Holoprosencephaly Panel, Sequencing and Deletion/Duplication

**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
  - Sanger sequencing is performed as necessary to fill in regions of low coverage and confirm reported variants
  - For fetal specimens, all clinically significant reported sequence variants are confirmed by Sanger 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, Sequencing and Deletion/Duplication 2008848**
  - Preferred test for individual with clinical phenotype of HPE and a normal karyotype
- **Holoprosencephaly Panel, Sequencing and Deletion/Duplication, 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, PTC1, SHH, SIX3, TDGF1, TGIF1, and ZIC2*

**Inheritance**

- Autosomal dominant – *DISP1, FOXH1, GLI2, NODAL, PTC1, 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
  - Detection of a pathogenic HPE gene variant in a symptomatic individual confirms etiology and aids in recurrence risk counseling
  - 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
  - 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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<td>Sonic hedgehog (Drosophila) homologue</td>
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