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
    - 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

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

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