Holoprosencephaly Panel, Sequencing and Deletion/Duplication

Holoprosencephaly (HPE) is a brain malformation resulting from partial or complete failure of the forebrain (prosencephalon) to divide into hemispheres. This malformation originates from failed midline delineation during early embryonic development. There are multiple types of HPE, detailed in the table below, with variable degrees of severity depending on the level of abnormal division in the brain. This condition can be an isolated finding (nonsyndromic) or associated with a broader syndrome such as Smith-Lemli-Opitz or Kallman syndrome. HPE is associated with multiple etiologies, including structural or numerical chromosomal abnormalities, copy number variations (CNVs), pathogenic variants in single genes, and environmental and teratogenic factors. Additionally, emerging evidence indicates that genetic and environmental modifiers likely play a role in modulating phenotypes.

Featured ARUP Testing

Holoprosencephaly Panel, Sequencing and Deletion/Duplication 2008848

Method: Massively Parallel Sequencing

Use to evaluate for a molecular etiology of HPE in an affected individual

Holoprosencephaly Panel, Sequencing and Deletion/Duplication, Fetal 2008863

Method: Massively Parallel Sequencing

Use to evaluate for a molecular etiology of HPE in an affected pregnancy

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Testing Strategy

Chromosome analysis, with or without reflex to genomic microarray, should be performed as a first-tier test since more than 50% of individuals with HPE may have an associated chromosomal or CNV abnormality.

Clinical Features

- Microcephaly (macrocephaly may be seen in cases of hydrocephalus)
- Central nervous system (CNS) malformations
- Seizures
- Pituitary dysfunction
- Craniofacial abnormalities
- Cognitive disabilities ranging from mild to severe
- Developmental delays

Types of HPE

Type	Range of Findings
Alobar HPE	• Single "monoventricle" • Cyclopia, with or without proboscis • Ethmocephaly or cebocephaly • Anopthalmia or micropthalmia • Bilateral cleft lip
Semilobar HPE	• Fusion of left and right frontal and parietal lobes; interhemispheric fissure only present posteriorly • Closely spaced eyes • Bilateral cleft lip or midline cleft
Lobar HPE	• Fusion of frontal lobes especially ventrally • Separation of most of right and left cerebral hemispheres and lateral ventricles • Closely spaced eyes • Bilateral cleft lip with median process
Middle interhemispheric fusion variant	• Posterior frontal and parietal lobes fail to separate; lack of cleavage of basal ganglia and thalami • Absence of the body of the corpus callosum, but presence of genu and splenium • Closely spaced eyes • Depressed or narrow nasal bridge
Microform HPE	• Presence of HPE-related craniofacial anomalies without structural brain defects on imaging • Microcephaly

Type	Range of Findings
	• Closely spaced eyes • Midface retrusion • Anosmia/hyposmia • Single central maxillary incisor

Genetics

Genes

Sequencing and deletion/duplication: *CDON*, *FGFR1*, *GLI2*, *PTCH1*, *SHH*, *SIX3*, *TGIF1*, *ZIC2*

Etiology

- Pathogenic variants in single genes
- Cytogenetic abnormalities
  - Numerical or structural chromosome anomalies
  - CNV anomalies
- Environmental and teratogenic factors
  - Maternal diabetes mellitus
  - Prenatal alcohol exposure

Prevalence

1/10,000 live births[1,2,3]

Inheritance

Dependent on etiology

For single gene variants: autosomal dominant with reduced penetrance and variable expressivity

Test Interpretation

Clinical Sensitivity

25% for molecular testing of genes included on this panel[4,5,6,7]

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Specificity (NPA)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

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

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Specificity (NPA)
	62.5 (38.3-82.6) [Single exon]	
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

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

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
  - SNVs and small deletions/insertions will not be called in the following exons due to technical limitations of the assay:
    - *FGFR1* (NM_001354367) exon(s) 18
    - *FGFR1* (NM_001354369) exon(s) 18
    - *FGFR1* (NM_001354370) exon(s) 17
    - *ZIC2* (NM_007129) partial exon(s) 3(Chr13:100637736-100637843)
- 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
  - Large duplications less than 3 exons in size
  - Single exon deletions/duplications in the following exons:
    - *FGFR1* (NM_001354367, NM_001354369) 18
    - *FGFR1* (NM_001354370) 17
  - Noncoding transcripts
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes and/or repetitive or homologous regions

Genes Tested

Gene	Alias Symbol(s)	MIM Number	Disorder
CDON	ORCAM, CDO, CDON1	608707	Holoprosencephaly 11
FGFR1	FLT2, KAL2, H2, H3, H4, H5, CEK, FLG, BFGFR, N-SAM, CD331	136350	Hypogonadotropic hypogonadism 2 with or without anosmia Hartsfield syndrome
GLI2	THP2, HPE9, THP1	165230	Holoprosencephaly 9 Culler-Jones syndrome
GLI3	GCPS, PHS, PAP-A, PAPA, PAPA1, PAPB, ACLS, PPDIV	165240	Pallister-Hall syndrome
PTCH1	NBCCS, PTCH, BCNS	601309	Holoprosencephaly 7
SHH	HPE3, HLP3, HHG1, SMMCI, TPT, TPTPS, MCOPCB5	600725	Holoprosencephaly 3 Solitary median maxillary central incisor
SIX3	HPE2	603714	Holoprosencephaly 2
TGIF1	HPE4, TGIF	602630	Holoprosencephaly 4

Gene	Alias Symbol(s)	MIM Number	Disorder
ZIC2	HPE5	603073	Holoprosencephaly 5

References

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