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.

### 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

<table>
<thead>
<tr>
<th>Type</th>
<th>Range of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alobar HPE</td>
<td>- Single &quot;monoventricle&quot;&lt;br&gt;- Cyclopia, with or without proboscis&lt;br&gt;- Ethmocephaly or cebocephaly&lt;br&gt;- Anophthalmia or microphthalmia&lt;br&gt;- Bilateral cleft lip</td>
</tr>
<tr>
<td>Semilobar HPE</td>
<td>- Fusion of left and right frontal and parietal lobes; interhemispheric fissure only present posteriorly&lt;br&gt;- Closely spaced eyes&lt;br&gt;- Bilateral cleft lip or midline cleft</td>
</tr>
<tr>
<td>Type</td>
<td>Range of Findings</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lobar HPE</td>
<td>- Fusion of frontal lobes especially ventrally</td>
</tr>
<tr>
<td></td>
<td>- Separation of most of right and left cerebral hemispheres and lateral ventricles</td>
</tr>
<tr>
<td></td>
<td>- Closely spaced eyes</td>
</tr>
<tr>
<td></td>
<td>- Bilateral cleft lip with median process</td>
</tr>
<tr>
<td>Middle interhemispheric fusion variant</td>
<td>- Posterior frontal and parietal lobes fail to separate; lack of cleavage of basal ganglia and thalami</td>
</tr>
<tr>
<td></td>
<td>- Absence of the body of the corpus callosum, but presence of genu and splenium</td>
</tr>
<tr>
<td></td>
<td>- Closely spaced eyes</td>
</tr>
<tr>
<td></td>
<td>- Depressed or narrow nasal bridge</td>
</tr>
<tr>
<td>Microform HPE</td>
<td>- Presence of HPE-related craniofacial anomalies without structural brain defects on imaging</td>
</tr>
<tr>
<td></td>
<td>- Microcephaly</td>
</tr>
<tr>
<td></td>
<td>- Closely spaced eyes</td>
</tr>
<tr>
<td></td>
<td>- Midface retrusion</td>
</tr>
<tr>
<td></td>
<td>- Anosmia/hyposmia</td>
</tr>
<tr>
<td></td>
<td>- Single central maxillary incisor</td>
</tr>
</tbody>
</table>

**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

**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

Analytic Sensitivity

For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytic Sensitivity (PPA) Estimate(^a) (%) and 95% Credibility Region</th>
<th>Analytic Specificity (NPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>&gt;99 (96.9-99.4)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Deletions 1-10 bp(^b)</td>
<td>93.8 (84.3-98.2)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Insertions 1-10 bp(^b)</td>
<td>94.8 (86.8-98.5)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Exon-level(^c) deletions</td>
<td>97.8 (90.3-99.8) [2 exons or larger]</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Exon-level(^c) duplications</td>
<td>83.3 (56.4-96.4) [3 exons or larger]</td>
<td>&gt;99.9</td>
</tr>
</tbody>
</table>

\(^a\)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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alias Symbol(s)</th>
<th>MIM Number</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CDON</strong></td>
<td>ORCAM, CDQ, CDON1</td>
<td>608707</td>
<td>Holoprosencephaly 11</td>
</tr>
</tbody>
</table>
| **FGFR1** | FLT2, KAL2, H2, H3, H4, 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, SMMC1, TPT, TPTPS, MCOPCB5 | 600725 | Holoprosencephaly 3  
Solitary median maxillary central incisor |
| **SIX3** | HPE2 | 603714 | Holoprosencephaly 2 |
| **TGIF1** | HPE4, TGIF | 602630 | Holoprosencephaly 4 |
| **ZIC2** | HPE5 | 603073 | Holoprosencephaly 5 |

## References


## Additional Resources

Related Tests

Chromosome Analysis, Constitutional Blood, with Reflex to Genomic Microarray 2005763  
**Method:** Giemsa Band/Genomic Microarray (Oligo-SNP Array)

Chromosome Analysis, Amniotic Fluid, with Reflex to Genomic Microarray 2008367  
**Method:** Giemsa Band/Genomic Microarray (Oligo-SNP Array)

Cytogenomic SNP Microarray 2003414  
**Method:** Genomic Microarray (Oligo-SNP Array)

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

Chromosome Analysis, Products of Conception, with Reflex to Genomic Microarray 2005762  
**Method:** Giemsa Band/Genomic Microarray (Oligo-SNP Array)

Cytogenomic SNP Microarray - Fetal 2002366  
**Method:** Genomic Microarray (Oligo-SNP Array)