Prenatal Testing for TP73L (TP63, p63) Gene Variants: Ectodermal Dysplasia

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:
Ectrodactyly-Ectodermal Dysplasia-Cleft Lip/Palate (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 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.

A detailed ultrasound examination, usually in the 2nd trimester of pregnancy, may identify abnormalities of the limbs or extremities. Prenatal molecular analysis of the TP73L gene could be considered in these cases even in the absence of a known family history. Ultrasound examination may be normal in affected fetuses; therefore, families at risk to inherit a specific known familial pathogenic variant can be offered targeted molecular testing regardless of ultrasound findings, if desired.

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

Test Methods:
Using genomic DNA, 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. For known variants, bi-directional sequencing of the relevant portion of the gene of the TP73L gene will be analyzed in duplicate.

Additionally, genotype analysis of maternal and fetal DNA for several polymorphic markers to test for maternal cell contamination will be performed.

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 perhaps 10% of cases. SHFM is genetically heterogeneous with multiple loci having been mapped.[1] In a recent 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] The sensitivity of TP73L testing in pregnancies with ultrasound anomalies suggestive of EEC or related syndromes is not currently known.

References:

1. Rinne, T. et al., (2006) Am J Med Genet A. 140A:1396-1406.
2. van Bokhoven, H. et al., (2001) Am J Hum Genet. 69:481-492.
3. van Bokhoven, H. and Brunner, H., (2002) Am J Hum Genet. 71:1-13.