Dyskeratosis Congenita and Telomere Biology Disorders: Diagnosis and Management Guidelines

First Edition, 2015
Editors: Sharon A. Savage, MD, and Elizabeth F. Cook, MD

We are deeply grateful to the many family and individual donors who made this book possible, as well as our sponsors:
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The authors, editors, and publisher of this guide have used their best efforts to provide up-to-date and accurate information that is generally accepted within medical standards at the time of publication. However, the information herein should not be construed as medical instruction or scientific endorsement. Always consult a physician before acting on any information.

There have been no clinical trials for most of the DC-associated medical complications. Thus, the clinical management suggested herein is based on the opinions and experience of the chapter authors and reviewers. These clinical care guidelines are meant to provide background and general clinical guidance as we await comprehensive clinical trials on the management of the multiple complications in DC.

Acknowledgements

The *Dyskeratosis Congenita and Telomere Biology Disorders Diagnosis and Management Guidelines* were developed over a period of months in the fall of 2014,when the authors met in consortia at a meeting focused on telomere-associated ailments.

This book wouldn't exist if not for the vision and leadership of Dr. Sharon Savage. Her guidance and direction helped make tangible a vital resource previously lacking shape. With deepest appreciation we thank Dr. Savage, not only for the tremendous effort required to organize and edit a medical text, but for her work chairing Dyskeratosis Congenita Outreach Incorporated's medical advisory board.

Instrumental in the emergence of DC Outreach was Dr. Blanche Alter. Even before this group had shape, Dr. Alter saw a means to help patients help themselves. For this, we thank you.

We sincerely thank all of our past and present medical advisors, including Drs. Suneet Agarwal, Jakub Tolar, Rodrigo Calado, Alison Bertuch, and Monica Bessler for their contributions to this book, but moreover for their commitment to families affected by this devastating disease.

We owe a debt of gratitude to the Dana-Farber Boston Children's Blood Disorders and Cancer Center for sponsoring the 2014 consortia that allowed our authors to meet in person.

We are so grateful for the contributions of every one of the book's authors—your combined knowledge has allowed for the creation of a powerful weapon for those affected by DC. The names and contact details for this book's contributors appear in the Contributors appendix, in the back of this book.

This book wouldn't have been possible if not for the Fanconi Anemia Research Fund. The *Fanconi Anemia Guidelines for Diagnosis and Management* has been an indispensable resource to us throughout the publishing process and with profound gratitude we thank the foundation for its support.

These guidelines are posted as a PDF at www.dcoutreach.org. To order additional print copies, send requests to:

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Donations to Dyskeratosis Congenital Outreach, Inc. accepted for printing and postage

Dyskeratosis Congenita Outreach, Inc., is proud to publish the first diagnosis and management guidelines for dyskeratosis congenita. We are a charity staffed by, and serving, families affected by DC globally. We have no paid staff, are governed by an elected seven-member board of directors, and served by a five-member medical advisory committee of physicians.

DC Outreach's mission is: *To provide information and support services worldwide to families affected by dyskeratosis congenita and telomere biology disorders, to encourage the medical community's research in finding causes and effective treatments, and to facilitate improved diagnosis by educating medical providers.*

Book design and layout by Joe Carlson

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Foreword:
DC Outreach and Its Role

Dyskeratosis Congenita Outreach, Inc. (DCO) was unofficially born in 2006 when two people affected by the rare, genetic condition connected over the common desire to reach out. Together they created a conduit of support among patients and families that had never before existed.

At its inception, DCO was simply a name, a website and an email address, yet a much-needed component of the dyskeratosis congenita landscape.

The absence of a family support group had also been recognized by physicians involved with the National Cancer Institute's (NCI) Inherited Bone Marrow Failure Syndrome Study. It was a void that a team of scientists, led by Dr. Blanche Alter, principal investigator of the study, set about filling by procuring funding to sponsor a family symposium for DC patients. Held in Bethesda in September 2008, the meeting allowed DC families to meet for the first time. Some of them had informally met through the DCO website, but most were coming face-to-face with another DC patient for the first time.

The meeting attendees, who likely would not have met otherwise, bonded over shared experiences. A number of them quickly organized into a group driven to expand the DC-community.

Symposium participants stepped forward and formed a volunteer group of directors. The nine-member board began holding monthly meetings via internet teleconference. In 2009 Dyskeratosis Congenita Outreach, Inc. received its official 501(c)3 status, giving it legitimacy as a charitable foundation.

A five-member medical advisory committee, comprised of some of the world's foremost authorities on DC, works closely with DCO to assist patients and educate the wider medical world on DC. The committee's current chair — Dr. Sharon Savage, chief of the Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, NCI — has not only been involved with the discovery of several genes linked to telomere disorders such as DC, but took the lead on creating the Clinical Treatment Guidelines.

Since its inception, the organization has grown to include many international families, which has been facilitated by DCO's expanding online presence. The site www.DCOutreach.org is continually updated with new features and information to better

serve the needs of the DC community. In addition to the website DCO maintains accounts with Twitter, Pinterest and Facebook, which have several hundred followers from dozens of countries.

In 2010, DCO initiated a biannual family retreat, which was held on Sebago Lake in Maine at Camp Sunshine, a retreat for families of children with life-threatening illnesses. These events have been resounding successes, attended by families from all over the world.

For many families one of the most difficult initial aspects of a DC diagnosis is the sense of isolation. So few people, doctors included, are familiar with or even aware of the disease, let alone have it. The chance for face-to-face interaction among patients and families—direct engagement with others who truly understand—is precious. Add to that the expert lectures, counseling sessions, opportunities for one-on-one time with some of the world's top DC-specialists, and a healthy dose of fun, and the experience becomes one that many attendees call "life changing."

These family retreats are free of charge to attendees, and DCO is committed to sponsoring them as long as possible.

Also in 2010 the group began publishing a semi-annual newsletter, the *DC Companion*, which is written and edited by DCO board members and alumni.

The group began hosting family support meetings, held via internet conference, in 2012. The monthly support calls are typically attended by a member of the medical advisory committee or another DC-specialist. The calls not only give participants the chance to gain an expert's perspective, but allow patients and family members the opportunity to relate to others who can empathize and understand.

In 2013, DCO was one of ten advocacy groups selected from hundreds of applicants to participate in a revolutionary research program organized by Genetic Alliance and funded by the Patient-Centered Outcomes Research Institute (PCORI). In autumn 2014, DC patients and family members began filling out "patient powered" surveys, the results of which have the potential to become part of a massive secure database allowing cross-referencing of patients, diseases and symptoms. The survey is optionally anonymous, yet the data will provide a wealth of information including symptom commonalities and interrelationships between diseases.

Genetic Alliance has stated it hopes to expand the study to include all disease advocacy groups. The DC Outreach community is fortunate to be involved from square one.

Attending scientific meetings is also among DC Outreach's initiatives, and since 2011 DCO has maintained a presence at the American Society for Hematology's annual conference.

Over 20,000 hematologists from around the world attend, and as an exhibitor the group spreads awareness about the condition by demystifying commonly held beliefs and distributing informational literature to attendees. Every year, as DCO representatives speak with numerous individuals who've never heard of or seen a DC-patient, the amount of outreach yet to be done remains evident.

The pronounced lack of both familiarity with DC and readily available information within the medical community are what prompted DCO to pursue the creation of this document. The number of stories told about children lost because of either misdiagnosis or sub-optimal medical treatment is both unbearable and unacceptable.

In line with DCO's mission to provide information and support services to families affected by DC and to educate medical providers, a goal has been to publish and disseminate a

definitive and comprehensive reference guide for the diagnosis, treatment, and management of DC and its related symptoms and manifestations.

DCO began as a two-person "support group." While it now has a seven-person board, five medical advisors, and a growing number of families and supporters, it's still an extremely small organization. Because of its size, the group depends on the dedication and contributions of so many to fulfill its mission.

Foremost among those contributors have been Drs. Alter and Savage of the National Institutes of Health. Their foresight has guided the creation of this foundation as well as the creation of this document.

This text has been written by some of the most practiced DC-clinicians and researchers. Their expertise on the disease's impact on each of the body's major organs and systems is unparalleled. We are profoundly grateful for the gift of their time and knowledge.

Our hope is that the availability of this resource will lead to more positive outcomes for Dyskeratosis Congenita patients all over the world.

—Nancy Cornelius, DC patient, daughter, and mother; founding member; and president of DCO from 2011-2014

Chapter 1:
Introduction to Dyskeratosis Congenita

Sharon A. Savage, MD

Introduction

Welcome to the first edition of the *Dyskeratosis Congenita and Telomere Biology Disorders: Diagnosis and Management Guidelines.*

These guidelines are the result of dyskeratosis congenita (DC) families, physicians, and scientists coming together for a common cause, to advance understanding of DC and its management. Chapter authors and their reviewers were purposely chosen because of their expertise in the field and also because of their varied experiences with DC.

The chapters were reviewed both at an in person meeting in Chicago, IL in October 2014 and through conference calls and email exchanges. There have been no clinical trials for most of the DC-associated medical complications. Thus, the clinical management suggested herein is based on the opinions and experience of the chapter authors and reviewers. Every effort

was made to illustrate points in which authors do not specifically agree or for which there are limited clinical data. These clinical care guidelines are meant to provide background and general clinical guidance as we await comprehensive clinical trials on the management of the multiple complications in DC.

A brief history of dyskeratosis congenita

The disorder now known as dyskeratosis congenita (DC) was likely first described in 1906 at a conference in Bern, Switzerland[1,2]. The skin manifestations were the focus of that report and it was described as poikilodermia vascularis atrophicans. A second report described a patient with abnormal skin, sparse hair and latticework skin pigmentation.

Professor F. Zinsser subsequently published a manuscript in 1910 on two brothers with skin, nail, and tongue abnormalities[3]. Additional reports led to its initial designation as Zinsser-Cole-Engman syndrome[2,4,5]. The mucocutaneous features and apparent congenital occurrence likely led to its designation as dyskeratosis congenita. DC was thought to be solely an X-linked disease because the early publications described the clinical manifestations in males only. In 1963, the first female case of DC was reported[6].

An expanded clinical phenotype, which included bone marrow failure and multi-organ system involvement, was subsequently documented. Variable expressivity, or a range of signs and symptoms in individuals with the same genetic condition, is now recognized in DC[7-10].

The causes of dyskeratosis congenita

Dyskerin (*DKC1*) was identified as the cause of X-linked DC in 1998[11].

This discovery also led to the first clues that DC was a disorder of telomere biology[12]. Understanding of DC etiology advanced significantly from 2004 to date, with the discovery of at least 10 other genes and recognition of autosomal recessive and autosomal dominant inheritance patterns (*TERC, TERT, NOP10, NHP2, TINF2, WRAP53, RTEL1, ACD, CTC1,* and *PARN*)[7-10,13,14].

Major technical advances in DNA sequencing have rapidly accelerated the pace our discoveries of the causes of inherited disorders. In fact, mutations in *PARN* were reported as a cause of autosomal recessive DC just one week before the final formatting of this book was completed and were thus unable to be incorporated into the final version of these guidelines[14].

What we have learned

The link between DC and telomere biology intersects several broad areas of study. Basic scientists are very interested in understanding the molecular biology of telomeres. Cancer researchers are actively pursuing studies of telomere length as a cancer risk factor as well as telomere biology in cancer cells[15].

The advent of telomere length diagnostic testing and expanded genetic testing have revealed a growing clinical spectrum of DC-associated telomere biology disorders[7,10,16,17]. We now understand that aberrant telomere biology may be present in patients without the classic mucocutaneous findings of DC but with one of the complications seen in DC, for example, *TERT* mutations patients with isolated aplastic anemia[18] or pulmonary fibrosis[19,20]. Biology has also served to connect the multisystem disorder Coats plus with DC due to the discovery of mutations in the telomere-capping gene *CTC1* as the primary cause of Coats plus[21-24].

The clinical management of DC requires a multidisciplinary approach. Most complications of DC are managed symptomatically. Outcomes after hematopoietic cell transplantation (HCT) for bone marrow failure have improved in recent years, but are still unsatisifactory[25-29]. Studies of the

progression of medical problems and case series of responses to therapy are helping us to understand DC but are limited by their observational nature[30,31].

What the future holds

Rapid advances in the understanding of telomere biology and thus the causes of DC have the potential to form the basis of studies aimed at treating the clinical complications. This will occur much more efficiently if clinicians, scientists, and families work together. These clinical care guidelines are an important first step in solidifying these collaborative efforts. As such, it is hoped they will form the foundation for advances in DC for years to come.

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Chapter 2:
Why Telomeres Matter

Roger R. Reddel, MD, PhD

Introduction

Biologists have studied telomeres for many decades – from long before their connection with human diseases became known. This chapter provides a background for the chapters that follow by summarizing information obtained from telomere research[a]. It begins with an overview of a few key aspects of biology required to understand what telomeres are, how they function, and the processes that protect and maintain them, and then describes how defects in these processes can cause disease.

Types of cells

Organisms are composed of microscopic building blocks called cells, and products (like the minerals and proteins that help form bone) that cells export into their environment. Each human contains many trillions of cells.

In the adult body, there are many types of cells with specialized roles, and many different shapes and sizes to suit

their functions. One example is peripheral nerve cells, which are very long so they can carry electrical impulses from the spinal cord to a muscle. Another is red blood cells, which are essentially small bags containing the oxygen-binding protein hemoglobin that get pumped around the body inside blood vessels, carrying oxygen from the lungs to other tissues.

One fundamental distinction between cell types relates to whether they are designed to pass on genetic information to the next generation or not. Ova and sperm, the cells that fuse to form a zygote and start the process of embryo formation, and the specialized cells that give rise to ova and sperm, are referred to as germ line cells. All other cells are called somatic cells.

Why cells need to make copies of themselves

Cells are able to replicate themselves via a process which usually involves growing in size and then dividing into two cells. The process is known as cell division, which means that this is one situation where division is the same as multiplication!

Throughout our lifetime, our cells need to replicate themselves a large number of times. We start off as a single fertilized egg cell (zygote), which needs to undergo a very large number of cell divisions to produce a fully formed baby. Growth

of a baby into an adult also occurs through the production of enormous numbers of new cells.

Further increasing the need for cell replication, a large number of cells are replaced many times over during a normal life span. There are some exceptions, like certain types of nerve cells that are made early on and can last for life, but cells of many other types are broken down and replaced by new ones.

Some of our cells are replaced regularly, which may be thought of as "programmed maintenance." One example is red blood cells, which are replaced with new cells every four months on average; the old ones are broken down and their molecular components are recycled.

Another example is skin cells, which are programmed to die off and shed as skin flakes, and are continuously replaced by new cells. The lining of the bowel is also being continuously replaced. Other types of cells are either replaced when they are damaged or are produced to meet a particular demand. For example, certain types of white blood cells are produced in large numbers when they are needed to fight an infection, and then mostly die off when their job is completed.

The molecules of life

Most cells contain a complete copy of the entire instruction set required for them to function and interact with each other.

This is encoded in a very long molecule – DNA (deoxyribonucleic acid). In contrast to the binary code used for computers (which consists of long strings of ones and zeroes), DNA contains four component nucleotides (represented by the letters A [adenine], C [cytosine], G [guanine], and T [thymine]) which constitute a four-letter code. The complete set of DNA is called the genome, and the DNA of the human genome is divided into 46 pieces called chromosomes. Twenty-three of these chromosomes come from one parent, and the other 23 from the other parent. Twenty-two of them are paired (essentially slightly different versions of the same genetic information) and referred to as autosomes; the remaining two chromosomes are the sex chromosomes, X and Y, which are similar in females (XX), but not in males (XY).

There are many other types of molecules within a living cell, but here just two other types will be mentioned: proteins and RNA (ribonucleic acid) molecules.

Proteins are particularly important because they form much of the intricate machinery that carries out a huge range of processes

required for life, including copying DNA and other molecules when cells are replicating. The precise makeup of individual proteins is encoded within specific regions (genes) of the DNA. Genes are used as the templates for production of RNA molecules, which are transported to areas within the cell responsible for manufacturing proteins (Figure 1).

Therefore, RNA acts as an intermediary molecule, taking instructions from the genome to the places where proteins are made. Biologists refer to the process of making RNA from the

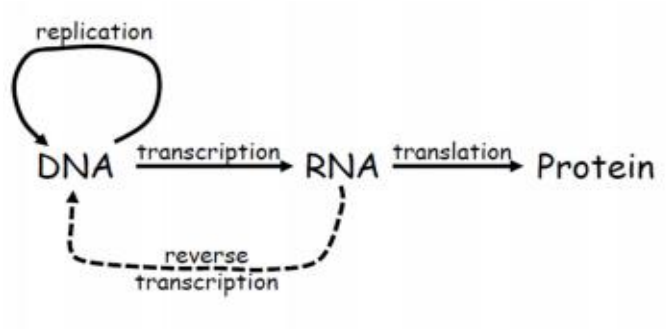

Figure 1: Relationships among key molecules of life. The human genome (which consists of 46 long DNA molecules) contains regions (genes), which are instruction sets for making (transcribing) RNA molecules. Many (but not all) RNA molecules contain an instruction set that is translated by the protein manufacturing machinery into a specific protein. Specialized proteins and RNA molecules assemble into large molecular machines that make a replicate copy of a cell's DNA (using the existing DNA as a template) when it is getting ready to divide into two cells. Sometimes, an RNA molecule is used as the template for making relatively small pieces of DNA, a process known as reverse transcription.

DNA code as transcription, and the process of making proteins according to the instructions in the RNA as translation. There are two functioning copies (alleles) of most genes, with many of the genes on the sex chromosomes being notable exceptions.

The way DNA gets copied when cells are being replicated is particularly interesting. DNA actually has two side-by-side strands, twisted to form the well-known double helix structure discovered by Watson and Crick. The strands are not identical; instead, they are complementary to each other. The relationship between the two strands in the double helix is determined by a very simple rule: wherever one strand has an A the other strand must have a T (and vice versa), and wherever one strand has a C the other strand must have a G (and vice versa).

To copy DNA, specialized proteins pull the strands apart and synthesize a new, complementary strand on each of the existing strands. This means that each DNA copy contains one pre-existing strand plus one newly synthesized strand.

Because RNA molecules are made according to the DNA code (but with different chemical building blocks), they can sometimes be "read backwards" by other specialized proteins to synthesize DNA. This process is called reverse transcription.

Telomeres

The arrangement of the human genome as a collection of 46 chromosomes, each with two ends, presents two big challenges that cells need to deal with. The first challenge is that the DNA copying machinery is incapable of copying all the way to the ends of a DNA molecule. The consequence is that chromosomes get slightly shorter every time cells are replicated.

The second is that cells need to be able to distinguish these 92 ends from accidental breaks elsewhere in the genome. Breaks in DNA have potentially serious consequences for cells, and cells therefore have elaborate sets of machinery for rejoining fractured ends. It is very important, however, that ends of different chromosomes not get "repaired" by being inappropriately joined together. This would result in one larger chromosome, which can then be pulled in two directions and break at some random location when the cell next divides.

Cells solve these two problems in the following ways. First, there is a specific DNA code at every chromosome end, which consists of a string of six letters (TTAGGG) repeated many hundreds of times. (Figure 2.) Because this repetitive DNA does

Figure 2. The DNA code at each chromosome end. One strand is a string consisting of hundreds of copies of the letters TTAGGG. The other strand contains the complementary letters, AATCCC.

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not code for a protein, it is partly dispensable: some of it can be lost due to normal shortening of chromosome ends without adverse consequences.

Second, there are specialized proteins within the cell that recognize DNA containing this specific code and bind to it, and there are other proteins which bind to the DNA-binding proteins. Together, these proteins form a complex structure that coats the chromosome ends and protects (or shelters) them from being mistakenly recognized as an accidental DNA break. Collectively, these proteins are therefore called the shelterin complex, and within this complex there are six different proteins, TRF1, TRF2, TIN2, TPP1, POT1, and hRAP1.

The repetitive DNA at the end of a chromosome is called a telomere. Sometimes, however, biologists use the same word to refer to the DNA plus the proteins that bind to it. Although this

is potentially confusing, in practice the meaning of the word is usually clear from the context.

Although telomeres still function despite a considerable amount of shortening, the amount of shortening that can occur without consequence is not unlimited. If too much shortening occurs, there is not enough TTAGGG left for shelterin to bind to, which results in the chromosome ends losing their protection from being treated as a DNA break.

Cells have a built-in mechanism to deal with shortened telomeres. Once a telomere reaches a minimum length, the cell is no longer permitted to divide again. In effect, it reaches its use-by date for replication. Telomere shortening can thus contribute substantially to the aging process. When there is a significant decline in the number of cells that are able to replicate, tissues and organs lose their capacity to undergo the renewal processes upon which healthy function depends. Telomere shortening can contribute to aging even in tissues that contain many non-dividing cells (like the brain) because their health depends on cells that do need to continue dividing. For example, the nutrition of the non-dividing cells of the brain depends on blood vessels lined by cells that must continue dividing to maintain normal function.

How telomeres can last a normal life span

Telomeres are part of a finely tuned biological system. Under normal circumstances, telomeres continue to function, protecting the chromosomes throughout all of the cell divisions of a normal human life span. Two critically important factors in their continued competence are their starting length and the rate at which they shorten.

Germ line cells require processes to provide an adequate starting length very early in the development of the embryo. These processes involve the action of a complex molecular machine called telomerase[b], which is able to add new DNA (containing many repeats of the TTAGGG sequence) to the ends of chromosomes, and thereby completely counteract the normal shortening process that accompanies cell division.

The rate of telomere shortening is influenced by environmental and lifestyle factors. For example, toxic chemicals and cancer chemotherapy agents can cause tissue damage, and therefore induce a lot of cell division, thus increasing the overall rate of telomere shortening. Treatments that are normally used to get a patient ready for a bone marrow transplant can also cause this, and some viral infections can have this effect. In addition, lifestyle factors, such as physical inactivity, smoking,

severe prolonged stress, and obesity are associated with shorter telomeres.

There are low levels of telomerase activity in the cells of many somatic tissues, which partially counteract normal telomere shortening. This slows down, but does not completely prevent the shortening in normal somatic cells. This is particularly important in organs that undergo a lot of cell division, including the bone marrow, which constantly produces huge numbers of new blood cells.

Telomerase is thus a key player in ensuring that our telomeres last for a normal human life span. It not only is important for providing a sufficient telomere length buffer at the start of life, but also for slowing down the rate of telomere loss through successive cell divisions. Inherited defects in telomerase can result in telomeres that are excessively shortened and therefore ineffective at preventing chromosome-related disease.

Telomerase

Telomerase is an enzyme that synthesizes the DNA sequence TTAGGG and adds it to the ends of telomeres. It does this by reverse transcribing an RNA molecule, which has a short sequence in the template region that is complementary to the TTAGGG DNA sequence. The RNA is sometimes referred to as

hTER or hTERC, but usually hTR (human Telomerase RNA), and is encoded by the *TERC* gene (Telomerase RNA Component).

Telomerase also contains a protein subunit called TERT (Telomerase Reverse Transcriptase), which does the reverse transcribing. The name of the gene encoding this protein is *TERT*.

A third component of the active telomerase complex is a protein called dyskerin, which binds to RNA molecules like hTR. The gene that encodes dyskerin is called *DKC1* because it was the first mutation confirmed to cause dyskeratosis congenita, one of the syndromes caused by short telomeres.

The active telomerase enzyme complex contains at least six molecules: two copies each of hTERT, hTR, and dyskerin. (Figure 3). Manufacturing and assembling this complex molecule requires the action of specialized proteins, including NOP10 and NHP2.

In order to lengthen telomeres, telomerase needs to be transported from the places where it is assembled to the ends of telomeres where is does its work. TCAB1 (encoded by the gene *WRAP53*) is a protein required for this transportation. TCAB1

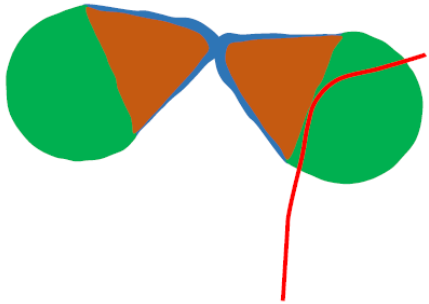

Figure 3. Schematic of telomerase components. It has not yet been possible to get a high-resolution "picture" of what telomerase looks like. However, the active form of the molecule is known to contain two copies each of TERT, hTR, and dyskerin. It latches on to the end of a telomere (red line) in order to lengthen it. For full-color illustrations, **see Color Photo Appendix, p. 399**.

(and also NOP10 and NHP2) may form part of the telomerase complex at various stages in its life cycle.

Once telomerase arrives at the chromosome end, it needs to dock with the telomere. A protein critically important for this is TPP1 (encoded by the *ACD* gene). TPP1 has a small region on its outer surface (the "TEL patch") with which it latches onto the surface of the telomerase enzyme.

Other molecules needed for normal telomere length

Considering data from other species, it would not be surprising to find that there are several hundred proteins that influence telomere length in humans to a greater or lesser extent. Of those that are already known, the shelterin proteins are very

important, because of their ability to influence telomerase activity and to protect the telomere. Telomerase synthesizes only the TTAGGG strand of telomere DNA. CTC1, STN1, and TEN1 are three proteins which form a molecular machine (the CST complex) which is thought to be involved in synthesizing the complementary CCCTAA DNA strand. The complex is also thought to be important in controlling the activity of telomerase.

The DNA of telomeres can be configured in a number of ways other than the helical Watson-Crick structure. The presence of many consecutive Gs in the telomere sequence means that telomeres are able to form complex structures (known as G-quadruplexes), whereby the Gs bind to each other instead of

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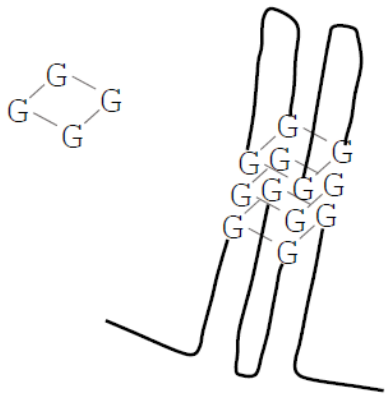
Figure 4:. Telomeres can form structures called G-quadruplexes. DNA that contains many runs of the letter G, can fold into complex structures, where the Gs bond together (instead of binding to the Cs on the strand of complementary DNA). Four Gs can bond to form a square-like structure called a G-quartet (left), and stacks of G-quartets (right) are called G-quadruplexes.



forming G-C pairs. Telomeres can also form a "t-loop" structure.

A number of proteins, including RTEL1, are required to prevent the G-quadruplex and t-loop structures from causing problems when telomeres are being copied during cellular replication.

Inherited causes of excessively short telomeres

Inherited defects in any of the genes that encode components of telomerase (*DKC1*, *TERC* or *TERT*) or of specific genes that encode proteins that are involved in telomerase's assembly (NOP10 or NHP2), transportation to the telomere (TCAB1), or docking with the telomere end (TPP1), can result in telomeres being too short, Figure 5. (See Color Photo Appendix for full page illustration.) In addition, defects in genes that encode specific proteins involved in other aspects of telomere protection and synthesis (*TINF2* [the gene encoding TIN2, one of the shelterin proteins], CTC1 and RTEL1) may also cause excessive telomere shortening. Some individuals who have excessively short telomeres do not appear to have mutations in any of these ten genes, so it is likely that there are additional inherited causes of short telomeres that have not yet been found.

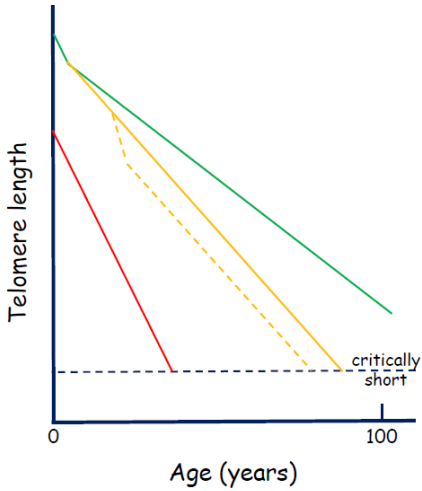
The consequence of deficient telomerase activity is two-fold. First, the normal shortening that accompanies cell division is

counteracted less effectively than when telomerase is normal, so telomeres shorten faster. Second, when there is less telomerase activity than normal, it may not be possible to restore telomere length in the germ line cells and early embryo. The result is that an individual in the next generation inheriting the defective gene may also inherit telomeres that start off shorter than normal, a "double whammy" effect. This results in a tendency for short telomere diseases to get worse from generation to generation, an unusual pattern of inheritance called genetic anticipation. Defects in the other genes which cause short telomeres may follow a similar pattern, even though they may not directly affect telomerase activity. Gene defects causing failure to protect the telomere or to copy the telomere DNA properly during cell division may speed up the rate of telomere shortening to an extent that normal levels of telomerase are not able to adequately counteract, either in somatic or germ line cells that pass DNA on to the next generation.

Why short telomeres cause disease

Cells with excessively short telomeres reach their proliferative "use-by date" much earlier than normal, which means that various tissues and organs are not able to maintain themselves

Figure 6. Telomeres need to last for a normal life span. The telomeres of many somatic cells shorten throughout life but, if they have a normal starting length and do not shorten too rapidly, we can live a long life and still have sufficient cells that do not have critically short telomeres (green line). Because of the amount of growth occurring, telomeres shorten more rapidly in early childhood than in adults. If the telomeres shorten faster than normal (which occurs, for example, when cells that undergo a lot of proliferation do not have enough telomerase), then some organs may lose the capacity to renew themselves later in life (amber line). Some environmental factors may cause cell death, which results in an increased need for proliferation and therefore an increased rate of telomere shortening, and this may result in problems occurring earlier in life (dotted amber line). Individuals who start out with short telomeres and also have an increased rate of telomere shortening (red line) may have problems from short telomeres early in life. **See Color Photo Appendix, p. 399.**



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by normal numbers of cell divisions. Eventually, this may result in an insufficient number of cells (cytopenia) in various organs.

The severity of the condition tends to be related to how short the telomeres are. If the telomere length deficit is very severe, there may even be insufficient cell division for organs to develop normally in specific embryonic tissues (for example, in the cerebellum and other parts of the brain). When short telomere

diseases become manifest first in childhood, they often affect the bone marrow, which is normally one of the most highly proliferative organs. This causes a deficiency in numbers of red blood cells (anemia), white cells (neutropenia), and platelets (thrombocytopenia). The combination of these three deficiencies is called aplastic anemia or bone marrow failure. When telomere shortening is less severe, problems may not surface until later in life.

Excessively short telomeres are also associated with an increased risk of cancer. The reasons for this may include the following. First, when telomeres become excessively short, they lose their ability to protect chromosome ends from the DNA repair machinery. This results in end-to-end fusion of chromosomes and the potential for the joined chromosomes to break at a random location when the cell next divides. This sets up a cycle where continued random chromosome breakage and random rejoining creates unpredictable changes in the genome, which may increase the risk of cancer. Second, organs that are depleted of normal cells may send increasingly powerful signals to stimulate the remaining cells to divide, which may inadvertently favor the growth of rogue cells on their way to becoming cancerous. Third, normal cells in a normal organ can

often restrain the growth of rogue cells, but this effect is progressively lost as cytopenia develops.

Excessive telomere shortening can affect almost any organ system, but it is still not clear why it causes bigger problems in some organs than others. It seems easy to understand why bone marrow, a highly proliferative tissue, may be affected.

It is difficult to understand, however, why there are more often serious problems in lungs, which are thought to have only moderate rates of cell division, than in the skin, or in the lining of the gastrointestinal tract, both of which constantly undergo high levels of cell division. It is also difficult to understand, for example, why some individuals who have no major problems with their bone marrow will develop lung disease. Even more baffling, there are individuals with very short telomeres who appear to be disease-free for a normal life span.

The answers may lie in part in the effects of environmental and lifestyle factors. In some families with short telomeres, pulmonary disease only occurs in individuals who have both inherited the defective gene and who smoke. In other families, an individual's short telomere-related problems may become manifest when treated with chemotherapy for cancer. The

answers may also lie in the modifying effects of other genes we do not yet know about.

This uncertainty also provides some grounds for optimism. An individual who inherits a short telomere mutation will not necessarily develop any manifestations of the condition, and even if one or more of these manifestations occur, disease progress may be quite unpredictable. The more that is understood about interactions between the environment and short telomere gene mutations, the better we may be able to prevent or modulate the adverse effects of the genes.

Notes

[a] This chapter will be posted at www.cmri.org.au so it can be updated from time to time to incorporate new research findings.

[b] Many people find the similarity between the words "telomere" and "telomerase" confusing. Telomeres are the DNA at chromosome ends (which become shorter with cell division), whereas telomerase is an enzyme (molecular machine) which lengthens telomeres.

Chapter 3:
Diagnosing Dyskeratosis Congenita and Related Telomere Biology Disorders

Alison A. Bertuch, MD, PhD, Gabriela Baerlocher, MD, and Blanche P. Alter, MD, MPH

Introduction

Dyskeratosis congenita (DC) was initially defined by the mucocutaneous triad of lacy reticulated skin pigmentation, nail dystrophy and oral leukoplakia (see Chapter 1).[1] However, it is now known that DC develops as a result of defective telomere maintenance, so this syndrome of telomere shortening is referred to as a telomeropathy or telomere biology disorder.

DC can impact every organ system and lead to a wide range of clinical manifestations, with bone marrow failure being a major clinical feature (see Table 1, end of chapter).[2,3] The identification of genetic mutations causative of DC and development of telomere length testing have facilitated diagnosis (see Chapters 2 and 4). As a result, diagnostic criteria for DC have evolved over the past two decades, although expert opinions vary in the details.[3-6]

In some cases, features of DC are present at birth or during infancy, while in others they present over the continuum of the first two decades of life. In some patients, they do not appear until adulthood.[7, 8] Genetic and telomere length testing provide early identification of individuals with a potential telomere disorder who have not yet manifested disease features. Serial physical examinations are warranted in individuals at risk of developing further symptoms —because DC features may develop over time.

Individuals should be considered to have DC if they have telomere lengths below the first percentile for age by multicolor flow cytometry with fluorescent in situ hybridization (flow FISH) in several subsets of leukocytes (granulocytes, CD45+ naïve T cells, CD45- memory T cells, CD20+ B cells, CD57+ NK/NKT cells) or a damaging or deleterious mutation in a DC-associated gene. In studies by Alter et al. with a selected patient cohort (patients referred with a diagnosis of dyskeratosis congenita or another inherited bone marrow failure syndrome such as Fanconi anemia, Shwachman-Diamond syndrome, or Diamond-Blackfan anemia), the results of telomere length measurements suggest that telomere lengths below the first percentile for at least 3 of 4 lymphocyte subsets are highly

sensitive and specific for DC.[9-11] The authors caution that the interpretation of telomere length results must be made in conjunction with the clinical context and by persons experienced in interpreting these results.

Major clinical features of DC

1. The mucocutaneous triad

The mucocutaneous triad of reticulated skin pigmentation, nail dystrophy, and oral leukoplakia typically manifests in mid-to-late childhood. The features need not present simultaneously nor do all need to be present to make a diagnosis of DC (see Chapter 10 for Dermatologic Manifestations of DC).

a. Reticulated skin pigmentation

Skin changes most often appear as reticular or lacy hypo- and hyperpigmentation, but may also be more punctate (Figure 1). All areas of skin may be affected, although changes may be restricted to neck, upper chest, and proximal parts of the limbs initially. In some cases, the pigmentation follows Blaschko lines.[12] Skin findings may simulate manifestations of graft versus host disease, a complication of hematopoietic cell transplantation (HCT). Some unrelated disorders also manifest reticular skin

pigmentation including dermatopathia pigmentosa reticularis, Naegeli syndrome, poikiloderma with neutropenia (also known as poikiloderma Clericuzio type), and Kindler syndrome.

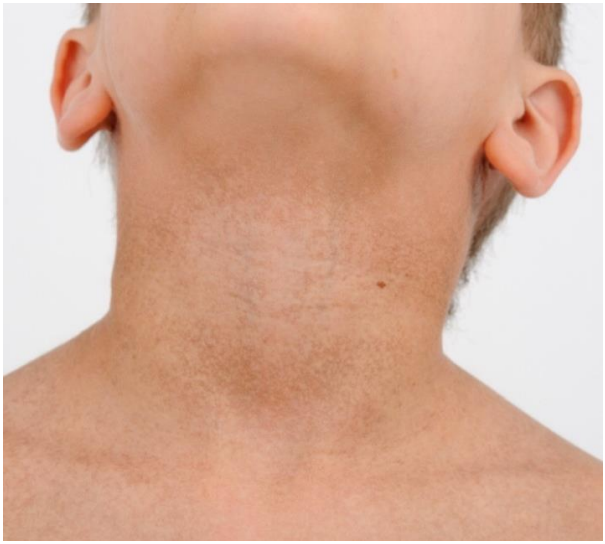
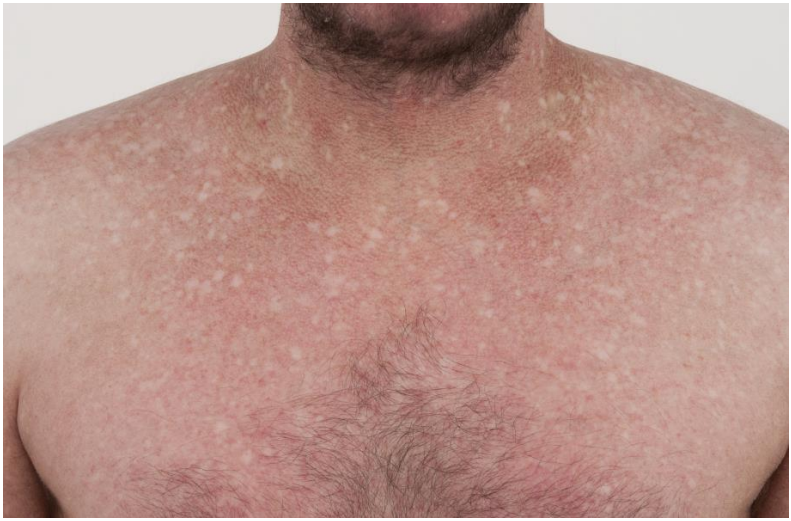


Figure 1: Skin pigmentation changes in DC.
(Reproductions in **Color Photo Appendix** on page 399.)



b. Nail dystrophy

Changes to the finger and toe nails may be subtle or severe, with ridging, thinning, peeling, or slow growth (Figure 2). Nail changes in a given patient may be asynchronous, with normal appearing nails adjacent to nails that are clearly affected. With age, nails may even seem to "disappear."

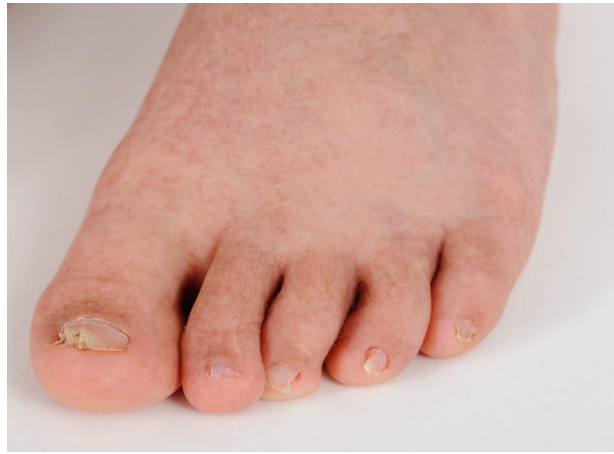
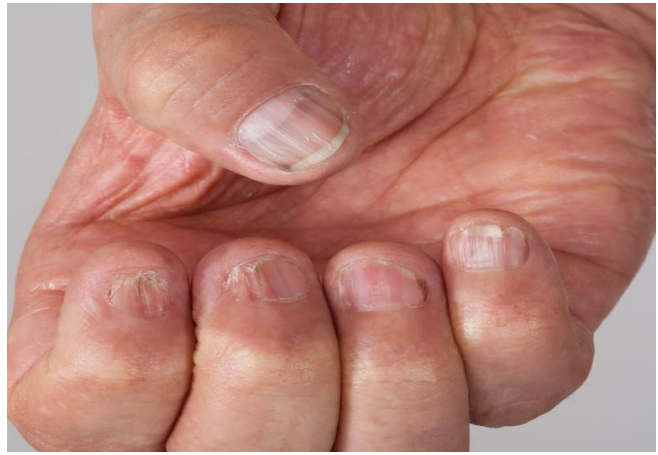


Figure 2: Nail dystrophy in DC



c. Oral leukoplakia

Oral leukoplakia appears as thickened, white patches that cannot be scraped off the buccal mucosa or along the edges and surface of the tongue (Figure 3). An experienced otolaryngologist or oral surgeon best evaluates oral leukoplakia.

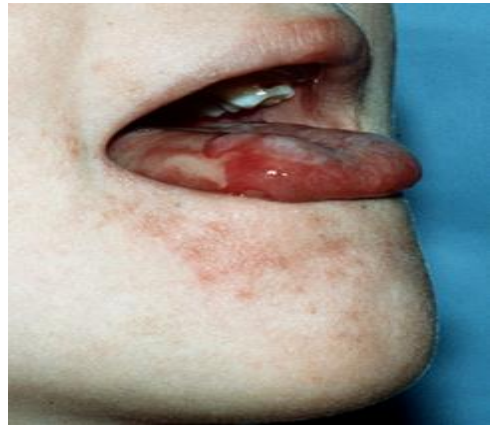
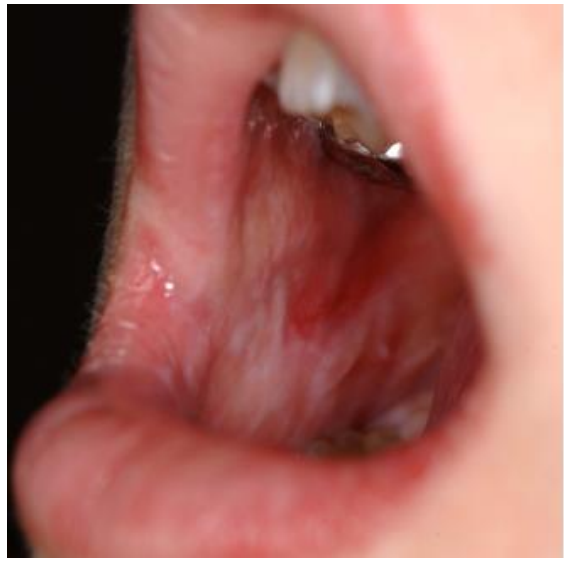


Figure 3: Leukoplakia in DC



2. Bone marrow failure

Bone marrow failure is generally defined as bone marrow cellularity less than normal for age, and with one or more peripheral blood cytopenias (absolute neutrophil count, hemoglobin, or platelet count below the lower limit of normal for age). It is a common feature of DC, with up to 85% of patients in the London Dyskeratosis Congenita Registry reporting bone marrow failure by the age of 30 years.[2] In a competing risk analysis, the cumulative incidence of bone marrow failure in the National Cancer Institute Inherited Bone Marrow Failure Syndrome Study was 50% by age 50.[13] The extent of bone marrow failure can be mild to severe, and can precede the mucocutaneous features of DC. Bone marrow failure at any age should prompt consideration of a diagnosis of DC.

Diagnostic evaluations for bone marrow failure include:

- Complete blood count, including mean corpuscular volume (MCV). An elevated MCV may indicate presence of an inherited syndrome such as DC, in distinction from immune-mediated acquired aplastic anemia.
- Absolute reticulocyte count
- Hemoglobin F measurement. Elevated hemoglobin F suggests inherited rather than acquired aplastic anemia.

- Bone marrow aspiration and biopsy
- Bone marrow cytogenetic analysis by G banding
- Bone marrow fluorescence in situ hybridization to detect 5q-, 7q-/monosomy 7, trisomy 8, and 20q-, if clinically indicated.

Additional evaluations that may be considered

- Chromosome breakage analysis to rule out Fanconi anemia
- RBC folate and vitamin B12 to assess stores, if MCV is elevated

The hematologic manifestations of DC and their treatment are presented in detail in Chapter 7, Management of DC.

Identifying additional features of dyskeratosis congenita

Table 1 lists the multitude of clinical findings that may be observed in DC. Some of these findings may be apparent on physical examination, whereas others require specific testing. Clinical evaluations that may be done to uncover additional features of DC are listed below. These should be considered on an individual patient basis, as clinically indicated.

Growth delay

- Birth weight and length measurements and gestational age at birth to assess for intrauterine growth retardation
- Current weight and length to assess for short stature and/or failure to thrive

Developmental delay/intellectual disability (see also Ch. 20)

- Neuropsychological testing

Neurologic manifestations

- Frontal-occipital head circumference measurement to detect microcephaly
- Brain magnetic resonance imaging to detect cerebellar hypoplasia (Figure 4)
- Head X-ray or brain computed tomography to detect calcification

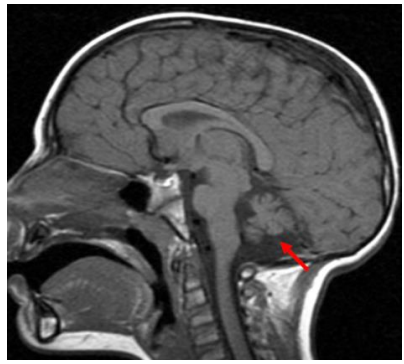


Figure 4: Cerebellar hypoplasia in Hoyeraal-Hreidarsson syndrome (red arrow)

Ophthalmologic manifestations (see also Chapter 11)[14]

Examination should be performed by an ophthalmologist and include a retinal exam. Findings may include:

- Epiphora (constant tearing) due to lacrimal duct stenosis or its congenital absence
- Blepharitis
- Exudative retinopathy
- Retinal neovascularization
- Retinal hemorrhages

Hearing loss

- Audiogram or auditory brain-stem evoked response testing

Dental involvement (see also Chapter 12)

In addition to oral leukoplakia, screening should allow for detection of:

- Extensive caries or tooth loss
- Periodontal disease
- Taurodontism (enlarged tooth pulp chambers) or decreased tooth root/crown ratio

Dental radiographs should be done with digital machines if possible, to reduce radiation exposure.

Lung involvement (see also Chapters 14 and 15)

Initial evaluations to assess lung involvement include:

- Pulse oximetry
- Pulmonary function tests (PFTs)
- Diffusion capacity of the lung for carbon monoxide (DLCO testing)
- Six minute walk test for young children unable to perform PFTs

In cases in which lung involvement is suspected, additional testing includes:

- Chest radiography
- Non-contrast high resolution chest computed tomography

Gastrointestinal tract and liver involvement (see also Chapters 16 and 17)

- A patient may report dysphagia (pain on swallowing) due to the presence of an esophageal web or stricture, which is diagnosed by barium swallow or esophagram.

- Upper and lower gastrointestinal tract bleeding due to ulceration, telangiectasias, or varices may be diagnosed by upper and lower tract endoscopy.
- Liver disease may be revealed by the following testing:
    - Aspartate aminotransferase (AST/SGOT)
    - Alanine aminotransferase (ALT/SGPT)
    - Alkaline
    - Gamma-glutamyltransferase (GGT)
    - Conjugated and unconjugated bilirubin
    - Albumin
    - Prothrombin time (PT)
    - Liver ultrasound, fibroscan, or magnetic resonance imaging
    - Liver biopsy, which may be indicated if the above studies are abnormal, should include assessment of liver iron stores in addition to histopathology.

Genitourinary tract involvement (see also Chapter 18)

- Physical examination may reveal
    - Urethral stricture
    - Hymenal stricture in females
    - Phimosis in males
    - Hypogonadism (small testes) in males

- Urinalysis may uncover microscopic hematuria due to hemorrhagic cystitis.

Musculoskeletal and endocrine disease (see also Chapter 13)

Complaints of hip or shoulder pain may be due to avascular necrosis (AVN) of the humeral or femoral head. AVN can be diagnosed by:

- X-ray – most sensitive for late stage disease
- Bone scan
- Magnetic resonance imaging – may pick up early changes in bone

Osteoporosis may be present and is diagnosed by:

- Dexascan
- Spine X-ray, which may also reveal compression fractures

Immunologic abnormalities (see also Chapter 9)

Patients may present with common variable immunodeficiency or severe combined immunodeficiency.[16, 17] Testing for immunodeficiency may include:

- Quantitative immunoglobulin levels for IgG, IgM, IgA, and IgE

- Determination of T, B, and NK cell percentages and absolute numbers
- Lymphocyte proliferation panel for mitogens and antigens

Additional mucocutaneous findings

- Atrophy of the papillae on the dorsum of the tongue
- Complete or patchy alopecia
- Premature graying of the hair
- Sparse eyebrows and lashes
- Telangiectasias
- Hyperpigmentation of the gums, tongue, palms, and soles have been anecdotally reported in individuals of African descent. *ACD* (*TPP1*)
- Glyphs (fingerprints) may disappear over time

Pertinent history

Cancer history of patient (see also Chapter 21)

Cancer may be the presenting feature of DC. The most common neoplasms seen in DC include:

- Myelodysplastic syndrome and acute myelogenous leukemia (AML)

- Head/neck cancer, especially squamous cell carcinoma of the tongue
- Anogenital squamous cell carcinoma

Family history

Obtaining a thorough family history is crucial. As discussed in Chapter 4, disease anticipation, with earlier onset and more severe disease manifestations, may be observed in successive generations. Patient pedigree should note if there is a history of:

- Dyskeratosis congenita
- Pulmonary fibrosis
- Liver fibrosis or cirrhosis of nonalcoholic, noninfectious etiology
- Bone marrow failure, myelodysplastic syndrome, or leukemia
- Cancer in young relatives (age less than 50 years), especially of the head and neck
- Infant or early childhood death due to immunodeficiency

* * *

Molecular diagnosis

Telomere length testing

Several methods have been developed to measure telomere length, including:

- Multicolor flow cytometry combined with FISH, which provides a measurement of telomere length in cells within a variety of leukocyte subsets,[18, 19] and
- Quantitative polymerase chain reaction (qPCR), which provides a relative estimate of telomere length with measurements of telomeric repeat-containing DNA and an internal single copy control.[20,21]
- Southern blot analysis, which uses an electrophoretic pattern of DNA to estimate the median telomere length of the total leukocytes within the sample.

Telomere length declines with normal aging. Additionally, there is a broad distribution of telomere length at any given age within a healthy population. For these reasons, a large number of individuals, from newborns to the aged, is needed to establish age-based normal values.

Clinically certified testing of telomere length by automated multicolor flow FISH is available in Canada (CLIA-certified) and

Switzerland (see Resources section). Importantly, since this testing is performed on fresh peripheral blood cells, it is best used as a diagnostic tool prior to HCT; after transplant, donor, rather than patient, cells would be assayed. Many investigators use qPCR or Southern blots to measure telomere length in white blood cells in the research setting; however, it is less accurate, reproducible, sensitive, and specific than telomere measurements by automated multicolor flow FISH.[22]

Individuals with DC have very short telomere length across cell types, defined as telomere length less than the first percentile for age.[9-11, 23] Specifically, very short telomere length in practically all leukocyte subsets (granulocytes, naïve T cells, memory T cells, B cells, and NK/NKT cells) as determined by automated multicolor flow FISH is both highly sensitive and specific for DC (see Figure 5, right, and Table 2, end of chapter).[9-11]

Telomere length slightly below the first percentile in three of the lymphocyte populations is only very rarely observed in patients with acquired aplastic anemia or inherited bone marrow failure syndromes other than DC, such as Fanconi anemia, Diamond-Blackfan anemia and Shwachman-Diamond syndrome.[9-11] Additionally, three patients with Dubowitz syndrome[24] and one with Coronin 1A deficiency syndrome[25]

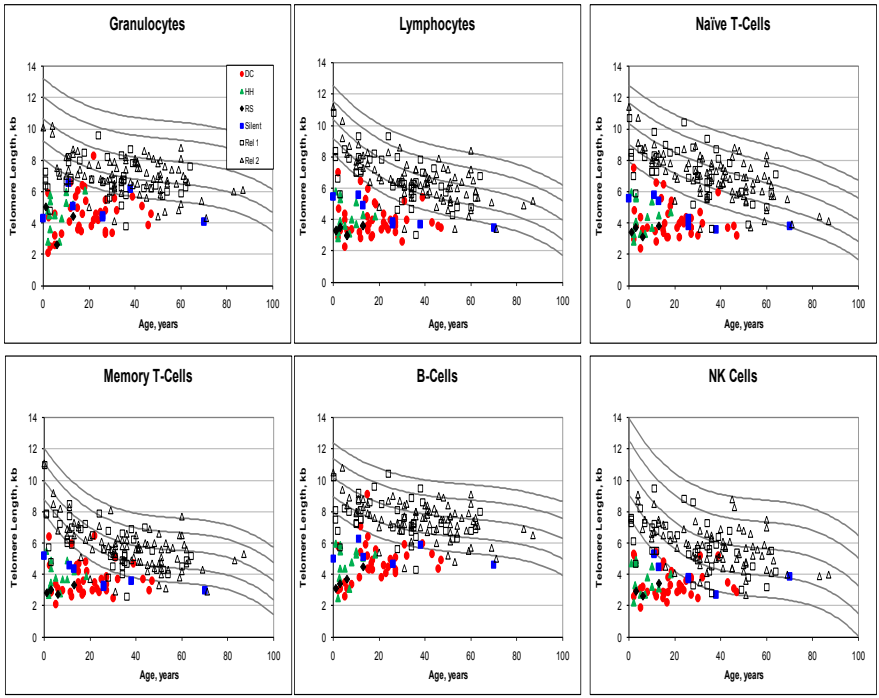


Figure 5: Telomere length according to age in patients with DC and their relatives. (See color version of the figure in the **Color Photos Appendix**.) The vertical axis represents telomere length in kb. The curved lines in the figures indicate the first, tenth, 50th, 90th, and 99th percentiles of results from 400 normal controls. Colored symbols represent patients with DC and their relatives. Red circles: classical DC patients; green triangles: Hoyeraal-Hreidarsson; black diamonds: Revesz syndrome; blue squares: silent carriers; open black squares: DC relatives in families with unknown genes; open black triangles: DC relatives without mutations in the probands' genes. Top panels show granulocytes, lymphocytes, and CD45RA^{+}/CD20^{-} naïve T cells. Bottom panels show CD45RA^{-} memory T cells, CD20^{+} B cells, and total NK/NKT cells. Figure and Figure Legend directly from Alter et al., Haematologica 2012.[10]

have been reported to have very short telomere lengths. Further study is needed in these rare disorders to better understand the significance of these findings. Thus, while highly sensitive and specific for DC, very short telomeres alone are insufficient to render its diagnosis. Results should be interpreted in the context of the patient's other clinical features and family history (see above "Features sufficient to establish a diagnosis of DC").

Bone marrow failure can precede the development of other DC features. Therefore, telomere length in leukocyte subsets by multicolor flow FISH testing is highly recommended for all patients with aplastic anemia. This is particularly true for patients being considered for HCT, as the diagnosis of DC has a major impact on the conditioning regimen and may influence donor selection. For example, siblings with very short telomeres would be considered suboptimal donors even in the absence of overt disease (see Chapter 8). Additionally, medical treatment for DC might include androgens, while immunosuppressive therapy might be indicated in cases of acquired bone marrow failure. Thus, telomere length testing has the potential to greatly influence treatment strategy. See Chapters 7 and 8 for further information.

Gene sequencing

To date, mutations in 11 genes have been found to cause DC: *DKC1, TINF2, TERT, TERC, WRAP53 (TCAB1), NOP10, NPH2, RTEL1, CTC1*, *ACD* and *PARN*.[26-28] (See Chapter 4 for further discussion of the genetics of DC). Clinical laboratories offer targeted sequencing of many of these genes, and whole exome sequencing is also available as an alternative approach (see Resources section). Sequencing of the known DC-associated disease in large cohorts of individuals, including both children and adults, with a clinical diagnosis of DC will identify causative mutations in ~70% of cases. It is important to recognize that the absence of a known mutation in a known gene does not rule out DC in a person who may yet have limited features of the disease. For instance, aplastic anemia and telomeres well below the first percentile may be seen in the absence of mucocutaneous or other features of DC. In addition to aiding the diagnosis of an individual patient, obtaining a molecular diagnosis through gene sequencing provides a mechanism to screen family members and to offer genetic counseling, as well as permit pre-implantation genetic diagnosis (see Chapter 5 on Genetic Counseling).

Additional considerations

Female carriers of DKC1 mutations

Although *DKC1* mutations result in X-linked recessive disease,[29] female carriers may occasionally manifest clinical features of DC, such as delayed wound healing, abnormal pigmentation, and nail dystrophy.[30] In addition, they may have skewed leukocyte X chromosome inactivation,[12] defined as greater than 90 percent of cells inactivating the same X chromosome (for example, the X chromosome inherited from the mother). Clinical X chromosome inactivation analysis utilizing the human androgen receptor assay is offered by numerous testing facilities (info on Repeat Diagnostics Inc. and University Hospital Bern in the Resources section) and may be useful in determining the carrier status of females when *DKC1* testing is not available or a variant of uncertain significance is identified.

Revertant somatic mosaicism

Similar to that seen in Fanconi anemia, revertant somatic mosaicism has been reported in autosomal dominant DC.[31] This phenomenon refers to the presence (within the same person) of cells bearing a mutation originating from the germline, as well as a subpopulation of cells in which the mutant allele has reverted

to wildtype. Reversion is thought to occur via mitotic homologous recombination. Hematopoietic stem cells no longer bearing a DC-associated mutation may have stabilized or possibly lengthened the telomeres. They may thereby have the potential to drive effective hematopoiesis. Such growth advantage is not observed in other somatic tissues like lung, liver, and skin. Patients may have clinical features suggestive of DC but with minimal hematopoietic abnormalities. Sequencing of blood cell DNA may fail to detect the presence of the mutant allele due to its relatively smaller proportion in peripheral blood. Therefore, in cases in which revertant somatic mosaicism is suspected, for example in patients with solely extrahematopoietic manifestations of DC, DNA from nonhematopoietic tissue, like skin fibroblasts, should be analyzed.

Dyskeratosis congenita subtypes

Three subtypes of DC have been recognized. They are frequently referred to as "severe" variants, reflecting their presentation in the first months to two years of life, and

association with neurodevelopmental defects [1]*. Their diagnostic criteria are listed below, and are also described in greater detail in Chapter 6.

1. Diagnosis of Hoyeraal-Hreidarsson syndrome (OMIM 300240)[32] Meets diagnostic criteria of DC (see above), plus

- Cerebellar hypoplasia

Additional features with high penetrance in Hoyeraal-Hreidarsson syndrome include

- Intrauterine growth retardation
- Developmental delay and intellectual disability
- Microcephaly
- Immunodeficiency

2. Diagnosis of Revesz syndrome (OMIM 2681300)[33]

Meets diagnostic criteria of DC (see above) plus

- Bilateral exudative retinopathy (bilateral Coats disease)

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[1]* The authors of this advise caution against the use of the term "severe" for these specific subtypes, as patients with classical DC or those with single system involvement such as pulmonary fibrosis or bone marrow failure also experience severe and life-threatening disease states.

Additional features may include:

- Intrauterine growth retardation
- Sparse hair
- Intracranial calcification

3. Diagnosis of Coats plus (OMIM 612199)[34]

- Distinctive pattern of intracranial calcification involving the thalamus, basal ganglia, dentate, and deep cortex, with associated leukoencephalopathy and brain cysts
- Retinal telangiectasia and exudates (as seen in Coats disease)
- Osteopenia with tendency to fracture and with poor bone healing
- Recurrent gastrointestinal hemorrhage due to vascular ectasias in the stomach, small intestine, and liver
- Intrauterine growth retardation
- Additional features overlapping with DC may be present: dystrophic nails, sparse hair, and abnormal skin pigmentation

Table 1: Diagnostic Findings in DC. These features present with variable severity and may not be present in all patients, modified from ref. 3.

Physical Features	
Mucocutaneous triad	Dystrophic nails
	Lacy reticulated pigmentation, especially neck and thorax
	Leukoplakia (white patches), usually oral
Additional features (in order of frequency[3])	
Eyes	Epiphora (tearing), lacrimal duct stenosis, blepharitis, exudative retinopathy
Hair	Early graying, loss, sparse eyelashes
Gastrointestinal	Esophageal stricture, liver fibrosis, cirrhosis, peptic ulceration, enteropathy
Stature	Short
Dental	Caries, missing teeth, periodontitis, decreased crown/root ratio, taurodontism
Skeletal	Osteoporosis, hip avascular necrosis
Head/Neurodevelopmental	Microcephaly, cerebellar hypoplasia (ataxia, spasticity, hypotonia), intracranial calcification
Perinatal	Low birth weight, intrauterine growth retardation
Lung	Fibrosis, restrictive; arterio-venous fistulas
Males	Small testes, undescended testes, phimosis, meatal stenosis, urethral stricture,

	hypospadias, leukoplakia
Skin	Hyperhidrosis
Neurodevelopmental	Learning disability, developmental delay, intellectual disability, depression, anxiety
Laboratory Features	
Blood	Anemia, and/or thrombocytopenia, and/or neutropenia
	High MCV for age
	High fetal hemoglobin (Hb F) for age
Bone Marrow	Aplastic: Hypocellular for age
	Myelodysplastic syndrome: significant dyspoieses (per WHO[28] +/- cytogenetic clone
	Leukemia: > 20% blasts in marrow
Telomeres	Below first percentile for age by automated multicolor flow-FISH in three of four lymphocyte subsets ($CD45^+$ naïve T cells, $CD45^-$ memory T cells, $CD20^+$ B cells, $CD57^+$ NK/NKT cells) and granulocytes
Genes	Deleterious/damaging mutations in a DC-associated gene

Table 2: Telomere lengths in DC patients compared with DC relatives.[10]

	DC Patients/ N abnormal	DC Relatives/ N abnormal	OR	95% CI	Sens %	Spec %	PPV %	NPV %
Granulocytes	60/62	22/123	138	31-1200	97	82	73	98
Lymphocytes	63/65	11/127	332	68-2942	97	91	85	98
CD45RA$^+$/CD20$^-$ naïve T cells	61/64	9/127	266	64-1468	95	93	87	98
CD45$^-$ memory T cells	61/64	11/127	214	53-1161	95	91	85	98
CD20$^+$ B cells	54/58	12/127	129	37-546	93	91	82	97
CD57$^+$ NK/NKT cells	50/59	12/119	50	18-140	85	90	81	92
≥4/6 lineages	61/64	9/117	244	58-1346	95	92	87	97
≥3/5 lymphocyte lineages	62/64	9/119	379	74-3390	97	92	87	98
4/4 lymphocyte subsets	42/55	7/127	55	19-170	76	94	86	90
≥3/4 lymphocyte subsets	54/55	7/127	926	113-37479	98	94	89	99
3/3 naïve and memory T and B cells	51/58	7/127	125	38-437	88	94	88	94
≥2/3 naïve and memory T and B cells	57/58	9/127	747	97-30241	98	93	86	99

	DC Patients/ N abnormal	DC Relatives/ N abnormal	OR	95% CI	Sens %	Spec %	PPV %	NPV %
2/2 naïve and memory T cells	59/64	7/127	202	55-806	92	94	89	96
1/2 naïve and memory T cells	63/64	13/127	552	77-22333	98	89	83	99
Granulocytes + lymphocytes	58/65	11/127	87	30-273	89	91	84	94

Denominators vary according to the number of patients in whom each included lineage had sufficient numbers of cells for analysis. The best performance characteristics are in lymphocytes alone, and at least three of the four lymphocyte subsets. Abnormal: below the first percentile for age in normals. OR: odds ratio in favor of being a DC patient compared with an unaffected relative. CI: confidence interval; sens: sensitivity; spec: specificity; PPV: positive predictive value; NPV: negative predictive value. Table reproduced from Alter et al., Haematologica 2012.[10]

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Chapter 4:
The Genetics of Dyskeratosis Congenita

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Introduction

Dyskeratosis congenita (DC) is inherited in X-linked recessive (XLR), autosomal dominant (AD), or autosomal recessive (AR) patterns.

De novo germline mutations are also relatively frequent in DC. To date, about 60-70% of DC patients have an identifiable germline mutation.[1,2] These mutations occur in genes responsible for the functioning and maintenance of telomeres (Figure 1, next page).

Currently, germline mutations in nine different telomere biology genes have been shown to cause DC (*DKC1, TERT, TERC, TINF2, WRAP53, NOP10, NHP2, CTC1,* and *RTEL1)*.[1,2] Mutations in *USB1* have been reported in patients with symptoms similar to those of DC but with normal telomere lengths. Most of the mutations reported are private (occur in a single patient or family). However, a few do occur repetitively in

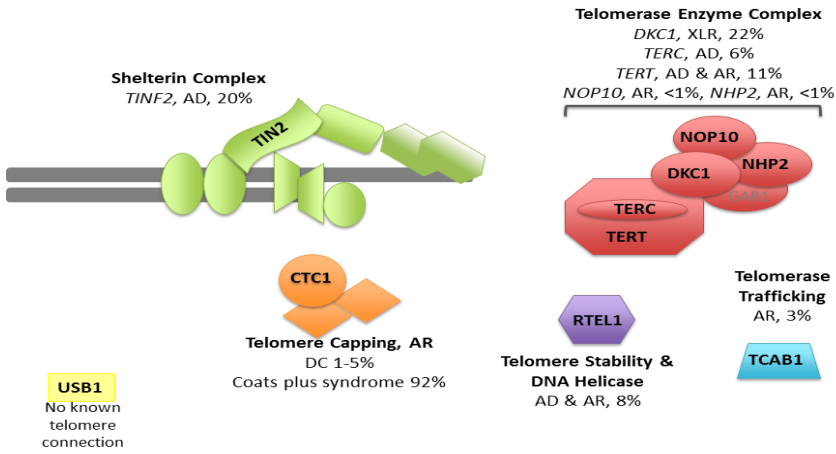

Figure 1: Schematic of the telomere and functions of the proteins affected in dyskeratosis congenita and the related telomere biology disorders. Protein names are shown. Abbreviations: XLR, X-linked recessive; AD, autosomal dominant; AR, autosomal recessive; DC, dyskeratosis congenita; *TCAB1*, telomere Cajal body-associated protein 1 (gene name: *WRAP53*); *TIN2*, *TRF1*-interacting nuclear factor 2 (*TINF2*); *TPP1*, telomere protection protein 1 (encoded by ACD, adrenocortical dysplasia homolog); *NOP10*, *NOP10* ribonucleoprotein (*NOP10*); *NHP2*, *NHP2* ribonucleoprotein (*NHP2*); *DKC1*, dyskerin (*DKC1*); *TERC*, telomerase RNA component (*TERC*); *TERT*, telomerase (*TERT*); *RTEL1*, regulator of telomere elongation helicase 1 (*RTEL1*); *CTC1*, CTS telomere maintenance complex component 1 (*CTC1*); *USB1*, U6 snRNA biogenesis 1 (*USB1*). Percentages are estimates and based on the literature and unpublished data from the National Cancer Institute's dyskeratosis congenita study. Color version in **Color Photo Appendix**, p. 399.

multiple unrelated patients, most notably p.Ala353Val in *DKC1* (more than 40 families) and p.Arg282His in *TINF2* (more than 30 families). As described elsewhere, there is a wide range of phenotypes associated with mutations in these genes, although a review of published variants shows that each gene has quite a distinctive spectrum (Table 1, at end of chapter).

Telomerase-associated genes

The first DC-associated gene, XLR *DKC1*, was discovered by linkage analysis in 1998.[3] The protein encoded by this gene, called dyskerin, was known by homology to be involved in the maturation of ribosomal RNA. The connection between DC and telomere length was made when dyskerin was shown to affect telomerase RNA. Primary fibroblasts and lymphoblasts from patients with DC bearing *DKC1* mutations exhibited low levels of telomerase RNA, reduced telomerase activity, and short telomeres compared to normal controls.[4]

The link between DC and telomere biology was supported by the subsequent discovery of *hTERT* and *hTR* (encoded by *TERT* and *TERC*, respectively) mutations in patients with AD forms of DC.[5,6] The *TERT* mutations found in these patients are generally nonsynonymous coding mutations that lead to telomerase haploinsufficiency (having half the amount of telomerase as

normal). *TERC* encodes the RNA template, which is required for the addition of telomeric nucleotide repeats by telomerase. In addition to these mutations affecting the template region of *TERC*, mutations in the promoter region, as well as other domains of *TERC* have been described.[7]

Rarely, *TERT* can be mutated in AR forms of DC; biallelic mutations are associated with more severe disease, and those patients have dramatically reduced levels of telomerase. AR DC can also be the result of biallelic mutations in *NOP10* or *NHP2* (encoded by genes of the same names), all of which affect telomerase biogenesis.

Disruption of telomerase trafficking in the nucleus can result from germline mutations in *TCAB1* (encoded by *WRAP53*).[8] Patients with compound heterozygous mutations in *TCAB1* were reported to have features of classic DC. Their clinically silent relatives who had one mutant allele had normal telomere lengths, suggesting that biallelic mutations are required for this phenotype. Compound heterozygous mutations in patient cells prevented telomerase from localizing to Cajal bodies for assembly. This results in misdirection of telomerase RNA to the nucleoli, precluding telomerase from elongating telomeres.

The Shelterin telomere protection complex

Germline mutations in *TIN2* (encoded by *TINF2*) are also responsible for AD DC, mostly occurring *de novo*.

TIN2 is not directly involved in telomerase function; rather, it is part of the shelterin complex, a six-protein telomere-specific complex that protects telomeres and participates in length regulation. Causative *TINF2* mutations cluster at the consensus site for heterochromatin protein 1-gamma (HP1ɣ). This association between *TINF2* and HP1ɣ is required for sister telomere cohesion, thereby preventing sister telomere loss.[9]

However, the exact mechanism by which mutations in *TIN2* result in very short telomeres and DC has not been determined.

Germline mutations in *TPP1* (encoded by ACD) have been reported in two families with DC.[10,11] One mutation is a deletion of the part of *TPP1* that binds to telomerase and is known as the TEL patch. The other reported mutation is a missense mutation that may act as a disease modifier and result in the more severe form of DC, Hoyeraal-Hreidarsson syndrome (HH).[11]

Mutations in the other four shelterin components (*TRF1, TRF2, POT1, RAP1*) have not yet been found in DC.

Telomere capping proteins

Compound heterozygous mutations in *CTC1* were first reported as a cause of Coats plus and in the phenotypically similar disorder termed cranioretinal microangiopathy with calcifications and cysts (CRMCC). Patients with those mutations had short telomeres and features that phenotypically overlapped with DC.[12-14]

Mutations in *CTC1* were subsequently demonstrated to cause AR DC[15,16] Telomere length in *CTC1*-associated DC was not as short as in DC due to other causes, but still shorter than controls. *CTC1* is part of the trimeric CST telomere capping complex, containing also *STN1* and *TEN1*. The CST complex has both extra-telomeric and telomeric roles; at the telomere, it cooperates with the shelterin complex to protect telomeres from degradation and aberrant recognition by DNA repair machinery.

Regulator of telomere elongation helicase 1 (*RTEL1*)

Several groups independently identified *RTEL1* mutations using whole exome sequencing in families with DC and Hoyeraal-Hreidarsson syndrome (HH).[17-19] The *RTEL1* protein regulates telomere length, may interact with PCNA (proliferating cell nuclear antigen), and also plays a role in DNA

repair.[17,18] Most of the *RTEL1* mutations appear to be AR, but AD mutations have been reported.[17]

U6 small nuclear RNA biogenesis 1 (*USB1*)

Linkage analysis led to the identification of mutations in C16orf57, which at the time was of unknown function.[20] It is now called *USB1*, and known to be involved in the maturation of a small nuclear RNA (U6), which plays a crucial role in RNA splicing.

USB1 mutations were first reported in individuals with Rothmund Thomson syndrome and Poikiloderma with Neutropenia, suggesting an overlapping clinical spectrum.[20] These patients, including those with a DC phenotype, tend to have normal telomere lengths. However, it is interesting to note that yeast cells which lack the ortholog of this protein (Δmpn1) display increased levels of telomeric repeat-containing RNA and short telomeres.[19]

Genetic heterogeneity

Our understanding of inheritance patterns in DC is complicated by the presence of silent carriers, arising because of incomplete clinical penetrance of disease-associated mutations. Incomplete penetrance occurs in genetic disorders when a

person with a disease-associated mutation does not develop the expected phenotype.

This is possibly due to a combination of genetic, environmental, and lifestyle factors. As more family members are tested for DC-associated mutations, more silent carriers are being recognized. Specifically, carriers of germline mutations in *TERT, TERC*, and *TINF2* with few symptoms consistent with DC have been identified because of the increased scrutiny brought about by the diagnosis of a family member. This occurs at least in part because the clinical signs and symptoms of DC can develop at different rates in different individuals, even within the same family.

Having the phenotype of very short telomeres is defined as having telomere length less than the first percentile expected for age, so 99 out of 100 people of the same age have longer telomeres. This observation in individuals from a family with variable clinical penetrance was used in the linkage scan that discovered mutations in *TINF2* as a cause of DC.[21] Silent carriers of DC-associated mutations should be counseled regarding their potential risk of disease.

Genetic anticipation refers to a younger age of onset and increased severity of the symptoms of a disease over successive

generations within a family. This has been reported in cases of telomerase haploinsufficiency: older generations are often asymptomatic, or may have adult-onset pulmonary fibrosis, but later generations with the same mutation can exhibit classic symptoms of DC or present with aplastic anemia in childhood.[5,22,23] A similar finding has been noted in a family with a TINF2 mutation.[21] It is also notable that in all of these reports the offspring have shorter telomeres than the parents.

Genetic analysis of DC is made more complex by the recent identification of somatic mosaic reversion. This phenomenon has been reported in DC families where a germline *TERC* mutation identified in skin fibroblasts was spontaneously corrected by mitotic recombination in blood cells.[23]

Summary

Causative germline mutations have been identified in about 60-70% of patients with DC. Scientists are using next-generation sequencing technologies to discover the genetic cause of DC in mutation-negative families. Genetic counseling for the patient and their family members is an integral component of DC clinical management (see Genetic Counseling Chapter 5). This can be particularly challenging in the context of the variable penetrance discussed above.

Table 1: Numbers of published variants in the 11 different DC-associated disease genes and their clinical manifestation.

	DC	HH	AA	MDS	AML	IPF
DKC1	48	14				1
TERC	14	1	25	14	3	7
TERT	14	6*	28	5	5	30
TINF2	24	3	8			1
WRAP53	6					
NOP10	1					
NHP2	3					
CTC1	4	2	2			
RTEL1	1	17				
ACD	1	2				
USB1	4					

The numbers of published variants in the 10 DC genes are given, not the number of cases. Only the primary phenotypes are given, and the occurrence of AA, MDS, and AML within DC is not included here. Several variants have been associated with more than one phenotype; in these instances the different phenotypes are scored separately. Only phenotypes described more than once are included. Abbreviations are as follows: DC, dyskeratosis congenita; HH, Hoyeraal Hreidarsson

	LC	RS	CR/P	CM	PN	RTS
DKC1						
TERC	2					
TERT	7					
TINF2		3				
WRAP53						
NOP10						
NHP2						
CTC1			17	10		
RTEL1						
ACD						
USB1					11	5

syndrome; AA, aplastic anemia; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; IPF, idiopathic pulmonary fibrosis; LC, liver cirrhosis; RS, Revesz syndrome; CR/P, Coat's retinopathy/plus; CM, cerebroretinal microangiopathy with calcification and cysts; PN, poikiloderma with neutropenia; RTS, Rothmund-Thomson syndrome. **Note that the TERT variants associated with HH are usually homozygous or compound heterozygotes or potential bystanders.*

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Chapter 5:
Genetic Counseling for Families with Dyskeratosis Congenita

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Introduction

The National Society of Genetic Counselors defines genetic counseling as the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.

This process integrates interpretation of family and medical histories to assess the chance of disease occurrence or recurrence. It also includes education about inheritance, genetic testing, and disease management. Patients are informed of resources and research opportunities as well as given disease-specific counseling (*National Society of Genetic Counselors, 2005,* http://www.nsgc.org*)*.

Genetic counselors are master's degree level health care professionals who typically work as part of a medical team. An appointment with a genetic counselor can result in better

understanding a diagnosis of dyskeratosis congenita (DC) through a discussion including family history, general and DC-specific genetic information, genetic testing options, psychological and social issues, risk assessment for other family members, family planning, and identifying support for families with DC.

Family and medical history

A family medical and cancer history is obtained to help determine whether only the individual being evaluated may have DC or whether other family members may also be at risk of having the disorder.

In preparation for a genetics visit, a family should spend time thinking about relatives on both sides of the family: do any individuals in the family have any signs of DC or cancer? This may require speaking with other family members, since some of the classic physical features of DC (abnormal fingernails and/or toenails, lacy rash on the chest and neck, and white spots in the mouth) may not be something one would normally notice in another individual.

Additionally, not everyone with DC will have these classic features. The family history may help the healthcare team in deciding which DC-associated gene(s) to test. For example, if

only males related through the same female relatives have DC, one would begin testing for the X-linked recessively inherited *DKC1* gene. However, if there were multiple family members of both genders affected over multiple generations, one would begin testing for the most common of the autosomal dominant DC genes. Since testing the relatives of someone known to have DC may uncover the fact that others in the family also have a mutation associated with DC, counseling of the entire family should be considered.

Cells, DNA, genes, amino acids, and proteins

Our cells contain 46 chromosomes that are made up of approximately 22,000 genes. These genes encode all the instructions needed for our bodies to function. The genes are composed of DNA (deoxyribonucleic acid), which is made up of a combinations of four bases called Adenine (A), Guanine (G), Thymine (T), and Cytosine (C). Combinations of the bases in groupings of three encode the twenty amino acids. Amino acids are assembled together, like beads on a string, to make proteins. Proteins contain the information necessary for cells to function.

If the A, T, G, and C letters of the code are not in the correct order, if one or more is deleted, or there are extras, the genes that instruct our cells how to perform their jobs will not be put

together properly, resulting in what is referred to as a mutation or a pathogenic variant. In the case of genes associated with DC, the mutation affects proteins important in maintaining telomeres that are essential for chromosomal stability. Thus, people with a DC-associated gene mutation will most likely have shorter than normal telomeres.

Inheritance of genes associated with DC

As of June 2015, there are 11 genes known to be associated with DC: *DKC1*, *TERC*, *TERT*, *TINF2*, *NOP10*, *NHP2*, *WRAP53*, *CTC1*, *RTEL1, ACD,* and *PARN* (see Chapter 4, Genetics of DC).

The *USB1* gene may be associated with DC, but those patients had normal telomere lengths. Several of these genes are associated with more than one inheritance pattern (autosomal dominant and autosomal recessive). Approximately 70% of people with DC have a mutation in one of these eleven genes[1-8].

We normally have two copies of each of our genes, one of which we inherit from our mother and the other from our father. Genes associated with DC can be inherited in one of three ways: autosomal dominant (AD), autosomal recessive (AR), or X-linked recessive (XLR).

One can also have DC because of a spontaneous mutation in a DC-associated gene, and so be the first in a family to have DC. In

this instance, neither of the parents would be carriers of the mutation.

AD inheritance means that a person needs only one copy of a abnormal gene in order to be at risk for having DC. Each of the children of someone with an AD mutation has an 50% chance of inheriting the mutation from that parent. AD genes for DC include *TERC*, *TERT*, *TINF2*, *RTEL1*, and *ACD*.

AR inheritance requires that a person inherit a mutation in the same gene for DC from both their mother and their father. Each child has a 1 in 4, or 25%, chance to inherit both mutations, a 2 in 4 (50%) chance of inheriting one mutation from either parent, and a 1 in 4, or 25%, chance of inheriting neither the maternal nor paternal mutation.

If a person were to inherit a mutation for each of two different AR genes for DC, they would be a carrier for each of the two AR gene mutations but would not likely be at risk for DC. If a person has a different AR mutation in each copy of the same gene for DC, each of their children will inherit one of the two mutations. If the other parent carries a mutation in the same DC gene, there is a 1 in 2 (50%) chance of each child having DC, and 1 in 2 (50%) chance for them to be a carrier of only one mutation.

AR genes for DC include *TERT*, *NOP10*, *NHP2*, *WRAP53*, *CTC1*, *USB1*, *RTEL1*, and *ACD*.

With XLR inheritance, a boy inherits a mutation on the X chromosome from his mother and will be at risk for DC. However, a female who inherits the mutation from her mother will carry the mutation and likely not have DC due to having another likely normal X chromosome, inherited from her father.

If a woman has an XLR mutation, each son has a 1 in 2 (50%) chance of inheriting the X chromosome with the mutation, and so be at risk for DC. Each daughter has a 1 in 2 (50%), chance of inheriting the X chromosome with the mutation, and so of being a carrier. Males with XLR DC will pass the mutation to all of their daughters on their X chromosome, and their daughters will be carriers. However, none of their sons will be affected, since males give a Y chromosome and not an X to each of their sons. The only known XLR gene for DC is *DKC1*.

It is important to note that not everyone who has a mutation in a DC gene will show signs or symptoms of the disease. This concept is referred to as reduced penetrance. Additionally, there may be variable expressivity. This term refers to the fact that even within the same family, one person may have severe physical manifestations, while another person may have only

abnormal nails and another person may only have pulmonary findings.

Testing for DC

Once a diagnosis of DC is confirmed clinically by the physician, a genetic counselor should speak with the individual and/or family to explain more about DC, possible inheritance patterns, testing options, and the testing process. Other issues may be addressed more accurately once mutation of a specific gene is identified (see Mutation Positive Test Results below).

Telomere testing

The first step in testing for DC is to assess the telomere length in a specific subtype of white blood cells. This test is very sensitive in screening for DC (see Chapter 3, Diagnosing DC). If all or nearly all of the white blood cells' telomeres are determined to be very short, the test result indicates a diagnosis of DC.[9,10] Diagnostic genetic testing can then be performed.

Genetic testing

A genetic counseling session prior to testing helps individuals understand general and DC-specific genetics concepts, as well as the process by which genetic testing occurs. It is also an

opportunity to explain the testing consent form, and discuss the risks, benefits and limitations of testing.

The decision regarding which DC genes will be tested is based on the gender of the affected individual, whether one or more people in the family are affected and how they are related to each other. If a mutation has already been identified in a family member, other family members only need to be tested for the specific mutation previously found. Testing may be performed in a sequential fashion, ordering testing of one gene at a time, or as a gene panel, whereby multiple genes are tested at the same time. The type of genetic testing may be based on healthcare provider or insurance preference.

Mutation positive test results

Once a mutation is identified, the genetic counselor reviews the results with the affected person and/or the parents. Discussion typically includes an explanation of the results and review of the inheritance of the gene, the risk of having a child with DC, and consideration of testing other family members. Psychosocial issues arising from confirmation of the DC diagnosis through genetic testing, as well as resources available to help affected families such as the DC Outreach family support group, may be discussed. Testing can determine whether one or

both parents have a mutation, or if the mutation is likely a new, "spontanteous" mutation in their child. If neither parent has the mutation, chances are low that any other children or their descendants will also have the mutation. However, there is still a small risk of there being other affected children due to germline mosaicism.

Germline mosaicism

Because the DNA in our cells must duplicate itself, mutations may occur in any cell. If a person has a mutation not found in either parent, this is referred to as a new, spontaneous, or *de novo* mutation. This mutation likely occurred to a gene in the egg or sperm that formed this person. In this case, there is a very small chance that other egg or sperm cells also have the same mutation, and other children may be at risk of inheriting the DC mutation.

Mutation negative test results

When the clinical presentation is consistent with DC but no mutation is found in known DC genes, an as yet unidentified DC gene may be responsible. One may wait until the next DC-associated gene is identified and available for testing. Alternatively, whole exome sequencing (testing most of the

DNA that codes for proteins) as part of a DC research study or clinical exome sequencing may identify a mutation in a new gene[11]. Exome sequencing involves obtaining samples from both parents and siblings when possible in order to interpret the data and identify a mutation. One of the possible negative consequences of exome sequencing is that the testing may identify misattributed paternity.

Reproductive options

Families may choose to conceive through a natural pregnancy without genetic testing until after the birth of the child. Other families may choose not to have children. A family with a DC-affected child may wish to conceive a child who is HLA (human leukocyte antigen) matched to the sibling with DC, in case the sibling were to need a bone marrow transplant. There are currently several means to have a child unlikely to have DC, including adoption, using a donor egg or sperm, prenatal testing (chorionic villus sampling [CVS] or amniocentesis) for a known mutation with the option of pregnancy termination based on a mutation positive result, and in vitro fertilization (IVF) with pre-implantation diagnosis (PGD). A genetic counselor can discuss the details of these options with the family.

Testing for DC prior to conception, during pregnancy, or after birth

Genetic testing cannot be offered prior to conception or during pregnancy when the DC-associated mutation has not been identified. Prenatal testing for DC-associated mutations during pregnancy can be performed by obtaining fetal cells via either CVS at about 10 – 12 weeks, or amniocentesis at about 15 – 18 weeks of pregnancy. DNA can be extracted from these fetal cells to test for the family mutation or HLA type.

A family may choose to have pre-conception or prenatal testing when a mutation has been identified in a family member with DC. IVF can be performed, and after a few days, PGD is done by taking cell(s) from each embryo and analyzing it for the DC mutation and/or desired HLA type. A family can then choose to implant the embryos that do not have the mutation and/or are an HLA match. The chance of having an embryo that will not have the mutation or will be HLA identical will vary based on the inheritance pattern of the specific gene. This procedure reduces the risk of having a child with DC and increases the likelihood of having a child who is an HLA match. However, there is a chance that errors can be made leading to a misdiagnosis. Performing confirmatory testing for the DC

mutation and HLA type during pregnancy with CVS or amniocentesis can corroborate the results of the PGD.

The process of IVF with PGD is time consuming, as well as physically, psychologically, and financially demanding. In order to confirm that the laboratory performing PGD will be able to identify the presence or absence of the mutation(s) in an embryo, DNA samples from the person with DC and their parents in order to perform preparatory genetic testing,. Multiple IVF and PGD cycles may be required to achieve a pregnancy that results in a live baby.

Summary

Genetic testing for DC requires a comprehensive clinical and family-oriented approach. Genetic counselors should be included as an integral part of the medical team for patients and families with DC.

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Chapter 6:
Subtypes of Dyskeratosis Congenita and the Telomere Biology Disorders

Alison A. Bertuch, MD, PhD

Introduction

Several clinical variants of dyskeratosis congenita (DC) have been described, each of which is linked to classic DC by shared medical features, very short telomeres, and mutations in genes important for telomere length maintenance.

In addition, several families have been described in which affected individuals experience predominantly a single clinical disorder, such as aplastic anemia with or without progression to myelodysplastic syndrome or acute leukemia, pulmonary fibrosis, or liver disease. Together with classic DC, these families and those with the severe variants represent the spectrum of clinical phenotypes associated with defective telomere maintenance. Each is discussed below.

Hoyeraal-Hreidarsson syndrome

Hoyeraal-Hreidarsson syndrome (HH)[1-5] is one of three recognized variants of DC.

Nearly all individuals with HH have cerebellar hypoplasia, which is associated with signs of cerebellar dysfunction such as ataxia.[6] Additional features of HH are intrauterine growth retardation, developmental delay, microcephaly, immunodeficiency, and bone marrow failure. The mucocutaneous triad (see Chapter 3) and additional features of DC may also be present.[7] As it is now known that HH is a variant of DC, some clinicians will consider an individual to have HH if they meet diagnostic criteria for DC and have cerebellar hypoplasia but lack other features of HH such as intrauterine growth retardation or immunodeficiency.

Hoyeraal-Hreidarsson syndrome typically presents in early childhood as a progressive, multisystem disorder. The immunodeficiency may progress to severe combined immunodeficiency syndrome (SCID) of the T+, B-, NK- cell type, with lethal viral infection in infancy.[8-10] This has raised the possibility that there are young patients with SCID who succumb to infection prior to the recognition of underlying HH. Gastrointestinal problems with chronic bloody diarrhea and

feeding difficulties, have also been reported.[11] Historically, the vast majority of individuals with HH reported in the literature have died within the first decade of life due to immunodeficiency or bone marrow failure.[12] However, with improved diagnosis, supportive care, and hematopoietic cell transplantation, longer term survival is possible today.

All of the genes associated with HH to date are associated with telomere maintenance (see also Chapter 4). These are:

- *DKC1*, which transmits X-linked recessive HH,[13] accounting for the large male preponderance
- *TINF2*, which results in sporadic HH due to *de novo* heterozygous mutations
- *TERT* and *RTEL1*, each of which result in autosomal recessive disease due to either compound heterozygous or homozygous mutations

The carrier frequency of the HH-associated *RTEL1* mutation c.3791G>A (p.R1264H) is 1% in the orthodox Ashkenazi Jewish and 0.45% in the general Ashkenazi Jewish populations.[14] Therefore, targeted sequencing may be considered initially in these populations.

In addition to mutation in the above genes, a heterozygous splice variant of *DCLRE1B* (*SMN1B*), which encodes the nuclease

Apollo, was reported in a child with HH.[15] Apollo is implicated in telomere maintenance, the hallmark abnormality of HH, but it also has a role in certain forms of general DNA repair.

As with classic DC, a significant proportion of patients with HH will not have a mutation in one of the currently known genes. Most individuals with HH, however, will have very short telomeres, even more so than patients with classic DC.[16] Some exceptions to this have been noted in the literature. In these cases, including the case with the *DCLRE1B* splice variant,[15] there is evidence of telomere dysfunction rather than a defect in telomere length.[10] Thus, telomere length above the first percentile does not necessarily rule out a diagnosis of HH.

Revesz syndrome

Revesz syndrome (RS) is another rare variant of DC, with the defining feature of bilateral exudative retinopathy, also known as Coats disease. (See Chapter 11 for further information on ophthalmologic manifestations of the DC spectrum disorders, including RS.) Additional features of RS include intrauterine growth retardation, intracranial calcification, sparse hair, and bone marrow failure.[17] Patients may also have microcephaly, cerebellar hypoplasia, and additional features of DC, including the mucocutaneous triad.

The phenotypic overlap of RS and DC has long been appreciated;[18] however, there are very few cases of RS that are well described in the medical literature.[17-26] Of those, the vast majority present to medical attention before the age of five years, with the original case described in a six month old infant.[17]

This early age of presentation, along with the severity and spectrum of disease manifestations, has led to the frequent description of RS as a severe variant of DC. Consistent with this, patients with RS not only have very short telomeres, but telomeres that are shorter than patients with classic DC, similar to what is observed with HH.[16] Lastly, the majority of reported cases are males; whether this reflects a true male predilection or simply represents a reporting or recognition bias remains unknown.

The only gene found to date to be mutated in RS is *TINF2*, which encodes TIN2, a member of the telomeric shelterin complex (see Chapter 4, Genetics of DC).[23,24] Therefore, targeted sequencing of *TINF2* is a reasonable first step toward a molecular diagnosis in a patient with RS. Not all patients with RS, however, will have a *TINF2* mutation.[16] Heterozygous *TINF2* mutations are also associated with classic DC and HH, and are often *de novo*.[23]

While it is probable that most cases of *TINF2*-associated RS are due to *de novo* mutations, there is one case in the literature of RS in which the *TINF2* mutation was inherited, although, the carrier parent was a mosaic.[25]

Recently, a family was described in which two siblings with exudative retinopathy were found to carry a novel *TERT* mutation, c.2603A>G, p.D868G.[27] Although these children had very short telomeres, bone marrow failure, and early pulmonary fibrosis, as seen in DC, they did not have the intracranial calcifications or neurodevelopmental deficits frequently observed in RS.

A large number of *TERT* mutations have been reported in the literature, including homozygous mutations with severe telomere shortening. These are not reported to be associated with exudative retinopathy, so it remains to be determined whether the ocular phenotype in this family is due to the *TERT* mutation or is unrelated.

Coats plus

Coats plus is the clinical entity most recently placed within the spectrum of telomere biology disorders.

Similar to RS, patients with Coats plus have bilateral exudative retinopathy or telangiectasias, as well as a

characteristic pattern of asymmetric intracranial calcification involving the thalamus, basal ganglia, dentate, and deep cortex, with associated leukoencephalopathy and brain cysts; osteopenia with tendency to fracture and poor bone healing; recurrent gastrointestinal hemorrhage due to vascular ectasias in the stomach, small intestines and liver; and pre- and postnatal growth retardation.[28]

Additional features include the mucocutaneous triad of DC and bone marrow involvement, although not typically marrow failure. Consistent with these overlapping clinical features of DC, the vast majority of patients with Coats plus have biallelic mutations in *CTC1,* a gene that encodes a factor important for telomere maintenance (see Chapter 4, Genetics of DC)[29,30] and patients diagnosed with classic DC have also been found to have biallelic *CTC1* mutations.[31,32]

Whether very short telomeres are a molecular feature of *CTC1*-associated disease remains to be determined. In the initial two reports on patients with Coats plus and *CTC1* mutations, one group found affected individuals had age-adjusted lymphocyte telomere length below the first percentile, as determined by flow FISH,[29] whereas the other group found no difference in the relative leukocyte telomere length between

affected and control individuals, as determined by qPCR.[30] Similarly, a report describing a patient with biallelic *CTC1* mutations and classic DC with intracranial calcifications and non-specific vascular retinal changes, found very short lymphocyte telomere length by flow FISH.[31] In contrast, another report describing six individuals with DC or related bone marrow failure disorders found no difference in relative telomere lengths between the affected individuals and controls. However these measurements were by qPCR.[32] Simultaneous measurements of telomere length using both methods in individual Coats plus and DC patient samples may ultimately resolve this question.

Distinguishing Revesz syndrome from Coats plus

As evident from the above descriptions, RS and Coats plus share several features: intrauterine growth retardation, bilateral exudative retinopathy, intracranial calcifications, sparse hair, nail dystrophy, and cutaneous changes.

However, they are distinct both clinically and genetically. Severe bone marrow failure is a dominant feature of RS, whereas this is not frequently described in patients with Coats plus. Patients with RS frequently have cerebellar hypoplasia, which is rare in Coats plus. Conversely, patients with Coats plus have a

very distinctive pattern of intracranial calcification. Further, gastrointestinal bleeding and a skeletal phenotype of osteoporosis and easy fracture are common. Genetically, *TINF2* mutations are associated with RS,[23,24] whereas *CTC1* mutations are associated with Coats plus.[29] Thus, the clinical features should lead to direct testing for mutation in either *TINF2* or *CTC1.*

Familial aplastic anemia, myelodysplastic syndrome and acute leukemia

Aplastic anemia associated with very short lymphocyte telomere length or with a mutation in a telomere biology gene should raise suspicion for a telomere disorder even in the absence of other features of DC. In young children, aplastic anemia may be the first manifestation of DC. As these children age, they may develop additional clinical features and eventually meet diagnostic criteria for DC.

In contrast, there are individuals who are well into adulthood when they develop aplastic anemia as the sole manifestation of a telomere disorder. Notably, mutation in *TERC* or *TERT*, and finding of short telomeres have been reported in isolated adult cases of aplastic anemia, as well as in up to 5 to 10% of

individuals in cohorts of seemingly acquired severe aplastic anemia.[33-36]

Although the reported individuals lacked physical features of DC, many had relatives who were also mutation carriers and had histories of macrocytosis, blood count abnormalities including aplastic anemia, myelodysplastic syndrome (MDS), or leukemia. Immunosuppressive therapy, which is typically effective in immune-mediated acquired aplastic anemia, was ineffective in these cases. Thus, a thorough family history and telomere length testing is recommended not only for children, but also adults with newly diagnosed MDS or aplastic anemia. This may reveal relatives also afflicted by MDS or with varying degrees of bone marrow failure, which would suggest a familial telomerase or other telomere maintenance gene mutation that presents predominantly as an isolated hematologic phenotype.[37,38]

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is the most common manifestation of disease due to shortened telomeres,[39] and approximately 8–15% of familial cases are associated with mutation in *TERT* or *TERC*.[40,41]

The reader is referred to Chapter 14, where IPF is discussed in more detail. In brief, IPF cases due to telomerase mutations generally present in mid-adulthood. The majority are familial.

The pedigrees of some the familial cases are characterized by pulmonary fibrosis as the predominant phenotype,[42] whereas other pedigrees evolve from a pulmonary fibrosis-predominant to bone marrow failure–predominant phenotype over successive generations.[43] The presence of an underlying germline telomerase mutation is highly suggested when IPF is accompanied by cytopenias or other hematologic abnormalities such as macrocytosis or cryptogenic liver disease. Thus, thorough medical histories, examination of peripheral blood counts and liver function, and detailed family history are warranted with IPF presentations.

Liver disease-predominant phenotype

Similar to familial IPF, pedigrees with a liver disease-predominant phenotype, as well as individuals with sporadic cryptogenic liver disease, have been described with germline *TERT* or *TERC* mutations.[44-46]

The reader is referred to Chapter 17, which describes in detail the hepatic manifestations associated with the telomere disorders. Here, we emphasize the importance of taking a

thorough family history focused not only on familial liver disease, but also surveying for bone marrow and lung disease as steps in uncovering these cases.[44]

Silent carriers

Uncovering a pathogenic mutation in an individual with a telomere-related disease has the potential to lead to genetic testing and the discovery of additional family members who carry the mutation but are asymptomatic, so-called silent carriers.

The ability to anticipate the likelihood of developing disease or having offspring with disease may vary from relatively easy (as for a newborn male sibling with a pathogenic *DKC1* mutation, who would be likely to develop disease) to more difficult (as for the highly unpredictable occurrence of MDS at 40 years of age in the offspring of a 60 year old with a pathogenic *TERT* mutation).

Even more difficult are cases in which a familial mutation is not identified, but testing revealed telomere lengths around the first percentile in asymptomatic relatives. As discussed in Chapter 5 on Genetic Counseling, knowledge of silent carrier status may impact health-related behaviors (like avoidance of smoking or alcohol use), facilitate decisions on pre-implantation

genetic counseling, and lead to disease surveillance (as with periodic CBCs or oral, head, and neck exams).

Lastly, silent carrier status would have significant implications with respect to related hematopoietic cell donation as such carriers would be unsuitable donors.

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Chapter 7:
Medical Management of Bone Marrow Failure in Dyskeratosis Congenita

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Introduction

Many individuals diagnosed with DC have some degree of abnormality in their complete blood count (CBC), and up to 80% with classic dyskeratosis congenita (DC) will develop bone marrow failure (BMF) by 30 years of age.[1,2]

This may range from minor findings such as macrocytosis (high mean corpuscular volume [MCV] for age due to large red blood cells) or mild asymptomatic cytopenias in one or more blood cell lineage, to symptomatic BMF (also referred to as severe aplastic anemia).

Low platelet count is usually the first cytopenia to appear, followed by anemia or neutropenia. Some patients may develop progressive abnormalities (dysplasia) in the bone marrow hematopoietic cells, which may evolve to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).[3]

The time of BMF onset is highly variable among individuals. Infants and young children with classic DC and DC variants, such as Hoyeraal-Hreidarsson syndrome, Revesz syndrome, or Coats' plus subtypes may present with progressive BMF early in life, even before other features of DC have appeared. Some individuals, particularly those with mutations in TERC or TERT, may never develop blood cell abnormalities, or they may appear much later in life (see Chapter 6, Subtypes of Dyskeratosis Congenita).[4,5]

Individuals with mutations in *TERC, TERT,* and some with other DC-related genes, may lack the classic mucocutaneous features diagnostic of DC.[4,5] They may instead present with isolated cytopenias or other manifestations related to having short telomeres seen in the clinical spectrum of telomere diseases.

However, since patients with classic DC, as well as those with short telomeres but without the DC mucocutaneous phenotype, are all classified as having a telomere biology disorder,[4] they are broadly grouped together here.

Definition of bone marrow failure

The diagnosis of BMF is made if blood counts are persistently below normal for age, and the bone marrow is hypocellular with

a blast count <5%. Other causes of low blood counts, such as infection, medications, peripheral blood cell destruction, or nutritional deficiencies must be excluded.

Bone marrow failure in DC can be broadly categorized as mild, moderate, or severe based on the degree of peripheral blood cytopenia in the most severely affected cell lineage (Table 1). This classification is modified from the Fanconi anemia consensus guidelines for the treatment of BMF,[6] and is meant to function as a guide for treatment planning.

Table 1: Classification of bone marrow failure

Peripheral Blood Cytopenia	Mild	Moderate	Severe
Absolute neutrophil count/mm^3	<1,500 – 1,000	<1,000-500	<500
Platelets/mm^3	<150,000 – 50,000	<50,000 – 20,000	<20,000
Hemoglobin gm/dL	<normal* - ≥ 8.0		<8.0

**Less than normal for age*

In an individual suspected or diagnosed with DC, a CBC and bone marrow examination are useful to determine baseline hematologic status, regardless of whether BMF is present or not. Diagnostic evaluations for BMF include:

- Complete blood count, including MCV
- Absolute reticulocyte count
- Bone marrow aspiration and biopsy
- Bone marrow cytogenetic analysis by G-banding
- Bone marrow fluorescence in situ hybridization (FISH) to detect 5q-, 7q-/monosomy 7, or trisomy 8 and 20q- if clinically indicated

Also refer to *Chapter 3, Diagnosing Dyskeratosis Congenita*, for more on evaluation of BMF.

Some investigators and clinicians may obtain fetal hemoglobin and erythropoietin levels because these parameters can be elevated in patients with inherited bone marrow failure syndromes (IBMFS).

Bone marrow examination consists of a biopsy and an aspirate. The biopsy assesses marrow architecture and cellularity. The aspirate determines whether cells within the bone marrow are morphologically normal or abnormal. Some degree of morphologic abnormality in erythroid, myeloid, or megakaryocytic lineages is common in patients with DC (and in other IBMFS), and does not necessarily indicate a diagnosis of MDS or portend progression to AML.

Recognizing progression from mild, stable dysplasia to MDS can be challenging in patients with IBMFS. Knowledge of the baseline nature and degree of cell lineage dysplasia, and routine surveillance of peripheral blood and bone marrow evaluation is necessary to track changes. Bone marrow aspirate should be sent for cytogenetic evaluation by G-banding. FISH studies to detect 5q-, 7q-/monosomy 7, or trisomy 8 and 20q- may be done when clinically indicated as an adjunct to G-banding to look for common clonal cytogenetic abnormalities associated with MDS.

An early consult with a hematopoietic cell transplantation (HCT) team may be initiated in patients with progressive cytopenias, or in those with morphologic MDS or cytogenetic clones (particularly monosomy 7) associated with MDS.

Monitoring of bone marrow failure

Periodic update of the medical history and physical exam, along with monitoring of blood counts and bone marrow, are important to assess progression of disease so appropriate therapeutic intervention can be initiated timely. It should be noted that disease presentation and progression to severe aplastic anemia (SAA) differ between DC subtypes (see Chapter 6). Therefore, guidelines for monitoring are determined by the trajectory of blood count decline or bone marrow changes. In

general, children have more rapidly progressive disease and thus need more frequent monitoring, whereas many older individuals have more stable hematological parameters—in these individuals, less frequent monitoring may be adequate.

Guidelines for the management of DC-associated BMF follow the model of Fanconi anemia and may change over time as new data on the clinical spectrum, heterogeneity of manifestations, progression, treatments, and associated complications become available.

In general, for patients with:

***Normal or mildly low blood counts and no cytogenetic abnormality**:*

- CBC may initially be checked every 4–6 months to determine the stability of blood counts. In patients with stable counts, annual monitoring of CBC may be sufficient.
- Bone marrow aspirate, biopsy, and cytogenetic studies should be performed if abnormalities appear in the blood counts.

Patients with blood counts falling or rising:

- The blood counts may drop considerably following an episode of infection in patients with limited bone marrow

reserve. Most often the counts return to the patient's baseline within a few weeks of recovery.

- In patients with progressively changing blood counts without a clinically apparent underlying cause, bone marrow morphology and cytogenetic evaluation may be indicated.

Patients with clonal cytogenetic abnormality:

- Clonal cytogenetic abnormalities, such as loss of chromosome 5, trisomy 8, 11q23 translocation, and deletion or loss of chromosomes 7, 20q, and 3q abnormalities are known to occur in patients with MDS and in association with transformation to AML. Presence of such clones may require more frequent monitoring of CBC and bone marrow evaluations, depending on the stability of blood counts and bone marrow findings.
- Bone marrow exam with cytogenetics and FISH studies may need to be repeated at 4–6 months interval to determine if there is clonal progression or evolution, or morphologic MDS.

Appropriate plans for intervention should be in place for progressively worsening cytopenias, increase in bone marrow

blast count to >5%, clonal progression or evolution, or development of morphological MDS or AML.

Note: Presence of a cytogenetic clone by itself (without morphologic evidence of MDS) does not necessarily indicate a diagnosis of MDS. Experience has shown that some patients have had clonal cytogenetic changes persisting for over 15 years without progression to MDS or leukemia.

Treatment Options for Bone Marrow Failure

Treatment is recommended for patients with persistent, severe BMF (SAA), that is, hemoglobin consistently below 8 g/dL, platelets lower than 20,000/mm^3, or neutrophils below 500/mm^3. Asymptomatic patients with mild or moderate cytopenias may be monitored by regular CBC checks without therapeutic intervention.

Unlike patients with acquired aplastic anemia, most patients with DC do not respond to immunosuppressive therapy,[7] so it is generally not recommended. Improvement in blood counts has been observed in some patients with mutations in *TERC* or *TERT*.[5] Current treatment options for DC-associated BMF include HCT or androgens.

Hematopoietic cell transplantion

HCT is the only curative treatment for DC-related BMF and other hematologic complications like MDS and leukemia. It is considered the treatment of choice in eligible patients if there is a matched, related donor proven to not have DC by physical and laboratory examinations, mutation testing or telomere length assay. HCT from an unrelated donor can be considered for those lacking a matched, related donor. HCT is discussed in detail in Chapter 8.

Androgens

Androgens are anabolic steroids that have been in use for a variety of conditions for over 50 years, including treatment of BMF in Fanconi anemia.[8] The published literature on androgen use in DC is limited,[9,10] but suggests that androgen treatment is a reasonable option in patients who are not candidates for HCT due to medical ineligibility, lack of suitable donors, or personal choice. As many as 50–70% of patients with DC receiving androgens showed a hematopoietic response with sustained improvement in hemoglobin, platelets, and neutrophil counts.[9] Androgens, however, have considerable side effects, and patients with DC seem to be particularly sensitive to them.

The most common side effects reported with androgens are:

- Virilization (or masculinization in females and children), with facial and pubic hair growth, scalp hair loss, acne, penile/clitoral enlargement, and deepening of the voice
- Behavioral changes (for example aggression and mood swings)
- Liver toxicity (increase in transaminase or bilirubin level)
- Alteration in blood lipid profile resulting in abnormally elevated low density lipoprotein (LDL) and low high density lipoprotein (HDL) levels.
- Growth spurt in children, which may result in premature closure of epiphyses (growth plates) and short adult height
- Liver adenomas, peliosis (blood lakes) in spleen or liver, and rarely hepatocellular carcinomas

Oxymetholone was the most commonly used androgen for DC-associated BMF until recently. The suggested starting dose is 0.5 to 1 mg/kg/day, half the dose used in Fanconi anemia, because patients with DC may be more sensitive to its side effects.[9,11] In recent years, the availability of oxymetholone has become very erratic.

Danazol is a synthetic androgen derivative that apparently causes less severe side effects and notably less masculinizing in

many patients, compared to oxymetholone. It is currently being studied in patients with DC and related telomere biology disorders.

Two recent reports showed that danazol effectively improved the blood counts in patients with Fanconi anemia and DC, and was well-tolerated with no severe or unacceptable side effects.[10,12] The suggested starting dose of danazol is 2.5-5 mg/kg/day in children, and 100-150 mg twice a day in adults. The dose can be increased or decreased based on the response while monitoring for androgen-associated side effects. A baseline CBC, serum lipid profile, liver function profile, liver and spleen ultrasound, and a hand X-ray for bone age (in a growing child) should be obtained prior to starting treatment.

Once treatment has begun, it may take up to three months at a constant dose to see an increase in hemoglobin, platelets, and sometimes neutrophil counts. After blood counts have stabilized, androgen dose may be gradually decreased over 2–6 months to the lowest effective dose required to maintain stable blood counts.

Every effort should be made to minimize or avoid toxicity from androgens. Close medical supervision and periodic

monitoring are important, with dose adjustment as required to achieve the minimum effective dose with the least side effects.

Androgen treatment should be discontinued in patients who have not shown a response to treatment after an adequate 3–4 month trial. Occasionally, patients who do not respond to one androgen may respond to a different one.

***Points to note in regard to androgen treatment*:**

- Androgen treatment does not cure bone marrow failure, but can produce a rise in blood counts for the duration of treatment. In some patients, this may be sustained for 15 years or even longer.
- Blood counts do not generally reach normal values with androgen treatment, but may improve to the extent that a previously transfusion-dependent patient may no longer need red blood cell or platelet transfusion support.
- Androgens are likely to be more effective in patients who have some degree of bone marrow reserve than in those whose marrow hematopoietic cellular content is severely depleted. In that case, patients may be or become refractory to androgen therapy.
- Androgens do not prevent or delay the progression to MDS or AML.

Monitoring for the side effects of androgens

Patients on androgen treatment should have baseline and regular follow-up clinical and laboratory evaluations while on treatment, as outlined in the table below.

Table 2. Monitoring while on androgens

Parameter	Before treatment	On treatment
CBC	Baseline CBC	Repeat every 4–6 weeks until counts stable, then every 2–3 months
Liver function test	Baseline AST, ALT, bilirubin, GGT	Every 6–12 weeks
Lipid profile	Baseline cholesterol, LDL, HDL, triglycerides	Every 6–12 months
Liver/spleen ultrasound	Baseline	Every 6 months
Bone age	Baseline in a growing child	Every 6 – 12 months
Endocrine evaluation	Baseline	Annually
Height/ weight	Baseline	Every visit

Patients receiving androgen therapy should be monitored regularly by an endocrinologist for androgen-associated side effects impacting growth, bone age (early fusion of epiphyses), gonadal function, and lipid profile in case there is a need for intervention. Persistently low HDL and high LDL levels may be of concern for future cardiovascular risk in patients on long-term (2–5 years or more) androgen therapy, but usually return to baseline values within 3–6 months after discontinuing this treatment. Thyroid function is not affected by androgen treatment, but thyroid binding globulin level has been found to be reduced in patients using oxymetholone.

Note: Prednisone 5 mg/day or every other day in combination with androgens was used in the past by some physicians to delay the early closure of epiphyses. This use is no longer recommended because there are no data to support its beneficial effects, and prednisone can cause avascular necrosis and bone density loss (osteopenia and osteoporosis).

Other treatments

Cytokines

Hematopoietic growth factors such as G-CSF and GM-CSF can achieve temporary improvement in counts and may be useful in patients with persistent neutropenia (neutrophil count

<500/mm^3), particularly in the presence of recurrent or serious infections. However, there is concern that growth factors may also stimulate proliferation of a malignant clone, resulting in malignant transformation. Splenic peliosis and splenic rupture have been reported in two individuals with DC who received G-CSF in combination with androgen treatment.[13] Thus, concurrent use of androgens with G-CSF, GM-CSF, and erythropoieten is contraindicated in patients with DC.

Thrombopoietin receptor agonists

Eltrombopag has not been studied in patients with dyskeratosis congenita, but there is concern for its inducing clonal evolution to MDS in aplastic anemia.[1,4] Thrombopoietin receptor agonists should therefore not be used in dyskeratosis congenita outside of an investigational protocol, and only with rigorous monitoring.

Investigational protocols

Investigational protocols may be considered for patients who are not candidates for HCT and who fail to respond to androgen treatment.

A list of ongoing therapeutic trials can be found at www.clinicaltrials.gov.

Management guidelines for treatment of bone marrow failure

The clinical management of DC and related telomere biology disorders is complex because several systems may be affected simultaneously to varying degrees, and presentation varies greatly between patients. The treatment approach that works for one patient may not be ideal for another. Therefore, the risks and benefits of a regimen should be discussed with the patient or family (of a pediatric patient) prior to initiating specific care.

A broad, general approach to treatment of BMF is outlined below:

At the time of diagnosis of dyskeratosis congenita:

- Consultation should be sought with a hematologist with expertise in DC who will evaluate, monitor, and manage the patient. A detailed assessment of all systems should be undertaken (as described in the DC Clinical Guidelines) to assess the degree of other system involvement.
- Older patients with mild cytopenias may be followed with regular blood counts. For younger patients with any degree of cytopenia, one should consider having a conversation about treatment options in case cytopenia progresses. Early discussion with a HCT team with

expertise in treating patients with DC should be considered. HLA-typing and testing of immediate family members for DC can be initiated to assess the availability of a potential HCT donor.

- Families should be referred for appropriate medical and genetic counseling. Those wishing to have more children may be interested in pursuing prenatal screening or preimplantation genetic diagnosis (PGD) with selection of an unaffected, HLA-matched embryo for the patient. (See also Chapter 5, Genetic Counseling).

Normal blood counts or mild to moderate bone marrow failure:

- Monitor CBC and bone marrow as discussed earlier (see monitoring of BMF) until further treatment is needed.
- Continue discussions regarding treatment options. For patients with declining counts, consider referral to the HCT team if not already done (as discussed above).
- For patients lacking an HLA-identical sibling, consultation with a transplant center to discuss the option of future unrelated donor HCT should be considered.

Severe bone marrow failure:

- Consider HCT for eligible patients.

- Consider androgen treatment for patients who are not candidates for HCT because they are unwilling, ineligible, or have risk factors conferring a high transplant risk.

Severe bone marrow failure of high transplant risk patients unresponsive to androgens:

- Offer supportive care
- Consider cytokines and investigational protocols.

MDS or AML

The diagnosis of MDS in a patient with DC or DC-related telomere biology disorder may need to be confirmed by a hematopathologist with expertise in these disorders. No standard effective therapy other than HCT has been established for MDS or AML associated with DC.

- Patients should be referred for HCT with or without prior induction chemotherapy.
- Experimental phase I or II clinical trials may be considered for patients ineligible for HCT.

Supportive care

Some patients with DC and related telomere biology disorders may need red blood cell and platelet transfusion support before definitive treatment can be initiated or becomes effective, or if

other measures have failed. Timely referral to a transplant center for consideration of HCT should be made for eligible patients.

Anemia

Red blood cell transfusions are indicated in anemic patients in order to maintain normal hemoglobin and quality of life. Patients on chronic red blood cell transfusions should be monitored for iron overload by serum ferritin, T2* MRI of the heart and liver, or other relevant studies. Appropriate treatment with iron chelators such as deferoxamine (Desferal) or deferasirox (Exjade) should be initiated in patients with iron overload.

Thrombocytopenia

Platelet transfusions may be indicated in patients undergoing invasive procedures or in those with mucosal bleeds. Aminocaproic acid (Amicar) may be used as an adjunct to platelet transfusions in patients with mucosal bleeds. Non-steroidal anti-inflammatory drugs, aspirin, and other medications that inhibit platelet function should be avoided. Activities carrying high risk of trauma, like contact sports, should be avoided.

Neutropenia

G-CSF may be considered in patients with fever and neutropenia (ANC <1,000/mm^3). As stated earlier, G-CSF should not be used in patients on androgens, as the risk of splenic peliosis and rupture is higher with this combination.

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Chapter 8:
Hematopoietic Cell Transplantation for Dyskeratosis Congenita

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Overview

Hematopoietic cell transplantation (HCT) can cure blood defects—bone marrow failure (BMF), myelodysplastic syndrome (MDS), and leukemia—in patients with dyskeratosis congenita [2*] (DC). However, HCT does not cure the other problems of DC. Early experience in HCT for DC was characterized by high morbidity and mortality, and raised concerns that conventional transplant regimens accelerated other disease manifestations in DC patients. HCT outcomes have improved in the past decade

[2*] Because of a lack of data to support differential management, in this chapter we do not distinguish classic dyskeratosis congenita from other telomere diseases (like Hoyeraal-Hreidarsson syndrome, Revesz syndrome, or aplastic anemia with very short peripheral blood cell telomere length or with mutations in telomere biology genes). The comments are intended to apply generally to patients with telomere diseases.

with advances in diagnosis, donor matching and supportive care, and by using reduced-intensity, disease-specific regimens.

History

Case reports in the 1980s and 1990s demonstrated that aplastic anemia in DC could be cured with HCT (reviewed in de la Fuente and Dokal[12]). [1-11]

However, the overall results in this era were dismal, with a 5-year overall survival of approximately 45%, and no long-term survivors of unrelated donor HCT.[12,13]. More than half of all patients died within 4 months of the HCT procedure, most often due to infections, graft failure, or graft versus host disease (GVHD).[12,13]

A striking increase in fatal lung and vascular complications was noted, attributed to both predisposition to pulmonary and endothelial disease in DC patients, and heightened sensitivity to cytotoxic chemotherapy and radiation used in the conditioning regimens.[2,7,8,12]. Other factors contributed to poor outcomes. The interval from onset of BMF to transplant was often years,[6] and identification of DC sometimes went undiagnosed until after HCT because the clinical syndrome was not recognized and genetic or functional testing was unavailable.[5]

With increased awareness, new diagnostic tests, and the application of lessons learned from reduced intensity conditioning (RIC) in Fanconi anemia (FA),[14] HCT outcomes have improved for DC in the past 15 years. In a retrospective study of data reported to the Center for International Blood and Marrow Transplantation Research (CIBMTR), the 5-year overall survival probability for DC patients undergoing HCT from 2000-2009 was 65%.[13]

Similarly, in a retrospective review of DC transplants using RIC regimens after 2000, approximately two-thirds of patients were alive with a median follow-up of 16 months, and included survivors of unrelated donor and cord blood transplants.[15] The improvement has been attributed to reduction or elimination of both radiation and alkylating agents (such as cyclophosphamide, busulfan, melphalan, thiotepa) in preparative regimens, and an increasing use of fludarabine- and antibody-based immunosuppressive conditioning.[15-22]

Better outcomes are also the result of improved supportive care of transplant patients, expanded availability of alternative donors and umbilical cord blood grafts, and advances in molecular human leukocyte antigen (HLA) matching techniques. Disease-specific, prospective HCT trials are underway for DC

patients.[15] These aim to exploit the telomere maintenance and cellular replication defects in DC patients, and ask whether minimally toxic conditioning regimens will permit successful engraftment. One can anticipate that outcomes will continue to improve in HCT for DC, with new knowledge and coordinated efforts aimed at decreasing adverse effects, and increasing overall length and quality of life for patients.

Proceeding to HCT

Diagnosis

Patients with DC can present with highly variable signs and symptoms, from classic findings in children to isolated hematological abnormalities in adults. Establishing the diagnosis of DC as the cause of the patient's hematological problems has major implications for how the transplant should be conducted. Therefore, a thorough investigation for DC should be conducted in all patients with BMF and MDS (and some patients with leukemia) who are being evaluated for HCT (see Chapter 3).

Indications for HCT

In general, the indication and timing of HCT depend on several factors, including:

- the nature of the patient's hematological problem and its severity;
- the degree of HLA match and the type of donor graft available to the patient;
- the patient's age and overall clinical condition;
- the transplant physician's recommendation; and
- the patient's or parents' decision.

For DC patients, several additional factors impact decision-making regarding the timing of HCT.

More than 80% of patients with classic DC will manifest BMF (defined as one or more peripheral cytopenias) by age 30.[23] Results of HCT are generally better for patients who are younger. The risk of graft failure is higher in patients who have received a higher number of red blood cell or platelet transfusions. DC patients have a high risk of MDS (>2500-fold over the general population) and acute leukemia (200-fold over the general population).[24]

HCT is curative for BMF in DC, and in theory eliminates the risk of MDS or leukemia originating from the patient's blood cells. Results of HCT are generally better for patients who present with BMF, compared to HCT outcomes of patients who

present with MDS or leukemia. These factors argue in favor of early intervention with HCT for DC patients manifesting hematologic defects, prior to significant transfusion exposure or evolution to MDS or leukemia. However, HCT is associated with a risk of transplant-related death of at least 15% and a risk of chronic GVHD of at least 10%. These risks are likely to be higher in DC patients compared to other patients because of disease-associated co-morbidities such as lung and liver dysfunction, which adversely influence the HCT outcomes.

The decision on HCT timing for each DC patient is therefore impacted by the individual's clinical status and predicted trajectory of hematologic disease, as well as the physician's and patient's assessment of relative risks and benefits.

The following are considered absolute and relative indications for HCT in DC patients:

Absolute indications:

- **Severe cytopenias**: defined as hemoglobin < 8 g/dL; absolute neutrophil count (ANC) < 500/mm^3; platelets < 20,000/mm^3 ; or requiring red blood cell or platelet transfusions to prevent significant symptoms of low hemoglobin or platelets. Immunosuppressive therapy

used for idiopathic aplastic anemia is unlikely to cure BMF in patients with DC and should not be trialed in this situation. Alternative treatments such as androgens or hematopoietic growth factors may be tried as temporizing measures, but for those without contraindications to HCT and with access to a suitable donor, it may be advisable to proceed to HCT without such a trial.

- **High-risk MDS and Acute leukemia** (that is, high-risk chromosomal abnormalities or marrow blast count >5%): May require chemotherapy before HCT, depending on the practice of the transplant center.

Relative indications

- **Moderate cytopenias**: If there is evidence of progression toward transfusion dependence, one may pursue HCT when a donor/graft with a suitable degree of HLA compatibility is available. Alternatively, it is reasonable to consider a trial of androgen therapy prior to proceeding with HCT.
- **Low-risk MDS** (morphologic bone marrow dysplasia with no chromosomal abnormalities or with low-risk chromosomal abnormalities): Depending on donor

availability, it may be preferred to proceed to HCT, given concerns for clonal evolution, rather than continue observation or trial androgen therapy.

Exclusions

In general, to undergo HCT, the patient must not have:

- uncontrolled bacterial, fungal, or viral infection
- severe organ dysfunction, such as kidney, liver, or respiratory failure
- an active pregnancy

Individual circumstances and specific conditioning regimens may permit consideration of HCT in patients with some of these conditions, and should be discussed with the transplant physician.

Assessment and planning for HCT

Referral to a transplant center

Because of disease-specific peri-transplant and long-term care considerations, and need for a tailored RIC regimen, patients should obtain a formal evaluation at a transplant center experienced in conducting HCT for DC. To determine the

experience of a transplant center, the physician or patient may wish to ask the questions listed in Table 1 at the end of this chapter. If a preferred transplant center is "out of network" for the patient's insurance, it may be possible to advocate for coverage of care through coordinated efforts of the patient, physician and the expert transplant center. A similar approach is advised for international patients working with government or private health care insurance.

There is no "standard" HCT regimen for DC that is used across centers; each transplant center may offer a different regimen for HCT, based on their own experience and opinion. Although this is not unusual in the practice of HCT, it can be unsettling for patients and families, who are in the position of having to decide between complex medical regimens, usually without a medical background to guide them. At the time of this writing, there is an effort to develop multi-institutional clinical studies employing consistent regimens for each HCT indication in DC. In the future, it is hoped that these types of coordinated efforts will yield more rapid advances in knowledge, which in turn will lead to more uniform standards of care among transplant centers.

Patient assessment

Time and advanced planning are required to gather the information needed for a comprehensive pre-transplant evaluation. For DC patients, such an evaluation will involve the following elements:

i. Past medical history

Because of the variability of DC clinical features, a thorough history is required to elicit factors that may complicate HCT. In particular, history should be obtained regarding infections, blood transfusion requirements, and use of prior therapies such as androgens and hematopoietic growth factors. Prenatal, birth, and developmental history, as well as neurologic, ophthalmologic, dental, gastrointestinal, pulmonary, hepatic, gynecologic/urologic, and oncologic conditions should be reviewed in detail. Prior surgeries and medical treatments, allergies, and current medications, including vitamins, supplements, and herbal therapies, should be detailed.

ii. Family history

The family medical history is extremely important. Without exception, any family members being considered as potential HCT donors must undergo telomere length analysis and genetic testing (if the genetic mutation is known), to determine disease risk and suitability as a donor. It has been shown that family members who appear to be completely healthy and without any manifestations suggestive of DC may still carry a genetic mutation associated with DC, and may not be suitable HCT donors.[25] Moreover, in families with telomere diseases, short telomeres can be inherited independent of the genetic mutation;[26] this raises the unanswered question of whether a well-matched unrelated donor is preferable to a fully matched related donor who does not carry the DC mutation but has short peripheral blood cell telomeres.

iii. Social history

Behavioral, school, and work performance issues should be reviewed. Alcohol and tobacco use should be examined because of elevated risk of cancer, liver, and

lung disease, both early on in the post-transplant period and long-term.

iv. Physical examination

Prior to HCT, the physician should systematically assess for physical abnormalities associated with DC that may alter the risk or plan of transplant therapy. The general examination should include particular attention to establishing a baseline for each organ system. This may include:

- neurological imaging to screen for brain cysts, white matter changes, and calcifications
- ophthalmological evaluation for retinal bleeding or exudate, and lacrimal duct obstruction
- oropharyngeal inspection for precancerous lesions, general dental health, and infection risk
- pulmonary function testing, with measurement of oxygen saturation, diffusion capacity of the lung for carbon monoxide (DLCO), and imaging for pulmonary fibrosis or arteriovenous malformations

- gastrointestinal status including liver function, and evaluation for evidence of cirrhosis, alimentary canal strictures, enteropathy, or gut bleeding
- urogenital examination for urethral strictures or precancerous lesions
- cutaneous inspection for baseline skin pigmentation and nail abnormalities, or precancerous skin lesions

The donor search

The compatibility of a patient and donor for HCT is determined primarily by their degree of donor/recipient HLA matching.

HLA antigens are encoded by several genetic loci, of which each individual has two copies or "alleles". The loci of primary importance are HLA-A, HLA-B, and HLA-DRB1. A "6 out of 6 match" refers to a match at both alleles for all three of these loci. Two additional loci of importance for HCT are HLA-C and HLA-DQB1, and identity at all five of these genetic loci yields a "10 out of 10 match." Donor/recipient mismatches may or may not be acceptable for HCT, depending on several factors,

including which HLA locus is mismatched and the type of donor or graft.

Determining whether or not the patient has a suitable donor is important for medical management decisions, even in the absence of an obvious short-term need for HCT. Therefore, it is essential that patients, siblings, and parents undergo HLA-typing as soon as the diagnosis of DC is made. A patient has a 25% chance of being HLA-identical to a full biological sibling. It is far less likely but possible for a parent to be a complete HLA match.

There is no given lower age limit for a potential sibling donor; infants can be used as sibling donors. However, because the number of cells transplanted per unit recipient weight correlates with success of engraftment, it may be difficult to use a sibling donor who is much smaller than the patient.

Generally speaking, a matched sibling is an ideal donor in that there is a higher degree of shared genetic identity with the patient, which reduces the risk of GVHD, and usually a sibling is readily available for donation, reducing the complexity and delays in transplant scheduling. The potential drawbacks of using sibling donors for HCT in patients with DC are that the sibling may be a silent carrier of the genetic mutations causing

the disease, and the sibling may have inherited short telomeres, and hematopoietic stem cells may not be ideal for transplantation.

Because of these issues, all potential sibling donors should undergo a complete blood count, telomere length testing, and genetic testing whenever possible. When there is uncertainty, a bone marrow examination should be performed on the donor to assess for hypocellularity or dysplasia.

If a sibling donor is unavailable, searching for an *unrelated* donor involves comparing the patient's HLA typing to information stored in worldwide donor registries. A preliminary donor search can be performed by a transplant center within a few days and without cost to the patient. The availability of stored umbilical cord blood (UCB) units that may be used for HCT is also determined this way. Again, it is essential that the availability of potential donors be determined as soon as the diagnosis of DC is made. In addition to family HLA typing, a preliminary search of existing registries for potential unrelated donors should be performed very early after diagnosis.

A formal unrelated donor search involves determining the willingness, compatibility, and suitability of one or more adult individuals to donate blood or bone marrow to a specific patient.

Because it involves blood tests, including high resolution HLA typing of potential donors, there are costs to the patient or insurance. The process of identifying a suitable donor can take anywhere from several weeks to months. Once a donor has been identified and the decision is made to proceed with HCT, it may still take several weeks to schedule the donor collection and complete the necessary pre-transplant evaluation and testing. Therefore, early planning is required to prevent delays in HCT.

The graft

The graft is the blood or bone marrow product containing the hematopoietic stem cells obtained from the donor for infusion into the patient. Various types of graft can be used:

- **Bone marrow (BM)***:* Liquid bone marrow, similar in appearance and consistency to blood, is typically removed from the pelvic bones of donors via needle aspiration. The donor is typically put under general anesthesia for this procedure. The amount of BM removed is dependent on the size of the patient, but ranges from 300–1200 milliliters (10–40 fluid ounces). It is filtered and may be further manipulated based on the donor and recipient ABO blood types and recipient size.

- **Peripheral blood stem cells (PBSC):** Granulocyte colony stimulating factor (GCSF) is given to the donor to mobilize hematopoietic stem cells from the marrow into the peripheral blood. The donor undergoes pheresis, which entails: (1) collection of blood via intravenous catheters, (2) separation and harvesting of white blood cells (which contain the mobilized stem cells), and (3) return of the remaining blood components to the donor. The donor is awake for the procedure, which may require multiple sessions over a few days. PBSC have the potential advantage of improved engraftment compared to bone marrow, but may be associated with higher risk of GVHD.
- **Umbilical cord blood (UCB) cells:** UCB is rich in hematopoietic stem cells. It is collected from the umbilical cord and placenta immediately after birth, HLA typed, and frozen at specialized blood banks. These banks serve as repositories for UCB units to be dispensed as needed for patients requiring this graft source. The potential advantages of using cord blood for transplantation are that it is readily available, and there is a decreased risk of GVHD. Therefore, less than perfect HLA matching at

HLA-A, -B, and -DRB1 is acceptable. In the United States, it is estimated that UCB units mismatched at one or two HLA loci are available for almost all patients younger than 20 years of age and for more than 80% of patients 20 years of age or older.[27] The disadvantage of UCB is that the volume of the product (and therefore the stem cell "dose") is fixed and may be insufficient. In this case, infusion of more than one UCB unit (a double UCB transplant) may be required. When obtained from a public bank, one cannot obtain more stem cells from the same donor. There may also be a higher risk of graft failure and certain post-transplant viral infections with UCB transplants because of fewer mature immune cells (T lymphocytes) in cord blood.

The choice of a BM, PBSC, or UCB graft for a given patient will depend on several factors including: (a) urgency of HCT; (b) degree of HLA match for a family donor versus unrelated donor versus UCB donor unit(s); (c) regimen-specific or transplant center requirement or preference; (d) donor preference (BM versus PBSC donation); (e) clinical considerations, most notably patient age and history of infections; and (f) donor/graft-specific

considerations (for example, the age, parity, and cytomegalovirus (CMV) status of the donor, or the cell count of the available UCB unit[s]).

Conditioning regimen

The conditioning regimen (also known as *preparative* or *cytoreductive* regimen) is the process by which the patient is treated with chemotherapy, radiation, and/or immunosuppressive drugs to allow engraftment of the donor hematopoietic stem cells. The "intensity" of a conditioning regimen refers to how aggressively the combination of agents depletes the blood-forming and immune cells of the patient. A higher intensity conditioning regimen more reliably enables engraftment of donor cells, but also causes increased toxicity and side effects. An ideal conditioning regimen would subject the patient to the least toxic agents (or no agents at all), and would achieve full replacement of the patient's blood and immune cells, as well as eradication of any dysplastic clones or leukemia cells.

Based on historical evidence showing an unacceptable rate of toxicity and death, fully myeloablative regimens consisting of high dosages of radiation or alkylating agents should not be used to treat patients with DC. Although higher intensity

conditioning regimens may be warranted to eradicate MDS or leukemia, the focus of current research trials is to decrease short- and long-term complications by minimizing conditioning intensity as much as possible for DC patients with BMF.

Relatively few agents are used in reduced intensity regimens for DC, but the combinations and dosages can vary significantly between transplant centers. The major classes of agents, as well as their typical dosages and range of toxic effects are listed in Table 2. At the time of this writing, there is no standard or "consensus" conditioning regimen for patients with DC, and therefore the physician and patient should give detailed consideration to the different regimens being offered at the centers where the patient is being evaluated for HCT. It is also important to note that given the high variability in symptoms and complications affecting different individuals with DC, it is unlikely that there will be one ideal regimen for all patients.

Graft versus host disease prophylaxis and treatment

All patients undergoing allogeneic HCT are at risk of GVHD, which occurs when the immune cells in the donor graft recognize the patient's tissues as "foreign", and cause inflammation and cell destruction. The two phases of GVHD—

acute and chronic—are characterized by different symptoms (Table 3). GVHD is a major cause of morbidity and death after HCT, and the risks of GVHD are higher in unrelated donor PBSC or BM transplants compared to sibling donor or UCB transplants. Chronic GVHD is of particular concern as it targets tissues that are often already affected in DC patients, and so may accelerate liver or lung failure, malignancy, or other disorders.

Several strategies are used to decrease the risk of GVHD, some of which may be preferable in DC patients:

- **Calcineurin inhibitors**: Cyclosporine A (CSA) and tacrolimus (FK506) are immunosuppressive agents that diminish the response of immune cells to foreign antigens, and are mainstays of GVHD prophylaxis. CSA or FK506 is used for several months after HCT, typically in combination with one or more other GVHD prophylactic strategies described below. The side effects and toxicity profiles of calcineurin inhibitors make them suitable for use in HCT regimens for DC patients.
- **Methotrexate (MTX)***:* MTX is given for several doses in the days immediately following graft infusion. Because it inhibits DNA synthesis, it destroys donor immune cells that otherwise divide rapidly in response to the patient's

"foreign" antigens. MTX effects are not specific to immune cells. It may cause mucositis, pulmonary fibrosis, and other cytotoxicity, so it is preferable to avoid using it as chronic GVHD prophylaxis in DC patients.

- **Mycophenolate mofetil (MMF)***:* MMF also inhibits immune cells in the donor graft but without significant toxicity to other cell types. It is given for several weeks after HCT. The side effect and toxicity profiles make MMF suitable for use in DC patients.
- **Graft modification:** Two types, ex vivo and in vivo T cell depletion:
    - *Ex vivo T cell depletion:* Removal of T cells from the donor graft prior to infusion significantly reduces the risk of GVHD without exposing the patient to pharmacological toxicity. T cell depletion may also permit a shorter duration of calcineurin inhibitor administration. The main risks of T cell depletion are graft failure and an increased susceptibility to viral infections. T cell depletion is not available at all transplant centers.
    - *In vivo T cell depletion:* Anti-thymocyte globulin (ATG), alemtuzumab, or other anti-

lymphocyte antibodies given as part of the conditioning regimen may persist in the patient after infusion of the graft and so effectively result in T cell depletion. The degree of GVHD protection afforded by this strategy is difficult to measure and is likely to be highly variable between patients. Like ex vivo T cell depletion, major risks may include increased graft failure and viral infections.

Despite preventive measures, patients may still develop GVHD, ranging in severity from limited skin involvement to life-threatening multi-organ failure. Corticosteroids such as methylprednisolone are first-line therapy for GVHD, and adequate control may require long-term immunosuppression. In DC patients with GVHD, consideration should be given early on to strategies that minimize cumulative exposure to high-dose, systemic corticosteroids, in order to reduce additive effects on musculoskeletal, endocrine, and other organ systems.

Transplant care timeline

The timeline of HCT for DC patients can be broken down into 4 periods: (1) conditioning/preparative therapy; (2) graft infusion

and supportive care until engraftment; (3) post-HCT care; and (4) long-term care. Patients are usually hospitalized from the period of conditioning through engraftment, approximately 4-6 weeks, followed by outpatient post-HCT care over the subsequent 9-12 months.

1. Conditioning/preparative therapy

Prior to or upon admission, a central venous catheter is placed to enable routine blood sampling and supportive care during the HCT procedure. In the 7–10 days prior to graft infusion, the patient is hospitalized and the conditioning regimen is administered. During this period and depending on the regimen, patients may experience immediate side effects such as nausea, vomiting, fever and fatigue. Medications to control these symptoms and prevent infections are administered. GVHD prophylaxis may begin during this time.

2. Graft infusion and supportive care until engraftment

The day of the graft infusion is termed "day 0." Hydration and medications to prevent infusion reactions are administered. The graft is administered intravenously, similar to a blood

transfusion. Blood counts fall in the days that follow due to the effects of the conditioning regimen, and transfusion support is administered. Pain management for oral mucosal breakdown and nutritional support are usually required during this phase of HCT; however, with some RIC regimens used for DC, the severity of these symptoms is decreased. In the subsequent weeks, patients are monitored closely for signs of complications such as infections, organ dysfunction, metabolic disturbances, and acute GVHD. Drugs for GVHD and infection prophylaxis continue to be administered. Neutrophil engraftment is defined as recovery of ANC to ≥ 500 cells/mm^3 for three days, and usually occurs between days 14 and 35 after graft infusion. Red blood cell and platelet transfusion dependence may continue even after neutrophil engraftment.

3. Post-HCT care

Patients are discharged from the hospital after neutrophil engraftment if: (a) there are no signs of infection or significant organ dysfunction, (b) they are able to maintain adequate hydration, nutrition and symptom control, and (c) an appropriate outpatient care management plan is in place. To reduce the risk of infections, patients are restricted from social

contacts for 6–12 months after HCT, including work/school and participation in crowded indoor functions. The first 100 days after transplant are considered the highest risk time period for HCT-related complications. Clinic visits are typically multiple times per week to administer medications or transfusions, and to assess for infection, graft function, GVHD, medication toxicity, metabolic derangements, and other post-HCT complications. If the patient is doing well after this period, the central venous catheter may be removed, and clinic visits may decrease in frequency. Also, if the patient has traveled to a transplant center for HCT, care may be transitioned to providers closer to the patient's home, depending on several factors. Immunosuppressive medications to prevent GVHD and infection prophylaxis are usually reduced or eliminated after 6–9 months, depending on the regimen, the patient's clinical status, and the transplant center's practice.

In an ideal scenario, by one year post-HCT, the patient will have discontinued almost all transplant-related medications, will be independent of transfusions, and resumed normal activities at home, school, or work. At this time, re-immunization can also start, as the transplant process will cause most patients to lose the protective effect of their previous immunizations.

The transplant physician or hematologist coordinating the patient's care should continue comprehensive surveillance for DC-related complications in the immediate post-transplant period. Several reports have documented the overlap of chronic GVHD symptoms and non-hematological manifestations of DC,[28-30] including oral mucosal, skin, and hair changes, musculoskeletal abnormalities, and lung disease. In some cases of presumed idiopathic aplastic anemia, these manifestations have led to a diagnosis of DC in the months to years following HCT. Awareness and careful evaluation is required to discern between HCT-related complications that may require aggressive interventions such as corticosteroids, versus the natural progression of DC.

4. Long-term care

Optimal care of all patients who have undergone HCT requires lifelong regular and comprehensive evaluation; late effects of the conditioning agents and immunosuppressive medications used in HCT, and complications such as GVHD and infections, demand ongoing surveillance. There is increased concern for significant post-HCT sequelae in patients with DC given the nature of the underlying disease.

At this time, there are no published studies specifically addressing post-HCT late effects in DC patients, but applicable guidelines for monitoring may be applied, such as those from the Children's Oncology Group (COG), or the joint recommendations of the European Society for Blood and Marrow Transplantation (EBMT), CIBMTR, and American Society of Blood and Marrow Transplantation (ASBMT).

DC patients should undergo regular, comprehensive multi-disciplinary evaluations with appropriate targeted testing in the years following HCT. Late effects of alkylating agents and radiation include malignancy, fertility problems, and endocrine defects, which are known DC-associated complications. Chronic GVHD and prolonged use of corticosteroids or other immunosuppressive therapies may exacerbate bone disease and magnify risk of malignancy in DC. Lung complications of HCT may decrease pulmonary reserve and accelerate respiratory decline in these patients. HCT late effects and their overlap with DC are listed in Table 4.

With HCT survival improving for DC patients, deliberate attention must be given to coordinating and facilitating ongoing multi-disciplinary care, preventing long-term complications, and optimizing quality of life. Patient encounters should include

counseling on a healthy lifestyle and avoidance of harmful habits such as smoking and excessive alcohol consumption, which may accelerate lung and liver disease. Ideally, to anticipate problems and intervene appropriately, post-HCT and long-term care of DC patients should be coordinated by a provider or combination of providers knowledgeable about both DC-related complications and the late effects of HCT.

Challenges and opportunities

In 2015, with early diagnosis, careful pre-transplant monitoring, and an individualized approach, HCT is an effective and feasible curative strategy for BMF in patients with DC. Efforts are underway to coordinate and execute multi-center prospective trials to more rigorously test the safety and efficacy of specific RIC HCT regimens for BMF in DC patients.

Ongoing challenges include tailoring HCT regimens for high-risk patients, such as those with allo-sensitization, as they will have a higher risk of graft rejection, those with significant DC-associated co-morbidities who may not even tolerate RIC, and those with MDS or leukemia who may require higher intensity regimens. Attention must also be given to long-term, multi-

disciplinary follow-up care to optimize outcome after a successful HCT.

Acknowledgement

We grateful to the Fanconi Anemia Research Foundation for permission to reprint material from "*Fanconi Anemia: Guidelines for Diagnosis and Management*" (3rd Edition, 2008).

Table 1: Transplant center interview questions

- How many allogeneic DC transplants has your center performed? How many in children? How many in adults? How many have survived beyond one year?
- How many unrelated donor transplants on DC patients has your center performed in the prior calendar year?
- What specific regimen(s) does your center offer/recommend? (Obtain the doses of each therapy, graft types, and GVHD prophylaxis.) Is this regimen part of a trial?
- What is your center's long-term follow-up plan for DC patients who undergo HCT?

Adapted from "Fanconi Anemia: Guidelines for Diagnosis and Management"; 3rd edition, 2008; Chapter 10, Table 3; used with permission from the Fanconi Anemia Research Fund.

Table 2: Conditioning agents

Radiation	Physically damages DNA and thereby kills and/or prevents division and growth of patient cells
	Very effective in destroying host blood and immune cells in preparation for donor stem cell engraftment
	Toxic effects are not specific to blood and immune cells: there are dosage-related toxic effects on all organs/tissues that are exposed
	Usually delivered to the whole body (TBI=total body irradiation); sometimes dose is focused on lymphoid organs (TLI=total lymphoid irradiation)
	Myeloablative dose is 1350-1400 cGy (centigray) total in several fractions
	Reduced intensity doses are approximately 200-400 cGy.
Alkylating Agents	Include cyclophosphamide, busulfan, melphalan, thiotepa
	Chemically modify and damage DNA, thereby killing and/or preventing division and growth of cells
	Very effective in destroying host blood and immune cells in preparation for donor stem cell engraftment
	Toxic effects are not specific to blood and immune cells: there are dosage-related toxic effects on multiple organs
	High-dosage ranges: cyclophosphamide 120-200 mg/kg total; busulfan 12.8-16 mg/kg total; melphalan 140-180 mg/m^2 total
	Reduced intensity dosages: cyclophosphamide 20-50 mg/kg total; busulfan 0.8-3.2 mg/kg total; melphalan 70 mg/m^2 total
Fludarabine phosphate	Interferes with DNA synthesis and thereby kills and/or prevents division and growth of patient cells

	Very effective in destroying host blood and immune cells in preparation for donor stem cell engraftment
	Toxic effects are largely limited to blood and immune cells, because the intravenously administered drug has limited penetration into other tissues
	Major component of reduced intensity conditioning regimens
	Dosage is typically 120 – 200 mg/m^2 total
Antibodies	Bind to and promote the destruction and clearance of hematopoietic and immune cells
	Long-lasting and powerful immunosuppressive agents; can destroy not only the donor immune cells, but depending on dosage and schedule, can deplete the immune cells in the graft; can create serum sickness-like reactions in the short-term; other toxic effects are limited to hematopoietic and immune cells
	i. Anti-thymocyte globulin: produced from different sources (horse or rabbit immune globulin raised against human immune cells; or rabbit immune globulin raised against human lymphocyte cell lines); long track record of use in HCT; limited by heterogeneity of formulations and lack of availability of particular formulations in different parts of the world
	<u>Anti-CD52 antibody (alemtuzumab; Campath-1H):</u> humanized monoclonal antibody causes rapid, profound and sustained lymphocyte depletion; may be associated with increased risk of viral reactivations/infections post-transplant; may be associated with decreased risk of GVHD

Table 3. Manifestations of GVHD

Acute GVHD	a. Skin (maculopapular rash to generalized erythroderma to desquamation and bullae)
	b. Liver (hyperbilirubinemia)
	c. Gastrointestinal system (secretory diarrhea, abdominal pain, ileus, hemorrhage, nausea/vomiting)
	d. Ocular (photophobia, hemorrhagic conjunctivitis, pseudomembrane formation, and lagophthalmos)
Chronic GVHD	a. Skin (lichen planus, scleroderma, maculopapular rash, hyperkeratosis, hair and nail loss)
	b. Liver (cholestasis, absent bile duct syndrome, cirrhosis, portal hypertension, hepatic failure)
	c. Gastrointestinal system (dysphagia, failure to thrive, aperistalsis, malabsorption syndrome)
	d. Lung: obliterative bronchiolitis (restrictive/obstructive airway disease)
	e. Sicca syndrome (keratoconjunctivitis sicca with burning, photophobia, irritation, pain; oral dryness, pain, lichenoid lesions, gingival atrophy, dental caries)
	f. Vaginitis, vaginal dryness/strictures
	g. Pancytopenia; eosinophilia
	h. Serositis (pleural, pericardial, joint effusions)
	i. Myofasciitis

From "Fanconi Anemia: Guidelines for Diagnosis and Management"; 3rd edition, 2008; Chapter 10, Table 8; used with permission from the Fanconi Anemia Research Fund

Table 4. Overlap of manifestations of DC and HCT late effects

	DC	HCT late effects
Hematology	Bone marrow failure, iron overload	Iron overload
Dermatology	Reticular pigmentation changes, skin thickening, nail changes	Chronic GVHD: rash, skin thickening and tightening, nail changes
Ophthalmology	Tear duct obstruction, loss of eyelashes	Ocular GVHD and dry eyes, cataracts
Oral	Leukoplakia, dental problems	Oral GVHD, dental problems
Endocrine	Skeletal defects, short stature, hypogonadism	Thyroid defects, growth hormone deficiency, fertility problems, hypogonadism, metabolic syndrome
Pulmonary	Fibrosis, arteriovenous malformations	Fibrosis, emphysema, pulmonary infections, idiopathic pneumonia syndrome, chronic GVHD
Gastroenterology	Esophageal stenosis, enteropathy, enterocolitis, cirrhosis, portal hypertension	Sequelae of gut GVHD, infectious colitis
Neurology, Psychiatry, Social	Development and psychiatric disorders, quality of life issues	Neurocognitive defects, post-traumatic stress disorder, anxiety, depression, social restrictions, quality of life issues
Oncology	MDS/leukemia, squamous cell cancers of head/neck/mucosal surfaces	Secondary MDS/leukemia, skin and other cancers

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Chapter 9: Immunologic Features of Dyskeratosis Congenita and Its Variant, Hoyeraal-Hreidarsson Syndrome

Fabien Touzot, Soma Jyonouchi, Patrick Revy

Introduction

Immune cells are highly proliferative when stimulated by microbial organisms; hence lymphocytes are particularly vulnerable to the effects of telomere dysfunction.

Cellular senescence, an accelerated decline in the number and function of mature peripheral immune cells, contributes to the pathophysiology of dyskeratosis congenita (DC) and its variant, Hoyeraal-Hreidarsson syndrome (HH) (see also Chapter 6 Subtypes of DC).[1,2] It is also possible that dysfunction of the hematopoietic environment from which these cells originate may also contribute to immune dysfunction in this disorder.[3] DC patients, particularly those with HH, exhibit a progressive immune deficiency manifesting as increased susceptibility to life-threatening infections, the severity of which worsens with age. Immunologic complications, although variable and

heterogeneous among patients, are one of the most common features of HH, and are a major cause of premature mortality in this disorder.[4]

Despite this, its immunologic manifestations remain underdiagnosed. Here we have summarized the most common immunologic characteristics of DC and HH and made recommendations for their evaluation and management.

Immunological features

Lymphopenia is the most common immunological abnormality observed in DC, occurring in 70% of patients.[1,2] Decreased B and natural killer (NK) cell count is its most distinctive immunologic signature. In fact, virtual absence of B lymphocytes is often observed in HH from birth.[5-12] As a result, marked hypogammaglobulinemia affecting potentially all subtypes (IgG, IgM, and IgA) occurs with high frequency. Antibody response to specific environmental and vaccine-associated antigens is impaired, rendering vaccination ineffective in these cases. Reduced T cell response to specific antigens like candida and tetanus, and less frequently to mitogens, has also been observed.[14]

Relatively increased cell division during B lymphocyte development causes acceleration of telomere shortening in this

cell compartment. This, combined with the shorter half-life of B cells compared with T lymphocytes, suggests B cells may be more affected than T cells.

While absolute number and function of T cell subsets is usually normal, some patients may have a decrease in CD4+ or CD8+ T cell counts, inversion of the CD4/CD8 ratio, or a prematurely advanced naïve-to-memory (CD45RA/CD45RO) T cell transition.[11]

Clinical presentation of immunodeficiency

Patients with DC can present with a spectrum of immunological features, ranging from HH-associated severe combined immunodeficiency (SCID) in infancy to much milder manifestation in adolescence, mimicking common variable immunodeficiency (CVID).

A prominent feature of DC presenting in infancy is severe, chronic, non-infectious enteropathy with intractable diarrhea. The histopathological hallmark of intestinal involvement is presence of mucosal inflammation and apoptosis (similar to what is observed in gut graft versus host disease). It is unclear if this is the result of a defect in digestive epithelium renewal or if mucosal immune dysfunction also participates in the pathogenesis of this feature.

Immunologic evaluation of patients with DC

Given immunologic abnormalities can precede development of clinically significant pancytopenia in DC patients, they may be underdiagnosed and undertreated, resulting in premature mortality from infection. All newly diagnosed patients would benefit from a complete immunological evaluation. Study should include complete blood cell counts, as well as quantifying of lymphocyte subsets using flow cytometry to evaluate $CD3^+CD4^+$ and $CD3^+CD8^+$ T cells (with naive and memory subsets based on the expression of CCR7 or CD62L and CD45RA), $CD56^+CD16^+$ NK cells, and $CD19^+$ cells.

In addition, examination of lymphocyte proliferative responses to mitogens (phytohemagglutinin, concanavalin A and pokeweed), as well as specific antigens (tetanus toxoid and candida) is recommended. Serum IgG, IgA, and IgM levels should be determined, as well as tetanus, diphtheria, poliomyelitis, and pneumococcal antibody titers. Measurement of IgM isohemagglutinin titers should also be considered.

Management of immune deficiency

Treatment depends on clinical presentation and degree of immune dysfunction. It should be managed in close consultation

with an immunologist and tailored to the patient's specific needs.

Opportunistic infections, such as Pneumocystis jirovecii and Cytomegalovirus, and recurrent sino-pulmonary infections occur with increased frequency in patients with T cell dysfunction and antibody deficiency. Antimicrobial prophylaxis with trimethoprim-sulfamethoxazole (20-30 mg/kg trimethoprim component three times a week) is recommended for patients with severe T cell lymphopenia. Intravenous immunoglobulin infusion (IVIG; 400 to 600 mg/kg every three weeks) is indicated for recurrent bacterial infections (ear, sinus, or pulmonary) resulting from impaired antibody immunity. Weekly subcutaneous immunoglobulin therapy (100 to 150 mg/kg) is also an acceptable alternative.

Annual influenza vaccination is recommended especially in cases with pulmonary involvement. This is so even for patients receiving immunoglobulin replacement therapy, because vaccination can stimulate cellular immunity, which plays an important role in combatting influenza virus infection.

Further, new strains of influenza are typically not represented in the antibody repertoire of immunoglobulin substitution.[15]

Immunologic improvement by hematopoietic stem cell transplantation

The immunologic sequelae of DC stem mainly from bone marrow failure and associated compromised development of the immune system.

Clinical benefit of even partial restoration of the immune system has been demonstrated in patients who experience spontaneous genetic reversion (correction of the genetic mutation) in cells from the patient's native immune/hematopoietic compartment.[16-18] In these cases, reversion confers a strong selective advantage to the corrected cells that can, at least in part, reconstitute an incompetent immune system and offer natural protection. Although rare, this phenomenon appears to be highly beneficial for patients by alleviating immunologic complications. Hematopoietic cell transplantation (HCT, see also Chapter 8) can improve a patient's immunological system by replacing it with a donor's. Severe immunodeficiency observed in HH patients can be cured by HCT. However, major adverse effects often complicate the post-HCT course. Moreover, this treatment does not prevent the development of pulmonary fibrosis or cancer, nor correct other non-hematopoietic aspects of the disease.

Table 1: Phenotypic and immunologic features in 3 HH patients in comparison with 3 DC patients

Patient	1 (HH)	2 (HH)	3 (HH)	4 (DC)	5 (DC)	6 (DC)
Age at diagnosis/testing	7mo	10mo	9mo	20yo	18yo	13yo
Mutation	DKC1	DKC1	DKC1	TERT	TERT	DKC1
IUGR	Yes	Yes	Yes	No	No	No
Cerebellar Hypoplasia	Yes	Yes	Yes	No	No	No
Colitis	Yes	Yes	Yes	No	No	No
Life-threatening infections	Yes	Yes	Yes	No	No	No
CD3 T cells (cells/uL)	969	1728	16899	890	798	1130
CD19 B cells (cells/uL)	93(L)	0(L)	3(L)	27(L)	17(L)	4(L)
CD56/16 NK cells (cells/uL)	8(L)	9(L)	57(L)	20(L)	5(L)	46(L)
IgG (mg/dL)	83(L)	10(L)	140(L)	724	591(L)	339(L)
IgA (mg/dL)	<6(L)	<10(L)	52	95	134	35(L)
IgM (mg/dL)	20(L)	33(L)	68	44(L)	30(L)	<4(L)

HH–Hoyeraal-Hreidarsson syndrome; DC–Dyskeratosis Congenita; IUGR–Intrauterine Growth Retardation; (L)–Low

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Chapter 10: Dermatologic Manifestations in Dyskeratosis Congenita

Vinod E. Nambudiri, MD, MBA, Edward W. Cowen, MD, MHSc

Introduction

Involvement of the skin, nails, and mucosal surfaces are hallmark features of dyskeratosis congenita (DC). The original description of the syndrome characterized a clinical triad of reticulated (net-like) skin pigmentation, nail deformities, and oral leukoplakia (whitish plaques). In addition to these diagnostic features, individuals with DC are at risk for several specific skin complications including hair loss, skin cancer, and hyperhidrosis (excessive sweating).

This chapter reviews dermatologic manifestations of DC and examines management and treatment strategies.

Skin cancer

Data from literature reviews and cohorts of individuals with DC have identified an overall increased risk of developing

various cancers in this patient population (see also Chapter 21, Cancer in DC).[1,2] This is thought to be associated with the finding of short telomeres, resulting in increased propensity for chromosomal abnormalities.

Head and neck and cutaneous squamous cell cancers (SCCs) are the most frequently reported solid organ tumors in this population. Individuals with DC tend to develop these malignancies at a younger age than the general population.[1] In a review of eight individuals with DC and cutaneous SCCs, the median age of onset was 21 years, significantly earlier than in the general population, in which the median age is 68.[1]

SCC of the skin generally presents as a slow-growing pink- or skin-colored papule/nodule (raised growth), and may be associated with overlying scale (flaking skin). The most common locations for SCC of the skin are the head and neck, upper trunk, and upper extremities–common locations for sun exposure; however, they may occur on any site of the body.

General risk factors for cutaneous SCC include sun (ultraviolet light) exposure, radiation, and the chronic use of immunosuppressant medication. Voriconazole, a medication used to treat fungal infections, may also increase the risk of squamous cell cancer.[3] There is also an association between

infection with human papillomavirus (HPV) and squamous cell cancer; however, data suggest that individuals with DC may develop squamous cell cancer independent of this association.[4]

There are multiple surgical (excision or Mohs micrographic surgery) and non-surgical (topical chemotherapy or radiation therapy) options to treat skin cancers. The most appropriate treatment depends on factors such as size and aggressiveness of the tumor, risk of recurrence, location on the body, and the anticipated cosmetic appearance following treatment.

Because of the increased risk of skin cancer, prevention strategies are recommended for individuals with DC. Useful approaches include:

- Regular use of sunscreen or sunblock when outdoors, and use of a daily moisturizing lotion with sunblock
- Wearing hats and sun-protective clothing when outdoors to prevent excessive sun exposure
- Limiting outdoor time during hours of peak sun exposure (between 10 am and 4pm)
- Being mindful of reflected sun from water and snow when engaging in outdoor activities
- Avoiding tanning beds

- Performing regular skin self-examination for any new or changing skin growths

For sun protection, individuals with DC should look for sunscreen agents with broad UVA and UVB protection, which cover the two most common types of ultraviolet light. Agents with a sun protection factor (SPF) of 30 or higher are recommended. Lip balm with SPF 30 or higher is also recommended. These should be applied regularly regardless of the season or amount of time spent outdoors.

Children with DC should be allowed to play outside and enjoy outdoor activities, mindful of the recommendations above. Reapplication of sunscreen to any exposed area is recommended every few hours while spending time outdoors. Maintaining a balance between sun protection and engaging in a healthy and active lifestyle is encouraged.

Additional helpful recommendations for sunscreen usage can be found online through organizations such as the American Academy of Dermatology (https://www.aad.org/media-resources/stats-and-facts/prevention-and-care/sunscreens) and the Skin Cancer Foundation (http://www.skincancer.org/prevention/sun-protection/sunscreen).

In addition to the above recommendations, annual full body skin examination by a dermatologist is advised.[5]

Thickening of palms and soles

Thickening of skin on the palms and soles seen in individuals with DC is referred to as *hyperkeratosis*. These changes are due to increased thickness of the skin's outer cell layers overlying these areas, Figure 1 below.

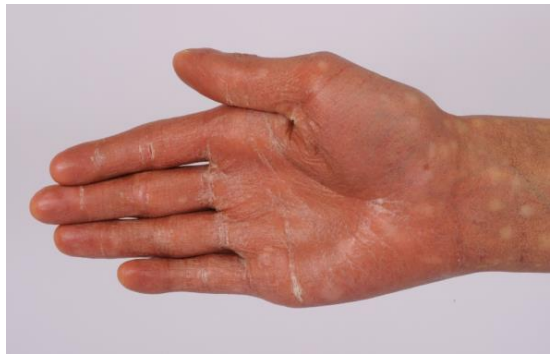


Figure 1: Hyperkeratosis: Thickening of the skin of the palm.
Color versions in **Color Photo Appendix**, p. 399

Changes in the palms and soles are analogous to thickening of the oral mucosa in DC, termed leukoplakia. Biopsies of oral leukoplakia may show evidence of chronic inflammation.[6]

The mainstay of treatment for hyperkeratosis of the palms and soles is the liberal use of topical moisturizers (emollients) which contain agents that break down keratin, the fundamental

component of the excess, thickened skin. Agents used for both moisturizing and breakdown of keratin include the following:

- Urea cream
- Salicylic acid cream or compounded ointment
- Lactic acid with ammonium hydroxide cream or lotion

Use of a moisturizer daily for maintenance of generally healthy skin on the remainder of the body is also recommended.

Hair changes

DC is associated with several changes in the appearance and quantity of hair. The hair of individuals with DC shows structural abnormalities in both the shaft and cuticle, which contribute to the thin appearance and early hair loss.[7]

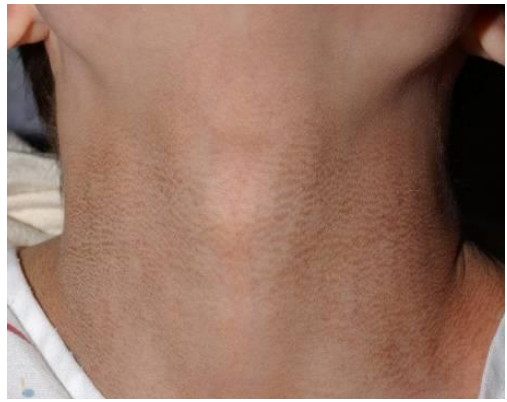
Individuals with DC are prone to premature graying of the hair. Commercially available hair dyes are useful for camouflaging this, if desired. Additionally, hair loss (alopecia) tends to occur at an early age in DC. This may involve hair anywhere on the body. Patients with loss of eyelashes may experience an increase in eye irritation from entry of dust particles or other foreign material and may benefit from protective eyewear. To date, no studies have looked specifically at treatments for hair loss in individuals with DC.

Minoxidil is an over-the-counter topical treatment that may be used for thinning hair of the scalp. Side effects of minoxidil include contact dermatitis and unwanted facial hair growth. Bimatoprost when applied to the base of the upper eyelashes causes the lashes to grow longer, fuller, and darker. Side effects of bimatoprost for eyelash regrowth include reversible hyperpigmentation of the eyelids. Off-label use of bimatoprost for eyebrow regrowth has also been reported.

Skin pigmentation

One of the diagnostic triad that characterizes DC is the net-like "reticulate" pattern of skin pigmentation. Most commonly, gray-brown skin discoloration occurs in areas of flexion, including the neck, shoulders, arms, and chest, seen in Figure 2**.** An additional finding of skin change in DC is poikiloderma. This thinning of the skin (atrophy) is characterized by appearance of fine blood vessels (telangiectasias) and areas of both increased (hyper-) and decreased (hypo-) pigmentation. While these features may aid in the diagnosis of DC, there are no studies examining the impact of treatments specifically aimed at reversing these changes. Liberal use of daily moisturizers may reduce roughness associated with symptomatic dry skin.

Figure 2: Reticulated pigmentation on the neck



Skin changes following allogeneic hematopoietic cell transplantation (HCT) for DC have not been extensively examined but deserve close medical attention. Individuals who have undergone HCT and their caregivers should be attuned to new or changing skin lesions in their surveillance for skin cancers, as well as the development of cutaneous graft versus host disease (GVHD), which may closely mimic the poikilodermatous skin and nail changes seen in DC.[6]

Dermatologic manifestations of chronic GVHD after transplant may also resemble cutaneous lichen planus. This chronic inflammatory skin condition often occurs in association with nail and oral mucosal changes.

Regular visits with a dermatologist are encouraged for evaluation of any cutaneous changes, as well as for skin cancer

screening in patients who have undergone allogeneic transplantation.

Hyperhidrosis

Up to 15% of patients with DC experience hyperhidrosis (excessive sweating).[8] Sweat glands are located in highest concentration in the palms, soles, and axillary regions of the body. Excessive sweating can have a significant impact on an individual's quality of life, and several treatment strategies exist for its management including:[9]

- Avoidance of specific triggers which may worsen the condition, such as consumption of alcohol or spicy foods
- Topical aluminum chloride powder, roll-on, or sprays
- Botulinum toxin injections
- Systemic anticholinergic agents such as oxybutynin or glycopyrrolate
- Iontophoresis using water or topical anticholinergic agents

No studies have been performed to date examining the efficacy of these treatments specifically in individuals with DC, but all have been shown to offer some relief of hyperhidrosis in various clinical scenarios.

Adermatoglyphia

Lack of fingerprints, adermatoglyphia (Figure3), is another potential dermatologic finding of DC. In some individuals born without fingerprints, the condition is thought to be secondary to a disorder in formation of the epidermis (the top layer of skin) while still an embryo.

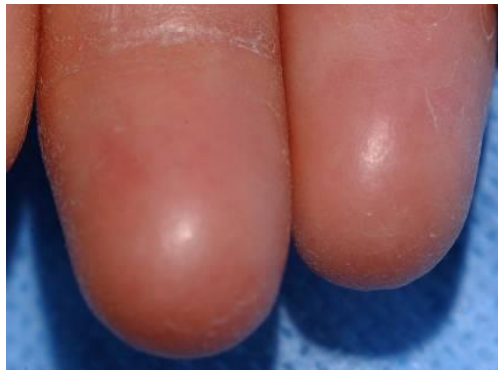


Figure 3: Adermatoglyphia: Loss of fingerprints

In contrast, the condition tends to develop over time in association with palmar hyperkeratosis[10,11] in individuals with DC. Caregivers and individuals with DC should be aware of this potential skin complication, as the inability to be fingerprinted may impact such processes as immigration and obtaining government identification.[11]

Nails

Nail involvement in DC can vary from nail malformation (onychodystrophy), to small nails (micronychia), or even complete absence of the nail plate (anonychia). Several nail changes are shown in Figure 4.

Common forms of onychodystrophy that occur in DC include longitudinal grooving of the nail plate (onychorrhexis) and splitting of the nail (onychoschizia). As with the skin findings of DC, nail involvement may mimic features of other conditions, like those seen in lichen planus and GVHD.[6,12]

There are limited data on management of DC-related nail changes. Brittle, fragile nails may impact quality of life due to repeated injury or discomfort. Keeping the nails trimmed and using an emery board to smooth rough or sharp nail edges may reduce the discomfort of incidental injury during day-to-day activities. Additional strategies may be useful in managing fragile nails:[13]

- Reduce excessive exposure to water, detergents, and prolonged hand washing.
- Avoid long-term use of artificial nails.
- Nail polishes and lacquers may help strengthen brittle nails.

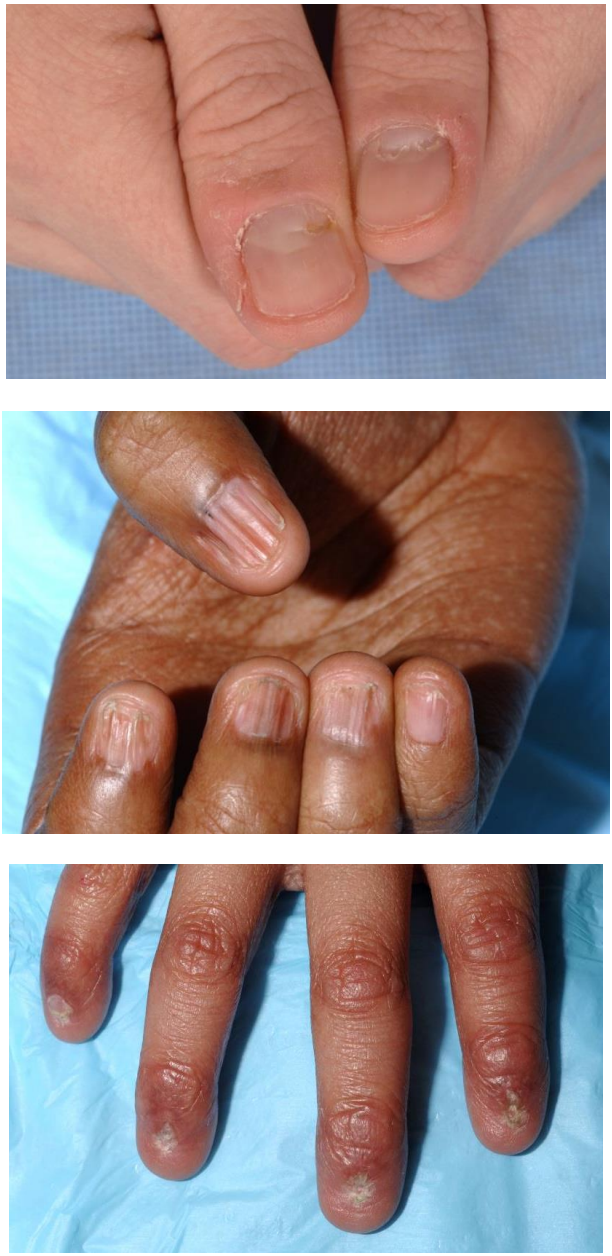


Figure 4: Nail changes in DC: onychoschizia,

longitudinal ridging, and micronychia

- Vitamin supplements such as biotin may provide strength to brittle nails.

Daily skin care

Skin is a clearly visible organ, and unhealthy or abnormal appearance has a potential impact on one's quality of life and self-esteem. Strategies to maintain skin health include:

- Review the daily sun protection strategies outlined above in the skin cancer section.
- Moisturize daily, after bathing, to help maintain the skin's natural water content.
- Stay well-hydrated throughout the day with adequate water intake.
- Avoid abrasive or overly-drying soaps and detergents.

In addition, annual full body skin examination by a dermatologist is recommended.[5]

Conclusion

Dermatologic manifestations of DC may involve the hair, nails, skin, and mucosal surfaces. Given the increased risk of cutaneous cancers in this population and the clinical overlap

with other skin conditions, we recommend close longitudinal surveillance by a dermatologist for individuals with DC for both diagnostic evaluation and therapeutic management.

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Chapter 11:
Ophthalmic Manifestations

Ekaterini Tsilou, MD and Rachel Bishop, MD

Introduction

Ophthalmic manifestations have been reported in approximately 40% of patients with dyskeratosis congenita (DC)[1]. These can be divided into changes affecting the anterior segment and adnexa (lids, lashes and lacrimal system) and those affecting the retina.

Anterior segment and adnexa

Changes to the anterior segment and adnexa include punctal atresia and nasolacrimal duct obstruction[1-6], trichiasis[3,7] (mis-directed eyelashes), loss of eyelashes[7], entropion (in-turning of the eyelids and eyelashes), ectropion (out-turning of the eyelids and eyelashes), conjunctivitis[7] (infection of the conjunctiva), corneal scarring[7,8], corneal ulceration (erosion of the outer surface of the eye) and perforation[3], and cataracts.

The most common finding in patients with DC is obliteration of the lacrimal drainage system, which can present with either

absent punctae or nasolacrimal duct obstruction. The patient might experience constant tearing, frequent episodes of conjunctivitis, episodes of blepharitis (inflammation of the eyelids), or corneal ulcers. Treatment of tear flow obstruction is surgical, by either dacryocystorhinostomy (DCR), whereby an opening is created between the lacrimal sac and the nasal cavity, or by insertion of Jones tubes, glass implants placed to allow direct drainage from the conjunctival fornix into the nose.

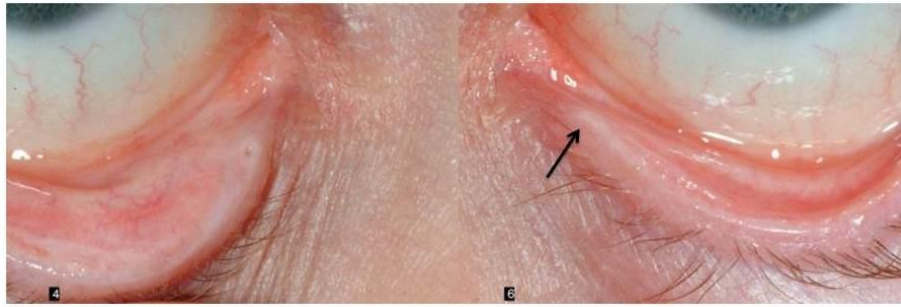


Figure 1: Photograph of a patient with dyskeratosis congenita demonstrating an absent punctum in the left eye (arrow). Color versions in **Color Photo Appendix**, page 399.

Entropion, ectropion, and trichiasis may be secondary to epithelial abnormalities of the skin and mucous membranes of the eye, and can lead to recurrent blepharitis, conjunctivitis, keratitis, corneal scarring, and eventually to decreased vision if untreated. Entropion and ectropion can be surgically repaired, and misdirected eyelashes seen in trichiasis can be either

temporarily or permanently removed. Early recognition of these potentially significant complications of DC leads to optimal management and outcomes.

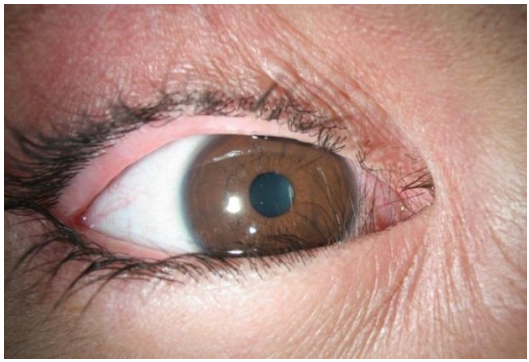


Figure 2. Entropion and trichiasis in a patient with dyskeratosis congenita.

Posterior segment

Optic nerve atrophy[2,9,10] and retinal vascular changes have been described in patients with DC. Retinal changes can include perivascular sheathing (atherosclerosis of the vessels), hemorrhages, areas of non-perfusion, retinal neovascularization, and exudative retinopathy[8,9,11-20]. While uncommon, these changes require early recognition and management to avoid the potentially devastating complication of vision loss if untreated.

Fluorescein angiography is indicated if any significant vascular abnormalities are identified during the retinal exam of a patient with DC.

Two clinical variants of DC are associated with a greater risk of retinal abnormalities. Patients with Revesz Syndrome develop exudative retinopathy, in addition to aplastic anemia and central nervous system abnormalities[17-19]. Patients with Hoyeraal-Hreidarsson syndrome display an increased frequently of retinal neovascularization.

Additional complications

In addition to the syndrome-specific manifestations of DC, side effects of treatment required for other DC-associated manifestations can result in other ocular complications. Radiation can cause radiation retinopathy, and systemic corticosteroid therapy associated with stem cell transplantation may cause glaucoma or cataract. Patients undergoing stem cell transplantation require a detailed eye examination and follow-up monitoring to identify potential problems.

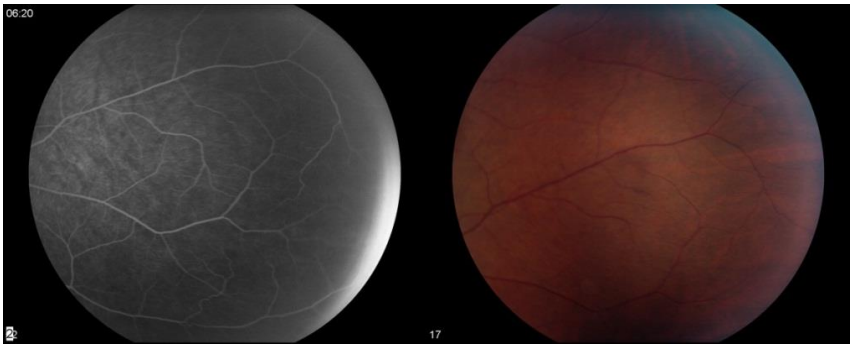
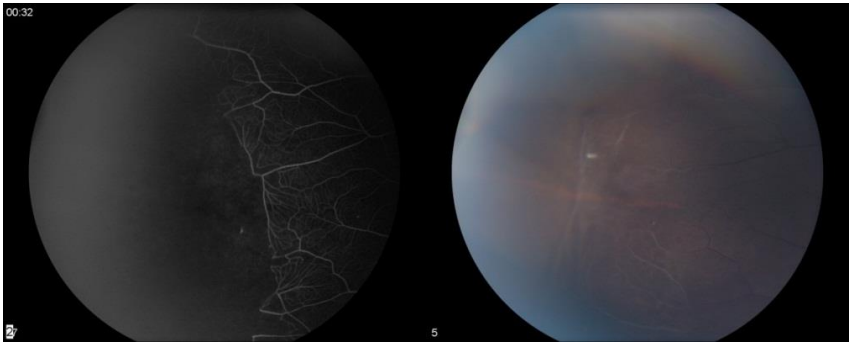


Figure 3: Fluorescein angiography (top left) and fundus photograph (top right) of normal retina. Fluorescein angiography (bottom left) and fundus photograph (bottom right) of a patient with dyskeratosis congenita, demonstrating perivascular sheathing and non-perfusion



Conclusions

A baseline ophthalmic evaluation should be part of the initial evaluation of every patient with DC, and subsequent periodic examinations should be part of routine care.

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Chapter 12:
Dental, Head and Neck Complications of Dyskeratosis Congenita

Pamela J. Gardner

Introduction

The oral phenotype of dyskeratosis congenita (DC) is characterized by leukoplakia and development anomalies of the permanent tooth, such as decreased root/crown ratio and mild taurodontism (vertically enlarged pulp chamber and shortened roots).[1] Individuals transplanted at an early age are susceptible to disruptions in tooth development, as well as development of chronic oral graft versus host disease (GVHD), reduced salivary flow (xerostomia), and thrush (oral candidiasis), each of which require medical management.

Oral leukoplakia

Oral leukoplakia associated with DC manifests clinically as a heterogeneous mucosal lesion and may develop at any age, from childhood to later in adult life. Localized to the dorsum of the tongue, buccal mucosa, palate and/or gingiva, the lesion(s) can

present as a fine reticular or a plaque-like white area, with or without peripheral erythema. The clinical presentation varies among individuals, with oral signs and symptoms developing at different rates. Very little is known about the clinical or histopathological features of oral leukoplakia in DC; however, they are thought to contribute to increased risk of developing head and neck squamous cell carcinoma (HNSCC).

Head and neck squamous cell carcinoma

Approximately 600,000 cases of HNSCC will arise globally each year, 40,000 of which will be in the United States,[2,3] making it the sixth most common cancer by incidence worldwide. Risk factors include exposure to carcinogens, most notably tobacco smoking and alcohol consumption, infection with high-risk types of human papillomavirus (HPV), and genetic predisposition, such as with DC.

HNSCC is considered a heterogeneous disease both at the molecular and clinical levels, with the existence of at least two genetic subclasses: HPV-positive and HPV-negative tumors.[4] Despite advances in diagnosis and treatment, the five-year survival rate for HNSCC continues to be approximately 50%.[5,6] Most individuals who develop HNSCC had a clinically visible

premalignant oral lesion (dysplasia) prior to developing cancer; early diagnosis and surgical management of oral dysplasia/HNSCC is extremely important in reducing patient morbidity.

Oral leukoplakia itself is not uncommon in the general population, with an estimated prevalence from less than 1% to more than 5%.[7-10] The rate of its malignant transformation into HNSCC varies from near nil to about 20% over one to thirty years.[11-13]

Individuals with DC have a very high risk of developing cancer. Specifically, the ratio of observed to expected (O/E) cancers was 11-fold greater in DC when compared with the general population (see Chapter 21). Forty percent of the most common solid tumors in DC were found to be HNSCC, including an approximately 1000-fold increase in the O/E ratio for cancer of the tongue.[14] While bone marrow failure continues to be the main cause of mortality in DC, these numbers suggest an independent high risk of mortality arising from oral leukoplakia-associated malignancy.

It has been suggested that non-homogeneous oral leukoplakia carries a higher degree of malignant transformation risk compared with the homogeneous variants; however, there is no

reliable method to identify which oral lesion will transform into cancer and which will not.[15]. Clinical,[16] histological,[17] and molecular markers[18,19] may aid in assessing the risk of an individual patient to develop cancer; however, currently there is no evidence-based and clinically useful predictor of malignant transformation.

Oral lichen planus

Lichen planus (LP) is an autoimmune T cell-mediated mucocutaneous inflammatory disease of unknown etiology.[23] Occurring in approximately 1% of the general population and most frequently in women 30 to 60 years of age,[24] LP can affect the oral mucosa, genitals, and skin. The clinical presentation of oral lichen planus (OLP) and the oral lesions associated with DC is phenotypically identical.

As with oral leukoplakia in DC, OLP has variable clinical characteristics and presentations. The most common type (reticular) is characterized by lacy white striae located bilaterally on the buccal mucosa, gingival, or tongue. The erosive (red or ulcerated), atrophic, and plaque-like versions of OLP are thought to have greater malignant potential than the reticular type, perhaps as a result of chronic inflammation. Reticular OLP

is often asymptomatic, but the atrophic and ulcerative forms can cause symptoms ranging from a burning sensation to severe, unremitting oral pain.[25,26]

The World Health Organization (WHO) classifies OLP as a precancerous disease in the general population. However, this designation is controversial. The frequency of malignant transformation in the general population has been found to range anywhere from 0.4% to more than 6%.[8,9] From 1-5% of OLP lesions will undergo malignant change to squamous cell carcinoma (SCC) of the mouth.[27-30] Between 1 and 3% of vulvar lichen planus lesions in the general population may develop into SCC,[31,32] while a small but unknown percentage of penile lesions will transform.[33,34] Chronic inflammation appears to play an important role in the promotion of malignant transformation of oral mucosa in some disorders. Both OLP with dysplasia and oral lesions of patients with DC show evidence of chronic inflammation coincident with a higher than normal rate of transformation to HNSCC. Therefore, OLP with dysplasia may serve as a unique disease model for studying the high rate of oral malignancy associated with DC.

NCI cohort study

The National Cancer Institute (NCI) cohort study of inherited bone marrow failure syndromes (02-C-0052) evaluated 44 individuals with DC between September 2003 and June 2012, and included detailed oral examinations, radiographs and clinical photos. The overall prevalence of oral leukoplakia was 64%: 75% in children and 50% in adults, with the youngest patient being 3 years old and the oldest 53. 93% of oral leukoplakia was localized to the dorsal tongue (plaque-like and reticular lichenoid white lesions with papillary atrophy). Of those with tongue lesions, 20 out of 26 (77%) had papillary atrophy. Only seven had oral ulcerations at the time of examination, and very few had accompanying erythema. The presence or absence of oral symptoms with DC-associated oral lesions is not known, but may be underreported.

Five genetic mutations were identified among 32 of the 44 individuals evaluated in this study: *WRAP53, DKC1, TERC, TINF2,* and *TERT*. The remaining patients were mutation-unknown. Ninety percent (9/10) of patients with *DKC1* mutations but only 17% (1/6) of those with *TERT* mutations had oral lesions, which suggests an association between

development of oral leukoplakia and the specific DC gene mutation. (Table 1).

DC Gene Mutation	n	Oral Lesions	No Oral Lesions	p value	RR	95% CI
TERT	6	1 (17%)	5 (83%)			
DKC1	10	9 (90%)	1 (10%)	**<0.0001***	**0.17**	**0.11-0.28**
TERC	3	2 (67%)	1 (33%)	**<0.0001***	**0.28**	**0.18-0.44**
TINF2	11	6 (55%)	5 (45%	**<0.0001***	**0.36**	**0.24-0.56**
Unknown	12	8 (67%)	4 (33%)	**<0.0001***	**0.28**	**0.18-0.43**
WRAP53	2	2 (100%)	0	**<0.0001***	**0.14**	**0.09-0.23**

Table 1: Presence of oral lesions by gene in patients with DC (unpublished data)

Eight subjects evaluated in the NCI cohort have had multiple oral biopsies with histopathological results that ranged from benign, chronic inflammation, pyogenic granuloma and hyperkeratosis to moderate dysplasia and HNSCC.

Clinical implications: Patients

Oral leukoplakia in DC develops at an unusually young age and is characteristic in appearance and location. Since most leukoplakias are asymptomatic, the need for treatment is primarily based on the precancerous nature of the lesion, and this can only be determined by tissue biopsy. A region of the oral

lesion may transform into oral cancer, but it is not currently known what that progression looks like. Early diagnosis and surgical management of oral dysplasia and HNSCC is extremely important in reducing morbidity. Therefore, it is recommended that a dentist or dental specialist (oral medicine doctor or oral and maxillofacial surgeon) screen DC patients for oral lesions every six months, in addition to otolaryngologist (ENT) evaluation every six to 12 months.

Fiber optic examinations are recommended from the age of 10 years to visualize the posterior oropharynx. The frequency of follow-up may be increased in the presence of histologically confirmed oral dysplasia, or a history of oral cancer. Clinical photos are recommended longitudinally to follow the progression of oral lesions. Persistent oral lesions should be biopsied when clinically indicated. Surgical removal of oral lesions in the absence of a precancerous histological diagnosis is not recommended since it may compromise surveillance efforts.

Oral leukoplakia associated with DC is similar in appearance to oral lichen planus. When symptomatic, it may present as sensitivity of the oral mucosae to spicy and acidic foods (orange juice, ketchup, salad dressing, tomato sauce), and mint flavored toothpaste. There may be ulcerations on one or both sides of the

tongue or buccal mucosa that do not resolve within two weeks or recur over time.

Topical steroids used to manage ulcerative oral lichen planus may be helpful in reducing the size and duration of the oral ulcerations in DC, and may include fluocinonide, dexamethasone rinse 0.5mg/5mL, and clobetasol cream or ointment (0.05%). Frequency of application should be determined by the prescriber. Associated pain is managed primarily via topical anesthetics. It is not known whether treatment of symptomatic oral leukoplakia in DC will alter the risk of malignant transformation.

Clinical implications: Clinicians

In distinction to lesions seen in the general population, oral leukoplakia of DC tends to occur in patients younger than 50 years of age and in the absence of risk factors, like smoking or alcohol use. Leukoplakia may be the first manifestation of DC, and can be easily identified during routine dental and medical examinations.

The gold standard for oral cancer diagnosis remains tissue biopsy with histological assessment; however, there are adjunctive clinical diagnostic tools that aid in early detection,

including toluidine blue dye (TB) and fluorescent visualization imaging systems.

Toluidine Blue

TB is a member of the thiazine group of metachromatic dyes. These dyes bind to DNA, and are partially soluble both in water and alcohol. Theoretically, dysplastic and malignant cells have higher nucleic acid content than normal, and thus staining of suspicious lesions with this dye can aid recognition of mucosal changes. Experience since the early 1980s in using TB as a vital stain found that lesions that take up the dye are six times more likely to become oral cancers[35]. The TB test appears to be highly sensitive (97.8%– 93.5%) but less specific (73.3% - 92.9%), mainly because of high false positive results.[36,37] TB has been shown in single- and multicenter studies to be useful in identifying OLPs and OSCC, and can provide information about lesion margins and so aid in biopsy site selection.[38-42]

Recently, molecular studies on TB stained lesions demonstrated a link between carcinoma and loss of heterozygosity (LOH). This concept refers to deletion of regions of chromosomes (for example 3p, 17p, and 9p) known to be frequently lost in head and neck cancers and dysplasia. LOH

occurs early in oral carcinogenesis, but the patterns of such loss can be predictive of the risk of progression. Oral lesions that stained positive with the TB dye were much more likely to have LOH.[35,43] The loss of heterozygosity has not been evaluated in dysplastic DC lesions.

Tissue autofluorescence

The value of tissue autofluorescence in the screening and diagnosis of precancerous lesions of the lung, uterus, cervix, and skin is well documented. In the past decade, several forms of autofluorescence technology have been developed to inspect the oral mucosa, including VELscope R (LEDDental, Inc., of White Rock, British Columbia, Canada). This U.S. Food and Drug Administration- and Health Canada-approved technology uses blue/violet light (400-460nm) to illuminate oral tissue. By visualizing these oral tissues through a light filter, normal tissue appears pale green, while abnormal tissue has a "loss of fluorescence" and appears dark brown or black. Like TB, autofluorescence may aid in choosing tissue biopsy sites, as well as visualizing surgical margins.[44,45]

There is general consensus that the clinical stage at time of diagnosis of HNSCC is the most important predictor of

recurrence and mortality in oral cancer patients. The time to diagnosis is influenced by multiple clinical and sociodemographic variables, including patient reluctance to consult a health-care professional due to lack of access to health care, especially in patients with low socioeconomic status. Clinicians can improve patient survival rate if a cancerous lesion is detected at an early stage, or if a precursor lesion (dysplasia) is discovered and treated prior to malignant progression. To this end, studies have shown that health-care providers would benefit from system-wide educational updates on oral cancer prevention and early detection.

Treatment of HNSCC

Treatment options are limited to the surgical removal of regions of oral dysplasia (moderate and severe), carcinoma in situ, and HNSCC. The extent of surgical resection depends upon the size and location of the tumor, so early detection is paramount to reduce morbidity and mortality. Laser ablation of regions of lichenoid striae in the absence of dysplasia is not recommended as the lesions are likely to recur. In addition, surgical alteration of normal oral architecture may compromise surveillance efforts.

Dental manifestations

In addition to oral leukoplakia, DC patients may exhibit alterations in tooth development. Short dental roots resulting in unfavorable root/crown ratios may affect dental restorative considerations. Root/crown ratios are a non-specific finding and normally vary between different races, genders and arch (maxillary versus mandibular teeth).[46] Short roots may complicate treatment planning in orthodontics, and must be considered in prosthodontic anchorage and estimating the ability of a tooth to carry masticatory forces. In Atkinson et al's study of 17 individuals with DC, a decreased root/crown ratio was found in 75% of patients with sufficient tooth development to permit evaluation.[1] Shortened roots were observed in individuals with mutations of the *TERT*, *DKC1*, or *TERC* genes.

Taurodontism affects the molars, and is characterized by vertical enlargement of the pulp chamber and reduced root size. It is a frequent finding in early humans and is found in some developmental syndromes. While the exposed portion of the teeth may look overtly normal without any particular anomalous characteristic on visual inspection, the floor of the pulp and furcation of the tooth may be shifted apically toward the root. This occurs from failure or late invagination of Hertwig's

epithelial root sheath, which is responsible for root formation and shaping.

Mild taurodontism was reported in Atkinson et al's study (57% with radiographs and sufficient tooth development to permit evaluation).[1] The clinical implication of taurodontism is increased risk of pulp exposure because of decay and dental procedures, endodontic treatment challenges, and with the shorter roots, prosthodontic and orthodontic issues as mentioned above.[47]

Other oral findings, such as aggressive periodontal disease, hypodontia, increased dental decay, and thin enamel, have been reported, but do not appear to be common in DC.

Post HCT oral manifestations

Individuals with DC who undergo hematopoietic cell transplantation (HCT) may develop chronic conditions such as oral graft versus host disease (GVHD), reduced salivary flow (xerostomia), and thrush (oral candidiasis), which may require medical management. Those transplanted at an early age (<10 years old) are more likely to experience disruptions in permanent tooth development. To a significant degree, the oral problems associated with HCT can be prevented or minimized

through optimal management. Consultation with a dental team experienced in caring for patients undergoing HCT procedures should be completed before the start of therapy.

Oral graft versus host disease

Signs and symptoms of oral GVHD are similar to autoimmune disorders like LP, and may present as sensitivity of the lining of the mouth to acidic foods and mint flavored toothpaste. There may also be mucosal ulcerations, erythema and lichenoid striae. Treatment of oral GVHD is only recommended when symptomatic, and may be managed with topical steroid rinses or creams, or systemic immunopsuppression. GVHD can also involve the salivary glands, resulting in xerostomia.

Xerostomia

Saliva serves a number of critical functions in the homeostasis of the oral ecosystem, in the oropharynx and larynx, and in speech and swallowing functions. Diminished saliva either from medications or oral GVHD results in an increased risk of dental demineralization and decay and oral infections such as candidiasis. A chronically dry mouth can also lead to an altered

sense of taste, difficulty speaking, halitosis, oral pain, and difficulty chewing and swallowing, culminating in decreased quality of life. Without saliva, teeth do not remineralize, and there is gradual softening of tooth matrix. The teeth bend and dentin may fracture and cavitate, and the coronal structure fractures from the supporting root.

In patients with residual salivary gland function, sugarless gum or lozenges may stimulate salivary secretion. Sugar-free popsicles, plain ice cubes, or ice water may be used to keep the mouth moist. Systemic sialagogues may increase production of natural saliva from functional glands. Medications that may be beneficial in stimulating salivary glands include pilocarpine (Salagen), cevimeline (Evoxac), anethole trithione (Sialor), and bethanechol (Urecholine). Saliva replacements like Oral Balance Gel may offer some relief. There is no ideal substitute for saliva when salivary glands are nonfunctional.

For the prevention of rampant dental demineralization and caries in a xerostomic mouth, patients should apply a 1.1% neutral sodium fluoride gel daily (for at least 5 minutes), using a custom-fitted vinyl tray if possible. This practice should be continued daily as long as the mouth remains dry because of low salivary flow rates. High-potency fluoride brush-on gels and

toothpastes may be considered in those who are unable or unwilling to comply with the use of fluoride trays.

To prevent dental damage associated with a lack of saliva, patients with xerostomia should increase oral hygiene efforts and avoid foods and medications (like Nystatin Rinse, Mycelex Oral Troches) with high sugar content.

Thrush/oral candidiasis

Candida albicans is a a yeast-like fungus naturally present in the oral cavity. It may overgrow in xerostomia, when there is disruption of oral bacteria (as caused by systemic antibiotics), or with the use of topical steroids. Infection presents as creamy white plaques on mucosal surfaces, and can be wiped off. Individuals may experience an increase in sensitivity localized to the lining of the mouth. Oral candidiasis may also present as cracking and redness at the angles of the mouth (angular chelitis).

Topical anti-yeast medications such as nystatin rinse and clotrimazole (Mycelex) oral troches have a high sugar content and should generally be avoided in patients with xerostomia since they can promote tooth decay. Patients using these medications should be warned of the risk and increase oral

hygiene efforts accordingly. Amphotericin B (available as a topical suspension [100mg/mL] 1mL up to 4 times daily) and fluconazole are effective systemic anti-fungals.

Tooth development

Dental abnormalities have been reported among survivors of childhood cancer. These include dental hypoplasia or agenesis, root stunting, and enamel hypoplasia. The severity of the problem is dependent upon the timing of chemotherapy and radiation, with the greatest impact occurring when treatment is between the ages of three and five.[48,49]

Clinical Management

Helping patients understand how cavities develop assists in preventing them.

DC in itself does not confer genetic susceptibility to developing caries; rather, dental decay is a multifactorial problem. Diet, oral bacteria (which form plaque), a decrease in the quality and quantity of saliva, and other factors are implicated. It has been shown that dental decay will not develop in the absence of fermentable dietary carbohydrates.[50] All dietary carbohydrates are cariogenic (dental decay causing) to some

degree, and this is influenced not only by the composition of carbohydrate-containing foods but by the sequence and frequency with which they are consumed. Sucrose appears to have the greatest cariogenic potential, and its frequency of intake is more important than the total amount consumed. Further, solid forms of the sugar are more easily retained on teeth, and appear to be more cariogenic than liquid forms.

The lowering of salivary pH (acidification) with the consumption of fruit juices, citric acid in soft drinks, canned pears and apples, for example, can also accelerate demineralization of tooth surfaces.[51] Certain foods appear to be protective. Cheddar cheese, regular milk consumption, and salted peanuts increase oral alkalinity. Cocoa contains substances that inhibit oral acidification. Starchy, fibrous foods require more chewing, and may inhibit the development of dental decay by stimulating saliva and maintaining a more neutral plaque pH. Polyols (sugar alcohols, including the 6-carbon sorbitol and 5-carbon xylitol) are noncariogenic and possibly even anticariogenic, since xylitol is not metabolized by oral bacteria.[52-54]

The composition and rate of saliva flow can impact development of dental decay in several ways. Saliva can act as a

buffer, neutralizing bacterial acid byproducts found on tooth surfaces and in carious lesions. The high concentrations of calcium and phosphorus and the low level of fluoride found in saliva may facilitate remineralization of early carious lesions and form caries-resistant surface enamel.[55] Saliva also contains several potentially bacteriostatic agents, including lysozyme, lactoferrin, and secretory immunoglobulins, which may inhibit the metabolism and growth of cariogenic bacteria.[56-58]

Reduction in salivary quantity may be a side effect of various medications, including antidepressants, anti-anxiety medications, and anti-histamines, or may be a component of post-transplant oral GVHD. Having a dry mouth can accelerate the rate of dental decay and significantly increased oral hygiene efforts are required. Patients should work with their general dentist and hygienist for strategies to prevent dental decay.

Fluoride is the most effective dietary component to exhibit a protective effect against root and surface caries. The mechanism by which it does so is not well understood,[59,60] but is thought to be related to its presence in enamel and dentin, and presumed role in promoting remineralization of early demineralized areas of the tooth.[55,61] By exerting an antimicrobial effect, it suppresses cavity causing oral bacteria.[62]

General hygiene recommendations include brushing teeth two to three times a day with fluoridated toothpaste and flossing once a day at a minimum to help prevent tooth decay. Some dentists recommend using prescription strength fluoride toothpaste or antibacterial mouth rinse to aid in reducing oral disease. Biannual dental checkups and cleanings are recommended to monitor for the presence of oral pathology and prevent the development of significant dental decay and gum disease. Precautions during routine dental treatment may be necessary in the presence of low platelet counts and white blood cell levels.

Access to quality dental care for medically compromised patients may be challenging outside of large urban centers. Regional dental schools offer clinics with multidisciplinary dental specialty practitioners and may provide economical dental treatment or be able to recommend a community dentist.

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Chapter 13:
Endocrine and Skeletal Disorders in Dyskeratosis Congenita

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Introduction

The endocrine system has not been prospectively studied in patients with dyskeratosis congenita (DC). Most knowledge regarding endocrine abnormalities is based on reports from the DC registry maintained by Dokal *et al* in the United Kingdom[1] and through clinical observations of the National Cancer Institute's (NCI) prospective DC cohort.

It appears that endocrine hormone deficiencies, such as hypothyroidism, growth hormone deficiency (GHD), hypogonadism, diabetes, or short stature, are not common in patients with DC. However, abnormalities related to the skeleton are seen with higher frequency compared to the general population.

There is an increased frequency of avascular necrosis (AVN) of the hips and shoulders, reduced bone mineral density (osteopenia/osteoporosis),[1] and an increased risk of fracture in some patients with DC[2] (also observed in the NCI cohort, unpublished data). In addition, therapies that treat hematological manifestations of DC, such as androgens and hematopoietic cell transplantation (HCT), may themselves lead to endocrine disorders, as described in this chapter.

Reported endocrine and skeletal abnormalities in DC

Features	Patients	Source
Short stature	20%	DC registry in United Kingdom1
Hypogonadism/undescended testes	6%	
Osteoporosis/avascular necrosis/scoliosis	5%	
Osteopenia/avascular necrosis	10%	Literature review[3]
Growth hormone deficiency	1 patient	Case report[4]

Skeletal complications

Bony abnormalities, including AVN of the hips and shoulders, osteopenia and osteoporosis, and scoliosis were reported in approximately 5% of patients with DC[1], but may be more frequent than reported to date (unpublished data – NCI cohort). Many patients with DC (~75%) also have dental abnormalities such as shortened roots or taurodontism.[5] Because of the phenotypic variability in DC, it is difficult to make generalizations about the onset and severity of these complications. The cells responsible for bone formation (osteoblasts) and for root development (cementoblasts) originate from mesenchymal stem cells. Mesenchymal stem cell defects have been reported in patients with DC,[6] and it is possible that these result in the increased frequency of dental and bony abnormalities.

Avascular necrosis of the hips and shoulders

AVN of the hip or shoulder affects approximately 10% of all DC patients.[3] Although this occurs most often in adults, children may be affected. AVN occurs when the blood vessels supplying

bone are compromised, leading to death of bone and bone marrow supplied by those vessels.[7] This results in pain, degenerative arthritis, and decreased function of the joint, and may require early joint replacement.[7,8]

Patients with DC and their parents should be educated at diagnosis regarding the early signs and symptoms of hip and shoulder AVN, since early conservative (restricted weightbearing, and antiresorptive medication, for example) and orthopedic surgical (core decompression, osteotomy, bone grafting) management can reduce disability and complications. In the presence of hip or shoulder pain in patients with DC, physicians should perform a thorough physical exam that includes assessment of pain level, range of motion, limb length, and X-ray imaging of the affected area. Physicians should have a low threshold for skeletal imaging, as well as orthopedic referral in these patients.

Osteopenia and osteoporosis

Osteopenia and osteoporosis have both been reported in patients with DC.[9] These occur when the rate of new bone production by osteoblasts is slower than the rate of resorption by osteoclasts.[10] The phenomenon occurs with normal aging, but is

accelerated in some patients with DC.[10] Premature thinning of bones may be due to reduced ability of the shortened-telomere osteoblasts of DC to differentiate and form normal bone.[6,10-12]

Bone fractures

Patients with severe manifestations of DC in childhood, particularly those with Coats' plus, Hoyeraal-Hreidarsson, or Revesz syndrome, may develop spontaneous fractures of bones.[13,14] The reason for this tendency is not completely understood, and is an area of ongoing research. Intrinsic dysfunction of the bone marrow mesenchymal cells may be a contributing factor.

Bone health screening

Dual energy absorptiometry (DXA) scan is done to evaluate bone mineral density (BMD). Although data may not correlate with the severity of bone disease and fracture risk in patients with DC, study should still be considered at or around 14 years of age to obtain a baseline BMD. Repeat studies may be performed according to patient-specific risk factors. DXA scan should also be performed in patients with hypogonadism or growth hormone deficiency, and prior to and one year after

HCT. Serum calcium, magnesium, and 25-hydroxy vitamin D levels should be monitored in those with low BMD, as well as in patients who have undergone HCT.[15] Patients with significant exposure to corticosteroids, bone fracture history, immobility, hypogonadism, or hormone deficiencies may benefit from being seen by an endocrinologist. Older patients with DC but without corticosteroid exposure, fracture history, or hormone deficiency may be screened and monitored according to age-specific DXA scan screening guidelines.

Maintaining and improving bone health

Patients with DC should include sufficient calcium and vitamin D in their diet to support appropriate bone growth and mineralization. Supplements may be required to meet the recommended daily allowance of vitamin D (> 30 ng/mL).[16] Patients with low BMD (after height adjustment in children ≤ 20 years of age) should increase their intake of calcium and vitamin D accordingly.

Growth and growth hormone

Short stature is reported in 12% of cases in the literature and in approximately 20% of patients in the UK DC registry of

patients with DC.[1,3] In contrast, the NCI cohort notes that short stature is very rare in individuals with DC, perhaps being more common in very severely affected patients. While the precise mechanism is unknown, their short stature does not appear to be related to growth hormone deficiency,[4] and growth hormone therapy is not recommended unless the patient is proven to have this deficiency.

Hypogonadism

A small number of severely affected males reported decreased sperm or testosterone production, or both, a condition known as hypogonadism.[8,17] Animal models have demonstrated that at least one of the DC mutations may lead to testicular atrophy in males and decreased fecundity in both males and females, but this has not been duplicated in human studies.[18,19] Physicians should check testosterone, LH, and FSH levels in patients with suspected deficiencies, and have an open dialogue about both the possibility and signs and symptoms of hypogonadism.

Interventions that affect the endocrine system: I. Androgen therapy

Patients with DC who have bone marrow failure and who are not candidates for HCT may be treated with androgens[20,21](see

Chapter 7 on Medical Management of Bone Marrow Failure). Low peripheral blood counts respond adequately enough in approximately 50-70% of patients with DC to obviate need for transfusion.[1,22,23] The duration of this effect varies from patient to patient. The androgen drugs most commonly used in DC are oxymetholone and danazol. Androgen therapy in patients with DC potentially affects the endocrine system in several ways, including decreasing thyroid binding globulin (TBG), rapid linear growth, masculinization, changes in behavior, lipid abnormalities, and changes in liver structure and function. Patients with DC receiving treatment with androgens need to be evaluated frequently for abnormal cholesterol, triglycerides, liver function, and liver adenomas (see Chapter 7).[24] It should be noted that patients with DC are often more sensitive to androgens than the general population, and therefore the dose should be adjusted accordingly.[8] It is important that individuals with DC and their families be aware of possible side effects of androgen therapy before beginning treatment.[24]

Thyroid binding globulin

Treatment with androgens may cause a significant decrease in TGB levels without affecting thyroid function.[21] Despite a low

TBG level, patients with normal thyroid glands maintain normal serum free thyroxine (T4) and thyroid stimulating hormone (TSH) levels, and do not experience any clinically noticeable adverse effects.[25]

Growth

Because androgens stimulate osteoblasts and the production of bone matrix, pre-pubertal children receiving this therapy may experience accelerated linear growth.[26,27] Premature skeletal maturation, with fusion of epiphyseal plates and reduced adult height has been reported, but this effect is relatively rare, especially in patients who received androgen therapy before puberty.[21,26,28] Pediatric patients should have a baseline bone age X-ray done before beginning androgen therapy and every 6-12 months while under this treatment, until reaching adult height.

Patients taking androgen therapy should avoid simultaneous use of growth factors like G-CSF or erythropoietin, as splenic and hepatic peliosis and splenic rupture have been reported in association with their combined use.[23,2629]

Masculinization and behavior changes

Androgen therapy may lead to masculinizing effects and behavior changes, including mood swings and aggression in both female and male patients.[8,21,30] Females receiving androgens have reported hoarseness and hirsutism, while males reported priapism.[21] The likelihood of onset and degree of virilization are proportional to androgen dose.[26,30]

Lipid and liver abnormalities

Patients with DC receiving androgen therapy may develop abnormal lipid profiles and impaired liver function[8,31]. Total cholesterol, triglycerides, and LDL (low-density lipoprotein) may be elevated, while HDL (high density lipoprotein) levels may be abnormally low.[21,31] There is no known dose-response relationship between androgens and lipid abnormalities, but cessation of androgen therapy results in a return to pre-treatment lipid levels within a few months.[26] Liver structure and function should be evaluated at baseline and at regular intervals during androgen therapy, as liver adenomas and carcinomas have been observed in patients on this regimen.[8]

II. Allogeneic hematopoietic stem cell transplants

HCT is the only curative treatment for bone marrow failure in DC; however, its preparative regimen is associated with significant toxicity (see Chapter 8).[32,33] With the development of new, less toxic conditioning regimens, HCT may become a more successful treatment modality for patients with DC.[34]

HCT survivors and their physicians need to be aware of an increased risk of several endocrine complications, including diabetes, cardiovascular disease, hypertension, hypogonadism, vitamin D deficiency, osteoporosis, adrenal dysfunction, pituitary disorders, and dyslipidemia.[35] Post-HCT screening and follow-up should be tailored to the specific conditioning regimen received by each patient.

Diabetes

HCT survivors need to have routine screening for diabetes, as they are much more likely to be insulin resistant than their healthy counterparts.[35] Steroid use, total body irradiation, and graft versus host disease (GVHD) all increase the likelihood of developing diabetes.[35] HCT survivors should be screened regularly for insulin resistance and receive pharmacotherapy if indicated.[35]

Cardiovascular disease

Patients who undergo HCT are at increased risk of developing cardiovascular disease compared to their healthy counterparts.[35] This risk is higher for males, older patients, and those who smoke.[35]

HCT survivors and their physicians should be aware of the signs and symptoms of cardiovascular disease, and should work toward cessation of smoking and the minimization of hypertension, diabetes, and other modifiable risk factors.[35]

Hypertension

Hypertension is three times as prevalent among HCT recipients as it is among non-HCT recipients.[35] It is associated with an increased risk of heart attack, heart failure, stroke, and kidney disease.[35] Transplant recipients should have blood pressure monitored at every medical appointment and should receive appropriate treatment to keep it within normal limits for age.[35]

Hypogonadism after HCT

Patients with DC occasionally experience hypogonadism as a result of the disease process, and undergoing HCT further increases this risk.[8,17,34] In males, hypogonadism is characterized

by decreased sperm production, erectile dysfunction, and low testosterone.[35] In women, signs of hypogonadism include primary ovarian failure, low libido, and vaginal changes.[35] In both males and females, doctors and patients need to have frank discussions regarding the likelihood of infertility following HCT and the options that exist regarding pre-HCT sperm banking and cryopreservation, as well as post-transplant *in vitro* fertilization.[35] Therapy for hypogonadism should be tailored to individual patient goals, as well as to preventing and treating bone loss.[35]

Vitamin D deficiency after HCT

Most patients are vitamin D deficient following HCT.[35] Levels should be checked by looking at serum 25-hydroxy vitamin D. Even in the absence of obvious signs and symptoms, physicians should be particularly suspicious of patients with high parathyroid hormone (PTH) and normal or low calcium and phosphorous levels.[35] Low serum vitamin D should be treated at least weekly with 50,000 IU of ergo-calciferol to normalize levels.[35] This should be monitored carefully by the patient's health care team.

* * *

Osteoporosis

Osteoporosis is common in post-HCT patients. Patients with DC who have undergone HCT and their physicians should be keenly aware of this complication, given the underlying disease mechanism. Steroid use, hypogonadism, direct damage to osteoprogenitor cells, hyperthyroidism, and calcium or vitamin D deficiency, all increase the risk of osteoporosis in HCT recipients.[35]

While T-scores are used to define impaired bone mineral density in adults, height-adjusted Z-scores are used in growing children.[36] After vitamin D levels have normalized, bisphosphonates may be considered in pediatric patients who have had two or more low-impact fractures and whose BMD T-score in adults, or height-adjusted Z-score in children is lower than -2.0 SD. Bisphosphonates prevent post-HCT bone loss in adults, but there is a lack of clear evidence to support their use as standard treatment of low BMD in pediatric patients; more data on treatment of children with secondary osteoporosis is necessary.[37] Side effects of bisphosphonates include the acute phase reaction, hypocalcemia, abdominal bloating, esophagitis

(oral agents), and bone or muscle pain. Delayed fracture healing and osteonecrosis of the jaw have also been reported in patients receiving bisphosphonates.[37] Side effects of these medications in patients with DC have not been studied. Patients and physicians should have frank discussions regarding the risks and benefits of treatment.

Post-HCT survivorship guidelines suggest that patients should have a DXA scan within one year of transplantation, especially in the face of prolonged corticosteroid exposure.[35] Oral bisphosphanates such as alendronate (Fosamax) or ibandronate (Boniva) are the first-line treatment of osteopenia and osteoporosis, but alternative treatment with once a year intravenous injection of zolendronic acid may be considered in patients with normal kidney function whose creatinine clearance is greater than 35 or are unable to tolerate oral formulations due to gastrointestinal side effects.[35]

AVN has been reported in 4-19% of allogeneic HCT patients.[35] Given the increased risk of AVN, post-transplant patients should be educated about its signs and symptoms. Physicians should have a high index of suspicion for this complication following onset of new joint or limb pain. Patients who have received total body irradiation, those who have received corticosteroids, and

those of advanced age are at particularly high risk of AVN, and should be evaluated accordingly.[35]

Adrenal dysfunction

All patients receiving either prolonged treatment with or intermittent supra-physiological doses of glucocorticoids (> 7.5 mg/d) may experience suppression of the hypothalamic pituitary axis (HPA), which may cause fatigue and weakness.[35] Adrenal insufficiency is assessed using an ACTH (adrenocorticotropic hormone) stimulation test, but providers should be aware that even low doses of steroids might produce an abnormal test result.[35] Patients suspected of adrenal insufficiency should be referred to an experienced endocrinologist for appropriate evaluation and replacement therapy.

Pituitary dysfunction

Growth failure is the main pituitary-associated complication of HCT: Radiation conditioning or transplantation before the age of ten may result in short stature.[35] Central hypogonadism and central hypothyroidism are also associated with HCT.[35] Patients should work with an endocrinologist to determine the best course of treatment.

Thyroid dysfunction

TSH levels are sometimes elevated following HCT. Age under ten at the time of transplant, administration of a conditioning regimen involving radiation or busulfan-cyclophosphamide, and presence of hematologic malignancy all further increase the risk of hypothyroidism among HCT survivors.[35] Patients experiencing constipation, diarrhea, weight gain, dry skin, fatigue, or changes in menstruation should have thyroid function checked.[35] Some patients may experience subclinical hypothyroidism which may resolve without any treatment, while others may require pharmacological intervention.[35]

Hyperthyroidism is occasionally seen in HCT survivors, but is much less common than hypothyroidism.[35] Patients with hyperthyroidism may experience anxiety, increased sweating, palpitations, weight loss, or diarrhea.[35] Symptomatic patients should have TSH and free thyroxine levels drawn, as well as assessment for thyroid antibodies.[35] Patients should be monitored for at least 6-8 weeks after starting thyroid therapy to ensure appropriate dosing.[35]

Radiation exposure during pre-transplant conditioning may lead to thyroid tumors in HCT recipients.[35] Thyroid tumors should be assessed with sonography and fine needle biopsy if appropriate, and malignancies should be removed surgically.[35] Benign tumors should be monitored with ultrasound at regular intervals and biopsied as necessary.[35]

Dyslipidemia

Dyslipidemia, an abnormal amount of fat or cholesterol in the blood, may be caused by or worsen following HCT.[35] GVHD of the liver, several of the immunosuppressive medications, diabetes, hypogonadism, thyroid dysfunction, and nephritic syndrome may also cause or exacerbate dyslipidemia[35]. Total and HDL cholesterol should be monitored every five years (starting by age 35 for men and 45 for women) in patients without additional risk factors.[35] Monitoring should begin at age twenty for individuals who smoke, have diabetes, or have a positive family history.[35] Patients with abnormal test results (total cholesterol above 200 mg/dL or HDL < 40 mg/dL) should receive a full fasting lipoprotein profile.[35] Patients and providers can use The Framingham Heart Study Calculator (available at

www.nhlbi.nih.gov) to estimate ten-year risk of cardiovascular disease and to help determine appropriate treatment.[35]

Successful treatment of dyslipidemia may lower the risk of cardiovascular disease-related adverse events and hypertrigliceridemia-induced pancreatitis.[15,35] Treatment should begin with therapeutic lifestyle changes and may also include decreasing immunosuppressant use, adding statins, niacin, omega-3 fatty acids, fenofibrates, and bile acid sequestrants.[15,35]

Patients and providers need to be aware of the possible increased risk of myopathy and rhabdomyolysis when statins and immunosuppressants are taken simultaneously, and patients should be closely monitored during the first four weeks of treatment.[15,35] Patients with GVHD of the liver should also be closely monitored for dyslipidemia.[15,35]

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Chapter 14:
Pulmonary Fibrosis

Christine Kim Garcia and Mary Armanios

Introduction

After bone marrow failure (BMF), pulmonary fibrosis (PF) is the most serious and life-threatening complication of dyskeratosis congenita (DC). In most cases, it presents later than BMF, and is associated with significant morbidity and mortality.

PF generally manifests in one of two patterns in DC patients. The first occurs early in life, following the onset of BMF.[1] In this setting, it may be accelerated by exposure to hematopoietic cell transplantation (HCT) conditioning regimens.[2,3] Historically, when myeloablative preparatory regimens were used for HCT, PF often presented within one year of transplantation and was rapidly fatal.[2] With more recent implementation of non-myeloablative regimens for this population, its onset has been delayed.[4] Alternatively, PF may be the first life-threatening complication of DC, and in this setting is usually seen in patients over the age of 30.[5-7]

After the fourth decade of life, PF may be the dominant feature of telomere-mediated disease occurring in the absence of DC mucocutaneous features and BMF.[8,9] Generally, this last group of patients is not always recognized clinically as having DC, although the development of PF in this population has been associated with telomere shortening and inherited mutations in genes encoding the telomerase complex. Considering the relatively higher incidence of PF in older adults,[10] the latter presentation may be the most common manifestation of telomere-related PF.[11] For the purposes of this review, we have considered all the above patients as having manifestations of telomere-related PF.

Clinical presentation and diagnosis

Symptomatic patients with PF usually present with respiratory complaints including exertional dyspnea and chronic cough. They may have inspiratory rales and digital clubbing on physical exam. The disease is associated with a restrictive pattern on pulmonary function tests and decreased diffusion capacity for carbon monoxide (DL_{CO}). High resolution non-contrast computed tomography (CT) imaging of the chest is the cornerstone diagnostic study and usually demonstrates diffuse interstitial markings. In adults with telomere-mediated PF, the

most common radiographic and histopathologic pattern is of usual interstitial pneumonia (UIP),[12] and the clinical diagnosis of idiopathic PF (IPF) is made in approximately 75% of cases.[13] This pattern has not been generally seen in pediatric DC cases.[5,7,14]

In PF that manifests post-HCT, the pattern of disease is often complex. Lung histopathology generally features a mixture of cellular inflammatory infiltrates and interstitial fibrosis that differs from the pattern seen in IPF.[15,16] Assessing these patients may be particularly difficult not only because the clinical findings and histopathology are non-specific, but because of the range of possible differential diagnoses, including lung involvement of graft versus host disease, opportunistic infection, and drug-induced lung injury. In these challenging cases, consultation with an experienced clinical team familiar with the presentations of telomere-mediated pulmonary disease may be helpful.

When the exact etiology of lung disease is unclear, bronchoscopy or thoracoscopic lung biopsy may be considered. Bronchoscopy with collection of bronchoalveolar lavage fluid and transbronchial biopsies may provide useful diagnostic material. This procedure is associated with a lower risk of adverse events than open surgical lung biopsy.

Patients with lung fibrosis have been known to experience acute postoperative worsening of their underlying interstitial lung disease or even death after surgical procedures.[17-19] Therefore, the risks and benefits of surgical (or thorascopic) lung biopsy need to be carefully weighed, especially if it is not anticipated that the biopsy will alter clinical management. It is recommended that the least invasive procedure be utilized to evaluate lung pathology in the DC population, given the potential for perioperative morbidity.

Screening

There are no clinical trials assessing the utility of screening protocols for PF in DC. The authors differ in their opinion in this area. Noting the prevalent adult-onset of PF in DC and the extremely low incidence in children, one of the authors (MA) feels that the risks of any testing, as well as unnecessary exposure to radiation, may be too high in asymptomatic children relative to the benefit. However, given the potential for treatment of PF with emerging drug therapies, the other author (CKG) feels that early detection may provide opportunities for earlier intervention. The following summarizes their opinions.

Children who have undergone hematopoietic stem cell transplant

Experts agree that in this post-HCT population, there should be an elevated suspicion for PF (see Chapter 8, Hematopoietic Cell Transplantation for Dyskeratosis Congenita).

In addition to the medical history and examination, noninvasive tests including spirometry, plethysmography, diffusion capacity measurement, and oxygen saturation are appropriate to establish a clinical baseline. The decision to repeat testing should be weighed against the patient's respiratory symptoms, physical exam, and level of impairment found on baseline testing.

The optimal frequency of repeat testing is unknown, although studies at regular intervals may be warranted given the higher frequency of PF in this patient population. If a PF diagnosis is suggested, it is recommended that the patient be evaluated by a pulmonologist or specialist with clinical expertise in this field, before chest imaging or more invasive procedures are pursued. Although non-contrast high-resolution chest CT imaging is routinely available, exposure to ionizing radiation is known to be carcinogenic and should be avoided when unnecessary in this already cancer-prone population (see Chapter 22, Radiation in

Dyskeratosis Congenita). For this reason, chest CT imaging should not be used as a routine screening tool in pediatric DC patients.

Asymptomatic children

The risk of developing PF in children is very low.

The authors differ in opinion on whether baseline evaluation is needed in this population. One (MA) asserts that tracking respiratory symptoms by clinical history and exam is sufficient, and this approach is associated with the lowest risk of unnecessary imaging, biopsies, and patient–family anxiety. The concern about variability in measured lung function in children also contributes to this view, since this increases the likelihood of false positive results, which in turn could contribute to unnecessary testing.

The other author (CKG) posits that baseline testing such as spirometry, plethysmography, diffusion capacity measurement, and oxygen saturation studies may be useful in establishing a clinical baseline from which objective changes can be assessed in conjunction with changes in the clinical status and exam. Measurement of lung volumes like forced vital capacity (FVC) and diffusion capacity (for example DL_{CO}) may vary by as much

as 15% between testing sessions, so only more significant changes in these parameters should warrant additional work-up. If a diagnosis of PF is suspected, it is strongly recommended that a specialist with clinical expertise in this area be consulted prior to additional chest imaging or more invasive procedures.

Asymptomatic adults

For middle-aged and older asymptomatic adults, non-invasive testing with spirometry, plethysmography and DL_{CO}, as well as non-contrast high-resolution chest CT scan may be considered to establish a clinical baseline.

Some asymptomatic adults predisposed to PF have been found to have subtle interstitial abnormalities on chest CT imaging and a reduction in the diffusion capacity, DL_{CO}. The predictive value of these findings for disease progression is unknown.[20] One study followed two sisters with the same rare telomerase mutation. Although each had evidence of preclinical lung disease on imaging at the start of the study, very different rates of progression were observed over the subsequent 27 years.[21] Thus, the significance of subtle interstitial abnormalities in asymptomatic individuals is unclear, and the appropriate interval for repeat testing is unknown.

The risks of undue radiation exposure in the form of routine, frequent, repeat imaging should be weighed against potential benefits. The development of suspicious new or worsening respiratory symptoms should obviously dictate evaluation and consultation with a pulmonologist, ideally one with experience with this patient population.

Exposures to avoid

The development of lung fibrosis can be associated with various environmental, iatrogenic and chemical exposures. Vigilance in avoiding these insults is critical to preserving lung function. The list below, although not comprehensive, includes relevant exposures to avoid:

- **Cigarette smoke**. Cigarette smoke is known to accelerate the onset of lung disease. Smoking should be strongly discouraged, and multi-disciplinary efforts should be made to support patients in avoiding both primary and secondary tobacco smoke. This may require referral to support groups and other counseling strategies used in high-risk populations.
- **Cytotoxic medications and radiation**. Ionizing radiation should be minimized if included in the HCT preparative regimen. In these cases, aggressive lung shielding should

be implemented (see Chapter 7). Busulfan should be strongly avoided because of its proven pulmonary toxicity in this population, and high dose busulfan is contraindicated. There are additional medications routinely used in oncology care and HCT that have pulmonary toxicities. These should be avoided in the DC population whenever possible.

- **Other medications.** Several medications are strongly associated with pulmonary toxicities, such as nitrofurantoin and amiodarone. A list of such medications and the strength of evidence supporting their association with interstitial lung disease is available at www.pneumotox.org. These fibrogenic medications should be avoided whenever possible.
- **Surgery risks**. Exacerbations of lung disease in adults with PF have been well-documented following both pulmonary and non-pulmonary surgeries. This risk should be weighed in planning elective procedures because this complication may be fatal. When feasible, elective surgery is preferably pursued using regional anesthesia and avoiding high partial pressure oxygen, which can trigger alveolar epithelial injury.

- **Occupational and environmental risk factors**. Occupations that have been associated with an increased risk of developing PF include farming, raising livestock and birds, stone cutting, hairdressing, and work involving exposure to metal dust.[22] Exposure to a number of different organic antigens (most commonly bird feathers, fungal and bacterial antigens) can result in an inflammatory condition termed hypersensitivity pneumonitis, which mimics IPF and other types of fibrosing lung disease. Changing occupations is not feasible for many individuals, and the quantitative benefit of doing so is unclear. Implementing respiratory protection plans that include wearing a particulate-filtering respirator is an alternative in order to reduce hazards associated with these exposures.
- **Respiratory illness**. Infections suspected or confirmed to be caused by bacterial pathogens should be promptly and appropriately treated with antibiotics. Immunizations to respiratory tract pathogens should be offered according to standard practice.

Medical treatment

Ongoing clinical trials are actively recruiting patients to investigate the effectiveness of various medications. In October 2014, two medications, pirfinidone (Esbriet in the United States, Intermune/Roche) and nintedanib (Ofev in the United States, Boehringer Ingerheim) were approved by the United States Food and Drug Administration for adults with IPF. Their approval was based on decreased rates of lung function decline in treated patients.[23,24]

Even so, these compounds have not been shown to improve survival, and lung transplantation remains the only modality to show this benefit. The approval trials did not explicitly include or exclude any genetically defined PF subsets (such as DC), so the benefits and toxicities in patients with telomere-related PF are currently not known. It is important to note that these drugs have not been tested and are not currently approved for children. Further, they have not been tested in patterns of idiopathic interstitial lung disease other than IPF. www.clinicaltrials.gov is a useful resource for ongoing clinical trials in PF.

Lung transplantation

The only known treatment that has been shown to prolong survival of end-stage PF is lung transplantation. In the post-HCT setting, this is often a high-risk procedure, because DC patients may already have evidence of non-pulmonary end organ damage (such as in the liver), and therefore the risks of transplant may be higher. There is at least one reported case of a child undergoing successful lung transplantation several years after bone marrow transplantation.[14] The patient's medical problems and the experience of the center are likely major factors to consider in the candidacy for lung transplantation after HCT.

There are some data regarding lung transplantation outcomes of adult telomere-related PF patients without classic features of DC.[4,25,26] In the reported series, patients had higher risk of recurrent morbidities including prolonged cytopenias and an increased transfusion requirement. There are also reports of increased calcineurin inhibitor nephrotoxicity and gastrointestinal bleeding.[25] Awareness of these potential complications should be taken into consideration during the pre-transplant evaluation and post-transplant management of telomere-related PF.

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Chapter 15:
Vascular Complications

Payal P Khincha, MD MSHS and Sharon A Savage, MD

Introduction

The development of gastrointestinal (GI), pulmonary, and retinal vascular telangectasias in DC has been described in small case series and case reports, but until recently such vascular abnormalities were not recognized as complications associated with dyskeratosis congenita (DC).[1-3]

The biological mechanism for vascular malformations in DC is not clear but may be related to defects in telomere biology. Von Willebrand factor levels were found to be significantly elevated in patients who developed fatal vascular complications after hematopoietic cell transplantation (HCT) for DC, suggesting there is an underlying predisposition to endothelial damage that may be related to high cell turnover.[4] It is prudent to note that there may be other organs whose vascular involvement in DC and its variants have not yet been characterized.

Retinal telangiectasias

Coats plus is a rare phenotypically complex disorder that encompasses bilateral exudative retinopathy, retinal telangiectasias, intrauterine growth retardation (IUGR), intracranial calcifications, bone abnormalities with poor healing, and gastrointestinal vascular telangiectasias (Figure 1, next page)[1,3] (see Chapter 6, Subtypes of Dyskeratosis Congenita and the Telomere Biology Disorders). Some patients also have premature graying of the hair, anemia, or nail dystrophy, which is similar to that of DC. The majority of Coats plus patients have biallelic mutations in *CTC1*, a telomere capping gene that is also known to cause DC. Notably, some features of Coats plus, such as bilateral exudative retinopathy and intracranial calcifications, overlap with those of Revesz syndrome, a variant of DC (see Chapter 6, Subtypes of Dyskeratosis Congenita and the Telomere Biology Disorders).[1-3] Therefore, patients with DC should be regularly screened by a trained ophthalmologist for presence of retinal pathology such as retinal telangiectasias.

Gastrointestinal telangiectasias

GI telangiectasias have thus far been described in the stomach, intestine, and liver of patients with Coats plus (Figure 2).[1]

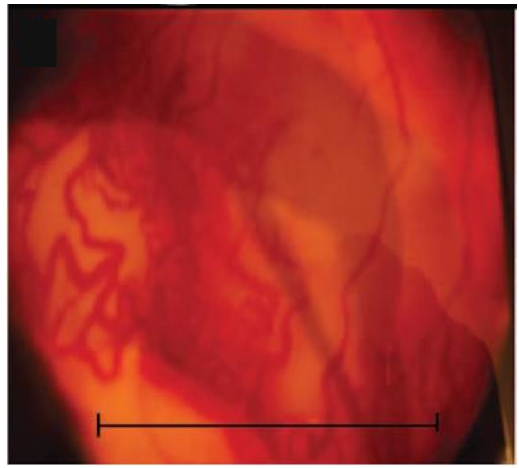

Figure 1: Retinal microangiopathy in Coats plus syndrome. Figure from Anderson BH, Kasher PR, Mayer J, et al. Mutations in *CTC1*, encoding conserved telomere maintenance component 1, cause Coats plus. Nature genetics. 2012;44(3):338-342. Color versions in **Color Photo Appendix**, page 399.

Vascular complications and severe GI bleeding from hemorrhagic colitis have been described in post-HCT DC patients, suggesting that these patients are particularly vulnerable to GI-related morbidity and mortality.[4,6,7] DC patients can also develop portal hypertension either from noncirrhotic liver disease or hepatic fibrosis, leading to development of porto-systemic varices.[5] GI telangiectasias in DC may present as life-threatening GI bleeding regardless of the underlying cause and are thus a potentially severe complication of DC. Diagnostic

modalities for GI telangiectasia include upper GI endoscopy, capsule endoscopy, or colonoscopy. Liver ultrasound and computed tomography (CT) scans may indicate the presence of liver disease or fibrosis that can potentially cause portal hypertension, and clinicians must be particularly vigilant about development of varices in these patients.

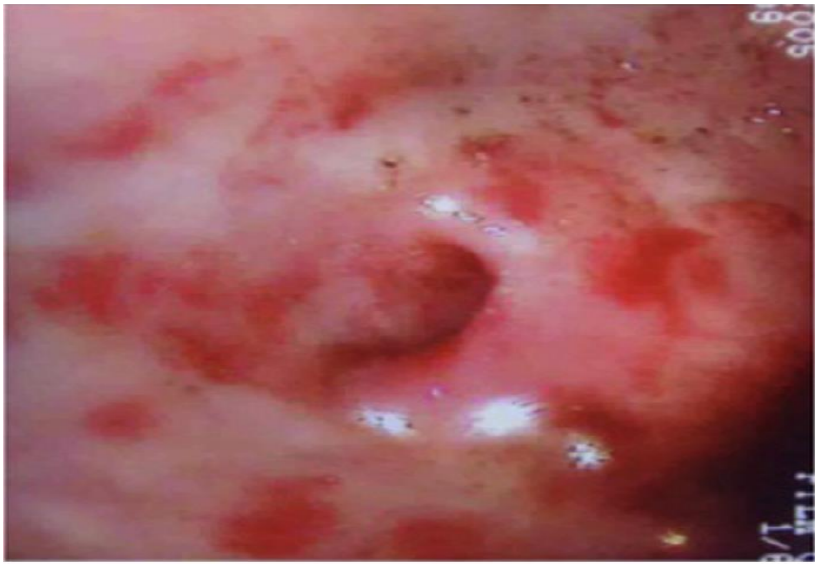

Figure 2: Gastric vascular ectasia in Coats plus syndrome. Figure from Anderson BH, Kasher PR, Mayer J, et al. Mutations in *CTC1*, encoding conserved telomere maintenance component 1, cause Coats plus. *Nature genetics*. 2012;44(3):338-342.

Pulmonary vascular malformations

Hepatopulmonary syndrome is described as pulmonary vascular dilation due to liver disease of any form that leads to a

deficit in arterial oxygenation.[8] It can occur in patients with or without portal hypertension. Patients with DC may be at risk of hepatopulmonary syndrome due to the increased frequency of underlying liver disease in this population.[5]

Pulmonary arteriovenous malformations (AVMs) unrelated to hepatopulmonary syndrome have been described in a few case reports of DC.[9-11] However, recent discussions with clinicians managing DC patients suggest that this complication may occur more frequently than has been previously appreciated (unpublished data). In DC, pulmonary AVMs have been reported to be microscopic and multiple, making diagnosis and treatment challenging.[9] Macroscopic pulmonary AVMs have been noted in at least one patient with DC.

In general, AVMs lead to right-to-left shunting of blood, which causes a deficit in arterial oxygenation and progressive respiratory insufficiency if undetected and untreated. Both of these manifestations can present with non-specific symptoms such as dyspnea on exertion, clubbing of the digits, cyanosis, or abnormal pulmonary function tests (PFT). The diagnosis of pulmonary AVM may be missed or delayed as it may present with symptoms similar to those of pulmonary fibrosis, a well described complication of DC (Chapter 14 Pulmonary Fibrosis).[5]

However, unexplained clubbing and lung diffusion capacity (DLCO) abnormality out of proportion to the degree of pulmonary fibrosis must alert clinicians to the possibility of pulmonary AVMs or hepatopulmonary syndrome (in the presence of liver disease).

Bubble echocardiography is a diagnostic modality that detects presence of right-to-left shunting and pulmonary vascular malformations. Further invasive testing such as angiography or cardiac catheterization may be necessary to confirm presence of these abnormalities, along with a workup to rule out cardiac causes of these symptoms.

Management

At present, there are no specific recommendations for treatment of DC-associated vascular malformations. Testing for other genetic syndromes, such as hereditary hemorrhagic telangiectasia, should be considered in the differential diagnosis for multi-organ vascular telangiectasias. Management guidelines follow medical and surgical recommendations appropriate for each entity, for example, photocoagulation for retinal telangiectasias, and coiling or nifedipine for pulmonary AVMs.

Currently, the only known successful treatment for hepatopulmonary syndrome is liver transplantation.[8]

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Chapter 16:
Gastrointestinal Disease

Naudia L. Jonassaint and Mary Armanios

Introduction

Dyskeratosis congenita (DC) affects rapidly dividing tissues such as the skin and bone marrow. The gastrointestinal (GI) tract is another high turnover compartment, and it may also be a site of disease in DC.

The penetrance of GI disease in DC is incomplete, and its prevalence varies depending on the population studied. In a cohort that included predominantly children with DC, as well as adults with telomere syndromes, GI disease was estimated to affect approximately 16% of individuals. There are three well-described GI manifestations of telomere-mediated disease. These are esophageal stenosis, enteropathy primarily affecting the small bowel, and enterocolitis, which primarily affects the colon (Jonassaint et al. 2013 and references therein).

Esophageal stenosis

Presentation

Esophageal stenosis is a narrowing of the esophagus that may interfere with swallowing. It is one of several examples of luminal stenotic lesions that appear in DC. Other examples include lacrimal duct and urethral stenosis.

The prevalence of esophageal stenosis in DC is not known, but most reported cases heretofore have been in patients with classic mucocutaneous features of the disorder. In cases where the esophageal stenosis is severe and congenital, it may manifest soon after birth as poor feeding, regurgitation and failure to thrive. In older children and adults, individuals may develop adaptive mechanisms such as selective thorough chewing and food avoidance. This may be because the narrowing is acquired or represents a milder, congenital presentation. Regardless, a high index of suspicion in young children and an explicit and detailed swallowing history in older children and adults is often necessary to elicit the symptoms in these chronic cases.

In addition to stenoses, esophageal webs and Schatzki's rings have been described in DC and other telomere syndromes, and

the management guidelines below are relevant to these more rare complications.

Diagnostic work-up and treatment

The ideal initial evaluation for esophageal stenosis is a cine esophagram (video contrast swallow study). It is typically done under the supervision of a speech language-pathologist.This study is preferred to a static barium swallow evaluation, which may miss subtle swallowing difficulties because it is not supervised by a speech language-pathologist. Interpretation of these diagnostic studies should include a thorough and focused evaluation of the cricopharynx and proximal esophagus, as these regions may be missed on routine exam, but are frequent sites of stenosis in DC.

Once the location of the stenosis is identified, endoscopic evaluation is necessary to confirm the diagnosis and proceed with therapeutic dilatation. Other causes of obstruction can be ruled out at this time, including head and neck squamous cell cancers. In cases where the obstruction is proximal, it may be important to have input from an interventional gastro-enterologist specializing in the esophagus (i.e. esophagologist) or an otolaryngologist. Stenoses may at times be severe and, in

these cases, pediatric endoscopy equipment may be required for dilatation in symptomatic adults.

Once completed, esophageal dilatation can significantly relieve symptoms. Multiple dilatations may be required if symptoms recur and have been performed successfully in several cases.

Enteropathy

Presentation

Patients with enteropathies often present with subtle and chronic complaints. Symptoms may include nausea, early satiety, non-specific abdominal pain, food intolerance, difficulty with weight gain, diarrhea, and food allergies. In extreme cases, it may present with failure to thrive. Telomere-associated enteropathy, including the one that complicates DC, causes significant morbidity.

Diagnostic work-up and treatment

In cases where the onset of symptoms is relatively recent, a diagnostic work-up that excludes other pathology, such as infection or malignancy, should be performed. This may include laboratory evaluation, upper endoscopy with biopsies of

the proximal small bowel, and colonoscopy with random biopsies even in the absence of gross pathology. An experienced pathologist may need to review these specimens to evaluate for subtle findings. The histopathology may reveal intraepithelial lymphocytosis, villous atrophy, and increased apoptosis. These findings are non-specific and are also seen in celiac disease and other enteropathies.

In some cases, affected patients spontaneously adjust and alter their diet, thus self-treating their symptoms. There is anecdotal clinical experience that a gluten-free diet improves symptoms even in patients who do not fulfill the criteria for celiac disease. In severe cases, weight loss and malabsorption cause morbidity, and require aggressive supportive care. Parenteral nutrition has been prescribed in these cases with variable degrees of success in reversing the failure to thrive symptoms.

DC and telomere syndrome patients may develop enteropathy after organ transplant. This may be related to transplant preparative regimens, immunosuppressive medications, or graft-versus-host disease. In cases where the enteropathy is exacerbated by medications (for example mycophenolate), discontinuing the offending agent may be necessary. A multi-disciplinary evaluation and familiarity with

the telomere-associated histopathology is ideal in formulating a treatment plan in these complicated patients.

Enterocolitis

Presentation

Enterocolitis is the most serious and life-threatening GI complication of telomere disorders, including DC. It is particularly prevalent in Hoyeraal-Hreidarsson syndrome (HH), and may be one of its initial presentations. Abdominal pain, failure to thrive, and bloody diarrhea are defining symptoms in enterocolitis. In some cases bacteremia, sepsis, and bowel perforation may occur. The pathophysiology of this condition is complex and likely reflects epithelial-intrinsic defects as well as immune abnormalities.

Diagnostic work-up and treatment

The diagnosis of enterocolitis is a clinical one, and is based on the patient's age and symptoms. Colonoscopy often reveals friable mucosa, gland drop-out, and inflammation. The diagnosis may be confused for inflammatory bowel disease. Treatment is supportive, including bowel rest, and antibiotic and nutritional support. Parental nutrition may be prescribed. In

cases of bowel perforation, surgical intervention is required. It is unclear whether other medical therapies that are used for inflammatory bowel disease are helpful in these settings. Immunosuppressive medications such as TNF-alpha inhibitors, may be considered in the treatment of inflammatory bowel disease but DC-specific data on response are not available. There is obvious theoretical risk of opportunistic infections when giving these medications, since patients have an underlying immune disorder. Immune reconstitution with stem cell transplantation has been performed, but in children with HH or DC who have developed enterocolitis, it is unclear from the authors' experience to date, whether it is possible to completely reverse this GI complication. Overall, this condition, when it is severe, may be associated with poor prognosis.

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Chapter 17:
Hepatic Complications in Dyskeratosis Congenita

Rodrigo T. Calado

Introduction

The gastrointestinal system is frequently affected in dyskeratosis congenita (DC), with pathology including oral features (leukoplakia and dental anomalies), esophageal stenosis, hepatic cirrhosis, and cancer (squamous cell carcinoma of the tongue, rectal adenocarcinoma, and hepatocellular carcinoma).[1,2]

Liver involvement may vary from mildly abnormal liver function tests only to end-stage cirrhosis and hepatocarcinoma. The time of onset of liver involvement also varies and depends on the mutated gene, the type of mutation, length of telomeres, disease anticipation, and interaction with environmental factors.

As indicated in *Chapter 4, Genetics of DC*, many patients with hepatic involvement are older and carry mutations in the *TERT* or *TERC* genes.[1,3] However, patients with DC from an X-linked

(*DKC1*) or autosomal dominant gene mutation are at high risk of developing liver disease in their youth. Children with DC who undergo hematopoietic stem cell transplantation (HSCT) for marrow failure in the first decade of life are particularly prone to liver complications, especially veno-occlusive disease and cirrhosis, in the post-transplant period.[4] Reduced intensity conditioning regimens may reduce liver toxicity.[5]

In patients with *TERT* or *TERC* mutations without the usual dermal abnormalities that characterize DC, liver disease may be the only clinical manifestation of this telomere biology disorder (also called a telomeropathy).[6] However, in a significant proportion of patients, liver disease accompanies aplastic anemia. It may also be found in relatives of patients with aplastic anemia who are otherwise silent carriers of a telomeropathy. Additionally, cryptogenic liver cirrhosis is found in a small proportion of patients with idiopathic pulmonary fibrosis, implicating telomere erosion in both fibrotic processes.[7] It is important to note that the same telomerase mutation may manifest differently in different individuals of the same family; whereas some may develop liver disease, others may be diagnosed with aplastic anemia or idiopathic pulmonary fibrosis.[8]

The pattern of hepatic involvement is variable. The most common liver pathologies associated with telomere diseases, especially DC, are described below.

Liver diseases

Hepatic cirrhosis

Hepatic cirrhosis is a late stage of progressive liver fibrosis and is characterized histologically by distortion of hepatic architecture and formation of regenerative nodules.[9] Although a liver biopsy is necessary to confirm the diagnosis of cirrhosis, it is usually not required in the clinic, as clinical, laboratory, and imaging findings may strongly indicate the diagnosis. Patients may complain of fatigue, jaundice (yellowing of the eyes and skin), hematemesis (vomiting blood), abdominal distension, and edema (swelling of the extremities), whereas physical examination may reveal signs of hepatic insufficiency (jaundice, spider telangieactasias, palmar erythema, gynecomastia) and portal hypertension (splenomegaly, ascites). Laboratory tests frequently show elevated hepatocellular enzymes (commonly with AST greater than ALT), elevated canalicular enzymes, low serum albumin, and prolonged prothrombin time, and imaging

may reveal ascites and a nodular hepatic surface with increased echogenicity.

Although the pathogenesis of cirrhosis is not completely understood, it appears that telomere attrition plays an important role. Chronic liver injury stimulates hepatocellular proliferation, cell turnover and telomere loss, which in turn promotes cell proliferation arrest and apoptosis.[10] In fact, telomere shortening by itself is associated with cirrhosis formation.[11]

In patients with telomerase mutations and liver damage, hepatocellular and canalicular enzymes are usually elevated, albumin may be low, and bilirubin may be mildly increased. When liver biopsy is performed, histology may reveal distortion of the hepatic architecture, with bridging fibrosis (fibrosis connecting portal areas) or perisinusoidal fibrosis. Inflammatory infiltrate is another common feature, and macrovesicular steatosis and Mallory bodies may be noted. Additionally, sinusoidal endothelial cells around the portal areas and central veins may stain positive for CD34, which suggests abnormal arterial blood flow to the sinuses. Iron accumulation in hepatocytes is usually noted. In more severe cases, portal hypertension with chronic congestive splenomegaly and esophageal varices may develop.

Liver cirrhosis may be cryptogenic, but *TERT* mutations also are risk factors for cirrhosis development in patients with hepatitis C virus or alcoholic hepatitis [10]. *TERT* mutations are more prevalent in patients with these conditions than in the normal population. However, it is not clear whether disease may be more severe when a *TERT* mutation is present.

Idiopathic non-cirrhotic portal hypertension

A variety of hepatic conditions, including nodular regenerative hyperplasia (NRH), have been unified into a single entity termed "idiopathic non-cirrhotic portal hypertension", which is clinically characterized by an increase in the portal venous pressure in the absence of a known liver disease or portal vein thrombosis.[12] Most patients present with signs of portal hypertension but with normal liver function, while others may already have developed impairment. Some patients demonstrate isolated elevated liver enzymes in the absence of an obvious cause. The association of bone marrow failure and hepatic NRH with or without pulmonary fibrosis has been described in several families.[3,13,14]

Histologically, the pattern is of NRH, with hepatocytes displaying variation in cell and nuclear sizes, and cell plate

dimensions alternating between areas which are widened with areas of compression.[3]

These findings on reticulin stain are consistent with regeneration. CD34 may be positive in sinusoidal endothelial cells, which is consistent with portal hypertension.

Hepatocellular carcinoma

Development of hepatocellular carcinoma in patients with telomerase mutations has been reported.[10,15] However, the number of cases reported so far is too small to determine whether the clinical behavior or tumor aggressiveness differs in patients with the mutations compared to the general population. It appears that the pattern of liver damage is similar to the involvement seen in hematopoietic tissue, in which telomere dysfunction results in organ failure and malignant transformation.

Other manifestations

Hepatic veno-occlusive disease is a frequent complication following HSCT for aplastic anemia in patients with DC.[4] In some patients with telomerase mutations, an enlarged, fatty liver

may be detected on ultrasound, and liver biopsy may reveal steatosis.[3]

Monitoring liver involvement in DC

Patients with telomere biology disorders, including dyskeratosis congenita, should be screened for liver dysfunction at diagnosis and monitored approximately once a year, depending on the patient's specific clinical manifestations. Complete liver function tests (aminotransferases and canalicular enzymes), prothrombin time, albumin, and bilirubin levels should be performed.

If tests are abnormal or physical examination suggests liver enlargement, abdominal ultrasound should be performed. Liver biopsy should be considered in all patients in whom the liver appears to be affected. Patients taking androgens are particularly susceptible to developing liver complications, although more recent work had not found an increased rate of abnormal liver function tests in these patients (see also Chapter 7).[16]

As in other complex multi-organ diseases, several subspecialties follow the patient, and medications prescribed by one specialist may interact with those prescribed by another, or have a synergistic toxic effect. The liver is of major concern for

side effects of polypharmacy. Patients should always inform their medical team of all prescribed medications.

Treatment options

There is no specific treatment for liver disease in DC. In more severe cases of liver failure or hepatocellular carcinoma development, liver transplant is an option, but reports on this treatment are anecdotal.[3,15]

Cirrhosis and portal hypertension are managed as they are for other etiologies, with a focus on prevention and treatment of additional liver and other organ injury, and managing symptoms. Patients may develop esophageal varices and hemorrhages, portal hypertensive gastropathy, ascites, spontaneous peritonitis, encephalopathy, hepatocellular carcinoma, or hepatopulmonary syndrome. Physicians should be extra careful in the adjustment of medications in the management of thrombocytopenia, as marrow failure may further decrease platelet counts.

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Chapter 18:
Genitourinary Complications in Dyskeratosis Congenita

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Introduction

Several genitourinary complications have been reported in patients with dyskeratosis congenita (DC), but there are limited data on their incidence. A review of the United Kingdom based DC registry found that 5% of males with DC had urethral stricture and/or phimosis.[1] Studies in a larger number of patients are underway.

The management of genitourinary complications in patients with DC should start with a detailed clinical evaluation based on the patient's symptoms and consultation with subspecialists as needed.

Males

Urethral strictures

Urethral strictures occur most commonly in males. This narrowing of the urethra can occur at any location along the

urethra. Men and boys with symptomatic urethral strictures typically present with obstructive voiding symptoms including straining with urination, incomplete bladder emptying, and a weak urine stream.[2] Patients may have a history of hematuria, frequent urinary tract infections, prostatitis, epididymitis, or bladder stones.[3,4] The diagnosis of urethral stricture should be made in consultation with a urologist.[2,5] Imaging studies, such as retrograde urethrography, voiding cystourethrography, or cystoscopy may be used to determine the location and extent of the stricture.

The pathogenesis of urethral stricture in males with DC is not known, but it is hypothesized to be due in part to the limited replicative capacity of the cells in these patients. In individuals without DC who develop urethral strictures, the normal pseudostratified columnar epithelium of the urethra is replaced by squamous metaplasia. The same mechanism is likely in DC, but this has not been studied.

Treatment is determined by the degree of symptoms and location of the narrowing,[2,6] and should be managed by a urologist with experience treating complex urethral strictures. Urethral dilation can be performed for relatively short strictures. Urethroplasty is used for strictures of the anterior urethra, while meatotomy is the preferred treatment for meatal stenosis.

Phimosis

Phimosis is a relatively common condition in which the foreskin cannot be retracted over the glans penis. The foreskin is not normally retractile in infants but gradually becomes so in childhood.[7] Scarring of the foreskin can result in phimosis, which in turn can cause difficulty in urination, balanitis, or urinary tract infections. Topical corticosteroids may be used for local irriation. Antibiotics may be required for infections.

It is not know if phimosis occurs more often in patients with DC than in the general population. It is thought that it will likely respond to the same management as for patients without DC, but this has not been systematically investigated.

Hypogonadism

Hypogonadism, manifesting as reduced testosterone production, has been reported in a small number of patients with DC. This is further reviewed in Chapter 13.

Females

There are anecdotal reports of labial adhesions, and hymenal and urethral strictures in females with DC. Incidence of these complications in DC is not known. However, these should be

considered in girls and women with DC who have frequent urinary tract infections, difficulty urinating, or abnormal menstrual bleeding. Labial leukoplakia has also been noted in some women with DC, but its contribution to adhesions or strictures is not understood. Women and girls with DC suspected of having these complications should be referred to a gynecologist and/or urologist with experience in treating these conditions.

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Chapter 19:
Dyskeratosis Congenita: Gynecologic and Obstetric Considerations

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Introduction

Female patients with dyskeratosis congenita (DC) may benefit from attention to their gynecologic and reproductive health. Although the gynecologic health and reproductive outcomes of patients with DC have not been systematically described, there are several key gynecologic issues faced by women with DC that merit discussion.

Patients with DC share an increased risk of developing some types of malignancy, although the risk of gynecologic cancer does not appear to be increased.[1] Women may undergo hematopoietic cell transplantation (HCT) to treat either bone marrow failure or malignancy, which presents unique concerns for gynecologic and reproductive health. The transplant may lead to early menopause or infertility. Additionally, if a patient undergoes HCT, there is increased risk of developing second cancers, or new cancers associated with the treatment itself.[2]

The most common HCT-related cancers are squamous cell cancer, including cervical cancer.[3]

Little is known about fertility and pregnancy outcomes in women with DC. Prenatal diagnosis can be undertaken to determine if a fetus is affected. Women with other inherited bone marrow failure syndromes are known to have problems with fertility and a higher rate of pregnancy complications related to low blood (hemoglobin) and platelet counts. Thus, women with DC benefit from care by a maternal-fetal medicine specialist. While early menopause has not been reported specifically in women with DC, women with other short-telomere disorders do have a higher risk of menopause before age 40 or premature ovarian insufficiency.[4]

In this chapter, issues regarding routine gynecologic surveillance, HCT, fertility, prenatal diagnosis, pregnancy, and obstetric complications are reviewed. Women with DC would benefit from inclusion of a gynecologist on their clinical care team to assess their gynecologic and reproductive health.

Malignancy risk

Patients with DC are at increased risk of squamous cell carcinoma.[5] Anogenital cancers in men with DC have been reported; however, affected women do not appear to share this

increased risk.[1] To date, only one case of cervical cancer has been reported,[1] making it less likely that its incidence is increased in DC.

Human papillomavirus and Pap smears

Human papillomavirus (HPV) is a sexually transmitted virus which can affect squamous cells in the genital area. It is associated with genital warts, lower genital tract precancer, and anogenital and oropharyngeal cancer. There are currently three vaccines which can prevent HPV infection, Gardasil®, Cervarix®, and a 9-valent HPV vaccine.

The Gardasil® vaccine prevents four types of HPV: types 16 and 18, which are associated with 70% of cervical cancer, and types 6 and 11, which cause 90% of genital warts.[6] The Cervarix® vaccine is designed to prevent only types 16 and 18. The 9-valent HPV vaccine is designed to prevent types 6, 11, 16, and 18, and five additional oncogenic types 31, 33, 45, 52, and 58. These vaccines are currently FDA approved for girls and boys ages 9-26 years old.[7,8]

These vaccines are given as a three-injection series with the subsequent shots given two and six months after the first. Due to the overall increase in malignancy, it is reasonable to recommend that patients with DC be vaccinated with the HPV vaccine. Vaccination has the greatest benefit if completed prior to becoming sexually active.

In the event of an abnormal Pap smear, established guidelines for colposcopy and HPV testing direct treatment.[9] Patients with an abnormal Pap smear undergo a procedure called colposcopy, whereby a gynecologist takes a closer look at the cervix and biopsies any areas that appear abnormal. At the time of colposcopy, the vagina and vulva are inspected for other lesions, which, if noted, are routinely biopsied, as well. Any biopsy finding of moderate dysplasia or worse warrants treatment. Counseling regarding safe sex practices may help limit exposure to sexually transmitted infections and is important given the impaired immune response in many women with DC.

Screening for and early detection of squamous cell abnormalities like precancer enable less invasive and successful treatment. The current recommendation for women is to start yearly comprehensive gynecologic exams when they become sexually active or by age 21.[9,10] It is reasonable to recommend that women with DC have a yearly Pap smear to screen for cervical cancer.[11] Additionally, after HCT, annual cytology testing is advised. HPV testing can be done at the same time as a Pap smear.

Management of gynecologic issues during HCT

HCT may be used for DC-related bone marrow failure (aplastic anemia). Excessive menstrual bleeding in the setting of severe

thrombocytopenia (very low platelets) or bone marrow failure warrants management with hormonal therapy in addition to platelet support.

Assessment with a complete blood count and pregnancy testing are important. Ultrasound is helpful to exclude other causes of bleeding, including fibroids, cysts, or polyps. Mild to moderate menstrual bleeding can usually be controlled with low dose combined oral contraceptives (35 mcg or less of ethinyl estradiol combined with a progestin). High dose estrogen decreases the risk of endometrial atrophy (thinning of the lining of the uterus), but can lead to excessive bleeding with long term use.[12,13]

A review of 33 patients seen for excessive menstrual bleeding during the transplant period showed hormonal therapy eliminated symptoms in 97% of patients. Of these women, a single oral contraceptive regimen was effective in 79%.[12] Low dose contraceptives can be given via transdermal patch, especially in women with poor oral tolerance and elevated liver enzymes. In cases of severe bleeding, high dose oral contraceptives containing 50 mcg or higher of ethinyl estradiol, or injectable estrogens (intravenous premarin 25 mcg every 6 hours for 24 hours) can be used. Higher doses are maintained until bleeding stops and then treatment is switched to a form of medication that can be continued

long-term, such as low dose combined oral contraceptives or leuprolide acetate.[12,14]

Leuprolide acetate is one of another class of medications called gonadotropin releasing hormone (GnRH) agonists. It is given by intramuscular injection and has been shown to be effective in suppression of menses in women undergoing transplant.[12,15-17] Injections may, however, be relatively contraindicated in some patients with severe thrombocytopenia because of the risk of bruising or bleeding at the injection site. Patients using leuprolide acetate who experience intolerable hypoestrogenic side effects such as hot flashes or vaginal dryness may benefit from additional treatment with hormone replacement, such as low dose combined oral contraceptives or progestins.

After HCT, annual cytology testing is advised because of increased risk of HPV-related disease, including genital tract squamous cell cancers.[2,3] This risk may be increased because of the loss of antibody titers after transplant, impaired immunity as the immune system is reconstituted, or the use of immunosuppression to prevent graft-versus-host disease.

Vaccination or revaccination for HPV should be considered as an additional strategy to decrease the risk of HPV-related neoplasia. Second cancers may arise after HCT, because of viral reactivation or because the patient has other risk factors for cancer.[2,3]

Fertility and pregnancy complications

Fertility has not been comprehensively studied in women with DC. A preliminary report, looked at fifteen females with DC compared to unaffected relatives and healthy unrelated volunteers. All eight women with DC who were post-pubertal underwent menarche at the same age as the general population[18].

Females with DC had significantly lower levels of anti-mullerian hormone, a marker of ovarian reserve, than both unaffected relatives or healthy unrelated volunteers. Three of eight (37.5%) had been pregnant, and only one in the cohort had experienced infertility, indicating women with DC can conceive and have children.

Women with DC are at increased risk of pregnancy complications. Some will require transfusion because of low platelet counts. Androgens, commonly the synthetic anabolic steroid oxymetholone, may be used to treat cytopenias in DC. These medications should be stopped if a patient becomes pregnant, as they can cause masculinization of the fetus. Bone marrow failure may worsen during pregnancy.

A maternal-fetal medicine specialist should monitor the prenatal health of the baby and mother. It is unknown whether bone

marrow failure that worsens during pregnancy will resolve after delivery.

Menarche

Most females begin menarche (first menstrual cycle) between the ages of 11 and 16 years, approximately three years after thelarche, or when the breast buds develop. Pubertal delay may occur in the face of bone marrow failure syndromes, chronic disease, after HCT, and if one is underweight. Sufficient body mass and endocrine hormonal signaling are required to begin menarche. Hormonal signaling can be interrupted by chronic illness, or medications such as oxymetholone. If menses does not occur within 3 years after breast buds develop or by age 16, evaluation by an adolescent medicine specialist or pediatric endocrinologist is warranted.

Menopause

In the general American population, the average age of menopause is around 51 years, and ranges anywhere from 40 to 61. There are limited data regarding timing of menopause in women with DC. Women without DC who have telomere shortening appear to be at higher risk of premature ovarian insufficiency.[4] Additionally, women with DC who are taking androgens may not easily recognize when they are experiencing menopause.

Radiation and chemotherapy of HCT may induce premature ovarian insufficiency, defined as menopause before age 40. Women with premature ovarian failure who do not use hormone replacement therapy (HRT) have increased rates of illness and death compared to women treated.[14] Hormone replacement may also help them feel more like their peers and maintain psychological and sexual health. Prior to age 35, these women may benefit from combined ethinyl estradiol (at least 30 mcg) and progestin contraception pills to maintain sexual function and enable development of peak bone density. Another option, especially in women over 35, is HRT, which usually contains lower amounts of hormones than contraceptive preparations.

Cancer treatment and fertility

Any woman undergoing cancer treatment or HCT will benefit from discussion with the care team about the potential effect of their regimen on fertility. In some cases, fertility preservation techniques may be possible prior to initiating therapy.[19,20] This process requires seeing a reproductive endocrinologist or fertility specialist. There are other options to consider as well, including egg donation, surrogacy, and adoption. Some patients may wish to use fertility methods, such as *in vitro* fertilization, which allow for

genetic testing of the embryos. Pre-implantation genetic diagnosis (PGD) is discussed in Chapter 5.

Breast cancer

There are currently no published reports of increased risk of breast cancer in women with DC. Therefore, breast cancer surveillance can conform to recommendations for otherwise healthy women, which includes mammograms and breast exams annually starting at age forty.[21]

Future research

Although the understanding of DC has grown tremendously in the past decade, there is still need for further work. Main areas of research include characterizing the obstetric and gynecologic health of women with DC and understanding the relationship between DC and cancer in women. Further information is also needed on the safety and immunogenicity of HPV vaccination in women with DC.

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Chapter 20:
Neuropsychiatric Complications in Dyskeratosis Congenita

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Telomeres and psychiatric disorders

There is significant research interest in the role of telomeres in psychiatric disorders. Cross-sectional studies have identified associations between shorter blood or buccal cell telomere length and psychiatric diagnoses such as major depressive disorder[1,2], bipolar disorder[2], schizophrenia[3], and post-traumatic stress disorder (PTSD) in adulthood following childhood trauma[4].

One study found reduced levels of lymphocyte telomerase in individuals with schizophrenia[5]. Shorter germline telomeres were also noted in subjects with significant psychosocial stress, such as adult caregivers of the chronically ill[6], women who have experienced domestic violence[7], and in chronically institutionalized children from Romania[8].

There is some suggestion that cumulative number of stressors may have a differential impact on later telomere length[9]. Stress-induced hypothalamic-pituitary-adrenal axis activation may play a

role in mediating the relationship between stressors and shortened telomeres[10], as cortisol is known to reduce telomerase activity.

Most of the above studies evaluated telomere length in peripheral blood leukocytes, which may not correlate with telomere length in other cells. A study of telomere length in cortical neurons showed no difference between patients with major depressive disorder and control subjects[11], while another study looking at cerebellar neurons demonstrated no link between telomere length and serious psychiatric illness[12]. It is important to note that in studies demonstrating telomere length association between cases and controls, the differences may be statistically significant, but are still relatively small when control telomeres are compared to the markedly short telomeres of dyskeratosis congenita (DC).

Thus, it remains unclear whether short telomeres predispose patients to develop certain neuropsychiatric conditions, or that telomere shortening is a downstream consequence of the physical effects of psychiatric symptoms and stress. Alternatively, telomere shortening in the face of neuropsychiatric conditions may be expressions of a common biological insult.

Neuropsychiatric disorders and DC

There are limited data on the relationship between DC and

neuropsychiatric conditions. Most individuals with DC have normal intelligence and achieve normal developmental motor milestones, although severely affected individuals may not. Developmental delay is present in two subtypes of DC: Hoyeraal Hreidarsson (HH)[13,14] and Revesz Syndrome[14,15]. Like classic DC, these disorders are characterized by the mucocutaneous triad described in Chapter 3.

In addition, Revesz syndrome is remarkable for bilateral exudative retinopathy and intracranial calcifications. Immunodeficiency is seen in HH, and changes reported in neuroimaging, including cerebellar hypoplasia or atrophy, small brainstem, thin corpus callosum, and cerebral calcifications, may be confused with TORCH syndrome, caused by a group of neonatally acquired infections (Toxoplasmosis, Other, Rubella, Cytomegalovirus and Herpes infections).

There are relatively scant data about psychiatric illness in patients with DC. Two case reports describe schizophrenia in these patients[16,17], and a study of six pediatric and eight adult patients with DC or DC-like conditions demonstrated a relatively high incidence of some form of neuropsychiatric disorder (Table 1)[18].

Lifetime prevalence of any psychiatric disorder was 83% in pediatric and 88% of adult subjects, much higher than the 25% for children[19] and 38% in adults[20] commonly reported among the

Table 1: Lifetime prevalence of neuropsychiatric disorders in patients with DC and DC-like conditions (derived from Rackley et al, Psychosomatics. 2012;53(3):230-23)

	Children		**Adults**		**All subjects** (n=14)
	DC (n=3)	DC-like (n=3)	DC (n=7)	DC-like (n=1)	
Any Primary Psychiatric Disorder	2	1	5	1	9 (64%)
Mood disorders	2	1	3		6
Anxiety disorders			2	1	3
Psychotic disorder				1	1
Adjustment disorder			2		2
Any Neurocognitive Disorder	1	2	2		5 (36%)
PDD			1		1
Learning disorders	1	1			2
ADHD	1	1			2
Intellectual Disability			2		2
Any DSM-IV TR Diagnosis	2	3	6	1	12 (86%)
No DSM-IV TR Diagnosis	1		1		2 (14%)

Abbreviations: DSM-IV TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; ADHD, Attention Deficit Hyperactivity Disorder; PDD, Pervasive Developmental Disorder

chronically ill of the general population. Subjects had a wide variety of psychiatric concerns, but mood disorders were the most common. Neurodevelopmental diagnoses such as attention deficit hyperactivity disorder (ADHD), intellectual disabilities, learning disabilities, or autism spectrum disorder were also very common in this sample, with half of pediatric subjects and a quarter of adults carrying at least one of these diagnoses.

It is worth noting that common treatments for DC, including androgen therapy and preparatory regimens for bone marrow and stem cell transplant, can precipitate or exacerbate psychiatric illness. As discussed more fully in Chapter 23, psychosocial sequelae of DC could also be associated with developing psychiatric problems. Living with a chronic illness that predisposes to the development of various cancers places additional psychological burdens on patients with DC and their families. Patient concerns arising from timing of diagnosis disclosure and management of aggressive treatments, such as bone marrow transplant, may initiate or aggravate pre-existing psychiatric symptoms.

Recommendations for patients with dyskeratosis congenita

Routine screening for neuropsychiatric conditions and referral to specialty mental health services as indicated may be a particularly

important component of comprehensive clinical care for patients with DC. The physiological and psychological impact of DC and its treatments can magnify underlying risks for development of psychiatric illness. Providers caring for DC patients should include, at a minimum, a check-in about emotional symptoms at each routine visit. A referral list of local mental health providers should be maintained for patients who would benefit from further evaluation or treatment.

The relatively frequent finding of intellectual disabilities, autism spectrum and other learning disorders in this patient population suggests a need to routinely monitor children with DC for problems in academic performance and achieving developmental milestones. For those patients with identified concerns, early neuropsychological assessment and close collaboration with support at the child's school can help guide academic and therapeutic interventions.

Future directions

Patients with DC may be a key population in which to study potential links between telomere biology and brain disorders. Longitudinal studies could help clarify the association between telomere shortening and psychiatric illness. Genotype-phenotype correlations between genes mutated in DC and neuropsychiatric

disorders may also yield important information on the contribution of these genes to neurodevelopment.

Conclusion

People living with DC have a higher risk for psychiatric illness and developmental disorders compared with the general population, and thus careful screening for these issues is indicated. Further study of this population has the potential to yield significant insights into the pathobiological connections between telomere biology and development of neuropsychiatric conditions.

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Chapter 21:
Cancer in Dyskeratosis Congenita

Blanche P Alter, MD, MPH, and Sharon A Savage, MD

Introduction

Dyskeratosis congenita (DC) is an inherited bone marrow failure (BMF) syndrome, which is associated with an increased risk of cancer. Most of the information in this chapter comes from reports in the medical literature published from 1910 through June 2014. There were 775 cases with sufficient data to determine whether they had or had not had cancer, and thus qualitative information about the types of cancer which occur in DC may be reasonably correct.

However, quantitative determination of the magnitude of risk, the relevant ages, and prior medical histories must be considered to be only approximations. Some of the reports did not include details, and thus all are subject to biased reporting. That is, cases with adverse events such as cancer may have been reported, but cases without such outcomes may not have been reported. Hence, information about cancer may present a picture that appears more dismal than reality. There are several aspects of being "cancer-

prone" which will be addressed here: development of cancer at unusually young ages, at higher frequencies than in the general population, and unique types of tumors.

Frequency of cancer in DC

Vulliamy et al suggested in 2006 that the crude rate (number of cancer cases divided by the total number of DC patients evaluated) of cancer in DC was around 10%.[1] We reviewed the literature from 1910 through 2008 and found reports of cancer in 52 of 552 patients, a similar crude rate of 9.4%.[2] Our updated review of the literature through July 2014 identified 775 DC cases, 60 with cancer, a slightly lower crude rate of 7.7%. Use of the crude rate to assess cancer incidence is misleading because it does not account for the ages at which the cancer occurs. Further, the total number of DC cases reported may be largely young children whose cancer risk has yet to be or may never be expressed, leading to an artificially low calculated cancer rate.

The literature cases without and with cancer are summarized in Tables 1 and 2, at the end of the chapter. There were 69 cancers among 60 cases; five had 2 cancers and two had 3 cancers. Eight patients (13% of those with cancer) were reported in whom the diagnosis of cancer preceded the diagnosis of DC by 6 months to 12 years; most of those cancers were head and neck squamous cell

carcinomas (HNSCC). This observation suggests that surgeons who deal with HNSCC need to keep DC in mind when they see an atypically young patient. Overall, the median age of HNSCC in the literature cases of DC was 32 years of age, compared with a median of 62 years in the general population. This pattern of early onset of cancer is consistent in most of the cancers listed in Table 2.

Two patients were reported to have developed cancer following hematopoietic cell transplantation (HCT). A male diagnosed with DC at age 10 years developed aplastic anemia by age 30, received a bone marrow transplant from his brother at age 33, and had rectal cancer at age 34.[3] A female was diagnosed with DC at age 17, developed BMF and was transplanted with bone marrow from a sibling at age 27, and was found to have metastatic stomach cancer at age 31.[4]

Half of those (the median) without cancer were diagnosed with DC by age 13 years, while in those with cancer the median age at diagnosis of DC was 25 years. The literature cases at the time of the report were older at the time of report among those who had cancer compared with those who did not (Table 1). This would seem to suggest that those with cancer live longer than those without, when in fact it indicates that young patients with DC have a high risk of early death because of aplastic anemia or complications of HCT.

Older patients may not have been diagnosed with DC until they developed cancer, as mentioned above.

The cumulative incidence of any cancer compared with age is shown in Figure 1, right, using the data derived from the 775 cases of DC in the literature. Most cancers, except leukemia and retinoblastoma, did not begin to appear until teenage and beyond. We had performed a similar analysis of the 50 patients in the NCI DC cohort up to 2008 (www.marrowfailure.cancer.gov), and reported the annual hazard rate and cumulative incidence of severe BMF, solid tumors, and leukemia in a competing risk analysis, in which each of the outcomes was the first event to occur.[5] Severe BMF was present at a rate of about 1% per year throughout childhood, but then increased to as high as 10% per year by age 50. Solid tumors rose to about 1.5% per year between ages of 5 to 40, and leukemia was rare. The cumulative incidence of BMF was close to 60% by age 50. Comparable to the literature data in Figure 2, the NCI cohort data in Figure 2, right, had a similar cumulative incidence of solid tumors. The literature incidence was 30% by age 50, and the NCI cohort incidence was 20% by the same age. These observations suggest that patients with DC develop cancer at ages younger than the general population.

An additional analysis was done with the data from the NCI cohort study, looking at the relative risk of cancer compared with

the general population (Table 3). The number of cases observed to have specific cancers was compared with the numbers expected

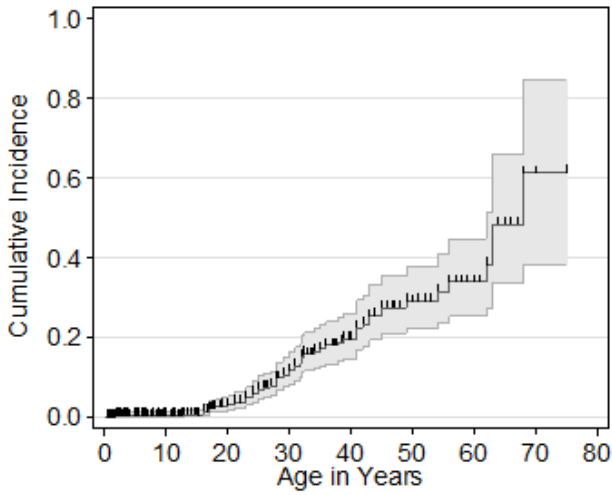

Figure 1: Cumulative incidence of cancer among 775 patients with DC reported in the literature. The median age was 67 years. Patients were censored at death; vertical lines indicate patients alive who had not developed cancer.

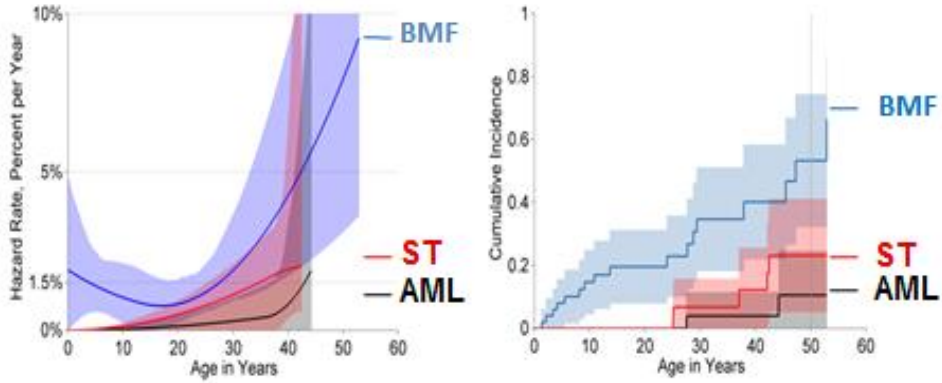

Figure 2: Annual hazard and cumulative incidence of competing adverse events in patients with DC in the NCI cohort through 2008. Shaded areas are the 95% confidence intervals. BMF, bone marrow failure. ST, solid tumor. AML, acute myeloid leukemia. From Alter el at.[2] ***For color version see Color Photos Appendix***

after taking into account age, sex, race, and birth cohort.[5] Cancer at all sites was increased by 11-fold, solid tumors by 8-fold, HNSCC (which was tongue cancer in all cases) by 1154-fold, and leukemia 196-fold. Other types of cancer were not significantly increased or even seen, perhaps due to the small size of the cohort, which had only 50 patients at that time. These numbers indicate that the relative risk of cancer in DC is increased well beyond that seen in the general population.

Types of cancer in DC

The types of cancers reported in patients with DC are summarized in Figure 3, right, and Table 2. Forty percent of the cancers were HNSCC, 12% stomach, and 10% each were anorectal and skin, mostly squamous cell carcinomas (SCCs). Liver was reported in 3, and lung, esophagus, and Hodgkin disease in 2 patients each. Single cases shown in Table 2 could have occurred by chance alone. All cancers except lung and lymphoma occurred at ages much younger than expected in the general population, reinforcing the concept that DC is a cancer-prone disorder.

The majority of the cancers in DC were solid tumors. However, there were 5 cases of leukemia in the literature reports. One was a 2 year old with acute lymphocytic leukemia (ALL), while the others had acute myeloid leukemia (AML) and were 28, 29, 30 and 40

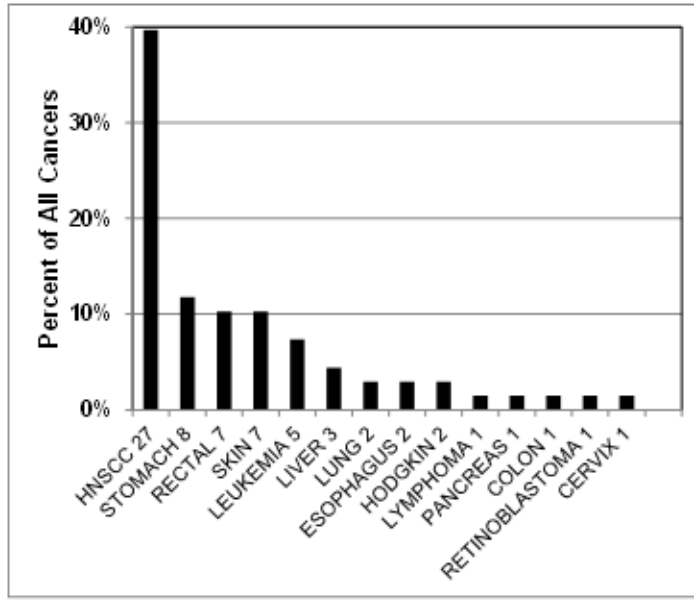

Figure 3: Distribution of types of cancer in patients with DC reported in the literature, 1910-2014. Data represent the percent among 60 patients who had any type of cancer; numbers are the actual number of patients with each cancer.

years old. ALL is the most common type of leukemia in children in the general population, while AML is seen in adults; both are rare in the 20-40 year old range. Myelodysplastic syndrome (MDS) was reported in 8 patients with DC with a median age of 30 years, and NCI cohort data indicated a relative risk of more than 1000-fold compared to the general population. MDS is not called a "cancer"

in this chapter, but it is considered to be on the pathway to leukemia in many patients.

Cancer prevention and surveillance

Strategies for surveillance and prevention of cancer are summarized in Table 4. Screening for HNSCC involves good oral examination during dental visits, and nasolaryngoscopy by a specialist in head and neck cancer (usually a subspecialty of ear, nose and throat physicians). We did not find any evidence to support involvement of the human papilloma virus (HPV) in HNSCC tumors in patients with DC.[6]

However, the HPV vaccine is recommended for all individuals (in the USA, males and females ages 9-26), and may play a role in prevention of the gynecologic and anorectal cancers that have been reported in DC. Patients with DC respond normally to HPV vaccine.[7] Certainly, annual physical examinations of the relevant areas are important for both women and men, with HPV testing of gynecologic specimens. Thorough dermatology examinations should be performed annually, as should routine blood tests for blood counts and liver function. Tests may also include bone marrow aspirates and biopsies, and lung function. The frequency of all examinations and tests should be at least annually, and more often if abnormalities are identified.

Individuals with DC should not smoke or drink alcohol. Limited sun exposure is highly recommended. Good oral hygiene is also important. Beyond that, any abnormality that might be cancer should be examined by an expert, and biopsies done at the first sign of anything abnormal. For example, oral leukoplakia, which is one component of the DC diagnostic triad, may evolve into cancer. Thus, any changes should be brought quickly to the attention of a physician or dentist.

Treatment of cancer in DC

There are very little data on the treatment of cancer in patients with DC. Consequently, early detection is very important. Many cancers can be completely surgically removed if they are small and have not metastasized (spread to other parts of the body). Patients with DC appear to be more sensitive to complications from treatment doses of radiation used in cancer therapy compared to the general population (see Chapter 22). The side effects of chemotherapy may also be more pronounced in patients with DC. It is important that people with DC who develop cancer work very closely with their medical providers to develop optimal treatment plans.

Summary

Patients with DC meet the criteria for "cancer-prone" as outlined in the first paragraph: most of the cancers present at ages younger than expected, occur at frequencies higher than predicted, and are of unusual types for individuals of those ages. The major solid tumors are HNSCC, stomach, anorectal, and skin. In addition, AML is more common than ALL in these patients despite their relative youth, and MDS is increased in frequency. DC belongs among the cancer-prone inherited bone marrow failure syndromes, and prevention, surveillance, and early diagnosis are critically important.

Tables on next page

Table 1: Cases of Dyskeratosis Congenita in the Literature, 1910-2014

Features	All Cases	Cases without Cancer	Cases with Cancer	p value, with vs without Cancer
Numbers	775	715	60	
Male:Female	553:215 (2.6)	507:201 (4.0)	46:14 (3.3)	0.5
Median age at DC diagnosis (range), years	14 (0-75)	13 (0-75)	25 (0.9-58)	<0.01
Median age at cancer diagnosis (range), years			29 (1.5-68)	
Median age at last report, alive (range), years	16 (0.3-75)	15 (0.3-75) N = 517	32 (2-42) N = 29	<0.01
Median age at last report, dead (range), years	19 (1-70)	15 (1-70) N = 173	32 (2-70) N = 31	<0.01

Table 2: Types of Cancer in Dyskeratosis Congenita in the Literature, 1910-2014

Cancer Type	Number of Cancers	Male:Female	Age at Cancer	Age at Cancer in General Population*
All sites	69 in 60 cases	46:14	29 (1.5-68)	66
All solid tumors	64 in 56 cases	44:12	32 (1.5-68)	66
HNSCC	27 in 25 cases	18:7	32 (16-54)	62
Stomach	8	6:2	29 (16-65)	69
Anorectal	7	7:0	23 (16-52)	60
Skin	7	5:2	21 (13-45)	68
Liver	3	3:0	32 (17-63)	63
Lung	2	2:0	56, 68	70
Esophagus	2	2:0	25, 41	67
Hodgkin	2	2:0	23, 28	39
Non-Hodgkin lymphoma	1	1:0	43	66
Pancreas	1	1:0	29	71
Colon	1	1:0	25	68
Retinoblastoma	1	1:0	1.5	2
Cervix	1	0:1	31	49
Leukemia (4 AML, 1 ALL)	5	2:3	29 (2-40)	66
MDS	8	8:0	30 (8-70)	70

Table 3: Relative Risk of Cancer in DC

Cancer Type	Number observed (O)	Number expected (E)	O/E ratio
All sites	7	0.6	11*
All solid tumors	5	0.5	8*
HNSCC	3	0	1154*
Cervix	1	0.02	43
Non-Hodgkin lymphoma	1	0.03	34
Skin basal cell	1	NA	NA
Leukemia	2	0.01	196*
MDS	5	0	2663*

*p<0.05, i.e. statistically significant. From Alter et al.[2]

Cancers were in patients who had not received a stem cell transplant. The observed number of cancers was compared with the expected number in the general population (O/E ratio) based on SEER, after adjustment for age, sex, race, and birth cohort (www.seer.cancer.gov).

Table 4: Cancer screening and prevention methods to consider for patients with DC. These recommendations are based on expert opinion and not on clinical trials of DC.

Cancer	Start Age	Screening Method	Prevention
HNSCC	10	Oral exam, nasolaryngoscopy	No smoking or drinking alcohol. Good oral hygiene
Gynecologic	16 or menarche	Gyn exam, pap smear, HPV test	HPV vaccine
Rectal	12	Physical exam, stool blood	
Esophagus	~20	Esophagoscopy	
Liver	Infancy	Liver enzymes, ultrasound	No drinking alcohol; chelate iron if transfused
Skin	Infancy	Dermatology exam	Sun protection
Leukemia	Infancy	Complete blood counts, bone marrow aspirate, biopsy	
Lung	40	Chest X-ray, lung function tests, as clinically indicated	No smoking
Other	At symptoms	Depends on symptoms	

Patients with DC should also follow the same cancer screening recommendations as the general population. More information is at http://www.cancer.gov/cancertopics/screening

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Chapter 22:
Radiation and Dyskeratosis Congenita

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Introduction

Patients with dyskeratosis congenital (DC) have abnormalities in telomere biology genes,[1] resulting in problems with their telomeres. These structures reside at the end of chromosomes, and are particularly sensitive to DNA damage caused by radiation and oxidative stress. Consequently, when compared to the general population, patients with DC may be more sensitive to the effects of both ionizing and non-ionizing ultraviolet radiation.[2]

When therapeutic or interventional radiation is being considered for patients with DC, precautions should be taken to prevent or minimize harm. It should be noted that there are very little data on radiation in these patients; there is still much unknown. This chapter reviews the types of radiation that may be of clinical importance in DC.

Types of radiation

Ionizing radiation is radiation that can pass through the body. It carries enough energy to liberate electrons from atoms, creating ions, which can in turn damage DNA and cause cell death. Examples include diagnostic medical X-rays and gamma rays .

Diagnostic radiation, such as X-rays used in bone density scans, radiography, diagnostic fluoroscopy, computed tomography (CT), and gamma rays used in single photon emission tomography (SPECT), and positron emission tomography (PET), typically use very low levels of ionizing radiation. Interventional radiation is sometimes used in interventional radiology, cardiology, and operating room procedures, and use moderate levels of X-ray ionizing radiation. Therapeutic radiation involves higher doses of ionizing radiation, including X-rays and gamma rays, and is designed to treat cancer or prepare a patient for hematopoietic stem cell transplant (HCT).

Ultraviolet radiation consists of light rays slightly more energetic than the color violet, and can excite electrons to move to a higher energy state. However, such radiation does not carry enough energy to produce charged ions, that is, it is "non-ionizing" when it strikes matter. For protection from ultraviolet radiation, patients with DC need to avoid tanning beds and take precautions to

minimize sun exposure as much as reasonably practical (see also Chapter 10).[1]

Ultrasounds (sonograms) and magnetic resonance imaging (MRI) do not use radiation, and are not considered in this chapter.

Effects of radiation

There are two types of radiation effects – tissue reactions and stochastic effects.

Tissue reactions

Tissue reactions are defined as those that cause cell death or an injury in populations of cells. The type of tissue reaction is based on the dose of radiation, sensitivity of the specific tissue type exposed, and the individual's underlying sensitivity to radiation. There is a threshold dose to producing a tissue reaction such that there are doses below which there is no reaction, and above which the severity of the tissue reaction increases as the dose increases.[3]

Therapeutic radiation (generally thought of as higher-dose radiation) is used to create a tissue reaction in order to kill cancer cells. It is also used as part of HCT preparation regimens to eliminate the patient's bone marrow cells so they can receive the donor's cells. Tissue reactions can also occur in healthy tissue near the area of the body targeted by therapeutic radiation. Very rarely,

tissue reactions occur when using moderate dose interventional radiation as part of a procedure that requires X-rays to see inside the body.

Stochastic effects

Stochastic effects of radiation might occur years after exposure to ionizing radiation. They can be thought of as the long-term consequences of radiation exposure. It is often difficult to know whether stochastic effects are caused by radiation or by chance. Stochastic effects generally refer to the occurrence of cancer in an individual who received radiation therapy, or to DNA damage occurring after radiation.[3] The risk of cancer is believed to increase with increasing radiation dose.

Therapeutic radiation

Patients with DC appear to have a lower threshold for tissue reactions than non-DC patients when exposed to therapeutic radiation.[1,4,5] However, detailed studies of ionizing radiation in DC have not been conducted to better define these lower thresholds. Even though tissue sparing techniques like proton therapy show promise,[5] more studies are needed to better determine optimal use of therapeutic radiation for cancer in patients with DC.[1] HCT protocols for patients with DC are being developed that use

reduced intensity total body irradiation,[6] or none at all (see also Chapter 8, HCT for DC).[7]

Diagnostic radiation

Diagnostic radiation (low dose radiation) is used for diagnostic imaging. This type of radiation includes X-rays used in mammography, bone density scans, radiography, diagnostic fluoroscopy, computed tomography (CT), and gamma rays used in nuclear medicine (NM) studies, including single photon emission computed tomography (SPECT) and positron emission tomography (PET). The doses used in diagnostic procedures are far too low to cause tissue reactions, but could cause stochastic effects in certain populations of patients.

Diagnostic radiation doses are often measured in relation to natural background radiation (see Table). For diagnostic imaging, the chances of stochastic effects are so low that they cannot be measured in an individual patient, but are estimated for patient populations. Although there are recent studies showing a slight increase in cancer rates from pediatric CT scans,[8,9] these studies are not without criticism.[10] The scientific consensus is that the effects are very small, and possibly not significant,[11] but the radiation safety community errs on the side of caution and assumes there is an affect for radiation safety purposes. Although patients with DC

might be more sensitive to stochastic effects from ionizing radiation than the general population, the doses required for diagnostic purposes are very low, and clinically indicated exams should be performed when needed.

Summary

Radiation exposure of patients with DC should be managed proactively. They are not as sensitive as those with ataxia telangiectasia (a condition most radiologists are familiar with) and they may or may not be as sensitive as individuals with Fanconi anemia. Patients with DC are more sensitive to therapeutic radiation (high dose radiation) than the general population, but the degree of this sensitivity has not been established. Clinically indicated diagnostic examinations (low dose radiation) should be performed as needed for optimal patient care while taking into consideration that the DC patient population might be more sensitive to the radiation effects.

Table 1. Patient dose from diagnostic X-ray exams[12,13] compared with natural background radiation to provide context. Background radiation dose varies from 1 to 10 mSv per year[11] depending on where one lives.

Diagnostic Exam	X-ray Dose	Amount of Time to Receive Similar Dose from Natural Background Radiation
Knee X-ray, Dental X-ray	0.005 mSv	4 hrs – 44 hrs
Dental panoramic X-ray	0.01 mSv	9 hrs – 3 ½ days
Bone Density Scan	0.015 mSv	13 hrs – 5 ½ days
Chest X-ray	0.02 mSv	18 hrs – 7 days
Lumbar spine X-ray	1.5 mSv	2 months – 20 months
Head CT	2 mSv	2 ½ months – 24 months
Chest CT	7 mSv	8 months – 7 years
Abdomen/Pelvis CT	14 mSv	17 months – 14 years

Abbreviation: millisievert (mSv), a measure of the effective dose of radiation. Effective dose is used to estimate stochastic risk in patient populations.

Table 2. Summary of Chapter Terminology

Types of Radiation	
Ultraviolet Radiation	• Ultraviolet (UV) light (UV radiation) is invisible to the human eye. It is not energetic enough to ionize atoms and is therefore considered non-ionizing radiation. It can, however, damage overexposed skin. • A beneficial effect of UV radiation exposure is vitamin D production in the body. • UV radiation comes from the sun and is filtered by the atmosphere. UV radiation is also produced by electrical arcs (like welding), tanning lamps, and blacklights.
Ionizing	• Ionizing radiation is powerful enough to remove electrons from atoms (ionize atoms), which can

Radiation	damage DNA and cause cell death. • Ionizing radiation can cause tissue reactions and stochastic effects (see below). • Most cosmic ionizing radiation is absorbed by the atmosphere. • Diagnostic, interventional, and therapeutic radiation in medicine eases pain and saves lives.
Patient Exposure to Ionizing Radiation	
Background Radiation	• Low dose radiation. • Background radiation comes from the sky, the soil, and what we eat. We naturally live in a bath of radiation.
Diagnostic Radiation	• Low dose radiation. • Medical uses include X-rays and gamma rays. • Ionizing radiation is used to see inside the body to aid with important diagnosis and monitor function. • Stochastic effects might occur from diagnostic radiation. • Patients with DC might be more sensitive to stochastic effects than the general population, but not so sensitive that clinicians should avoid clinically appropriate diagnostic imaging.
Interventional Radiation	• Moderate dose radiation. • Ionizing radiation is used in minimally invasive procedures to see inside the body while performing treatments or surgeries. • Very rarely, radiation levels exceed a threshold where tissue reactions occur. • Based on what has been observed from therapeutic radiation, there is reason to believe that tissue reactions might occur at a lower threshold than in the general population for interventional radiation.
Therapeutic Radiation	• High dose radiation. • The purpose of therapeutic radiation is to create controlled tissue reactions as part of a clinical protocol.

	• Examples where this type of radiation is used include cancer therapy and total body irradiation for hematopoietic stem cell transplants. • Case studies of cancer therapy in patients with DC have shown that tissue reactions occur in non-cancerous tissue at lower doses than the general population. Total body irradiation is more toxic to these patients, which has led to the development of reduced intensity or elimination of radiation in conditioning in hematopoietic stem cell transplant protocols.
Stochastic Effects	• Effects that can occur by chance, especially malignancies or genetic mutations. The probability of occurrence increases with radiation dose, but the severity is independent of dose. • There is no threshold; severity of effect is not dose-dependent.
Tissue Reactions	• Injury in populations of cells or cell death. • There is a threshold dose. Once above the threshold, the severity of the reaction increases as dose is increased.

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Chapter 23:
Psychosocial Issues of Dyskeratosis Congenita

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DC is part of my life, but DC does not define me.
—Young adult with Dyskeratosis Congenita

A diagnosis of dyskeratosis congenita (DC) comes with complex concerns. Living with a rare diagnosis whose course is unpredictable is filled with layers of uncertainty. It is a challenge that places many people with DC on an uncharted path with few fellow travelers. The growing knowledge base afforded by a committed cohort of scientists and clinicians affords hope and the promise of greater potential for the treatment and management of DC.

Depending on one's coping style, adapting to an illness with multiple, varied manifestations can create unprecedented anxiety. Not knowing what the road ahead holds can be immobilizing and can create self-imposed limitations. DC is in the family of inherited bone marrow failure disorders, so the potential need for hematopoietic cell transplantation looms, as does the potential later development of cancer.

In addition, there is the possibility of pulmonary fibrosis. As an illness with concerns for the future, coping with DC means learning to adapt to those possibilities. Part of coming to terms with DC means acquiring the knowledge to manage the illness, and not having the illness manage the patient.

While there are visible components to DC, there are also issues that are less apparent. When families facing DC are brought together, one hears the subtext: regardless of what is shared, there are also so many differences. Each person's story will not be same. DC often presents with a unique illness course, which adds to its emotional complexity. There can be comfort in the differences as well. Uncertainty is cumbersome emotionally, but it also holds hope as one of its components.

The emotional journey

When I was diagnosed, I wished it was breast cancer, because it would be something people knew, understood, and for which there were specific treatments.

—Adult with DC

Although all life-threatening illnesses can cause an individual or family to feel isolated, isolation is more prevalent with less-prevalent diagnoses. There is often no societal support for rare diseases. The creation of illness-specific organizations can

dramatically change one's experience of the illness. Dyskeratosis Congenita Outreach serves that role for families affected by DC.

There are many coping styles that develop as an individual goes through life with a chronic, life-limiting illness. One can be proactive, coping assertively by choice. For example, one can choose to compensate for limited knowledge about DC by seeking out all possible relevant medical information. This style does not work for everyone. Some people choose to know less, managing things as they happen, while others may try to ignore the illness altogether.

The type of information seeker one is will influence how one proceeds to gain knowledge about DC and what one does with that knowledge. In illnesses that are more common, even a passive person can be inundated with information from media, colleagues, friends, and family. With information not overly abundant for DC, one has to be willing to seek out knowledge to obtain it.

Part of the barrier of a rare disease is that throughout the journey you always feel alone.

—Parent of a child with DC

It is difficult to understand how the multitude of illness-related factors, or the potential of such issues, impacts the day-to-day emotional well-being and sense of self for an individual with DC.

The rarity of the illness and the wide range of symptoms can make DC difficult to diagnose. For some, symptoms precede the diagnosis for an extended period of time. Knowing that something is wrong but being unable to give a name to it can create uneasiness, loneliness, and an ongoing sense of anxiety. Even after the diagnosis is established, that period of uncertainty may have established a prevailing pattern of coping in response to the illness.

A common challenge of DC is having an illness that is difficult to explain to others. Most people have not heard of telomeres. Telling someone that you have a bone marrow failure disorder with an unusual name, with short telomeres, does not automatically engender resounding support or compassion.

Common questions

How do you describe DC?

When do you introduce DC into a relationship?

What are the implications for the relationship?

What is the best way to enhance a partner's understanding of the disease and its ramifications?

What is the role of involved family members in the illness journey?

Dyskeratosis Congenita Connections

Attending DC camp allowed us to reconnect as a family.

Because it was unknown, people did not know how devastating, even fatal it was.

—Adult with DC

DC is a family affair in every way. The number of affected family members and their ages will affect the emotional profile and needs of a family at any given time. More than one person can be affected, and in some families the illness will span more than one generation. The inheritance pattern of DC presents an emotionally complex story. The fact that both parent and child can be affected at the same time creates multiple layers of mutual concern.

I knew I had what my father had.

—Adult patient with DC

Prior to diagnosis, not knowing what is wrong, but in some cases understanding that you and other family members share similar symptoms, can be unnerving. Alternatively it can cause family members to believe that those symptoms carry less significance as they are present in more than one family member. Implication of the diagnosis is complicated, both for those in the family who are affected and for those who are not.

I have learned that the "non-affected" family members are impacted as much by my diagnosis as I am.

—33 year-old adult with DC

Parents' journeys

When a child is diagnosed with DC, orchestrating the child's medical care, sustaining family life, and managing responsibilities and the family finances, all while maintaining hope, fall to the child's parents. Caregivers must explore and assimilate tremendous amounts of information to stay the course.

Receiving a diagnosis of DC can present an emotional crisis. It takes time before parents can move from shock and disbelief to a more proactive mode of coping.

Many parents feel anxious or depressed upon learning the diagnosis, unsure of what to expect. The ability to contain the anxiety, manage the emotion, make decisions, enjoy life, and continue to function, are all skills to be mastered in a new context.

If a marital relationship was previously stressed, difficulties in the relationship may be further exacerbated by having to also deal with the illness. However, in some situations, couples felt that the strain and magnitude of the issues they faced enabled them to become stronger together. Individual parents may cope differently. One parent may need to learn everything there is to learn to

strategically plan for the future, whereas the other may choose to stay focused in the moment. One parent may need to talk and to cry, while the other may appreciate silence. Differences in coping styles may relate to gender, culture, age, and personality, and should be recognized so that each parent can be supported for his or her strengths, insight, and ability to adapt during the course of the illness.

Depending on the parents' ages at the child's time of diagnosis, or age of an adult newly diagnosed with DC, implications are great with regard to having more children. There are increasing numbers of options with regard to having another child. Growing success and refinement of preimplantation genetic diagnosis (PGD) and surrogacy options present methods that can be used to conceive an unaffected child, one who would be a potential donor for hematopoietic cell transplantation for the child with DC.

Assisted reproduction can be physically, emotionally, and financially draining. Unsuccessful PGD attempts result in delaying having more children and can create other conflicts. This phase can be an emotional one in the life of a family affected by DC, as treatment options, as well as ability to have additional children, stand in the balance. Successful PGD attempts can simultaneously set the course of a family toward having a baby and planning a hematopoietic cell transplantation of the sibling. Whether one has

DC or a child with DC, actively choosing to have a child without it can present an existential experience.

The journey for children with DC

Visible manifestations of the disorder serve as constant reminders to those with DC and to the rest of the world that the individual with DC is different. Whether it is about stature, dysplastic nails, skin, bone marrow failure, or lung disease, it is not always possible to keep DC private. The things that cannot be seen (like low blood counts, fertility issues, liver disease, etc.), though invisible, may dictate many aspects of the life of the person with DC.

Physical and other differences may set children with DC apart from their peers and can be factors that cause children to feel isolated, lonely, or depressed, affecting self-esteem and ability to focus on age-appropriate achievements. Counseling and meeting others in similar situations can be a great benefit during these times. Children also need to feel that they can confide in their parents, their medical team, and important people in their lives when they feel limited physically or emotionally by DC. How parents accept and face the illness will influence how their children with DC develop and adapt to it. If parents can create an environment that allows for dialogue, children will find it easier to

DC parents' advice to families,
2014 DCO family meeting at Camp Sunshine

Dominant themes

Be proactive, advocate wisely.
You are not alone; there are more families like us.
This is a worldwide illness. Don't feel isolated.
Be positive in general and be positive about the future.
Live as normal a life as possible.
Use DCO. It is a great support.

About social support

Find other families with DC and connect with others.
Share your story; it can help others.
Know that others know what you are talking about and are experiencing.
Don't hide things; share the journey.

About living

Take more time with your loved ones.
Enjoy every day.
Focus on making memories with your family and friends.
Remember to enjoy the good days.

Emotional and personal themes

Take care of yourself so you are able to take care of the affected individual.
Do not try to do it all yourself.
Understand that people genuinely want to help; reach out.

Know yourself and when you are taking on too much.
Stand up for yourself and your loved ones.
Listen to your intuition; you are wiser than you may realize.
Relax during the highs so you can weather the lows.
Don't let a diagnosis of DC destroy your life.
Always, always, find the good in things.
Try not to get too discouraged.
Don't let the illness overtake your life.
Ask for strength from a higher power.
Find Help.
Stay Calm.

Medical themes

Get educated and stay ahead of things.
Don't be scared to ask questions.
Research, research, research.
Research physicians to find knowledgeable doctors experienced with DC.
Get another opinion if you are not comfortable with answers you are given.
Follow your gut; don't take no for an answer, if you truly believe that you are right.
Be diligent about staying in tune with the disease process. Know your or your child's lab numbers and trend if things are changing.
Keep medical records organized.
Make sure your or your child's diet is as healthy as possible.

ask their parents questions about their illness and treatment. An open environment will enable children, as they grow, to become more active participants in discussions about DC and its management. This is true whether it is the adult or the child (or both) who has DC.

Children often know much more about DC than adults might realize. They have independent interactions with professionals while in the hospital setting and may overhear information from ambient conversation. They surmise things from the emotional climate around them, and at increasingly earlier ages have access to social media and the Internet. They will ask questions when they want to know, and will often shy away from questions to which they do not want the answers. Children tend to be good regulators of their own knowledge base, providing insights about the things they know and what they want to know.

Children of all ages and stages of illness need to be allowed to continue to grow, regardless of the status of their medical condition. Maximizing the capacity of the child with DC inherently helps everyone in the family. Children living with a life-threatening illness need to be prepared to be successful and motivated in life. Recognition of achievements of all magnitudes, cultivated and applauded at all ages, will enable the development of emotional strength and can support continued growth.

At any age, the school environment may present unique issues for children with DC, because of illness-related short- or long-term absence. Upon entering school, children begin to compare themselves to other children. For the youngest of children, school may be where they learn that not everyone has DC or a family member with DC, not everyone has so many doctor visits, needs blood drawn frequently, or takes medication.

This age becomes a time of further inquiry and therefore presents an opportunity for further understanding. If a child is sick and unable to attend school, or is unable to participate in activities because of physical or stamina limitation, or is perceived as different from peers, the child may begin to feel sad or uncomfortable in a manner not previously experienced.

Children need support in learning how to adapt, respond, and connect with peers around matters related to DC. As school-age children grow, they begin to differentiate themselves from their families and develop increasingly strong relationships with their peers. Physical limitations or medical care (like hematopoietic cell transplantation), may influence a child's social activities and relationships. Children need help finding a balance between social and family relationships in the context of living with DC, allowing them to feel nurtured while gaining a sense of independence.

Development of a child's sense of self and how that relates to illness will be influenced by the age and developmental stage in which they learn of the diagnosis. A frequent concern for parents is what and when to tell children about DC. At each stage of development, children need age-appropriate explanations of the condition and its required treatment. Such information should grow in sophistication as the child grows. Developmentally appropriate explanations and access to information throughout the illness experience enhances the child's ability to understand and deal with DC.

As children get older, they begin to actively participate in decision-making about their care. Parents may feel relief that they are now making decisions with, rather than for, their child. At the same time, they may feel concern about their child's decision-making skills compared with their own.

Some parents express anxiety about how their child will learn to make well thought out, difficult decisions. Of equal concern for parents is whether their child will continue to include them as an integral component of medical care decision-making. Taking care of one's child's illness is a job that no parent ever wants in the first place, yet once proficient at it, is not a job most parents want to give up.

Adolescents

As children with DC mature, they are confronted with age-appropriate challenges of development. Adolescents have the capacity to understand DC in increasing depth and may need assistance integrating newfound knowledge into day-to-day life.

For adolescents, challenging "the system" is age-appropriate and functional, at times facilitating emotional growth. It allows teens to assert themselves as individuals and take responsibility for their actions. Rebelling against the "rules" of DC can be expected, even with the most mild-tempered child, as the child ages into adolescence and young adulthood. Compliance with medical regimens may be incomplete or non-existent and should be given particular attention at this stage. Risk-taking behaviors that relate to peer pressure, including drug and alcohol use, and sex are all components of the adolescent's developmental landscape.

Growing to and through adulthood

Many individuals with DC have lived with the knowledge of their illness since birth or early childhood and continue as young adults to make decisions in collaboration with their parents. Having grown up in a "medical partnership," these youth are accustomed to collaborative medical care.

Growth for the individual with DC can also be a time of growth for other family members. Parents will sometimes need assistance enabling their children to become more responsible for their own care. In turn, parents need to educate and begin to empower their children while learning to trust them and their judgment. As with growth in all facets of life, there can be occasional dissonance between parents and children living with DC. Ultimately parents need to learn to support and appreciate their grown children's choices.

Young adults may find themselves torn between the desire to be proactive about their health and the desire to fit in socially. This struggle can be exacerbated by the complexities of the emotional journey with DC, combined with a sense that life may be on an accelerated path. As people with DC age and medical problems emerge, groundwork set in earlier years enables patients to rely on health care providers for treatment and support.

Finding their own voices, taking responsibility for managing their illness, becoming primary decision-makers, using their parents as partners or consultants, and truly becoming independent, are appropriate and very significant steps for young adults. It is important to help individuals with DC gain independence while helping them understand that they can still rely on their families for assistance, support, and guidance. Medical

partnerships with parents should be well-established before children "age out" of pediatric care. DC impacts the entire family, from the period of diagnosis throughout the course of the illness, and family members need to work together to find the best decision-making strategies for their family.

Becoming a young adult leads to a more comprehensive understanding of DC, along with new intellectual and emotional realizations. Salient issues that may otherwise have been dormant at earlier developmental stages will need to be addressed. Young adults who face the most severe manifestations of DC may, of necessity, remain more physically and emotionally dependent on family members. At each stage, issues of dependence and independence may need to be negotiated.

Growing up with DC while establishing and mastering life goals presents unique challenges. Individuals with DC have to deal with issues of partnership, sexuality, children, and financial and insurance concerns, while managing a complex illness, organizing a variety of medical specialty care, and addressing potential medical risks. An adult with DC who parents a child with DC has to negotiate medical issues and concerns while anticipating and taking care of the child's needs. In this situation, the affected child is exposed to the parent's medical trajectory, leaving open the

question of whether the child will experience a parallel illness course.

Who one is in the world is often amplified by the friendships one creates. Whom do you tell that you have DC, and what and when do you tell them? These are complex issues inherently related to whom you trust, combined with an ongoing evaluation of the relevance of who needs to know, and sense of what will be done with the information.

Each individual must decide how to incorporate DC into the structure of one's life. This issue can frame early stages of relationships with friends, roommates, and romantic partners. When someone who has DC embarks on a relationship, questions emerge about the nature of the illness, as well as the personal implications for the person with DC and the partner. The revealing of DC, "the short version," and then DC, "the long version," becomes a component of the "dating" process.

Partners of individuals with DC may need an outlet for information, expression, and assistance as issues present themselves. Components of DC may be understood intellectually. When the individual's condition worsens, new concerns may emerge for the partner. Negotiating the partner's and parents' caregiver role presents an additional challenge.

Meetings with family members

There are several types of family meetings, some involving only family members and others in which the medical team participates in discussing the illness and treatment choices. In complex rare illnesses such as DC, such meetings can serve to educate and inform family members, garnering both practical and emotional support for individuals facing DC. There is real value in an ongoing dialogue among family members to discuss what is happening medically, and to create mutual support in dealing with DC.

The value in holding a broader meeting and including medical staff is that a wide range of issues and questions can be explored, vastly increasing family members' knowledge about DC, thereby increasing ability to support one another.

The family meeting

We had never met anyone with dyskeratosis congenita before. We both arrived scared and nervous and are leaving excited and hopeful.

—Two parents after the DC Family Meeting at Camp Sunshine

Another type of meeting is the DC Family Meeting at Camp Sunshine (www.campsunshine.org). Dyskeratosis Congenita Outreach, in collaboration with Camp Sunshine, has hosted

biennial sessions since 2010 for families affected by DC. This program serves as a vehicle to educate and support individuals with DC and their families. The retreat blends educational sessions—directed by research and medical experts—with psychosocial support and recreational activities. It has proven to be invaluable in the lives of individuals with DC and their family members.

Value of the Dyskeratosis Congenita Outreach–Camp Sunshine session: Family comments

- "Camp Sunshine has given us hope for the first time in seven years."
- "We are not alone."
- "My son was transformed from being 'the boy with weird skin and nails' to being accepted and meeting two other kids his age."
- "It gave us a directed path of information and help."
- "We laughed for the first time in years, truly laughed."

Siblings

Siblings often use each other as reference points in life. These relationships can be exceptionally significant but may not always be the priority in a family when a diagnosis of DC occurs. Sibling

relationships are among the strongest bonds in life and need to be maintained and nurtured during the DC journey. It is important that affected and non-affected siblings have the opportunity to talk with each other and with their parents.

I was diagnosed after my brother's autopsy results came back.
—DC patient and sibling

Siblings of children with DC present their own unique concerns, some more and some less apparent. Children may feel guilty that a sibling was diagnosed and that they are healthy. In the case of genetic disorders, this feeling of guilt can often be further exaggerated. Siblings, whether affected or unaffected, worry about each other, and worry about themselves.

Why did he inherit the DC? It could have as likely been me: the odds were the same.
—Sibling of a teen with DC

The already complex relationship between siblings may be further complicated if there is more than one child with DC in the family. Anxiety, jealousy, guilt, and worry are among the dominant emotions experienced by siblings. Sometimes all of these emotions remain private. The universe of younger children is often defined by the relationship to siblings. They see themselves in a

comparative context. "I am one of three; I am the oldest; I am the youngest of six; I have no brothers or sisters."

Depending on the situation, children can exhibit emotional responses to the illness equal to or even stronger than that of the affected sibling. Some children who do not have DC feel they are less important to their parents, because they do not get as much attention. Just having such feelings, even when not verbalized, can cause a child to experience guilt.

Open communication, education, and the ability to process experiences enable siblings to find solace on the DC family journey. It is important to address unaffected children's feelings and questions, while including them in illness-related activities when possible. Siblings need their own time with parents, to have age-appropriate explanations of DC, feel that their voices are heard, and truly be and feel that they are an integral part of the family.

Ongoing impact

Embracing the moment, living in the present (while planning for tomorrow), and developing one's personal style of coping, help those with DC and their families so grownget through the day.

However, in the context of a rare, progressive illness there often lingers the concern about what will happen next. It can be difficult to live in the present when worrying about the future.

Living with DC inevitably exposes one to someone who dies from a complication of the illness, either in the greater DC community or in one's own family. As the community of people with DC becomes more cohesive and individuals become more connected, so grows a network of support, information and hope. At the same time, additional exposure to loss and grief emerges. Creating rituals to honor the life of someone who dies from the same illness you have honors not only the individual, but the entire community.

Questions from adults about dyskeratosis congenita

What will the future bring?

How can I plan?

What types of career can I pursue?

How do I negotiate DC in a relationship?

If I want a family, how should I proceed?

How would I manage my DC and manage a family?

How will I integrate DC into my life, but not have it stop me from doing things I want to do?

How do I live with the uncertainty in my future?

What if my symptoms cannot be controlled?

Family matters

The diagnosis of DC has a strong impact on the family. As a genetic disorder, at times the diagnosis of one member may lead to that in another family member.

At times, families may be making decisions about experimental procedures and protocols that have been used on very few patients. Families experience vulnerability and a unique anxiety when allowing themselves, once again, to recognize the rarity of DC and the frailty of life.

Should a child/individual's condition deteriorate and alternate treatment options be considered, the family may be thrown into emotional crisis again. A partial antidote to such an experience can come in the guise of empowerment. Being prepared to take appropriate action, feeling informed, and being supported by a community can mitigate against the stress and loneliness of this experience and help reduce the sense of impotence, helplessness, or hopelessness.

At all points there is inevitably a concern for what could happen next.

Medical understanding of DC continues to evolve, allowing for the emotional and physical sequelae to also continue to evolve. At

every point there is concern about preparing for the future while living in the present.

Parent-doctor relationships

Relationships with physicians are of tremendous significance to families affected by DC. Finding a physician who has expertise in DC or is willing to work in collaboration with such a specialist is critical. The quality of these relationships often influences the patient and family's entire experience of DC and quality of life.

Individuals with DC or their caregivers must become experts on DC and understanding their medical care. Having providers who help navigate the course of the illness and talk through decisions with patients and family can help those facing DC feel much less isolated and more in control.

Encountering researchers or doctors who have devoted a significant amount of their professional career to gain knowledge or treat persons with DC inspires those affected. Such a commitment, and the connection between patients, researchers and clinicians, represents a very hopeful paradigm and the best medicine for patients and their families.

Guidelines for physicians, parents, and patients

- Psychosocial assessment of an individual diagnosed with DC (and parents if the patient is a child) can serve as a helpful tool.
- Make referrals to appropriate counseling and other resources, including support groups.
    - Group support:
        - Encourage dialogue among children or adults with DC and other bone marrow failure illnesses (or with those with other life-threatening illnesses) to minimize isolation and enhance self-esteem.
        - Encourage support group attendance for parents.
- Present information that is developmentally appropriate for patients to enhance understanding of and comfort with the diagnosis of DC.
- Encourage involvement with DC Outreach to help families develop and maintain a current knowledge base, gain support, and afford families an active role in supporting research. Encourage families to utilize:
    - Webinars/Websites
    - Family meetings
    - Educational Programs
    - Individual support

• Encourage families to create a working partnership between the physician/medical team and the family.

• Encourage patients to become responsible and proactive in regard to their illness and medical care.

• Encourage all children, teenagers, young adults, and adult patients to pursue their academic, vocational, and social goals and dreams.

    • Help establish obtainable goals, with a "next goal" ever present.

• Encourage patients/family members to learn and stay abreast of potential treatment options.

• Encourage prevention and proactivity as they relate to illness manifestations.

• Work to make decisions with—not for—families.

• Help the patient and family to imagine the next illness steps.

• Help families adjust to living each day, focusing on activities apart from the illness as crucial components of day-to-day coping.

• Stay current on research and the ever-growing knowledge base and potential treatment options.

• Facilitate relationships and communication with professionals with specialty expertise in DC.

• Seek specialists at times of decision-making

• Follow up with counseling referrals at times of crisis

Support groups

Support groups serving people facing rare disorders offer the opportunity for people to connect, share information and learn from each other about the medical and psychosocial aspects of DC. Group experiences can enable coping and give individuals very practical, as well as emotional tools to take on the day-to-day challenges of DC.

In parents' groups, parents are be able to compare and learn about their child's experience in relationship to other children, seek companionship of other parents in similar situation, share information, and unite to seek a cure, empowered in the face of the illness.

Conclusion

In one situation an undiagnosed individual had the presence of mind to have a bone marrow biopsy done post mortem on her mother. She saved it and was able to confirm the diagnosis a decade later.

—Adult with DC

DC remains a difficult diagnosis to deliver and a complicated illness to live with. However, many family members of persons with DC feel the connections within their family may reach deeper levels than those of their healthy peers, as their experiences teach them a great deal about life.

Parents and persons with DC sometimes describe having a greater appreciation for the things they do with their children, learning how to experience each day to its fullest and enjoy life. Both parents and patients talk about being stronger than they realized they were and their ability to endure. Resilience exhibited in many family members and persons with DC can seem nothing short of remarkable.

Chapter 24:
Transitioning from Pediatric to Adult Medical Care for Patients with DC

Tim Olson, MD, PhD, Kim J. Overby, MD, MBE, Monica Bessler, MD, PhD, David B Wilson, MD, PhD

How strange that the nature of life is change, yet the nature of human beings is to resist change.

— Elizabeth Lesser, *Broken Open: How Difficult Times Can Help Us Grow*

Introduction

Unlike Peter Pan, pediatric patients with dyskeratosis congenita (DC) eventually grow up and therefore require the expertise of physicians who care for adults.

Pediatric–adult transition was originally defined over 20 years ago as "the purposeful, planned movement of youth with special health care needs from child-centered to adult-oriented care".[1] This pivotal developmental milestone, however, remains a major source of anxiety for patients and their caregivers. Pediatric–adult transition for patients with DC is specifically fraught with challenges related to the rarity of the disorder, its diverse disease

manifestations, the need for multispecialty care coordination, difficulties in maintaining health insurance, and the identification of a suitable "medical home." This chapter highlights the pediatric–adult transition process for individuals with DC. Practical suggestions and links to resources are provided.

You are not alone

The challenges associated with the transition from pediatric to adult health care are not unique to patients with DC.

Approximately 10 million children in the United States have chronic diseases,[2] and 750,000 individuals with childhood-acquired conditions enter adulthood each year.[3] Recognizing the need for a systematic approach to optimize care for this young adult population, the American Academy of Pediatrics, the American Academy of Family Physicians, and the American College of Physicians-American Society of Internal Medicine issued a consensus statement[4] that included several specific recommendations for providing these patients with the knowledge and skills necessary to successfully navigate this transition. Despite increased awareness of this issue, recent studies have shown that only about 40% of patients receive the necessary, core elements of transition preparation.[5]

Pediatric and adult care in DC: a contrast in styles and the need for a medical home

As any individual who has made the transition can attest, there are broad differences between pediatric and adult care that go beyond clinic décor and staff demeanor. Examples of these differences are listed in Table 1, at the back of the chapter. Young adults transitioning to the adult care model need to be aware of these differences in order to avoid lapses in quality of care.

The task of establishing a "medical home" in the adult care system is particularly challenging for patients with DC. A medical home is the provider who serves as the hub of the medical wheel, ensuring the successful delivery of individually tailored health care even in the setting of complex disease processes. The medical home serves as the critical source of care coordination to maximize efficient and effective use of resources and services required by patients with special medical needs.

Generally, pediatric hematology subspecialists provide this medical home to children with DC. Owing to disparate practice models and lack of familiarity with DC, general adult hematology practices are less likely to serve as the medical home for patients with DC. Furthermore, with an increasing number of patients with DC undergoing hematopoietic cell transplantation prior to

transition to adult care (see Chapter 8), the role of the general adult hematologist in DC management may be diminished further. Many patients with DC, therefore, identify a dedicated primary care physician (PCP) office as their medical home. Successful management depends on consistent communication between this PCP and regional experts in DC management.

The pediatric–adult transition is a gradual process rather than an isolated event

At age 18, a person has the right to vote, make medical decisions and sign consent forms, control who has access to their medical information, designate a health care power of attorney/health care agent, and create an advanced directive/living will.

Whereas this legal transition from childhood to adulthood is abrupt, the real-world transition to adulthood is a gradual process that differs widely among individuals. Moreover, the transition from pediatric- to adult-oriented health care coincides with emerging adulthood in other life domains such as education, employment, social relationships, and independent living. Ideally, the knowledge and skills needed for transition are learned over time and tailored to the developmental stage of the individual. Young children are primarily recipients of care, with management provided by parents and medical providers.

Even so, children should be provided with developmentally appropriate information and can often participate in aspects of their care. As patients mature through adolescence, parents and providers should make efforts to engage adolescents in a shared management model, thereby beginning the transition process by having teens play an active participatory role in their care management.[6] By the end of the transition process, patients should have the skills to be the primary supervisor of their own care, with parents and providers primarily serving as resources for support and consultants.

A number of factors influence transition readiness for patients with chronic health care needs. In a recent focus group study of adolescent and young adult survivors of childhood cancer, Schwartz et al. validated a model of transition readiness known as SMART.[7] This model delineates a number of factors critical to successful transition, distinguishing between preexisting factors that can be challenging to change in the short term, and those which are more amenable to modification through a comprehensive transition program (Table 2).

One approach may not fit all

Because pediatric–adult transition is a gradual process influenced by a variety of personal, condition-specific, and

sociocultural factors, it is important to keep in mind that there is no standard approach, and that one set of recommendations and milestones (see Tables 1 and 2) might not be applicable to all patients. This limitation is particularly true of patients with DC, a condition marked by heterogeneity in clinical manifestations and age of disease onset.

It is crucial to recognize specific challenges that are not directly related to DC but nonetheless have a significant impact on the health and wellbeing of these young adults, such as literacy deficits, anger management concerns, or concomitant risk-taking behaviors. Transition programs must provide adolescents and young adults with the tools to recognize and overcome these obstacles. By identifying resources for support, health care providers can help patients envision and achieve goals in other domains of emerging adulthood.

Disease-specific factors influencing timing of DC transition

Patient-specific pre-existing factors heavily influence the timing and nature of transition to adult care for patients with DC. For those with severe forms of DC in whom the diagnosis has been made in early childhood, the focus of pediatric–adult transition is often the adjustment to the myriad challenges of young adulthood in the context of long-standing medical limitations. Other patients

with DC, however, are diagnosed in mid to late adolescence at the onset of bone marrow failure; for these patients, the need to transition to adult care comes at a time when they are just coming to terms with the diagnosis and learning what medical services they need.

Because DC is a rare condition, access to disease-specific expertise may be quite limited for patients living in certain regions. This limited access may result in patients being justifiably reluctant to leave local pediatric providers with whom they have a strong, well-established relationship. A related problem affecting transition is that private- and state-sponsored health insurance programs for children are often flexible in allowing children with chronic medical needs to seek out medical expertise, even if this means crossing state boundaries to do so. In contrast, health insurance programs for adult patients may impose restrictions in accessing the same degree of expertise, particularly if expert providers are not part of the treatment network.

A number of clues can help patients, families, and pediatric health care providers decide that it is time to consider transitioning to adult care (see Table 3). For most youth, transition takes place around age 22 or whenever formal education has been completed. Another major factor determining transition timing is the set of organ-specific disease manifestations that an individual with DC

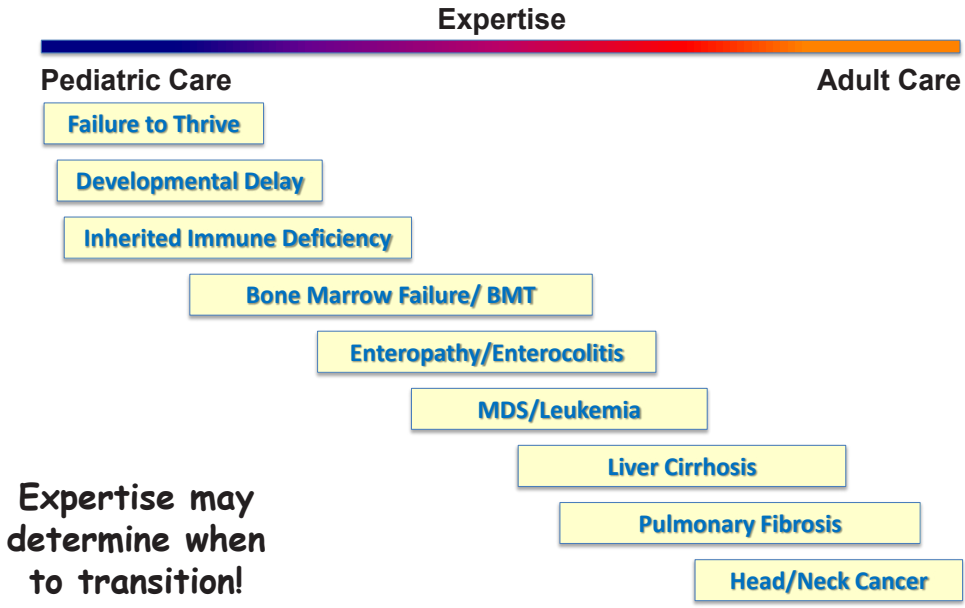

Figure 1. Example of how medical expertise for the various disease manifestations of dyskeratosis congenita may be divided between pediatric and adult practitioners. N.B. the depicted spectrum may not accurately reflect expertise at all centers.

may possess, and the availability of local or regional adult versus pediatric providers to address these complications (Figure 1). For example, patients with DC whose major ongoing medical issues are bone marrow failure and complications of chronic immune deficiency, may be better served by staying longer in an experienced pediatrics clinic, particularly if no local adult providers are available that have experience in these areas.

For patients with DC who are diagnosed with bone marrow failure during adolescence, treatment with hematopoietic cell

transplantation may be indicated prior to transition to adult providers in order to maximize transplant outcomes (see Chapter 8). In contrast, patients with *TERC* or *TERT* mutations who experience pulmonary or hepatic complications (see Chapters 14 and 16), and patients with concerning symptoms of head/neck cancer (see Chapter 12) may find an earlier transition beneficial in order to streamline regular care by adult pulmonology, hepatology, or oral pathology specialists experienced in managing these conditions. Thus, it is critical that patients with DC work closely with their pediatric providers to tailor an individualized approach to the timing of transition to adult care.

Unfortunately, many patients with DC also experience neurocognitive or neuropsychiatric deficits (see Chapter 20). In severe forms of DC such as Hoyeraal-Hreidarsson and Revesz syndromes, the severity of neuropsychiatric deficits may make transition to independent medical management unfeasible. Nonetheless, many of these patients will develop complications that are best managed using expertise from adult providers. These patients particularly benefit from formal identification of a medical home, whether from a pediatric provider or one specializing in caring for adults with disabilities, as long as there is the capability of efficiently involving all necessary subspecialists to create an individualized, yet cohesive network of care.

Persons with neurocognitive disabilities may have the capacity to designate a health care power of attorney or health care agent, even if they lack the capacity to make more complicated medical decisions for themselves. Most states have laws that automatically designate a family member to act as the surrogate decision-maker for individuals who lack the capacity to make medical decisions. However, when significant neurocognitive concerns exist, transition planning should also include providing information regarding the process of pursing legal guardianship for families who wish to do so.

General tips for focusing on modifiable factors to improve transition outcomes

Despite the many challenges encountered during the transition process, families and providers who focus on factors that are most easily modified (Table 2) can overcome these obstacles and ensure optimal care through this critical period and beyond. Of utmost importance for enabling a smooth transition, adolescents must be provided with necessary skills and knowledge to maintain high quality health care (see Table 4). Their parents, who must initially continue to play a vital role in this process, require continued support (see Table 5).

As a basic guideline, between the ages of 11 and 13, most patients are developmentally able to:

- gain in-depth knowledge and understanding of their disease
- briefly explain their condition to others
- know their allergies and medication names
- take their medications without reminders

Patients in this age range, with the help of techniques such as a 3-sentence health summary (see Table 6, adapted from www.sickkids.ca/good2go), should be able to easily discuss health information with their regular providers, as well as in emergency situations.

By 14 to 16 years of age, patients should be directing most of their communications with health care providers. They should also have the opportunity to discuss aspects of their care privately with providers. Patients in mid-adolescence should know each of their health care providers by name and know why they see them. In addition, they should begin to understand the processes of health insurance and making appointments.

By late adolescence (17-22 years of age), patients should be able to schedule their own appointments and arrange necessary transportation. They should have full knowledge of their health insurance coverage, and have a sense of how they will maintain

coverage in the future, based on career plans and goals. They should also play the primary role in maintaining health records through the use of a "care binder" notebook or other system for organizing health information. They should be able to update and maintain access to written health summaries and emergency care cards. Resources that can help adolescents and young adults acquire all of these skill sets are listed in Table 7.

Transition as a challenge that must be met

Becoming a successful young adult is challenging, even for adolescents who do not have DC or other chronic medical conditions. Transitioning medical care from pediatric into adult systems is unmistakably an added burden for young adults with DC during this already difficult developmental period. However, youth who experience a successful, systematic transition are more likely to have better health outcomes and report improved rates of fulfillment, achievement, and higher self-esteem compared to those who do not attain a smooth transition. Pediatric providers and parents have an obligation to provide these patients with DC not only with exceptional medical care, but also the knowledge and skills necessary to ensure an optimal transition experience.

"Look on every exit as being an entrance somewhere else."
— **Tom Stoppard**, *Rosencrantz and Guildenstern Are Dead*

Pediatric Care	Adult Care
Parents and medical providers are in charge of care and monitor symptoms	Care is self-directed and health status is primarily self-monitored
Parents schedule appointments and identify new specialty providers as needed	Patients must schedule and keep appointments, and find new providers on their own
Support services are offered for financial and emotional issues	Patient must seek support services for financial and emotional issues
Parents are responsible for insurance coverage, finances, and payment	Patient is responsible for securing insurance, and managing finances and payment
Transportation provided by parents	Patient must provide own transportation
Parents manage home medications and other treatments	Patient must obtain prescriptions and refills, and must manage any complex home care needs.
Pediatric clinic staff are typically tolerant of immature patient behavior	Adult clinic staff are likely to be intolerant of immature behavior
Parents request and manage information about treatment options, and will often shield patients from specifics regarding prognosis.	Patients must research and make informed decisions regarding treatment options, and must be able to handle information regarding prognosis.

Table 2: SMART: a social-ecological model of adolescent and young adult readiness to transition [7]	
Preexisting factors	**Modifiable Factors**
• Social and demographic factors • Health care access/insurance • Medical status • Cognition	• Knowledge • Self-sufficiency • Expectations • Maturity • Motivation • Communication • Emotions

Table 3: Clues that it is time to transition to an adult care provider
• You lack comfort in addressing important areas of your health with a pediatric provider. • You are a passive participant during visits and not a partner in medical decision-making. • The office equipment is too small. • You feel out of place in the overall environment of a pediatric clinic. • You prefer to bring a boyfriend or girlfriend to the clinic visit. • Your pediatric provider is unable to interface with adult providers in • other subspecialties. • You have completed formal education (e.g., graduating high school or college).

Table 4: Key skills for the transitioning patient
• Understanding your condition and health needs • Communicating with healthcare professionals • Knowing and managing medications and treatments • Scheduling and keeping appointments • Having an emergency plan • Keeping a health summary • Maintaining health insurance • Navigating adult clinic and hospital settings • Accessing community resources

Table 5: Optimizing transition – general tips for parents
• Start early • Teach developmentally appropriate information about your child's condition • Encourage teen to assume responsibilities • Provide coaching opportunities and practice independence • Help your teen understand the future health implications of their condition • Discuss career and educational goals and their impact on health insurance • Address decision-making and guardianship issues when necessary

Table 6: 3 sentence health summary technique

(adapted from www.sickkids.ca/good2go)

Method:

Sentence 1: state your age, diagnosis and most important points about your medical history

Sentence 2: state any treatment you are currently receiving

Sentence 3: state what your concerns or symptoms are now.

Example:

1: *I am 16 and have Dyskeratosis Congenita. I have bone marrow failure and problems with my immune system, and I have had several severe lung and skin infections.*

2: *I receive red blood cell and platelet transfusions once in a while when my counts are low and have taken G-CSF injections before when I have had an infection.*

3: *I am here today because I have a fever and a cough, and I just don't feel well.*

Table 7: Tools and resources

Websites focused on pediatric to adult transition:

- National Health Care Transition Center: http://gottransition.org
- Health Care Transitions Initiative: http://hscj.ufl.edu/jaxhats/DocumentsResources.aspx
- Florida Health and Transition Services: http://www.floridahats.org
- The Hospital for Sick Children (Toronto)-Sick Kids, Good 2 Go Transition Program: http://www.sickkids.ca/good2go
- Children's Hospital of Philadelphia-Transition to Adulthood:

http://www.chop.edu/centers-programs/transition-adulthood-program

- Aplastic Anemia & MDS International Foundation: http://www.aamds.org/facts-for-life/transition-pediatric-adult-health-care

https://live.blueskybroadcast.com/bsb/client/CL_DEFAULT.asp?Client=680927&PCAT=944&CAT=1725

Building health care summary and maintaining medical records:

- 2-page health summary: http://www.floridahats.org/wp-content/uploads/2010/03/HCT-Summary.pdf
- Electronic Transition Information Form: www.healthytransitionsny.org
- Care Binder: http://www.medicalhomeinfo.org/for_families/care_notebook

Communicating with health care professionals:

- G.L.A.D.D. model of health care visit communications: http://education.ufl.edu/education-healthcare-transition/
- 3-sentence health summary: www.sickkids.ca/good2go

Emergency plans/cards:

My Health Passport: http://www.sickkids.ca/MyHealthPassport

CHOP Emergency Information Card: http://vec.chop.edu/export/download/pdfs/articles/pfe/emergency-information-wallet-card.pdf

RxResponse Medical Information Card:

http://www.rxresponse.org/rx-on-the-run

Tips for college:

http://childrenshospitalblog.org/transitioning-healthcare-at-college

www.gottransition.org/resources/index.cfm

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Chapter 25:
Advocating for a Loved One with a Rare Disease

Rachel Godfrey, mother of Ronan, 2

When first entering the world of rare disease, one of the greatest challenges is relinquishing control over the situation at hand. Not only do you not know what you are dealing with, but more often than not the medical care providers are also at a loss.

Test after test may bring no answers, and in this case you feel that no news is definitely not good news. With each test, you dive further and further into the realm of the unknown until, if you are fortunate, you finally find out what it is that you are dealing with. Then you realize that you are in yet another strange place, and your first step through this doorway is often learning how to pronounce the name of this rare disease, this new label that will forever shape your life. Once you have wrapped your tongue around that you ask, "So what *is* it? What does that *mean*?"

People come from diverse backgrounds, and we respond to this news in different ways. Some of us choose to tune out and let those whom they trust take over, often feeling we can't handle the stress

this news brings. The emotional journey can just be too much for us to process all at once, and we take small steps down the path we now find ourselves on. At times we may not even recognize ourselves when faced with overwhelming information and uncertainty. Some of us can feel angry that we are watching our loved one go through the ups and downs of the unknown.

For patients and caregivers alike, who want or need to feel like they have even a small bit of control, this is where they start to grasp at any small piece of the puzzle they can. This puzzle consists of symptoms, treatments, specialists, institutions, published medical writings, and finally, support groups. Anyone that knows or understands even an inkling of what this rare disease will mean becomes a lifeline of sorts. We will do anything to grab it and hold on. This is the journey I took when my son was diagnosed with dyskeratosis congenita (DC) in 2011 at the age of two.

The term "advocate" was new to me when I became one. As I pushed through the never-ending appointments and hospitalizations, making the tough decisions, I was told by many that I was my son's best advocate. I wasn't sure what people meant at first. In my mind and my heart I was simply my son's mother, and this is what a mother does for her child. But as time went on and more decisions had to be made, more signs of disease were discovered; I came to learn just what it meant.

The term "advocate" is defined as "a person who pleads on someone else's behalf", and I couldn't agree more, as I have done my fair share of pleading along Ronan's journey thus far.

I can think of nothing worse than being unable to help one's child or loved one. That was how I found myself one day when my son had a nosebleed and we began our rollercoaster ride through the discovery, diagnosis, and treatment of DC. To be an advocate for somebody who can't advocate himself can be a challenge in so many ways, especially when you yourself, and possibly even the medical care team involved, don't fully understand the condition.

This is often the case with DC; so few of us truly understand the disease and what it means to each patient can vary so drastically. We often long to hear the journeys of other families and what they have gone through, hoping to determine what we can or should expect next. The DC community has become a family, a team of advocates for each other in many ways, since even though our experiences vary greatly, we are the only ones that truly know what it's like to have DC in our lives.

Advocating takes inner strength that you may feel you don't have or can't begin to imagine summoning from your already exhausted self. I like to think of advocating as many *small acts of courage*. Taking each day as it comes (often times we are taking each hour as it comes), and approaching each situation, finding the

strength and courage to focus on the one issue at hand, and working toward a positive outcome. This work will not be on your shoulders alone; you will have many decisions to make, and as your journey progresses, you will likely have a medical team working with you. Teaming *with* doctors and establishing an equal part on the care team can be vital – you as the parent or primary caregiver for someone who can't make decisions for themselves may want to show medical care providers how much you want to be involved.

Here are some things to consider when advocating for your loved one:

Listen to others and try to understand their point of view. They may have thought of something you have not that is vital to the care of your loved one. They may understand an aspect of the situation you do not. Be open to learning from others.

Rather than being adversarial, focus on being assertive. Hostility between family and doctors, though easy to jump to, can hurt these important relationships. Egos can be hurt and the priority must be to focus on the needs of the patient.

Fostering positive collaboration is key, so consider keeping correspondence kind and positive. Emotions can run high and get in the way of clearly articulating thoughts and ideas. Reply in a timely matter to correspondence from those who can help you, and

keep all of your appointments whenever possible. Showing others that their meetings and messages are a priority to you should gain you respect and good standing.

Remember that adults can work together to effect change. Respectful, assertive communication is worth your effort and can be a lifeline for your loved one. If difficulties arise in communicating with the medical team, consider inquiring about another doctor being assigned to your case. This is not always possible for many reasons, but may need to be considered if you feel the care and treatment your loved one is receiving is not in their best interests.

Their well-being is priority number one and should be the very first thing you and your medical care team agree upon. If you find this challenging or you find you are in need of assistance or support, there are many people who want to do just that:

Social workers or a patient advocate are often assigned to children in hospital settings to assist the family with navigating the health care system and provide resources that can help make the situation as agreeable as possible. They may be able to connect you to government agencies, or local non-profits or disease advocacy organizations that can provide assistance. These groups can make a big difference in such things as financial aid and special needs accommodations.

Support groups such as Dyskeratosis Congenita Outreach, Inc.

DCO can help in many ways.

They can connect you to doctors and researchers that specialize in the condition. These specialists may be open to communicating directly with your medical team to ensure they are aware of the nature of the condition and help them move forward with the best care protocol for your family member. This can prove to be invaluable with a rare disease such as DC, when so few doctors and researchers truly know what needs to be taken into consideration when going forward with such procedures as hematopoietic cell transplantation, medication, or even standard diagnostic studies such as genetic screening, blood tests and various radiological scans.

Support groups can also be a wealth of information on the condition, providing materials and information not only on the condition, but also on current clinical trials and advances in science and research, potentially leading you to a discovery that may be helpful for your loved one's situation.

Another way an advocacy group like DCO can help is by connecting you to other people who are in or have been in similar situations. Having a connection to someone who can truly understand what it's like to go through what you are living can be a lifeline during difficult times. You might find inspiration in

hearing about their successes, or find that they have some helpful hints and ideas that can make every day challenges a bit easier. You may even learn from others' choices and experiences. Research and discovery are currently progressing very quickly with DC, and what we knew three years ago seems light years behind us at times.

Friends and family may be a wonderful source of support and even be a part of your advocacy team. Having a partner that knows you, knows your loved one, and knows what your hopes are for them can be truly valuable. We all find ourselves in varying situations, often alone whether or not we want to be, sometimes surrounded by too many people who seem to care too much about things that do not seem to matter, or arguing with the ones we love the most because tensions are running high in these often stressful situations.

Many families find that strangers come out of the woodwork and become life-long friends during these times, while the people they were sure would be there are not. This might be something you try not to take too personally. When our friends and family don't understand, they might not know what to say and so they say nothing so as to not say the wrong thing. Some families choose not to share the diagnosis with their closest friends or family. Some people literally broadcast it on the nightly news. We are all different, but be sure to do what is most comfortable for you, what

is going to help you the most, and ultimately, what is best for the one you are advocating for.

As I sat with my son during his many transfusions before transplant, I was surrounded by children in the pediatric cancer clinic, all of them hooked up to something, be it blood or chemotherapy. Yet I always felt alone being the only one with a child with DC. I remember having all kinds of thoughts about how I wish we were dealing with "this" instead of "that", or thinking that we were in a better place than others for whatever reason.

As I went through this, then transplant, then recovery, and finally getting into a "new normal" with my son, I learned that each journey is different. Each journey has its good and bad days, breakthroughs and setbacks, and successes and failures. I can always think of someone who is in a better situation, and also someone who is in a worse one. What is best for one is not what's best for another, even from one DC patient to the next. As difficult as it may be, try not to compare your situation with others', or wish you were in someone else's position.

One day you might be, and it may turn out not to be so great, or you might end up in an even better place than you expected. Keep your focus on what will get your loved one to the next step that is in the right direction, ask for help when you need it, and accept help that is offered. Accepting help can be one of the most difficult

things to do, but you will tire, and when you do, the help will be there for you when you need it.

A dear friend once told me as I sat outside my son's hospital room, "People want to help. Letting them help is giving them a gift."

And one day, when you get to your "new normal" as we all do, you will be given the gift of helping others, too.

Resources

For information on the National Institutes of Health Inherited Bone Marrow Failures Syndromes study please go to: http://marrowfailure.cancer.gov/index.html.

For information on ongoing clinical trials focused on DC-related topics go to www.clinicaltrials.gov.

Telomere length testing laboratories certified through the Clinical Laboratories Improvement Amendments or CLIA, which govern testing on human subjects, are able to measure telomere lengths according to standards accepted by DC-specialists.

Among facilities suggested by DC Outreach are:

Repeat Diagnostics Inc./Geraldine Aubert, PhD
309-267 West Esplanade Ave.
North Vancouver, BC V7M 1A5
T. 604-985-2609
F. 778-340-1144
www.repeatdiagnostics.com

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Color Photo Appendix

Figures from Chapter 2

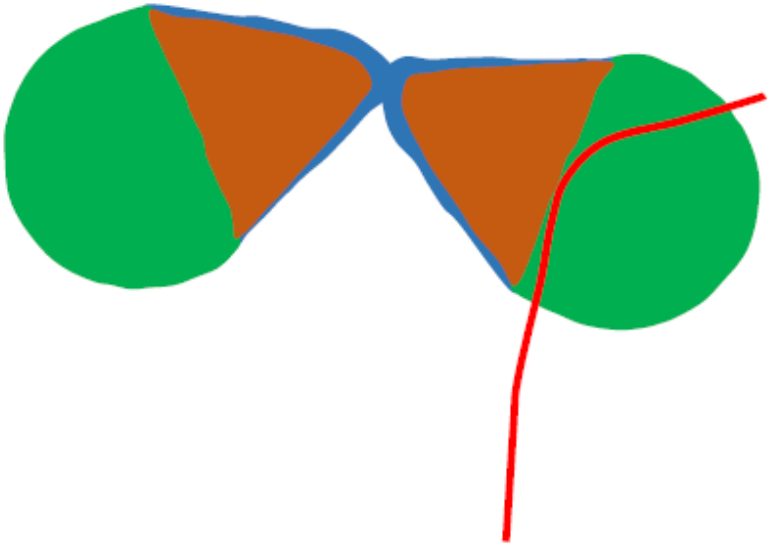


Figure 3. Schematic of telomerase components. It has not yet been possible to get a high-resolution "picture" of what telomerase looks like. However, the active form of the molecule is known to contain two copies each of TERT (green), hTR (orange), and dyskerin (blue). It latches on to the end of a telomere (drawn here as a red line) in order to lengthen it.

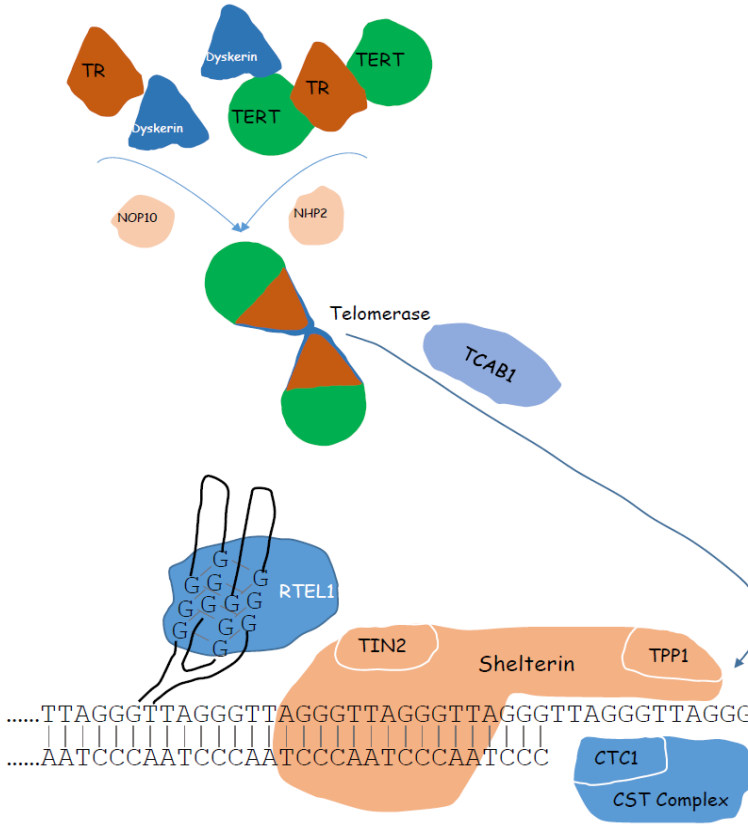


Figure 5. Mutations in ten different genes are known to cause excessively short telomeres. These include the genes (TERT, TERC and DKC1) encoding components of active telomerase (TERT, hTR and dyskerin), and the genes encoding two of the proteins (NHP2 and NOP10) which help assemble the telomerase components. TCAB1 (encoded by the WRAP53 gene) is involved in transporting telomerase to the telomere end, where it docks with one of the shelterin subunits, TPP1 (encoded by the ACD gene). Mutations in the gene (TINF2) encoding another shelterin subunit (TIN2), also result in excessive telomere shortening, as do mutations in RTEL1 (a protein needed for dealing with complex DNA structures) and a gene coding for a subunit (CTC1) of the CST complex, which is involved in processing of the telomere's AATCCC strand.

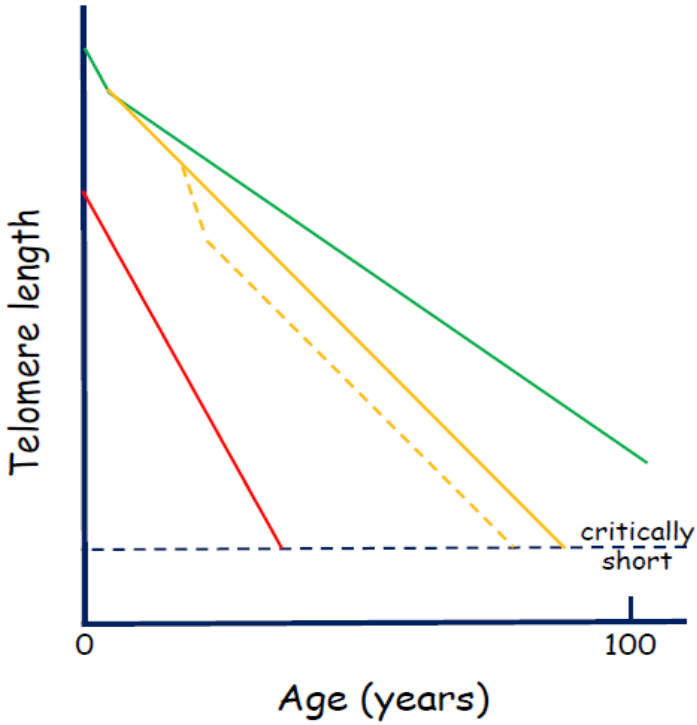


Figure 6. Telomeres need to last for a normal life span. The telomeres of many somatic cells shorten throughout life but, if they have a normal starting length and do not shorten too rapidly, we can live a long life and still have sufficient cells that do not have critically short telomeres (green line). Because of the amount of growth occurring, telomeres shorten more rapidly in early childhood than in adults. If the telomeres shorten faster than normal (which occurs, for example, when cells that undergo a lot of proliferation do not have enough telomerase), then some organs may lose the capacity to renew themselves later in life (amber line). Some environmental factors may cause cell death, which results in an increased need for proliferation and therefore an increased rate of telomere shortening, and this may result in problems occurring earlier in life (dotted amber line). Individuals who start out with short telomeres and also have an increased rate of telomere shortening (red line) may have problems from short telomeres early in life.

Figures from Chapter 3

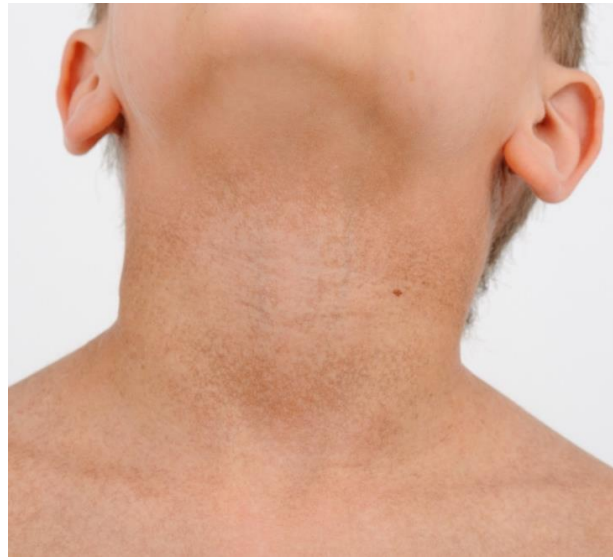
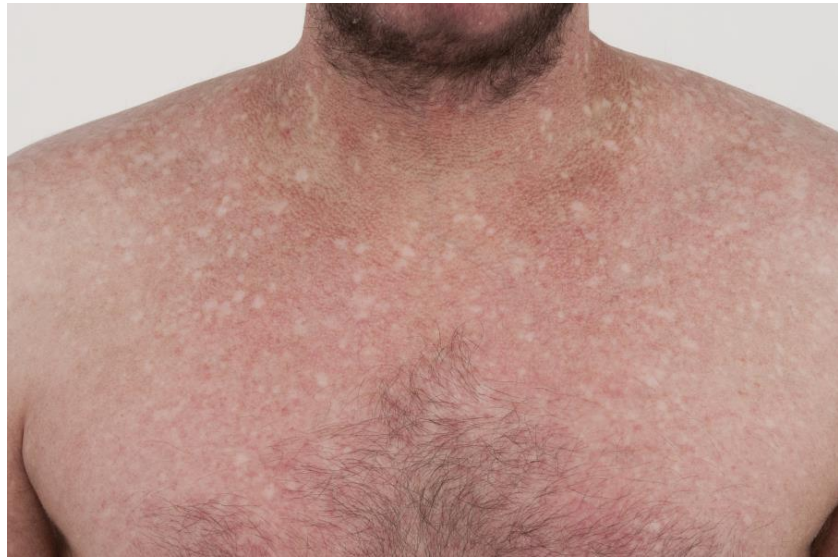


Figure 1: Skin pigmentation changes in DC



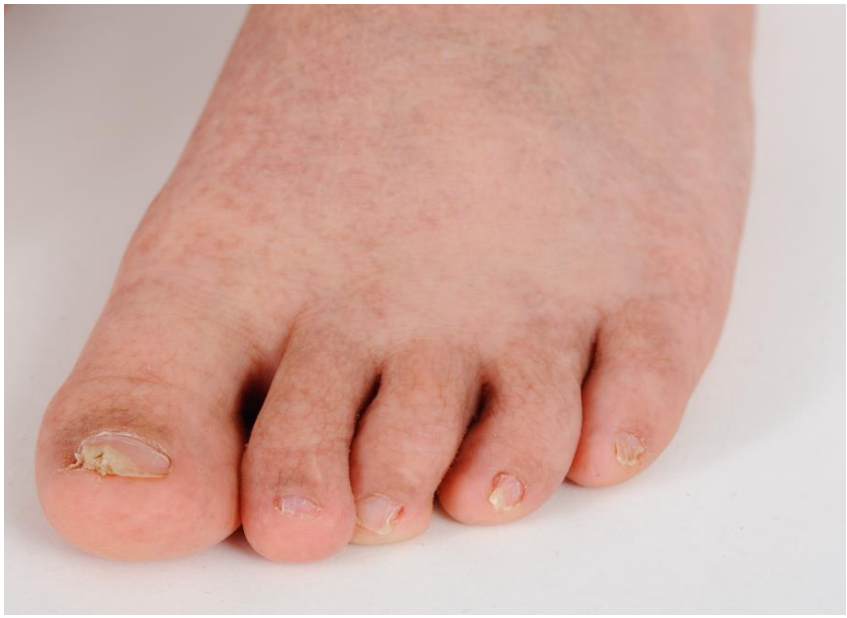
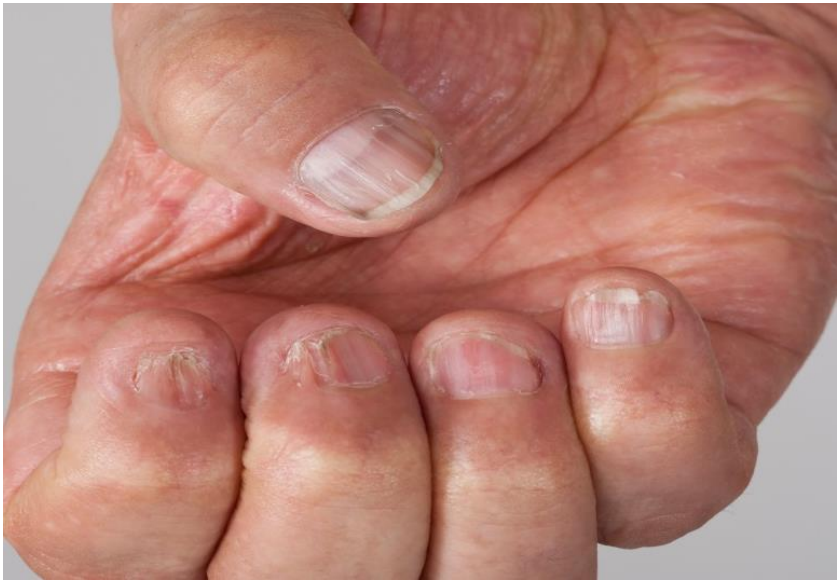
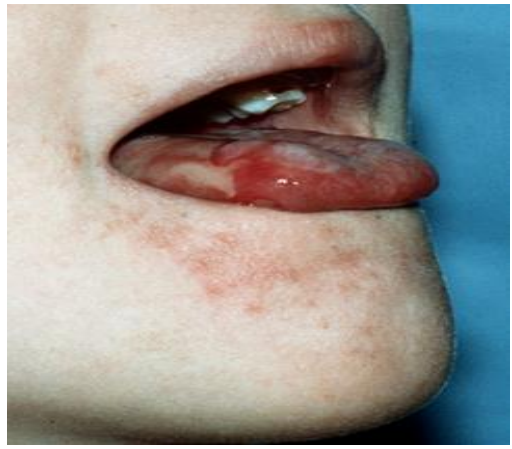


Figure 2: Nail dystrophy in DC





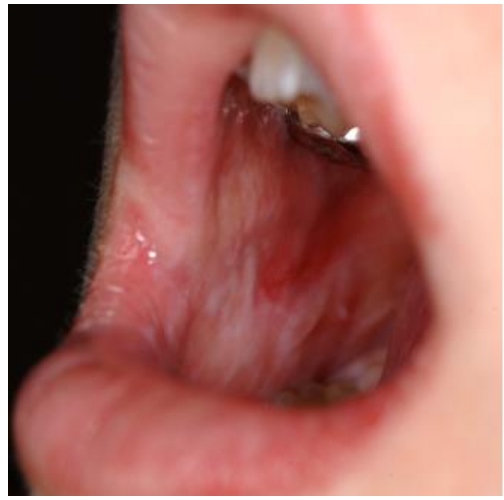


Figure 3, top and center: Leukoplakia in DC.

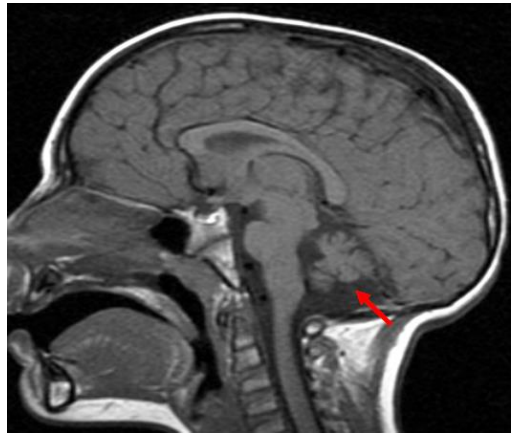


Figure 4, bottom: Cerebellar hypoplasia in Hoyeraal-Hreidarsson syndrome (red arrow)

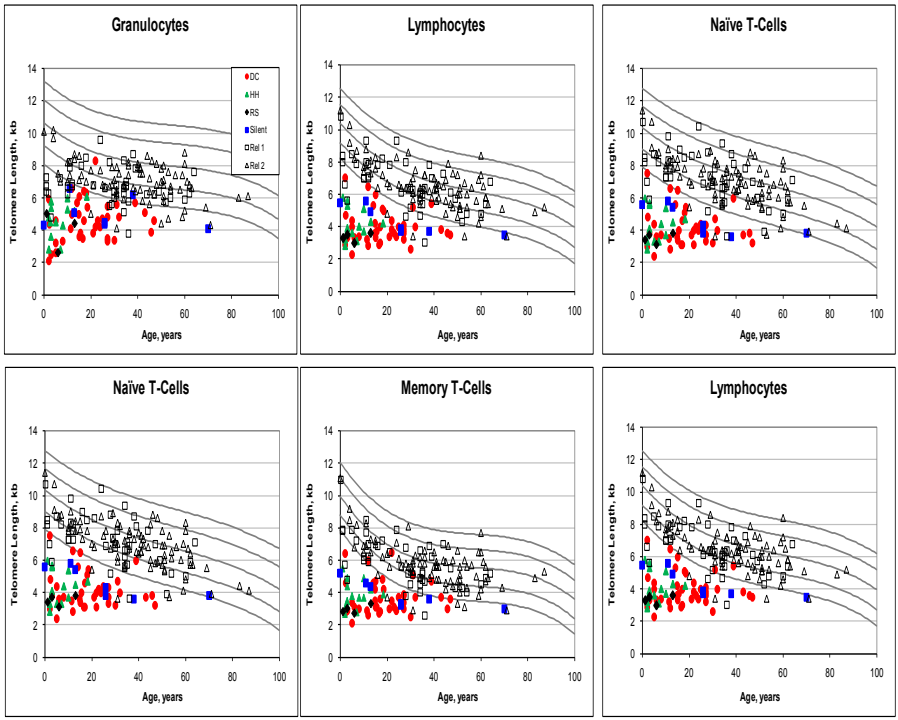


Figure 5: Telomere length according to age in patients with DC and their relatives. The vertical axis represents telomere length in kb. The curved lines in the figures indicate the first, tenth, 50th, 90th, and 99th percentiles of results from 400 normal controls. Colored symbols represent patients with DC and their relatives. Red circles: classical DC patients; green triangles: Hoyeraal-Hreidarsson; black diamonds: Revesz syndrome; blue squares: silent carriers; open black squares: DC relatives in families with unknown genes; open black triangles: DC relatives without mutations in the probands' genes. Top panels show granulocytes, lymphocytes, and CD45RA^{+}/CD20^{-} naïve T cells. Bottom panels show CD45RA^{-} memory T cells, CD20^{+} B cells, and total NK/NKT cells. Figure and Figure Legend directly from Alter et al., Haematologica 2012.

Figure from Chapter 4

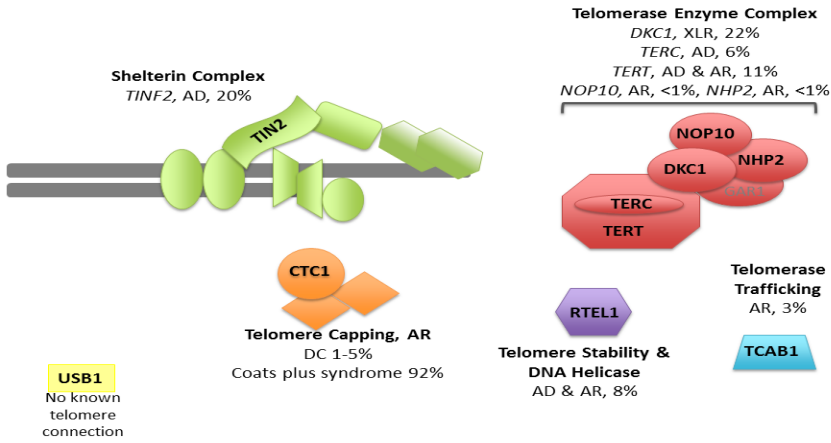


Figure 1: Schematic of the telomere and functions of the proteins affected in dyskeratosis congenita and the related telomere biology disorders. Protein names are shown. Abbreviations: XLR, X-linked recessive; AD, autosomal dominant; AR, autosomal recessive; DC, dyskeratosis congenita; TCAB1, telomere Cajal body-associated protein 1 (gene name: WRAP53); TIN2, TRF1-interacting nuclear factor 2 (TINF2); TPP1, telomere protection protein 1 (encoded by ACD, adrenocortical dysplasia homolog); NOP10, NOP10 ribonucleoprotein (NOP10); NHP2, NHP2 ribonucleoprotein (NHP2); DKC1, dyskerin (DKC1); TERC, telomerase RNA component (TERC); TERT, telomerase (TERT); RTEL1, regulator of telomere elongation helicase 1 (RTEL1); CTC1, CTS telomere maintenance complex component 1 (CTC1); USB1, U6 snRNA biogenesis 1 (USB1). Percentages are estimates and based on the literature and unpublished data from the National Cancer Institute's dyskeratosis congenita study.

Figures from Chapter 10

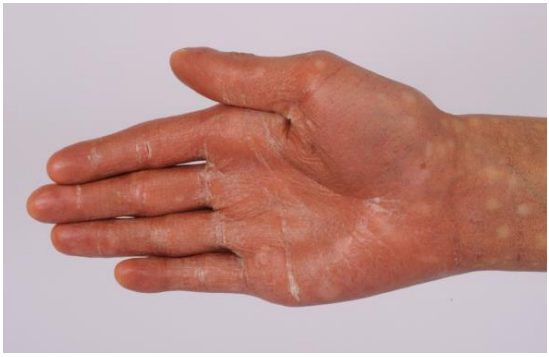


Figure 1: Hyperkeratosis: Thickening of the skin of the palm

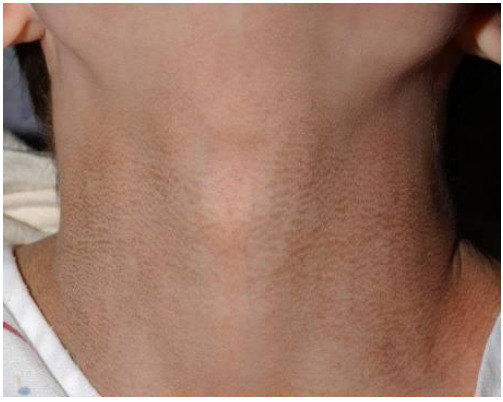


Figure 2: Reticulated pigmentation on the neck

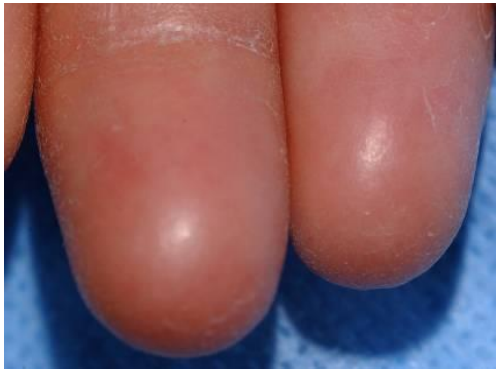


Figure 3: Adermatoglyphia: Loss of fingerprints

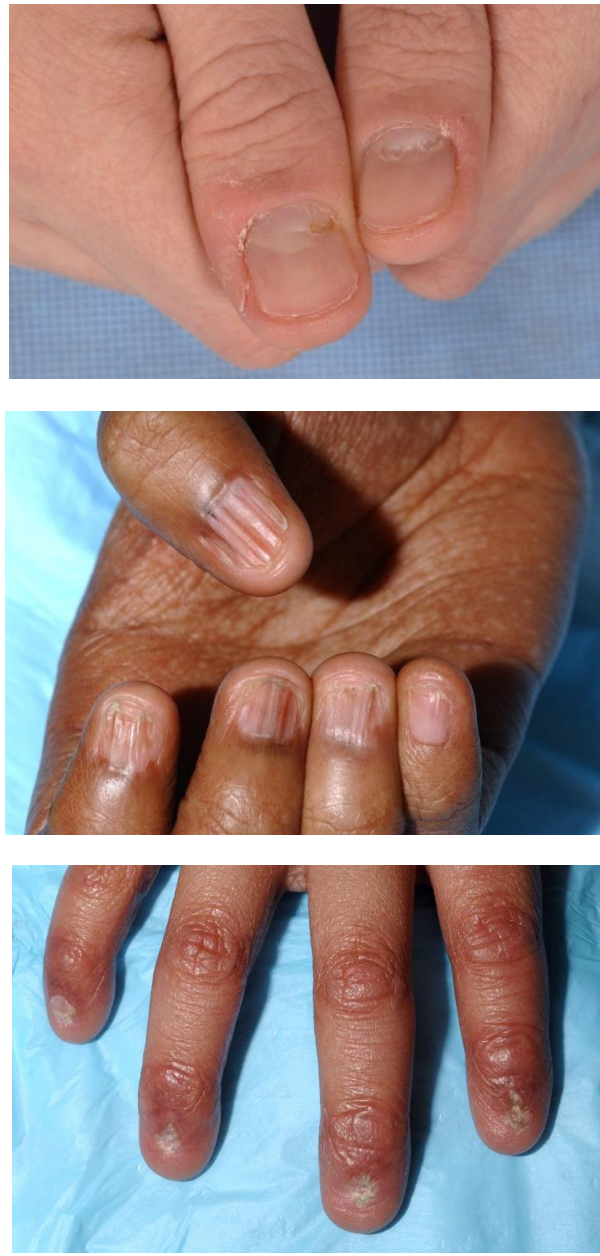


Figure 4: Nail changes in DC: onychoschizia, longitudinal ridging, and micronychia.

Figures from Chapter 11

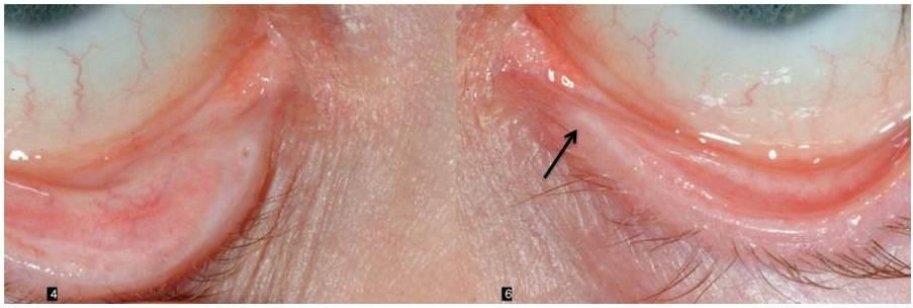


Figure 1: Photograph of a patient with dyskeratosis congenita demonstrating an absent punctum in the left eye (arrow).

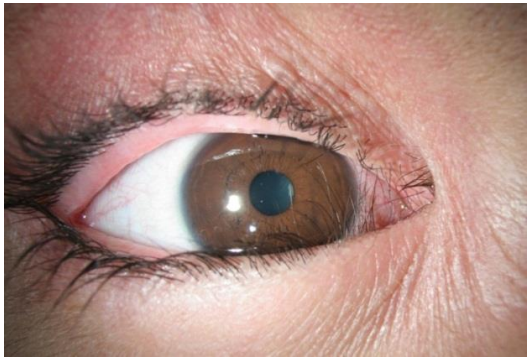


Figure 2: Entropion and trichiasis in a patient with dyskeratosis congenita.

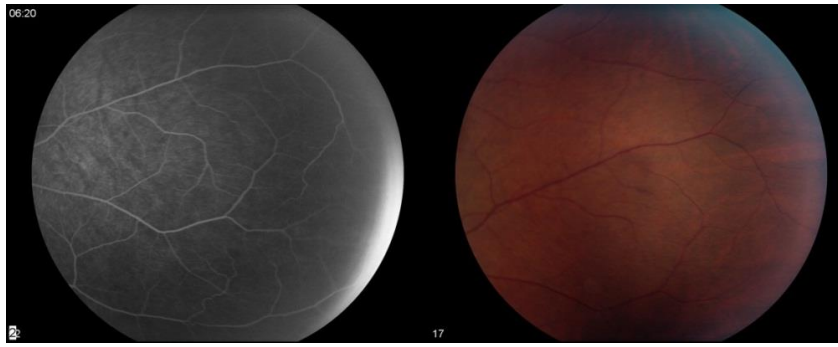
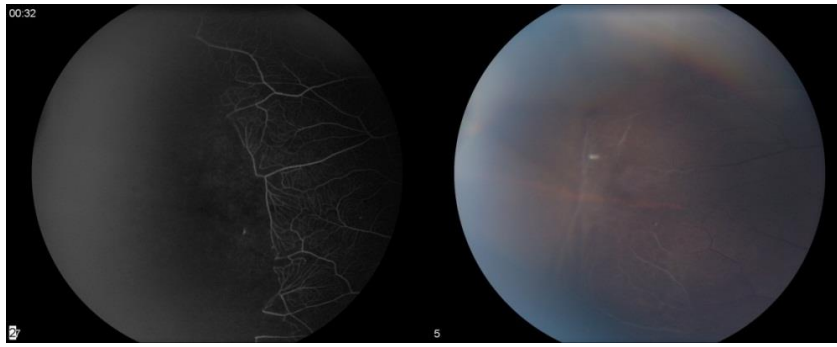


Figure 3: Fluorescein angiography (top left) and fundus photograph (top right) of normal retina. Fluorescein angiography (bottom left) and fundus photograph (bottom right) of a patient with dyskeratosis congenita, demonstrating perivascular sheathing and non-perfusion.



Figures from Chapter 15

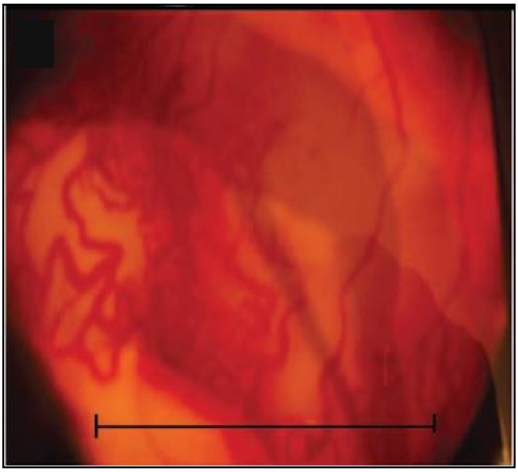


Figure 1, top: Retinal microangiopathy in Coats plus syndrome. Figure from Anderson BH, Kasher PR, Mayer J, et al. Mutations in CTC1, encoding conserved telomere maintenance component 1, cause Coats plus. Nature genetics. 2012;44(3):338-342.

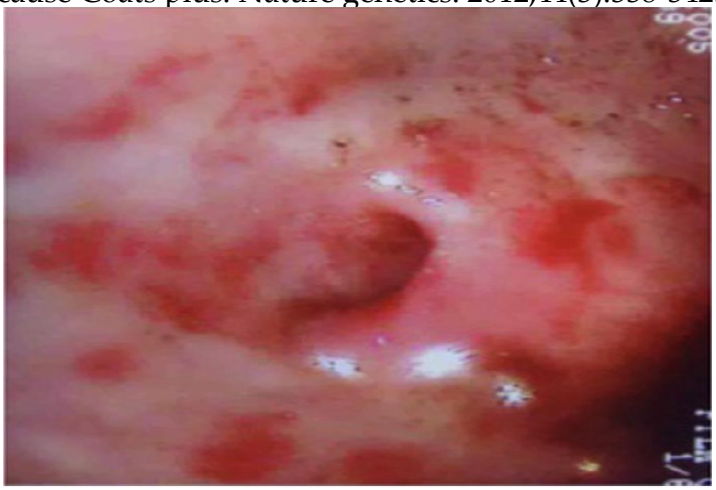


Figure 2, **bottom**: Gastric vascular ectasia in Coats plus syndrome. Figure from Anderson BH, Kasher PR, Mayer J, et al. Mutations in CTC1, encoding conserved telomere maintenance component 1, cause Coats plus. *Nature genetics*. 2012;44(3):338-342.

Figures from Chapter 21

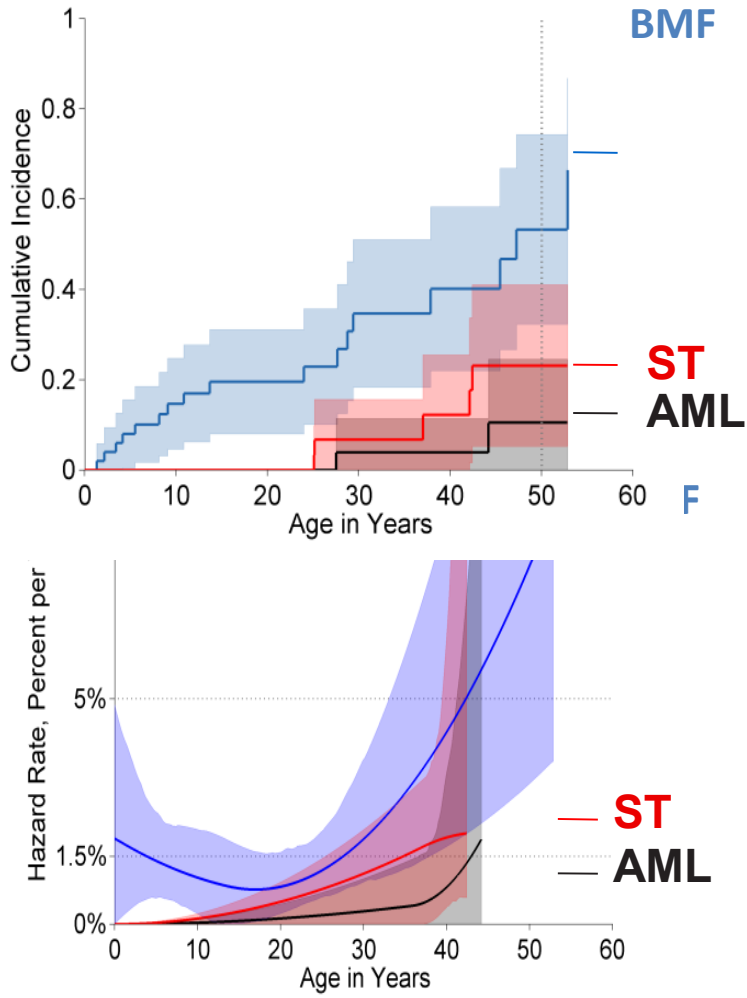


Figure 3: Annual hazard and cumulative incidence of competing adverse events in patients with DC in the NCI cohort through 2008. Shaded areas are the 95% confidence intervals. BMF, bone marrow failure. ST, solid tumor. AML, acute myeloid leukemia. From: Alter BP, Giri N, Savage SA, Rosenberg PS. Cancer in 7192 dyskeratosis congenita. Blood 2009;113:6549-6557.

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Glossary

Sources: The Centers for Disease Control and Prevention, U.S. Food and Drug Administration, MediLexicon, Merriam Webster, the National Library of Medicine, Orphanet. (https://www.nlm.nih.gov, http://www.medilexicon.com, http://www.orpha.net, http://www.fda.gov, http://www.cdc.gov, accessed June 2015.)

<Sharp brackets> mean "also known as."

Absolute Neutrophil Count (ANC): The percentage of neutrophils multiplied by the total number of white blood cells. Includes both mature neutrophils (segs) and immature neutrophils (bands)

Acute Myeloid Leukemia (AML): A quickly progressive cancer of the myeloid line of blood cells, characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells.

Adenoma: A benign tumor of a glandular structure or of glandular origin.

Adermatoglyphia: A genetic disorder which causes an individual to have no fingerprints.

Alanine Aminotransferase (ALT): An enzyme found in highest amounts in the liver. Injury to the liver results in release of ALT into the blood.

Alkylating Agent: A substance with mutagenic activity that inhibits cell division and growth and is used to treat some cancers.

Allele: A copy or alternate format of a gene

Allogeneic: Involving, derived from, or being individuals of the same species that are sufficiently unlike genetically to interact antigenically.

Alopecia: Loss of hair.

Aminotransferases: As enzyme that catalyzes a reaction between an amino acid and an a-keto acid.

Androgens: A synthesized, male sex hormone (testosterone)

Anemia: A condition in which the blood is deficient in red blood cells, in hemoglobin, or in total volume.

Anonychia: Congenial absence of the nails.

Antibody: Any of a large number of proteins produced normally by specialized B cells after stimulation by an antigen and act specifically against the antigen in an immune response. Some are produced abnormally by some cancer cells, and typically consist of four subunits including two heavy chains and two light chains. <immunoglobulin>

Antigen: Any substance foreign to the body that evokes an immune response either alone or after forming a complex with a

larger molecule (as a protein) and that is capable of binding with a product (as an antibody or T cell) of the immune response.

Aplastic Anemia: Anemia characterized by defective function of the blood-forming organs (as the bone marrow) and can be caused by toxic agents (as chemicals or X-rays) or is idiopathic in origin. <hypoplastic anemia>

Apoptosis: A genetically determined process of cell self-destruction that is marked by the fragmentation of nuclear DNA. It is activated either by the presence of a stimulus or by the removal of a stimulus or suppressing agent and is a normal physiological process eliminating DNA-damaged, superfluous, or unwanted cells. When halted (as by genetic mutation), it may result in uncontrolled cell growth and tumor formation. *<programmed cell death>*

Arteriovenous malformations: Vascular anomaly characterized by abnormal connections between the arteries and the veins.

Ascites: Abnormal accumulation of serous fluid in the spaces between tissues and organs in the cavity of the abdomen. <hydroperitoneum>

AST/Aspartate Aminotransferase: An enzyme found in highest amounts in the liver. Injury to the liver results in release of AST into the blood.. *<aspartate transaminase>, <glutamic-oxaloacetic transaminase>*

Ataxia: The inability to coordinate voluntary muscular movements.

Autosomal Dominant (AD): A trait requiring only one copy of the genetic mutation at a particular locus in order to express observable phenotype.

Autosomal Recessive (AR): Describes a trait or disorder requiring the presence of two copies of a gene mutation at a particular locus in order to express observable phenotype.

Avascular Necrosis: Death of bone tissue due to impaired or disrupted blood supply (as that caused by traumatic injury or disease) and marked by severe pain in the affected region and by weakened bone that may flatten and collapse. <osteonecrosis>

B cells: A type of white blood cell lymphocyte that can either mature into plasma cells or memory B cells.

Biallelic mutations: Mutations that occur on both copies of a gene.

Blepharitis: Inflammation of the eyelids.

Bone Marrow: The soft tissue filling the cavities of bones. Bone marrow exists in two types, yellow and red. Yellow marrow is found in the large cavities of large bones and consists mostly of fat cells and a few primitive blood cells. Red marrow is a hematopoietic tissue and is the site of production of erythrocytes and granular leukocytes. Bone marrow is made up of a framework of connective tissue containing branching fibers with the frame being filled with marrow cells**.**

Buccal mucosa: Cheek tissue

Bullae: Blisters on the skin

Carcinogen: A cancer-causing agent

Carcinoma: A malignant tumor of epithelial origin

Carcinoma in situ (CIS): Carcinoma in the stage of development when the cancer cells are still within their site of origin (as the mouth or uterine cervix).

CBC: Complete Blood Count

Cerebellar hypoplasia: A neurological condition in which the cerebellum is smaller than usual or not completely developed.

Chemotherapy: The use of chemical agents in the treatment or control of disease.

Cholestasis: Any condition in which the flow of bile from the liver is slow or blocked.

Cirrhosis: Widespread disruption of normal liver structure by fibrosis and the formation of regenerative nodules that is caused by any of various chronic progressive conditions affecting the liver.

Coats Plus Syndrome/Retinopathy: The disorder causes blood vessels in the retina to be abnormally enlarged (dilated) and twisted. The abnormal vessels leak fluid, which can eventually cause the layers of the retina to separate (retinal detachment). These eye abnormalities often result in vision loss.

Common Variable Immunodeficiency (CVID): A disorder characterized by low levels of immunoglobulin (antibodies) and an increased risk of infection.

Co-morbidity: A medical condition that exists simultaneously with and usually independently of another medical condition.

Compound heterozygous: Usually refers to autosomal recessive disorders where an individual has two different abnormal alleles at a particular locus, one of each chromosome of a pair.

Conjunctival fornix: The loose arching folds connecting the conjunctival membrane lining the inside of the eyelid with the conjunctival membrane covering the eyeball.

Corpus callosum: The band of commissural fibers uniting the cerebral hemispheres.

Cortecosteroids: Any of various adrenal-cortex steroids used medically, especially as anti-inflammatory agents.

Cutaneous: Relating to the skin

Cytopenias: Deficiency of the cellular elements of the blood

Cytotoxic: Toxic to cells

De novo mutation: An alteration in a gene that is present for the first time in one family member as a result of a mutation in a germ cell (egg or sperm) of one of the parents or in the fertilized egg itself.

Dual energy X-ray absorptiometry (DEXA or DXA): A test which uses two different X-ray beams to estimate bone density in the vertebrae and hip.

Dyslipidemia: A condition marked by abnormal concentrations of lipids or lipoproteins in the blood.

Dysphagia: Difficulty swallowing

Dysplasia: Cells that look abnormal under a microscope but are not cancer.

Dysplastic nails: Ridging, flaking or poor growth of the nails

Ectropion: Abnormal turning out or a part, as in an eyelid

Edema: An abnormal excess accumulation of serous fluid in connective tissue or in a serous cavity.

Effusion: Escape of fluid from an anatomical vessel due to rupture.

Endocrinologist: Physician treating problems associated with the endocrine glands.

Engraftment: The process by which donor stem cells establish themselves successfully the recipient.

Enterocolitis: Inflammation affecting both the small and large intestine.

Enteropathy: Disease of the intestinal tract.

Esophageal stenosis: A narrowing of the esophagus that may interfere with swallowing. It is one of several examples of luminal stenotic lesions that appear in DC.

Esophageal web: Membranous structure in which a thin fold of tissue creates at least a partial obstruction of the esophageal lumen.

Excision: In a biopsy, the removal of the entire lump or suspicious area.

Exudative retinopathy: A condition where blood vessels in the retina become abnormally enlarged and twisted. The abnormal vessels leak fluid, which can eventually cause the layers of the retina to separate (retinal detachment). This eye abnormality often results in vision loss.

Familial: Tending to occur in more members of a family than expected by chance alone

Fanconi Anemia: A genetically heterogeneous rare autosomal recessive disorder characterized by congenital malformations, hematological problems and predisposition to malignancies. To date 16 distinct FANC genes have been reported

Gene: A specific sequence of nucleotides in DNA or RNA that is located usually on a chromosome and that is the functional unit of inheritance controlling the transmission and expression of one or more traits by specifying the structure of a particular polypeptide and especially a protein or controlling the function of other genetic material. <determinant>

Genetic anticipation: The phenomenon in genetic diseases where symptoms occur earlier and with increased severity in succeeding generations.

Germline: The cellular lineage of a sexually reproducing organism from which eggs and sperm are derived. Also: the genetic material contained in this cellular lineage which can be passed to the next generation.

Graft versus host disease (GVHD): A complication that can occur after a stem cell or bone marrow transplant. With GVHD, the

newly transplanted donor cells attack the transplant recipient's body.

Hematologic: Of or relating to blood or to hematology.

Hematopoietic: Of, relating to, or involved in the formation of blood cells <hematopoietic stem cells>.

Hematopoietic growth factor: Any of a group of glycoproteins that promote the proliferation and maturation of blood cells.

Hematopoietic stem cell transplant (HCT or HSCT): The intravenous infusion of autologous or allogeneic stem cells collected from bone marrow, peripheral blood, or umbilical cord blood to reestablish hematopoietic function in patients whose bone marrow or immune system is damaged or defective.

Hemorrhage: A copious discharge of blood from the blood vessels

Hepatic: Of, relating to, affecting, or associated with the liver <hepatic injury> <hepatic insufficiency>

Hepatocellular: Of or involving hepatocytes <hepatocellular carcinomas> <hepatocellular necrosis>

Heterozygous: Having the two genes at corresponding loci on homologous chromosomes different for one or more loci.

Hirsutism: Excessive growth of hair of normal or abnormal distribution.

Homozygous: Having the two genes at corresponding loci on homologous chromosomes identical for one or more loci.

Human papillomavirus (HPV): A sexually transmitted virus. It is passed on through genital contact (such as vaginal and anal sex). It is also passed on by skin-to-skin contact.

Hyperhidrosis: Generalized or localized excessive sweating.

Hyperkeratosis: Excessive thickening of the outer layer of the skin.

Hypogammaglobulinemia: A deficiency of gamma globulins and especially antibodies in the blood.

Hypogonadism: Functional incompetence of the gonads especially in the male with subnormal or impaired production of hormones and germ cells.

Hypothyroidism: The clinical syndrome that results from decreased secretion of thyroid hormone from the thyroid gland. It leads to a slowing of metabolic processes and in its most severe form to the accumulation of mucopolysaccharides in the skin, causing a nonpitting edema termed myxedema.

Idiopathic: Arising spontaneously or from an obscure or unknown cause.

Immunodeficiency: Inability to produce a normal complement of antibodies or immunologically sensitized T cells especially in response to specific antigens.

Immunoglobulin: Glycoproteins present in the blood (antibodies) and in other tissue. They are classified by structure and activity into five classes (immunoglobulin A; immunoglobulin D; immunoglobulin E; immunoglobulin G; immunoglobulin M).

Immunosuppression: Suppression (as by drugs) of natural immune responses.

In vivo: In the living body of a plant or animal.

Incomplete penetrance: The probability of a gene or genetic trait being expressed. "Incomplete" penetrance means the genetic trait is expressed in only part of the population. "Complete" penetrance means the gene or genes for a trait are expressed in all the population who have the genes. The percent penetrance also may change with the age range of the population.

Intrauterine growth retardation: The failure of a fetus to attain its expected fetal growth at any gestational age.

Iron chelation: Removal of iron from the blood through medication or phlebotomy.

LDL: A lipoprotein of blood plasma that is composed of a moderate proportion of protein with little triglyceride and a high proportion of cholesterol and that is associated with increased probability of developing atherosclerosis <*bad cholesterol*>, <*beta-lipoprotein*>, <*low-density lipoprotein*>

Leukemia: An acute or chronic blood cancer characterized by the type of white blood cell most prominently involved.

Leukoencephalopathy: Any of various diseases affecting the brain's white matter.

Leukoplakia: A white patch lesion found on a mucous membrane that cannot be scraped off. Leukoplakia is generally considered a precancerous condition, however its appearance may also result from a variety of hereditary diseases.

Liver function tests (LFT): A blood test that detects inflammation and damage to the liver.

Luteinizing hormone (LH): A female hormone that, in combination with follicle stimulating hormone, stimulates the secretion of estrogen from ovarian follicles. In men, it is important in the development of interstitial tissue in the testis and for the secretion of testosterone <interstitial-cell stimulating hormone> <lutropin>

Lymphocyte: Any of the colorless weakly motile cells that originate from stem cells and differentiate in lymphoid tissue (as of the thymus or bone marrow), that are the typical cellular elements of lymph, that include the cellular mediators of immunity, and that constitute 20 to 30 percent of the white blood cells of normal human blood.

Lymphopenia: Reduction in the number of lymphocytes circulating in the blood of humans or animals.

Macrocytosis: The occurrence of larger-than-normal red blood cells.

Microcephaly: A condition of abnormal smallness of the head usually associated with intellectual delays.

Mucocutaneous Triad: Reticulated skin pigmentation, nail dystrophy, and oral leukoplakia

Multifactorial: Having characters or a mode of inheritance dependent on a number of genes at different loci.

Mutation: A relatively permanent change in hereditary material involving either a physical change in chromosome relations or a biochemical change in the codons that make up genes

M**yeloablative**: Total depletion of bone marrow cells, such as through the administration of chemotherapy and radiation therapy prior to a stem cell transplant.

Myelodysplastic syndrome (MDS): Disease in which the bone marrow does not function normally. Also called preleukemia or smoldering leukemia

Nail dystrophy: This general term is used to describe malformed fingernails and toenails. The nails are often ridged, pitted or abnormally curved.

Nasolacrimal duct: The duct transmits tears from the lacrimal sac to the inferior meatus of the nose. It is also called the nasal duct.

Neoplasia: A process of tumor formation.

Neutropenia: Neutropenia is an abnormal decrease in the number of neutrophils, a type of white blood cells.

Neutrophil: A granulocyte that is the chief phagocytic white blood

cell is called a neutrophil.

Next-generation sequencing technologies: This recent new technology has been developed to speed up the process to sequence a human genome, DNA. It now takes only a few days to weeks to complete.

Ophthalmic: Relating to the eye. Draining the eye or structures in the region of the eye

Opportunistic infection: An infection caused by bacterial, viral or fungal pathogens that occurs more frequently and are more severe in individuals with weakened immune systems is said to be opportunistic.

Osteonecrosis: This disease is caused by reduced blood flow to the bones and joints. The lack of blood causes the bone to break down faster than the body can make enough new bone. The bone starts to die and may break down.

Osteopenia: This can cause bones to be weak and brittle, and increases the risk for broken bones. It is a decrease in the amount of calcium and phosphorous in the bone. It is also called bone loss.

Palliative treatment: It is treatment of the discomfort, symptoms, and stress of serious illness. It provides relief from distressing symptoms including pain, shortness of breath, fatigue, constipation, nausea, loss of appetite and problems with sleep.

Pancytopenia: It is the reduction in the number of red and white blood cells as well as platelets. It results in fatigue due to the low numbers of red blood cells, frequent infections due to the low

number of white blood cells, clotting problems due to the low number of platelets.

Parathyroid Hormone (PTH): The hormone of the parathyroid gland regulates the metabolism of calcium and phosphorus in the body. <parathormone.>

Peliosis: This purplish or brownish red discoloration is caused by hemorrhage into the tissues. It is easily visible through the epidermis.

Phenotype: A phenotype is an individual's observable traits, such as height, eye color, and blood type. The genetic contribution to the phenotype is called the genotype.

Platelet Count: A platelet count is a test to measure how many platelets you have in your blood. Platelets are tiny fragments of cells that are essential for blood clotting.

Poikiloderma: Several disorders that are characterized by patchy discoloration of the skin.

Portal Hypertension: This type of hypertension in the hepatic portal system is caused by venous obstruction or occlusion that produces splenomegaly and ascites in its later stages.

Pulmonary Fibrosis: Pulmonary fibrosis is a condition in which the tissue deep in your lungs becomes scarred over time. This tissue gets thick and stiff. That makes it hard for you to catch your breath, and your blood may not get enough oxygen.

Reticulated Skin Pigmentation: Skin pigmentation, or coloring, resembling a net. <hyperpigmentation>

Retinopathy: Any of various noninflammatory disorders of the retina including some that causes blindness.

Revesz Syndrome: A variant of dyskeratosis congenita involving abnormalities in the light-sensitive tissue at the back of the eye (retina).

Schatzki's Rings: A local narrowing in the lower part of the esophagus that may cause dysphagia, or difficulty in swallowing.

Severe Combined Immunodeficiency (SCID): A rare congenital disorder of the immune system that is characterized by inability to produce a normal complement of antibodies and T cells and that usually results in early death.

Silent Carrier: A person who has a genetic defect but does not develop any symptoms or signs of the defect. The carrier's offspring may inherit the defect and develop the associated disorder.

Squamous Cell Cancer (SCC): Cancer of a kind of epithelial cell. Is one of the major forms of skin cancer but can also occur in the digestive tract, lungs, and other areas of the body.

Strictures: Abnormal narrowing of bodily passages (as from inflammation, cancer, or the formation of scar tissue).

Syndrome: A group of signs and symptoms that occur together and characterize a particular abnormality.

Taurodontism: A dental condition marked by the enlargement of the pulp cavities and the reduction of the roots.

Telangiectasias: A permanent dilation of preexisting blood vessels (capillaries, arterioles, venules) creating small focal red lesions, most commonly in the skin or mucous membranes.

Telomerase: A ribonucleoprotein (RNA) that is an enzyme that adds DNA sequence repeats to the end of DNA strands in the telomere regions, which are found at the end of chromosomes.

Telomere: The end of a chromosome. Telomeres are made of repetitive sequences of non-coding DNA that protect the chromosome from damage. Each time the cell divides, the telomeres become shorter. Eventually, the telomeres become so short that the cell can no longer divide and it dies.

Thrombocytopenia: Persistent decrease in the number of blood platelets.

Trichiasis: A turning inward of the eyelashes often causing irritation of the eyeball.

Urethral Stenosis: A narrowing of the diameter of the urethra.

Urogenital: Of, relating to, affecting, treating or being the organs or functions of excretion and reproduction.

Veno-Occlusive Disease: Disorder in which veins are partially or completely obstructed or the blood flow through the veins is less than optimal.

X-linked recessive (XLR): A mode of inheritance in which a mutation in a gene on the X chromosome causes the phenotype to be expressed in males and in females who inherit the same alleles for a particular gene from both parents.