

Holoprosencephaly Panel

Holoprosencephaly (HPE) is a brain malformation resulting from incomplete separation of the forebrain at 3-5 weeks postconception. Diagnosis is confirmed by brain magnetic resonance imaging (MRI) or computed tomography (CT) imaging. Genetic testing helps families understand the cause of HPE and the risk for recurrence.

Disease Overview

Associated Findings

- Microcephaly (or macrocephaly due to hydrocephalus)
- Central nervous system (CNS) malformations
- Seizures
- Pituitary dysfunction
- Craniofacial abnormalities
- Intellectual disabilities ranging from mild to severe

Types of HPE

Based on degree of brain separation:

- Alobar
- Semilobar
- Lobar
- Middle interhemispheric fusion variant
- Microform HPE

Etiology

Multifactorial, with both genetic and environmental contributions:

- Maternal diabetes mellitus is known environmental risk factor
- Numerical or structural chromosome abnormalities ~25-50%
- Pathogenic single-gene variants

Prevalence

1/250 embryos and 1/10,000-16,000 live births^{1,2,3}

Inheritance

Dependent on etiology

- Autosomal dominant for all genes tested on HPE panel

Genotype-Phenotype Correlation

- Reduced penetrance
- Variable expressivity depending on gene and variant

Test Description

See [Genes Tested](#) table for genes included in the panel.

Tests to Consider

[Holoprosencephaly Panel, Sequencing and Deletion/Duplication 2008848](#)

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Indications for ordering:

To determine etiology of holoprosencephaly (HPE) or determine if parents of an affected individual are carriers (the affected individual should be tested first, if possible).

[Holoprosencephaly Panel, Sequencing and Deletion/Duplication, Fetal 2008863](#)

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Testing strategy:

Because clinical sensitivity of chromosome analysis may approach 50% for HPE, chromosome analysis should be performed before the HPE panel.

[Familial Mutation, Targeted Sequencing 2001961](#)

Method: Polymerase Chain Reaction/Sequencing

- Recommended test for a known familial sequence variant previously identified in a family member.
- A copy of the family member's test result documenting the known familial variant is required.

For chromosome analysis testing, see [Related Tests](#)

Clinical Sensitivity

- 35-45% for familial holoprosencephaly^{4,5,6,7,8,9,10}
- Unknown for sporadic cases

Limitations

- A negative result does not exclude a heritable form of holoprosencephaly.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be affected if the individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
 - Variants outside the coding regions and intron-exon boundaries of the targeted genes
 - Regulatory region variants and deep intronic variants
 - Breakpoints of large deletions/duplications
 - Deletions/duplications in *CDON*, *FGFR1*, and *GLI3*
 - Noncoding transcripts
- The following exons are not sequenced due to technical limitations of the assay: *ZIC2* (NM_007129) 3
- The following may not be detected:
 - Deletions/duplications/insertions of any size by massively parallel sequencing
 - Deletions/duplications less than 1kb in the targeted genes by array
 - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
 - Low-level somatic variants
 - Single exon deletions/duplications in the following exons:
 - *FGF8* (NM_033163) 1; *PTCH1* (NM_001083602) 1; *SHH* (NM_001310462) 2

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate ^a (%)	Analytical Sensitivity (PPA) 95% Credibility Region ^a (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

^aGenes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Genes Tested

Gene	Alias Symbol(s)	MIM Number	Disorder
<i>CDON</i>	ORCAM, CDO, CDON1	608707	Holoprosencephaly 11
<i>DISP1</i>	DISPA, MGC13130, DKFZP434I0428, MGC16796	607502	Holoprosencephaly 10, microform

Gene	Alias Symbol(s)	MIM Number	Disorder
<i>FGF8</i>	AIGF	600483	Hypogonadotropic hypogonadism 6 with or without anosmia
<i>FGFR1</i>	FLT2, KAL2, H2, H3, H4, H5, CEK, FLG, BFGFR, N-SAM, CD331	136350	Hypogonadotropic hypogonadism 2 with or without anosmia Hartsfield syndrome
<i>FOXH1</i>	FAST1	603621	
<i>GLI2</i>	THP2, HPE9, THP1	165230	Holoprosencephaly 9 Culler-Jones syndrome
<i>GLI3</i>	GCPS, PHS, PAP-A, PAPA, PAPA1, PAPB, ACLS, PPDIV	165240	Pallister-Hall syndrome
<i>NODAL</i>		601265	Nodal-related holoprosencephaly
<i>PTCH1</i>	NBCCS, PTCH, BCNS	601309	Holoprosencephaly 7
<i>SHH</i>	HPE3, HLP3, HHG1, SMMCI, TPT, TPTPS, MCOPCB5	600725	Holoprosencephaly 3 solitary median maxillary central incisor
<i>SIX3</i>	HPE2	603714	Holoprosencephaly 2
<i>TGIF1</i>	HPE4, TGIF	602630	Holoprosencephaly 4
<i>ZIC2</i>	HPE5	603073	Holoprosencephaly 5

References

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Related Tests

[Chromosome Analysis, Amniotic Fluid 2002293](#)

Method: Giemsa Band

[Chromosome Analysis, Constitutional Peripheral Blood 2002289](#)

Method: Giemsa Band

[Chromosome Analysis, Products of Conception 2002288](#)

Method: Giemsa Band

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