EDAR Gene Testing in Hypohidrotic Ectodermal Dysplasia

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.

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

Test Methods:
Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the 11 coding regions and splice sites of the EDAR gene (exons 2-12) is analyzed. If a sequence change is identified, the variant is confirmed by a second analysis, using sequence, heteroduplex or restriction fragment analysis or another appropriate method.

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.

Variant Spectrum:

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%).

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.