Chapter 5

Genetic Counseling for Families

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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 (*National Society of Genetic Counselors*, http://www.nsgc.org; *About Genetic Counselors*, https://www.aboutgeneticcounselors.org/).

The process of genetic counseling integrates the interpretation of family and personal medical histories to assess the chance of disease occurrence or recurrence. Genetic counseling may include a discussion of the diagnosis of and/or screening for inherited disease(s), types of inheritance, available genetic testing options, genetic test results, disease management, referral to genetic disease support groups and/or other resources, as well as potential research

opportunities.

Genetic counselors are generally master's degree level healthcare professionals who typically work as part of a medical care team. An appointment with a genetic counselor may provide individuals and families with a better understanding of a telomere biology disease (TBD) diagnosis through discussions including family history, clinical findings, general and TBD-specific genetic information, genetic testing options and results, psychological and social issues, risk assessment for other family members, family planning, and identification of support options for families with a TBD. A local genetic counselor can be found through the findageneticcounselor.nsgc.org website.

Overview of the Genetics of Telomere Biology

Our cells contain all of our genetic material, called DNA, in 23 pairs of chromosomes. Chromosome pairs 1-22 are autosomal meaning they are the same between males and females. The last pair of chromosomes are called the sex chromosomes. Males have an X and a Y sex chromosome while females have two X chromosomes. Individual genetic instructions in our DNA are called genes. Genes encode all the instructions needed for our bodies to function properly. The genes in our DNA are made up of four bases called adenine (A), guanine (G), thymine (T), and cytosine (C). Combinations of these bases in groupings of three encode twenty amino acids. Amino acids are assembled together, like beads on a string, to make proteins. Proteins contain the information necessary for cells to perform their specific functions.

If the A, T, G, and C bases of the amino acid code are changed, the protein will not be assembled or function properly. Changes in the gene are called variants (historically called mutations). In the case of genes associated with TBD, the variants affect proteins

important in maintaining the ends of our chromosomes called telomeres. Telomeres are essential for the stability of our chromosomes, thus individuals with TBD-associated genetic variant(s) will most often have shorter than normal telomeres for an individual of their age (see also Chapter 2, Why Telomeres Matter).

The Genetics & Inheritance of TBD

As of March 2021, there are 15 established genes known to be associated with TBDs: *ACD*, *CTC1*, *DKC1*, *NAF1*, *NHP2*, *NOP10*, *PARN*, *POT1*, *RTEL1, STN1*, *TERC*, *TERT*, *TINF2*, *WRAP53*, and *ZCCHC8*. There are other genes for which there is limited evidence for an association with TBDs: *DCLRE1B*/*SMN1B*/*Apollo*, *GRHL2*, *LIG4*, *MDM4*, *NPM1*, *RPA1*, and *USB1*. At least 70% of individuals who meet clinical diagnostic criteria for DC have a disease-causing variant in one of the established genes [1].

TBDs can be inherited in an autosomal or X-linked pattern. Both males and females have two copies of autosomal genes. Autosomal dominant (AD) inheritance means that an individual only needs a disease-causing variant on one copy of an autosomal gene to have a TBD. Each child of an individual with an AD variant has a 50% chance of inheriting the variant from that parent (Table 1).

Autosomal recessive (AR) inheritance means that an individual has a TBD from having a disease-causing variant on both copies of the same autosomal gene associated with TBD. When a child has an AR form of TBD, each of their parents is typically a “carrier” of one of the disease-causing variants identified in the child. In each pregnancy for two carriers together, there is a 25% chance to have a child inherit both variants and have a TBD, a 50% chance to have a child who inherits one variant and is a carrier of TBD, and a 25% chance of having a child who does not inherit either variant. For two individuals to have a child with AR TBD, they must both carry a variant in the same TBD-associated gene (Table 1).

Some of the TBD autosomal genes can be associated with both autosomal dominant

and autosomal recessive disease (Table 1). Typically, individuals with a disease-causing variant in one copy of the TBD-associated gene (AD) have milder disease than individuals with a disease-causing variant on both copies of the same gene (AR).

While the majority of the genes associated with TBDs are autosomal, one TBD-associated gene called *DKC1* is located on the X chromosome and is inherited in an X-linked (XL) pattern (see Table 1). Since female sex chromosomes are XX, they have two X chromosomes and two copies of the *DKC1* gene. Since male sex chromosomes are XY, they only have one X chromosome and only one copy of the *DKC1* gene. Males who have a disease-causing variant on their only copy of the *DKC1* gene are expected to have symptoms since they no longer have any functioning *DKC1*. Females with a disease-causing variant on one of their two copies of *DKC1* gene tend to be either unaffected or have more mild symptoms because they have a second, working copy of *DKC1*. Historically, females with a *DKC1* gene variant were referred to as “carriers” as they have an increased chance of having a child with a TBD. This term has faced some opposition, as it does not account for the symptoms that some women with this form of TBD may experience.

Any child of a female with an XL variant will have a 50% chance of inheriting the X chromosome with the variant. Males who inherit the variant are expected to have disease symptoms while females who inherit the variant could have an increased chance of developing some symptoms in their lifetime. Each daughter has a 50% chance of inheriting the X chromosome with the variant. Males with XL TBD will pass the variant to all of their daughters (who inherit the X chromosome with the *DKC1* gene variant) and none of their sons (who inherit the Y chromosome).

In the majority of cases, the variant(s) that is causing the TBD symptoms in an individual was inherited from one or both parents. However, in some cases the disease-causing variant was new in the individual with a TBD. This is called a *de novo* variant. If a TBD-associated variant is found in a proband but not found in a parent, it is considered likely *de novo*. Due to the small chance of gonadal mosaicism in a parent

with negative testing, there remains a small residual chance of disease recurrence in a future pregnancy.

Table 1: Mode of Inheritance of TBD and Possible TBD Associated Genes

Mode of Inheritance	TBD Gene(s)
X-linked (XL)	*DKC1*
Autosomal Dominant (AD)	*NAF1*, *TERC*, *TINF2*, *ZCCHC8*
Autosomal Dominant (AD) or Autosomal Recessive (AR)	*ACD*, *NHP2*, *PARN*, *RTEL1*, *TERT*
Autosomal Recessive (AR)	*CTC1*, *NOP10*, *POT1*, *STN1* (*OBFC1*), *WRAP53*

Genotype/Phenotype Correlations and Symptom Variability

The variant(s) and the TBD-associated gene that is impacted is called the genotype. The phenotype refers to the clinical symptoms identified in an individual. Genotype/phenotype correlations refers to the association between the possible or likely clinical symptoms based on the identified genotype. This section highlights some of the genotype/phenotype findings for various TBD-associated genes. It is important to know that even within individuals in the same family with the same genetic cause of TBD, the symptoms that each individual experiences and the age of symptom onset can vary. This is called variable expressivity. Further, not everyone with the gene variant associated with TBD may show symptoms of the disease. This is called reduced penetrance. Finally, in some families with TBD, subsequent generations may be more severely affected or have an earlier onset of disease than in previous generations. This is called anticipation.

These concepts help explain why the term telomere biology disorders, or TBD, is used in this second edition of the Clinical Guidelines instead of dyskeratosis congenita. While historically dyskeratosis congenita was defined by the classic clinical triad (see Chapters 3, Diagnosing TBDs & Subtypes of TBDsand 6, Dermatologic Manifestations), it is now known that the spectrum of disease extends from pediatric patients with classic presentations to individuals presenting with a single symptom, such as pulmonary fibrosis, in adulthood. Based on this understanding, the term TBD is used to describe families with telomere disease, as it encompasses the full spectrum of symptoms in disorders of telomere maintenance.

***ACD*:** Heterozygous (AD) and compound heterozygous (AR) variants in *ACD* have been reported. A three generation family with a heterozygous *ACD* variant presented with short telomeres, bone marrow failure, and oral cancer without dysmorphism, mucocutaneous manifestations, or anomalies of the skeletal, cardiac or urogenital system [2]. A compound heterozygous case was reported with clinical features consistent with Hoyeraal Hreidarsson syndrome including microcephaly, cerebellar hypoplasia, developmental delay, oral leukoplakia, nail dystrophy, and esophageal stenosis [3].

CTC1: Homozygous and compound heterozygous variants (both AR) in *CTC1* have been associated with Coats Plus and less commonly with classic dyskeratosis congenita [4-7]. Limited information is available on possible disease symptoms in carriers [8]. Some reports have demonstrated telomere lengths at or less than the first percentile for age in homozygous/compound heterozygous cases while heterozygous relatives had telomere lengths on the lower end of normal [7, 9]. Others have reported normal telomere length studies in cases, carriers and controls [5, 6].

DKC1: Males with a hemizygous (XL) variant in the *DKC1* gene can present with a wide range of clinical phenotypes. The classic triad is commonly seen in males with *DKC1* variants. The classic dyskeratosis congenita and Hoyeraal Hreidarsson syndrome phenotypes predominate; however, more isolated disease symptoms or later onset

disease severity has been reported [10-13]. Females with *DKC1* (previously called carriers) can be asymptomatic or show more mild disease symptoms such as features of the classic triad, dental anomalies, hair abnormalities although some isolated cases of women with more pronounced disease symptoms have been reported [14-17].

***NAF1*:** Heterozygous (AD) frameshift variants have been identified in individuals with short telomere length, pulmonary fibrosis, and bone marrow failure [18]**.**

NHP2: Homozygous and compound heterozygous variants (both AR) in *NHP2* were originally reported in cases with classic dyskeratosis congenita findings [19, 20]. A subsequent publication demonstrated a compound heterozygous case with the Hoyeraal Hreidarsson syndrome phenotype including intrauterine growth retardation, microcephaly, cerebellar hypoplasia, developmental disability, lymphopenia, and the classic triad. In addition, multiple heterozygous (AD) cases were reported with aplastic anemia, interstitial lung disease, and pulmonary fibrosis. While both the individuals with apparent autosomal recessive and autosomal dominant disease had telomere lengths at or less than the 1st percentile for age, the parents of the child with HH who are heterozygotes had normal telomeres and were reportedly asymptomatic in young adulthood [21].

NOP10: A homozygous (AR) variant in *NOP10* was reported in three siblings with reticular skin pigmentation and nail dystrophy without leukoplakia. Other symptoms included abnormal dentition, thickening of the skin on the palms and soles, and short telomeres. One individual had hypocellular bone marrow and pancytopenia. Heterozygous relatives had telomeres that were significantly shorter than controls but not as short as the homozygous cases [22]. A more recent report identified two second cousins once-removed with the same homozygous variant in the *NOP10* gene presenting in infancy with cataracts, hearing impairment, nephrotic syndrome, enterocolitis and short telomeres. One child was also found to have cerebellar hypoplasia and hypomyelination. One relative with a heterozygous variant had hearing

impairment [23].

***PARN*:** Homozygous/compound heterozygous (both AR) and heterozygous (AD) variants in *PARN* present with a severe phenotype in some individuals, while others have pulmonary fibrosis. Clinical findings may include short telomeres [24] and immunologic abnormalities [25], as well as intrauterine growth retardation, microcephaly, central nervous system calcifications, severe developmental delay, cerebellar hypoplasia, esophageal and urethral stenosis, hip avascular necrosis, bone marrow failure abnormal skin pigmentation, oral leukoplakia, nail dysplasia, hyperkeratosis of palms and soles, and multiple fractures [26, 27].

POT1: Homozygous (AR) variants in the *POT1* gene have been associated with a very early onset and rapidly progressing form of Coats Plus (CP). The reported symptoms included intrauterine growth retardation, leukoencephalopathy, gastrointestinal ectasia, bone fracture, developmental disabilities, and sparse hair in addition to the intracranial calcifications and retinal exudates that are typical of CP [28]. Heterozygous (AD) variants in *POT1* have also been associated with an increased risk of developing certain malignancies [29].

***RTEL1*:** Heterozygous (AD) and homozygous/compound heterozygous (both AR) variants have been reported in *RTEL1* in association with short telomeres and disease. A founder *RTEL1* variant, R1264H, has been identified in the Ashkenazi Jewish population [30, 31]. Clinical findings for individuals with homozygous or compound heterozygous variants may be suggestive of DC or Hoyeraal Hreidarsson syndrome and may be more severe than those with heterozygous variants [31-33]. Multiple families with heterozygous variants in *RTEL1* have presented with adult-onset disease, often with an isolated feature such as pulmonary fibrosis, liver disease, or bone marrow failure [32-35]. Importantly, these phenotypes are not necessarily uniform in families, and other disease features may be seen, including the dyskeratosis congenita phenotype [36-37].

STN1: Two patients with homozygous (AR) variants in the *STN1* gene have been

reported with a Coats Plus phenotype. Symptoms included intrauterine growth retardation, premature greying, poor growth, liver fibrosis, portal hypertension, esophageal varices, brain calcifications with white matter changes, osteopenia, gastrointestinal hemorrhage, telangiectasia, and pancytopenia with hypocellular bone marrow. One patient developed significant neurologic disease including spasticity, dystonia, and ataxia. One of the reported cases had normal telomere lengths while the other had short telomeres [38].

TERC: Variants in the *TERC* gene have been associated with a wide phenotypic spectrum from unaffected adults to pediatric onset disease. Some individuals present with isolated features of telomere disease such as lung, liver or hematologic abnormalities in later adulthood while others present with more classic dyskeratosis congenita symptoms with some or all of the classic triad including a possible case with the Hoyeraal Hreidarsson phenotype [39-43]. While telomere lengths are often less than the first percentile for age, some affected individuals have telomere lengths that are more moderately short [44-46]. While TERC is associated with an autosomal dominant form of TBD, a case of more pronounced disease in an individual with two *TERC* gene variants has been reported [47].

***TERT*:** Heterozygous (AD) and homozygous/compound heterozygous (both AR) variants in the *TERT* gene have been associated with disease symptoms. Some individuals with one variant in *TERT* may have classical DC findings such as the clinical triad, bone marrow failure, cancer, and liver cirrhosis [46, 48, 49]. However, others may only have an isolated disease symptom such as pulmonary fibrosis [50] or be asymptomatic. Additionally, those with homozygous/compound heterozygous *TERT* variants may have a severe Hoyeraal-Hreidarsson phenotype [51]. As with the *TERC* gene, telomere lengths are often less than the first percentile for age, some affected individuals have telomere lengths that are more moderately short [44-46].

***TINF2*:** Variants in the *TINF2* gene are heterozygous (AD), often identified in exon 6 of the gene, and commonly *de novo*. Patients with *TINF2* variants usually have very short

telomeres. Clinical findings may be severe (some *TINF2* variants have been identified in those with Hoyeraal Hreidarsson or Revesz syndromes) and include aplastic anemia, bone marrow failure, dystrophic nails, skin abnormalities, leukoplakia, oral cancer, osteoporosis, avascular necrosis of the hip, epiphora, pulmonary fibrosis, gastrointestinal hemorrhage, bilateral exudative retinopathy, intracranial calcification, microcephaly, developmental delay, and immune deficiency [49, 52, 53].

WRAP53: Patients with compound heterozygous (AR) variants in the *WRAP53* gene have been reported with classic dyskeratosis congenita symptoms including the classic triad, bone marrow failure, and telomere lengths less than the 1st percentile for age [54, 55]. In addition, *WRAP53* variants have been reported in association with the Hoyeraal-Hreidarsson variant of telomere disease including cerebellar hypoplasia, developmental disabilities, microcephaly, intrauterine growth retardation, hypotonia, gastrointestinal abnormalities and progressive bone marrow failure among other findings [55]. Heterozygotes were reported as healthy with normal telomere lengths.

***ZCCHC8*:** Heterozygous (AD) variants in the *ZCCHC8* gene have been associated with pulmonary fibrosis, bone marrow failure and short telomeres [56].

Genotype/Phenotype for Possible TBD-Associated Genes

***DCLRE1B/SMN1B/Apollo*:** A patient with clinical features of Hoyeraal-Hreidarsson syndrome (severe intrauterine growth retardation, microcephaly, cerebellar hypoplasia, lack of B lymphocytes, progressive aplastic anemia, severe enteropathy, severe bone marrow failure) was identified as having a heterozygous (AD) variant in *Apollo* [57].

***GRHL2*:** Two consanguineous families with an original diagnosis of dyskeratosis congenita were found to have different homozygous (AR) variants in the *GRHL2* gene. Variants in *GRHL2* have been associated with ectodermal dysplasia/short stature syndrome with clinical features that overlap with TBD including nail dystrophy, abnormal oral pigmentation, and keratoderma and hyperkeratosis of the hands and feet. Telomere

lengths were not reported to be short [58].

***LIG4*:** Two families with an original diagnosis of dyskeratosis congenita were found to have compound heterozygous (AR) variants in the *LIG4* gene. Variants in *LIG4* have been associated with *LIG4*/Dubowitz syndrome. Some overlapping features of TBD and *LIG4/*Dubowitz include bone marrow failure, various skin abnormalities, immune deficiency, microcephaly, and developmental delay. Telomere lengths were not reported to be short [58].

***MDM4*:** One report identified four heterozygous (AD) *MDM4* gene cases and one obligate carrier in one family. Phenotypes included neutropenia, bone marrow hypocellularity, AML, HNSCC, B cell deficiency, vague gastrointestinal symptoms, and chronic pain [59].

***NPM1*:** Two patients have been reported with heterozygous (AD) *NPM1* variants located in the same region of the gene. One patient had severe growth defects at birth, thumb abnormalities and thrombocytopenia, and the other had skin pigmentation abnormalities, nail dystrophy, microcephaly, developmental delay, short stature, skeletal abnormalities in the radius, and bone marrow failure [60].

***RPA1*:** A child presenting with pancytopenia, hypocellular bone marrow, the mucocutaneous triad, a congenital renal anomaly, and short telomeres had a *de novo* heterozygous (AD) variant in *RPA1*. The allelic frequency of the variant was higher in fibroblasts than bone marrow, and two somatic compensatory events were identified, likely consistent with a gain-of-function effect [61].

***USB1*:** Eight families with an original diagnosis of dyskeratosis congenita were found to have homozygous (AR) variants in the *USB1* gene. Variants in *USB1* have been associated with poikiloderma with neutropenia. Overlapping findings between TBD and poikiloderma with neutropenia include bone marrow failure, abnormal skin pigmentation and nail abnormalities. Telomere lengths were not reported to be short [58].

Evaluation and Testing

Family and Medical History

A family, individual medical, and cancer history is obtained to help determine whether only the individual being evaluated may have a TBD or whether other family members may also be at risk of having the disorder. In preparation for a genetics evaluation, a family should spend time thinking about relatives on both sides of the family: do any individuals in the family have any findings related to TBD or cancers? This may require speaking with other family members, since some of the features of a TBD are subtle and some individuals may be more private with their health information.

It is important to remember that not every individual with a TBD will have disease features. The symptoms in the family and the age that disease symptoms present may vary. The family history may help the healthcare team in deciding which family member(s) would be the most helpful to evaluate and/or offer testing. Testing the relatives of an individual known to have a TBD may identify other unsuspected family members who have the TBD-associated variant for whom genetic counseling would be beneficial.

Testing for TBD

Once the healthcare provider suspects the diagnosis of a TBD, a genetic counseling consultation with the individual and/or family can be helpful in explaining more about TBD, possible inheritance patterns, telomere and molecular genetic testing options, the testing process, and insurance concerns relating to genetic testing. Other concerns may be addressed more precisely once the variant for a specific gene is identified (see “Positive Results” below). Testing may be helpful for other family members to identify their chance of having a TBD or being a carrier of TBD based on the inheritance pattern of the TBD in the family. Individuals with the variant(s) identified in the family should be offered clinical consultation with a qualified medical provider to discuss the screening

recommendations for early detection and appropriate clinical care. (see Chapter 3, Diagnosing TBDs & Subtypes of TBDs.)

Telomere Length Measurements

The first step in testing for a suspected TBD is to assess the telomere length in specific subtypes of white blood cells. This test is very sensitive in screening for a TBD known to be associated with short telomeres (see Chapter 3, Diagnosing TBDs & Subtypes of TBDs). If all or nearly all of the white blood cells' telomere lengths (tests commonly evaluate either 2 or 6 subtypes of white blood cells) are determined to be very short (less than 1% length for their age), the test result is consistent with the diagnosis of a TBD. However, it is possible that not all individuals with a TBD will have all very short telomeres.

Genetic Testing Methodologies

Once an individual has been identified to have clinical features and/or telomere lengths that are consistent with or suggestive of a TBD, genetic testing is recommended for TBD-associated genes to try to identify a causative gene variant. Historically the term "mutation" was used for many years to refer to a change in the DNA that was thought to be responsible for causing genetic disease. All changes in the DNA are now referred to as "variants" and further described as one of five types of variants: pathogenic (disease causing), likely pathogenic, variant of uncertain significance, likely benign, or benign (does not cause disease). The interpretation of a variant may change over time as more information is known about a specific gene or variant or if additional information becomes available from familial testing. It is important to check in with the testing laboratory periodically as additional information on the familial variant may become available over time that impact the classification.

A genetic counseling session prior to testing for TBD provides individuals with an understanding of general and TBD-specific genetics concepts, as well as the process by which genetic testing occurs and results that may be identified. It is also an opportunity

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

The decision regarding which TBD genetic test to offer is based on many factors such as whether or not a variant has been previously identified in a family member or whether there are other clinical findings that may suggest a larger set of genes should be evaluated (whole exome or whole genome sequencing).

Targeted testing is appropriate if a variant in a TBD gene has already been identified in a family member. Other family members can then be tested for the specific variant in the TBD gene previously found in the family. However, additional family and medical history should be evaluated prior to testing any individual to determine if there are other findings in them or their family members who are not related to the side of the family with the identified TBD variant that suggest that testing with a larger gene panel would be more appropriate.

The first individual in a family to be tested for TBD genes will most often have Next Generation Sequencing (NGS) panel testing where multiple TBD genes are tested at the same time. Many NGS panels do not test for all known TBD genes due to the constantly expanding number of TBD-associated genes. NGS panels should include sequencing and copy number variant (CNV) analysis of the TBD-associated genes. Analysis of genes by sequencing and CNV testing involve different technologies and look for different types of variants in genes.

Whole exome sequencing (WES) and/or whole genome sequencing (WGS) may be beneficial if an individual has a complex clinical phenotype with atypical findings or if the NGS TBD panel testing was negative. WES will sequence our exons and splice sites, which account for about 2% of our genome. WGS analyzes the whole genome, but currently the interpretation of variants identified in areas outside of the exons and splice sites is often limited. WES/WGS testing increases the complexity of testing, often requiring specimens from family members and creating a greater potential to uncover incidental or secondary findings. As with all genetic testing, comprehensive, informed

consent is needed prior to initiating testing.

Interpretation of Test Results

Positive Results

If a pathogenic or likely pathogenic variant(s) is identified, the results are considered positive or diagnostic for a TBD. The positive results are provided to the patient. This discussion typically includes an explanation of the specific gene variant and the associated gene, a review of the inheritance of the specific gene in their family, the reproductive implications of the finding, medical screening and management recommendations, and consideration for testing of other family members. The psychosocial implications of a TBD diagnosis are considered and additional resources for support are discussed.

Negative Results

When the clinical presentation and telomere length analysis in the individual is consistent with a TBD but no variant is found in a known TBD gene, an as yet unidentified TBD gene may be responsible. Once testing of the clinically available TBD genes has been completed, testing can be put on hold until additional TBD genes have been identified. Alternatively, WES/WGS or research study enrollment may help identify a novel or previously undetectable genetic cause of disease. Individuals with disease can continue to be managed based on their clinical diagnosis at the guidance of their medical team.

Variants of Uncertain Significance

A variant of uncertain significance (VUS) is a change in the DNA for which there is not enough current information to determine whether the variant alters how the gene works in the body and is related to disease. It may be that the variant is rare, or has never previously been identified. An assumption that it causes disease cannot be made from

the available evidence. If an individual has a VUS, their clinical care and management should be based on their personal and/or family history and not the VUS. Genetic testing technology is rapidly evolving and, in time, may lead to a more certain interpretation of variants currently identified as a VUS.

Familial Implications of Genetic Findings

It is important to realize that the results of genetic testing for an individual have health and reproductive implications for family members as well. Further, if the individual with a TBD is being considered for a bone marrow or organ transplant from a relative, testing to assure that the donor relative does not also have a TBD is critical.

After a positive test result, other family members can pursue testing targeting the familial variant, unless there are other indications to consider additional testing for that individual. Information on the specific gene and variant identified will determine which relatives could benefit from testing.

Testing can determine whether one or both parents of the individual have the variant(s), or if the variant is likely a new (*de novo)* variant in their child with a TBD. In rare cases, individuals with a child with a likely *de novo* variant will have another child with a TBD. This is due to germline mosaicism where a parent has a TBD-causing variant in their egg or sperm cells but not in the tissue used in their genetic studies for the TBD. Based on this information, negative parental testing for a variant identified in a child with TBD cannot completely rule out the possibility that a future child will be affected.

After a negative test result, other relatives can be screening with telomere length measurement studies. Telomere length testing may identify other individuals who should follow screening guidelines for TBD findings.

In families where a variant of uncertain significance is identified, additional assessments in family members that include clinical evaluation and telomere length studies can both help identify other relatives with TBD and can help with the

interpretation of the familial variant if other individuals with TBD symptoms are also found to have the familial variant. In the absence of confirmed pathogenicity, relatives should be screened and managed based on their clinical symptoms and telomere length measurements under the guidance of their medical team.

Samples for Telomere and Molecular Genetic Testing

Different samples may be obtained from an individual for testing based on the technology used for testing and/or other indications. Currently, blood is the sample of choice for telomere length testing. Molecular testing of TBD-associated genes can be performed on blood, saliva, buccal (the area of the cheek inside the mouth) scrapings, bone marrow, or skin. If an individual has myelodysplastic syndrome (MDS), leukemia, previously underwent hematopoietic cell transplant, or is receiving certain treatments like transfusions, germline molecular genetic testing from blood, saliva, buccal scraping, or bone marrow samples may not be accurate. In such situations, genetic testing should be performed on a skin biopsy.

In some cases, genetic testing can be complicated by mosaicism. Mosaicism for a specific genetic disorder may occur after conception in one of two ways. An individual may acquire a somatic disease-causing variant that was not in their original germline cells. Additionally they may have a revertant mosaicism in which they originally had a disease-causing variant that was changed back to the “normal” DNA sequence. It is difficult to know when the mosaicism associated variant occurred, so which organ system(s) are involved usually cannot be identified. Suspected revertant mosaicism has been reported in TBD and has the potential to lead to a false negative finding on samples containing blood [62]. If an individual with clinical symptoms highly suggestive of TBD has negative testing, repeat studies on an alternate tissue such as skin can be considered.

Reproductive Options

There are multiple reproductive options available for individuals with an increased chance of having a child with TBD that can be reviewed in detail by a preconception or prenatal genetic counselor. Decisions regarding reproductive planning are personal choices based on individual beliefs, religious practices and ethical values. Families may choose to have an unassisted pregnancy without genetic testing until after the birth of the child and/or wait until the child shows clinical signs of the TBD. Other families may choose not to have children or may consider adoption.

Other individuals may wish to have children with the help of various reproductive technologies. There are currently several options for reducing the chance a child will have the familial TBD including using donor gametes (egg or sperm), prenatal diagnostic testing (chorionic villus sampling [CVS] or amniocentesis) for known variant(s), and in vitro fertilization (IVF) with preimplantation genetic testing (PGT). Prenatal diagnosis is not expected to impact treatment during pregnancy, thus prenatal diagnosis is most commonly sought either for medical management planning following delivery, for consideration of pregnancy termination, or to confirm IVF-PGT results. IVF-PGT can also select for the HLA (human leukocyte antigen) type of an embryo to have a child who is both unaffected with TBD and a potential bone marrow donor to an affected sibling who may need a transplant in the future.

The process of IVF with PGT is time consuming, as well as physically, psychologically, and financially demanding. In order to confirm that the laboratory performing PGT will be able to identify the presence or absence of the variant(s) in an embryo, DNA samples from the individual with TBD and their parents and possibly other family members are requested in order to develop an accurate genetic test. Multiple IVF and PGT cycles may be required to achieve a pregnancy. PGT is not a guarantee that a child will be unaffected but rather a test that reduces the possibility that a future child will have a TBD.

Telomere length measurements cannot be performed as a part of IVF-PGT or prenatal diagnostic testing at this time, thus families who do not have a known familial variant have fewer reproductive options available to them. A blood sample can be obtained after birth for telomere length analysis. For families with a VUS in a TBD-associated gene, our incomplete understanding of the genetic finding limits the availability and utility of reproductive options. Families with uncertain findings should seek genetic counseling to learn more about their options based on the current interpretation of the familial variant. Women with a TBD who are considering pregnancy should be offered consultation with a medical provider to discuss potential health risks during pregnancy (See Chapter 21, Gynecologic and Obstetric Considerations). Surrogacy may be an option for women with a TBD depending on laws and services in their area.

Summary

Genetic testing for TBD 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 TBD. A local genetic counselor can be found through the https://www.aboutgeneticcounselors.org/ website.

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