EDARADD Gene Analysis in Anhidrotic/Hypohidrotic Ectodermal Dysplasia

Clinical Features:
The group of disorders known as ectodermal dysplasia is both clinically and genetically heterogeneous. Anhidrotic/hypohidrotic ectodermal dysplasia is characterized by reduced or absent sweating, hypotrichosis and hypodontia. The autosomal dominant and recessive forms, due to pathogenic variants in EDAR and EDARADD genes, are clinically indistinguishable from the far more common form which is seen primarily in males and is due to pathogenic variants in the X-linked EDA1 gene.[1,2]

In addition, a heterozygous variant in EDARADD has been found in one individual with isolated oligodontia, without other characteristics of ectodermal dysplasia.[3]

Genetics:
The EDARADD gene consists of six exons and codes for a death domain adaptor that interacts with the death domain of the EDAR protein. The EDAR protein and its ligand, ectodysplasin (coded for by the EDA1 gene), are members of the tumor-necrosis factor receptor family. The EDARADD gene is the human homolog of mouse *crinkled*, while EDAR is the homolog of *downless* and EDA1 of *tabby*, all of which have identical phenotypes in mouse.

Pathogenic variants in the EDARADD gene are inherited in an autosomal dominant or autosomal recessive manner, and autosomal dominant variants may occur de novo. The spectrum of variants is not characterized since the disorder is rare; however, missense, frameshift, and small in-frame deletion variants have been described and appear to cluster in the last exon of the gene affecting the death-domain of the protein.[1] A dominant-negative mechanism has been suggested for pathogenic variants in EDARADD associated with autosomal dominant inheritance.[1]

Test Methods:
Using genomic DNA from a submitted specimen, bi-directional sequence analysis of the complete coding region (exons 1-6) and splice sites of the EDARADD gene is performed. The presence of a sequence change is confirmed by repeat analysis using sequencing, restriction fragment analysis, or other appropriate method.

Test Sensitivity:
Four genes (EDA1, EDAR, WNT10A, and EDARADD) account for 90% of hypohidrotic/anhidrotic ectodermal dysplasia.[2] Of these, EDARADD is responsible for the

fewest cases, likely less than 1-2%. Due to the rarity of EDARADD pathogenic variants, no genotype-phenotype correlations can be drawn at this time.

References:

1. Bal et al. (2007) Human Mutation 28 (7):703-9.
2. Cluzeau C. et al., (2011) Hum Mutat 32:70-71.
3. Bergendal B. et al., (2011) Am J Med Genet Part A 155:1616-1622.