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

**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.
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 \textit{CDON}, \textit{FGFR1}, and \textit{GLI3}
  - Noncoding transcripts
- The following exons are not sequenced due to technical limitations of the assay. \textit{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:
    - \textit{FGF8} (NM_033163) 1; \textit{PTCH1} (NM_001083602) 1; \textit{SHH} (NM_001310462) 2

Analytical Sensitivity

For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA) Estimate(^{a}) (%)</th>
<th>Analytical Sensitivity (PPA) 95% Credibility Region(^{a}) (%)</th>
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</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>99.2</td>
<td>96.9-99.4</td>
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<tr>
<td>Deletions 1-10 bp</td>
<td>93.8</td>
<td>84.3-98.2</td>
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<tr>
<td>Deletions 11-44 bp</td>
<td>100</td>
<td>87.8-100</td>
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<tr>
<td>Insertions 1-10 bp</td>
<td>94.8</td>
<td>86.8-98.5</td>
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<tr>
<td>Insertions 11-23 bp</td>
<td>100</td>
<td>62.1-100</td>
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</tbody>
</table>

\(^{a}\)Genes 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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alias Symbol(s)</th>
<th>MIM Number</th>
<th>Disorder</th>
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</thead>
<tbody>
<tr>
<td>\textit{CDON}</td>
<td>ORCAM, CDO, CDON1</td>
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<td>\textit{DISP1}</td>
<td>DISPA, MGC13130, DKFZP434I0428, MGC16796</td>
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<tr>
<td>Gene</td>
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<td>MIM Number</td>
<td>Disorder</td>
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<td>FGF8</td>
<td>AIGF</td>
<td>600483</td>
<td>Hypogonadotropic hypogonadism 6 with or without anosmia</td>
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<tr>
<td>FGFR1</td>
<td>FLT2, KAL2, H2, H3, H4, H5, CEK, FLG, BFGFR, N-SAM, CD331</td>
<td>136350</td>
<td>Hypogonadotropic hypogonadism 2 with or without anosmia Hartsfield syndrome</td>
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<td>FOXH1</td>
<td>FAST1</td>
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<tr>
<td>GLI2</td>
<td>THP2, HPE9, THP1</td>
<td>165230</td>
<td>Holoprosencephaly 9 Culler-Jones syndrome</td>
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<tr>
<td>GLI3</td>
<td>GCPS, PHS, PAP-A, PAPA, PAPA1, PAPB, ACLS, PPDIV</td>
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<td>Pallister-Hall syndrome</td>
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<td>NODAL</td>
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<td>Nodal-related holoprosencephaly</td>
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<td>PTCH1</td>
<td>NBCCS, PTCH, BCNS</td>
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<td>HPE3, HLP3, HHG1, SMMCI, TPT, TPTPS, MCOPCB5</td>
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<td>SIX3</td>
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<td>TGIF1</td>
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<td>ZIC2</td>
<td>HPE5</td>
<td>603073</td>
<td>Holoprosencephaly 5</td>
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</table>

References


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