Hypohidrotic Ectodermal Dysplasia

Indications for Ordering

Confirm clinical diagnosis of hypohidrotic ectodermal dysplasia (HED) or related disorders

Test Description

Hypohidrotic ectodermal dysplasia sequencing
- Targeted capture of all coding exons and intron/exon junctions followed by massively parallel sequencing of *EDA, EDAR, EDARADD, IKBKG/NEMO* genes
- Sanger sequencing
  - Confirms reported variants for exons 5-12 of *IKBKG* gene, due to presence of pseudogene
  - Provides data for bases with insufficient coverage in all four genes

Hypohidrotic ectodermal dysplasia deletion/duplication
- Exonic oligonucleotide-based comparative genomic hybridization (CGH) microarray detects large deletions and/or duplications in *EDA*, *EDAR*, *EDARADD* genes, and exons 1-4 of *IKBKG* gene

Tests to Consider

Primary tests

Hypohidrotic Ectodermal Dysplasia Panel, Sequencing and Deletion/Duplication, 4 Genes 2010203
- Recommended test for confirming a diagnosis of HED

Hypohidrotic Ectodermal Dysplasia Panel, Sequencing, 4 Genes 2010766
- Detects the majority of causative HED variants, but will not detect rare large deletions or duplications

Hypohidrotic Ectodermal Dysplasia Deletion/Duplication, 3 Genes 2010763
- Order only if HED sequencing has been performed, or if there is a known familial large deletion/duplication

Related test

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Hypohidrotic ectodermal dysplasia (HED)/anhidrotic ectodermal dysplasia (EDA)
- May affect males or females
- Symptoms
  - Sparse scalp and body hair
  - Congenital absence of or abnormally formed teeth
  - Hyperthermia caused by reduced sweating

Hypohidrotic ectodermal dysplasia with immunodeficiency (HED-ID or XL-EDA-ID)
- Affects only males
- Symptoms – features of HED, plus
  - Dysgammaglobulinemia
  - Increased susceptibility to infection
  - Lymphedema
  - Osteoclast abnormalities

Incontinentia pigmenti (IP)
- Affects only females
- Generally, prenatally lethal in males
- Symptoms
  - Skin lesions
  - Alopecia
  - Hypodontia
  - Dystrophic nails
  - Neurological abnormalities

Genetics

Genes – see table for gene-specific information

Test Interpretation

Clinical sensitivity – see table for gene-specific sensitivity

Variants
- Most causative HED variants are sequence variants
  - Rare large deletions/duplications reported in *EDA* and *EDARR* genes
- Loss of function variants in *EDAR* gene cause autosomal recessive HED
- Dominant negative variants in *EDAR* gene cause autosomal dominant HED
- *IKBKG* gene variants with some residual protein activity cause HED-ID in males
- *IKBKG* gene variants that eliminate activity altogether
  - Lethal in males
  - Causative for IP in females
- Apparent de novo variants are frequent in HED and IP
- Germ line and somatic mosaicism reported

Results

- Positive – variant(s) detected
  - One pathogenic variant detected in *EDA* gene
    - Causative for HED in males
    - Females are carriers and variably affected
  - One pathogenic variant detected in *EDAR* or *EDARADD* gene
    - May cause mild autosomal dominant HED
    - May indicate a carrier of autosomal recessive HED
  - Two pathogenic variants detected in *EDAR* or *EDARADD* gene
    - Causative for autosomal recessive HED, regardless of gender
  - One pathogenic variant detected in *IKBKG* gene
    - Causative for HED-ID or prenatally lethal in males
    - Females are carriers of IP and variably affected
- Negative – no causative variants identified
  - Cause of HED unknown
  - Consider testing for other ectodermal dysplasias
- Inconclusive – variants of uncertain clinical significance
  - Unable to determine if detected variants are benign or pathogenic
  - Definitive cause of HED unknown

Limitations

- Rare diagnostic errors can occur due to primer- or probe-site variants
- Not detected
  - Regulatory region and deep intronic variants
  - Variants in genes other than *EDA, EDAR, EDARADD*, and *IKBKG*
  - Exons 5-12 of *IKBKG* gene not evaluated by CGH array due to technical limitations caused by a pseudogene
    - Common 11.7 kb deletion of exons 6-12 (aka exons 4-10) associated with IP not detected
    - Large deletions/duplications exclusively in exons 5-12 not detected
- Deletions smaller than 2.1 kb may not be detected

Gene Symbol	Gene Name	NM #	OMIM #	Associated Syndromes	Inheritance	Clinical Sensitivity
EDA	ectodysplasin A	001399	300451	HED	XL	50-60%
EDAR	ectodysplasin A receptor	022336	604095	HED	AR, AD	15-20%
EDARADD	*EDAR*-associated death domain	145861	606603	HED	AR, AD	1-2%
IKBKG/*NEMO*	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma	001099857	300248	HED-ID, IP	XL	rare for HED-ID; ~10% for IP

HED = hypohidrotic ectodermal dysplasia, HED-ID = hypohidrotic ectodermal dysplasia with immunodeficiency, IP = incontinentia pigmenti, AD = autosomal dominant, AR = autosomal recessive, XL = X-linked