The biology and management of dyskeratosis congenita and related disorders of telomeres

Hemanth Tummala⁴, Amanda Walne⁴ and Inderjeet Dokal⁴,⁵

Center for Genomics and Child Health, Blizard Institute, Barts and The London Faculty of Medicine and Dentistry, Queen Mary University of London, London, UK; Department of Haematology, Barts Health, London, UK

ABSTRACT

Background: Dyskeratosis congenita (DC) is a multisystem syndrome characterized by mucocutaneous abnormalities, bone marrow failure, and predisposition to cancer. Studies over the last 25 years have led to the identification of 18 disease genes. These have a principal role in telomere maintenance, and patients usually have very short/abnormal telomeres. The advances have also led to the unification of DC with a number of other diseases, now collectively referred to as the telomeropathies or telomere biology disorders.

What is covered: Clinical features, genetics, and biology of the different subtypes. Expert view on diagnosis, treatment of the hematological complications and future.

Expert view: As these are very pleiotropic disorders affecting multiple organs, a high index of suspicion is necessary to make the diagnosis. Telomere length measurement and genetic analysis of the disease genes have become useful diagnostic tools. Although hematological defects can respond to danazol/oxymetholone, the only current curative treatment for these is hematopoietic stem cell transplantation (HSCT) using fludarabine-based conditioning protocols. New therapies are needed where danazol/oxymetholone is ineffective and HSCT is not feasible.

1. Clinical abnormalities

The range of clinical features associated with DC has expanded significantly since its initial description by Zinsser in the beginning of the 20th century. In its syndromic form, it is characterized by the mucocutaneous triad of nail dystrophy, abnormal skin pigmentation and leukoplakia (Figure 1). A wide range of other features (Table 1) affecting different body systems have been recognized [1–3]. Three modes of inheritance have been identified: X-linked recessive (OMIM, 305000), autosomal recessive (OMIM, 224230), and autosomal dominant (OMIM, 127550). The clinical features associated with each subtype can vary widely (as detailed below). The main causes of mortality are bone marrow (BM) failure/immune deficiency (~60–70%), cancer (~10%), and pulmonary disease (~10–15%).

Clinical features frequently appear in childhood. Skin pigmentation abnormalities and nail changes typically appear first, usually below the age of 10 years. The BM failure develops by the age of 20 years with up to 80% of patients having signs of BM failure by the age of 30 years. There is considerable variation between patients with respect to the age of onset and severity of disease, even within affected individuals of the same family. This causes difficulty in making a diagnosis. Equally, it is not uncommon for the BM failure or immune deficiency or another abnormality to present before the more classic mucocutaneous abnormalities.

The minimal clinical criteria for diagnosis of DC include the presence of at least two out of the four major features (nail dystrophy, abnormal skin pigmentation, leukoplakia, and BM failure) and at least two of the other extra-hematopoietic features (Table 1) known to occur in DC [2]. Since 1998, 18 disease genes have been identified and these account for approximately 75% of cases (Table 2).

2. Genetics and different subtypes of DC and related disorders

2.1. X-linked recessive DC and the Hoyeraal–Hreidarsson syndrome due to DKC1 variants

The disease gene (DKC1) responsible for X-linked DC was identified in 1998. DKC1 is highly conserved and encodes dyskerin [4]. With the identification of DKC1 the first genetic test became available. It also provided conclusive evidence that DC is a genetically heterogeneous disorder and that other syndromes with overlapping features can share the same genetic variants (Figure 2(a)). The first example of this was the Hoyeraal–Hreidarsson (HH) syndrome, a severe pediatric disorder characterized by intrauterine growth restriction, microcephaly, cerebellar hypoplasia, BM failure, and variable immune deficiency [5]. Due to overlap in clinical features, it was demonstrated that HH is a severe variant of DC associated with hemizygous DKC1 variants [6]. A diagnosis of HH can be made if an individual has four of the six commonly recognized

ARTICLE HISTORY
Received 23 May 2022
Accepted 29 July 2022

KEYWORDS
Bone marrow failure; dyskeratosis congenita; Hoyeraal–Hreidarsson syndrome; immune deficiency; Revesz syndrome; telomerase; telomeres

CONTACT Inderjeet Dokal i.dokal@qmul.ac.uk Centre for Genomics and Child Health, Blizard Institute, Barts and The London, Faculty of Medicine and Dentistry, Queen Mary University of London, 4 Newark Street, London, England E1 2AT, UK

© 2022 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
features of HH listed above [2]. However, DKC1 variants are not the only cause of HH, variants in other genes (discussed later) can also lead to HH. It is notable, while the majority of patients with hemizygous DKC1 variants have a classic DC phenotype, only a subgroup of DKC1 variants are associated with HH phenotype. Furthermore, some patients with DKC1 variants have features that overlap with both classic DC and HH. DKC1 encodes for the ribonucleoprotein (RNP) dyskerin involved in regulating the stability of H/ACA family RNAs, which includes several members, among which is telomerase RNA (TERC). The molecular impact of DKC1 variants identified appears to destabilize TERC leading to short or abnormal telomeres in DC patients.

2.2. Autosomal dominant DC and its link to telomerase and telomeres

2.2.1. TERC (telomerase RNA component) and TERT (telomerase reverse transcriptase)

In 2001, heterozygous TERC variants were identified in one subtype of autosomal dominant DC. This was a major advance in the field as it provided the first direct link of telomerase to DC [7]. Telomerase is a complex enzyme made up of two main components: TERC (telomerase RNA component) which acts as the template and TERT (telomerase reverse transcriptase) which is the catalytic component. Telomerase functions as a specialized polymerase, adding TTAGGG repeats to the end of the 3' lagging strand of DNA after replication. As a consequence of the semi-conservative nature of DNA replication, telomerase is critical for maintaining telomere length in dividing cells such as hematopoietic stem cells. Without functional telomerase, telomeres shorten with each successive round of cell division, when they become critically short the cells enter senescence. Telomerase is restricted to cells such as stem cells, germ cells and their immediate progeny. In cells that do not express telomerase (e.g. skin fibroblasts), telomere shortening is part of normal process of cellular aging [8].

Germline variants were initially identified in TERC (Figure 2 (b)) in patients with one subtype of autosomal dominant DC [7]. This key discovery rapidly led to expansion of the DC phenotype to include a diverse range of other diseases (Figures 3 and 4). First, heterozygous TERC variants were demonstrated in a subset of patients with aplastic anemia (AA) and subsequently in myelodysplastic syndrome (MDS) [9,10]. This started to push the clinical diagnosis away from the classic mucocutaneous abnormalities to BM failure being the up-front presenting abnormality.

The identification of germline variants in DKC1 and TERC led to the recognition that the principal pathology in DC is defective telomere maintenance; both TERC and dyskerin (DKC1) are now considered to be key components of the telomerase enzyme complex and patients harboring germline TERC and DKC1 variants have very short telomeres [2,11]. This advance focussed further studies on the genes encoding

---

Table 1. Abnormalities associated with classic DC.

| Clinical abnormality/feature | % of patients* |
|------------------------------|----------------|
| A. Common/major abnormalities |
| Skin pigmentation abnormalities | 89 |
| Nail dystrophy | 88 |
| Bone marrow failure | 85.5 |
| Leukoplakia | 78 |
| B. Other recognized abnormalities |
| Epiphora | 30.5 |
| Learning difficulties/developmental delay/mental restriction | 25.4 |
| Pulmonary disease | 20.3 |
| Short stature | 19.5 |
| Extensive dental caries/loss | 16.9 |
| Esophageal stricture | 16.9 |
| Premature hair loss/greying/sparse eyelashes | 16.1 |
| Hyperhidrosis | 15.3 |
| Cancer | 9.8 |
| Intrauterine growth restriction | 7.6 |
| Liver disease/enteropathy/peptic ulceration | 7.3 |
| Ataxia/cerebellar hypoplasia | 6.8 |
| Hypogonadism/undescended testes | 5.9 |
| Microcephaly | 5.9 |
| Urethral stricture/phimosis | 5.1 |
| Osteoporosis/scoliosis/aseptic necrosis | 5.1 |
| Deafness | 0.8 |

*These percentages refer to the first 118 DC patients recruited to the Dyskeratosis Congenita Registry (DCR) in London before the identification of any disease genes.

---

Figure 1. Mucocutaneous abnormalities of DC: Nail dystrophy (a and b), abnormal skin pigmentation (c), and leukoplakia (d).
Table 2. Dyskeratosis congenita and related disease subtypes.

| Disease subtype                  | Approximate % of patients | Chromosome location | Gene name | No. of exons | Associated hematological phenotype |
|----------------------------------|---------------------------|---------------------|-----------|--------------|-----------------------------------|
| X-linked recessive               | 25                        | Xq28                | DKC1      | 15           | DC, HH                            |
| Autosomal dominant               |                           |                     |           |              |                                   |
|                                  | 12                        | 14q11               | TINF2     | 6            | DC, HH, AA, RS                    |
|                                  | 5                         | 3q26                | TERC      | 1            | DC, AA, MDS, AML                  |
|                                  | 4                         | 3p15.33             | TERT      | 16           | DC, AA, MDS, AML                  |
|                                  | <1                       | 10q24.33            | STN1      | 9            | Coats plus                        |
|                                  | <1                       | 4q32.2              | NAF1<sup>a</sup> | 13          | DC-like                           |
|                                  | <1                       | 12q24.31            | ZCCHC8<sup>a</sup> | 17          | DC-like                           |
|                                  | <1                       | 1q32.1              | MDM4<sup>a</sup> | 13          | DC-like                           |
|                                  | <1                       | 16q22.1             | ACD       | 12           | AA, MDS                           |
|                                  | <1                       | 20q13.3             | RETL<sup>1</sup><sup>a</sup> | 35          | DC-like/MDS                       |
|                                  | <1                       | 17p13.3             | RPA1      | 17           | DC-like                           |
| Autosomal recessive              | 3                         | 20q13.3             | RETL<sup>1</sup><sup>a</sup> | 35          | HH                                |
|                                  | 1                         | 17p13.1             | CTC1      | 23           | DC, Coats plus                    |
|                                  | 1                         | 5p15.33             | TERT<sup>b</sup> | 16          | DC, HH                            |
|                                  | <1                       | 15q14               | NOP10     | 2            | DC                                |
|                                  | <1                       | 5q35.3              | NHP2      | 4            | DC                                |
|                                  | <1                       | 17p13.1             | WRAP53    | 13           | DC                                |
|                                  | <1                       | 16p13.12            | PARN<sup>b</sup> | 27          | DC/HH                             |
|                                  | <1                       | 16q22.1             | ACD       | 12           | DC-like                           |
|                                  | <1                       | 1p13.2              | DCLRE1B   | 4            | HH-like                           |
|                                  | <1                       | 7q31.33             | POT1      | 15           | DC-like                           |
| Uncharacterized<sup>a</sup>      | 25                        |                     |           |              |                                   |

The data are based on the Dyskeratosis Congenita Registry in London. The major subtypes of disease are due to variants in DKC1, TINF2, TERC, and TERT.<sup>a</sup>Heterozygous variants in these genes are also associated with pulmonary disease in adulthood. <sup>b</sup>These are likely to represent more than one genetic locus. Abbreviations: AA, aplastic anemia; AML, acute myeloid leukemia; Coats plus, complex syndrome characterized by intracranial calcifications and leukoencephalopathy, retinal vasculature abnormalities, skeletal abnormalities and recurrent gastrointestinal hemorrhage; MDS, myelodysplastic syndrome; RS, Revesz syndrome.

Figure 2. The diverse clinical phenotypes associated with DKC1 and TERC variants. (a) A schematic representation of the variants in DKC1/dyskerin found in cases of DC and HH including the recurrent A333V variant that accounts for approximately 40% of all X-linked DC. NLS, nuclear localization signal, TruB, RNA binding domain PUA, pseudouridine synthase, and archaeosine transglycosylase. (b) The TERC molecule has three domains: the Pseudoknot, scaRNA, and CR4-CRS domains. The majority of variants cluster in the pseudoknot domain. Patients harboring heterozygous TERC variants can present with a variety of phenotypes including dyskeratosis congenita, aplastic anemia, myelodysplastic syndrome/leukemia, and pulmonary disease. These variants refer to patients enrolled on the Dyskeratosis Congenita Registry in London.

other telomerase components in uncharacterized cases of DC. The next significant discovery was the identification of variants in TERT. The clinical presentation in patients with heterozygous TERT variants is very variable ranging from near DC phenotype to AA<sup>[12,13]</sup>. Heterozygous variants in TERT and TERC have also been identified in patients with pulmonary fibrosis, liver disease, and acute leukemia<sup>[14-17]</sup>. 


2.2.2. TINF2 (TRF1-interacting nuclear factor 2) and the shelterin complex

Heterozygous variants in TINF2, which encode a component (TIN2) of the shelterin complex, were identified in 2008 in one subtype of AD-DC. The shelterin complex is composed of six proteins: TRF1 (telomeric-repeat binding protein 1), TRF2 (telomeric-repeat binding protein 2), TINF2 (TRF1-interacting nuclear factor 2), RAP1 (TERF2-interacting protein), TPP1 (TIN2-interacting protein 1), and POT1 (protection of telomeres) [18]. TRF1, TRF2, and POT1 of the shelterin complex (Figure 3) bind directly to the telomeric DNA: TRF1 and TRF2 bind to double stranded DNA and POT1 to the single stranded DNA overhang. The shelterin complex has several functions: it determines the structure of the telomeric terminus, generates t-loops and controls the synthesis of telomeric DNA by telomerase. Without shelterin, telomeres are not protected and chromosome ends are incorrectly processed by the DNA repair pathways. The composition and interactions of components of the shelterin complex are highly ordered with TIN2 (encoded by TINF2) occupying a central role.

In some patients with clinical features of DC, HH, AA, and Revesz syndrome (RS), heterozygous TINF2 variants have been identified [19,20]. This discovery extended the spectrum of diseases even further. RS is characterized by bilateral exudative retinopathy, nail dystrophy, BM failure, fine hair, cerebellar hypoplasia, and growth restriction [21]. Patients with TINF2 variants frequently have severe disease associated with very short telomeres. A significant number of the variants affect

---

**Figure 3. Structural representation of the complexes involved in telomere maintenance to highlight the major disease subtypes.** The telomerase complex includes TERC (telomerase RNA component), TERT (telomerase reverse transcriptase), dyskerin, NOP10, NHP2, GAR1, and NAF1. The shelterin complex is made up of the six proteins TRF1, TRF2, TPP1, POT1, RAP1, and TIN2. The telomere capping (CST) complex is composed of CTC1, STN1, and TEN1. Protein/RNA names indicated by (*) asterisks are mutated in DC and related disorders: Hemizygous DRC1 (dyskerin) variants are observed in X-linked DC and HH. Heterozygous TERC and TERT variants are associated with DC, AA, MDS, AML, and pulmonary/liver fibrosis. Biallelic variants in TERT can cause DC and HH. Heterozygous TIN2 variants have been observed in DC, AA, HH, and Revesz syndrome. Biallelic NOP10, NHP2, TCA1, CTC1 variants are seen AR-DC. Biallelic RTEL1 variants are observed in AR-HH, Biallelic ACD and PARN variants have been reported in AR-DC/HH. Biallelic DCLRE1B variants are associated HH-like disease. Heterozygous NAF1 variants have been observed in AD-DC. Heterozygous variants in RPA1 and ZCCHC8 are associated with DC-like disease. Heterozygous RTEL1 and PARN variants have been associated with pulmonary fibrosis.

Abbreviations: AR, autosomal recessive; AA, aplastic anemia; DC, dyskeratosis congenita; HH, Hoyeraal–Hreidarsson syndrome; MDS, myelodysplastic syndrome; RS, Revesz syndrome.

---

**Figure 4. Schematic highlighting the diverse presentations of DC and related diseases: classic, severe variants and ‘cryptic’ variants.** The year (in brackets) indicates first genetic recognition. These disorders are now increasingly referred to as the telomeropathies or telomere biology disorders because affected individuals usually have short/abnormal telomeres compared to age-matched controls.
amino acids 280–292 of TIN2. It is notable that in TINF2 families, the majority of patients have de novo variants. This is a very different situation to families with TERT and TERC variants, where affected individuals in the first generation usually have minimal or no clinical features and those in succeeding generations have more severe disease. It has been noted that patients in the second and third generations usually have shorter telomeres compared to the first generation. This phenomenon of genetic anticipation adds complexity to making prognostic predictions [22,23].

In recent years germline variants in genes encoding other shelterin proteins have been identified. This includes ACD (encoding TPP1) variants in patients with BM failure [24]. POT1 heterozygous variants have been identified in some familial Hodgkin lymphoma patients, chronic lymphocytic leukemia, melanoma, and glioma, and usually have long telomeres [25–29]. A homozygous POT1 variant has been documented in a case of Coats plus [30]. In contrast, a recent study has identified a germline POT1 variant in family members with DC-like features and short telomeres [31]. As a functional shelterin sub-complex, TIN2 along with TPP1 and POT1 stimulate telomerase processivity and protects telomere integrity.

2.2.3. NAF1 (nuclear assembly factor 1)
Heterozygous NAF1 variants were described in 2016 in two families with DC-like disease [32]. Akin to dyskerin, NAF1 is also an RNP, and its haploinsufficiency selectively disrupts telomere length homeostasis in DC patients.

2.2.4. ZCCHC8 (zinc finger CCHC-type domain containing 8 protein)
In 2019, a heterozygous variant was identified in a multiplex family with pulmonary fibrosis and short telomeres [33]. ZCCHC8 is a nuclear exosome targeting component required for telomerase RNA maturation as well as degradation during various stages of telomerase biogenesis (Figure 4).

2.2.5. MDM4 (mouse double minute 4)
In 2020, a germline heterozygous variant in MDM4 was found to be associated with DC-like phenotype and short telomeres [34]. MDM4 is a negative regulator of p53, and therefore loss of MDM4 causes germline activation of p53-driven transcriptional program that may cause defects in telomere maintenance.

2.2.6. RPA1 (replication protein A)
In 2022, germline heterozygous missense variants in RPA1 were identified in four unrelated families [35]. These patients had short telomeres and varying clinical features including BM failure, MDS, immune defects, pulmonary fibrosis, and cutaneous abnormalities. Functional studies suggested the RPA1 variants led to gain-of-function, where its increased binding to telomeric 3’ overhangs counteracts or restrains telomerase activity leading to short telomeres.

2.3. Autosomal recessive DC
Since 2007, much progress has been made in the genetic basis of autosomal recessive (AR) DC. A large genetic linkage study in 16 consanguineous families did not identify a single common locus suggesting there is genetic heterogeneity within AR-DC [36]. Since this observation, biallelic variants in nine genes have been identified as causing AR disease.

2.3.1. NOP10 (nucleolar protein 10)
The first AR-DC gene [36] to be identified was NOP10 (2007). The homozygous NOP10 variant in a large family with classical DC impacted a highly conserved residue (p.Arg34Trp). Affected individuals in the family had short telomeres and reduced levels of TERC. NOP10 association with the TERC, snoRNP complex plays a critical role in telomere synthesis.

2.3.2. TERT (telomerase reverse transcriptase)
In a subset of AR-DC, biallelic variants have been identified in TERT in addition to the heterozygous variants described above [12,13,23]. These variants give a very different profile of telomerase activity and telomere length with both being greatly reduced compared with heterozygous TERT variants [37]. Patients with biallelic TERT variants can have a clinical phenotype that is close to HH. They can also have significant immune defects.

2.3.3. NHP2 (non-histone ribonucleoprotein 2 homolog)
Biallelic NHP2 variants were identified in families with AR-DC. Patients harboring these variants had reduced TERC levels and short telomeres [38]. NHP2 and NOP10 are both components of the HACA RNP (ribonucleoprotein) complex. This complex is comprised of an RNA molecule and four highly conserved proteins, dyskerin, NOP10, NHP2, and GAR1. The HACA RNP complex has an important role in ribosome biogenesis, pre-mRNA splicing, and telomere maintenance [39]. Variants have been identified in all components of this HACA RNP complex in DC patients except for GAR1.

2.3.4. TCAB1 (telomerase Cajal body protein 1)
Biallelic TCAB1 variants (alias WRAP53) were observed in 2011 in families with AR-DC [40]. TCAB1 has an important function in trafficking telomerase to Cajal bodies. TCAB1 variants disrupt telomerase localization to Cajal bodies. This leads to misdirection of telomerase RNA to nucleoli and prevents telomerase from elongating telomeres thereby resulting in short telomeres.

2.3.5. CTC1 (conserved telomere maintenance component 1) and the CST complex
Biallelic variants in CTC1 were identified in DC and related diseases in 2012 [41,42]. Their effect on telomere length is variable. CTC1 is part of the telomere capping CST complex. This complex is made up of the three proteins CTC1, STN1, and TEN1. (Figure 3). CTC1 promotes efficient DNA replication and thereby helps to maintain telomere length. Patients with biallelic CTC1 variants tend to have pancytopenia that is non-severe and usually do not have immune deficiency. While no DC patients have been described with TEN1 variants, biallelic
STN1 variants are reported in few cases presenting with short telomeres and features of Coats plus syndrome [43].

2.3.6.  RTEL1 (regulator of telomere length 1)
Biallelic RTEL1 variants were first identified in 2013 in a subset of patients with features of HH [44,45]. An autosomal recessive founder mutation was also been reported in HH patients from two unrelated families of Ashkenazi Jewish ancestry [46]. RTEL1 functions as a helicase (Figure 3). It is critical for telomere maintenance. It also has a role in homologous recombination. Patients with biallelic RTEL1 variants usually have very short telomeres as there is impaired resolution of T-loops. However, patient cells do not have significant defects in homologous recombination, since peripheral blood lymphocytes usually have normal chromosomal breakage score following treatment with diepoxybutane or mitomycin-C [45]. These patients have very homogeneous clinical features which include global BM failure, immune deficiency, and cerebellar hypoplasia. Subsequently, it has been observed heterozygous RTEL1 variants are responsible for some cases of pulmonary fibrosis [47]. Furthermore, a subgroup of patients with a combination of MDS and liver disease are associated with heterozygous loss of function variants in RTEL1 [48].

2.3.7.  PARN (poly(A)-specific ribonuclease)
Biallelic PARN variants were identified in 2015 in some patients with severe DC [49]. Many of these patients had global BM failure, cerebellar hypoplasia, as well as a range of other features. In the same year, heterozygous PARN variants were identified in some families with pulmonary fibrosis [50]. PARN is an exonuclease and its deadenylation activity is important in RNA stability. In this context, it has a role in the regulation of a large number of genes including many genes (e.g. TERC, DKC1, RTEL1) important in telomere maintenance and activation of TP53.

2.3.8.  ACD (Adrenocortical dysplasia)
Biallelic variants in two families with DC or DC-like disease have been reported [51]. ACD encodes the shelterin protein TPP1. Patients with these variants have short to very short telomeres. These variants disrupt TERT interaction with the TPP1-TEL patch region, causing disruption in telomerase trafficking to telomeres. It should be noted that a heterozygous ACD variant affecting the TPP1-TEL patch interaction with TERT is also reported in two autosomal dominant families with DC/DC-like disease [24,52].

2.3.9.  DCLRE1B (DNA crosslink repair 1B)
Families with disease resembling HH syndrome were reported in 2022 with biallelic variants in DCLRE1B (alias APOLLO) [53]. These patients had global defects of genome stability leading to fragile telomeres but normal telomere length.

It is notable, that variants in several components of the telomere maintenance machinery have helped to unify

Figure 5. Age of onset and clinical spectrum of disease abnormalities seen in different genetic subtypes of DC. Patients with DKC1 and TINF2 variants usually present at an early age (a) and typically have many more (frequently >5) abnormalities (b) compared to those with heterozygous TERC and TERT variants. This demonstrates that while patients are unified by having defects in genes that are important in telomere maintenance, they exhibit many clinical differences. The number in brackets refers to the number of cases of each subtype in the analysis [54].
a number of different clinical disorders (Figures 3 and 4). Equally, it is also important to appreciate that there is marked variability in the age of onset and constellation of features observed in the different genetic subtypes [54]. For example, patients with TINF2 and DCK1 variants typically have a larger number of abnormalities and early onset of disease compared to patients with TERT and TERC variants [Figure 5]. This detailed information is critical in the management of individual patients. It is also important to acknowledge that while the principal function of the disease genes listed above relates to telomere maintenance some of these genes also have other biological roles. For example, DCK1, NOP10, NHP2 and NAF1 are all important in ribosome biogenesis. It is also noteworthy, there are variants in other genes that can produce a DC/DC-like phenotype [55] where the function of the gene is not principally linked to telomere maintenance. This includes biallelic variants in USB1 and heterozygous variants in NPM1 [56,57] USB1 function as RNA exonuclease, by facilitating the displacement of uridine nucleoside on RNA substrates to stabilize U6 small nuclear RNA, during RNA splicing. NPM1 regulates 2′-O’-methylation of ribosomal RNA by directly binding C/D box small nucleolar RNAs and modulate translation. The disease associated variants in these genes will be useful for clinical purposes specifically in the interpretation of pathogenic status in the suspected cases of DC.

2.4. Hematological defects

It has become clear that BM failure is a common complication of DC. Typically, this develops in the second or third decade, but it can develop any time after birth to the seventh decade of life. Initially, the BM failure can just involve a single lineage (frequently isolated thrombocytopenia or anemia) and then become global and evolve into severe BM failure. The progressive development of BM failure (in up to 80% of patients) resulting in reduction of mature blood cells is one of the major causes of early mortality in these patients. Features of dysplasia in one or more hematopoietic lineage are common; in some cases, these can be tri-lineage. The BM abnormalities can evolve into MDS and leukemia. The initial clinical presentation may be as just BM failure, particularly in patients harboring TERC, TERT, and TINF2 variants.

In-vitro studies have shown that there is a reduction or absence of the multi-lineage colony forming cells consistent with a hematopoietic stem defect [58,59]. There are also differences in progenitor colonies according to the gene variant; for example, patients with TERC variants show a greater a reduction in peripheral blood colony number compared to those with DCK1 variants. This correlation is noteworthy, as patients with TERC variants frequently present with BM failure before mucocutaneous features, whereas in those with DCK1 variants, the presentation usually tends to be more classical.

2.5. Immune deficiency

It has become recognized that immune defects (such as abnormal immunoglobulin levels and altered B and/or T-lymphocyte counts) can occur in patients. These may occur in the absence of significant BM failure. In some cases, mortality from sepsis is therefore attributable to immune defects rather than BM failure. Indeed life-threatening infections such as Cytomegalovirus and Pneumocystis jirovecii have been reported and this aspect with special consideration of immunological abnormalities was initially reviewed by Solder et al. in 1998 [1,60]. Following the demonstration that HH syndrome is a severe DC variant in 1999, there is now recognition that in some patients, the initial clinical presentation may be with severe immune deficiency, typically this is T+B-NK-’. Pediatric patients with this presentation may require prompt treatment with allogeneic HSCT (hematopoietic stem cell transplant). Overall, the immune defects can be very variable. Frequently in the early stages, there is a reduction in the B and NK (natural killer) cells while T cells are relatively spared.

Published literature and the patient registry in London point to significant immune defects in patients with HH and RS phenotypes which are frequently observed in patients with variants in DCK1, TINF2, and RETL1 (Table 2) [1,60]. It is notable immune deficiency is seen in virtually all patients with biallelic variants in RETL1, while in the other genetic subtypes, the immune defects are much more variable.

2.6. Telomere length and pathophysiology

Telomeres are complex structures that are essential for chromosome/genomic integrity as they prevent chromosome ends from being recognized as DNA breaks. They are composed of long TTAGGG repeats and the associated proteins of the shelterin complex. In 1999 Mitchell et al. first reported the association between shortened telomere lengths in X-linked DC [61]. Following this, it was recognized that patients with other genetic subtypes also have short telomeres compared to age-matched controls [62]. These observations have led to DC being now regarded as principally a disorder of defective telomere maintenance (Figure 6). A model for the pathophysiology of DC is given in Figure 7. Germline variants (primary defect) in key components (telomerase, shelterin, etc.) important in telomere maintenance result in excessive telomere attrition. This, together with environmental factors (such as smoking) and the overall genetic constitution of the individual, lead to premature cell death and chromosome instability. With increasing age this combination of interactions reduces/exhausts stem cell reserve and results in clinical abnormalities such as bone marrow failure and predisposition to cancer.

In a study employing flow-FISH [63], telomere lengths were measured in a range of different blood cells from patients with DC and other BM failure patients. This showed that DC patients had very short telomeres (below the first centile) compared to age-matched controls in the majority of leucocytes studied. It also showed that telomere length in DC patients was shorter compared to other BM failure syndromes and because of this telomere length can, with caution, be treated as a surrogate marker for DC [64].
3. Expert opinion

3.1. General aspects of diagnosis and management

As DC and related disorders are complex with very pleotropic clinical abnormalities, diagnosis can sometimes be difficult. It is important to consider the diagnosis when there are two or more of the common features listed in Table 1. A diagnosis of DC and related disorders should also be considered in patients with isolated BM failure or immune deficiency. DC has several abnormalities which overlap with the inherited BM failure
syndrome Fanconi anemia (FA). It is therefore important to exclude a diagnosis of FA. The chromosomal breakage test employing diepoxybutane or mitomycin-C enables FA to be distinguished from DC.

Patients with the following categories of features can be considered to have DC or DC-like disease [65]:

(i) Those with all three mucocutaneous (nail dystrophy, abnormal skin pigmentation, and leukoplakia) abnormalities.
(ii) Those with one or two of these mucocutaneous features together with BM failure and at least two other extra-hematopoietic features of DC.
(iii) Those with AA or MDS or pulmonary fibrosis who are found to have a pathogenic TERC, TERT, TINF2, RTEL1, or PARV variant.
(iv) Those with four or more features of HH (growth restriction, developmental delay, microcephaly, BM failure, immune deficiency, cerebellar hypoplasia).
(v) Those with two or more features observed in DC associated with very short telomeres (<1st centile).

It is noteworthy ‘syndromic-DC’ often presents as a multisystem disorder in children, whereas adult patients presenting with one or more feature of DC display a very variable phenotype. DC and related disorders clearly represent a very diverse clinical and genetic spectrum (Figures 4 and 5).

Measurement of telomere length, particularly using Flou-FISH (flow fluorescence in situ hybridization), can be very informative in the diagnosis of DC [63]. However, it does not have 100% specificity or 100% sensitivity. Genetic analysis for the known disease genes (which now include DKC1, TERC, TERT, NOP10, NHP2, TINF2, TCAB1, CTC1, RTEL1, ACD (TPP1), PARV, POT1, STN1, NAF1, ZCCHC8, MDM4, RPA1, DCLRE1B) as part of targeted gene panel or exome/genome sequencing can help to substantiate the diagnosis at the molecular level. However, this is not straightforward (according to ACM guidelines, many variants are classified as variants of unknown significance) as it can be difficult to assign clear status to many identified variants and in approximately ~25% of the patients the genetic basis will remain unknown even after testing for all the known disease genes.

Once a diagnosis of DC or telomereopathy has been made, it is important to clearly explain to the patient/family that the disease is very variable and that accurate prognostic predictions are not possible. Patients need to have follow-up throughout life together with regular investigations. The frequency of investigations (such as blood, BM, imaging, respiratory, and other tests) is difficult to stipulate precisely because of the marked clinical heterogeneity in different patients (Figure 5). However, regular follow-up, possibly on a yearly basis, is advisable; with more frequent monitoring and focused investigations being undertaken if a particular symptom develops.

In view of the increased cancer risk, it is important for patients to avoid smoking. They should also be advised to avoid sunbathing and to keep alcohol intake to a minimum. The most common non-hematological malignancies are squamous cell carcinomas of the head and neck. Treatment for cancer will depend on the specific cancer, but in general, patients with telomere defects will require a reduction in drug dosages and more supportive care. There is some evidence that suggests acquisition of somatic mutations in driving cancer phenotypes such as MDS and acute myeloid leukemia in DC patients.

Avoidance of smoking is also important with regard to pulmonary disease, which is more common in these patients. Danazol has been found to have some benefits in this context. Lung transplantation may be an appropriate option in some cases.

Liver disease, which may include cirrhosis, is more common than in the general population. Patients therefore need to be advised to keep alcohol intake to a minimum and all medical treatments require close monitoring.

Advice on skin care and avoidance of sunlight is important. Patients should also avoid occupations that expose them to hazardous chemicals or repeated physical trauma. Avoidance of extremes of temperature is desirable as the skin is fragile compared to the normal population.

Patients with DC and related disorders are generally more sensitive to a variety of medical drugs. All drugs (including danazol which is associated with increase in lipid triglyceride/cholesterol and other affects) need to be used carefully and drug doses have to be significantly modified in patients undergoing allogeneic HSCT.

3.2. Therapy of the hematological and immune complications

BM failure and/or immune deficiency are the principal causes of early mortality. For patients with significant peripheral cytopenia supportive therapy (blood and platelet transfusions) is important. They also need to be treated promptly with antimicrobials if they develop pyrexia.

In patients who have significant peripheral cytopenias (Hb <80 g/L, neutrophils <0.5 × 10^9/L, platelets <20 × 10^9/L), the first-line medical therapy in many countries is frequently with oxymetholone. Tri-lineage hematological improvements can be observed in many patients with oxymetholone. While its precise mechanism of action is still not understood, it is thought to function by promoting the growth of hematopoietic progenitors indirectly. There is also some data to suggest that it may increase telomerase activity by action on the TERT gene [66]. In some cases, the hematopoietic improvement with oxymetholone can last years. Patients with DC can respond to a dose as low as 0.25 mg/kg body weight/day and this can be increased, if necessary to 2–5 mg/kg body weight/day. It is important to monitor for side effects (e.g. liver toxicity, hypertension). More recently, it has been recognized that danazol can also produce tri-lineage hematological responses in approximately 70% of DC and related diseases [67,68]. As danazol is less virilizing and generally has a better toxicity profile, it is now used in preference to oxymetholone. Patients can respond to relatively low doses of danazol (e.g. 1 mg/kg/day) but some patients may need a higher dose (e.g. 5–10 mg/kg/day). It is therefore reasonable to start at a low dose and gradually work up to a higher dose, if necessary. It can take 4–8 weeks after the start of danazol before a clear improvement is seen in the peripheral blood counts. Patients
who have no response to danazol/oxyphenbutazone and who do not have significant comorbidities are good candidates for HSCT.

Allogeneic HSCT is currently the only curative treatment for the hematopoietic and/or immunologic abnormalities, but this is not without risk. There is significant mortality associated with HSCT for DC patients compared with other BM failure syndromes. One of the principal reasons for this is the high level of pulmonary/vascular complications that occur in these patients. The precise drugs used in the conditioning regimen also has an important impact on patient survival. It has now become established that the standard myeloablative conditioning regimes are generally associated with poor outcome. In more recent times, the use of low-intensity fludarabine-based conditioning regimens have led to lower toxicity and significantly improved clinical outcomes [69–71]. Nevertheless, it can be difficult to know when to proceed to HSCT. Reasonable indications include BM failure that has not responded to danazol or there is response but with significant side effects from the danazol. Equally, it might be reasonable to proceed straight to HSCT without prior treatment with androgens if there is a compatible stem cell donor. It is important to have full discussion with the patient/family of the relative advantages (cure of hematopoietic defects) and disadvantages (e.g., premature morbidity/mortality from severe infection, graft-versus-host disease) of HSCT and that it will not cure the extra-hematopoietic abnormalities.

### 3.3. Future view

In the future, treatments that target and correct the disease-specific defects may emerge. In this context, it is noteworthy that exogenous TERC alone can correct the telomerase defect, restore telomere length and improve cell growth in lymphocytes harboring DKC1 or TERC variants [72]. There are also reports of an improvement of blood counts in individuals with an acquired somatic mutation in TERC [73,74]. It would be interesting to determine if increased TERC expression/telomerase activity, using this or other approaches [75] can lead to viable new treatment strategies.

Furthermore, over the last 5 years, the mechanisms that control synthesis of TERC have been better defined. These studies have also revealed that inhibition of PAPD5 (poly(A) RNA polymerase D5), and possibly TGS1 (trimethylguanosine synthase 1), can restore mature TERC levels. This leads to increase in telomerase activity and improvement in hematopoietic function. Compounds capable of inhibiting PAPD5 already exist. Recent data from cell and animal models suggest small-molecule PAPD5 inhibitors may represent an efficacious future treatment for a significant subset of patients [76,77]. They therefore warrant further detailed investigation to determine their overall benefit/toxicity profile.

A significant subset of DC and related disorders still remain uncharacterized at the genetic level. New genomic and biological approaches may lead to their characterization in the coming years. This could also suggest new targets for therapy.

In conclusion, since the first disease gene (DKC1) was identified in 1998, there has been considerable progress in the genetics and biology of DC and related disorders (Figure 7). This has led to the recognition of a new set of diseases collectively termed the telomeropathies or telomere biology disorders. There have also been significant improvements in their diagnosis and management. Repurposing of drugs such as danazol and use of fludarabine-based allogeneic HSCT has already had a major positive impact on treatment of this group of patients. In the coming years, drugs such as PAPD5 inhibitors that are able to target the disease-specific defects may emerge. These represent great hope as they may be able to treat abnormalities that currently remain a challenge.

### Acknowledgments

We would like to thank all colleagues, past (Jenna Alnajar, Richard Beswick, Shirley Cardoso, Laura Collopy Alicia Ellison, Mike Kirwan, Stuart Knight, Anna Marrone, Jasmin Sidhu, David Stevens and Philip Mason) and present (Upal Hossain and Tom Vulliamy) and all the patients and clinicians upon whom the research in our laboratory depends.

### Funding

This paper was funded by Blood Cancer UK (14032) and the Medical Research Council (MR/P018440/1).

### Declaration of interest

The authors declare no competing interest.

### Reviewer disclosures

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

### References

Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.

1. Dokal I. Dyskeratosis congenita in all its forms. Br J Haematol. 2000;110(4):768–779.
2. Vulliamy TJ, Marrone A, Knight SW, et al. Mutations in dyskeratosis congenita: their impact on telomere length and the diversity of clinical presentation. Blood. 2006;107(7):2680–2685.
3. Niewisch MR, Giri N, McReynolds LJ, et al. Disease progression and clinical outcomes in telomere biology disorders. Blood. 2022;139(12):1807–1819.
4. Heiss NS, Knight SW, Vulliamy TJ, et al. X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions. Nat Genet. 1998;19(1):32–38.
5. Hoyeraal HM, Lamvik J, Moe PJ. Congenital hypoplastic thrombocytopenia and cerebral malformations in two brothers. Acta Paediatr Scand. 1970;59(2):185–191.
6. Knight SW, Heiss NS, Vulliamy TJ, et al. Unexplained aplastic anaemia, immunodeficiency, and cerebellar hypoplasia (Hoyeraal-Hreidarsson syndrome) due to mutations in the dyskeratosis congenita gene, DKC1. Br J Haematol. 1999;107(2):335–339.
7. Vulliamy T, Marrone A, Goldman F, et al. The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. Nature. 2001;413(6854):432–435.
This article provided definitive link of DC to telomerase.
8. Blasco MA. Telomere length, stem cells and aging. Nat Chem Biol. 2007;3(10):640–649.
9. Vulliamy T, Marrone A, Dokal I, et al. Association between aplastic anemia and mutations in telomerase RNA. Lancet. 2002;359(9324):2168–2170.

This is the first description of DC and telomeres to AA.
10. Yamaguchi H, Baelerchter GM, Landsdorp PM, et al. Mutations of the human telomerase RNA gene (TERC) in aplastic anemia and myelodysplastic syndrome. Blood. 2003;102(3):916–918.
11. Cohen SB, Graham ME, Lovrecz GO, et al. Protein composition of catalytically active human telomerase from immortal cells. Science. 2007;315(5820):1850–1853.
12. Vulliamy TJ, Walne A, Baskaradas A, et al. Mutations in the reverse transcriptase component of telomerase (TERT) in patients with bone marrow failure. Blood Cells Mol Dis. 2005;34(3):257–263.
13. Yamaguchi H, Calado RT, Ly H, et al. Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia. N Engl J Med. 2005;352(14):1413–1424.

This is the first description of TERT variants in AA.
14. de Leon A D, CronkHITE JT, Katzenstein AL, et al. Telomere lengths, pulmonary fibrosis and telomerase (TERT) mutations. PLoS One. 2010;5(5):e10680.
15. Calado RT, Regal JA, Kleiner DE, et al. A spectrum of severe familial liver disorders associated with telomerase mutations. PLoS One. 2009;4(11):e7926.
16. Calado RT, Regal JA, Hills M, et al. Constitutional hypomorphic telomerase mutations in patients with acute myeloid leukemia. Proc Natl Acad Sci USA. 2009;106(4):1187–1192.
17. Kirwan M, Vulliamy T, Marrone A, et al. Defining the pathogenic role of telomerase mutations in myelodysplastic syndrome and acute myeloid leukemia. Hum Mutat. 2009;30(1):1567–1573.
18. de Lange T. Shelterin: the protein complex that shapes and safeguard human telomeres. Genes Dev. 2005;19(18):2100–2110.
19. Savage SA, Giri N, Baerlocher GM, et al. TINF2, a component of the shelterin telomere protection complex, is mutated in dyskeratosis congenita. Am J Hum Genet. 2008;82(2):501–509.
20. Walne AJ, Vulliamy T, Beswick R, et al. TINF2 mutations result in very short telomers. analysis of a large cohort of patients with dyskeratosis congenita and related bone marrow failure syndromes. Blood. 2008;112(9):3594–3600.
21. Revesz T, Fletcher S, Al-gazali LL, et al. Bilateral retinopathy, aplastic anemia, and central nervous system abnormalities: a new syndrome? J Med Genet. 1992;29(9):673–675.
22. Vulliamy T, Marrone A, Szyllo R, et al. Disease anticipation is associated with progressive telomere shortening in families with dyskeratosis congenita due to mutations in TERC. Nat Genet. 2004;36(5):447–449.

This is the first demonstration of disease anticipation in DC.
23. Armanios M, Chen JL, Chang YP, et al. Haploinsufficiency of telomerase reverse transcriptase leads to anticipation in autosomal dominant dyskeratosis congenita. Proc Natl Acad Sci USA. 2005;102(44):15960–15964.
24. Guo Y, Kartawinata M, Li J, et al. Inherited bone marrow failure associated with germline mutation of ACD, the gene encoding telomere protein TPP1. Blood. 2014;124(18):2767–2774.
25. McMaster ML, Sun C, Landi MT, et al. Germline mutations in protection of telomeres 1 in two families with Hodgkin lymphoma. Br J Haematol. 2018;181(3):372–377.
26. Speedy HE, Kinnersley B, Chubb D, et al. Germ line mutations in shelterin complex genes are associated with familial chronic lymphocytic leukemia. Blood. 2006;112(19):2319–2326.
27. Potrany M, Puig-Butille JA, Ribera-Sola M, et al. POT1 germline mutations but not TERT promoter mutations are implicated in melanoma susceptibility in a large cohort of Spanish melanoma families. Br J Dermatol. 2019;181(1):105–113.
28. Bainbridge MN, Armstrong GN, Gramatges MM, et al. Germline mutations in shelterin complex genes are associated with familial glioma. J Natl Cancer Inst. 2015;107(1):384.
29. Shi J, Yang XR, Ballew B, et al. Rare missense variants in POT1 predispose to familial cutaneous malignant melanoma. Nat Genet. 2014;46(5):482–486.
30. Takai H, Jenkinson E, Kabir S, et al. A POT1 mutation implicates defective telomere end fill-in and telomere truncations in Coats plus. Genes Dev. 2016;30(7):812–826.
31. Kelich J, Aramburu T, van der Vis JJ, et al. Telomere dysfunction implicates POT1 in patients with idiopathic pulmonary fibrosis. J Exp Med. 2022;219(5). DOI:10.1084/jem.20211681.
32. Stanley SE, Gable DL, Wagner CL, et al. Loss-of-function mutations in the RNA biogenesis factor NAF1 predispose to pulmonary fibrosis-empysema. Sci Transl Med. 2016;8(351):351ra107.
33. Gable DL, Gaysinskaya V, Atik CC, et al. ZCCHC8, the nuclear exosome-targeting component, is mutated in familial pulmonary fibrosis and is required for telomerase RNA maturation. Genes Dev. 2019;33(19–20):1381–1396.
34. Toufektsian E, Lejour V, Durand R, et al. Germline mutation of MDM4, a major p53 regulator, in a familial syndrome of defective telomere maintenance. Sci Adv. 2020;6(15):eaay3511.
35. Sharma R, Sahoo SS, Honda M, et al. Gain-of-function mutations in RPA1 cause a syndrome with short telomeres and somatic genetic rescue. Blood. 2022;139(7):1039–1051.
36. Walne AJ, Vulliamy T, Marrone A, et al. Genetic heterogeneity in autosomal recessive dyskeratosis congenita with one subtype due to mutations in the telomerase-associated protein NOP10. Hum Mol Genet. 2007;16(13):1619–1629.
37. Marrone A, Walne A, Tamary H, et al. Telomerase reverse-transcriptase hozygous mutations in autosomal recessive dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome. Blood. 2007;110(13):4198–4205.
38. Vulliamy T, Beswick R, Kirwan M, et al. Mutations in the telomerase component NHP2 cause the premature ageing syndrome dyskeratosis congenita. Proc Natl Acad Sci USA. 2008;105(23):8073–8078.
39. Meier UT. How a single protein complex accommodates many different H/ACA RNAs. Trends Biochem Sci. 2006;31(6):311–315.
40. Zhong F, Savage SA, Shkrelli M, et al. Disruption of telomerase trafficking by TCA81 mutation causes dyskeratosis congenita. Genes Dev. 2011;25(1):11–16.
41. Keller RB, Gagne KE, Usmani GN, et al. CTCl mutations in a patient with dyskeratosis congenita. Pediatr Blood Cancer. 2012;59(2):311–314.
42. Walne AJ, Bhagat T, Kirwan M, et al. Mutations in the telomere capping complex in bone marrow failure and related syndromes. Haematologica. 2013;98(3):334–338.
43. Simon AJ, Lev A, Zhang Y, et al. Mutations in STN1 cause Coats plus syndrome and are associated with genomic and telomere defects. J Exp Med. 2016;213(8):1429–1440.
44. Ballew BJ, Yeager M, Jacobs K, et al. Germline mutations of regulator of telomere elongation helicase 1, RTEL1, in Dyskeratosis congenita. Hum Genet. 2013;132(4):473–480.
45. Walne AJ, Vulliamy T, Kirwan M, et al. Constitutional mutations in RTEL1 cause severe dyskeratosis congenita. Am J Hum Genet. 2013;92(3):448–453.
46. Ballew BJ, Joseph V, De S, et al. A recessive founder mutation in regulator of telomere elongation helicase 1, RTEL1, underlies severe immunodeficiency and features of Hoyeraal-Hreidarsson syndrome. PLoS Genet. 2013;9(8):e1003695.
47. Cogan JD, Kropski JA, Zhao M, et al. Rare variants in RTEL1 are associated with familial interstitial pneumonia. Am J Respir Crit Care Med. 2015;191(6):646–655.
48. Cardoso SR, Ellison ACM, Walne AJ, et al. Myelodysplasia and liver disease extend the spectrum of RTEL1 related telomeropathies. Haematologica. 2017;102(8):e293–e6.

EXPERT REVIEW OF HEMATOLOGY 695
49. Tummala H, Walne A, Collopy L, et al. Poly(A)-specific ribonuclease deficiency impacts telomere biology and causes dyskeratosis congenita. J Clin Invest. 2015;125(5):2151–2160.

50. Stuart BD, Choi J, Zaidi S, et al. Exome sequencing links mutations in PARN and RTEL1 with familial pulmonary fibrosis and telomere shortening. Nat Genet. 2015;47(5):512–517.

51. Tummala H, Collopy LC, Walne AJ, et al. Homozygous 08-fold variants in telomere protein TPP1 are associated with dyskeratosis congenita-like phenotypes. Blood. 2018;132(12):1349–1353.

52. Kocak H, Ballew BJ, Bish K, et al. Hoyeraal-Hreidarsson syndrome caused by a germline mutation in the TEL patch of the telomere protein TPP1. Genes Dev. 2014;28(19):2090–2102.

53. Kermasson L, Churikov D, Awad A, et al. Inherited human Apollo deficiency causes severe bone marrow failure and developmental defects. Blood. 2022;139(16):2427–2440.

54. Vulliamy TJ, Kirwan MJ, Beswick R, et al. Differences in disease severity but similar telomere lengths in genetic subgroups of patients with telomerase and shelterin mutations. PLoS One. 2011;6(9):e24383.

55. Walne AJ, Collopy L, Cardoso S, et al. Marked overlap of four genetic syndromes with dyskeratosis congenita confounds clinical diagnosis. Haematologica. 2016;101(10):1180–1189.

56. Hilcenko C, Simpson PJ, Finch AJ, et al. Aberrant 3′ oligoadenylation of spliceosomal U6 small nuclear RNA in poikiloedermia with neutropenia. Blood. 2013;121(6):1028–1038.

57. Nachmani D, Bothmer AH, Grisendi S, et al. Germline NPM1 mutations lead to altered rRNA 2′-O-methylation and cause dyskeratosis congenita. Nat Genet. 2019;51(10):1518–1529.

58. Marsh JC, Will AJ, Hows JM, et al. “Stem cell” origin of the hematopoietic defect in dyskeratosis congenita. Blood. 1992;79(12):3138–3144.

59. Goldman FD, Aubert G, Klingelhoitz AJ, et al. Characterization of primitive hematopoietic cells from patients with dyskeratosis congenita. Blood. 2008;111(9):4523–4531.

60. Solder B, Weiss M, Jager A, et al. Dyskeratosis congenita: multisystemic disorder with special consideration of immunologic aspects. A review of the literature. Clin Pediatr. 1998;37(9):521–530.

61. Mitchell JR, Wood E, Collins K. A telomerase component is defective in the human disease dyskeratosis congenita. Nature. 1999;402 (6761):551–555.

**This is the first link of DC to telomerase.**

62. Vulliamy TJ, Knight SW, Mason PJ, et al. Very short telomeres in the peripheral blood of patients with X-linked and autosomal dyskeratosis congenita. Blood Cells Mol Dis. 2001;27(2):353–357.

63. Alter BP, Baerlocher GM, Savage SA, et al. Very short telomere length by flow fluorescence in situ hybridization identifies patients with dyskeratosis congenita. Blood. 2007;110(5):1439–1447.

64. Du HY, Pumbo E, Ivanovich J, et al. TERC and TERT gene mutations in patients with bone marrow failure and the significance of telomere length measurements. Blood. 2009;113(2):309–316.

65. Dokal I, Vulliamy T, Mason P, et al. Clinical utility gene card for: dyskeratosis congenita - update 2015. Eur J Hum Genet. 2015;23 (4):558.

66. Calado RT, Yewdell WT, Wilkerson KL, et al. Sex hormones, acting on the TERT gene, increase telomerase activity in human primary hematopoietic cells. Blood. 2009;114(1):2236–2243.

67. Islam A, Rafiq S, Kirwan M, et al. Haematological recovery in dyskeratosis congenita patients treated with danazol. Br J Haematol. 2013;162(6):854–856.

68. Townsley DM, Dumitriu B, Liu D, et al. Danazol treatment for telomere diseases. N Engl J Med. 2016;374(20):1922–1931.

* First randomized study showing benefit of danazol in DC and related disorders.

69. de la Fuente J, Dokal I. Dyskeratosis congenita: advances in the understanding of the telomerase defect and the role of stem cell transplantation. Pediatr Transplant. 2007;11(6):584–594.

70. Dietz AC, Orchard PJ, Baker KS, et al. Disease-specific hematopoietic cell transplantation: nonmyeloablative conditioning regimen for dyskeratosis congenita. Bone Marrow Transplant. 2011;46 (1):98–104.

71. Agarwal S. Evaluation and management of hematopoietic failure in dyskeratosis congenita. Hematol Oncol Clin North Am. 2018;32 (4):669–685.

72. Kirwan M, Beswick R, Vulliamy T, et al. Exogenous TERC alone can enhance proliferative potential, telomerase activity and telomere length in lymphocytes from dyskeratosis congenita patients. Br J Haematol. 2009;144(5):771–781.

73. Revy P, Kannengiesser C, Fischer A. Somatic genetic rescue in Mendelian haematopoietic diseases. Nat Rev Genet. 2019;20 (10):582–598.

74. Jongmans MC, Verwiel ET, Heijdra Y, et al. Revertant somatic mosaicism by mitotic recombination in dyskeratosis congenita. Am J Hum Genet. 2012;90(3):426–433.

75. Agarwal S, Loh YH, McLoughlin EM, et al. Telomere elongation in induced pluripotent stem cells from dyskeratosis congenita patients. Nature. 2010;464(7286):292–296.

76. Shukla S, Jeong HC, Sturgeon CM, et al. Chemical inhibition of PAPD5/7 rescues telomerase function and hematopoiesis in dyskeratosis congenita. Blood Adv. 2020;4(12):2717–2722.

* This study shows benefit of PAPD5 inhibitors in DC cells.

77. Nagpal N, Wang J, Zeng J, et al. Small-molecule PAPD5 inhibitors restore telomerase activity in patient stem cells. Cell Stem Cell. 2020;26(6):896–909 e8.

* This study shows benefit of PAPD5 inhibitors in DC model.