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Evaluation and Management of Hematopoietic Failure in Dyskeratosis Congenita

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INTRODUCTION

Dyskeratosis congenita (DC) is a rare, inherited bone marrow failure (BMF) syndrome characterized by variable manifestations and ages of onset, and predisposition to cancer. Genetic discoveries in the past 20 years have revealed DC as one of a spectrum of diseases caused by mutations in genes regulating telomere maintenance, collectively referred to here as telomere biology disorders (TBDs). Hematologic disease is a frequent finding in patients with DC and in children presenting with TBD. Timely diagnosis of an underlying TBD in patients with BMF affects treatment and has been facilitated by increased awareness and availability of diagnostic tests in recent years. This article summarizes the pathophysiology, evaluation, and management of hematopoietic failure in patients with DC/TBD.

A SPECTRUM OF TELOMERE DISEASES

DC in its classic form was described more than 100 years ago and is characterized by manifestations regarded as the diagnostic triad of reticular skin pigmentation abnormalities, oral leukoplakia, and dystrophic nails. These symptoms are now recognized as the outward manifestations of a systemic degenerative disease with myriad disorders emerging variably over the lifespan.¹ Hematologic disease is frequent: clinically significant BMF manifested in 50% of patients with DC by age 50 year in one prospective cohort, whereas 90% of patients with DC developed at least a single lineage cytopenia by the fourth decade of life in a registry study.^{2,3} Patients with DC have increased risks of myelodysplastic syndrome (MDS) (>500 times) and acute myeloid leukemia (AML) (~73 times) compared with the general population.⁴ The elucidation of gene mutations in classic DC led to the discovery of a broad and variable spectrum of disease, affecting individuals of all ages.^{5,6} Early-onset, multisystem disorders manifesting as Hoyeraal-Hreidarsson syndrome, Revesz syndrome, or Coats plus disease are caused by mutations in genes also disrupted in patients presenting

with classic DC.^{7–10} In contrast, some patients without overt syndromic features diagnosed in childhood or adulthood with idiopathic aplastic anemia or familial MDS/AML carry germline mutations in the same telomere biology genes implicated in DC.^{11–14} Still other patients with TBDs may remain asymptomatic from a hematologic standpoint throughout life, but present in the fifth to seventh decades of life with progressive and ultimately fatal hepatic or pulmonary fibrosis.^{15,16} An increasing awareness of the highly variable presentation of TBD and the availability of clinically validated telomere length and genetic testing have led to refined estimates of the rarity of TBD. Although early-onset phenotypes with multisystem disease such as DC are generally said to affect ~1 in 1 million children, the prevalence of the broader spectrum of TBD that includes adults with late-onset manifestations may be 10 to 100 times higher.¹⁷ In these individuals, recognizing subtle hematologic defects in the absence of overt symptoms can have important clinical consequences, such as anticipating complications of medical therapy for other TBD-associated disorders (eg, organ transplant for lung or liver disease), and assessing their suitability as bone marrow donors for affected family members.^{18,19}

TELOMERES IN STEM CELL SELF-RENEWAL

Telomeres are repetitive protein-DNA structures that protect the ends of chromosomes (Fig. 1). Hundreds to thousands of copies of the hexanucleotide repeat TTAGGG are complexed with shelterin proteins (TRF1, TRF2, RAP1, TIN2, POT1, TPP1) to prevent the recognition of free DNA ends as double-stranded breaks. The ends of linear DNA cannot be replicated by DNA polymerase, and therefore telomere length decreases with each cell cycle. At a critically short telomere length, senescence is triggered and cells stop dividing.^{20,21} Adult self-renewing cells such as hematopoietic stem cells (HSCs) counteract telomere-associated senescence by activating telomerase (encoded by the *TERT* gene), a ribonucleoprotein that replaces hexanucleotide repeats by reverse transcription of an RNA template (encoded by the *TERC* gene). The balance of replication-associated telomere attrition and telomerase-mediated repeat addition is an important determinant of stem cell self-renewal capacity and therefore tissue regenerative capacity throughout the lifespan. Telomere length can be considered an endowment from a tissue-specific stem cell that determines the number of times its telomerase-negative, differentiated progeny can divide.

GENETICS OF DYSKERATOSIS CONGENITA/TELOMERE BIOLOGY DISORDERS

The pioneering work of Dokal, Vulliamy and colleagues^{22,23} in the 1990s established a registry of patients with DC that enabled genetic linkage studies and led to the discovery of *DKC1*, the first DC-associated gene. The protein encoded by *DKC1*, dyskerin, was found to have homology to Cbf5p, a yeast pseudouridine synthase that binds an RNA motif called the H/ACA box. Independently, Mitchell and Collins²⁴ identified an H/ACA box motif in the long noncoding RNA component of human telomerase, *TERC*, leading to their insight that disruption of telomere maintenance pathways may underlie DC. This hypothesis was confirmed by their subsequent demonstrations that dyskerin was indeed a novel component of human telomerase, and that *TERC* RNA levels were decreased in *DKC1*-mutant cells in

patients with DC.²⁵ Subsequently, the discovery of germline *TERC* mutations in autosomal dominant DC pedigrees solidified a role for defective telomere maintenance in DC.²⁶ In the ensuing 20 years, mutations in 13 genes involved in various aspects of telomere maintenance have been identified to account for ~70% of DC cases^{27–30} (Table 1), including genes encoding telomerase-associated components (*TERC*, *TERT*, *DKC1*, *NOP10*, *NHP2*, *TCAB1*, *NAF1*, *PARN*), shelterin proteins (*TIN2*, *TPP1*), and other regulators of telomere length and replication (*RTEL1*, *CTC1*, *STN1*) (see Fig. 1).

The inheritance of short telomeres has been shown to contribute to disease manifestations and patient phenotypes. Genetic anticipation is seen in autosomal dominant forms of DC/TBD, with hematopoietic and multisystem disease presenting earlier in life, and with an increasing penetrance in each generation.^{31,32} This anticipation is thought to be caused by the combined effect of inheriting shortened telomeres (ie, diminished telomere endowment) in addition to a telomere maintenance defect caused by the underlying genetic mutation. Intriguingly, it has also been observed in animal models and human studies of pedigrees with known autosomal dominant mutations that inheritance of short telomeres without the genetic mutation may result in hematologic or nonhematologic phenotypes of DC.^{33–35}

CAUSE OF HEMATOPOIETIC FAILURE IN DYSKERATOSIS CONGENITA

Genetically determined defects in telomere length provide an intuitive pathophysiologic link between premature telomere attrition, compromised HSC self-renewal, and hematopoietic failure. HSC self-renewal and differentiation are required to maintain the homeostatic production of billions of blood cells per day. HSCs express telomerase, and HSC self-renewal is governed in part by telomere length.^{36–38} Blood cell telomere length decreases as people age, indicating that telomerase levels are limiting in the HSC compartment.³⁶ Telomere length of donor hematopoietic cells decreases rapidly on transplant into another host, consistent with accelerated telomere attrition in human HSCs during periods of replicative stress.^{39–41} Defects in telomere length inheritance and/or maintenance are therefore consistent with impairments in hematopoietic output over the lifespan. Across the spectrum of TBD, hematopoietic failure as a presenting manifestation tends to correlate with the severity of telomere shortening.⁴²

Several correlative studies have linked short telomere length in the hematopoietic compartment to various diseases perhaps reflective of external pressures such as high turnover and immune attack. Shorter than normal telomere length is found in the blood cells of patients with aplastic anemia and MDS, and is associated with evolution of acquired aplastic anemia to MDS.^{43–47} Short telomere length also portends poor outcome to therapeutic interventions such as immunosuppressive therapy (IST)⁴⁸ and bone marrow transplant,⁴⁹ independent of germline mutations in telomere biology genes. These findings indicate a direct role of telomere attrition in hematopoietic failure and transformation.

The observation of clonal dominance in carriers of DC-associated mutations provides strong evidence for a causal role of HSC-intrinsic telomere maintenance defects in BMF. Early studies of maternal carriers of pathogenic X-linked *DKC1* gene mutations showed skewing of X inactivation in the peripheral blood.⁵⁰ This finding indicates that hematopoietic

progenitors expressing the mutant *DKC1* allele are compromised in survival, self-renewal, and/or differentiation compared with those expressing the normal allele. In autosomal dominant DC, somatic reversion of pathogenic *TERC* mutations has been observed in the peripheral blood.⁵¹ Multiple independent episodes of reversion by somatic recombination were documented to occur at the level of a multi-potent hematopoietic progenitor, and the derivatives of individual clones could be shown to comprise most of the peripheral blood cells. Collectively, these striking observations indicate a strong selective pressure for intact telomere maintenance mechanisms in HSCs to ensure adequate hematopoietic output.

DIAGNOSTIC TESTING FOR TELOMERE BIOLOGY DISORDER

Patients presenting with persistent peripheral blood cytopenias and a hypocellular bone marrow undergo extensive testing for infectious, immune, genetic, and other causes of BMF. Because of the implications for management, this evaluation should routinely include testing for constitutional defects in telomere maintenance. The absence of classic mucocutaneous or other signs of DC does not exclude the possibility of an inherited TBD. With the increased availability of appropriate diagnostic testing in the past several years, it has become clear that a substantial number of patients diagnosed with a TBD do not manifest the classic DC triad or other overt findings at the time of presentation with hematopoietic failure.⁴²

Telomere length measurement (TLM) provides a functional test for constitutional telomere maintenance, and is an important adjunct to a comprehensive clinical assessment of patients presenting with BMF and/or suspected TBD. Several methods exist to measure telomere length, including Southern blot, quantitative polymerase chain reaction (qPCR), and flow cytometry-fluorescence in situ hybridization (flow-FISH).⁵² Flow-FISH of peripheral blood cells is a clinically validated diagnostic test for DC. Flow-FISH entails hybridization of fluorescent probes to telomere ends in blood cells. The overall fluorescent intensity of a cell reflects the telomere length of all of the chromosome ends in the cell. A mean fluorescence intensity is measured for a population of cells (eg, total nucleated blood cells or particular blood cell lineage such as lymphocytes) and compared with age-adjusted normal values. Applying flow-FISH to a registry of patients with known or suspected inherited BMF syndromes, Alter and colleagues^{53,54} determined that a mean lymphocyte telomere length less than or equal to 1st percentile (%ile) for age was highly sensitive for identifying patients with a constitutional TBD among patients with various forms of BMF. On this basis, age-adjusted mean lymphocyte telomere length less than or equal to 1%ile has been proposed to be diagnostic of DC/TBD when evaluating children with BMF.⁵⁴

Although clinical flow-FISH has transformed diagnostic testing for DC since it became available approximately 10 years ago, the results must be taken within the clinical context. The diagnostic performance of flow-FISH as defined by the studies described earlier depends largely on the assumption that very low lymphocyte telomere length reflects a constitutional telomere length defect in patients with myeloid failure. However, other acquired or genetic disorders that cause high HSC turnover, or primary immunodeficiency syndromes that affect lymphoid development or homeostasis, may also manifest very low lymphocyte telomere length. In these cases, caution is warranted in interpreting lymphocyte TLM. There remains a need for a constitutional TLM strategy that does not involve

hematopoietic cells, which may avoid these confounding situations. A recent study has shown that some children and most older patients with TBD can manifest leukocyte telomere length greater than the 1%ile.⁴² In this study, TLM was always less than the 50%ile for age and usually less than 10%ile in patients with TBD. These data argue that, taking all ages and presentations into account, the majority of patients with a genetic disorder of telomere biology will not have telomere length less than 1%ile by flow-FISH. Therefore, the finding of lymphocyte TLM greater than 1%ile should not be used to rule out TBD in adult patients. Other limitations to flow-FISH telomere length testing include the geographic locations of the test centers, need for transport of a fresh specimen within a certain time frame to the testing center, sensitivity of the sample to environmental effects in transit, and lack of insurance coverage for this specialized test.

In terms of other approaches for TLM, qPCR of blood cell telomere length has been shown in several recent studies to be inferior to flow-FISH in diagnostic performance and is therefore not recommended for clinical decision making.^{55,56} Southern blot can be considered a gold standard of telomere length measurement but is technically cumbersome and has not been standardized for specific tissues or across age distributions, and therefore its clinical utility is not yet realized.

Genetic testing is an important complement to functional telomere length testing in establishing a diagnosis of TBD. The development of next-generation sequencing panels targeting BMF genes by several investigators and centers has ushered in an era in which genetic testing might be pursued early in the clinical assessment, perhaps before or instead of telomere length testing. However, a major limitation of these exome capture panels is the incomplete genetic characterization of DC/TBD. Other confounders include incomplete coverage of genes of interest, incorrect filtering of potentially pathogenic variants, the interpretation of variants of uncertain significance, and failure to capture noncoding mutations or germline mutations because of somatic reversion. Simultaneous Sanger sequencing or orthogonal methods are useful to address coverage issues. Family studies combined with telomere length testing could be helpful in establishing the pathogenicity of variants of undetermined significance and addressing somatic reversion. Whole-genome sequencing may reveal relevant noncoding variants in patients suspected to have DC/TBD. Given these considerations, our usual practice is to send both the flow-FISH telomere length testing and a BMF genetics panel early in the evaluation of patients with BMF whenever possible.

EVALUATION OF CYTOPENIAS IN PATIENTS WITH DYSKERATOSIS CONGENITA

Peripheral blood cytopenias are common in DC and TBD, more frequently in children and in patients with multisystem disease. Characteristic findings in children presenting with hematopoietic failure caused by DC typically include myeloid defects with a predominance of thrombocytopenia; a high mean corpuscular volume; and more variably anemia, neutropenia, and reticulocytopenia. Lymphocyte numbers may be normal, but in early-onset forms of TBD such as Hoyeraal-Hreidarsson syndrome, a characteristic T cell-positive, B

cell-deficient, and natural killer cell-deficient lymphopenia may be present, with or without immune dysregulation or immunodeficiency.

Although hematopoietic failure predominates, other disorders may contribute to low blood counts in patients with DC and TBD, and these are important to evaluate. Pancytopenia may result from transformation to MDS or AML. Hematologic malignancy is a less frequent manifestation of DC than BMF in children, whereas it may be the presenting manifestation of TBD in adults.² In patients with liver disease and splenomegaly caused by portal hypertension, hypersplenism may contribute to thrombocytopenia and neutropenia, and may also cause delayed hematopoietic reconstitution after bone marrow transplant. Gastrointestinal bleeding caused by esophageal varices from liver disease or caused by gastric vascular abnormalities, as is seen in Coats plus syndrome,^{30,57} may contribute to anemia. Cytopenias from these causes can accompany and be exacerbated by concurrent hematopoietic failure. Bone marrow evaluation on presentation and serially is thus essential to evaluate for morphologic and cytogenetic changes to help distinguish aplasia versus transformation versus consumptive causes of cytopenias in DC.

MANAGEMENT OF HEMATOPOIETIC FAILURE IN DYSKERATOSIS CONGENITA

The optimal management of hematopoietic failure in patients with DC or TBD depends first and foremost on diagnosing the underlying genetic disease. For this reason, all patients presenting with BMF should be assessed for DC/TBD by telomere length and genetic testing in conjunction with a careful clinical assessment. Arguably, the same may hold true for patients with MDS and AML presenting at any age because of the implications for patient management and family counseling. However, the frequency of TBD in these patients, and therefore the diagnostic yield, is unknown. Careful assessment of the family history for pulmonary or liver disease, hematologic defects or malignancy, and other manifestations such as early graying should be undertaken, and may be the primary findings that lead to testing and eventual diagnosis of DC/TBD.

Supportive Care

Transfusion support with red blood cells and platelets may be required for patients with severe cytopenias. Platelet refractoriness following transfusion may reflect hypersplenism caused by liver disease. Exposure to a large number of transfusions increases the risk of allosensitization and graft failure in hematopoietic stem cell transplant (HSCT). Transfusion dependence is therefore considered an indication for intervention with androgens or allogeneic HSCT (discussed later). Erythropoietin and granulocyte colony-stimulating factor are not expected to produce durable improvements in red cell or neutrophil production in patients with DC, and generally are not used.

Immunosuppressive Therapy

IST with cyclosporine and antithymocyte globulin is a standard therapy for patients with severe aplastic anemia (SAA) who do not have a suitable sibling donor for HSCT. Anecdotally some patients with DC who were initially diagnosed with SAA and treated with

IST may have had a transient response to IST. However, in general, IST has not been shown to yield a response in patients with DC,⁵⁸ and a priority of early diagnosis in DC is to avoid unnecessary exposure to IST and delays to more appropriate therapies.

Eltrombopag

Eltrombopag is a small molecule agonist of the thrombopoietin receptor (c-Mpl), which initially gained approval for the treatment of refractory immune thrombocytopenic purpura. Trials undertaken to determine whether eltrombopag could decrease platelet transfusion requirements in patients with acquired SAA unexpectedly revealed trilineage improvement in a number of cases.⁵⁹ Based on the fact that the c-Mpl receptor is present on HSCs, it is thought that eltrombopag may directly stimulate HSC self-renewal to improve hematopoietic function in SAA. Recently, based on additional clinical trial experience, eltrombopag has gained US Food and Drug Administration approval as front-line therapy in combination with IST for SAA. With respect to DC, however, anecdotes and case reports suggest there may be no response to eltrombopag in patients with TBD.⁶⁰ The use of eltrombopag in patients with DC is therefore not recommended outside of a clinical trial.

Androgens

Based on the observation that males of various species generally have higher hemoglobin levels than females, male sex steroids were trialed in patients with SAA several decades ago.⁶¹ In some patients, improvements in multiple lineages were seen. It is now apparent that androgens can elicit a hematologic response in a substantial proportion of patients with specific inherited BMF syndromes, namely Fanconi anemia (FA) and DC.^{62,63} In retrospective reports in DC, various androgens (eg, oxymetholone, fluoxymesterone, nandrolone, and danazol) have been documented to produce hematologic response rates of 60% to 70%, frequently yielding transfusion independence.^{64,65} Common and therapy-limiting side effects of androgens such as oxymetholone include dyslipidemia and virilization, which may limit use in female patients and requires careful monitoring.^{64,65} In the only prospective trial of androgen therapy for DC/TBD, adult patients were treated with high doses of danazol over a 24-month period, and a hematologic response was achieved in ~80% of patients during the period of evaluation.⁶⁶ However, several patients (10 of 24) discontinued therapy before the 24-month time point, and liver enzyme abnormalities were common (41%). Based on its efficacy in this report and apparently decreased side effect profile, danazol can be considered the androgen of choice for treatment of DC/TBD. In general, the timeline to effect of androgens differs between lineages but is on the order of 1 to 3 months.^{64–66} The durability of response to androgens is difficult to predict; some patients require dose escalation or lose their response altogether. Although androgens can sustain patients in a transfusion-independent state for months to years, they are not considered curative for hematopoietic defects in DC.

The mechanisms by which androgens improve hematopoietic function in different BMF syndromes are not clear. It has been shown in vitro that androgens that are aromatized into estrogens can upregulate the *TERT* gene via nuclear hormone receptors,⁶⁷ which would in theory counteract telomere attrition and restore HSC self-renewal in patients with DC/TBD. In keeping with this, adults with TBD treated with danazol in the prospective trial were

found to have telomere elongation in peripheral blood cell DNA over the course of the treatment period, as measured by qPCR.⁶⁶ However, several issues have been raised about the proposed mechanism and effect seen in this study:

1. Neither danazol nor its derivatives aromatize to an estrogen.⁶⁸
2. Overexpression of *TERT* alone is insufficient to elongate telomeres in *DKC1* or *TERC* mutant patient cells.^{69,70}
3. Telomere length was measured in DNA from total peripheral blood cells, which are likely to differ in composition between pretreatment and convalescent states.
4. Telomere length was measured by qPCR, which may be inferior to methods such as flow-FISH.^{55,56}

A prior report on the effects of androgens in patients with DC showed no increase in telomere length when measured longitudinally by flow-FISH, albeit with small numbers of patients.⁶⁴ Thus, it remains unknown whether telomere restoration is the mechanism by which androgens exert their hematologic benefits in DC/TBD. Moreover, it is unclear whether androgens affect telomere length or organ function in patients with DC/TBD outside the blood. Therefore, androgens should only be trialed for nonhematopoietic manifestations in patients with DC/TBD in the context of a proper clinical study.

In summary, androgen therapy can be considered a standard transfusion-sparing approach for hematopoietic failure in patients with DC/TBD. The utility of androgens is limited by variability in response; durability of response; side effects, including liver toxicity; and adherence to the medication. There are no clear extra-hematopoietic benefits of androgens in patients with DC. Whether or not androgens should be tried before HSCT in patients with DC is not clear and depends on individual patient characteristics, available HSCT options, and physician and patient choice.

Hematopoietic Stem Cell Transplant

HSCT is the only definitive therapy for the hematopoietic and immunologic defects in DC. Case reports as early as the 1980s and 1990s showed that BMF in DC could be cured with HSCT.^{71–81} The observation of long-term hematologic reconstitution after allogeneic HSCT indicates an HSC-intrinsic defect as the major contributor to hematopoietic failure in DC and children with TBD. However, a high morbidity and mortality from conventional HSCT approaches was apparent across the experience. In retrospective analyses, more than 50% of patients died within 4 months of the HSCT procedure, most often because of infections, graft failure, or graft-versus-host disease (GVHD).^{82,83} The 5-year overall survival was approximately 45%, with no long-term survivors of unrelated donor HSCT.^{82,83} An unusual frequency of fatal lung and vascular complications was noted, attributed to both predisposition to pulmonary and endothelial disease in patients with DC and increased sensitivity to myeloablative conditioning with DNA alkylating agents and radiation.^{72,77,78,82} Other factors that likely contributed to poor outcomes in the early experience include the long time interval from onset of BMF to transplant,⁷⁶ and inferior unrelated donor matching capabilities and supportive care. DC also sometimes went undiagnosed until

after HSCT, because the clinical syndrome was not recognized at the time of hematopoietic failure, and genetic and functional testing were unavailable.⁷⁵

With more awareness of the increased transplant-related mortality in DC, better diagnostics, and application of lessons learned from FA,⁸⁴ HSCT outcomes seem to be improving. Reduced-intensity conditioning regimens have been used increasingly in patients with DC since the early 2000s. Progress has been attributed in large part to reduction of DNA alkylating agents (cyclophosphamide, busulfan, melphalan, thiotepa) and ionizing radiation in preparative regimens, and an increasing use of fludarabine and antibody-based immunosuppressive conditioning.^{85–92} In a retrospective study of data reported to the Center for International Blood and Marrow Transplantation Research (CIBMTR), the 5-year probability of overall survival for patients with DC undergoing HSCT from 2000 to 2009 was 65%.⁸³ Similarly, in a review of DC transplants using reduced-intensity conditioning regimens after 2000, approximately two-thirds of patients were alive with a median follow-up of 16 months, and included survivors of unrelated donor and cord blood transplants.⁸⁷ A retrospective case series of 7 patients with DC undergoing HSCT with a preparative regimen of fludarabine, alemtuzumab, and lower-dose melphalan showed a 100% engraftment rate and survival of 5 out of 7 patients at a median follow-up of 44 months.⁹³ However, a retrospective review of 109 patients with DC transplanted since 1976 was unable to show a statistically significant improvement in overall survival using reduced-intensity versus myeloablative conditioning in HSCT for DC, possibly due to short follow-up and small numbers of patients.⁹⁴

In the past decade, prospective HSCT trials tailored for patients with DC with BMF have been developed and executed in the United States. The first ([clinicaltrials.gov NCT00455312](https://clinicaltrials.gov/ct2/show/study/NCT00455312)) was conducted by the University of Minnesota and featured fludarabine and alemtuzumab-based immunosuppression, decreased (50 mg/kg) cyclophosphamide dosing, and a single 200-cGy fraction of total-body irradiation with anatomic lung shielding. GVHD prophylaxis was tailored to avoid cytotoxic agents such as methotrexate and corticosteroids. Early interim results reported by Dietz and colleagues⁸⁷ in 2010 described 6 patients treated on this regimen, 5 of whom received unrelated bone marrow or cord blood; 4 patients had successful HSCT, whereas 2 had early mortality from graft rejection and infection. Short-term pulmonary and liver toxicity were not seen, and 3 of the 5 unrelated donor transplants were successful. This trial is completed and results of longer follow-up are expected. A second prospective trial for BMF in DC/TBD originated at Boston Children's Hospital (BCH)/Dana-Farber Cancer Institute in 2012 ([clinicaltrials.gov NCT01659606](https://clinicaltrials.gov/ct2/show/study/NCT01659606)). The study asks whether myeloid engraftment can be achieved in HSCT for BMF in patients with DC without any exposure to radiation or DNA alkylating agents. This approach is based on the theory that, in the context of BMF, defective telomere maintenance and cellular replication results in a competitive disadvantage of HSCs in patients with DC compared with healthy donor HSCs, which could enable engraftment without using nontargeted cytotoxic agents. This regimen, consisting of alemtuzumab and fludarabine conditioning alone, if successful, would represent the first time a series of patients achieved myeloid engraftment in allogeneic HSCT without alkylators or radiation. An early report in 2014 of 4 patients who received unrelated HSCT under this protocol indicated durable engraftment.⁹⁵ The protocol has been

expanded to the first multicenter, prospective treatment trial for patients with DC, with completion expected in 2018.

Based on the early results of these prospective trials, it can be anticipated that outcomes will continue to improve in HSCT for BMF in DC. Important questions remain. What is the optimal HSCT regimen for patients with TBDs presenting with MDS/AML? Can patients with TBDs with simultaneous hematopoietic failure and comorbidities such as lung and liver disease tolerate and benefit from minimal intensity HSCT? Does a successful minimal intensity HSCT for BMF alter the overall survival and natural history of the disease? Answers to these questions will come from carefully planned prospective trials and coordinated efforts designed to decrease adverse events and increase overall length and quality of life for patients with DC/TBD.

SUMMARY AND FUTURE PROSPECTS

Advances in diagnosing and treating BMF caused by DC have been driven by genetic discovery in the past 2 decades, and the ensuing translation of basic biology to the bedside. Hematopoietic failure caused by an impairment in telomere maintenance “makes sense” and has provided a conceptual framework that has been useful for tailoring therapy and generating hypotheses to be tested in prospective clinical trials. Much remains to be learned about the pathophysiology and treatment of other disease manifestations in the TBDs. With a continued focus on understanding DC, new insights into normal human telomere biology can be expected, that will lead to novel therapeutic approaches to restore telomere maintenance in TBD and other disorders.

REFERENCES

1. Kirwan M, Dokal I. Dyskeratosis congenita: a genetic disorder of many faces. *Clin Genet* 2008;73(2):103–12. [PubMed: 18005359]
2. Alter BP, Giri N, Savage SA, et al. Malignancies and survival patterns in the National Cancer Institute inherited bone marrow failure syndromes cohort study. *Br J Haematol* 2010;150(2):179–88. [PubMed: 20507306]
3. Dokal I Dyskeratosis congenita in all its forms. *Br J Haematol* 2000;110(4): 768–79. [PubMed: 11054058]
4. Alter BP, Giri N, Savage SA, et al. Cancer in the National Cancer Institute Inherited Bone Marrow Failure Syndrome Cohort After Fifteen Years of Follow-up. *Haematologica* 2018;103:30–9. [PubMed: 29051281]
5. Armanios M, Blackburn EH. The telomere syndromes. *Nat Rev Genet* 2012; 13(10):693–704. [PubMed: 22965356]
6. Calado RT, Young NS. Telomere diseases. *N Engl J Med* 2009;361(24):2353–65. [PubMed: 20007561]
7. Keller RB, Gagne KE, Usmani GN, et al. CTC1 Mutations in a patient with dyskeratosis congenita. *Pediatr Blood Cancer* 2012;59(2):311–4. [PubMed: 22532422]
8. Knight SW, Heiss NS, Vulliamy TJ, et al. Unexplained aplastic anaemia, immuno-deficiency, and cerebellar hypoplasia (Hoyeraal-Hreidarsson syndrome) due to mutations in the dyskeratosis congenita gene, DKC1. *Br J Haematol* 1999; 107(2):335–9. [PubMed: 10583221]
9. Glusker G, Touzot F, Revy P, et al. Unraveling the pathogenesis of Hoyeraal-Hreidarsson syndrome, a complex telomere biology disorder. *Br J Haematol* 2015;170(4):457–71. [PubMed: 25940403]

10. 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):501–9. [PubMed: 18252230]
11. 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):309–16. [PubMed: 18931339]
12. 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(11):1567–73. [PubMed: 19760749]
13. Yamaguchi H, Baerlocher GM, Lansdorp PM, et al. Mutations of the human telomerase RNA gene (TERC) in aplastic anemia and myelodysplastic syndrome. *Blood* 2003;102(3):916–8. [PubMed: 12676774]
14. 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):1413–24. [PubMed: 15814878]
15. Armanios MY, Chen JJ, Cogan JD, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. *N Engl J Med* 2007;356(13):1317–26. [PubMed: 17392301]
16. Tsakiri KD, Cronkhite JT, Kuan PJ, et al. Adult-onset pulmonary fibrosis caused by mutations in telomerase. *Proc Natl Acad Sci U S A* 2007;104(18):7552–7. [PubMed: 17460043]
17. Armanios M. Telomerase and idiopathic pulmonary fibrosis. *Mutat Res* 2012; 730(1–2):52–8. [PubMed: 22079513]
18. Fogarty PF, Yamaguchi H, Wiestner A, et al. Late presentation of dyskeratosis congenita as apparently acquired aplastic anaemia due to mutations in telomerase RNA. *Lancet* 2003;362(9396):1628–30. [PubMed: 14630445]
19. Parry EM, Alder JK, Qi X, et al. Syndrome complex of bone marrow failure and pulmonary fibrosis predicts germline defects in telomerase. *Blood* 2011; 117(21):5607–11. [PubMed: 21436073]
20. Allsopp RC, Harley CB. Evidence for a critical telomere length in senescent human fibroblasts. *Exp Cell Res* 1995;219(1):130–6. [PubMed: 7628529]
21. Harley CB, Futcher AB, Greider CW. Telomeres shorten during ageing of human fibroblasts. *Nature* 1990;345(6274):458–60. [PubMed: 2342578]
22. 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):32–8. [PubMed: 9590285]
23. Knight SW, Vulliamy TJ, Heiss NS, et al. 1.4 Mb candidate gene region for X linked dyskeratosis congenita defined by combined haplotype and X chromosome inactivation analysis. *J Med Genet* 1998;35(12):993–6. [PubMed: 9863595]
24. Mitchell JR, Cheng J, Collins K. A box H/ACA small nucleolar RNA-like domain at the human telomerase RNA 3' end. *Mol Cell Biol* 1999;19(1):567–76. [PubMed: 9858580]
25. Mitchell JR, Wood E, Collins K. A telomerase component is defective in the human disease dyskeratosis congenita. *Nature* 1999;402(6761):551–5. [PubMed: 10591218]
26. Vulliamy T, Marrone A, Goldman F, et al. The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. *Nature* 2001; 413(6854):432–5. [PubMed: 11574891]
27. Stanley SE, Gable DL, Wagner CL, et al. Loss-of-function mutations in the RNA biogenesis factor NAF1 predispose to pulmonary fibrosis-emphysema. *Sci Transl Med* 2016;8(351):351ra107.
28. Townsley DM, Dumitriu B, Young NS. Bone marrow failure and the telomeropathies. *Blood* 2014;124(18):2775–83. [PubMed: 25237198]
29. Bertuch AA. The molecular genetics of the telomere biology disorders. *RNA Biol* 2016;13(8):696–706. [PubMed: 26400640]
30. 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): 1429–40. [PubMed: 27432940]
31. Vulliamy T, Marrone A, Szydlo 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):447–9. [PubMed: 15098033]

32. Diaz de Leon A, Cronkhite JT, Katzenstein AL, et al. Telomere lengths, pulmonary fibrosis and telomerase (TERT) mutations. *PLoS One* 2010;5(5):e10680. [PubMed: 20502709]
33. Collopy LC, Walne AJ, Cardoso S, et al. Triallelic and epigenetic-like inheritance in human disorders of telomerase. *Blood* 2015;126(2):176–84. [PubMed: 26024875]
34. Armanios M, Alder JK, Parry EM, et al. Short telomeres are sufficient to cause the degenerative defects associated with aging. *Am J Hum Genet* 2009;85(6): 823–32. [PubMed: 19944403]
35. Hao LY, Armanios M, Strong MA, et al. Short telomeres, even in the presence of telomerase, limit tissue renewal capacity. *Cell* 2005;123(6):1121–31. [PubMed: 16360040]
36. Vaziri H, Dragowska W, Allsopp RC, et al. Evidence for a mitotic clock in human hematopoietic stem cells: loss of telomeric DNA with age. *Proc Natl Acad Sci U S A* 1994;91(21):9857–60. [PubMed: 7937905]
37. Broccoli D, Young JW, de Lange T. Telomerase activity in normal and malignant hematopoietic cells. *Proc Natl Acad Sci U S A* 1995;92(20):9082–6. [PubMed: 7568077]
38. Chiu CP, Dragowska W, Kim NW, et al. Differential expression of telomerase activity in hematopoietic progenitors from adult human bone marrow. *Stem Cells* 1996;14(2):239–48. [PubMed: 8991544]
39. Notaro R, Cimmino A, Tabarini D, et al. In vivo telomere dynamics of human hematopoietic stem cells. *Proc Natl Acad Sci U S A* 1997;94(25):13782–5. [PubMed: 9391104]
40. Brummendorf TH, Rufer N, Baerlocher GM, et al. Limited telomere shortening in hematopoietic stem cells after transplantation. *Ann N Y Acad Sci* 2001;938:1–7 [discussion: 7–8]. [PubMed: 11458496]
41. Akiyama M, Asai O, Kuraishi Y, et al. Shortening of telomeres in recipients of both autologous and allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2000;25(4):441–7. [PubMed: 10723589]
42. Alder JK, Hanumanthu VS, Strong MA, et al. Diagnostic utility of telomere length testing in a hospital-based setting. *Proc Natl Acad Sci U S A* 2018;115(10): E2358–65. [PubMed: 29463756]
43. Calado RT, Cooper JN, Padilla-Nash HM, et al. Short telomeres result in chromosomal instability in hematopoietic cells and precede malignant evolution in human aplastic anemia. *Leukemia* 2012;26(4):700–7. [PubMed: 22005790]
44. Scheinberg P, Cooper JN, Sloand EM, et al. Association of telomere length of peripheral blood leukocytes with hematopoietic relapse, malignant transformation, and survival in severe aplastic anemia. *JAMA* 2010;304(12):1358–64. [PubMed: 20858879]
45. Lange K, Holm L, Vang Nielsen K, et al. Telomere shortening and chromosomal instability in myelodysplastic syndromes. *Genes Chromosomes Cancer* 2010; 49(3):260–9. [PubMed: 19998444]
46. Ohyashiki JH, Ohyashiki K, Fujimura T, et al. Telomere shortening associated with disease evolution patterns in myelodysplastic syndromes. *Cancer Res* 1994; 54(13):3557–60. [PubMed: 8012981]
47. Ball SE, Gibson FM, Rizzo S, et al. Progressive telomere shortening in aplastic anemia. *Blood* 1998;91(10):3582–92. [PubMed: 9572992]
48. Sakaguchi H, Nishio N, Hama A, et al. Peripheral blood lymphocyte telomere length as a predictor of response to immunosuppressive therapy in childhood aplastic anemia. *Haematologica* 2014;99(8):1312–6. [PubMed: 24816243]
49. Peffault de Latour R, Calado RT, Busson M, et al. Age-adjusted recipient pretransplantation telomere length and treatment-related mortality after hematopoietic stem cell transplantation. *Blood* 2012;120(16):3353–9. [PubMed: 22948043]
50. Vulliamy TJ, Knight SW, Dokal I, et al. Skewed X-inactivation in carriers of X-linked dyskeratosis congenita. *Blood* 1997;90(6):2213–6. [PubMed: 9310472]
51. Jongmans MC, Verwiel ET, Heijdra Y, et al. Revertant somatic mosaicism by mitotic recombination in dyskeratosis congenita. *Am J Hum Genet* 2012;90(3): 426–33. [PubMed: 22341970]
52. Aubert G, Hills M, Lansdorp PM. Telomere length measurement-caveats and a critical assessment of the available technologies and tools. *Mutat Res* 2012; 730(1–2):59–67. [PubMed: 21663926]

53. 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):1439–47. [PubMed: 17468339]
54. Alter BP, Rosenberg PS, Giri N, et al. Telomere length is associated with disease severity and declines with age in dyskeratosis congenita. *Haematologica* 2012; 97(3):353–9. [PubMed: 22058220]
55. Gadalla SM, Khincha PP, Katki HA, et al. The limitations of qPCR telomere length measurement in diagnosing dyskeratosis congenita. *Mol Genet Genomic Med* 2016;4(4):475–9. [PubMed: 27468421]
56. Gutierrez-Rodriguez F, Santana-Lemos BA, Scheucher PS, et al. Direct comparison of flow-FISH and qPCR as diagnostic tests for telomere length measurement in humans. *PLoS One* 2014;9(11):e113747. [PubMed: 25409313]
57. Anderson BH, Kasher PR, Mayer J, et al. Mutations in CTC1, encoding conserved telomere maintenance component 1, cause Coats plus. *Nat Genet* 2012;44(3): 338–42. [PubMed: 22267198]
58. Al-Rahawan MM, Giri N, Alter BP. Intensive immunosuppression therapy for aplastic anemia associated with dyskeratosis congenita. *Int J Hematol* 2006; 83(3):275–6. [PubMed: 16720563]
59. Olnes MJ, Scheinberg P, Calvo KR, et al. Eltrombopag and improved hematopoiesis in refractory aplastic anemia. *N Engl J Med* 2012;367(1):11–9. [PubMed: 22762314]
60. Trautmann K, Jakob C, von Grunhagen U, et al. Eltrombopag fails to improve severe thrombocytopenia in late-stage dyskeratosis congenita and diamond-black-fan-anaemia. *Thromb Haemost* 2012;108(2):397–8. [PubMed: 22739569]
61. Shahidi NT, Diamond LK. Testosterone-induced remission in aplastic anemia of both acquired and congenital types. Further observations in 24 cases. *N Engl J Med* 1961;264:953–67. [PubMed: 13750594]
62. Allen DM, Fine MH, Necheles TF, et al. Oxymetholone therapy in aplastic anemia. *Blood* 1968;32(1):83–9. [PubMed: 5658392]
63. Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. *Blood Rev* 2010;24(3):101–22. [PubMed: 20417588]
64. Khincha PP, Wentzensen IM, Giri N, et al. Response to androgen therapy in patients with dyskeratosis congenita. *Br J Haematol* 2014;165(3):349–57. [PubMed: 24666134]
65. Islam A, Rafiq S, Kirwan M, et al. Haematological recovery in dyskeratosis congenita patients treated with danazol. *Br J Haematol* 2013;162(6):854–6. [PubMed: 23782100]
66. Townsley DM, Dumitriu B, Liu D, et al. Danazol treatment for telomere diseases. *N Engl J Med* 2016;374(20):1922–31. [PubMed: 27192671]
67. 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(11):2236–43. [PubMed: 19561322]
68. Grossmann M Danazol treatment for telomere diseases. *N Engl J Med* 2016; 375(11):1095.
69. Westin ER, Chavez E, Lee KM, et al. Telomere restoration and extension of proliferative lifespan in dyskeratosis congenita fibroblasts. *Aging Cell* 2007;6(3): 383–94. [PubMed: 17381549]
70. Wong JM, Collins K. Telomerase RNA level limits telomere maintenance in X-linked dyskeratosis congenita. *Genes Dev* 2006;20(20):2848–58. [PubMed: 17015423]
71. Mahmoud HK, Schaefer UW, Schmidt CG, et al. Marrow transplantation for pancytopenia in dyskeratosis congenita. *Blut* 1985;51(1):57–60. [PubMed: 3893572]
72. Berthou C, Devergie A, D'Agay MF, et al. Late vascular complications after bone marrow transplantation for dyskeratosis congenita. *Br J Haematol* 1991;79(2): 335–6. [PubMed: 1958493]
73. Chessells JM, Harper J. Bone marrow transplantation for dyskeratosis congenita. *Br J Haematol* 1992;81(2):314. [PubMed: 1643034]
74. Dokal I, Bungey J, Williamson P, et al. Dyskeratosis congenita fibroblasts are abnormal and have unbalanced chromosomal rearrangements. *Blood* 1992; 80(12):3090–6. [PubMed: 1361371]
75. Phillips RJ, Judge M, Webb D, et al. Dyskeratosis congenita: delay in diagnosis and successful treatment of pancytopenia by bone marrow transplantation. *Br J Dermatol* 1992;127(3):278–80. [PubMed: 1390173]

76. Langston AA, Sanders JE, Deeg HJ, et al. Allogeneic marrow transplantation for aplastic anaemia associated with dyskeratosis congenita. *Br J Haematol* 1996; 92(3):758–65. [PubMed: 8616050]
77. Yabe M, Yabe H, Hattori K, et al. Fatal interstitial pulmonary disease in a patient with dyskeratosis congenita after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1997;19(4):389–92. [PubMed: 9051251]
78. Rocha V, Devergie A, Socie G, et al. Unusual complications after bone marrow transplantation for dyskeratosis congenita. *Br J Haematol* 1998;103(1):243–8. [PubMed: 9792316]
79. Ghavamzadeh A, Alimoghadam K, Nasser P, et al. Correction of bone marrow failure in dyskeratosis congenita by bone marrow transplantation. *Bone Marrow Transplant* 1999;23(3):299–301. [PubMed: 10084264]
80. Lau YL, Ha SY, Chan CF, et al. Bone marrow transplant for dyskeratosis congenita. *Br J Haematol* 1999;105(2):571. [PubMed: 10233444]
81. Shaw PH, Haut PR, Olszewski M, et al. Hematopoietic stem-cell transplantation using unrelated cord-blood versus matched sibling marrow in pediatric bone marrow failure syndrome: one center's experience. *Pediatr Transplant* 1999; 3(4):315–21. [PubMed: 10562977]
82. 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):584–94. [PubMed: 17663679]
83. Gadalla SM, Sales-Bonfim C, Carreras J, et al. Outcomes of allogeneic hematopoietic cell transplantation in patients with dyskeratosis congenita. *Biol Blood Marrow Transplant* 2013;19(8):1238–43. [PubMed: 23751955]
84. Socie G, Devergie A, Girinski T, et al. Transplantation for Fanconi's anaemia: long-term follow-up of fifty patients transplanted from a sibling donor after low-dose cyclophosphamide and thoraco-abdominal irradiation for conditioning. *Br J Haematol* 1998;103(1):249–55. [PubMed: 9792317]
85. Ayas M, Nassar A, Hamidieh AA, et al. Reduced intensity conditioning is effective for hematopoietic SCT in dyskeratosis congenita-related BM failure. *Bone Marrow Transplant* 2013;48(9):1168–72. [PubMed: 23542225]
86. Cossu F, Vulliamy TJ, Marrone A, et al. A novel DKC1 mutation, severe combined immunodeficiency (T1B-NK-SCID) and bone marrow transplantation in an infant with Hoyeraal-Hreidarsson syndrome. *Br J Haematol* 2002;119(3):765–8. [PubMed: 12437656]
87. 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. [PubMed: 20383216]
88. Dror Y, Freedman MH, Leaker M, et al. Low-intensity hematopoietic stem-cell transplantation across human leucocyte antigen barriers in dyskeratosis congenita. *Bone Marrow Transplant* 2003;31(10):847–50. [PubMed: 12748659]
89. Gungor T, Corbacioglu S, Storb R, et al. Nonmyeloablative allogeneic hematopoietic stem cell transplantation for treatment of dyskeratosis congenita. *Bone Marrow Transplant* 2003;31(5):407–10. [PubMed: 12634734]
90. Nishio N, Takahashi Y, Ohashi H, et al. Reduced-intensity conditioning for alternative donor hematopoietic stem cell transplantation in patients with dyskeratosis congenita. *Pediatr Transplant* 2011;15(2):161–6. [PubMed: 21176016]
91. Nobili B, Rossi G, De Stefano P, et al. Successful umbilical cord blood transplantation in a child with dyskeratosis congenita after a fludarabine-based reduced-intensity conditioning regimen. *Br J Haematol* 2002;119(2):573–4. [PubMed: 12406104]
92. Vuong LG, Hemmati PG, Neuburger S, et al. Reduced-intensity conditioning using fludarabine and antithymocyte globulin alone allows stable engraftment in a patient with dyskeratosis congenita. *Acta Haematol* 2010;124(4):200–3. [PubMed: 21042011]
93. Nelson AS, Marsh RA, Myers KC, et al. A reduced-intensity conditioning regimen for patients with dyskeratosis congenita undergoing hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2016;22(5):884–8. [PubMed: 26845033]
94. Barbaro P, VEDI A. Survival after hematopoietic stem cell transplant in patients with dyskeratosis congenita: systematic review of the literature. *Biol Blood Marrow Transplant* 2016;22(7):1152–8. [PubMed: 26968789]

95. Agarwal S, Williams DA, London WB, et al. Full donor myeloid engraftment with minimal toxicity in dyskeratosis congenita patients undergoing allogeneic bone marrow transplantation without radiation or alkylating agents. *Blood* 2014; 124(21):2941.

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KEY POINTS

- Genetic discovery in the rare inherited bone marrow failure syndrome dyskeratosis congenita (DC) has revealed a spectrum of diseases caused by mutations in genes regulating telomere maintenance.
- Defects in telomere maintenance provide a molecular framework for understanding hematopoietic stem cell failure in DC.
- Timely diagnosis of an underlying telomere biology disorder greatly affects patient management and is facilitated by telomere length testing and genetic testing.
- Prospective trials and coordinated efforts are driving therapeutic advancements for hematopoietic failure in DC.

Fig. 1.

Components of telomere biology disrupted in DC. Telomeres are composed of thousands of TTAGGG repeats. The telomere repeats are bound by several proteins (TRF1, TRF2, TIN2, RAP1 [not shown], TPP1, and POT1), collectively called shelterin. The telomere ends in a loop (t loop) with a 3' overhang, which must be unwound by RTEL1 for telomere replication. The figure depicts the unwound telomere end bound by telomerase, a ribonucleoprotein (RNP) complex that elongates telomeres by reverse transcription. Telomerase is composed of the reverse transcriptase TERT and the RNA template TERC, which add telomere repeats to the 3' end. Several other proteins make up the telomerase RNP (dyskerin, NOP10, NHP2, GAR1, TCAB1), and are responsible for stabilizing and trafficking telomerase to the Cajal body, where telomeres are elongated. NAF1 is responsible for early assembly of the dyskerin RNP but is replaced by GAR1 in the mature RNP. PARN is required for maturation and stabilization of nascent TERC RNA. Components of the CST (CTC1, STN1, TEN1) complex are responsible for filling in the lagging C-strand of the elongating telomere end. Components of the telomere maintenance machinery that have been found to be disrupted in DC are shown in color with bold labels.

Table 1

Genetics of dyskeratosis congenita

#	Gene (Product)	Inheritance	Presenting Manifestations/Syndrome and Genetic Features	Frequency Estimate in DC ^a	Functional Consequence
1	<i>DKC1</i> (dyskerin)	X-linked recessive	DC, HHS, AA, PF; female carriers may have subtle findings	More common	Reduced TERC and telomerase activity ^b
2	<i>TERC</i> (TERC)	AD	DC, AA, PF, LD, CA; genetic anticipation	Less common	Reduced telomerase activity
3	<i>TERT</i> (TERT)	AD	DC, HHS, AA, PF, LD, CA; genetic anticipation	Less common	Reduced telomerase activity or recruitment to telomeres
		AR	DC, HHS	Less common	Reduced telomerase activity or recruitment to telomeres
4	<i>NOP10</i> (NOP10)	AR	DC	Very rare	Reduced TERC and telomerase activity ^b
5	<i>NHP2</i> (NHP2)	AR	DC	Very rare	Reduced TERC and telomerase activity ^b
6	<i>TINF2</i> (TINF2)	AD, often de novo	DC, HHS, RS, PF; mutations clustered in exon 6	More common	Unclear
7	<i>WRAP53</i> (TCAB1)	AR	DC	Very rare	Impaired telomerase trafficking to Cajal body ^b
8	<i>CTC1</i> (CTC1)	AR	DC, CP	Less common	Impaired telomere replication; telomere fragility
9	<i>RTEL1</i> (RTEL1)	AD	PF, AA	NA	Impaired telomere replication; telomere fragility
		AR	DC, HHS, AA, PF	Less common	Impaired telomere replication; telomere fragility
10	<i>ACD</i> (TPP1)	AD	AA	NA	Impaired telomerase recruitment to telomeres
		AR	DC, HHS	Very rare	Impaired telomerase recruitment to telomeres
11	<i>PARN</i> (PARN)	AD	PF, AA	NA	Reduced TERC and telomerase activity ^c
		AR	DC, HHS, AA, PF, LD	Less common	Reduced TERC and telomerase activity ^c
12	<i>NAF1</i> (NAF1)	AD	DC, AA, PF, LD, CA; genetic anticipation	Very rare	Reduced TERC and telomerase activity ^b
13	<i>STN1</i> (STN1)	AR	DC, CP	Very rare	Impaired telomere replication; telomere fragility

Presenting manifestations. DC: mucocutaneous triad (dystrophic nails, leukoplakia, and skin pigmentation abnormalities); BMF; or other associated features, including increased risk of malignancy, pulmonary fibrosis, vascular abnormalities; includes atypical forms with some features but not full triad.

Abbreviations: AA, plastic anemia; AD, autosomal dominant; AR, autosomal recessive; CA, myelodysplastic syndrome, acute leukemia, head/neck squamous cell cancers; CP, Coats plus syndrome - cerebroretinal microangiopathy with calcification and cysts; gastrointestinal bleeding; osteopenia; DC, mucocutaneous triad (dystrophic nails, leukoplakia, and skin pigmentation abnormalities); BMF; or other associated features, including increased risk of malignancy, pulmonary fibrosis, vascular abnormalities; includes atypical forms with some features but not full triad; HHS, Hoyer-Hreidarsson syndrome - early onset with multiple manifestations with cerebellar hypoplasia, immunodeficiency; LD, liver disease including cirrhosis; NA, not applicable; PF, pulmonary fibrosis and other interstitial lung diseases; RS, Revesz syndrome - early-onset with multiple manifestations including retinal vascular disease.

^aFrequency estimates. "More common": found mutated in greater than 10% of patients with classic DC. "Less common": found mutated in less than 10% of patients with classic DC. "Very rare": case reports of approximately 1 to 5 patients presenting with classic DC.

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Potential dysregulation of other box H/ACA RNAs.
Potential dysregulation of other RNAs.