Dyskeratosis Congenita Test

GENETICS LIST
ACD, CTC1, DKC1, NHP2, NOP10, PARN, RTEL1, TERC, TERT, TINF2, USB1, WRAP53

CLINICAL FEATURES
Individuals with dyskeratosis congenita (DC) most commonly present with abnormal skin pigmentation, nail dystrophy, bone marrow failure and oral leukoplakia. Other features that may present include: epiphora, developmental delay, pulmonary disease, short stature, poor dentition, esophageal stricture, premature hair loss and an increased risk for a variety of malignancies. Individuals typically present during early childhood, often with abnormal skin pigmentation and nail dystrophy as the first clinical signs. By age 30, most individuals with DC have signs of bone marrow failure. However, there is a large degree of disease heterogeneity and severity, especially for heterozygous variants in the TERT gene. Some patients may initially be characterized as having constitutional or idiopathic aplastic anemia or myelodysplastic syndromes. In addition, variants in the TERC and TERT genes have been identified in individuals with reported idiopathic pulmonary fibrosis.[10]Hoyeraal-Hreidarsson (HH) and Revesz Syndromes are severe forms of DC. HH is characterized by microcephaly, growth and mental retardation, spastic paresis, ataxia and immunodeficiency. Individuals with Revesz syndrome present with bilateral retinal exudative retinopathy and intracranial calcifications, in addition to many of the common DC features. Genetic anticipation can also be observed, with children displaying clinical features at an earlier age and/or with a more severe presentation as compared to a parent harboring the same variant. In all forms of DC, telomere protection or maintenance is defective.

TEST METHODS
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

TEST SENSITIVITY
Approximately 50% of individuals with DC have a detectable pathogenic variant.[8,9] Most patients with DC are males with pathogenic variants in the X-linked DKC1 gene, which is rarely involved in affected females. About 1/3 of sporadic cases and 2/3 of families with more than one affected male have DKC1 pathogenic variants.[1] Another 11-24% of sporadic cases of DC (male and female) can be attributed to pathogenic variants in exon 6 of the TINF2 gene.[5,9] A smaller percent of DC cases can be attributed to pathogenic variants in the TERC (6-10%) and the TERT genes (1-7%).[9] The USB1 and CTC1 genes are responsible for no more than 2% of DC cases each; these genes are unique in DC cases in that they are not associated with shortened telomeres. Additional genes

(PARN, ACD, NHP2, WRAP53, and NOP10) are responsible for a rare number of cases. All known variants in TINF2 have been identified in exon 6, and comprise single base pair substitutions or small insertions/deletions, which are expected to be detected by sequence analysis.

Gene	Protein	Inheritance	Disease Association	Sensitivity
DKC1	Dyskerin	X-linked	DC,HH	30%[11]
TINF2	TERF1 (TRF1)-interacting nuclear factor 2	AD	DC, aplastic anemia	11-24%[5,9]
TERC	Telomerase RNA component	AD	DC, aplastic anemia, pulmonary fibrosis	6-10%[9]
TERT	Telomerase reverse transcriptase	AD; AR (rare)	DD, HH, aplastic anemia, pulmonary fibrosis	1-7%[9]
RTEL1	Regulator of telomere elongation helicase 1	AD; AR	DC, HH	5%[12,13]
USB1	U6 small nuclear RNA biogenesis phosphodiesterase 1	AR	DC, poikiloderma with neutropenia; normal-length telomeres	2%[11,14]
CTC1	Conserved telomere maintenance component 1	AR	CRMCC, Coats plus, DC; normal-length telomeres	<2%[15]
PARN	Poly(A)-specific ribonuclease	AD; AR	Recessive DC, HH; dominant pulmonary fibrosis	Rare[16,19]
ACD	Adrenocortical dysplasia homolog	AD	DC	Rare[19-20]
NHP2	H/ACA ribonucleoprotein complex subunit 2	AR	DC	Rare[21]
WRAP53	WD repeat-containing protein antisense to TP53	AR	DC	Rare[22]
NOP10	H/ACA ribonucleoprotein complex subunit 3	AR	DC	Rare[23]

DKC –Dyskeratosis Congenita
HH –Hoyeraal-Hreidarsson syndrome
CRMCC –Cerebroretinal microangiopathy with calcifications & cysts

REFERENCES

1.Vulliamy TJ et al. Mutations in dyskeratosis congenita: their impact on telomere length and the diversity of clinical presentation. Blood. 2006 107(7):2680-5.16332973
2.Vulliamy T et al. The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. Nature. 2001 Sep 27 413(6854):432-5.11574891
3.He J et al. Targeted disruption of Dkc1, the gene mutated in X-linked dyskeratosis congenita, causes embryonic lethality in mice. Oncogene. 2002 Oct 31 21(50):7740-4.12400016
4.Goldman F et al. The effect of TERC haploinsufficiency on the inheritance of telomere length. Proceedings Of The National Academy Of Sciences Of The United States Of America. 2005 102(47):17119-24.16284252
5.Walne AJ et al. TINF2 mutations result in very short telomeres: analysis of a large cohort of patients with dyskeratosis congenita and related bone marrow failure syndromes. Blood. 2008 112(9):3594-600.18669893

6.Savage SA et al. TINF2, a component of the shelterin telomere protection complex, is mutated in dyskeratosis congenita. American Journal Of Human Genetics. 2008 82(2):501-9.18252230
7.Vulliamy TJ et al. Differences in disease severity but similar telomere lengths in genetic subgroups of patients with telomerase and shelterin mutations. Plo S One. 2011 6(9):e24383.21931702
8.Walne AJ and Dokal I. Advances in the understanding of dyskeratosis congenita. British Journal Of Haematology. 2009 145(2):164-72.19208095
9.Savage SA and Bertuch AA. The genetics and clinical manifestations of telomere biology disorders. Genetics In Medicine : Official Journal Of The American College Of Medical Genetics. 2010 12(12):753-64.21189492
10.Armanios MY et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. The New England Journal Of Medicine. 2007 356(13):1317-26.17392301
11.Dokal and I. Dyskeratosis congenita. Hematology / The Education Program Of The American Society Of Hematology. American Society Of Hematology. Education Program. 2011 2011:480-6.22160078
12.Ballew BJ et al. Germline mutations of regulator of telomere elongation helicase 1, RTEL1, in Dyskeratosis congenita. Human Genetics. 2013 Apr 132(4):473-80.23329068
13.Walne AJ et al. Constitutional mutations in RTEL1 cause severe dyskeratosis congenita. American Journal Of Human Genetics. 2013 Mar 7 92(3):448-53.23453664
14.Walne AJ et al. Mutations in C16orf57 and normal-length telomeres unify a subset of patients with dyskeratosis congenita, poikiloderma with neutropenia and Rothmund-Thomson syndrome. Human Molecular Genetics. 2010 Nov 15 19(22):4453-61.20817924
15.Walne AJ et al. Mutations in the telomere capping complex in bone marrow failure and related syndromes. Haematologica. 2013 Mar 98(3):334-8.22899577
16.Moon DH et al. Poly(A)-specific ribonuclease (PARN) mediates 3'-end maturation of the telomerase RNA component. Nature Genetics. 2015 Dec 47(12):1482-8.26482878
17.Stuart BD et al. Exome sequencing links mutations in PARN and RTEL1 with familial pulmonary fibrosis and telomere shortening.Nature Genetics. 2015 May 47(5):512-7.25848748
18.Tummala et al. (2015) The Journal Of Clinical Investigation 125 (5):2151-60 (PMID: 25893599)
19.Guo Y et al. Inherited bone marrow failure associated with germline mutation of ACD, the gene encoding telomere protein TPP1.Blood. 2014 Oct 30 124(18):2767-74.25205116
20.Kocak H et al. Hoyeraal-Hreidarsson syndrome caused by a germline mutation in the TEL patch of the telomere protein TPP1. Genes & Development. 2014 Oct 1 28(19):2090-102.25233904
21.Vulliamy T et al. Mutations in the telomerase component NHP2 cause the premature ageing syndrome dyskeratosis congenita. Proceedings Of The National Academy Of Sciences Of The United States Of America. 2008 Jun 10 105(23):8073-8.18523010
22.Zhong F et al. Disruption of telomerase trafficking by TCAB1 mutation causes dyskeratosis congenita. Genes &Development. 2011 Jan 1 25(1):11-6.21205863
23.Walne AJ et al. Genetic heterogeneity in autosomal recessive dyskeratosis congenita with one subtype due to mutations in the telomerase-associated protein NOP10. Human Molecular Genetics. 2007 Jul 1 16(13):1619-29.17507419