Dyskeratosis Congenita

Synonym: Zinsser-Cole-Engman Syndrome

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Go to:

Summary

Clinical characteristics.

Dyskeratosis congenita (DC), a telomere biology disorder, is characterized by a classic triad of dysplastic nails, lacy reticular pigmentation of the upper chest and/or neck, and oral leukoplakia. The classic triad may not be present in all individuals. People with DC are at increased risk for progressive bone marrow failure (BMF), myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML), solid tumors (usually squamous cell carcinoma of the head/neck or anogenital cancer), and pulmonary fibrosis. Other findings can include: abnormal pigmentation changes not restricted to the upper chest and neck, eye abnormalities (epiphora, blepharitis, sparse eyelashes, ectropion, entropion, trichiasis), and dental abnormalities (caries, periodontal disease, taurodauntism). Although most persons with DC have normal psychomotor development and normal neurologic function, significant developmental delay is present in the two variants in which additional findings include cerebellar hypoplasia (Hoyeraal Hreidarsson syndrome) and bilateral exudative retinopathy and intracranial calcifications (Revesz syndrome). Onset and progression of manifestations of DC vary: at the mild end of the spectrum are those who have only minimal physical findings with normal bone marrow function, and at the severe end are those who have the diagnostic triad and early-onset BMF.

Diagnosis/testing.

All individuals with DC have abnormally short telomeres for their age, as determined by multicolor flow cytometry fluorescence in situ hybridization (flow-FISH) on white blood cell (WBC) subsets. To date, *ACD*, *CTC1*, *DKC1*, *NHP2*, *NOP10*, *PARN*, *RTEL1*, *TERC*, *TERT*, *TINF2*, and *WRAP53* are the genes in which pathogenic variants are known to cause DC and

result in very short telomeres. Pathogenic variants in one of these 11 genes have been identified in approximately 70% of individuals who meet clinical diagnostic criteria for DC.

Management.

Treatment of manifestations: Treatment is tailored to the individual. Hematopoietic cell transplantation (HCT) is the only curative treatment for BMF and leukemia but historically has had poor long-term efficacy; if a suitable donor is not available, androgen therapy may be considered for BMF. Treatment of other cancers is tailored to the type of cancer. Of note, cancer therapy may pose an increased risk for prolonged cytopenias as well as pulmonary and hepatic toxicity. Treatment of pulmonary fibrosis is primarily supportive, although lung transplantation may be considered.

Surveillance: For BMF: complete blood count (CBC) annually if normal and more often if abnormal; consider annual bone marrow aspirate and biopsy. For those on androgen therapy: routine monitoring of liver function. For cancer risk: monthly self-examination for oral, head, and neck cancer; annual cancer screening by an otolaryngologist and dermatologist; annual gynecologic examination. For pulmonary fibrosis: annual pulmonary function tests starting either at diagnosis or when the individual can perform the test (often around age eight years). Routine dental screening every six months and good oral hygiene are recommended.

Agents/circumstances to avoid: Blood donation by family members if HCT is being considered; non-leukodepleted and non-irradiated blood products; the combination of androgens and G-CSF in treatment of BMF (has been associated with splenic rupture); toxic agents implicated in tumorigenesis (e.g., smoking).

Evaluation of relatives at risk: If a relative has signs or symptoms suggestive of DC or is being evaluated as a potential HCT donor, telomere length testing is warranted or molecular genetic testing if the pathogenic variant(s) in the family are known.

Genetic counseling.

The mode of inheritance of DC varies by gene:

- X-linked: *DKC1*
- Autosomal dominant: *TERC* and *TINF2*
- Autosomal dominant or autosomal recessive: *ACD*, *RTEL1*, and *TERT*
- Autosomal recessive: *CTC1*, *NHP2*, *NOP10*, *PARN*, and *WRAP53*

Genetic counseling regarding risk to family members depends on accurate diagnosis, determination of the mode of inheritance in each family, and results of molecular genetic testing. Once the DC-related pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk for DC is possible.

Go to:

GeneReview Scope

Dyskeratosis Congenita: Included Phenotypes

- Classic dyskeratosis congenita
- Hoyeraal Hreidarsson syndrome
- Revesz syndrome

Go to:

Diagnosis

Individuals with characteristic clinical findings described below who have very short telomeres and/or a pathogenic variant in one of the genes known to be associated with dyskeratosis congenita (DC) should be considered as having DC. The phenotypic spectrum of telomere biology disorders is broad and includes individuals with classic DC as well as those with very short telomeres and an isolated physical finding [Savage & Bertuch 2010, Dokal 2011, Ballew & Savage 2013, Bertuch 2016].

The criteria for classic dyskeratosis congenita (DC) were described by Vulliamy et al [2006] and are described below. Note, however, individuals may develop features of DC at variable rates and ages, which can make proper diagnosis challenging.

Suggestive Findings

Dyskeratosis congenita (DC) **should be suspected** in individuals with the following findings [Vulliamy et al 2006, Savage & Bertuch 2010]:

Physical abnormalities

- At least two features of the classic DC clinical triad (Figure 1):
  - Dysplastic nails. May be subtle with ridging, flaking, or poor growth, or more diffuse with nearly complete loss of nails
  - Lacy reticular pigmentation of the upper chest and/or neck. May be subtle or diffuse hyper- or hypopigmentation. Note that abnormal pigmentation changes are not restricted to the upper chest and neck.
  - Oral leukoplakia (white patches in the mouth)
- One feature of the classic triad plus two or more of the following [Vulliamy et al 2006]:
  - Epiphora (excessive watering of the eye[s])
  - Blepharitis (inflammation of the eyelids, often due to epiphora)
  - Abnormal eyelashes
  - Prematurely gray hair
  - Alopecia
  - Periodontal disease
  - Taurodontism (enlarged tooth pulp chambers) or decreased tooth root/crown ratio
  - Developmental delay
  - Short stature
  - Microcephaly
  - Hypogonadism
  - Esophageal stenosis

- Urethral stenosis
- Liver disease
- Osteoporosis
- Avascular necrosis of the hips or shoulders.

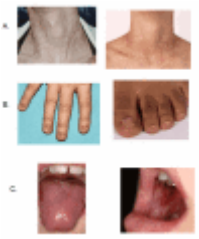

Figure 1.

Examples of the dyskeratosis congenita diagnostic triad A. Skin pigmentation

Note: Individuals with DC may have none of the above additional findings; the findings may appear or worsen with age.

Progressive bone marrow failure (BMF). May appear at any age and may be a presenting sign. Macrocytosis and elevated hemoglobin F levels may be seen.

Myelodysplastic syndrome (MDS) or **acute myelogenous leukemia (AML).** May be the presenting sign.

Solid tumors, usually head/neck squamous cell cancer or anogenital adenocarcinoma, in persons younger than age 50 years and without other risk factors. Solid tumors may be the first manifestation of DC in individuals who do not have BMF.

Pulmonary fibrosis. See Familial Pulmonary Fibrosis.

Shortened telomere length. Individuals with suspected DC should undergo leukocyte telomere length testing by automated multicolor flow-FISH in the six-cell panel assay. (Click here for details on this testing). Telomere length less than the first percentile for age in lymphocytes is 97% sensitive and 91% specific for DC. In individuals with complex or atypical DC, the six-cell panel may be more informative than the two-panel test of total lymphocytes and granulocytes [Alter et al 2012].

For more information about telomeres, see Supplemental Material-Telomeres (pdf).

Establishing the Diagnosis

The diagnosis of DC **is established** in a proband with identification of a pathogenic variant (or variants) by molecular genetic testing in one of the genes listed in Table 1A or 1B.

Molecular testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Serial single-gene testing can be considered if clinical findings, laboratory findings, ancestry, or inheritance pattern indicate that mutation of a particular gene is most likely. See Table 1A for information on mode of inheritance and relative frequency of the most common genes associated with this condition.

- Sequence analysis of the gene of interest is performed first, followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- Targeted analysis for pathogenic variants can be performed first in individuals of Ashkenazi Jewish ancestry for the c.3791G> A (p.Arg1264His) pathogenic variant in *RTEL1*.

A multigene panel that includes the genes listed in Table 1A and Table 1B, and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

More comprehensive genomic testing (when available) including exome sequencing and genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel that includes the genes listed in Table 1A and 1B) fails to confirm a diagnosis in an individual with features of DC. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene that results in a similar clinical presentation).

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Approximately 70% of individuals who meet clinical diagnostic criteria for DC have a pathogenic variant(s) in one of the 11 known DC-related genes.

See Table 1A for the most common genetic causes (i.e., pathogenic variants of any one of the genes included in this table account for >1% of DC) and Table 1B for less common genetic causes (i.e., pathogenic variants of any one of the genes included in this table are reported in only a few families).

Table 1A.

Molecular Genetics of Dyskeratosis Congenita (DC): Most Common Genetic Causes

Gene [1, 2]	MOI	Proportion of DC Attributed to Pathogenic Variants in Gene [3]	Proportion of Pathogenic Variants [4] Detected by Method	
			Sequence analysis [5]	Gene-targeted deletion/duplication analysis [6]
CTC1	AR	1%-3%	~100%	Unknown [7]
DKC1	XL	20%-25%	~100% [8]	Unknown [7]
RTEL1	AD or AR	2%-8%	~100%	Unknown [7]
TERC	AD	5%-10%	~100%	Unknown [7]
TERT	AD or AR	1%-7%	~100%	Unknown [7]
TINF2	AD	12%-20%	~100%	Unknown [7]
Unknown		20%-30%	NA	

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

1. Genes are listed in alphabetic order

2. See Table A. Genes and Databases for chromosome locus and protein.

3. Data from Ballew & Savage [2013], Dokal et al [2015], Glousker et al [2015], Bertuch [2016], and Author [personal observation]

4. See Molecular Genetics for information on allelic variants detected in this gene.

5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex

ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

7.

No data on detection rate of gene-targeted deletion/duplication analysis are available.

8.

Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis

Table 1B.

Molecular Genetics of DC: Less Common Genetic Causes

Gene [1, 2, 3]	Comments
ACD	AD or AR; 2 families identified [Guo et al 2014, Kocak et al 2014]
NHP2	AR; 2 families, 6/6 reported alleles [Vulliamy et al 2008]
NOP10	AR; 1 family, 2/2 reported alleles [Walne et al 2007]
PARN	AR; 6 families [Tummala et al 2015, Moon et al 2015, Burris et al 2016]
WRAP53 (*TCAB1*)	AR; 2 families with 4/4 reported alleles [Zhong et al 2011]

Pathogenic variants of any one of the genes listed in this table is reported in only a few families (i.e., <1% of DC)

AD = autosomal dominant; AR = autosomal recessive

1.

Genes are listed in alphabetic order.

2.

See Table A. Genes and Databases for chromosome locus and protein.

3.

Genes are not described in detail in Molecular Genetics but may be included here (pdf).

Tissue-restricted mosaicism has been observed in a limited number of individuals heterozygous for a *TERC* germline pathogenic variant. Specifically, a *TERC* germline pathogenic variant that was not observed by molecular genetic testing of DNA extracted from peripheral blood cells was detected in DNA extracted from other cells (e.g., skin fibroblasts) of the individual [Jongmans et al 2012]. Tissue-restricted mosaicism resulted from revertant somatic mosaicism (i.e., loss of heterozygosity for the deleterious allele) in peripheral blood

cells, particularly in individuals with DC without bone marrow failure. The assumption is that the selective advantage of the revertant hematopoietic cells allows them to populate the bone marrow, resulting in the inability to detect the pathogenic variant in DNA extracted from these cells. This has only been observed in individuals with germline *TERC* pathogenic variants. Molecular genetic testing of a second tissue source should be considered in individuals who meet the diagnostic criteria for DC but do not have a pathogenic variant identified on molecular genetic testing of peripheral blood cells.

Go to:

Clinical Characteristics

Clinical Description

The classic dyskeratosis congenita (DC) triad of abnormal fingernails and toenails, lacy, reticular pigmentation of the neck and upper chest, and oral leukoplakia is diagnostic (Figure 1); however, these features are not present in all individuals with DC and may or may not develop over time after the appearance of other complications listed below [Savage & Bertuch 2010, Dokal 2011]. The time of onset for these medical problems varies considerably among individuals even within the same family and thus the manifestations of DC do not progress in a predictable pattern. The spectrum ranges from individuals who develop bone marrow failure (BMF) first, and then years later develop other classic findings such as nail abnormalities, to others who have severe nail problems and abnormalities of skin pigmentation but normal bone marrow function.

Two forms of DC with more severe manifestations have been identified: **Hoyeraal Hreidarsson syndrome** and **Revesz syndrome** (see Severe Forms of DC).

Dermatologic. Lacy, reticular pigmentation primarily of the neck and chest may be subtle or diffuse hyper- or hypopigmentation. Changes in skin pigmentation may become more pronounced with age.

Dysplastic fingernails and toenails may worsen significantly over time and nails may eventually "disappear."

People with DC may lose dermatoglyphics with age.

Hyperhidrosis is noted in some individuals.

Growth and development. Short stature has been reported but height is variable.

Intrauterine growth retardation has been noted in children with the more severe Hoyeraal Hreidarsson syndrome or Revesz syndrome variants.

Developmental delay may be present in some. It can be more pronounced in persons with the Hoyeraal Hreidarsson syndrome or Revesz syndrome variants.

Ophthalmic. Epiphora caused by stenosis of the lacrimal drainage system can result in blepharitis.

Abnormal eyelash growth includes sparse eyelashes, ectropion, entropion, and trichiasis, which can lead to corneal abrasions, scarring, or infection if not treated.

Bilateral exudative retinopathy seen in the Revesz syndrome variant can lead to blindness.

Dental. Dental caries and periodontal disease had been reported to occur at early ages and at higher rates than in the general population; however, they may currently be less frequent because of improved dental hygiene.

Decreased root/crown ratio is attributed to abnormal tooth development.

Taurodontism (enlarged pulp chambers of the teeth) may be noted on dental x-ray.

Ears, nose, and throat. Oral leukoplakia is part of the diagnostic triad. It may be a presenting sign found in childhood or it may develop over time.

Deafness has been reported but is rare.

Squamous cell carcinoma of the head and neck. Persons with DC are at very high risk for these cancers.

Cardiovascular. Rare reported congenital heart defects include atrial and ventricular septal defects, myocardial fibrosis, and dilated cardiomyopathy.

Respiratory. Pulmonary fibrosis may be a presenting sign or may develop over time. It may be more common in individuals who have had a hematopoietic cell transplant. Pulmonary fibrosis is manifest as bibasilar reticular abnormalities, ground glass opacities, or diffuse nodular lesions on high-resolution computed tomography and abnormal pulmonary function studies that include evidence of restriction (reduced vital capacity with an increase in FEV1/FVC ratio) and/or impaired gas exchange (increased $P_{(A-a)}O_2$ with rest or exercise or decreased diffusion capacity of the lung for carbon monoxide).

Pulmonary arterio-venous malformations have recently been reported in individuals with DC. They may be present in individuals with hypoxia in the absence pulmonary fibrosis and can be diagnosed by bubble echocardiography.

Gastrointestinal. Esophageal stenosis has been reported in several persons with DC and may worsen over time.

Enteropathy, which may result in poor growth, has been reported.

Liver fibrosis is a potential complication that has been noted and may occur at variable rates.

Hepatopulmonary syndrome has been reported.

Vascular ectasias and bleeding may occur.

Elevated risk of anorectal adenocarcinomas has been reported in DC.

Genitourinary. Urethral stenosis in males may be present at diagnosis or develop over time.

Elevated risk of cervical squamous cell cancer has been reported in DC.

Musculoskeletal. Osteoporosis and osteopenia have been reported. The contribution of prior treatment and co-morbid conditions to these complications is not known.

Avascular necrosis of the hips and shoulders can result in pain and reduced function. Several individuals have required hip replacement surgery at young ages.

Neurologic. Although most persons with DC have normal psychomotor development and normal neurologic function, significant developmental delay is present in the Hoyeraal Hreidarsson syndrome and Revesz syndrome variants. Cerebellar hypoplasia is present in the Hoyeraal Hreidarsson syndrome variant (Figure 2) and intracranial calcifications have been reported in the Revesz syndrome variant. In addition, microcephaly has been reported in some persons with DC.

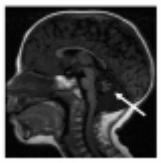

Figure 2.

MRI of cerebellar hypoplasia in an individual with the Hoyeraal Hreidarsson variant of dyskeratosis congenita. Arrow indicates the hypoplastic cerebellum.

Psychiatric. Schizophrenia has been reported in two persons. A small study of six children and eight adults with DC found higher than expected rates of neuropsychiatric complications. However, the true prevalence of disorders such as depression and bipolar disorder in individuals with CD is unknown [Rackley et al 2012].

Endocrine. Hypogonadism has been noted in a small number of severely affected males.

Hematologic. Bone marrow failure is a common presenting sign, may develop at any age and may progress over time. Approximately one-half of individuals with DC develop some degree of bone marrow failure by age 40 years.

Individuals with DC are at increased risk for leukemia (see **Cancer**).

Immunologic. Immunodeficiency of variable severity has been reported in DC. It has not been fully characterized, but it appears that some individuals may have reduced numbers of B-cells, T-cells, and/or NK cells.

Cancer. Persons with DC are at high risk for leukemia and squamous cell cancer of the head and neck or anogenital region.

The first study to quantify these risks evaluated reports of cancer in persons with DC from the DC cohort study at the National Cancer Institute (NCI) and from the scientific literature [Alter et al 2009]. The median age of onset for all cancers was 37 years (range 25-44 years) in the NCI cohort and 29 years (range 19-70 years) in the literature cases.

The most frequent solid tumors were head and neck squamous cell carcinomas (40% in both groups), followed by squamous cell skin cancers and anorectal adenocarcinoma. In the NCI cohort, the ratio of observed to expected (O/E) cancers was 11-fold greater in persons with DC compared to the general population. The highest O/E ratios were for tongue cancer (1154-fold increase) and acute myeloid leukemia (AML) (195-fold increase). Myelodysplastic syndrome (MDS) also occurs at increased rates in persons with DC [Alter et al 2009]. In this study, the median age of MDS was 35 years (range 19-61 years) and the O/E ratio of MDS was 2362-fold that of the general population.

Severe Forms of DC

Hoyeraal Hreidarsson syndrome, a very severe form of DC, presents in early childhood [Walne & Dokal 2008]. In addition to features of DC, cerebellar hypoplasia is required to establish the diagnosis (Figure 2). The findings in the original cases included cerebellar hypoplasia, developmental delay, immunodeficiency, intrauterine growth retardation, and BMF, as well as the DC diagnostic triad [Hoyeraal et al 1970].

Revesz syndrome has many of the features of DC and presents in early childhood [Revesz et al 1992]. In addition to features of DC, bilateral exudative retinopathy is required to establish the diagnosis. The original cases included individuals with intracranial calcifications, intrauterine growth retardation, BMF, and sparse, fine hair in addition to nail dystrophy and oral leukoplakia.

Genotype-Phenotype Correlations

Genotype-phenotype correlations have not yet been studied comprehensively.

Individuals with Hoyeraal Hreidarsson and Revesz syndrome have shorter telomeres than individuals with classic DC.

In general, persons with *DKC1*, *TINF2*, and autosomal recessive *PARN*, *RTEL1*, and *ACD* pathogenic variants appear to have more clinical features and complications than persons with pathogenic variants in other genes known to cause DC [Alter et al 2012, Ballew et al 2013a, Ballew et al 2013b, Deng et al 2013, Le Guen et al 2013, Walne et al 2013, Guo et al 2014, Kocak et al 2014, Moon et al 2015, Tummala et al 2015]. Persons with *DKC1* or *TINF2* pathogenic variants may have Hoyeraal Hreidarsson syndrome. Persons with Revesz syndrome may have *TINF2* pathogenic variants. Some individuals with *TINF2* pathogenic variants developed bone marrow failure manifest as aplastic anemia by age ten years; others may be asymptomatic heterozygotes [Ballew & Savage 2013, Dokal et al 2015, Glousker et al 2015, Bertuch 2016].

Individuals with autosomal dominant heterozygous *RTEL1* or *ACD* pathogenic variants may develop clinical manifestations at older ages than those with recessive pathogenic variants in these genes.

Persons with autosomal dominant, heterozygous *TERT* pathogenic variants may present as adults with isolated bone marrow failure or isolated pulmonary fibrosis, and thus may be the least affected of all those with DC. Individuals with autosomal recessive *TERT* pathogenic variants may have the severe phenotype Hoyeraal Hreidarsson syndrome.

Those with *TERC* pathogenic variants appear to have variability in severity. Some individuals with *TERC* pathogenic variants may present with isolated bone marrow failure rather than the classic mucocutaneous features seen with (for example) *DKC1* pathogenic variants.

Individuals with DC who do not have a pathogenic variant in one of the 11 known genes often have the most clinically severe phenotypes, including multiple features of DC, Hoyeraal Hreisdarsson syndrome, or Revesz syndrome [Alter et al 2012, Ballew et al 2013a, Ballew et al 2013b, Deng et al 2013, Le Guen et al 2013, Walne et al 2013, Guo et al 2014, Kocak et al 2014, Moon et al 2015, Tummala et al 2015].

The two individuals reported with *WRAP53* compound heterozygous pathogenic variants had classic DC with the mucocutaneous phenotype and bone marrow failure. One of these individuals also had tongue squamous cell cancer.

Persons with *CTC1* pathogenic variants may not have the mucocutaneous triad but often do have cytopenias, retinal exudates, intracranial calcifications or cysts, ataxia, IUGR, osteopenia, and/or poor bone healing.

Penetrance

The penetrance of DC and DC-associated medical complications is not well understood. Due to the variability between individuals (even within the same family) and the observation that medical complications may increase with age, penetrance may appear incomplete, but additional studies are needed.

Anticipation

Some studies have suggested that shorter telomeres and an earlier age of onset of symptoms may occur in successive generations in families affected by DC; however, it is unclear whether this observation reflects anticipation or the bias of ascertainment that occurs when diagnosis of a severely affected individual results in identification of mild manifestations in earlier generations in a family. The families in which the younger generations had more severe clinical features than their parents had pathogenic variants in *TERC*, *TERT*, or *TINF2* [Armanios et al 2005, Vulliamy & Dokal 2008, Savage & Bertuch 2010].

Nomenclature

Revesz syndrome [Revesz et al 1992] and Hoyeraal Hreidarsson syndrome [Hoyeraal et al 1970, Hreidarsson et al 1988], previously thought to be distinct disorders, are now recognized to be part of the phenotypic spectrum of dyskeratosis congenita.

A few case reports of a syndrome of ataxia and pancytopenia are actually describing DC caused by pathogenic variants in *TINF2* [Tsangaris et al 2008].

Prevalence

The prevalence of DC in the general population is not known and believed to be rare. As of 2015, the author is aware of at least 400 families in the world.

Go to:

Genetically Related (Allelic) Disorders

Aplastic anemia has been associated with germline pathogenic variants in *ACD*, *TERC*, and *TERT* [Yamaguchi et al 2003, Yamaguchi et al 2005]. Some persons with apparently acquired aplastic anemia may actually have undiagnosed DC or a milder form of this telomere biology disorder.

Autosomal dominant idiopathic pulmonary fibrosis has been associated with heterozygous pathogenic variants in *PARN* (OMIM 616371), *RTEL1* (OMIM 616373), *TERT* (OMIM 614742), and *TERC* (OMIM 614743) [Armanios et al 2007, Tsakiri et al 2007, Alder et al 2008, Moon et al 2015, Stuart et al 2015]. This is also a telomere biology disorder closely related to DC (see Familial Pulmonary Fibrosis).

Liver cirrhosis associated with germline pathogenic variants in *TERT* or *TERC* has been reported in up to 7% of affected individuals [Calado et al 2011, Hartmann et al 2011].

Cerebrobretinal microangiopathy with calcifications and cysts (CRMCC) or Coats Plus syndrome (OMIM 612199) is associated with compound heterozygous pathogenic variants in *CTC1*. Many features of these related disorders overlap with those of DC. These features include: hair, skin, and nail changes; anemia; thrombocytopenia; osteopenia; intracranial calcifications; exudative retinopathy; and developmental delay. Individuals with *CTC1* pathogenic variants have very short telomeres.

All of these disorders overlap clinically with features of DC and appear to be part of the spectrum of telomere biology disorders, of which classic DC is the most severe [Dokal 2011, Ballew & Savage 2013, Dokal et al 2015, Glousker et al 2015, Bertuch 2016].

Go to:

Differential Diagnosis

Disorders with clinical features that overlap those of DC include the following.

Disorders with nail dysplasia

- Nail-patella syndrome
- Twenty-nail dystrophy (OMIM 161050)
- Keratoderma with nail dystrophy and motor-sensory neuropathy (OMIM 148360)
- Poikiloderma with neutropenia

Inherited bone marrow failure syndromes. These are a complex set of related disorders that may have bone marrow failure as the first presenting sign.

- **Fanconi anemia (FA)** is characterized by physical abnormalities, bone marrow failure, and increased risk of malignancy. Progressive bone marrow failure with pancytopenia typically presents in the first decade, often initially with thrombocytopenia or leukopenia. By age 40 to 50 years, the estimated cumulative incidence of bone marrow failure is 90%. The diagnosis of FA rests on the detection of chromosome aberrations (breaks, rearrangements, radials, exchanges) in cells after

culture with a DNA interstrand cross-linking agent such as diepoxybutane (DEB) or mitomycin C (MMC). At least 15 genes are known to be associated with FA; inheritance is autosomal recessive for most of the FA complementation groups; *FANCB* pathogenic variants are inherited in an X-linked manner. The first clinical manifestation of both FA and DC may be bone marrow failure.

- **Diamond-Blackfan anemia (DBA),** in its classic form, is characterized by a profound isolated normochromic and usually macrocytic anemia with normal leukocytes and platelets; congenital malformations in approximately 50% of affected individuals; and growth retardation in 30%. The hematologic complications occur in 90% of affected individuals during the first year of life (median age of onset: 2 months). DBA is associated with an increased risk of acute myelogenous leukemia, myelodysplastic syndrome, and solid tumors including osteogenic sarcoma. DBA has been associated with pathogenic variants in 16 genes that encode ribosomal proteins and in *GATA1* and *TSR2*. DBA is most often inherited in an autosomal dominant manner; *GATA1*-related and *TSR2*-related DBA are inherited in an X-linked manner. DBA and DC may first present with bone marrow failure.
- **Shwachman-Diamond syndrome (SDS)** is characterized by: exocrine pancreatic dysfunction with malabsorption, malnutrition, and growth failure; hematologic abnormalities with single- or multilineage cytopenia and susceptibility to myelodysplasia syndrome and acute myelogeneous leukemia; and bone abnormalities. In almost all affected children, persistent or intermittent neutropenia is a common presenting finding, often before the diagnosis of SDS is made. Short stature and recurrent infections are common. *SBDS* is the only gene currently known to be associated with SDS; inheritance is autosomal recessive. Like DC, SDS may first present as bone marrow failure or GI malabsorption.

Acquired aplastic anemia, characterized by tri-lineage bone marrow cytopenias [Young et al 2008]. It is often progressive and may occur at any age. Telomere length testing helps identify the subset of individuals with later-onset aplastic anemia who have a telomere biology disorder; these individuals may have a few or none of the other clinical findings of DC. Other known causes of aplastic anemia include an immune process, infection, or drug reaction. In many individuals the cause of acquired aplastic anemia is unknown.

Idiopathic pulmonary fibrosis (IPF), the most frequent idiopathic interstitial pneumonia. It results in progressive fibrotic lung disease and has high morbidity and mortality. Persons with DC may develop IPF and it is conceivable that IPF in a young person could be the first manifestation of DC; thus, DC should be considered in young persons with IPF. In some individuals, IPF (like aplastic anemia) may be a manifestation of a telomere biology disorder. See Familial Pulmonary Fibrosis.

Go to:

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with dyskeratosis congenita (DC), it is important to note that the clinical spectrum of DC is broad and signs and symptoms develop at various ages and rates. Suggested studies to consider include:

- **Dermatologic.** Thorough skin and nail examination
- **Growth and development evaluation**
- **Ophthalmic.** Thorough examination for complications related to lacrimal duct stenosis, abnormal eyelash growth, and retinal disorders including exudative retinopathy
- **Dental.** Baseline evaluation for oral hygiene, leukoplakia, and oral squamous cell cancer
- **Otolaryngology.** Baseline evaluation for leukoplakia and squamous cell head/neck cancer
- **Gastrointestinal and hepatic.** History of potential swallowing difficulties and/or enteropathy; baseline liver function tests
- **Genitourinary.** For males, assessment for urethral stenosis
- **Musculoskeletal.** Consideration of baseline bone mineral density scan; history of any joint problems
- **Neurologic.** If early-onset neurologic findings (e.g., ataxia) or many of the complications listed above are present, consideration of brain MRI to evaluate for cerebellar hypoplasia or intracranial calcifications
- **Hematologic**
    - Evaluation by a hematologist to determine if signs of bone marrow failure are present. Evaluation may include complete blood count and bone marrow aspiration and biopsy.
    - Consideration of HLA typing of the affected individual, unaffected sibs, and parents in anticipation of possible need for hematopoietic cell transplantation (HCT)
- **Pulmonary**
    - Baseline pulmonary function tests (PFTs) including carbon monoxide diffusion capacity
    - Consideration of bubble echocardiography to evaluate for pulmonary arteriovenous malformations
    - Evaluation by a pulmonologist if the individual is symptomatic or PFTs are abnormal
- **Increased risk of cancer**
    - Evaluation by an otolaryngologist and dentist as soon as the individual is able to cooperate with the examination
    - Gynecologic examination for females starting by age 16 years or when sexually active
- **Consultation** with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

The specific treatment for DC-related complications must be tailored to the individual. The recommendations in this section were first discussed at a DC clinical research workshop in 2008 and subsequently at a meeting of experts convened to review the publication of the first edition of the *Dyskeratosis Congenita and Telomere Biology Disorders: Diagnosis and Management Guidelines* [Savage et al 2009, Savage & Cook 2015] Because of the rarity of DC, the recommendations are not based on large-scale clinical trials. Affected individuals may have few or many of the complications associated with DC. Comprehensive coordinated care among specialties is required.

Bone marrow failure (BMF). Following the model of the Fanconi anemia consensus guidelines [Eiler et al 2008] and updated on the DC treatment guidelines [Savage & Cook 2015], treatment of BMF is recommended if the hemoglobin is consistently below 8 g/dL, platelets lower than 30,000/mm^3, and neutrophils below 1000/mm^3. If a matched-related donor is available, hematopoietic cell transplantation (HCT) should be the first consideration for treatment for hematologic problems such as BMF or leukemia regardless of age.

HCT from an unrelated donor can be considered, although a trial of androgen therapy (e.g., oxymetholone or danazol) may be considered first [Khincha et al 2014].

Persons with DC may be more sensitive to androgens than individuals with Fanconi anemia, and the dose must be adjusted to reduce side effects such as impaired liver function, virilization, or behavioral problems (e.g., aggression, mood swings). The suggested starting dose of oxymetholone is 0.5 to 1 mg/kg/day, half the dose used in Fanconi anemia. It may take two to three months at a constant dose to see a hematologic response.

Side effects, including liver enzyme abnormalities, need to be monitored carefully. Baseline and follow-up liver ultrasound examinations should be performed for individuals receiving androgen therapy because of the possibility of liver adenomas and carcinomas, which have been reported in Fanconi anemia and in persons using androgens for benign hematologic diseases or for non-hematologic disorders [Velazquez & Alter 2004].

Hematopoietic growth factors may be useful in BMF. However, splenic peliosis ("blood lakes") and splenic rupture have been reported in two individuals with DC receiving androgens and G-CSF [Giri et al 2007]. G-CSF with erythropoietin has occasionally been useful but perhaps should also not be used in combination with androgens [Khincha et al 2014].

HCT is the only curative treatment for severe BMF or leukemia in DC. It should be performed at centers experienced in treating DC. Reported problems include graft failure, graft-versus-host disease (GVHD), sepsis, pulmonary fibrosis, hepatic cirrhosis, and veno-occlusive disease [Berthou et al 1991, de la Fuente & Dokal 2007] that is caused in part by underlying pulmonary and liver disease [Yabe et al 1997, Dror et al 2003, Brazzola et al 2005, de la Fuente & Dokal 2007, Ostronoff et al 2007]. As a result, long-term survival of persons with DC following HCT has been poor. Reduced-intensity preparative regimens being studied in a few institutions may improve long-term outcomes [Dietz et al 2011, Nishio et al 2011, Vuong et al 2010, Gadalla et al 2013, Algeri et al 2015].

The range of clinical phenotypes seen in DC and the possibility of non-manifesting or very mildly affected heterozygotes within families may complicate the selection of related HCT donors [Fogarty et al 2003, Denny et al 2008]. Potential related HCT donors should be tested either for the pathogenic variant present in the proband or, if the pathogenic variant is not known, for telomere length.

Cancer. Specific treatment should be tailored to the type of cancer.

Affected individuals undergoing chemotherapy for cancer may be at increased risk for prolonged cytopenias as a result of underlying BMF. This risk has not been quantitated; studies are ongoing.

Individuals with DC may be at increased risk for therapy-related pulmonary and hepatic toxicity. Pulmonary function tests and liver function should be monitored carefully.

Long-term data on the effects of cancer radiotherapy in DC are not available. Affected individuals may be at increased risk for radiotherapy-related complications based on observations in persons undergoing radiotherapy in HCT [Author, personal observation].

Although the risk of myelodysplastic syndrome (MDS) is high in DC, many persons have abnormal cytogenetic clones and/or morphologic changes consistent with abnormal myelopoiesis but may not have severe cytopenias.

Pulmonary fibrosis. The options for therapy in persons with DC and pulmonary fibrosis are primarily supportive care. Lung transplantation may be considered in severe cases, although long-term outcomes have not been studied (see Familial Pulmonary Fibrosis).

Prevention of Secondary Complications

Individuals with DC should not smoke cigarettes or drink alcohol.

Surveillance

The recommendations in this section were discussed at the first DC clinical research workshop in 2008 and updated in 2014 at a consensus conference that led to publication of the first edition of the *Dyskeratosis Congenita and Telomere Biology Disorders: Diagnosis and Management Guidelines* [Savage et al 2009, Savage & Cook 2015]. Because of the rarity of DC, the recommendations are not based on large-scale clinical trials.

Bone marrow failure

- Consider repeating a complete blood count (CBC) once a year if CBCs are normal. CBCs should be obtained more frequently at the discretion of the treating hematologist.
- Consider annual bone marrow aspirate and biopsy that includes morphologic examination and cytogenetic studies.

Individuals on androgen therapy for bone marrow failure

- Check liver function tests prior to starting and then every three months.
- Perform liver ultrasound examination semiannually for adenomas.
- Check cholesterol and triglycerides prior to starting and every six months.

Cancer surveillance. Most solid tumors develop after the first decade (median age of onset: 28 years).

- Monthly self-examination for oral, head, and neck cancer
- Annual cancer screening by an otolaryngologist
- Annual gynecologic examination
- Annual skin cancer screening by a dermatologist

Pulmonary fibrosis. Perform annual pulmonary function tests starting either at diagnosis or at an age when the individual is able to appropriately perform the test (typically age ~8 years).

Oral and dental surveillance

- Schedule routine screening and dental hygiene visits every six months.
- Maintain good oral hygiene.
- The individual's dentist should be made aware of the increased risk of head and neck squamous cell cancers and perform a thorough examination at each visit.
- Oral leukoplakia should be monitored carefully and suspicious lesions should be biopsied.

Agents/Circumstances to Avoid

Blood transfusions

- Transfusions of red cells or platelets should be avoided or minimized for those who are candidates for HCT.
- To minimize the chances of sensitization, family members must not act as blood donors if HCT is being considered.
- All blood products should be leukodepleted and irradiated.

Radiation. It is prudent to minimize exposure to therapeutic radiation since data on radiation side effects are limited.

Androgens and growth factors. The combination of androgens and G-CSF was associated with splenic peliosis ("blood lakes") and rupture in two individuals; thus, the combination should be avoided [Giri et al 2007].

Cancer prevention. Given the increased susceptibility of individuals with DC to developing leukemias and other malignancies, individuals with DC are advised to avoid toxic agents that have been implicated in tumorigenesis, including smoking.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures.

Evaluations can include:

- Telomere length testing;
- Molecular genetic testing if the pathogenic variant(s) in the family are known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Individuals with DC who become pregnant may develop pancytopenia or existing cytopenias may worsen. They should be followed closely by a perinatologist.

Therapies Under Investigation

Studies of the effectiveness of danazol, a modified testosterone, are under way in DC and the related telomere biology disorders. Danazol may have fewer side effects than oxymetholone. The response and optimal dosing in DC is not yet defined.

Studies to improve the clinical and molecular characterization of DC are under way at the National Cancer Institute (marrowfailure.cancer.gov).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Go to:

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Dyskeratosis congenita (DC) caused by mutation of *DKC1* is inherited in an X-linked manner.

DC caused by mutation of *TERC* or *TINF2* is inherited in an autosomal dominant manner.

DC caused by mutation of *ACD*, *RTEL1*, or *TERT* is inherited in an autosomal dominant or autosomal recessive manner.

DC caused by mutation of *CTC1*, *NHP2*, *NOP10*, *PARN*, or *WRAP53* is inherited in an autosomal recessive manner.

X-Linked DC

Risk to Family Members

Parents of a male **proband**

- The father of an affected male will not have the disorder nor will he be hemizygous for the *DKC1* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected male, the mother of an affected male is an obligate heterozygote (carrier). If a woman has more than one affected son and the

DKC1 pathogenic variant cannot be detected in her leukocyte DNA, she has germline mosaicism. (Although no instances of germline mosaicism have been reported in *DKC1*-related DC, it remains a possibility.)
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or the affected male may have a *de novo* *DKC1* pathogenic variant, in which case the mother is not a carrier.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the variant will be heterozygotes (carriers) and will usually not be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *DKC1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the empiric recurrence risk to sibs is approximately 1% because of the theoretic possibility of parental germline mosaicism.

Offspring of a male proband. Affected males transmit the *DKC1* pathogenic variant to:

- All of their daughters who will be (heterozygotes) carriers and will usually not be affected;
- None of their sons.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the *DKC1* pathogenic variant and the aunts' offspring, depending on their gender, may be at risk of being heterozygotes for the pathogenic variant or of being affected.

Heterozygote (Carrier) Detection

Carrier testing of female relatives at risk for X-linked DC is possible if the *DKC1* pathogenic variant has been identified in the family.

Note: (1) The development of clinical manifestations in females who are heterozygous for a *DKC1* pathogenic variant is extremely rare. (2) Identification of female carriers requires either prior identification of the pathogenic variant in the family or, if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Autosomal Dominant DC – Risk to Family Members

Parents of a proband

- Some individuals diagnosed with autosomal dominant DC have an affected parent.
- A proband with autosomal dominant DC may have the disorder as the result of a *de novo* DC-related pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is unknown.
    - The majority of *TINF2* pathogenic variants appear to occur *de novo* in the proband [Savage et al 2008, Walne et al 2008, Sasa et al 2012].

- Recommendations for the evaluation of apparently asymptomatic parents include molecular genetic testing for the pathogenic variant identified in the proband or, if the genetic alteration in the proband is not known, telomere length testing.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, two possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (the frequency of germline and somatic mosaicism in DC is not known).

  Walne et al [2008] reported a family with two affected sibs, in one of whom a *TINF2* pathogenic variant was identified (the other was deceased and could not be tested); neither parent had the pathogenic variant, suggesting germline mosaicism in a parent.

- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.
- Note: If the parent is the individual in whom the pathogenic variant first occurred s/he may have somatic mosaicism for the pathogenic variant and may be mildly/minimally affected.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents: if a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still at increased risk because of the possibility of reduced penetrance in a parent.
- If the DC-related pathogenic variant found in the proband cannot be detected in the DNA of either parent, the empiric recurrence risk to sibs is approximately 1% because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant DC has a 50% chance of inheriting the DC-related pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, his or her family members may be at risk.

Autosomal Recessive DC

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one DC-related pathogenic variant).
- Heterozygotes for a pathogenic variant in *CTC1*, *NHP2*, *NOP10*, *PARN*, or *WRAP53* are predicted to be asymptomatic. Heterozygotes for a pathogenic variant in *ACD*, *RTEL1*, or *TERT* may or may not be affected (see Heterozygote Detection).

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of inheriting two DC-related pathogenic variants, a 50% chance of inheriting one pathogenic variant, and a 25% chance of inheriting neither of the familial DC-related pathogenic variants.
- Heterozygotes for a pathogenic variant in *CTC1*, *NHP2*, *NOP10*, *PARN*, or *WRAP53* are predicted to be asymptomatic. Heterozygotes for a pathogenic variant in *ACD*, *RTEL1*, or *TERT* may or may not be affected (see Heterozygote Detection).

Offspring of a proband. The offspring of an individual with autosomal recessive DC are obligate heterozygotes for a DC-related pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier for a DC-related pathogenic variant.

Heterozygote (Carrier) Detection

Carrier testing for at-risk relatives requires prior identification of the DC-related pathogenic variants in the family.

Note: Heterozygotes may or not may not be affected. Pathogenic variants in *ACD*, *RTEL*, or *TERT* can cause both autosomal dominant and autosomal recessive DC; the effect of heterozygosity for one *ACD*, *RTEL*, or *TERT* pathogenic variant in individuals from families in which DC has been inherited in an autosomal recessive manner is not known.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Predictive testing for at-risk asymptomatic family members requires prior identification of the pathogenic variant in the family or, if a pathogenic variant is not identified in an affected family member, documentation of short telomere length in an affected relative.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the DC-related pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for DC are possible.

Go to:

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Dyskeratosis Congenita Outreach, Inc.**

  1562 First Avenue #205-4093

  New York NY 10028-4004

  Email: dcoutreach@dcoutreach.org

  www.dcoutreach.org

- **My46 Trait Profile**

  Dyskeratosis Congenita

- **Dyskeratosis Congenita Outreach Registry**

  Solve the Puzzle

- **National Cancer Institute Inherited Bone Marrow Failure Syndromes (IBMFS) Cohort Registry**

  Phone: 800-518-8474

  Email: NCI.IBMFS@westat.com

  www.marrowfailure.cancer.gov

Go to:

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.

Dyskeratosis Congenita: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

ACD	16q22.1	Adrenocortical dysplasia protein homolog		ACD	ACD
CTC1	17p13.1	CST complex subunit CTC1	CTC1 @ LOVD	CTC1	CTC1
DKC1	Xq28	H/ACA ribonucleoprotein complex subunit DKC1	DKC1 @ LOVD Telomerase Database (DKC1) DKC1base: Mutation registry for Hoyeraal-Hreidarsson syndrome	DKC1	DKC1
NHP2	5q35.3	H/ACA ribonucleoprotein complex subunit 2	Telomerase Database, Nola2 (NHP2) mutations NHP2 database	NHP2	NHP2
NOP10	15q14	H/ACA ribonucleoprotein complex subunit 3	Telomerase Database, Nola3 (Nop10) mutations NOP10 database	NOP10	NOP10
PARN	16p13.12	Poly(A)-specific ribonuclease PARN		PARN	PARN
RTEL1	20q13.33	Regulator of telomere elongation helicase 1		RTEL1	RTEL1
TERC	3q26.2	Not applicable	Telomerase Database, TR mutations (TERC)	TERC	TERC
TERT	5p15.33	Telomerase reverse transcriptase	Telomerase Database (TERT) TERT database	TERT	TERT
TINF2	14q12	TERF1-interacting nuclear factor 2	Telomerase Database, TINF2 mutations TINF2 database	TINF2	TINF2
WRAP53	17p13.1	Telomerase Cajal body protein 1	Telomerase Database (WRAP53)	WRAP53	WRAP53

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B.

OMIM Entries for Dyskeratosis Congenita (View All in OMIM)

127550 DYSKERATOSIS CONGENITA, AUTOSOMAL DOMINANT 1; DKCA1
187270 TELOMERASE REVERSE TRANSCRIPTASE; TERT
224230 DYSKERATOSIS CONGENITA, AUTOSOMAL RECESSIVE 1; DKCB1

300126 DYSKERIN; DKC1
305000 DYSKERATOSIS CONGENITA, X-LINKED; DKCX
602322 TELOMERASE RNA COMPONENT; TERC
604212 POLYADENYLATE-SPECIFIC RIBONUCLEASE; PARN
604319 TRF1-INTERACTING NUCLEAR FACTOR 2; TINF2
606470 NUCLEOLAR PROTEIN FAMILY A, MEMBER 2; NOLA2
606471 NUCLEOLAR PROTEIN FAMILY A, MEMBER 3; NOLA3
608833 REGULATOR OF TELOMERE ELONGATION HELICASE 1; RTEL1
609377 ACD SHELTERIN COMPLEX SUBUNIT AND TELOMERASE RECRUITMENT FACTOR; ACD
612661 WD REPEAT-CONTAINING PROTEIN ANTISENSE TO TP53; WRAP53
613129 CONSERVED TELOMERE MAINTENANCE COMPONENT 1; CTC1
613987 DYSKERATOSIS CONGENITA, AUTOSOMAL RECESSIVE 2; DKCB2
613988 DYSKERATOSIS CONGENITA, AUTOSOMAL RECESSIVE 3; DKCB3
613989 DYSKERATOSIS CONGENITA, AUTOSOMAL DOMINANT 2; DKCA2
613990 DYSKERATOSIS CONGENITA, AUTOSOMAL DOMINANT 3; DKCA3
615190 DYSKERATOSIS CONGENITA, AUTOSOMAL RECESSIVE 5; DKCB5
616353 DYSKERATOSIS CONGENITA, AUTOSOMAL RECESSIVE 6; DKCB6
616553 DYSKERATOSIS CONGENITA, AUTOSOMAL DOMINANT 6; DKCA6

Molecular Pathogenesis

Dyskeratosis congenita (DC) is a disorder of telomere biology. The telomere is a complex structure (Figure 3). The TTAGGG nucleotide repeats at the chromosome end fold back to create a t-loop. Many proteins bind to the t-loop and others bind to those proteins to form a stable telomere "cap." Eleven different genes (*DKC1*, *TERC*, *TERT*, *TINF2*, *NOP10*, *NHP2*, *WRAP53*, *ACD*, *RTEL1*, *PARN*, *CTC1*) encoding critical components of the telomere have been found to be mutated in individuals with DC.

Figure 3.

Telomere length and structure are regulated by a host of proteins. Pathogenic variants affecting a subset of these proteins have been implicated in telomere biology disorders. The percentages indicate the approximate number of cases resulting from variants (more...)

The proteins encoded by *DKC1*, *NHP2*, and *NOP10* are members of the H/ACA snoRNPs (small nucleolar ribonucleoproteins) gene family, which is involved in various aspects of rRNA processing and modification [Walne & Dokal 2008]. The proteins encoded by the genes *DKC1*, *NHP2*, and *NOP10* localize to the dense fibrillar components of nucleoli and to coiled (Cajal) bodies in the nucleus. Both 18S rRNA production and rRNA pseudouridylation

are impaired if any one of the four proteins is depleted. These H/ACA snoRNP proteins are also components of the telomerase complex.

Telomerase (TERT) is a reverse transcriptase that uses its RNA component, TERC, to add the TTAGGG nucleotide repeats to the chromosome ends. *WRAP53* (*TCAB1*) is required for the transport of telomerase to Cajal bodies for assembly of the holoenzyme complex. *TINF2* encodes the TIN2 protein, which is a part of the shelterin telomere protection complex (reviewed in Palm & de Lange [2008]). Shelterin consists of six proteins encoded by the genes *TINF2*, *TERF1*, *TERF2*, *POT1*, *ACD* (*TPP1*), and *TERF2IP* (*RAP1*). TERF1 (TRF1), TERF2 (TRF2), POT1, and ACD (TPP1) proteins bind to the telomeric DNA and their interactions with TIN2 and TERF2IP (RAP1) create a stable complex.

The CST complex is an essential telomeric capping complex that consists of CTC1 (encoded by *CTC1*), STN1 (*OBFC1*), and TEN1 (*TEN1*) [Miyake et al 2009, Surovtseva et al 2009]. This complex is proposed to promote efficient priming of telomeric C-strand synthesis.

RTEL1 encodes regulator of telomere elongation helicase 1. It is an essential DNA helicase and also important in the stability of telomeric t-loops.

PARN, poly(A)-specific ribonuclease was recently shown to be important in the interaction of the TERC (telomerase RNA component) with the telomere.

Figure 3 shows some of these interactions.

CTC1

Gene structure. *CTC1* comprises 23 exons spanning 23,273 bp of genomic sequence on chromosome 17p13.1. The primary isoform results from the NM_025099.5 transcript. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. *CTC1* pathogenic variants reported include missense variants and frameshift-causing deletions.

Normal gene product. CTC1 is a 134.5-kd protein which consists of 1,217 amino acids (NP_079375.3). The CTC1 protein is an essential component of the CST complex which is implicated in telomere protection and DNA metabolism. The human CST complex has only recently been defined.

Abnormal gene product. Compound heterozygous pathogenic variants in *CTC1* appear to result in short telomeres for age. *CTC1* pathogenic variants reported include pathogenic missense variants and deletions causing a frameshift. The specific effect of the pathogenic variants on protein function is currently being studied.

DKC1

Gene structure. *DKC1* comprises 15 exons and spans a genomic region of 15,734 base pairs. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 40 pathogenic variants are described for *DKC1*; the majority are pathogenic missense variants that change an amino acid residue (see **Abnormal gene product**).

For detailed information about specific variants, see Table 2 (pdf).

Normal gene product. The primary transcript of *DKC1* (isoform 1, NP_001354.1) encodes a protein of 514 amino acids. Isoform 2 uses an alternate in-frame splice site in the 3' coding region, compared to variant 1, resulting in a shorter isoform of 509 amino acids (NP_001135935.1). Dyskerin plays multiple roles in human cells. It binds H/ACA and telomerase RNAs (TERC) via its PUA domain. It also functions in ribosomal (r)RNA processing, ribosomal subunit assembly, and centromere and microtubule binding.

Abnormal gene product. Most pathogenic variants in *DKC1* occur in the PUA domain, suggesting that DC arises from abnormal RNA binding.

RTEL1

Gene structure. *RTEL1* comprises 35 exons spanning 39,382 bp of genomic DNA on chromosome 20q13.3.

Pathogenic variants. *RTEL1* pathogenic variants reported include missense variants, frameshift-causing deletions, and stop codons. A founder variant (c.3791G>A; p.Arg1264His) with a carrier frequency of 0.4%-1% has been identified in individuals of Ashkenazi Jewish ancestry.

Table 3.

RTEL1 Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.3791G>A [1]	p.Arg1264His [1]	NM_001283009.1 NP_001269938.1

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1.

The variant is alternately named c.3028C>T (p.Arg1010Ter) on transcript NM_032957.4.

Normal gene product. RTEL1 (regulator of telomere elongation helicase 1) is an essential DNA helicase and is important for the stability of telomeric t-loops.

Abnormal gene product. Disease-associated variants in the RTEL1 protein have been reported in different domains of RTEL1, including the helicase domain, C4C4 domain, PIP, and PCNA domains. The specific functional consequences of these variant are not known.

TERC

Gene structure. *TERC* is a noncoding RNA of 451 bp comprising one exon. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Nearly 50 nucleotide changes and small deletions in *TERC* have been associated with disease.

For detailed information about specific variants, see Table 4 (pdf).

Normal gene product. *TERC* encodes a noncoding RNA; no protein product is made. It serves as the RNA template for telomerase, the reverse transcriptase that adds nucleotide repeats to the telomere.

Abnormal gene product. Pathogenic variants in *TERC* result in an abnormal RNA structure and abnormal template for telomerase.

TERT

Gene structure. *TERT* comprises 16 exons. NM_198253.2 is a transcript of 4,018 nucleotides. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Nearly 50 variants in *TERC* have been associated with idiopathic pulmonary fibrosis, aplastic anemia, interstitial pneumonia, or dyskeratosis congenita. Pathogenic variants include missense as well as loss-of-function (frameshift, splice site) variants [Vulliamy et al 2005, Yamaguchi et al 2005, Armanios et al 2007].

For detailed information about specific variants, see Table 5 (pdf).

Normal gene product. The telomerase protein comprises 1,132 amino acids. Telomerase is a ribonucleoprotein polymerase (reverse transcriptase) that maintains telomere ends by addition of the telomere repeat TTAGGG. The enzyme consists of a protein component with reverse transcriptase activity encoded by this gene and an RNA component that serves as a template for the telomere repeat. Telomerase expression plays a role in cellular senescence, as it is normally repressed in postnatal somatic cells resulting in progressive shortening of telomeres. Deregulation of telomerase expression in somatic cells may be involved in oncogenesis [Armanios 2009].

Abnormal gene product. Pathogenic variants in telomerase that are associated with DC, IPF, or aplastic anemia typically result in loss or reduced expression of the enzyme.

TINF2

Gene structure. *TINF2* comprises nine exons (isoform 2, NM_012461.2). An alternative isoform consists primarily of the first six exons (NM_001099274.1). NM_001099274.1 is a transcript of 1869 base pairs.

The contribution of these alternative isoforms to human disease is not yet known. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. All of the *TINF2* pathogenic variants described to date have been located in exon 6. It is not yet known if pathogenic variants elsewhere in the gene cause disease.

For detailed information about specific variants, see Table 6 (pdf).

Normal gene product. *TINF2* encodes the TIN2 protein, which is an important part of the shelterin telomere protection complex. TIN2 binds to TERF1 and TERF2, which bind directly to the telomeric DNA.

Abnormal gene product. The functional consequences of *TINF2* pathogenic variants are not yet known. They occur in a highly evolutionarily conserved region of the protein and are predicted to have significant effects on protein function.

For information on the genes in Table 1B, click here (pdf)

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Go to:

Chapter Notes

Author Notes

Website: marrowfailure.cancer.gov

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