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