Dyskeratosis Congenita

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KEYWORDS

• Dyskeratosis congenita • Telomere • *DKC1* • *TERC* • *TERT*
• *TINF2* • Bone marrow failure

Dyskeratosis congenita (DC) is an inherited bone marrow failure (BMF) 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. BMF, pulmonary fibrosis, liver disease, neurologic and ophthalmic abnormalities, and increased risk for cancer also occur.[1,2] The known clinical complications are listed in **Table 1**.

Patients who have DC have very short germline telomeres compared with those of their healthy relatives, normal controls, and patients who have inherited BMF syndromes (IBMFS).[3,4,5] Mutations in genes important in telomere biology have been identified in approximately half of the patients who have DC.[5] Genotype-phenotype correlations may exist but often are complex to interpret. A broader spectrum of disorders resulting from defects in telomere biology is now appreciated, such as pulmonary fibrosis without other physical or hematologic findings associated with DC. Patients who have DC have a high risk for many medical problems, the most serious of which are BMF, cancer, and pulmonary fibrosis. Accurate diagnosis is critical, because patients who have DC and who develop BMF do not respond to immunosuppression and have a high risk for hematopoietic stem cell transplantation (HSCT)-related complications. This article reviews the clinical features of DC and describes its molecular pathogenesis. The usefulness of telomere length as a diagnostic test and of genetic testing in families is discussed and guidelines for medical management and clinically indicated screening are proposed.

CLINICAL FEATURES

The name, *dyskeratosis congenita*, was derived after the description by Zinsser, in 1910, of two brothers who had nail dystrophy, oral leukoplakia, and skin pigmentation anomalies.[6] Additional reports of patients who had similar features appeared by Engman[7] and by Cole and colleagues,[8] leading to the designation Zinsser-Engman-Cole

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Table 1
Clinical findings in dyskeratosis congenita

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

The diagnostic triad is noted in bold type. Revesz syndrome and Hoyeraal-Hreidarsson syndrome indicate findings specific to those syndromes.