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# Syndromes Associated with Holoprosencephaly

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## Abstract

Holoprosencephaly (HPE) is partial or complete failure of the forebrain to divide into hemispheres and can be an isolated finding or associated with a syndrome. Most cases of HPE are associated with a syndrome and roughly 40–60% of fetuses with HPE have trisomy 13 which is the most common etiology of HPE. Other syndromes associated with HPE include additional aneuploidies like trisomy 18 and single gene disorders such as Smith-Lemli-Opitz syndrome. There are a number of syndromes such as pseudotrisomy 13 which do not have a known molecular etiology; therefore, this review has two parts: syndromes with a molecular diagnosis and syndromes where the etiology is yet to be found. As most HPE is syndromic, this review provides a comprehensive list and description of syndromes associated with HPE that may be used as a differential diagnosis and starting point for evaluating individuals with HPE.

## INTRODUCTION

Holoprosencephaly is a relatively common forebrain malformation, occurring in 1 in 1298 fetuses (1st and 2nd trimesters) (Kagan, Staboulidou, Syngelaki, Cruz, & Nicolaides, 2010). Holoprosencephaly (HPE) is characterized by complete or partial failure of the prosencephalon (forebrain) to separate in early embryogenesis into two cerebral hemispheres. HPE is often accompanied by midline facial anomalies such as hypotelorism, cleft lip/palate, and in severe cases, cyclopia and a proboscis (Figure 1A). HPE is a relatively common finding in fetal surveys with one large prenatal ultrasound screening study finding 44 cases in 55,117 cases screened or 1:1298 (Kagan et al., 2010). HPE may occur in isolation (nonsyndromic) and is often associated with pathogenic variants in the genes *SHH, SIX3,* and *ZIC2;* however, HPE most commonly occurs as part of a syndrome. The most common syndromes include aneuploidies such as trisomies 13, 18 and 22, Smith-Lemli-Opitz syndrome, and Hartsfield syndrome (Dubourg et al., 2007; Solomon, Gropman, & Muenke, 1993).

Advances in genomic technology during the last three decades has allowed for a molecular diagnosis to accompany many of the syndromes comprising HPE. As with any major malformation such as HPE, the clinician is obligated to look for findings in other organ systems that may lead to a syndromic diagnosis. The purpose of this review is to summarize syndromes associated with holoprosencephaly.

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## METHODS

PubMed was queried for the terms holoprosencephaly, syndromes, and the list of specific syndromes known by our group to be associated with HPE. Additionally, reference lists of journal articles where queried for relevant studies. Table I summarizes reported syndromes in the medical literature that have had at least one case of holoprosencephaly.

## SYNDROMES ASSOCIATED WITH MOLECULAR DIAGNOSES

### Trisomy 13

Trisomy 13 is the most common cause of HPE. Multiple organ systems can be affected in trisomy 13 and common physical exam findings include microphthalmia/anophthalmia, cleft lip and palate, postaxial polydactyly, and rocker bottom feet. Holoprosencephaly has been reported in 8%–39% of individuals with trisomy 13 (Hsu & Hou, 2007; Lehman et al., 1995; H. Y. Lin et al., 2007; Papp et al., 2006). Much of the data associating trisomy 13 HPE has come from prenatal testing. In a screen of over 50,000 pregnancies, Kagan et al. found that 65.9% of fetuses with holoprosencephaly had abnormal karyotypes and the majority (86%) of these abnormal karyotypes were trisomy 13 (Kagan et al., 2010). In another large study in Argentina of 13,883 ultrasounds with prenatal genetic testing, 28 fetuses were found to have holoprosencephaly (0.2%) and 12 cases (43%) had trisomy 13. (Petracchi, Crespo, Michia, Igarzabal, & Gadow, 2011). Figure 1A shows the most severe form of holoprosencephaly in a patient with trisomy 13, born with cyclopia and a proboscis (Capobianco et al., 2007). Due to the high incidence of trisomy 13 in HPE cases, trisomy 13 is at the top of the differential diagnosis for HPE. The mechanism of trisomy 13's relationship to HPE is not understood. *ZIC2,* a gene commonly associated with HPE is located at 13q32.3, but *ZIC2* variants are loss of function (Roessler et al., 2009). There currently is no available mouse model for trisomy 13, but human chromosome 13 has synteny with six mouse chromosome segments, making a model possible (Sheppard, Wiseman, Ruparelia, Tybulewicz, & Fisher, 2012). Promising models for understanding the pathogenicity of trisomy 13 are stem cell and gene expression research (Biancotti et al., 2010; Zhang et al., 2013).

### Other aneuploidies

After trisomy 13, the most common aneuploidies associated with HPE are trisomy 18, trisomy 21 and trisomy 22. Central nervous system anomalies found in trisomy 18 include corpus callosum agenesis, spina bifida, and cerebellar hypoplasia (Cereda & Carey, 2012). Holoprosencephaly is a less common CNS manifestation in trisomy 18. In a study of 14 fetuses with trisomy 18, only one (7.1%) had holoprosencephaly (Rosa et al., 2017). Petracchi et al. in their study of 13,883 prenatal diagnoses, found 2 cases of trisomy 18 in 28 fetuses with holoprosencephaly (Petracchi et al., 2011). More research is needed to know why trisomy 18 infrequently presents with holoprosencephaly. *TGIF*, which is one of the known gene associations with HPE (Gripp et al., 2000), is located at 18p11.31; additionally 10–15% of individuals with monosomy 18p present with HPE (Turleau, 2008). At least 5 cases of Down syndrome with holoprosencephaly have been individually reported (Basu, Kumar, & Das, 2009; Epstein, Seto, & Golabi, 1988; Hamada et al., 1991; Martinez-Frias, 1989; Urioste et al., 1988). Down syndrome is common and holoprosencephaly associated

with Down syndrome is very rare; thus, the question of coincidence versus causation remains to be answered (Epstein et al., 1988; Martinez-Frias, 1989). Trisomy 22 is a rare condition. Three cases of trisomy 22 and HPE has been reported (Fahmi, Schmerler, & Hutcheon, 1994; Isada, Bolan, Larsen, & Kent, 1990; Kehinde et al., 2014). One case of trisomy 16 has been associated with HPE, Petracchi et al. in their study of 13,883 prenatal diagnoses, found 1 case of trisomy 16 presenting with holoprosencephaly.

### Triploidy

Common findings in triploidy include lethality, microcephaly, limb anomalies and rarely holoprosencephaly. In a study of 54 triploidy fetuses at Brigham and Women's Hospital in Boston, 3 were found to have holoprosencephaly (Toufaily, Roberts, Westgate, & Holmes, 2016). In the Kagan et al. study, 3 of the 29 cases of holoprosencephaly with abnormal karyotypes were found to be triploidy (Kagan et al., 2010).

### 13q deletion syndrome

Not surprisingly, there have been multiple reports of chromosome 13q (location of *ZIC2*) deletions associated with holoprosencephaly, known as 13q deletion syndrome (Araujo Junior, Filho, Pires, & Filho, 2006; Garcia-Rodriguez, Garcia-Garcia, Perez-Sanchez, & Pavon-Delgado, 2015; Marcorelles et al., 2002; Mimaki et al., 2015; Quelin et al., 2009). In a series of 12 patients with varying 13q deletions, the 4 cases with holoprosencephaly all had *ZIC2* in the deletion interval (Quelin et al., 2009). Other manifestations of 13q deletion syndrome include cognitive impairment, growth delay, facial anomalies, and limb, kidney, eye, and heart malformations (Quelin et al., 2009). The phenotype and genotype of 13q deletion syndrome is variable; the Online Medelian in Man ((Online Mendelian Inheritance in Man)) website defines 13q deletion syndrome as a 13q14 deletion syndrome comprising a 16Mb interval, which does not contain *ZIC2* [OMIM, accessed 3/15/2018]; however, the medical literature in general labels most deletions on 13q as part of this syndrome (Araujo Junior et al., 2006; Mimaki et al., 2015; Quelin et al., 2009).

### 18p deletion syndrome

*TGIF1,* associated a very small fraction of HPE, is located on at this locus (Gripp et al., 2000; Mercier et al., 2011). Adding to evidence of pathogenicity are multiple reports of 18p deletions involving *TGIF1* found with HPE (Chen et al., 2013; Portnoi et al., 2007; Yi et al., 2014).

### Smith-Lemli-Opitz syndrome

Smith-Lemli-Opitz syndrome (SLOS) is a multiple congenital anomaly syndrome that presents with intellectual disability, facial dysmorphisms, congenital heart anomalies, and external genitalia defects in males. Multiple case reports have associated SLOS with HPE (Caruso et al., 2004; Kelley et al., 1996; Nowaczyk et al., 2001; Travessa, Dias, Rocha, & Sousa, 2017; Weaver, Solomon, Akin-Samson, Kelley, & Muenke, 2010). Even though only 5% of individuals with Smith-Lemli-Opitz syndrome (SLOS) present with HPE (Caruso et al., 2004), it remains the classic example of a single gene variant associated with syndromic HPE, and its cholesterol metabolism perturbation makes this syndrome more interesting.

Low cholesterol has been proposed to affect the SHH signaling pathway (Haas & Muenke, 2010) and SLOS is caused by a deficiency of the enzyme 7-dehyrocholestol reductase resulting in a block in the last step of cholesterol synthesis where 7-DHC is not converted to cholesterol. Figure 1D demonstrates clinical findings in a 24 week gestation fetus with SLOS and HPE including cyclopia, ambiguous genitalia, and syndactyly of toes 2 and 3 on the right (Weaver et al., 2010).

### Hartsfield syndrome

Hartsfield syndrome is characterized by holoprosencephaly, cleft lip and palate, and unilateral or bilateral split hands/feet (Figure 1B–C), also known as ectrodactyly (Hong et al., 2016; Simonis et al., 2013). Simonis et al. found heterozygous variants in *FGFR1* in six of seven patients with Hartsfield syndrome, four with heterozygous variants in the intracellular kinase domain and two individuals with homozygous variants located in the extracellular domain (Simonis et al., 2013). Our group recently screened 200 probands with holoprosencephaly and found 7 cases of pathogenic variants in *FGFR1* (Hong et al., 2016). In Hong et al., zebrafish studies demonstrated that the variants in *FGFR1* acted in a dominant negative fashion.

### Steinfeld syndrome

Steinfeld first reported a female child with HPE, bilateral reduction defects in upper limbs, midline cleft lip and palate, congenital heart disease, and renal anomalies (Steinfeld, 1982). Four further cases have been reported since this report (Jones et al., 2016; Nothen, Knopfle, Fodisch, & Zerres, 1993; Siebert, Schoenecker, Resta, & Kapur, 2005; Stevens, 2010). Steinfeld syndrome is characterized by holoprosencephaly and limb anomalies. One report has connected Steinfeld to a variant in *CDON* (Jones et al., 2016); however, this was not classic HPE, but microform. Another report has associated isolated (nonsyndromic) HPE with *CDON* variants but did not classify the patients as having Steinfeld syndrome, as the patients did not have limb anomalies (Bae et al., 2011).

### Culler-Jones syndrome

Special mention is made of Culler-Jones syndrome, a syndrome that is associated with *GLI2,* a gene which has been associated with “holoprosencephaly-like” features in the past (Roessler et al., 2003). Culler-Jones syndrome (CJS) is characterized by hypopituitarism and postaxial polydactyly. Bear et al. screened approximately 400 individuals with HPE spectrum phenotype for *GLI2* variants and found variants in 112 individuals, with 43 of these variants being truncating variants. Of the 43 individuals with truncating variants, only one had a brain malformation consistent with HPE (Bear et al., 2014). Thus, individuals with *GLI2* variants and CJS have a well-defined phenotype that does not usually include HPE.

## SYNDROMES WITHOUT MOLECULAR DIAGNOSES

### Pseudotrisomy 13

Pseudotrisomy 13 syndrome, also known as holoprosencephaly-polydactyly syndrome, refers to HPE associated with postaxial polydactyly and a normal karyotype. Because HPE and polydactyly are features of trisomy 13, Hewitt et al. suggested the term pseudotrisomy

13 for this presentation given the normal karyotype (Hewitt, Seller, Bennett, & Maxwell, 1989), and Cohen and Gorlin later “coined” the term pseudotrisomy 13 syndrome (Cohen & Gorlin, 1991). Bous et al. reviewed 40 cases of pseudotrisomy 13 syndrome and reported 80% of cases with classic HPE (MRI evidence of HPE), 80% with polydactyly, and 58% with a cardiac anomaly (Bous et al., 2012). There is no known molecular diagnostic association and research with next generation sequencing is needed to more thoroughly interrogate pseudotrisomy 13 for a molecular diagnosis.

### Hydrolethalus syndrome

Hydrolethalus syndrome is characterized by a lethal form of brain malformations, usually hydrocephalus and absent midline structures, micrognathia, polydactyly, and defective lobation of the lungs (Salonen, Herva, & Norio, 1981). We mention hydrolethalus syndrome as Bachman et al. found a case of holoprosencephaly, hydrocephalus, and polydactyly in a consanguineous Mexican-American family and proposed that pseudotrisomy 13 cases were part of hydrolethalus syndrome (Bachman, Clark, & Salahi, 1990). Subsequent to Bachman et al.’s 1990 study, hydrolethalus syndrome was found to be an autosomal recessive condition associated with two genes, *HYLS1* and *KIF7* (Mee et al., 2005; Putoux et al., 2011). However, no cases of hydrolethalus syndrome with a molecular diagnosis have been associated with HPE. A review of 21 cases with molecularly confirmed variants in the gene *HYLS1* found that all cases had a complete interhemispheric fissure, and in a few cases, a hypothalamic hamartoma was found (Paetau et al., 2008). Holoprosencephaly is not a common finding in hydrolethalus syndrome.

### Pallister-Hall syndrome

Pallister-Hall syndrome is diagnosed in the presence of a hypothalamic hamartoma and mesoaxial polydactyly, with confirmation in a heterozygous pathogenic variant in *GLI3.* Verloes et al. presented a case with alobar HPE, hypothalamic hamartoma, and polydactyly, and reviewed an additional 27 cases of hypothalamic hamartoma with other congenital anaomalies (Verloes, Gillerot, Langhendries, Fryns, & Koulischer, 1992). This group proposed a classification that would combine cases with hypothalamic hamartomas and HPE (i.e. Pallister-Hall syndrome) and cases of HPE and polydactyly without hypothalamic hamartomas under a classification of Cebro-Acro-Visceral Early Lethality (CAVE) Multiplex Syndrome (Verloes et al., 1992). Additionally, SLOS type II, hydrolethalus, pseudotrisomy 13 (holoprosencpehaly-polydactyly syndrome), orofacialdigital type IV were included in this umbrella. Since the availability of a molecular test for Pallister-Hall syndrome, there has been no confirmed PHS case with HPE. We conclude that HPE is not a frequent finding in HPS.

### Agnathia-Otocephaly Complex

Agnathia-Otocephaly complex (AGOTC) is a rare malformation with failure of the first arch development and is characterized by agnathia, ventromedial ear position, microstomia, and holoprosencephaly (Figure 1E) (Faye-Petersen et al., 2006). The gene *PRRX1* (Celik et al., 2012; Dasouki, Andrews, Parimi, & Kamnasaran, 2013) has been associated with AGOC; however, there are no cases of AGOTC with HPE associated with *PPRX1* (Dasouki et al., 2013).

### CHARGE syndrome

Lin et al. evaluated 144 patients with CHARGE syndrome, and three were found to have holoprosencephaly (Lin, Siebert, & Graham, 1990); however, these patients did not have a molecular diagnosis as *CHD7* would not be associated with CHARGE syndrome for another 14 years.

### Genoa syndrome

Camera et al. reported 2 siblings with semilobar HPE and craniosynostosis involving the coronal and lambdoid sutures and called this Genoa syndrome (Camera, Lituania, & Cohen, 1993). There have been other reports of individuals with both HPE and craniosynostosis; however, and etiology remains elusive (Hacihamdioglu et al., 2010; Lapunzina, Musante, Pedraza, Prudent, & Gadow, 2001; C. H. Lin, Tsai, Ho, & Lin, 2009; Raam, Solomon, Shalev, & Muenke, 2010).

### Lambotte syndrome

Lambotte et al. in 1978 first reported a new multiple congenital anomaly condition in two siblings with microcephaly, intrauterine growth retardation (IUGR), cerebral malformation, and early lethality in two siblings. Verloes et al. later reported 4 siblings from one family with Lambotte syndrome where one of the siblings had semilobar HPE (Verloes, Dodinval, Beco, Bonnivert, & Lambotte, 1990). Subsequently, an unaffected sister in the family described by Verloes et al. gave birth to an affected child, and a t(2;4)(q37.1;p16.2) translocation was found in the mother, suggesting a combination of 2q/4p trisomy/monosomy in all of the affected children of this family (Herens et al., 1997).

### Agnathia-microstomia-synotia syndrome

Agnathia-microstomia-synotia syndrome is a rare lethal congenital malformation of the first branchial arch that presents with agnathia, mandibular hypoplasia, anteromedial malposition of ears, microstomia, and aglossia or microglossia. A number of case reports of agnathia-microstomia-synotia have shown HPE (Chaoui, Heling, Thiel, & Karl, 2011; Faye-Petersen et al., 2006; Wai & Chandran, 2017).

### Amelia, cleft lip, and holoprosencephaly

Five cases of amelia, cleft lip, and holoprosencephaly have been reported (Kariminejad, Goodarzi, Asghari-Roodsari, & Kariminejad, 2009; Thomas & Donnai, 1994; Zimpfer et al., 2007). The association of HPE with limb defects is of special interest as SHH signaling directs digit number and identity in the vertebrate limb (Vokes, Ji, Wong, & McMahon, 2008); however, the mechanism responsible for the association between holoprosencephaly and amelia remains unknown.

## DISCUSSION

Most cases of holoprosencephaly are associated with a syndrome and trisomy 13 is the most common etiology. Syndromes associated with single gene variants are much less common and make up a limited amount of cases. Over the last two decades, the advancement of

molecular diagnoses attached to syndromes has better defined genetic syndromes. As next generation sequencing becomes more available (Roessler, Hu, & Muenke, 2018), larger sets of genes will be able to be tested per sample, allowing for expansion of syndrome associated with HPE. As noted above, there are still a number of syndromes associated with HPE that do not have a molecular etiology such as pseudotrisomy 13, Genoa syndrome and Agnathia-microstomia-synotia syndrome. Additionally, there are syndromes such as CHARGE syndrome with a known genetic etiology that was associated with HPE before available genetic testing and a case with HPE and a pathogenic variant is missing from the medical literature. In the coming years, many of these questions will be answered from the research community.

In addition to the diagnostic value to families and patients of associating syndromes with HPE, the connection of HPE with multiple congenital anomaly syndromes inform us about the pathophysiology of embryonic brain development. HPE is a midline malformation disorder; however, HPE syndromes are associated with other midline brain anomalies. As an example, Smith-Lemli-Opitz syndrome (SLOS) is often associated with brain malformations other than HPE. In the largest brain imaging study of 55 individuals with SLOS, Lee et al. found 53 of 55 (96%) individuals to have aberrant brain MRI scans (Lee, Conley, Gropman, Porter, & Baker, 2013). Abnormalities of the septum pellucidum were found in 42/55 (76%) and of the corpus callosum in 38/55 (69%). Knowing that sonic hedgehog processing and signaling is dependent on cholesterol (Cooper et al., 2003; Porter, Young, & Beachy, 1996), Lee et al. correlated the severity of the brain malformations to sterol levels in these patients with SLOS. We next direct our attention to Hartsfield syndrome and *FGFR1* variants as a second example of midline brain malformations (Lee et al., 2013). Although Hartsfield syndrome is defined by the co-occurrence of HPE, ectrodactyly, and *FGFR1* variants (Simonis et al., 2013), there a number of other conditions caused by *FGFR1* variants including Pfeiffer syndrome, Kallmann syndrome, Hartsfield syndrome, and normosmic hypogonadotropic hypogonadism (nIHH) (Hong et al., 2016). Kallmann syndrome may be associated with agenesis of the corpus callosum and dysgenesis of the olfactory bulbs, neural structures in vertebrate forebrains. Klein et al. reported a case of choanal atresia in a family with Kallmann syndrome, suggesting that Kallmann syndrome may be the least severe form of the holoprosencephaly-hypopituitarism complex (Klein, Friedman, Brookshire, Brown, & Edman, 1987). The anterior neural ridge located at the rostral edge of the embryonic neural plate is one of three organizing centers in the developing prosencephalon (embryonic forebrain) and secretes fgf ligands and reduction of fgf signaling in the mouse model in the telencephalon results in HPE-like malformations (Paek, Gutin, & Hebert, 2009; Storm et al., 2006). Hong et al. determined that in families affected by Hartsfield syndrome, *FGFR1* acted in a dominant negative fashion which is consistent with known loss of function mechanism in Kallmann syndrome (Hong et al., 2016). SLOS and Hartsfield are excellent examples of how syndromic disease has advance our knowledge of brain development and there is room for much more to learn.

In summary, we present a comprehensive list and description of syndromic HPE in this review. As most HPE is syndromic, this paper will serve as a differential diagnosis in individuals diagnosed with HPE.

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## Biographies

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years. His group has discovered numerous genes contributing to HPE, including the first and most well-known gene, Sonic Hedgehog. His other research interests include cardiac disease, craniofacial malformation syndromes, attention-deficit-hyperactivity disorder (ADHD), and the genetics of diverse populations.


**Figure 1.**

**A)** Trisomy 13 fetus with cyclopia and proboscis. Reprinted by permission from Springer Nature (Capobianco et al., 2007). **B)** Bilateral split foot. Reprinted by permission from Oxford University Press (Hong et al., 2016). **C)** Bilateral split foot and the absence of second digit phalanges bilaterally on X-ray. Reprinted by permission from Oxford University Press (Hong et al., 2016). **D)** Frontal view of a 24-week-old fetus. Note cyclopia (synophthalmia), ambiguous genitalia, and partial syndactyly of 2nd and 3rd toes on the right Reprinted by permission from John Wiley and Sons (Weaver et al., 2010). **E)** Agnathia–otocephaly complex with cyclopia, agnathia, microstomia and ventromedial ear position. Reprinted by permission from BMJ Publishing Group Ltd. (Wai & Chandran, 2017).

**Table I**

Syndromic cases of holoprosencephaly (HPE) with a molecular diagnosis. Case reports are not listed. In the “cases screened column”, the phenotype is clarified in parentheses to specify how a cohort was ascertained.

| Condition | HPE cases | Cases screened (denominator) | Holoprosencephaly type | Extra-CNS anomalies | Molecular findings | Reference |
|---|---|---|---|---|---|---|
| Trisomy 13 | 1 | 13 (trisomy 13) | holoprosencephaly not specified | multiple congenital anomalies | karyotype | (Hsu & Hou, 2007) |
| Trisomy 13 | 13 | 33 (trisomy 13) | holoprosencephaly not specified | multiple congenital anomalies | karyotype | (Lehman et al., 1995) |
| Trisomy 13 | 4 | 23 (trisomy 13) | holoprosencephaly not specified | multiple congenital anomalies | karyotype | (H. Y. Lin et al., 2007) |
| Trisomy 13 | 5 | 28 (trisomy 13) | fetal ultrasound: holoprosencephaly | multiple congenital anomalies | karyotype | (Papp et al., 2006) |
| Trisomy 13 | 12 | 28 (HPE) | fetal ultrasound: holoprosencephaly | multiple congenital anomalies | karyotype | (Petracchi et al., 2011) |
| Trisomy 18 | 2 | 28 (HPE) | fetal ultrasound: holoprosencephaly | multiple congenital anomalies | karyotype | (Petracchi et al., 2011) |
| Trisomy 18 | 1 | 14 (trisomy 18) | fetal ultrasound: holoprosencephaly | multiple congenital anomalies | karyotype | (Rosa et al., 2017) |
| Trisomy 16 | 1 | 28 (HPE) | fetal ultrasound holoprosencephaly | multiple congenital anomalies | karyotype | (Petracchi et al., 2011) |
| Triploidy | 3 | 54 (triploidy) | holoprosencephaly not specified | multiple congenital anomalies | karyotype | (Toufaily et al., 2016) |
| 13q deletion syndrome | 4 | 12 (13q deletion) | holoprosencephaly not specified | multiple congenital anomalies | 13q31.1–13qter; 13q31.1–13qter; 13q31.3–13q33.1; 13q32.3 | (Quelin et al., 2009) |
| Smith-Lemli-Opitz syndrome | 1 | 18 (SLOS) | holoprosencephaly not specified | multiple congenital anomalies | (elevation of 7-DHC and 8-DHC/ decreased cholesterol | (Caruso et al., 2004) |
| Smith-Lemli-Opitz syndrome | 1 | 50 (sporadic cases of HPE) | semi-lobar | polydactyly of the right hand and mild cutaneoussyndactyly of toes 2 and 3 | increased 7-DHC/cholesterol ratio | (Kelley et al., 1996) |
| Smith-Lemli-Opitz syndrome | 2 | 28 (HPE) | fetal ultrasound holoprosencephaly | multiple congenital anomalies | *DHCR7*: c.964-1G > C; c.440 G>A | (Petracchi et al., 2011) |

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| Condition | HPE cases | Cases screened (denominator) | Holoprosencephaly type | Extra-CNS anomalies | Molecular findings | Reference |
|---|---|---|---|---|---|---|
| Hartsfield syndrome | 7 | 200 (HPE) | semi-lobar; microform; not specified; microform; lobar; semi-lobar/lobar (sisters) | limb anomalies | FGFR1: p.Asp641Asn; p.Arg627Thr; p.Asp623Glu; p.Met535Lys; p.Gly487Asp; Glu294Lys | (Hong et al., 2016) |
| Hartsfield syndrome | 6 | 7 (Hartsfield syndrome) | alobar; lobar; semi-lobar; lobar; semi-lobar; lobar | limb anomalies | p.L165S*; p.L191S*; p.G490R; p.D623Y; p.N628K; p.C725Y | (Simonis et al., 2013) |