DKC1, TINF2, TERC and TERT Gene Analysis in Dyskeratosis Congenita

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:

Analysis is performed by bi-directional sequencing of the coding regions and splice sites of exons 1-15 of the DKC1 gene (encoding dyskerin), of the non-translated single coding region of TERC (encoding the RNA component of telomerase), of exon 6 of the TINF2 gene (encoding amino acids 204-353) or of exons 1-16 of the TERT gene. Targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available as a reflex test to evaluate for rare exonic deletions in the DKC1 and TERC genes. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

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 gene5,9. A

smaller percent of DC cases can be attributed to pathogenic variants in the TERC (6-10%) and the TERT genes (1-7%).9 Additional genes (NOP10 and NHP2) 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. For DKC1, TERC and TERT, sequencing is expected to be able to detect >95% of cases with typical variants, including any deletions of DKC1 exons in males. ExonArrayDx deletion/duplication testing is available as an added test in DKC1 (for females) and in TERC and TERT (for males and females), although the added sensitivity is not known.

References:

1. Vulliamy TJ, et al, Mutations in dyskeratosis congenita, Blood 107:2680-2685, 2006.
2. Vulliamy TJ, et al, The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenital, 2001, Nature 413:432.
3. He J, et al, Targeted disruption of Dkc1, the gene mutated in X-linked dyskeratosis congenital causes embryonic lethality in mice. 2002, Oncogene 21:7740.
4. Goldman F et al, The effect of TERC haploinsufficiency on the inheritance of telomere length, 2005, PNAS 102:17119.
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. 2008, Blood 112:3594-3600.
6. Savage SA et al, TINF2, a Component of the Shelterin Telomere Protection Complex, Is Mutated in Dyskeratosis Congenita. 2008, The American Journal of Human Genetics 82:501-509.
7. 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.
8. Walne et al., Advances in the understanding of dyskeratosis congenita. 2009. British Journal of Haematology. 145:164-172.
9. Savage et al., (2010) The genetics and clinical manifestations of telomere biology disorders. Genet Med. 12(12):753-64.
10. Armanios et al., (2007) Telomerase Mutations in Families with Idiopathic Pulmonary Fibrosis. N Engl j Med. 356:1317-1326.