

# Chapter 4

## The Genetics of Dyskeratosis Congenita and Telomere Biology Disorders

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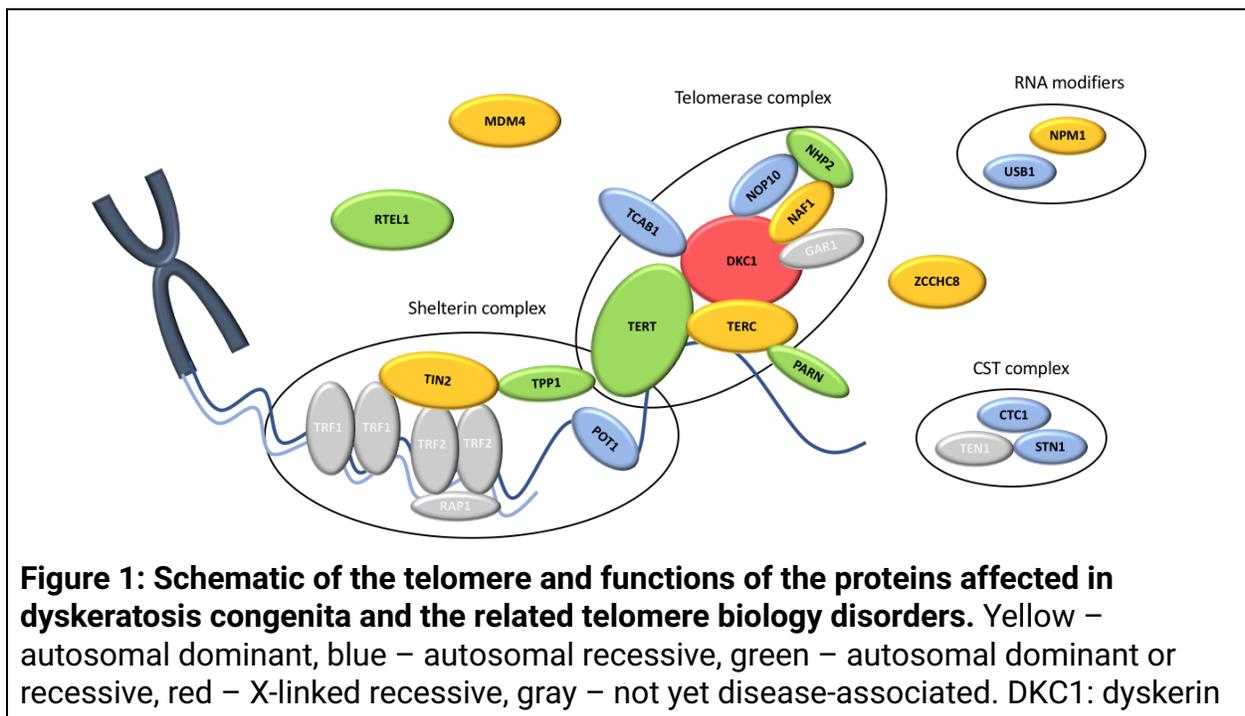
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### Introduction

Pathogenic germline variants, also called mutations, in genes essential for telomere biology are the primary cause of dyskeratosis congenita (DC) and related Telomere Biology Disorders (TBDs) and can be inherited in X-linked recessive (XLR), autosomal dominant (AD), or autosomal recessive (AR) patterns (see Chapter 5, Genetic Counseling for Families). *De novo* germline mutations are also relatively frequent in DC/TBDs. To date, about 70-80% of patients with DC/TBDs have an identifiable pathogenic variant [1-3]. Currently, germline mutations in sixteen different telomere biology genes have been shown to cause DC/TBDs

(Figure 1) [1-4]. Seven of them are well-established disease genes (*DKC1*, *TERT*, *TERC*, *TINF2*, *CTC1*, *RTEL1* and *PARN*) while nine have so far been reported in only a small number of families (*NOP10*, *NHP2*, *WRAP53*, *ACD*, *POT1*, *STN1*, *NAF1*, *ZCCHC8* and *MDM4*). Genetic variants in *USB1* have been reported in patients with symptoms similar to those of DC/TBDs but with normal telomere lengths and more recently, variants in *NPM1* that affect a modification of ribosomal RNA, have been reported in two DC/TBD patients. Most of the DC/TBD-associated pathogenic variants reported occur in a single patient and/or their family members (*i.e.*, a private mutation). However, a few do occur repetitively in multiple unrelated patients, most notably p.Ala353Val in *DKC1* (more than 40 families), p.Arg282His in *TINF2* (more than 30 families), and p.Arg1264His in *RTEL1* (a founder mutation in people of Ashkenazi Jewish ancestry) [5, 6]. As described elsewhere, there is a wide range of phenotypes associated with pathogenic variants in these genes (Table 1).



(encoding gene *DKC1*); TERC: hTR, human telomerase RNA component (*TERC*); TERT: human telomerase reverse transcriptase (*TERT*); NOP10: nuclear protein family A, member 3 (*NOP10*); NHP2: NOLA2 nucleolar protein family A, member 2 (*NHP2*); NAF1: nuclear assembly factor 1 ribonucleoprotein (*NAF1*); GAR1: nucleolar protein family A, member 1 (*GAR1*); PARN: poly (A)-specific ribonuclease (*PARN*); TCAB1: telomere Cajal body associated protein 1 (*WRAP53*); TPP1: telomere protection protein 1 (*ACD*); STN1: CST complex subunit (*STN1*); CTC1: conserved telomere maintenance component 1 (*CTC1*); RTEL1: Regulator of telomere elongation helicase 1 (*RTEL1*); TIN2: TERF1 interacting nuclear factor 2 (*TINF2*); TRF1: telomeric repeat binding factor 1 (*TERF1*); TRF2: telomeric repeat binding factor 2 (*TERF2*); RAP1: TERF2 interacting protein (*RAP1*).  
Components are grouped based on their function.

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## Telomerase-Associated Genes

The first DC-associated gene, XLR *DKC1*, was discovered by linkage analysis in 1998 [7]. The protein encoded by this gene, called dyskerin, was known by homology to be involved in the maturation of ribosomal RNA. The connection between DC/TBDs and telomere length was made when dyskerin was shown to affect telomerase RNA. Primary fibroblasts (skin cells) and lymphoblasts (made from lymphocytes, a type of white blood cell) from patients with DC bearing *DKC1* mutations exhibited low levels of telomerase RNA, reduced telomerase activity, and short telomeres compared to normal controls [8].

The link between DC/TBDs and telomere biology was supported by the subsequent discovery of pathogenic variants in hTERT or hTR (encoded by *TERT* and *TERC*, respectively) in patients with AD forms of DC/TBDs [9, 10]. The *TERT* variants found in these patients are generally nonsynonymous coding mutations that lead to reduction of telomerase activity due to changes in key amino acids. *TERC* encodes the RNA template required for the addition of the (TTTAGG)<sub>n</sub> telomeric DNA nucleotide repeats by telomerase. In addition to mutations affecting the template region of *TERC*, mutations in other domains as well as the promoter region of *TERC* have been described [11]. Rarely, *TERT* can be a cause of AR forms of DC/TBD; biallelic pathogenic variants are

associated with more severe disease and patients have dramatically reduced levels of telomerase. AR DC/TBD can also be the result of biallelic mutations in *NOP10* or *NHP2*, (encoded by genes of the same names), both of which affect telomerase biogenesis, while heterozygous mutations in *NHP2* have been reported in families with AD pulmonary fibrosis (PF) [12-14]. Loss of function variants in *NAF1*, another factor involved in telomerase biogenesis, have been found in two families presenting with AD inheritance of DC/TBD and affected individuals diagnosed with PF, myelodysplastic syndrome (MDS), and/or liver disease [15].

Disruption of telomerase trafficking in the nucleus can result from germline mutations in *TCAB1* (encoded by *WRAP53*) [10]. Patients with compound heterozygous mutations in *TCAB1* were reported to have features of classic DC. Their relatives who had one mutant allele had normal telomere lengths, suggesting that biallelic mutations are required for clinical manifestations. Compound heterozygous mutations in patient cells prevented telomerase from localizing to Cajal bodies for assembly. This results in misdirection of telomerase RNA to the nucleoli and precludes telomerase from elongating telomeres.

Defects in the maturation of hTR can also cause DC/TBDs. Biallelic mutations in *PARN*, a deadenylase which mediates 3'-end processing of hTR, were shown to cause severe early onset DC resembling the Hoyeraal Hreidarsson syndrome (HH) [16-19].

Heterozygous mutations in *PARN*, on the other hand, are associated with AD inheritance of PF [20]. More recently, a mutation *ZCCHC8*, which is also required for hTR 3'-end maturation, has been found in a family with AD PF [21].

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## The Shelterin Telomere Protection Complex

Germline pathogenic variants in *TIN2* (encoded by *TINF2*) are also responsible for AD DC, mostly occurring *de novo* [22, 23]. *TIN2* is not directly involved in telomerase function; rather, it is part of the shelterin complex, a six-protein telomere-specific complex that protects telomeres and participates in length regulation. Causative *TINF2*

mutations cluster at the consensus site for heterochromatin protein 1-gamma (HP1 $\gamma$ ). This association between *TINF2* and HP1 $\gamma$  is required for sister telomere cohesion, thereby preventing sister telomere loss [24].

Pathogenic variants in two other shelterin components, *ACD* (encoding TPP1), and *POT1* (encodes POT1), have been described in rare patients with TBDs. Patients with *ACD* variants presented with variable phenotypes, including HH with AR inheritance and aplastic anemia/myelodysplasia with AD inheritance [25, 26]. *POT1* biallelic variants were identified in a patient with Coats plus [27].

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## Telomere Capping Proteins

Compound heterozygous pathogenic variants in *CTC1* were first reported as a cause of Coats plus and in a clinically similar disorder termed cranioretinal microangiopathy with calcifications and cysts [28, 29]. Patients with those mutations had short telomeres and features that phenotypically overlapped with DC/TBDs [28-30]. Mutations in *CTC1* were subsequently demonstrated to cause AR DC/TBDs [31, 32]. Patient telomere length in *CTC1*-associated DC/TBD was not as short as in DC/TBD due to other causes, but still shorter than unaffected individuals. *CTC1* encodes part of the CST complex along with *STN1* and *TEN1*. Two individuals with Coats plus due to pathogenic germline variants in *STN1* have also been described [33]. The CST complex has both extra-telomeric and telomeric roles; at the telomere, it cooperates with the shelterin complex to protect telomeres from degradation and aberrant recognition by DNA repair machinery [34].

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## Regulator of Telomere Elongation Helicase 1 (*RTEL1*)

Several groups independently identified *RTEL1* mutations using whole exome sequencing in families with DC and HH [35-37]. The *RTEL1* protein regulates telomere length, may interact with PCNA (proliferating cell nuclear antigen), and also plays a role in DNA repair [4, 38]. Most of the *RTEL1* mutations appear to be AR, but AD mutations

have also been reported, particularly in patients presenting with late onset pulmonary disease [14, 39]. As many as 1 in 100 to 1 in 200 individuals of Ashkenazi Jewish ancestry may carry the RTEL1 p.Arg1264His founder mutation, which has led to the inclusion of *RTEL1* in prenatal genetic testing panels for this population [6, 40, 41].

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## U6 Small Nuclear RNA Biogenesis 1 (*USB1*)

Linkage analysis led to the identification of mutations in *C16orf57*, which at the time was of unknown function [27]. It is now called *USB1* and known to be involved in the maturation of a small nuclear RNA (U6), which plays a crucial role in RNA splicing. *USB1* mutations were first reported in individuals with Rothmund Thomson syndrome and poikiloderma with neutropenia, suggesting an overlapping clinical spectrum [42]. These patients, including those with a DC/TBD phenotype, tend to have normal telomere lengths. However, it is interesting to note that yeast cells which lack the orthologue of this protein ( $\Delta mpn1$ ) display increased levels of telomeric repeat-containing RNA and short telomeres [29].

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## MDM4 Regulator of P53

MDM4 is a key regulator of the tumor suppressor protein p53 (encoded by *TP53*). AD inheritance of a pathogenic variant in *MDM4* was discovered in a family with a history of bone marrow failure, early-onset head and neck squamous cell carcinoma, and short telomeres. Laboratory and animal model studies showed that the *MDM4* variant activated the p53 pathway which, in turn, caused telomere dysfunction [43].

**Table 1. Genes associated with DC/TBDs.**

<b>Gene</b>	<b>Gene Product</b>	<b>Patterns of Inheritance</b>	<b>Role</b>	<b>Predominant Phenotypes</b>
<i>ACD</i>	TPP1	AD, AR	Shelterin component	DC-like
<i>CTC1</i>	CTC1	AR	Telomere extension	DC, CP, CM
<i>DKC1</i>	Dyskerin	XLR	Telomerase component	DC, HHS
<i>MDM4</i>	MDM4	AD	Telomere associated regulation of p53	DC-like
<i>NAF1</i>	NAF1	AD	Telomerase component	PF
<i>NHP2</i>	NHP2	AR, AD	Telomerase component	DC, PF
<i>NOP10</i>	NOP10	AR	Telomerase component	DC
<i>NPM1</i>	NPM1	AD	No telomere association (rRNA modification)	DC
<i>PARN</i>	PARN	AR, AD	hTR maturation	DC, HHS, PF
<i>POT1</i>	POT1	AR	Shelterin component	CP
<i>RTEL1</i>	RTEL1	AR, AD	Telomere replication	DC, HHS, PF, MDS, LC
<i>STN1</i>	STN1	AR	Telomere extension	CP
<i>TERC</i>	hTR	AD	Telomerase component	DC, AA, MDS, PF
<i>TERT</i>	hTERT	AD, AR	Telomerase component	DC, AA, MDS, PF, LC

<i>TINF2</i>	TIN2	AD	Shelterin component	DC
<i>USB1</i>	USB1	AR	No telomere association (snRNA maturation)	DC-like, PN, RTS
<i>WRAP53</i>	TCAB1	AR	Telomerase component	DC
<i>ZCCHC8</i>	ZCCHC8	AD	hTR maturation	PF

Abbreviations: DC, dyskeratosis congenita; HHS, Hoyeraal Hreidarsson syndrome; AA, aplastic anaemia; MDS, myelodysplastic syndrome; AML, acute myeloid leukaemia; PF, pulmonary fibrosis; LC, liver cirrhosis; RS, Revesz syndrome; CR, Coat's retinopathy/plus; CM, cerebroretinal microangiopathy with calcification and cysts; PN, poikiloderma with neutropenia; RTS, Rothmund-Thomson syndrome.

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## Genetic Heterogeneity

Our understanding of the genetic causes of DC/TBDs is complicated by the presence of silent carriers and variable clinical manifestations that progress with time. This variability results in incomplete clinical penetrance of disease-associated pathogenic variants. Incomplete penetrance occurs in genetic disorders when a person with a disease-associated mutation does not develop the expected clinical features. This is possibly due to a combination of genetic, environmental, and lifestyle factors. As more family members are tested for TBD-associated mutations, more silent carriers are being recognized. Specifically, carriers of germline mutations in *TERT*, *TERC*, *RTEL1*, and *PARN* with few symptoms consistent with DC/TBDs have been identified because of the increased scrutiny brought about by the diagnosis of a family member. This occurs at least in part because the clinical signs and symptoms of DC/TBDs can develop at different rates in different individuals, even within the same family. For example, the phenotype of very short telomeres (less than the first percentile for age – 99 of 100 people of the same age have longer telomeres) in individuals from a family with variable

clinical penetrance was used in the linkage scan that discovered mutations in *TINF2* as a cause of DC [30]. Silent carriers of DC/TBD-associated mutations should be counseled regarding their potential risk of disease.

As next generation sequencing technologies become widely available to aid in the molecular diagnosis of DC/TBDs, the number of genetic variants of unknown significance identified increases significantly. The status of these variants remains uncertain until further laboratory, population, and/or family studies are conducted to determine whether they are clinically significant or benign. This is true for all rare diseases and as a result, more stringent criteria have been introduced in order to assign pathogenic status to novel variants. In genes such as *TERT* where private (occurring in one family only) missense (amino acid changing) mutations with variable penetrance are the most common cause of disease, new sporadic variants will often not meet sufficient criteria to be classified as pathogenic.

Genetic anticipation refers to a younger age of onset and increased severity of the symptoms of a disease over successive generations within a family. This has been reported in cases of telomerase haploinsufficiency: older generations are often asymptomatic or may have adult-onset pulmonary fibrosis and/or liver disease, but later generations with the same mutation can exhibit classic symptoms of DC or present with aplastic anemia in childhood [9, 44, 45]. A similar finding has been noted in a family with a *TINF2* mutation [46]. It is also notable that in all of these reports the offspring have shorter telomeres than the parents.

Genetic analysis of DC/TBDs is made more complex by the recent identification of somatic mosaic reversion. This phenomenon has been reported in DC families where a germline *TERC* mutation identified in skin fibroblasts was spontaneously corrected by mitotic recombination in blood cells [33].

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## Summary

Causative germline pathogenic variants (*i.e.*, mutations) have been identified in about 70-80% of patients with DC/TBDs. Scientists are using next-generation sequencing technologies to discover the genetic cause of DC/TBDs in mutation-negative families. Genetic counseling for the patient and their family members is an integral component of DC/TBD clinical management (see Chapter 5, Genetic Counseling for Families). This can be particularly challenging in the context of the variable penetrance and variants of unknown significance, discussed above.

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