Holoprosencephaly Panel, Nonsyndromic Sequencing and Deletion/Duplication, 11 Genes

Indications for Ordering

- Determine the etiology of holoprosencephaly (HPE) to aid in counseling and assessing recurrence risk
- Determine if parents of an affected individual are carriers (the affected individual should be tested first, if possible)

Test Description

- Targeted capture of all coding exons and exon-intron junctions followed by massively parallel sequencing
- Deletion/duplication analysis by the tiled, custom-designed comparative genomic hybridization (CGH) array
- 11-gene panel covers most nonsyndromic HPE

Tests to Consider

Primary tests

Holoprosencephaly Panel, Nonsyndromic, Sequencing and Deletion/Duplication, 11 Genes 2008848
- Preferred test for individual with clinical phenotype of HPE and a normal karyotype

Holoprosencephaly Panel, Nonsyndromic, Sequencing and Deletion/Duplication, 11 Genes, Fetal 2008863
- Preferred test for fetuses with HPE that is not caused by a structural or numerical chromosome abnormality

Related tests

- Chromosome Analysis, Peripheral Blood 2002289
- Chromosome Analysis, Amniotic Fluid 2002293
- Chromosome Analysis, Chorionic Villus Sampling 2002291
- Chromosome Analysis, Products of Conception, with Reflex to Genomic Microarray 2005762

Disease Overview

Incidence – 1/250 embryos and 1/10,000-16,000 live births

Classification – HPE is a brain malformation
- Results from incomplete separation of the forebrain at 3 to 5 weeks post conception
- HPE classification – ranges from the most severe to the least severe depending on the degree of brain separation
  - Alobar variant
  - Semilobar variant
  - Lobar variant
  - Middle interhemispheric variant
  - Microform

Symptoms

Most common symptoms
- Microcephaly
- Macrocephaly in cases with hydrocephalus
- Seizures
- Pituitary dysfunction
- Characteristic midline facial defects
- Intellectual deficits – range from very mild to severe
- Cardiac, gastrointestinal, urogenital, and skeletal malformations
- Diabetes insipidus
- Only 20-30% of infants with alobar HPE survive 1 year
- MRI provides confirmation of the diagnosis

Genetics

Genes – DISP1, FGF8, FOXH1, GLI2, NODAL, PTCH1, SHH, SIX3, TDGF1, TGIF1, and ZIC2

Inheritance

- Autosomal dominant – DISP1, FOXH1, GLI2, NODAL, PTCH1, SHH, SIX3, TDGF1, TGIF1, and ZIC2 genes
- Autosomal recessive – FGF8 gene

Penetrance – depends on the specific gene and variant; higher penetrance for ZIC2 gene variants

Variants

- 25-50% of HPE caused by structural or numerical chromosomal abnormalities – best detected by chromosomal studies
- 25% of HPE occurs as part of a recognizable syndrome resulting from single gene variants
- 25% of HPE is nonsyndromic monogenic
Test Interpretation

Clinical sensitivity – unknown

Results

• Positive
  o Detection of a pathogenic HPE gene variant in a symptomatic individual confirms etiology and aids in recurrence risk counseling
  o Detection of a pathogenic gene variant in an asymptomatic individual indicates the individual has a 50% risk of passing the variant on to offspring

• Inconclusive
  o Variants of unknown clinical significance may be identified

Limitations

• Only the following genes are tested – DISP1, FGF8, FOXH1, GLI2, NODAL, PTCH1, SHH, SIX3, TDGF1, TGIF1, and ZIC2
• Structural and numeric chromosomal abnormalities will not be detected
• Diagnostic errors can occur due to rare sequence variations
• Deep intronic and regulatory region variants will not be evaluated
• Breakpoints for large deletion/duplications will not be determined

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Description</th>
<th>NM #</th>
<th>OMIM #</th>
<th>Inheritance</th>
<th>Disorder</th>
<th>Frequency</th>
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<tr>
<td>SHH</td>
<td>Sonic hedgehog (Drosophila) homologue</td>
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<td>HPE Stalk interruption syndrome</td>
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