

Dyskeratosis Congenita Test

Gene 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 Associations	Sensitivity
<i>DKC1</i>	Dyskerin	X-linked	DC, HH	30% ¹¹
<i>TINF2</i>	TERF1 (TRF1)-interacting nuclear factor 2	AD	DC, HH, aplastic anemia	11-24% ^{5,9}
<i>TERC</i>	Telomerase RNA component	AD	DC, aplastic anemia, pulmonary fibrosis	6-10% ⁹
<i>TERT</i>	Telomerase reverse transcriptase	AD; AR (rare)	DC, HH, aplastic anemia, pulmonary fibrosis	1-7% ⁹
<i>RTEL1</i>	Regulator of telomere elongation helicase 1	AD; AR	DC, HH	5% ^{12,13}
<i>USB1</i>	U6 small nuclear RNA biogenesis phosphodiesterase 1	AR	DC, poikiloderma with neutropenia; normal-length telomeres	2% ^{11,14}
<i>CTC1</i>	Conserved telomere maintenance component 1	AR	CRMCC, Coats plus, DC; normal-length telomeres	<2% ¹⁵
<i>PARN</i>	Poly(A)-specific ribonuclease	AD; AR	Recessive DC, HH; dominant pulmonary fibrosis	Rare ¹⁶⁻¹⁸

<i>ACD</i>	Adrenocortical dysplasia homolog	AD	DC	Rare ¹⁹⁻²⁰
<i>NHP2</i>	H/ACA ribonucleoprotein complex subunit 2	AR	DC	Rare ²¹
<i>WRAP53</i>	WD repeat-containing protein antisense to TP53	AR	DC	Rare ²²
<i>NOP10</i>	H/ACA ribonucleoprotein complex subunit 3	AR	DC	Rare ²³

DKC – Dyskeratosis Congenita

HH – Hoyeraal-Hreidarsson syndrome

CRMCC – Cerebroretinal microangiopathy with calcifications & cysts

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