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Dyskeratosis Congenita

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Synopsis

Dyskeratosis congenita (DC) is an inherited bone marrow failure syndrome characterized clinically by the triad of abnormal nails, reticular skin pigmentation, and oral leukoplakia, and associated with very high risks of developing aplastic anemia, myelodysplastic syndrome, leukemia, and solid tumors. Patients have very short germline telomeres, and approximately half have mutations in one of six genes encoding proteins that maintain telomere function. Accurate diagnosis of DC is critical to ensure proper clinical management because patients with DC and bone marrow failure do not respond to immunosuppressive therapy and may have increased morbidity and mortality associated with hematopoietic stem cell transplantation.

Keywords

dyskeratosis congenita; telomere; *DKC1*; *TERC*; *TERT*; *TINF2*; bone marrow failure

Dyskeratosis congenita (DC) is an inherited bone marrow failure and cancer predisposition syndrome caused by defects in telomere biology. The consequences of DC affect all body systems; these may include the diagnostic triad of abnormal nails, reticular skin pigmentation, and oral leukoplakia; bone marrow failure, pulmonary fibrosis, liver disease, neurological and ophthalmic abnormalities, as well as increased risk of cancer also occur [1;2]. The known clinical complications are shown in Table 1.

Patients with DC have very short germline telomeres compared with those of their healthy relatives, normal controls, and patients with inherited bone marrow failure syndromes (IBMFS) [3-5]. Mutations in genes important in telomere biology have been identified in approximately half of the patients with DC [5]. Genotype-phenotype correlations may exist but are often quite complex to interpret. A broader spectrum of disorders due to defects in telomere biology is now appreciated, such as pulmonary fibrosis without other physical or hematologic findings associated with DC. Patients with DC have a very high risk of numerous medical problems, of which the most serious are bone marrow failure (BMF), cancer, and pulmonary fibrosis. Accurate diagnosis is critical, because patients with DC who develop BMF do not respond to

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immunosuppression, and have a very high risk of hematopoietic stem cell transplantation (HSCT)-related complications. Here we review the clinical features of DC and describe its molecular pathogenesis. The utility of telomere length as a diagnostic test and of genetic testing in families will be discussed, and guidelines for medical management and clinically indicated screening will also be proposed.

Clinical Features

The name “dyskeratosis congenita” was derived after the description of two brothers with nail dystrophy, oral leukoplakia, and skin pigmentation anomalies by Zinsser in 1910 [6]. Additional reports of patients with similar features appeared by Engman [7], and by Cole *et al* [8] leading to the designation of Zinsser-Engman-Cole syndrome [2]. Early reports focused on the dermatologic findings. However, as more cases were described with other medical complications, it became clear that DC is a complex, multi-system disorder [1-3].

The clinical diagnosis of classical DC requires at least two features of the triad of dysplastic nails, lacey reticular pigmentation of the upper chest and/or neck, and oral leukoplakia (Figure 1) [1;9]. This diagnostic triad is still important in defining clinically significant disease, but additional features are now appreciated, including BMF, epithelial cancers, myelodysplastic syndrome (MDS), leukemia, epiphora, blepharitis, prematurely gray hair, alopecia, developmental delay, short stature, cerebellar hypoplasia (Figure 2), microcephaly, esophageal stenosis, urethral stenosis, pulmonary fibrosis, liver disease, and avascular necrosis of hips or shoulders (Table 1) [1;9;10]. The median age at diagnosis of DC reported by the Dyskeratosis Congenita Registry (DCR) was 15 years (range 0-75 years) [9;11]. Thus, many patients may not present until their late teens or adulthood. The DCR required the presence of either two of the three features of the triad, or one of the triad with at least two minor features [9;11]. However, the development of the telomere length assay as a diagnostic test for DC coupled with the discovery of more genes as causative of DC has led us to modify the definition of DC [3;12]. We accept as DC patients with the triad described above, or any of the other findings, hematologic and/or neoplastic complications consistent with DC who also have a mutation in a DC gene, and/or very short telomeres. We also call a healthy individual “DC” who has very short telomeres and is a member of a pedigree with bona fide cases, where the gene has not yet been identified.

There are two major severe subsets of DC. The first is Hoyeraal-Hreidarsson Syndrome (HH), a severe form of DC characterized by cerebellar hypoplasia, microcephaly, developmental delay, immunodeficiency, intrauterine growth retardation (IUGR), and BMF. The original descriptions of HH all included cerebellar hypoplasia [13-15], and we suggest that documentation of cerebellar hypoplasia (Figure 2) is required to make the diagnosis of HH. More than 30 such cases have been described, and recent studies showed that patients with HH have very short telomeres. Several patients with HH have now been found to have mutations in DC genes proven to cause DC, including *DKC1*, *TINF2*, or *TERT* [16-18].

The second subset is Revesz Syndrome (RS), first described in case reports of young children with BMF and exudative retinopathy [19;20]. These children had bilateral exudative retinopathy (similar to acquired unilateral Coat’s retinopathy), IUGR, BMF, sparse, fine hair, and central nervous system (CNS) calcifications; some patients also had nail dystrophy and oral leukoplakia. CNS calcification was reported in 15 of the 20 cases in the literature, cerebellar hypoplasia in 2, and 2 cases had both CNS calcifications and cerebellar hypoplasia [12;17;19]. Patients with RS also have abnormally short telomeres and so far mutations have been found in *TINF2* [12;17].

We propose that the appellation of HH be restricted to DC patients who have documented cerebellar hypoplasia, and that the RS category requires bilateral exudative retinopathy, and perhaps also CNS calcifications.

Molecular Pathogenesis

The inheritance of DC can be X-linked recessive (XLR), autosomal dominant (AD), or autosomal recessive (AR). There is also a high frequency of sporadic cases, which are presumably due to new mutations in dominant genes. Six genes in the telomere biology pathway have been identified to date as mutated in patients with DC (Table 2): *DKC1*, *TERC*, *TERT*, *TINF2*, *NOLA2*, and *NOLA3* [1;12;18;21-23]. Approximately half the patients with DC have a mutation in one of these six genes, while the other half await discovery of mutations in additional telomere genes.

Telomeres consist of long nucleotide (TTAGGG)_n repeats and an associated protein complex located at chromosome ends that are essential for the maintenance of chromosomal integrity [24]. Telomeric repeats are lost with each cell division, in part due to incomplete replication of the 3' end of the chromosome. Telomere attrition can result in critically short telomeres prompting cellular senescence or cellular crisis, apoptosis, genomic instability, or a reduction in cellular lifespan [24]. Telomerase (*TERT*) is a reverse transcriptase which uses an RNA template (*TERC*) to extend nucleotide repeats at the chromosome end. A protein complex, termed "shelterin", consists of six proteins that act as a cap at the telomere and regulate telomere length (gene names: *TERF1*, *TERF2*, *TINF2*, *TERF2IP*, *ACD*, and *POT1*). Additional proteins interact with and regulate the activity of the shelterin complex. Thus, telomere length regulation and telomeric stability require complex interactions of multiple proteins at many different levels.

The locus for the XLR form of DC was mapped in the mid-1980s, and the first DC gene, dyskerin (*DKC1*), was cloned in 1998 [21]. Primary fibroblasts and lymphoblasts of males with *DKC1* mutations had very short telomeres [4]. The dyskerin protein is involved in post-transcriptional pseudouridylation and forms a ribonucleoprotein (RNP) complex with three other proteins, NOP10, NHP2, and GAR1. AR inheritance of mutations in NOP10 or NHP2 (gene names *NOLA3* and *NOLA2*, respectively) have been identified in three consanguineous families with DC [22;23].

TERC, a member of the family of H/ACA small RNAs, serves as the reverse transcription template for the telomerase enzyme [25]. Mutations in the *TERC* gene are present in patients with DC and occur in an AD manner or *de novo* [26]. *TERC* mutations have also been identified in patients with aplastic anemia but without other clinical features consistent with DC [27]. These findings prompted subsequent studies which evaluated the telomerase enzyme, *TERT*, in patients with DC. Mutations in *TERT* were found in patients with both AD and AR DC, in patients with aplastic anemia and no other signs of DC, as well as in patients with pulmonary fibrosis [18;28-32]. The variability in clinical features in patients with *TERC* or *TERT* mutations suggests the existence of a broad spectrum of telomere biology disorders, often manifest by abnormal levels of telomerase activity and short telomeres.

We identified the first component of the shelterin complex as mutated in DC, *TINF2* (protein name: TIN2, TRF1-interacting nuclear factor 2) [12]. Patients with *TINF2* mutations can have severe forms of DC, with young age at onset, but the phenotypic spectrum is broad, and includes patients with mild or even no findings [12;17]. *TINF2* is the only gene identified to date as mutated in the Revesz Syndrome variant of DC [12;17]. The mechanism by which *TINF2* mutations cause DC has not yet been elucidated, but it is notable that most patients with *TINF2* mutations have extremely short telomeres [12;17].

The primary molecular consequences of mutations in the DC-associated genes are very short telomeres, low levels of telomerase activity, and/or reduced expression of *TERC*. Genetic anticipation of symptoms and of short telomeres have been suggested in family pedigrees with either *TERC* or *TERT* mutations [26;33]. Decreased *TERC* expression and short telomeres were present in patients with mutations in *NOP10* as well as *NHP2* [22;23]. It is possible that the *TINF2* mutations may lead to instability of the shelterin complex and telomere dysregulation. Based on these data, DC appears to be a disorder of telomere biology, and the consistent feature in all patients is abnormally short telomeres [3;5].

Making the Diagnosis

Patients may develop signs and symptoms of DC at any age, which usually become more severe with increasing age. The accurate diagnosis of DC is critical, especially since therapy for complications such as BMF or cancer is often urgent. Telomere length has been extensively evaluated in DC and to some extent in other IBMFS [5]. Multiple methods were used, including terminal restriction fragment (TRF) measurement on Southern blots, fluorescence *in situ* hybridization (FISH) with immunostaining, quantitative PCR, single telomere length analysis, and flow-cytometry with FISH (flow-FISH) [reviewed in 34,35]. Earlier studies used TRF to determine telomere length in DNA isolated from white blood cells (WBCs) or mononuclear cells (MNCs) and reported either mean telomere length in patients compared with a small number of age-matched controls, or the difference between the average telomere lengths of patients and controls (deltaTEL) (reviewed in [5]). Those studies found that patients with DC had shorter telomeres than controls; the use of telomere length as a diagnostic test was not evaluated at that time.

Flow-FISH, which uses fresh blood samples, has the advantage of providing telomere length data on specific white blood cell subsets [36]. Telomere length in total leukocytes and in leukocyte subsets (granulocytes, total lymphocytes, naïve T-cells, memory T-cells, B-cells, and NK cells) was determined by flow-FISH on cells from patients with DC, their relatives, and patients with other IBMFS. Data from 400 healthy controls (newborn through 100 years) was used to generate percentiles of normal telomere length, and values below the 1st percentile for age were considered “very short.” The diagnostic sensitivity and specificity of very short telomeres was >90% in total lymphocytes, naïve T-cells, and B-cells for the diagnosis of DC in comparison with healthy relatives of patients with DC or non-DC IBMFS patients. Rare healthy relatives with very short telomeres were later shown to have mutations in the same DC genes as the affected probands. Evaluation of the panel of six leukocyte subsets provided the greatest degree of sensitivity and specificity; the best statistical performance characteristics were obtained by finding very short telomeres in at least three or four of the subsets [3].

It is important to note that this study found that many patients with non-DC IBMFS also had very short telomeres in granulocytes; a similar result was reported in patients with acquired AA [37]. This could be due to increased granulocyte turnover and short lifespan in comparison with other cell types, resulting in more cell divisions of early myeloid progenitor cells (since telomeres shorten with each cell division). In our experience, granulocyte telomere length results are sensitive but are not specific for the diagnosis of DC, and we rely on the results from lymphocytes and lymphocyte subsets.

In cross-sectional data from normal individuals, as well as those with a non-DC IBMFS, telomere length decreases with age in a nonlinear, S-shaped manner. However, telomere length did not appear to decrease with age in our cross-sectional analysis of DC, and in some cell types even appeared to increase slightly [3]. If this finding is sustained in longitudinal studies, then deltaTEL would also decrease with age (since the difference between DC patients and healthy controls would narrow with age, rather than decreasing in parallel), and thus deltaTEL

should not be used to compare telomere lengths across ages. The lack of age-associated decline in telomere length in DC was not known at the time of the earlier publications using deltaTEL.

Another group recently concluded that telomere length was sensitive but not specific in screening for DC [38]. The flow-FISH method used to determine telomere length differed from previously established methods in several ways [3;39;40]. It used total MNCs, and compared patient telomeres to telomeres from a tetraploid acute lymphocytic leukemia cell line, which was arbitrarily assigned as “100%”, and then reported patient results as a percentage of the control cell line. The published results did not show the nonlinear, S-shaped distribution of telomere length in healthy individuals which is well-described in the literature [41-44]. Future studies are required for the interpretation of this method in the context of diagnosis of patients with DC.

The development of cytopenias is often the first sign in DC and thus early and accurate diagnosis is essential. Patients with BMF due to DC do not respond to immunosuppressive therapy [45]. They are also at high risk of HSCT-related complications due to underlying pulmonary and liver disease [46-50]. In addition, recent studies have shown individuals can be “silent” carriers of a pathogenic mutation in a DC gene [12]. Therefore, we suggest that patients with BMF in whom Fanconi anemia is ruled-out (by a normal chromosome breakage test with crosslinking agents) have telomere length tested by flow-FISH in leukocyte subsets to evaluate for DC. This is the most sensitive and specific screening test for DC at this time. Telomeres that are less than the 1st percentile for age in 4 of the 6 leukocyte subsets described above, excluding granulocytes, are highly correlated with the diagnosis of DC in our experience.

Reasons to consider dyskeratosis congenita in the differential diagnosis of patients with bone marrow failure or cancer

- Bone marrow failure with normal chromosome breakage responses to DEB or MMC
- Head/Neck Cancer in a young person (<50 years of age)
- Anogenital Cancer in a young person (<50 years of age)
- Family history of pulmonary fibrosis
- Family history of bone marrow failure
- Family history of cancer in young people, especially head and neck cancer

Genetic testing for DC should begin with a careful assessment of the patient’s personal and family medical history. Genetic counseling must be provided both before and after mutation testing, because testing may identify unsuspected affected or silent carrier diagnoses of DC, which will have effects on an individual’s health care, and on family dynamics. Complex issues regarding counseling and testing of children and adolescents need to be considered [51]. Pre-pregnancy and/or prenatal genetic counseling is available for families considering the risk to future offspring. Pre-implantation genetic diagnosis as well as prenatal testing can also be considered in families with a known mutation in a gene for DC.

The physical findings of a patient should also be considered in relation to mutation testing. For example, in male patients with clinical DC and no affected female relatives XLR inheritance may be suspected and testing for *DKC1* should be performed. Patients with *TINF2* mutations may have multiple physical findings and early onset BMF, although a smaller subset of patients with mutations in *TINF2* may be very mild [12;17]. There can be variability in the severity of clinical and hematologic findings associated with mutations in *TERC* [52]. Patients with heterozygous *TERT* mutations may present at slightly older ages with more varied and milder

phenotypes than patients with mutations in other genes [28-32]. AR mutations in *NOLA2* and *NOLA3* have only been reported in consanguineous families [22;23].

Since mutations have been identified in only about half of the known patients with DC, the absence of a mutation in a known DC gene in a patient with very short telomeres and clinical findings consistent with DC does not rule-out the diagnosis. Due to the high rates of complications, including cancer, we suggest that patients with BMF and/or other clinical signs consistent with DC who have telomeres below the <1st percentile for age be considered to have a disorder of telomere biology. The National Cancer Institute's cohort study of DC, a part of its IBMFS cohort (<http://marrowfailure.cancer.gov>), is evaluating all such patients in a standardized manner in order to prospectively study the complication rates in these patients as well as to identify new DC genes [53;54].

Complications of Dyskeratosis Congenita

The clinical features and related medical complications in DC are shown in Table 1. It is important to note that nearly all systems can be affected and the findings may vary greatly between patients. BMF is a common finding in DC and may occur before or after (or even in the absence of) the appearance of the diagnostic triad or other features of DC. The DCR reported an incidence of BMF of 86% [55], and the NCI cohort study has noted a 91% incidence (Alter and Savage, unpublished data). However, both of these cohorts may be biased due to ascertainment primarily by hematologists and/or oncologists.

A review of literature reports of cancer in patients with DC indicated that head and neck squamous cell carcinomas (SCC) were the most common type, followed by anorectal SCC, stomach, and lung cancers [56]. MDS and AML have also been reported in DC. The age at diagnosis of cancer in DC is much younger than the average age of cancer in the NCI's Surveillance, Epidemiology, and End Results (SEER) population-based sporadic cancer registry [56].

Pulmonary fibrosis is a very serious complication in patients with DC, particularly following HSCT. Studies of patients with idiopathic pulmonary fibrosis (IPF) revealed that a sub-group have mutations in *TERT* or *TERC*, as well as shorter telomeres than healthy controls [28;32; 52]. The first studies focused on patients with a family history of IPF; a subsequent study found shorter telomeres and *TERT* or *TERC* mutations in sporadic cases [57]. Although the telomere shortening in these patients was not as dramatic as that seen in patients with more common features of DC, it does suggest that there is a spectrum of disorders of the telomere maintenance pathway caused by mutations in telomere biology genes.

The neurological consequences of DC are complex. Ataxia may result from cerebellar hypoplasia in the HH variant of DC [9;11;13-15]. Patients who present with pancytopenia and ataxia in whom DC is not initially suspected may actually have HH; a mutation in *TINF2* was recently identified in a patient with these signs [58]. Patients with DC may have variable degrees of developmental delay and/or learning disorders, as well as microcephaly; two patients were reported to have had schizophrenia [59;60].

There are numerous other clinical complications that significantly affect the quality of life of patients with DC. There may be gastrointestinal problems of varying severity. Esophageal stenosis requiring dilatation was reported in 17% of patients [9]. Enteropathies and liver fibrosis have also been reported [9;11]. Osteopenia and/or osteoporosis have occurred at unusually young ages. These bone density complications may be further exacerbated by the use of corticosteroids after HSCT for graft versus host disease (GVHD) prophylaxis and/or treatment. Avascular necrosis of the hips has led to hip replacement surgery in some patients [30]. Ophthalmic problems include obstruction of the lacrimal drainage system leading to constant

tearing (epiphora), and abnormal eyelash growth which can cause corneal erosions or ulcers [54;61]. Bilateral exudative retinopathy is the hallmark of the RS variant of DC, and may result in blindness [12;19;20]. Several other ophthalmic complications have been reported, including proliferative retinopathy, retinal or vitreous hemorrhage, glaucoma, and other problems [61].

The median survival was 44 years of age in cases of DC without HH or RS reported in the medical literature (Figure 3A). The median survival for those with HH was 5 years; those with RS had a 75% survival plateau at age 11 (Figures 4B and 4C). However, no patients with either HH or RS have been reported so far who were older than 20 years of age. Thus, survival appears to be shortened in DC, and particularly in those with the severe subsets. One note of caution is that reports of cases or case series may be biased towards inclusion of those with severe complications.

Medical Management of Dyskeratosis Congenita

The medical management of DC is complex and must be based on patient-specific needs as randomized clinical trials have not been conducted. Patients with DC and BMF do not respond to immunosuppressive therapy [45]. Failure of response to immunosuppressive therapy in apparently acquired BMF should lead to the consideration of DC as the proper diagnosis. Following the model of the Fanconi anemia consensus guidelines [62], treatment of BMF is recommended if the hemoglobin is consistently below 8 g/dL, platelets less than 30,000/mm³, and neutrophils below 1000/mm³. The first consideration for treatment for hematologic problems such as BMF or leukemia should be HSCT, if there is a matched related donor. HSCT from an unrelated donor can be considered, although a trial of androgen therapy (e.g. oxymetholone) may be chosen.

In our experience, patients with DC are more sensitive to androgens than patients with Fanconi anemia, and the dose must be adjusted to reduce side effects such as impaired liver function, virilization, or behavioral problems (e.g. aggression, mood swings). We use a starting oxymetholone dose of 0.5 to 1 mg/kg/day, half the dose used in Fanconi anemia. It may take two to three months at a constant dose to see a hematologic response. Side effects, including liver enzyme abnormalities, need to be monitored carefully. Baseline and follow-up liver ultrasounds should be performed for patients on androgens because of the possibility of liver tumors, both adenomas and carcinomas, which have been reported in patients with Fanconi anemia and in patients whose use of androgens was for other benign hematologic diseases or for non-hematologic reasons [63].

Hematopoietic growth factors are occasionally considered in patients with BMF. We do not recommend using androgens combined with G-CSF, since splenic rupture occurred in two of our patients with DC receiving this combination [64]. G-CSF with erythropoietin has occasionally been useful but perhaps should also not be used in combination with androgens [65].

HSCT is the only curative treatment for BMF in patients with DC. It should also be noted that the major indications for HSCT are severe BMF or AML. Although there is a high risk of MDS in DC, many of the cases have abnormal cytogenetic clones and/or morphologic dyspoieses, but do not necessarily have severe cytopenias. HSCT is clearly a life-saving measure, but has substantial risks either from toxicity from radiochemotherapy or immune-related complications. Reported problems include graft failure, GVHD, sepsis, pulmonary fibrosis, cirrhosis, and veno-occlusive disease [49;66], due, in part, to underlying pulmonary and liver disease [46-50]. As a result, long-term survival of patients with DC following HSCT has been very poor [49;66]. Studies of reduced-intensity preparative regimens are ongoing in a few institutions which may improve long-term outcomes [54;67].

The selection of related hematopoietic stem cell donors may be complicated by the variable phenotype seen in DC, including silent carriers. In one family, peripheral blood stem cell (PBSC) mobilization from a matched-sibling HSCT donor yielded suboptimal numbers of CD34+ cells and the HSCT to the proband was complicated by delayed engraftment and sepsis. In a second family, peripheral blood stem cell mobilization was unsuccessful from an apparently healthy matched sibling donor, who was subsequently shown to have a markedly hypocellular bone marrow. The probands and sibling donors were later found to have mutations in *TERC* [68].

We recently identified a potential donor who was a silent carrier of a *TINF2* mutation. The individual was an apparently healthy, HLA-matched sibling of a patient with DC in need of HSCT. The sibling was found to have very short telomeres prior to the discovery of the *TINF2* gene mutation [12]. The presence of very short telomeres in this potential donor was the basis of our recommendation that he not be used as the donor [51]. Another HLA-matched sibling with normal telomeres was successfully used as the donor and was subsequently shown not to have a *TINF2* mutation (which was found in the proband after the transplant). The sibling with the short telomeres was a silent carrier for the *TINF2* mutation [12]. The relatives of patients with DC who are being considered as HSCT donors should be carefully evaluated for DC. If the causative gene is known in the patient, then it should be tested in the donor. If the gene has not yet been identified, the donors should have telomere length testing done in leukocyte subsets by flow-FISH to rule-out silent carriers.

Since patients with DC are at very high risk of SCC of the head and neck or anogenital region, as well as hematologic malignancies, we recommend frequent monitoring of patients for early detection of these complications. Monthly self-examination for oral and head and neck cancer is warranted, as well as annual screening by a head and neck specialist and semiannually by a dentist, similar to screening recommendations for patients with Fanconi anemia [62]. Other clinical tests to consider for disease surveillance for patient with DC include at least twice yearly complete blood counts; annual bone marrow aspirates, biopsies, and cytogenetics; liver ultrasounds especially for, but not limited to, those on androgens; and annual pulmonary function tests; gynecologic exams; and skin cancer screening by a dermatologist. These screening measures are being studied prospectively in the NCI DC cohort [54].

Summary

The identification of large numbers of patients with DC has led to the recognition of a broad clinical phenotype, and the appreciation that these patients have abnormalities in telomere biology. DC is a multi-system disorder which includes a very high risk of BMF and cancer. Patients should be monitored closely for these and other complications. Mutations in six telomere biology genes have been identified in DC, representing about half of the known patients. Measurement of telomere length in leukocyte subsets determined by flow-FISH is a sensitive and specific screening test for DC in patients with BMF and normal chromosome breakage tests. If telomeres are less than the 1st percentile for age, we suggest prospective management and screening for DC-related complications as well as genetic testing for mutations in DC genes. Such studies are required to better understand the clinical consequences of DC, identify the basis for BMF response to androgens, define the best HSCT regimen, and determine the best measures for surveillance and prevention of cancer and other complications.

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A.

B.

C.

Figure 1.
The dyskeratosis congenita diagnostic triad. A. Dystrophic fingernails. B. Lacey, reticular pigmentation of the neck and upper chest. C. Oral leukoplakia

Figure 2.
Brain MRI of a patient with Hoyeraal-Hreidarsson Syndrome. The arrow indicates the characteristic cerebellar hypoplasia.

Figure 3. Survival of patients with dyskeratosis congenita (DC) based on review of the literature. A: Patients with DC, not including those with Hoyerall Hreidarsson or Revesz Syndromes, B: Hoyerall Hreidarsson Syndrome (HH), C: Revesz Syndrome (RS)

Table 1**Clinical Findings in Dyskeratosis Congenita**

The diagnostic triad is noted in **bold** type. RS and HH indicate findings specific for Revesz Syndrome and Hoyeraal Hreidarsson Syndrome, respectively.

System	Findings
Dermatologic	<p>Lacy, reticular pigmentation, primarily of the neck and chest; may be subtle or diffuse hyper- or hypopigmentation</p> <p>Abnormal fingernails and toenails, may be subtle with ridging, flaking, or poor growth, or more diffuse with nearly complete loss of nails</p> <p>Early gray hair or hair loss</p> <p>Hyperhidrosis</p> <p>Short stature</p>
Growth and Development	<p>Intrauterine growth retardation</p> <p>Developmental delay</p> <p>Epiphora due to stenosis of the lacrimal drainage system</p>
Ophthalmic	<p>Blepharitis</p> <p>Sparse eyelashes, ectropion, entropion, trichiasis</p> <p>Exudative retinopathy (RS)</p>
Dental	<p>Dental caries, may be less frequent now due to improved dental hygiene</p> <p>Periodontal disease</p> <p>Decreased root/crown ratio</p> <p>Taurodontism (enlarged pulp chambers of the teeth)</p> <p>Oral leukoplakia</p>
Ears, Nose, Throat	<p>Deafness (rare)</p> <p>Squamous cell head and neck cancer</p>
Cardiovascular	Rare reported defects include atrial or ventricular septal defects, fibrosis, and dilated cardiomyopathy
Respiratory	<p>Pulmonary fibrosis</p> <p>Esophageal stenosis</p>
Gastrointestinal	<p>Enteropathy</p> <p>Liver fibrosis</p>
Genitourinary	<p>Urethral stenosis in males</p> <p>Epithelial cancers</p>
Musculoskeletal	<p>Osteoporosis</p> <p>Avascular necrosis of the hips and shoulders</p>
Neurologic	<p>Developmental delay</p> <p>Microcephaly</p> <p>Cerebellar hypoplasia (HH)</p> <p>Intracranial calcifications (RS)</p>
Psychiatric	Schizophrenia (2 case reports)
Endocrine	<p>Hypogonadism</p> <p>Bone marrow failure: a common presenting sign</p>
Hematologic	<p>Myelodysplastic syndrome</p> <p>Leukemia</p>
Immunologic	Immunodeficiency

Dyskeratosis Congenita Genes

The genes proven to be mutated in DC and their frequency estimates are shown. Depending on the study, approximately 40 to 50% of patients remained molecularly uncharacterized.

Table 2

Gene Name	Protein Name	Function	Inheritance	Chromosomal location ^a	MIM identifier	Frequency in NCI cohort ^b	Frequency in DCR ^c
<i>DKC1</i>	DKC1: Dyskerin	Component of H/ACA snoRNP's and telomerase RNA (TERC)	XLR	Xq28 NC_000023.9: 153644344 - 153659154	300126	17%	36%
<i>TERC</i>	TERC: telomerase RNA component	TERC is the RNA component of telomerase. It acts as a template for the addition of telomeric repeat sequences	AD	3q21-q28 NC_000003.10: 170965542 - 170965091	602322	10%	6%
<i>TERT</i>	TERT: telomerase	A reverse transcriptase that adds the TTAGGG _(n) repeats to telomeres	AD, AR	5p15.33 NC_000005.8 1348162 - 1306282	187270	7%	1%
<i>TINF2</i>	TIN2: TRF1-interacting nuclear factor 2	Interacts with telomeric repeat-binding factor-1 and -2 (TRF1, and TRF2) and other shelterin components.	AD	14q12 NC_000014.7: 23781720 - 23778689	604319	24%	11%
<i>NOLA3</i>	NOP10: nucleolar protein family A, member 3	Associates with NHP2, DKC1, and GAR1 in structures corresponding to H/ACA snoRNP's	AR	15q14-q15 NC_000015.8: 32422654 - 32421209	606471	0%	<1%
<i>NOLA2</i>	NHP2: nucleolar protein family A, member 2	Associates with NOP10, DKC1, and GAR1 in structures corresponding to H/ACA snoRNP's	AR	5q35.3 NC_000005.8: 177513567 - 177509070	606470	0%	<1%

Abbreviations: NCI, National Cancer Institute; DCR, Dyskeratosis Congenita Registry; snoRNP, small nucleolar ribonucleolar proteins; XLR, X-linked recessive; AD, autosomal dominant; AR, autosomal recessive

^aBased on Human genome build 36.3, information available on October 7, 2008.

^bData from (12) and unpublished data from NCI cohort as of December 1, 2008.

^cData derived from references 11,17, and 23.