TP73L (*TP63, p63*) Gene Analysis in Ectodermal Dysplasia and Related Syndromes

Disorder Also Known As: Ectrodactyly-Ectodermal Dysplasia-Cleft Lip/Palate (EEC); Nonsyndromic Split Hand-Split Foot Malformation (SHFM4); Hay-Wells Syndrome (HWS); Limb-Mammary Syndrome (LMS); ADULT syndrome; Rapp-Hodgkin syndrome (RHS)

Clinical Features:

EEC consists of limb malformations, ectodermal dysplasia, and cleft lip and palate (in ~40% of patients; isolated cleft lip or palate is rare). The disorder shows variable expressivity and reduced penetrance. The ectodermal dysplasia in EEC is characterized by hypohidrosis, hypotrichosis, and anodontia. The limb anomalies include ectrodactyly (in 2/3 of patients), split-hand/split-foot, or polysyndactyly. Associated findings may include lacrimal-duct abnormalities, urinary tract anomalies, dysmorphic facies, and developmental delay.

Split Hand-Split Foot Malformation (SHFM) is characterized by limb malformation involving the central rays of the autopod and presenting with syndactyly, median clefts of the hands and feet, aplasia or hypoplasia of the phalanges, metacarpals, and metatarsals.

Hay-Wells syndrome (HWS) has phenotypic overlap with the EEC syndrome. Its major characteristics include eyelid fusion (~44%), ectodermal dysplasia, and cleft lip and palate (~80%). Many affected newborns have severe skin erosions. Nail and teeth defects occur in 75-80% of cases, and about half of patients experience lacrimal duct atresia. Alopecia also can be seen. The distinguishing feature of HWS is the *absence* of limb malformations. Sweating abnormalities and mammary gland/nipple hypoplasias are rarely observed.

Limb-Mammary syndrome (LMS) includes hand/foot anomalies and hypoplasia/aplasia of the mammary gland and nipple. Less frequent findings include lacrimal-duct problems, ectodermal dysplasia (hypohidrosis (~ 30% of cases), hypodontia, nail dysplasia), cleft palate, and bifid uvula.

ADULT syndrome is clinically similar to LMS in that both have mammary gland hypoplasia. However, orofacial clefting has not been observed in affected patients, while the nails, skin, and teeth are affected in almost all cases. Hypohidrosis is seen rarely.

Rapp-Hodgkin syndrome overlaps with HWS. Patients usually have mid-facial hypoplasia, cleft palate, bifid uvula, nail hypoplasia, dry skin and coarse hair.

Inheritance Pattern/Genetics:
Each of these disorders is inherited in an autosomal dominant manner, and *de novo* variants are common.

Test Methods:
Analysis is performed by bi-directional sequencing of exons 5-8, 13, and 14 of the TP73L (p63; TP63) gene, where the vast majority of variants have been identified in this group of disorders. The sequencing approach employed by GeneDx is expected to identify >95% of small intragenic variant. If no variant is identified in these six exons, sequencing of remainder of the TP73L gene can be performed upon request. 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:
Test sensitivity varies depending on the clinical diagnosis. In EEC syndrome, TP73L variants have been identified in ~98% of classically-affected patients, while in SHFM, TP73L variants account for ~10% of cases. SHFM is genetically heterogeneous with multiple loci having been mapped.[1] In a study of 8 families with HWS, all were found to have variants in the TP73L gene.[2] To date, there are six families who have been described with the LMS syndrome, the majority with identifiable TP73L variants. Likewise, the few families published with features of ADULT syndrome have been found to carry TP73L variants (most affecting the R337, also commonly reported as codon R298 in a different isoform). Due to the small number of families with LMS, Rapp-Hodkin syndrome and ADULT syndromes, sensitivity data is not well defined.[1,3]

There is growing evidence of genotype/phenotype correlation in this group of disorders. Variants in EEC are nearly always missense, and occur in the DNA binding domain of the TP73L gene. Hotspot missense changes of five codons, R243, R266, R318, R319, and R343 (also commonly reported as R204, R227, R279, R280, and R304 in the literature when using a different isoform) account for almost 90% of EEC cases. Specifically, variants of amino acid R266 (R227) are associated with a lack of cleft lip and palate, fewer limb malformations, and increased incidence of genitourinary abnormalities. Other EEC variant-specific phenotypic patterns have been elucidated. Variants in SHFM have included missense, nonsense, and splice site, with no particular predilection to a gene region. Frameshift variants affecting the Sterile Alfa Motif (SAM) domain of the TP73L protein have been identified in LMS. HWS variants identified to date have all been missense changes in exon 13 that affect the SAM domain, while ADULT syndrome typically is associated with a hotspot variant affecting R337 (R298) in exon 8.[1] In Rapp-Hodgkin syndrome, missense and frameshift variants have been reported in the SAM domain and tail (exon 14) as well as in the DNA binding domain (exon 7) of the TP73L protein.

References:

1. Rinne, T. et al., (2006) Update. Am J Med Genet A. 140A: 1396-1406.
2. van Bokhoven, H. et al., (2001) Am J Hum Genet. 69: 481-92, 2001.
3. van Bokhoven, H. and Brunner, H., (2002) Am J Hum Genet. 71: 1-13.