Dyskeratosis Congenita: Genetic Counseling and Inheritance Patterns

Ann Garrity Carr, MS, CGC
Certified Genetic Counselor

Sharon A. Savage, MD
Chief, Clinical Genetics Branch
Division of Cancer Epidemiology and Genetics

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Who are Genetic Counselors?

- Master’s-trained health care professionals who combine their knowledge of basic science, medical genetics, epidemiological principles, and counseling theory with their skills in genetic risk assessment, education, interpersonal communication and counseling to provide services to clients and their families for a diverse set of genetic or genomic indications.

- Genetic counselors help people “. . . understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.” The process of genetic counseling “. . . integrates the following: interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; education about inheritance, testing, management, prevention, resources and research; counseling to promote informed choices and adaptation to the risk or condition.” (National Society of Genetic Counselors’ Definition Task Force, 2006.)
Genetic Counseling for DC

• Pre-test
  - Evaluate
    ▪ Understanding of risk and reasons for testing
    ▪ Genetic risk for individual family members
  - Educate
    ▪ Findings associated with mutations in the DC genes
    ▪ General genetics and inheritance
    ▪ Inheritance patterns of DC-related genes
  - Discuss
    ▪ Risks, benefits, and limitations of genetic testing
    ▪ Testing procedure for DC genes
    ▪ Alternatives to genetic testing

• Testing
  - Consent for genetic testing
  - Obtain sample for DNA analysis
  - CLIA laboratory testing for mutations in DC genes

• Post-test
  - Patient/family contacted that results are available
  - Disclosure of results by genetic counselor and/or physician
Cell

DNA base

DNA (Deoxyribonucleic acid)

Gene

Chromosome
Chromosomes of a Male
Genes for Dyskeratosis Congenita

- TERT
- DKC1
- TERC
- NHP2
- TINF2
- NOP10
- WRAP53
- AND
- CTC1
- TERT
- PARN
- ACD
- RTEL1

http://www.biologia.uniba.it/rmc/0-internal-images/z-ideograms/ideograms.html
DNA Genetic Code Dictates Amino Acid Identity and Order

DNA Sequence Is the Genetic Code.

GCA AGA GAT AAT TGT...

Ala Arg Asp Asn Cys... Growing Protein Chain
DNA Replication

- DNA opens up like a zipper to make an exact copy of itself:
  - A matches with T
  - C matches with G
- The copied DNA is identical to the original DNA
Disease-Associated Pathogenic Variants (Mutations)

- A **pathogenic variant (mutation)** is a change in the order of the bases (A, T, C, or G) when the DNA does not copy itself correctly, resulting in altered function of the protein.
The gray cat ran down the hall.
The gray cat ran down the ball.

Changes in DNA might change the way a gene works.
X-Linked Recessive Inheritance

- DC gene is on the X, a sex determining chromosome
- Men who inherit the pathogenic variant (mutation) from their mother have a high risk of DC-related findings (men have only one X chromosome)
- Carrier females – rarely affected
X-Linked Recessive

Parents

- Father Affected
- Mother Unaffected

Children

- Son Unaffected
- Daughter Carrier
- Son Unaffected
- Daughter Carrier

- Son Affected
- Daughter Carrier
- Son Unaffected
- Daughter Unaffected

NIH
U.S. National Library of Medicine

Autosomal Dominant Inheritance

- Each child of a parent with a DC pathogenic variant (mutation) has a 50% chance of inheriting the mutation.
- No “skipped generations”
- Men and women have the same chance to pass a DC pathogenic variant (mutation) on to their sons or daughters.
Autosomal Recessive Inheritance

- Two pathogenic variants (mutations) (one from each parent) are needed to be at risk for DC
- Each child has a 1 in 4, or 25%, chance of inheriting both parents’ pathogenic variants (mutations) associated with DC
- Men and women have the same chance to pass a DC pathogenic variant (mutation) on to their sons or daughters

No DC pathogenic variant (mutation) – not at increased risk
One DC pathogenic variant (mutation) - carrier
Two DC pathogenic variants (mutations) – high risk for DC-related findings
## Inheritance Pattern of DC Genes

<table>
<thead>
<tr>
<th>X-Linked Recessive</th>
<th>Autosomal Dominant</th>
<th>Autosomal Recessive</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>DKC1</em> (DC, HH)</td>
<td><em>TERC</em> (DC, AA, PF)</td>
<td><em>NOP10</em> (DC)</td>
</tr>
<tr>
<td><em>TINF2</em> (DC, HH, RS)</td>
<td></td>
<td><em>NHP2</em> (DC)</td>
</tr>
<tr>
<td><em>TERT</em> (DC, AA, MDS, AML, PF)</td>
<td></td>
<td><em>TERT</em> (HH)</td>
</tr>
<tr>
<td><em>RTEL1</em> (PF, AA)</td>
<td></td>
<td><em>RTEL1</em> (DC, HH)</td>
</tr>
<tr>
<td><em>PARN</em> (PF)</td>
<td></td>
<td><em>PARN</em> (HH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>WRAP53</em> (DC, HH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>CTC1</em> (CP, DC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>ACD</em> (HH)</td>
</tr>
</tbody>
</table>

**Annotations:**
- AA = aplastic anemia
- AML = acute myeloid leukemia
- CP = Coates plus
- DC = Dyskeratosis congenita
- HH = Hoyeraal-Hreidarsson syndrome
- MDS = myelodysplastic syndrome
- PF = pulmonary fibrosis
- RS = Revesz syndrome
- **BOLD** = multiple inheritance patterns for the same gene
Genetic Testing

• Analyzing DNA to look for a genetic alteration (mutation, variant, change) that may indicate an increased risk of developing DC

• Performed on a small sample of body fluid or tissue
  – Usually blood, but sometimes saliva, cells from inside the cheek, skin cells, amniotic fluid (the fluid surrounding a developing fetus), or other tissues

• Clinical genetic testing
  – Find out whether a disease associated gene for DC can be identified in an individual patient and/or family member
  – Results of a clinical test are disclosed and may help an individual make decisions about medical care or reproductive issues
  – Clinical tests may be diagnostic, predictive/presymptomatic, or carrier testing
  – Prenatal clinical tests may be screening (indicate an increased risk but not conclusive) or diagnostic; preimplantation tests are diagnostic

• Research genetic testing
  – Finding unknown genes, learning how genes work, developing tests for future clinical use, and advancing our understanding of genetic conditions
  – Research results are usually not available to patients or their healthcare providers
Ideally, Begin Testing with a Person in the Family Who Has DC

Once a mutation/disease-associated genetic variant is identified in a family member with DC, testing will be more informative for individuals than if they were only tested for telomere length.
DNA Sequencing
Gene panel testing

Variants in any of these genes cause similar disease
Genomic testing to find cause of rare disease
Whole genome vs. whole exome

Genome 100%

Exome 1-2%
Whole genome sequencing vs. whole exome sequencing

**Whole Genome Sequencing**

- **GENE**
  - Exon Intron Exon Intron Exon Intron

  **SEQUENCING**

  AATCGATGGACTAGCAAGTAATTACCGTTCTAGATCGTA

**Whole Exome Sequencing**

- **GENE**
  - Exon Intron Exon Intron Exon Intron

  **SEQUENCING**

  GGACTAGCAAGTAATTACCGT
Exome Sequencing

• Our DNA has 3 billion building blocks or “letters”
• Only a small amount of those letters code for our proteins
• The “exome” contains all of our exons (the part that codes for our proteins)
• Exome sequencing looks at every letter in a DNA sequence, so it can reveal rare mutations
Uncovering Genetic Causes of DC by Whole Exome Sequencing

Variant Filtering Strategy

- Total variants
- Remove synonymous SNPs
- In ESP <4x
- In internal control group <3x
- Segmental duplications
- In proband
- In family members with short telomeres

Technical Validation and Functional Characterization

Sequencing done at Cancer Genomics Research Lab, DCEG, NCI using Nimbelgen v2 Capture Arrays, Illumina HiSeq (Bari Ballew)
What Results Might I Get from Genetic Testing?

- Genetic testing can be interpreted as positive, negative, true negative, uninformative negative, or benign polymorphism.
- Specific genetic variants may be classified as pathogenic, likely pathogenic, variant of unknown significance, likely benign, or benign.
- Results of preimplantation genetic diagnosis (PGD) guides a doctor and woman/couple to decide which embryo(s) to implant in a woman’s uterus.
X-linked Recessive Inheritance: Genetic Testing Results

<table>
<thead>
<tr>
<th>Result</th>
<th>Gender</th>
<th>Genetics</th>
<th>Affected with DC?</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Mutation</td>
<td>Female</td>
<td>$XX - 2\ DKC1\ genes\ without\ mutation$</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>$XY - 1\ DKC1\ gene\ without\ mutation$</td>
<td>No</td>
</tr>
<tr>
<td>1 Mutation</td>
<td>Female</td>
<td>$XX - 1\ DKC1\ gene\ with\ and\ 1\ without\ mutation$</td>
<td>Rarely - Carrier</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>$XY - 1\ DKC1\ gene\ with\ mutation$</td>
<td>Yes</td>
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# Autosomal Dominant Inheritance: Genetic Testing Results

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<th>Genetics</th>
<th>Affected with DC?</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Mutation</td>
<td>Both</td>
<td>2 genes without DC mutation</td>
<td>No</td>
</tr>
<tr>
<td>1 Mutation</td>
<td>Both</td>
<td>1 gene with and 1 gene without DC mutation</td>
<td>Yes</td>
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### Autosomal Recessive Inheritance: Genetic Testing Results

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<tr>
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<td>Both</td>
<td>2 genes without DC mutation</td>
<td>No</td>
</tr>
<tr>
<td>1 mutation</td>
<td>Both</td>
<td>1 gene with and 1 gene without DC mutation</td>
<td>No, Carrier</td>
</tr>
<tr>
<td>2 of the same mutation</td>
<td>Both</td>
<td>2 genes with DC mutation</td>
<td>Yes</td>
</tr>
<tr>
<td>2 different mutations in same gene</td>
<td>Both</td>
<td>2 genes with DC mutation</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Informed Consent for Testing

• Potential Benefits
  - Improved medical management of DC-related disorders
  - Relief from uncertainty and anxiety regarding DC-related disorders
  - Information for individual and family/lifestyle decision making

• Potential Risks
  - Physical (generally small) to obtain sample for testing
  - Discovering persons with unsuspected affected or carrier diagnoses for DC
  - Emotional distress, impact on family dynamics, sibling issues
  - Loss of privacy
  - Discrimination by employers and insurers

• Limitations of Genetic Testing
  - Significance of some genetic variations is unknown
  - Negative molecular genetics test result is fully informative only if mutation(s) identified in family
  - Identification of DC mutation(s) indicates an increased risk, not certainty, of developing physical or hematologic findings associated with DC or cancer
An Important Limitation of Genetic Testing
Use Family History to Help Decide About:

• Inheritance pattern
  – X-linked Recessive (XLR)
  – Autosomal Dominant (AD)
  – Autosomal Recessive (AR)

• Risks to patient and family members

• Offering genetic testing

• Referrals for screening, prevention, and support
Genetic Testing Has Implications for the Entire Family

- Consider the impact of testing on all family members
- Ultimately, testing is the choice of the individual or their guardian
Potential Issues for Female Carriers of a \textit{DKC1} Mutation

- **Genetic**
  - 50\% chance for any child to inherit the \textit{DKC1} mutation
    - Sons will be affected if they inherit the mutation
    - Daughters will be carriers if they inherit the mutation

- **Psychological and Social**
  - Possible stigma of being a carrier
  - Not affected - relief/survivor guilt

- **Medical**
  - Most \textit{DKC1} female carriers are healthy
  - A few \textit{DKC1} female carriers may have mild manifestations of DC due to incomplete X inactivation
Potential Issues for Persons Found to be Affected with DC by Genetic Testing

- Risk of children inheriting DC associated mutation depends on inheritance pattern
  
  - X-linked recessive inheritance
    - Affected males: no affected sons, all daughters are carriers
    - Carrier females: 50% chance for each son to be affected and 50% chance for each daughter to be a carrier

  - Autosomal dominant inheritance
    - 50% chance for any child to be affected

  - Autosomal recessive inheritance
    - 50% chance for any child to be a carrier
    - 25% chance for any child to be affected if partner is also a carrier
Potential Family Issues for Individuals with DC

- Amount of attention received from parents
- May/may not want to be treated as a “normal” child
- Issues surrounding possible bone marrow/stem cell donation – indebted to sib
- Wonder why they were the “unlucky” one compared to sibs
- How to talk to family and/or friends about why they are different from sibs
Potential Family Issues for Individuals without DC

- Amount of attention paid to affected sibling
- Issues surrounding possible bone marrow/stem cell donation
- Relief/survivor guilt
- How to talk to family and/or friends about sibling or other family member with DC
Reproductive Options for Persons Who Have a Mutation in a Gene for DC

• Natural pregnancy with no preimplantation or prenatal testing
  — Test child soon after birth

• Natural pregnancy with no preimplantation or prenatal testing
  — Test child when symptoms develop (follow screening guidelines for DC-related diseases if parents choose not to test the child after birth)

• Prenatal diagnosis
  — Amniocentesis
  — CVS

• Future: prenatal testing by maternal blood sample
  — Non-invasive prenatal testing with cell-free DNA to test for the specific mutation(s) in the parent(s)
Reproductive Options for Persons Who Have a Mutation in a Gene for DC (2)

• Conception/Preimplantation
  – Donor egg or sperm
  – In Vitro Fertilization (IVF)
    ▪ Eggs and sperm combined in the laboratory (in vitro)
    AND
  – Preimplantation Genetic Diagnosis (PGD)
    ▪ Cell(s) removed from the embryo after a few days
    ▪ Molecular testing for single gene disorders and/or HLA type

• Adoption
Cord Blood Banking

• A baby’s umbilical cord contains blood which is a source of stem cells
• Banked cord blood stem cells may be used if/when a family member needs a transplant for DC if the donor and recipient are an HLA match
DNA Banking

- Genetic testing results for at-risk family members are most accurate when testing is first performed on a relative with the condition
- Involves obtaining genetic material (blood, cheek cells, saliva, or other tissues) from an individual to extract DNA and store the sample for future use
- Reasons for obtaining a sample for DNA banking:
  - Current genetic testing technology has not identified the cause of the disorder in a person/family
  - Having a DNA sample from an affected family member will allow discovery of the genetic basis of a disorder based on future advances in genetic testing
  - A terminally ill family member does not have time for a genetic evaluation and testing
  - The current cost of testing is prohibitive
- Laboratories in the United States from the Genetic Testing Registry (GTR) - Information accessed 8/28/18
Inherited bone marrow failure syndromes (IBMFS) are rare disorders; usually these patients have some form of aplastic anemia (failure of the bone marrow to produce blood), and may have a family history of the disorder. There are several well-described syndromes that can be recognized by healthcare experts either by physical characteristics in the patients or from laboratory findings. There are also patients who are harder to classify.

Patients with these syndromes are of interest to the NCI because they have a very high risk of developing cancer (either leukemia or certain solid tumors). At the moment, we cannot predict which specific patient with an IBMFS is going to develop cancer, and we want to study all patients with an IBMFS to learn more about those without and those who may develop cancer.

The NCI IBMFS Cohort Study enrolls families from North America that have at least one member with an IBMFS. The study includes individuals known to have an IBMFS as well as their first degree relatives (brothers, sisters, parents, and children) as well as other relatives where appropriate.

Our overall goal is to reach a better understanding of how cancers develop in persons with IBMFS, so that we may improve the health care that can be offered to persons with these disorders.

How can I join?

Individuals with one of the inherited bone marrow failure syndromes and their family members are encouraged to participate.

Phone: 1-800-518-9474 to speak with the referral nurse
Email: NCI.IBMFS@westat.com
Genetic Counseling Resources

National Society of Genetic Counselors
- http://aboutgeneticcounselors.com/
- https://www.nsgc.org/page/find-a-genetic-counselor

Genetic Alliance: Making Sense of Your Genes: A Guide to Genetic Counseling
- http://www.geneticalliance.org/publications/guidetogeneticcounseling
Genetics Resources

• Genetics Home Reference – Help Me Understand Genetics

• Genetic Alliance: Genes in Life – Genetics 101
  – http://www.genesinlife.org/genetics-101

• National Cancer Institute

• National Human Genome Research Institute
  – https://www.genome.gov/education/

• Wellcome Trust Sanger Institute
  – https://www.yourgenome.org/