Anhidrotic/Hypohidrotic Ectodermal Dysplasia, Autosomal Dominant (EDARADD)

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 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.

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 NCBI RefSeq

transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

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.