

TERC Gene Sequencing

CLINICAL FEATURES

Pathogenic variants in the *TERC* gene are associated with dyskeratosis congenita (DC) and related telomere biology disorders.² Individuals with DC most commonly present with abnormal skin pigmentation, nail dystrophy, bone marrow failure and oral leukoplakia. Other features may 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.^{2,5} However, there is a large degree of disease heterogeneity and severity.³ Some patients may initially be characterized as having constitutional or idiopathic aplastic anemia or myelodysplastic syndromes.⁴ In addition, variants in the *TERC* gene have been identified in individuals with reported idiopathic pulmonary fibrosis.⁶ 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.¹ Individuals with biallelic pathogenic variants in the *TERC* gene have been reported to have more severe disease than heterozygotes and present with the classical dyskeratosis congenita phenotype.^{7,8} In all forms of DC, telomere protection or maintenance is defective.

TEST METHODS

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method is used to confirm all potentially pathogenic variants. If present, apparently homozygous variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. Sequence alterations are reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Reportable variants include pathogenic variants, likely pathogenic variants, and variants of uncertain significance. Likely benign and benign variants are not routinely reported but are available upon request.

TEST SENSITIVITY

Approximately 6–10% percent of DC cases can be attributed to pathogenic variants in the *TERC* gene.⁵ The methods used by GeneDx are expected to be greater than 99% sensitive in detecting variants identifiable by sequencing. This analysis will not detect large deletions or duplications. ExonArrayDx deletion/duplication testing is available as an added test for copy number variants involving the *TERC* gene, although the added sensitivity is not known.

REFERENCES:

1. Vulliamy TJ, et al, Mutations in dyskeratosis congenita: their impact on telomere length and the diversity of clinical presentation, *Blood* 107:2680–2685, 2006.
2. Vulliamy TJ, et al, The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita, 2001, *Nature* 413:432.
3. Vulliamy et al., Differences in Disease Severity but Similar Telomere Lengths in Genetic Subgroups of Patients with Telomerase and Shelterin Mutations. 2011. *PLoS One*. 6(9) e24383.
4. Walne et al., Advances in the understanding of dyskeratosis congenita. 2009. *British Journal of Haematology*. 145:164–172.

5. Savage et al., (2010) The genetics and clinical manifestations of telomere biology disorders. Genet Med. 12(12):753-64.
6. Armanios et al., (2007) Telomerase Mutations in Families with Idiopathic Pulmonary Fibrosis. N Engl J Med. 35
7. Ly H et al. Identification and functional characterization of 2 variant alleles of the telomerase RNA template gene (TERC) in a patient with dyskeratosis congenita. Blood. 2005 106(4):1246-52.
8. Bessler M et al. Dyskeratosis congenita. FEBS Lett. 2010 Sep 10 584(17):3831-8.