



Telomere Biology Disorder/Dyskeratosis Congenita Panel

The telomere biology disorders (TBDs) are a set of complex diseases related to aberrant telomere biology. Genetic defects in telomeres and telomere repair appear in multiple human diseases including constitutional marrow failure as dyskeratosis congenital (DC), some apparently acquired aplastic anemia, myelodysplasia and acute myeloid leukemia; pulmonary fibrosis; and hepatic nodular regenerative hyperplasia and cirrhosis [1]. DC is a highly heterogeneous disorder characterized by abnormal skin pigmentation, nail dystrophy and oral leukoplakia (mucosal keratosis appearing as white patches in the oral cavity) [2]. This classic triad of findings is present in 80-90% of affected individuals [3]. Idiopathic pulmonary fibrosis (IPF) can also be caused by mutations in the same genes as are associated with DC, and that *TERT* and *TERC* mutations are the most common cause of IPF identified to date [4]. Anticipation may be observed in affected families, and is thought to be due to the inheritance of shortened telomeres from an affected parent [3]. TBD/DC can be inherited in either an autosomal dominant, autosomal recessive or X-linked manner, depending on the causative gene. Clinically silent carriers of a TBD-associated genetic mutation have also been reported. Variable penetrance of the phenotype and/or variable expressivity of the disease-associated mutations are common [5].

Our Telomere Biology Disorder/Dyskeratosis Congenita Panel includes sequence and deletion/duplication analysis of the 14 genes listed below.

Telomere Biology Disorder/Dyskeratosis Congenita Panel				
ACD	C16orf57 (USB1)	CTC1	DKC1	NAF1
NHP2	NOLA3 (NOP10)	PARN	POT1	RTEL1
TERC	TERT	WRAP53 (TCAB1)	TINF2	

Gene	Clinical Features
ACD	Guo Y <i>et al.</i> (2014) reported germline mutations of <i>ACD</i> , the gene encoding telomere protein TPP1 in Inherited bone marrow failure [6]. Hoyeraal-Hreidarsson syndrome can also be caused by a germline mutation in the TPP1 [7].
C16orf57 (USB1)	<i>C16orf57</i> has been identified to be mutated in poikiloderma with neutropenia (PN), an inherited poikiloderma displaying significant clinical overlap with DC [8, 9]. Mutations in <i>C16orf57</i> have also been identified in patients with Rothmund-Thomson syndrome (RTS) [10].
CTC1	Keller <i>et al.</i> (2012) identified compound heterozygous mutations in <i>CTC1</i> in a patient with DC [11]. The <i>CTC1</i> gene is also associated with Coats syndrome, which is characterized by bilateral exudative retinopathy, intracranial calcifications and cysts, premature hair greying, osteoporosis and anemia [12].
DKC1	Mutations in the X-linked <i>DKC1</i> gene are the most common cause of DC [13]. Age of onset and severity of symptoms is highly variable, but affected males typically present in the first decade of life, and typically die in their twenties due to complications from bone marrow failure [13]. Many mutations occur <i>de novo</i> . Female heterozygous carriers are typically asymptomatic [13].
NAF1	Mutations in <i>NAF1</i> have been described in patients with short telomere length, pulmonary fibrosis, low telomerase RNA levels, and extrapulmonary manifestations including myelodysplastic syndrome and liver disease [14].
NHP2	Biallelic mutations in <i>NHP2</i> have been described in two patients with DC [15].
NOLA3 (NOP10)	A homozygous mutation in <i>NOLA3</i> was identified in 3 individuals with DC in a consanguineous family [16]. All three individuals had the mucocutaneous features of DC, one individual also developed bone marrow failure [16].
PARN	Biallelic mutations in <i>PARN</i> have been reported to be associated with severe aplastic anemia and marked hypomyelination [17, 18]. Monoallelic mutations of <i>PARN</i> can cause developmental/mental illness [17]. Heterozygous mutations in <i>PARN</i> have also been reported in patients with familial pulmonary fibrosis and telomere shortening [19].
POT1	A <i>POT1</i> mutation has been recently reported implicating defective telomere end fill-in and telomere truncations in Coats plus [20].

RTEL1	Both dominant and recessive mutations in the <i>RTEL1</i> gene have been associated with Hoyeraal Hreidarsson syndrome, a clinically severe variant of DC with cerebellar hypoplasia, severe immunodeficiency, enteropathy, and intrauterine growth retardation [21]. Anticipation has been described in one family where two affected males inherited a heterozygous mutation from a clinically unaffected female with short telomeres [21]. Heterozygous mutations in <i>RTEL1</i> have also been reported in patients with familial pulmonary fibrosis and telomere shortening [19].
TERC	Heterozygous mutations in the TERC gene account for approximately 4% of all cases of DC [13]. Anticipation has been observed in families with TERC-associated DC, with increased disease severity and earlier age of onset seen with successive affected generations [13]. Idiopathic pulmonary fibrosis can be caused by mutations in TERC [4].
TERT	Heterozygous mutations in TERT have been associated with DC or aplastic anemia [13]. Penetrance of these mutations appears to be reduced, with some individuals being asymptomatic [13]. Variable expressivity has also been described, with some individuals being mildly affected [13]. Idiopathic pulmonary fibrosis can be caused by mutations in TERT [4].
WRAP53 (TCAB1)	Biallelic mutations in TCAB1 have been described in individuals with classical DC from two different families [22].
TINF2	Dominant mutations in TINF2 have been described in patients with DC [23]. Both inherited and de novo mutations have also been described [23, 24].

Test methods: Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Telomere Biology Disorder/Dyskeratosis Congenita panel

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube. **NOTE: blood samples are not accepted if patient has a history of MDS or leukemia. Please send 2 T-25 flasks of cultured skin fibroblasts instead.**

Cost: \$3500
 CPT codes: 81406, 81407
 Turn-around time: 6 weeks

Note: We cannot bill insurance for this panel.

Results:

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire Telomere Biology Disorders/Dyskeratosis Congenita Sequencing Panel or Deletion/Duplication Panel. All abnormal results are reported by telephone or email.

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