

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*, *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
 - 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

Gene Symbol	Gene Description	NM #	OMIM #	Inheritance	Disorder	Frequency
<i>SHH</i>	Sonic hedgehog (Drosophila) homologue	000193	600725	Autosomal dominant	HPE	30-40%
<i>ZIC2</i>	Zic family member 2 (odd-paired Drosophila homologue)	007129	603073	Autosomal dominant	HPE	5%
<i>SIX3</i>	Sine oculis homeobox (drosophila homolog 3)	005413	603714	Autosomal dominant	HPE	1%
<i>TGIF1</i>	Transforming growth factor beta induced factor homeobox 1	173208	602630	Autosomal dominant	HPE Stalk interruption syndrome	1%
<i>GLI2</i>	GLI - Kruppel family member GLI2 - Transcriptional factor mediating hedgehog signaling	005270	165230	Autosomal dominant	HPE	Unknown
<i>PTCH1</i>	Patched (Drosophila) homologue	000264	601309	Autosomal dominant	HPE	Rare
<i>FGF8</i>	Fibroblast growth factor 8 (androgen induced)	033163	600483	Autosomal recessive	HPE	Rare
<i>FOXH1</i>	Forkhead box H1	003923	603621	Autosomal dominant	HPE	Rare
<i>NODAL</i>	Nodal, mouse, homologue of establishment	018055	601265	Autosomal dominant	HPE	Rare
<i>TDGF1</i>	Teratocarcinoma-derived growth factor 1	003212	187395	Autosomal dominant	HPE	Unknown
<i>DISP1</i>	Dispatched homologue 1 (Drosophila)	005270	607502	Autosomal dominant	HPE	Unknown