



## Holoprosencephaly Overview

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### Summary

The purpose of this overview is to increase the awareness of clinicians regarding the genetic causes of holoprosencephaly and to inform genetic counseling of family members. The following are the goals of this overview.

#### Goal 1

Describe the clinical characteristics of holoprosencephaly.

#### Goal 2

Review the genetic causes of holoprosencephaly.

#### Goal 3

Provide an evaluation strategy to identify (when possible) the genetic cause of holoprosencephaly in a proband.

#### Goal 4

Inform genetic counseling of family members of an individual with holoprosencephaly.

## 1. Clinical Characteristics of Holoprosencephaly

Holoprosencephaly (HPE), the most common malformation of the forebrain in humans, is a structural anomaly of the brain resulting from failed or incomplete forebrain division in the third to fourth weeks of gestation; the forebrain (prosencephalon) incompletely cleaves into right and left hemispheres, deep brain structures, and the olfactory and optic bulbs and tracts [Gropman & Muenke 2005, Dubourg et al 2007, Grinblat & Lipinski 2019].

While HPE is often first identified on prenatal ultrasound examination [Kousa et al 2018], it is most frequently diagnosed during the newborn period when abnormal facial findings and/or neurologic presentation prompt

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further evaluation. Infants with normal facies or only mildly abnormal facies and either mild or intermediate brain anomalies may not be diagnosed until the first year of life when neuroimaging studies obtained during evaluation for developmental delay and/or failure to thrive reveal HPE [Weiss et al 2018b].

Imaging of the brain by CT scan or MRI defines the type of HPE and identifies associated CNS anomalies [Hahn & Barnes 2010, Griffiths & Jarvis 2016, Kousa et al 2018]. The study of choice is cranial MRI examination, preferably obtained with adequate sedation at a pediatric center experienced in evaluating children for structural brain anomalies. Review of the study by a radiologist and/or other clinician familiar with the clinical subtypes of HPE is essential, as subtle midline anomalies may be missed, and non-HPE-related malformation findings may be mistaken for findings of HPE [Solomon et al 2009b].

## Types of HPE

HPE, a continuum of brain malformations, is traditionally divided into the following types (in decreasing order of severity) (reviewed in Hahn & Barnes [2010]):

**Alobar HPE**, in which there is a single "monoventricle" and no separation of the cerebral hemispheres (Figure 1), is the most severe form. The range of findings includes:

- Cyclopia: single eye or partially divided eye in single orbit with a proboscis above the eye
- Cyclopia without proboscis
- Ethmocephaly: extremely closely spaced eyes but separate orbits with proboscis between the eyes
- Cebocephaly: closely spaced eyes with single-nostril nose
- Closely spaced eyes
- Anophthalmia or microphthalmia
- Premaxillary agenesis with median cleft lip, closely spaced eyes, depressed nasal ridge
- Bilateral cleft lip
- Relatively normal facial appearance (especially in persons with pathogenic variants in *ZIC2*)

**Semilobar HPE**. The left and right frontal and parietal lobes are fused and the interhemispheric fissure is only present posteriorly (Figure 2). The range of findings includes:

- Closely spaced eyes
- Anophthalmia/microphthalmia
- Depressed nasal ridge
- Absent nasal septum
- Flat nasal tip
- Bilateral cleft lip with median process representing the philtrum-premaxilla anlage
- Midline cleft (lip and/or palate)
- Relatively normal facial appearance

**Lobar HPE**. Most of the right and left cerebral hemispheres and lateral ventricles are separated but the frontal lobes, most rostral aspect of the telencephalon, are fused, especially ventrally (Figure 3). The range of findings includes:

- Bilateral cleft lip with median process
- Closely spaced eyes
- Depressed nasal ridge
- Relatively normal facial appearance

**Middle interhemispheric fusion variant** (MIHF/MIHV or syntelencephaly). The posterior frontal and parietal lobes fail to separate, with varying lack of cleavage of the basal ganglia and thalami and absence of the body of the corpus callosum but presence of the genu and splenium of the corpus callosum (Figure 4).

The range of findings includes:

- Closely spaced eyes
- Depressed nasal bridge
- Narrow nasal bridge
- Relatively normal facial appearance

**Septopreoptic type.** Nonseparation is restricted to the septal and/or preoptic regions; described in small case series [Hahn et al 2010].

**Microforms of HPE (also termed "microform HPE")** are clinical subtypes of HPE defined by the presence of HPE-related craniofacial anomalies without structural brain defects on imaging. They may occur in simplex HPE (i.e., a single occurrence of HPE in a family) or in relatives of probands with classic forms of HPE (Figure 5). Their clinical spectrum includes the following:

- Microcephaly [Solomon et al 2009a]
- Single central maxillary incisor [Lacbawan et al 2009, Richieri-Costa & Ribeiro 2010]
- Closely spaced eyes
- Anosmia/hyposmia (resulting from absence of olfactory tracts and bulbs)
- A broad range of ophthalmologic anomalies, including refractive errors, ptosis, microcornea, and coloboma [Pineda-Alvarez et al 2011]
- Sharp, narrow nasal bridge [Solomon et al 2009a]
- Absent superior labial frenulum
- Midface retrusion
- Congenital nasal pyriform aperture stenosis [Ruda et al 2020]
- Developmental delay (variably present). Of note, individuals with classic HPE-spectrum facial features and pathogenic variants seen in severely affected relatives may be intellectually gifted [Lacbawan et al 2009, Solomon et al 2010b, Solomon et al 2012b].

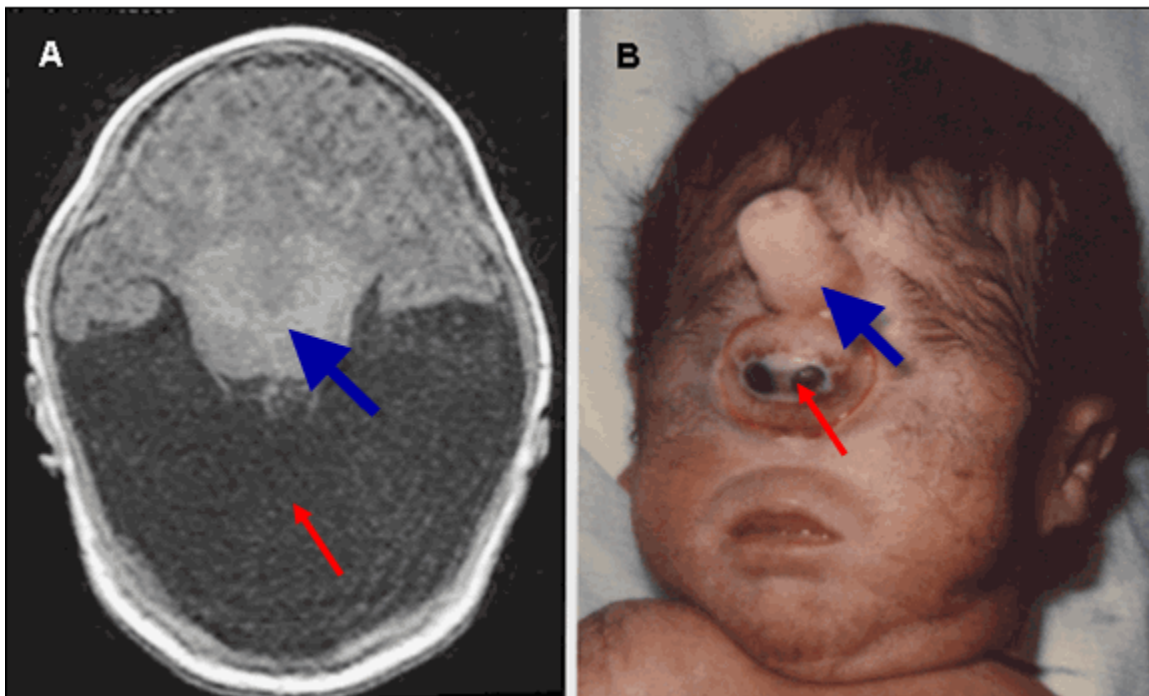
## Other Structural CNS Findings

Other structural CNS findings that may occur with but are not specific to HPE:

- Anomalies of midline structures: undivided thalami, agenesis of the corpus callosum (OMIM 217990), callosal dysgenesis [Kidron et al 2016], absent septum pellucidum, and absent or hypoplastic olfactory bulbs and tracts (arrhinencephaly) and optic bulbs and tracts
- Macrocephaly secondary to hydrocephalus
- Dandy-Walker malformation
- Neuronal migration anomalies
- Abnormal circle of Willis
- Caudal dysgenesis

## Craniofacial Anomalies

The continuum of craniofacial anomalies, present in approximately 80% of individuals with HPE, includes cyclopia, synophthalmia, or a proboscis at the severe end and normal facies in individuals who have, but are not expressing, an HPE pathogenic variant inherited in an autosomal dominant manner. Common subtle facial features in individuals without obvious craniofacial findings include microcephaly (although hydrocephalus can result in macrocephaly), closely spaced eyes (also known as hypotelorism; potentially severe), depressed nasal ridge, and cleft lip and/or palate. A single maxillary central incisor may be present; although a nonspecific finding, it is a distinctive microform in autosomal dominant HPE [Lacbawan et al 2009, Richieri-Costa & Ribeiro 2010].



**Figure 1.** Alobar HPE

A. MRI of alobar holoprosencephaly (HPE), the most severe form of HPE, characterized by an enlarged midline monoventricle (holoventricle, red/thin arrow) with fusion of the frontal lobes and the midline gray matter structures (thalami and basal ganglia, blue/thick arrow). Typically, the corpus callosum and the third ventricle are absent.

B. Facial features seen in the alobar HPE spectrum, characterized by a single eye-like structure (cyclopia, red/thin arrow) and an overriding nose-like structure (proboscis, blue/thick arrow)

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Of note, subtle facial anomalies in mildly affected family members can be easily overlooked [Lacbawan et al 2009, Solomon et al 2009a].

Malformations of the nose include complete absence, agenesis of the nasal cartridge, and proboscis (flat nose with a single central nostril without nasal bones).

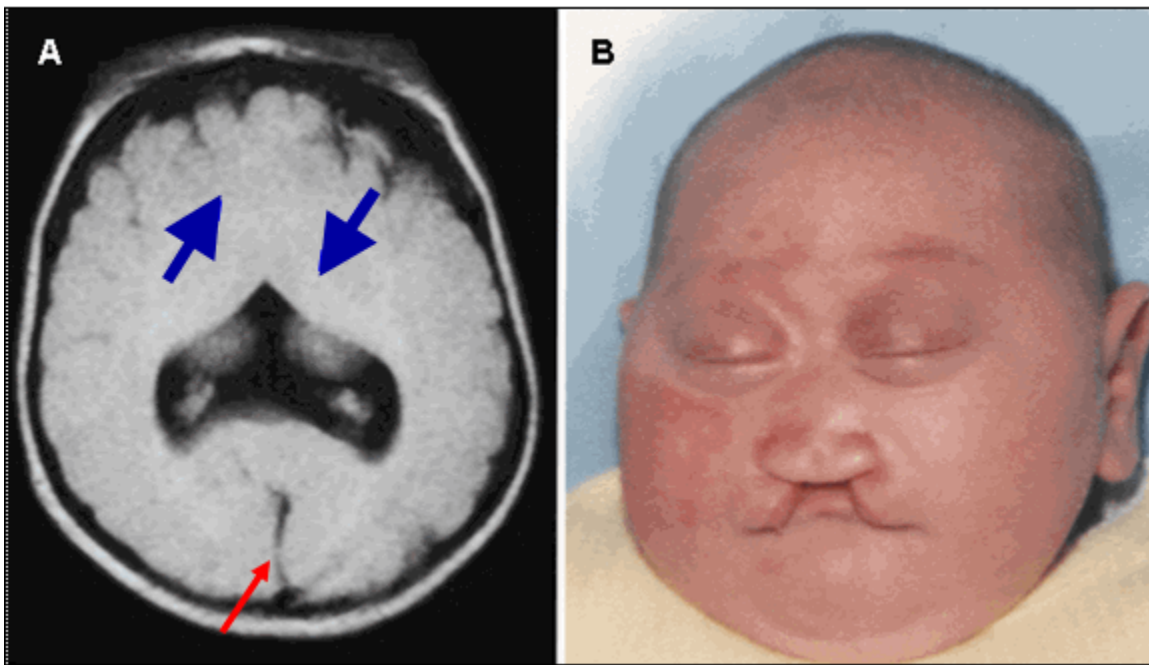
Palatal anomalies include various midline and lateral clefts, midline palatal ridge, bifid uvula, high-arched palate, and absence of the superior labial frenulum [Solomon et al 2010a].

The extremely variable phenotypic expression occurs both in simplex HPE (i.e., a single occurrence in a family) and among members of the same family with an inherited form of HPE.

## Clinical Manifestations of HPE

Clinical manifestations (reviewed in Levey et al [2010] and Solomon et al [2010a]) commonly observed in children with HPE include the following:

- **Developmental delay** is present in all individuals with the HPE spectrum of CNS anomalies. The degree of delay is variable, correlating with the severity of the brain malformation, but tends to be severe.
- **Seizures** are common, and may be difficult to control.
- **Hydrocephalus** can occur, and may result in macrocephaly, rather than the more commonly observed microcephaly.
- **Neural tube defects** occur in a small proportion of individuals.



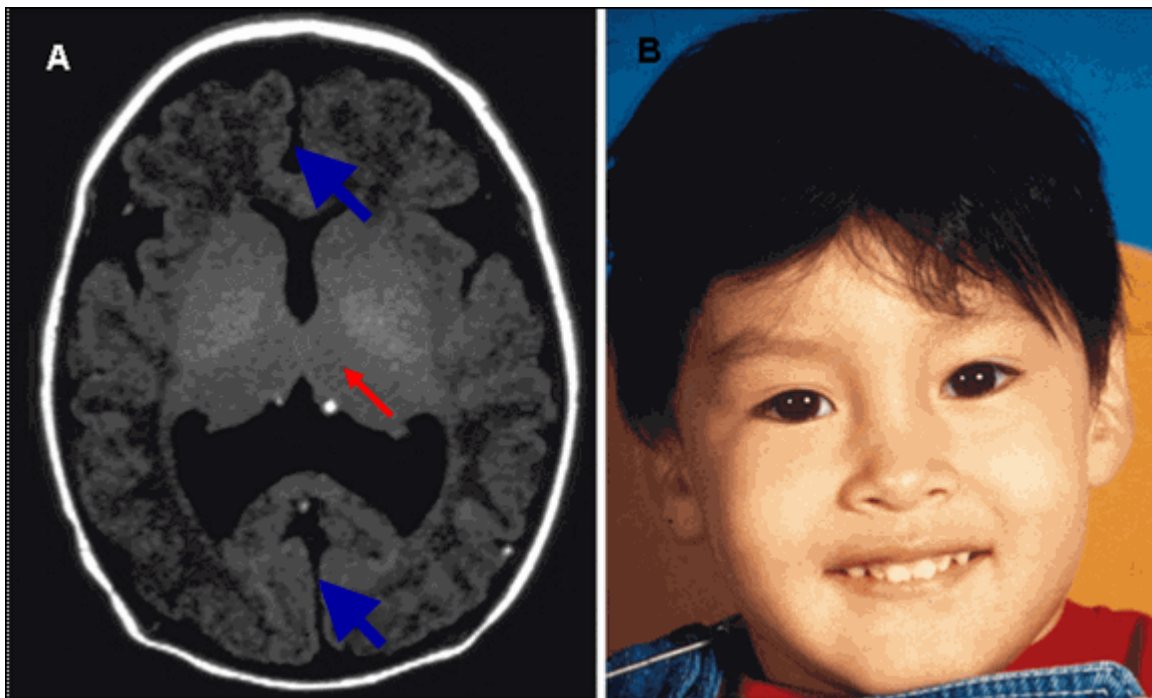
**Figure 2.** Semilobar HPE

A. MRI showing semilobar HPE. Note fusion of the frontal lobes, but presence of some septation posteriorly with presence of a falx and interhemispheric fissure (red/thin arrow). The splenium of the corpus callosum is present but more anterior portions are usually absent. A small, partially formed third ventricle is seen. More significant fusion of anterior brain structures (cortex, basal ganglia, thalamus) persists in this variant (blue/thick arrows). A dorsal cyst may be seen. In mild cases, lack of frontal horn development distinguishes this from the lobar type.

B. Note microcephaly, closely spaced eyes, depressed nasal ridge with cleft lip.

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- **Hypothalamic and brain stem dysfunction** may lead to swallowing difficulties and instability of temperature, heart rate, and respiration.
- **Pituitary dysfunction** is manifest by partial or complete panhypopituitarism with abnormal function of any or all of the anterior and/or posterior pituitary hormones, though central diabetes insipidus is by far the most common finding in persons with nonchromosomal, nonsyndromic HPE [Lacbawan et al 2009, Solomon et al 2010a].
- **Short stature and failure to thrive** are common, especially in more severely affected children. Growth hormone deficiency and/or chromosome anomalies may in part be responsible for poor growth in some individuals.
- **Feeding difficulties** may be a major problem in children with HPE. At least part of the difficulty may derive from axial hypotonia, poor suck as a result of neurologic complications, lethargy, seizures and their effects, side effects of medications, and lack of interest. Often gastroesophageal reflux, choking, and gagging occur with feeds. Additional common problems include slowness in eating, frequent pauses, and frank vomiting with risk of aspiration. Oral-sensory dysfunction may affect feeding especially when associated with textural aversion and labial and lingual weakness. Children with cleft lip and/or palate often have additional difficulties with oral feeding.
- **Excessive intestinal gas/colic**, irritability, and constipation frequently occur [Levey et al 2010].
- **Aspiration pneumonia** can be a complication of poor coordination of swallowing.
- **Erratic sleep patterns** can occur.



**Figure 3.** Lobar HPE

A. MRI in axial plane depicting lobar HPE, the least severe of the major types of HPE. The cerebral hemispheres are separated (blue/thick arrows); the ventricles are misshapen as a result of absence of the septum pellucidum. The posterior portion of the corpus callosum may be normally formed. There is a varying degree of fusion of the midline gray structures (thalami, basal ganglia, red/thin arrow).

B. Relatively normal facial appearance of a child with lobar HPE resulting from a pathogenic variant in *ZIC2*. Subtle dysmorphisms include narrow forehead (not apparent in this photo), upslanted palpebral fissures, relatively large ears, a relatively depressed nasal bridge, and a broad and well-defined philtrum.

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**Life expectancy.** A common misperception is that children with HPE do not survive beyond early infancy. While this is the case for the most severely affected children, a significant proportion of more mildly affected children (as well as some severely affected children) survive past age 12 months. In fact, a proportion of individuals with HPE of various subtypes, including severe subtypes, survive until adulthood.

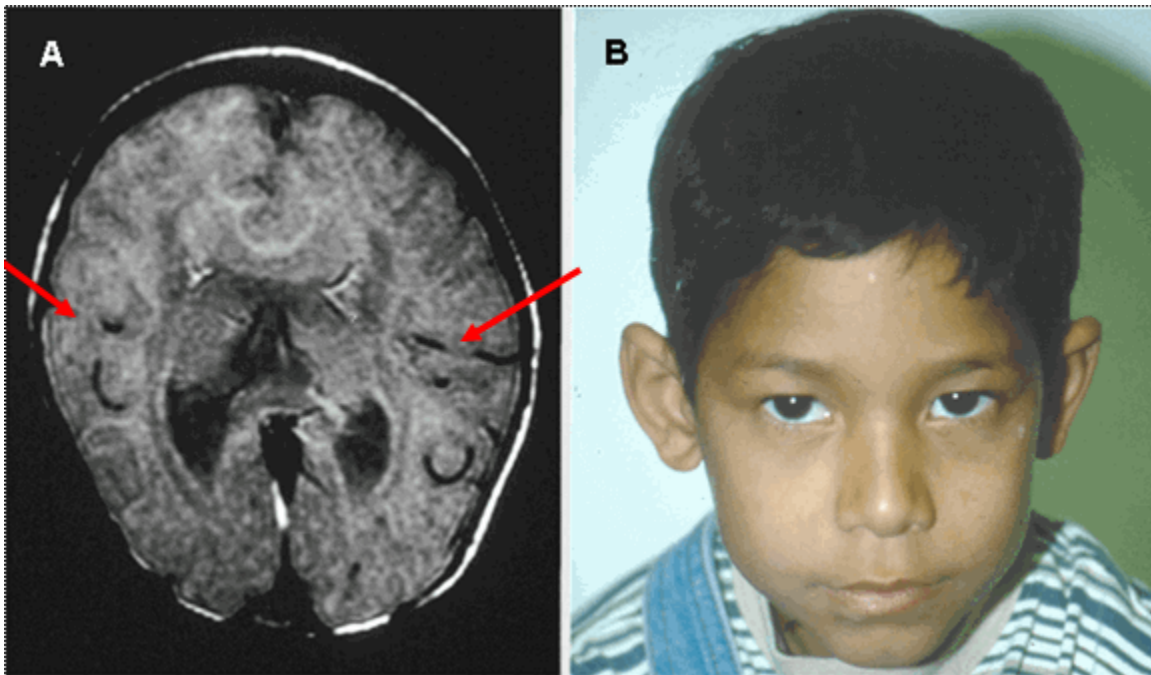
The longer survival may be on account of recent advances in diagnostic methods, including brain imaging methods that allow for early detection of both severe and mild malformations. Improvement in the management of HPE over time may have also contributed to longer survival [Levey et al 2010, Pineda-Alvarez et al 2010, Weiss et al 2018b].

The distribution of HPE subtypes appears to be similar among children, adolescents, and adults, with semilobar HPE representing approximately 50% of HPE in both children and adults. The exception is alobar HPE, which appears to be less frequent in adults than children [Weiss et al 2018a].

Among affected individuals with abnormal chromosome complement, an inverse relationship exists between the severity of the facial phenotype and length of survival.

- Infants with cyclopia or ethmocephaly generally do not survive beyond age one week.
- Approximately 85% of adults with HPE have a mild or nonclassic facial phenotype [Weiss et al 2018a].

Among affected adolescents and adults, sensorineural hearing loss is found in approximately 30% and cortical vision impairment in approximately 20% [Weiss et al 2018a].



**Figure 4.** Middle interhemispheric fusion (MIHF)

A. MRI in axial plane depicting middle interhemispheric variant of HPE in which the anterior portions of the frontal lobes and the occipital lobes are well separated. The sylvian fissures are oriented nearly vertically and are abnormally connected across the midline over the vertex of the brain (red/thin arrows). The genu and splenium of the corpus callosum appear normally formed, but the callosal body is typically absent. The hypothalamus and lentiform nuclei are normally separated; however, the caudate nuclei and the thalami remain incompletely separated.

B. The facial appearance is usually normal.

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Of note, 60% of adolescent and adult survivors have severe involvement: they are nonambulatory and nonverbal with minimal hand function, and full dependence on caregivers [Weiss et al 2018a]. There is a correlation between the degree of developmental delay and the severity of the brain malformation or HPE subtype [Levey et al 2010, Weiss et al 2018a].

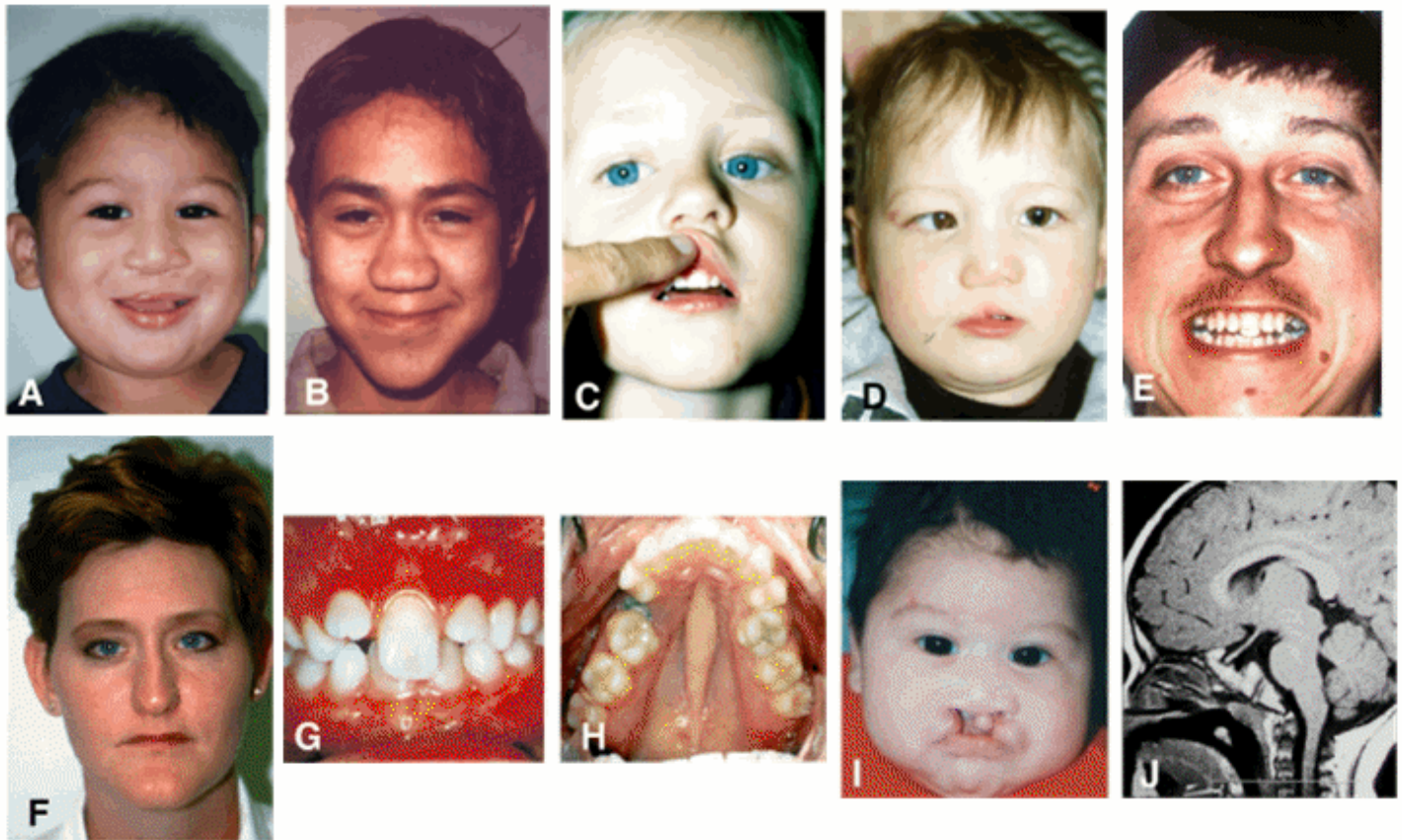
## 2. Genetic Causes of Holoprosencephaly

### Chromosome Abnormalities with Holoprosencephaly

Approximately 25%-50% of individuals with HPE have a chromosome abnormality. Chromosome abnormalities are nonspecific and either numeric or structural, and can involve any chromosome [Dubourg et al 2018].

Individuals with HPE and a normal chromosome complement cannot be distinguished from those with an abnormal chromosome complement based on craniofacial abnormality or HPE subtype; however, individuals with HPE caused by a chromosome abnormality are more likely to have other organ system involvement, resulting in a more severe clinical course in most.

**Numeric chromosome abnormalities.** Trisomy 13, the most common cause of HPE, is observed in 40%-60% of HPE of all causes and about 75% of HPE caused by chromosome abnormalities. Birth prevalence of trisomy 13 is 1:5000. Arrhinencephaly is seen in about 70% of individuals with trisomy 13.



**Figure 5.** Microforms of holoprosencephaly (HPE) spectrum with milder craniofacial anomalies in the absence of neurologic findings

- A. Premaxillary agenesis with repaired bilateral clefts of the lip
- B. Absence of nasal bones and cartilage with a narrow nasal bridge
- C. Single central maxillary incisor
- D. Premaxillary agenesis, repaired unilateral cleft of the lip, and bilateral iris coloboma
- E. Close-up showing single central maxillary incisor
- F. This woman has a child with HPE. She has closely spaced eyes and narrow nasal bridge as her only manifestations.
- G. Single central incisor
- H. Prominent midline palatal ridge
- I. Premaxillary agenesis with bilateral cleft lip and palate in a child with pituitary hypoplasia and growth hormone deficiency
- J. Sagittal T<sub>1</sub>-weighted MRI showing pituitary hypoplasia (red arrow)

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The other common aneuploidies associated with HPE include trisomy 18 and triploidy. Various other aneuploidies have been reported [Kagan et al 2010, Solomon et al 2010c, Petracchi et al 2011, Toufaily et al 2016, Rosa et al 2017].

**Structural chromosome abnormalities** associated with HPE have been reported in virtually all chromosomes. The most frequent are deletions or duplications involving various regions of 13q, and del(18p), del(7)(q36), dup(3)(p24-pter), del(2)(p21), and del(21)(q22.3) [Hu et al 2018]. Many of these regions contain genes known to be associated with autosomal dominant nonsyndromic HPE (Tables 2a, 2b).

**Pathogenic copy number variations (CNVs).** Chromosomal microarray (CMA) includes array-based comparative genomic hybridization (array CGH) and SNP array. CMA has identified pathogenic CNVs



(including loci already known to be associated with HPE) in 10% of all individuals with HPE. Note that CNV detection rates may vary by testing laboratory and methodology [Dubourg et al 2018, Hu et al 2018].

## Monogenic Syndromes with Holoprosencephaly as an Occasional Finding

Approximately 18%-25% of individuals with HPE have a pathogenic variant in a single gene causing syndromic HPE. At least 25 different conditions in which HPE is an occasional finding have been described; the majority of these disorders are rare. Some of the more common are summarized in Table 1 [Kruszka & Muenke 2018].

**Table 1.** Syndromes with Holoprosencephaly as an Occasional Finding: Monogenic Causes

MOI	Gene	Disorder	Clinical Subtype(s) of HPE	Craniofacial Findings	Other Key Features / Comment	Citation
AD	<i>CDON</i>	Steinfeld syndrome (OMIM 184705)	Microform HPE		CHD, absent gallbladder, renal dysplasia, & radial defects	Jones et al [2016]
	<i>FGFR1</i>	Kallman syndrome 2 (See Isolated GnRH Deficiency.)		Cleft lip & palate	Assoc of isolated hypogonadotropic hypogonadism & HPE	Dubourg et al [2016]
		Hartsfield syndrome		HPE-related craniofacial features	Unique assoc of HPE & ectrodactyly	Simonis et al [2013], Hong et al [2016], Palumbo et al [2019]
AR	<i>CENPF</i>	Strømme syndrome	Alobar HPE	Microcephaly	Intestinal atresia & variable ocular abnormalities	Alghamdi et al [2020]
	<i>DHCR7</i>	Smith-Lemli-Opitz syndrome	Alobar HPE	Microcephaly, short nose & anteverted nares	~5% of affected persons have HPE.	Weaver et al [2010]

AD = autosomal dominant; AR = autosomal recessive; CHD = congenital heart disease; HPE = holoprosencephaly; MOI = mode of inheritance

## Single-Gene Disorders with Isolated (Nonsyndromic) Holoprosencephaly

The nonsyndromic forms of HPE best understood at a molecular genetic level are inherited in an autosomal dominant manner (see Tables 2a, 2b).

The phenotype of individuals with pathogenic variants in genes associated with nonsyndromic HPE is extremely variable even within the same family, ranging from alobar HPE with cyclopia to clinically normal [Solomon et al 2010a, Solomon et al 2010b, Dubourg et al 2018].

In the majority of individuals with HPE, a correlation exists between the facial anomalies and the gene involved and/or type of pathogenic variant (see Figure 6 and Types of HPE). However, it is important to note that in many cases this correlation cannot be made.

**Table 2a.** Nonsyndromic Holoprosencephaly: Most Common Monogenic Causes

Gene <sup>1</sup>	% of All Nonsyndromic HPE	Craniofacial Findings	Other Key Features / Comment	Selected OMIM Entries
<i>SHH</i>	5.4%-5.9% <sup>2</sup>	Spectrum of HPE-related craniofacial features	<ul style="list-style-type: none"> <li>Affected persons may be part of large kindreds segregating the variant; many of these families are not identified until ascertainment of the severely affected proband. <sup>3</sup></li> <li>Renal/urinary anomalies may be more common than in those w/pathogenic variants in other HPE genes. <sup>4</sup></li> </ul>	142945
<i>ZIC2</i>	4.8%-5.2% <sup>2</sup>	Bitemporal narrowing, upslanted palpebral fissures, large ears, short nose w/anteverted nares, & broad & deep philtrum <sup>3</sup>	<ul style="list-style-type: none"> <li>Renal/urinary anomalies may be more common than in those w/pathogenic variants in other HPE genes. <sup>4</sup></li> <li>Pathogenic variants are more frequently <i>de novo</i> than are variants in other HPE genes &amp; appear to have high penetrance w/relatively few mildly manifesting persons. <sup>5</sup></li> </ul>	609637
<i>SIX3</i>	~3% <sup>6</sup>	Spectrum of HPE-related craniofacial features	<ul style="list-style-type: none"> <li>Affected persons may be part of large kindreds segregating the variant; many of these families are not identified until ascertainment of the severely affected proband. <sup>3</sup></li> <li>May be assoc w/more severe types of HPE</li> </ul>	157170
<i>TGIF1</i>	<1% <sup>2</sup>	Spectrum of HPE-related craniofacial features	May demonstrate the entire spectrum of severity <sup>7</sup>	142946

AD = autosomal dominant; AR = autosomal recessive; CHD = congenital heart disease; DD = developmental delay; HPE = holoprosencephaly; LOF = loss of function; MOI = mode of inheritance

1. Genes are listed in order of most commonly involved.

2. Roessler et al [2012], Dubourg et al [2018]

3. Solomon et al [2009a], Mercier et al [2011], Solomon et al [2012a]

4. Solomon et al [2010a], Solomon et al [2010b], Mercier et al [2011]

5. Solomon et al [2010a]

6. Dubourg et al [2018]

7. Solomon et al [2010b], Keaton et al [2010], Dubourg et al [2018]

**Table 2b.** Nonsyndromic Holoprosencephaly: Less Common Monogenic Causes

Gene <sup>1</sup>	% of All Nonsyndromic HPE	Craniofacial Findings	Other Key Features / Comment	Selected OMIM Entries
<i>CDON</i>	Rare	Rare	Range of classic HPE-spectrum features described in several unrelated persons <sup>2</sup>	614226
<i>CNOT1</i>	<1.5%	Microtia, microcephaly, epicanthal folds, long philtrum	<ul style="list-style-type: none"> <li>Semilobar HPE described in 2 unrelated persons</li> <li>Neonatal diabetes mellitus requiring insulin may be a feature.</li> <li>Pancreatic exocrine insufficiency may be present.</li> <li>May be assoc w/sensorineural &amp; conductive hearing loss w/ossicle anomalies <sup>3</sup></li> </ul>	
<i>DISP1</i>	<1.2%	Bilateral cleft lip/palate, hypotelorism, single central maxillary incisor	Facial features may be consistent w/HPE-spectrum anomalies w/o corresponding brain anomalies. <sup>4</sup>	607502
<i>DLL1</i>	<1%	Rare	Facial features may be consistent w/HPE-spectrum anomalies. <sup>5</sup>	606582

Table 2b. continued from previous page.

Gene <sup>1</sup>	% of All Nonsyndromic HPE	Craniofacial Findings	Other Key Features / Comment	Selected OMIM Entries
<i>FGF8</i>	<2.2%	Spectrum of HPE-related craniofacial features	Range of classic HPE-spectrum features described in several unrelated persons <sup>6</sup>	600483
<i>FGFR1</i>	~ 1.2%	Spectrum of HPE-related craniofacial features	Isolated HPE <sup>7</sup>	
<i>KMT2D</i>	Rare	Spectrum of HPE-related craniofacial features	Range of classic HPE-spectrum features described in 2 unrelated persons <sup>8</sup>	
<i>PPP1R12A</i>	Rare	Wide spectrum of craniofacial features	HPE, urogenital malformations, & DD <sup>9</sup>	
<i>RAD21</i>	Rare	Spectrum of HPE-related craniofacial features	<ul style="list-style-type: none"> <li>Range of HPE-spectrum features described in 5 unrelated persons.</li> <li>May be assoc w/mild forms of HPE <sup>10</sup></li> </ul>	
<i>SMC1A</i>	Rare	Spectrum of HPE-related craniofacial features	Range of classic HPE-spectrum features described in 5 unrelated females <sup>10</sup>	
<i>SMC3</i>	Rare	HPE-related craniofacial features	HPE-spectrum features described in 1 person w/ semilobar HPE <sup>10</sup>	
<i>STAG2</i>	Rare	Spectrum of HPE-related craniofacial features	Range of classic HPE-spectrum features described in 6 unrelated females <sup>10</sup>	
<i>STIL</i>	Rare	Rare	<ul style="list-style-type: none"> <li>May present w/a range of classic HPE-spectrum features</li> <li>AR inheritance in all reported persons <sup>11</sup></li> </ul>	

AR = autosomal recessive; DD = developmental delay; HPE = holoprosencephaly

1. Genes are listed in alphabetic order.

2. Bae et al [2011]

3. Kruszka et al [2019a]

4. Roessler et al [2009], Dubourg et al [2016]

5. Dupé et al [2011], Dubourg et al [2016]

6. Arauz et al [2010], Dubourg et al [2016], Hong et al [2018]

7. Dubourg et al [2016]

8. Tekendo-Ngongang et al [2019]

9. Hughes et al [2020]; see [PPP1R12A-Related Urogenital and/or Brain Malformation Syndrome](#).

10. Kruszka et al [2019b]

11. Kakar et al [2015], Mouden et al [2015]

Variants in other candidate genes including *FOXH1*, *GAS1*, *NODAL*, *PTCH1*, *SUFU*, and *CRIPTO* (formerly *TDGF1*) have seldom been reported in individuals with nonsyndromic HPE. However, because investigations of several large HPE cohorts have failed to reproduce these findings, more data may be needed to confirm the possible role of these genes in HPE pathogenesis.

Although *GLI2* pathogenic variants were described as a cause of HPE, it has become clear that *GLI2* variants do not cause HPE, but rather a distinct phenotype characterized by pituitary anomalies, polydactyly, and subtle facial features (sometimes similar to HPE facial features) consistent with Culler-Jones syndrome (OMIM 615849) [Bear et al 2014, Bear & Solomon 2015].

## Holoprosencephaly of Unknown Cause

**Autosomal dominant vs multifactorial.** Microtia-anotia (OMIM 600674) and other anomalies



**Figure 6.** Facial findings in holoprosencephaly (HPE)

- A. Alobar HPE with cyclopia and proboscis above the single eye
- B. Alobar HPE with cebocephaly and closely spaced eyes
- C. Semilobar HPE with microcephaly, premaxillary agenesis, and midline cleft lip and palate
- D. Semilobar HPE with closely spaced eyes, midface retrusion, and mild dysmorphism

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#### Unknown mode of inheritance [Kruszka & Muenke 2018]

- Caudal dysgenesis (OMIM 600145)
- Pseudotrisonomy 13 (OMIM 264480)
- Genoa syndrome (OMIM 601370)
- Brachial amelia, cleft lip, and holoprosencephaly (OMIM 601357)

### 3. Evaluation Strategies to Identify the Genetic Cause of Holoprosencephaly in a Proband

Establishing a specific genetic cause of holoprosencephaly (HPE) can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling.

Evaluations to determine a specific genetic cause of holoprosencephaly usually involve the following.

**Prenatal history to identify possible environmental causes.** The most common teratogen in humans known to cause HPE is diabetes mellitus. While both gestational and pre-gestational diabetes are risk factors for HPE, pre-gestational diabetes requiring insulin confers the highest (>10-fold increased) HPE risk [Johnson & Rasmussen 2010, Tinker et al 2019].

**Physical examination.** A detailed physical examination should be conducted with special emphasis on extracranial features, especially those associated with syndromic forms of HPE (see Table 1) [Kruszka & Muenke 2018]. Of note, it is not uncommon to find extracranial anomalies in individuals with nonsyndromic HPE (see Tables 2a, 2b) [Martinez et al 2018].

**Family history.** A three-generation family history should be taken with attention to pregnancy loss, neonatal deaths, and relatives with manifestations of holoprosencephaly and/or developmental delay with documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing.

**Focused examination of the parents** and apparently normal sibs (whenever possible) to identify milder manifestations of HPE.

**Molecular genetic testing.** Approaches can include a combination of gene-targeted testing (multigene panel or single-gene testing) and comprehensive genomic testing (chromosomal microarray analysis, genome sequencing, exome sequencing, or exome array). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

- **Chromosomal microarray analysis (CMA)** using oligonucleotide or SNP arrays detects genome-wide large deletions/duplications in all forms of HPE, including apparently nonsyndromic HPE and HPE with associated anomalies. CMA has been successful in identifying pathogenic variants in up to 14% of individuals with HPE who have a normal karyotype and no causative gene identified on multigene panel testing.
- **Chromosome analysis.** Diagnostic methods for detecting chromosome abnormalities in individuals with HPE are not different from those routinely used in the investigation of numeric and structural cytogenetic abnormalities in those with other genetic conditions or birth defects. Recommended methods include: G-banding karyotype and CMA [Kruszka et al 2018]. If there is clinical suspicion for trisomy 13, a karyotype should be done first; otherwise, a CMA should be done first [Pineda-Alvarez et al 2010, Solomon et al 2010c], including trisomy 13.
- **Single-gene testing.** When a specific syndromic cause of HPE is considered (Table 1), sequence analysis of the gene of interest is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used and the gene involved, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to consider gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes some or all of the genes listed in Tables 1, 2a, and 2b is most likely to identify the genetic cause of HPE while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of some of the genes associated with HPE, some panels may not include all the genes mentioned in this overview. (3) In some laboratories, panel options

may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant or mendelian inheritance – exome array (when clinically available) may be considered to detect multiexon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

## 4. Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

If a genetic etiology (chromosome abnormality, monogenic condition, or pathogenic variant in a HPE-associated gene) is established in a proband with HPE, specific counseling for recurrence risk is indicated [Hadley et al 2018].

### Chromosome Abnormality – Risk to Family Members

#### Parents of a proband

- Parents of a child with a numeric chromosome abnormality (e.g., trisomy or triploidy) are expected to be chromosomally and phenotypically normal.
- Parents of a child with a structural unbalanced chromosome rearrangement (e.g., deletion, duplication) are at risk of having a balanced chromosome rearrangement and should be offered chromosome analysis.

#### Sibs of a proband

- Sibs of a child with a numeric chromosome abnormality are at a slightly increased risk of having a similar chromosome abnormality (depending on the specific abnormality and the age of the mother) with a similar or different phenotype.
- The risk to the sibs of a child with a structural unbalanced chromosome rearrangement depends on the chromosome status of the parents:
  - If neither parent has a structural rearrangement, the risk to sibs is negligible.
  - If a parent has a balanced structural rearrangement, the risk is increased and depends on the specific rearrangement and possibly other variables.

**Offspring of a proband.** Individuals with HPE and a chromosome rearrangement are unlikely to reproduce.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has a chromosome rearrangement, the parent's family members are at risk and can be offered chromosome analysis.

## Autosomal Dominant Inheritance – Risk to Family Members

### Parents of a proband

- Many individuals diagnosed with autosomal dominant nonsyndromic HPE (Tables 2a, 2b) inherited a pathogenic variant from a heterozygous parent who may or may not have HPE-spectrum anomalies [Mouden et al 2015].
- Some individuals with autosomal dominant nonsyndromic HPE may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by a *de novo* variant is estimated at 10%-30% for *SHH*, 70%-80% for *ZIC2*, and 10%-20% for *SIX3* [Lacbawan et al 2009, Solomon et al 2010a, Solomon et al 2010b, Weiss et al 2018a].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant. Recommendations may also include evaluation of the parents for mild manifestations of HPE.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent.\* Germline mosaicism has been suggested based on the finding of several families [Nanni et al 1999, Brown et al 2001, Lacbawan et al 2009, Solomon et al 2010a; Solomon et al 2010b].  
\* Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.
- The family history of some individuals diagnosed with HPE may appear to be negative because of reduced penetrance and failure to recognize the disorder in family members; this is particularly true for families with HPE caused by pathogenic variants in *SIX3* [Stokes et al 2018]. In some cases, a single mild manifestation is the only clue that a given individual has autosomal dominant nonsyndromic HPE and thus is at increased risk of having affected offspring. Note, however, that none of the mild manifestations is pathognomonic for HPE and each can occur as an isolated finding apart from the HPE spectrum. Therefore, an apparently negative family history cannot be confirmed unless appropriate molecular genetic testing has been performed on the parents of the proband.

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the parents:

- If a parent is affected or has an HPE pathogenic variant (with or without clinical manifestations), the risk to sibs of inheriting the variant is 50%. Empiric studies indicate that sibs who inherit a pathogenic variant have a 20% risk for HPE, 15% risk for an HPE microform, and a 15% likelihood of a normal phenotype.
- If the proband has a known HPE pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is low, but slightly greater than that of the general population because of the possibility of parental germline mosaicism [Nanni et al 1999, Brown et al 2001, Lacbawan et al 2009, Solomon et al 2010a, Solomon et al 2010b].
- If the parents have not been tested for the HPE pathogenic variant in the proband but are clinically unaffected and the family history is negative, the risk to the sibs of the proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for HPE because of the possibility of reduced penetrance in a parent or parental germline mosaicism.

### Offspring of a proband

- Every child of an individual with a pathogenic variant for autosomal dominant nonsyndromic HPE has a 50% chance of inheriting the pathogenic variant.

- Although severely affected individuals do not reproduce, individuals with mild forms and microforms of autosomal dominant HPE may do so. The clinical manifestations and severity in offspring may range from mild to severe.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent is affected or has a pathogenic variant, the parent's family members may be at risk.

## Autosomal Recessive Inheritance – Risk to Family Members

### Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *STIL* pathogenic variant; see Tables 2a, 2b).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *STIL* pathogenic variant and to allow reliable recurrence risk assessment. (Although a *de novo* pathogenic variant has not been reported in *STIL*-HPE to date, *de novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic.

### Sibs of a proband

- If both parents are known to be heterozygous for a *STIL* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic.

**Offspring of a proband.** To date, individuals with *STIL*-HPE are not known to reproduce.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of a *STIL* pathogenic variant.

**Carrier detection.** Carrier testing for at-risk relatives requires prior identification of the *STIL* pathogenic variants in the family.

## X-Linked Inheritance – Risk to Family Members

### Parents of a female proband

- A female proband with X-linked HPE caused by a pathogenic variant in *STAG2* or *SMC1A* may have inherited a pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*.
- To date, the majority of individuals with X-linked HPE are female, represent simplex cases (i.e., a single occurrence in the family), and have the disorder as the result of a *de novo* pathogenic variant.
- Molecular genetic testing is recommended for both parents of a female proband.
- If the *STAG2* or *SMC1A* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the proband most likely has a *de novo* pathogenic variant. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism.
- Note: The mother of a proband who is found to be heterozygous for a *STAG2* or *SMC1A* pathogenic variant may have favorable skewed X inactivation that results in her being mildly affected or unaffected.

### Parents of a male proband

- If a male is the only affected family member (i.e., a simplex case), the mother may be heterozygous or the affected male may have a *de novo* pathogenic variant, in which case the mother is not heterozygous. To



date, X-linked HPE has been reported in only one male; the affected male had the disorder as the result of a *de novo* *STAG2* truncating variant [Aoi et al 2019]; *SMC1A*-HPE has not been reported in a male proband.

- Molecular genetic testing is recommended for the mother of a male proband.
- The father of an affected male will not have the disorder nor will he be hemizygous for an X-linked HPE-causing pathogenic variant; therefore, he does not require further evaluation/testing.

**Sibs of a female proband.** The risk to sibs depends on the genetic status of the parents:

- If the mother of the proband has a *STAG2* or *SMC1A* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Females who inherit the pathogenic variant are at high risk of developing HPE, although skewed X inactivation may result in variable phenotypic expression.
  - Because the large majority of individuals affected with X-linked HPE identified to date are females, it is very likely that males who inherit *STAG2* or *SMC1A* variants either do not survive or present a severe HPE phenotype [Aoi et al 2019, Kruszka et al 2019b].
- If the father of the proband has a *STAG2* or *SMC1A* pathogenic variant, he will transmit it to all his daughters and none of his sons.
- If the proband represents a simplex case and if the *STAG2* or *SMC1A* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of parental germline mosaicism.

**Sibs of a male proband.** The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a *STAG2* or *SMC1A* pathogenic variant, the chance of transmitting it in each pregnancy is 50% (see **Sibs of a female proband**).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *STAG2* or *SMC1A* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is greater than that of the general population because of the possibility of maternal germline mosaicism.

**Offspring of a proband**

- Each child of a female proband with X-linked HPE has a 50% chance of inheriting the *STAG2* or *SMC1A* pathogenic variant. Female probands with frank HPE are very unlikely to reproduce.
- Each daughter of a male proband with X-linked HPE has a 50% chance of inheriting the *STAG2* or *SMC1A* pathogenic variant. Surviving male probands with frank HPE are very unlikely to reproduce.

**Other family members.** The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected or has a *STAG2* or *SMC1A* pathogenic variant, the parent's family members may be at risk.

## Prenatal Testing and Preimplantation Genetic Testing

### High-Risk Pregnancies

**Molecular genetic testing.** Once the HPE-causing pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk for HPE and preimplantation genetic testing are possible.

**Fetal ultrasound examination.** For families with nonsyndromic HPE and no identifiable etiology, alobar HPE can be diagnosed by prenatal ultrasound examination between ten to 14 weeks of gestation based on abnormal facial morphology (as seen in many cases) and absence of the normal configuration of the choroid plexuses

within the lateral ventricles, called "butterfly sign" [Kousa et al 2018, Calloni et al 2019]. Milder degrees of HPE including semilobar or lobar HPE cannot reliably be detected by prenatal ultrasound examination.

Lobar HPE can be recognized in utero with ultrasound. However, a specific diagnosis is often difficult and relies on qualitative evaluation of the morphology of the ventricles. Though not specific, antenatal demonstration of an echogenic linear structure running anterior-posterior within the third ventricle is highly suggestive of lobar HPE, and can assist this difficult diagnosis.

Fetal MRI is routinely used as a second-line investigation in several centers to evaluate CNS structure when ultrasound studies have suggested the presence of an anomaly [Edwards & Hui 2018]. MRI is useful for the evaluation of the posterior fossa and the median telencephalon as well as for etiologic clarification of hydrocephalus. Fetal MRI is particularly valuable for clarifying the anatomic subtypes of HPE, and thus informing on its severity [Edwards & Hui 2018, Kousa et al 2018, Calloni et al 2019]. Ultrafast MRI minimizes artifacts caused by fetal motion. Because MRI involves no exposure to radiation, it appears to be safe.

## Low-Risk Pregnancies

When HPE is found on routine prenatal ultrasound examination in a fetus not known to be at increased risk for HPE, an extensive fetal examination, preferably using high-resolution ultrasound examination (e.g., examination with 3D ultrasound) to determine the presence of additional structural anomalies is indicated [Edwards & Hui 2018]. Additional testing on amniotic fluid may be done to both establish the cause of HPE and assist in the management of the pregnancy and the recurrence risk counseling of the parents. Such testing can include the following [Kruszka et al 2018]:

- Fetal karyotype to detect numeric and structural chromosome abnormalities. Fetal karyotype is usually the first test ordered in the context of low-risk pregnancies.
- CMA if the karyotype is normal (or instead of karyotype) to detect pathogenic deletions or duplications (and aneuploidies if no previous karyotype) in the genes known to cause HPE (see Tables 2a, 2b). Of note, alternative assays such as MLPA may be used for this purpose.
- Multigene panel sequencing including at least the three following genes: *SHH*, *ZIC2*, and *SIX3*

It is essential to bear in mind that if the fetus has HPE identified by ultrasound examination, medical and parental decision making about the pregnancy may occur independent of a specific genetic diagnosis.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **Families for Hope**  
1219 North Wittfield Street  
Indianapolis IN 46229  
**Phone:** 888-533-4443  
**Email:** [Info@FamiliesforHoPE.org](mailto:Info@FamiliesforHoPE.org)  
[www.familiesforhope.org](http://www.familiesforhope.org)
- **Genetic and Rare Diseases Information Center (GARD)**  
[Holoprosencephaly](#)
- **National Human Genome Research Institute (NHGRI)**  
[Learning About Holoprosencephaly](#)

- **National Institute of Neurological Disorders and Stroke (NINDS)**  
PO Box 5801  
Bethesda MD 20824  
**Phone:** 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)  
[Holoprosencephaly Information Page](#)
- **National Organization for Rare Disorders (NORD)**  
[Holoprosencephaly](#)

## Chapter Notes

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- 11 March 2005 (me) Comprehensive update posted live
- 27 January 2003 (me) Comprehensive update posted live
- 27 December 2000 (pb) Overview posted live
- August 2000 (mm) Original submission

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