

## Hypohidrotic Ectodermal Dysplasia (EDAR)

**Disorder also known as:** Autosomal recessive hypohidrotic ectodermal dysplasia; autosomal dominant hypohidrotic ectodermal dysplasia

### **Clinical Features:**

The recessive form of hypohidrotic ectodermal dysplasia that is due to pathogenic variants in the EDAR gene (coding for the human homolog of the mouse downless gene) is clinically indistinguishable from the X-linked form. It affects males and females equally. Clinical features include hypotrichosis with fine, sparse and light-colored scalp and body hair, decreased ability to sweat leading to heat intolerance, hypodontia and conical or peg shaped teeth. Hypoplastic breasts are not uncommon. Typical facial features are periorbital hyperpigmentation, saddle nose and full lips. Affected individuals in families in which the disease behaves in a dominant manner are similarly affected. The X-linked form of hypohidrotic ectodermal dysplasia due to a pathogenic variant in the EDA1 gene is much more common than pathogenic variant(s) in the EDAR/downless gene.

### **Inheritance Pattern:**

Pathogenic variants in the EDAR gene are responsible for both autosomal dominant and autosomal recessive forms of hypohidrotic ectodermal dysplasia.

### **Test Sensitivity:**

Pathogenic variants in the EDAR gene have been reported in up to 25% of individuals with hypohidrotic ectodermal dysplasia who do not have an EDA1 gene variant (Chassaing et al., 2006). The overall frequency of EDAR variant in hypo-/anhidrotic ectodermal dysplasia is only about 7%. The method used by GeneDx to screen the EDAR gene is expected to identify nearly all variants that occur in the coding and flanking splice sites of the gene. Two families with HED due to autosomal recessive or dominant variants in another gene, EDARADD, have been reported, thus providing evidence for further genetic heterogeneity in this condition (Headon et al., 2001; Bal et al., 2007); therefore variants in the EDAR gene will not be identified in a proportion of individuals with a recessive form of the disease. Clinical diagnostic testing of the EDARADD gene is not available in the United States, to our knowledge.

To date, more than 20 distinct variants have been found in the EDAR gene, the vast majority of which represent missense changes, with occasional splice site variants and deletions. Most variants (79%) are autosomal recessive, while autosomal dominant variants are less common (21%).

## 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. Chassaing et al. Hum Mutat. 27(3):255-259, 2006
2. Monreal et al. Nat Genet 22:366-369, 1999.
3. Headon et al. Nature. 414:913-916, 2001.
4. Bal, E et al. Hum Mutat. 28:703-709, 2007.