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. 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-CN). 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.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease Associations</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DKC1</td>
<td>Dyskerin</td>
<td>X-linked</td>
<td>DC, HH</td>
<td>30%(^{11})</td>
</tr>
<tr>
<td>TINF2</td>
<td>TERF1 (TRF1)-interacting nuclear factor 2</td>
<td>AD</td>
<td>DC, HH, aplastic anemia</td>
<td>11-24%(^{5,^9})</td>
</tr>
<tr>
<td>TERC</td>
<td>Telomerase RNA component</td>
<td>AD</td>
<td>DC, aplastic anemia, pulmonary fibrosis</td>
<td>6-10%(^9)</td>
</tr>
<tr>
<td>TERT</td>
<td>Telomerase reverse transcriptase</td>
<td>AD; AR (rare)</td>
<td>DC, HH, aplastic anemia, pulmonary fibrosis</td>
<td>1-7%(^9)</td>
</tr>
<tr>
<td>RTELI</td>
<td>Regulator of telomere elongation helicase 1</td>
<td>AD; AR</td>
<td>DC, HH</td>
<td>5%(^{12,^{13}})</td>
</tr>
<tr>
<td>USB1</td>
<td>U6 small nuclear RNA biogenesis</td>
<td>AR</td>
<td>DC, poikiloderma with neutropenia; normal-length telomeres</td>
<td>2%(^{11,^{14}})</td>
</tr>
<tr>
<td>CTC1</td>
<td>Conserved telomere maintenance component 1</td>
<td>AR</td>
<td>CRMCC, Coat's plus, DC; normal-length telomeres</td>
<td>&lt;2%(^{15})</td>
</tr>
<tr>
<td>PARN</td>
<td>Poly(A)-specific ribonuclease</td>
<td>AD; AR</td>
<td>Recessive DC, HH; dominant pulmonary fibrosis</td>
<td>Rare(^{16-18})</td>
</tr>
</tbody>
</table>
**Test Information Sheet**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Inheritance</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD</td>
<td>Adrenocortical dysplasia homolog</td>
<td>AD DC</td>
<td>Rare[^19-20]</td>
</tr>
<tr>
<td>NHP2</td>
<td>H/ACA ribonucleoprotein complex subunit 2</td>
<td>AR DC</td>
<td>Rare[^21]</td>
</tr>
<tr>
<td>WRAP53</td>
<td>WD repeat-containing protein antisense to TP53</td>
<td>AR DC</td>
<td>Rare[^22]</td>
</tr>
<tr>
<td>NOP10</td>
<td>H/ACA ribonucleoprotein complex subunit 3</td>
<td>AR DC</td>
<td>Rare[^23]</td>
</tr>
</tbody>
</table>

DKC – Dyskeratosis Congenita
CRMCC – Cerebroretinal microangiopathy with calcifications & cysts

**References:**

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
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

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