Published in final edited form as:

Clin Dysmorphol. 2012 October ; 21(4): 183–190. doi:10.1097/MCD.0b013e3283551fd0.

Holoprosencephaly–polydactyly/pseudotrisomy 13: a presentation of two new cases and a review of the literature

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Abstract

Patients with a combination of holoprosencephaly and polydactyly, but with apparently normal chromosomes, may be clinically diagnosed with holoprosencephaly–polydactyly syndrome (HPS), also termed pseudotrisomy 13. However, the criteria for HPS have been controversial since the advent of the diagnostic term, and a clear understanding of the condition lacks definitive delineation. We review the historical and current perspectives on the condition and analyze findings in 40 patients with apparent HPS, including cases from the literature and two previously unreported patients. Overall, our analysis suggests previously unrecognized trends in patients diagnosed with HPS. Specifically, there appears to be a higher prevalence of visceral anomalies, most significantly cardiac and genitourinary, but also with increased gastrointestinal, pulmonary, adrenal, skeletal, and renal abnormalities, in patients with HPS. Although these visceral anomalies may not be essential for the identification of HPS, clinicians should be aware of the presence of such characteristics in these patients to optimize management and help establish etiologies.

Keywords

holoprosencephaly; holoprosencephaly and polydactyly; polydactyly; pseudotrisomy; pseudotrisomy 13

Introduction

Holoprosencephaly (HPE) is the most common malformation of the human forebrain, occurring in one in 250 gestations, although only approximately one in 10 000 live-born

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Conflicts of interest There are no conflicts of interest.

infants present with the condition because of the high proportion of intrauterine lethality (Orioli and Castilla, 2010). In addition to characteristic structural brain abnormalities, patients typically have accompanying midline facial anomalies, which range from cyclopia or synophthalmia at the most severe end of the spectrum to findings such as hypotelorism and a single central maxillary incisor in less severely affected patients. The causes of HPE are highly heterogeneous. HPE may occur as one component in a syndrome, may be because of cytogenetic anomalies, or may occur because of mutations in over 10 identified genes associated with nonchromosomal, nonsyndromic HPE (Pineda-Alvarez *et al*., 2010; Solomon *et al*., 2010).

HPE is classified into four major types, depending on the degree of severity of brain malformations: alobar (the most severe type), semilobar, lobar, and the more recently described middle interhemispheric variant-type HPE (Hahn and Barnes, 2010). Patients may also have ‘microform’ HPE, in which conventional neuroimaging shows no brain anomalies consistent with frank HPE, but patients may have subtle facial features consistent with a midline deficit. Many patients with microform HPE are identified because of the birth of a severely affected relative (Solomon *et al*., 2010).

Although the causes of some types of syndromic HPE have been elucidated, others remain less well delineated. Holoprosencephaly–polydactyly syndrome (HPS) is one of the less understood entities, although several lines of enquiry provide interesting hints. Classically diagnosed in patients with a combination of HPE, polydactyly, and apparently normal chromosomes, the criteria for HPS, also called pseudotrisomy 13, have been controversial since the use of the term began (Cohen, 1989a, 1989b, 1989c; Hewitt *et al*., 1989). Here, we analyze findings in 40 patients with apparent HPS and review the historical and current perspectives on the condition. Our analysis shows key trends in HPS. First, normal chromosomes as a required criterion may not be justified, as cytogenetic abnormalities have been discovered in some patients, pointing to possible genetic causes. Second, along these lines, cytogenetic analysis, including newer microarray and large-scale sequencing techniques, may allow increased molecular understanding of the cause of HPS. Third, clinicians should be aware that patients may have other anomalies (e.g. cardiac and genitourinary), which are highly associated with HPS and should be evaluated for when encountering a patient with HPS.

Diagnostic controversies

There have been difficulties both in defining HPS and in clearly showing its existence as a unified phenotype. The similarity to hydrolethalus syndrome led to the proposal that they are manifestations of the same disorder (Bachman *et al*., 1990). Others disagreed, arguing that HPS is a separate entity (Cohen and Gorlin, 1992). Further delineation of the syndrome led to the suggestion that pseudotrisomy 13 can manifest without polydactyly, an anomaly previously believed essential to the diagnosis (Ramos-Arroyo *et al*., 1994). In an attempt to resolve the debate, new criteria were established, taking into account sporadic and familial types of HPS. According to this formulation, a sporadic occurrence would fulfill the diagnostic criteria in the case of a normal karyotype and one of the following: HPE and postaxial polydactyly; HPE and other abnormalities not including polydactyly; or postaxial

polydactyly, brain abnormalities such as microcephaly, agenesis of corpus callosum, and/or hydrocephalus, as well as other abnormalities. Patients with familial HPS/pseudotrisomy 13 would require an affected sibling to have a normal karyotype and the same clinical criteria outlined for sporadic cases would apply (Lurie and Wulfsberg, 1993).

The controversy grew with the discovery that a normal karyotype, the third classic diagnostic criterion, may not always be evident in patients with HPS. Of the 40 cases described in Table 1, only 82% have seemingly normal karyotypes. Further, there may be underappreciated cytogenetic anomalies not apparent on conventional chromosome analysis that may account for the presence of HPS (Hewitt *et al*., 1989; Brown *et al*., 1993; Chen *et al*., 1998, 2005; Chang, 2003; Koolen *et al*., 2006; Bendavid *et al*., 2010; Marquis-Nicholson *et al*., 2011). As an aggregate, these developments are not surprising, given the growing availability and use of high-density microarrays. Microalterations on chromosome 13 may be the cause of HPS in some. Evidence suggests that the region in question lies in chromosome arm 13q, which includes the locus for *ZIC2*, a gene frequently mutated in HPE (Hewitt *et al*., 1989; Brown *et al*., 1993; Koolen *et al*., 2006). Other cytogenetic anomalies in patients with pseudotrisomy 13 include the partial deletion of chromosome 8p and duplication of 5q35.1 (Chen *et al*., 1998, 2005; Chang, 2003; Koolen *et al*., 2006). Another study described multiple (21) long contiguous stretches of homozygosity in a patient showing the features of pseudotrisomy 13 (Marquis-Nicholson *et al*., 2011).

Theories of causation

The molecular pathogenesis of HPS is poorly understood and is likely complex. Traditionally, HPE is thought to be a result of a loss-of-function mutation, while polydactyly is thought to be a result of a gain-of-function mutation (Clark *et al*., 2001). One hypothesis for why both loss-of-function and gain-of-function effects may result from the same pleiotropic mutation is that the response to the signals from the gene(s) responsible for HPS may differ because of varying embryologic patterning of the brain and limbs. Alternatively, the phenotype may result from two or more mutations involving different genes or an as yet undiscovered contiguous gene syndrome, resulting in brain and limb anomalies (Cordero *et al*., 2008).

Sonic hedgehog (SHH) is a key molecule in the pathogenesis of HPE and many genes implicated in HPE are tied to the SHH signaling pathway (Solomon *et al*., 2010). The presence of HPE because of diverse causes such as Smith–Lemli–Opitz syndrome, maternal alcohol use, and the use of the cholesterol-lowering statin class of medications during pregnancy may all be tied to SHH signaling (Lanoue *et al*., 1997; Edison and Muenke, 2004; Li *et al*., 2007). Further, aberrant SHH signaling is also associated with disorders that manifest polydactyly, including Pallister–Hall syndrome, Greig cephalopolysyndactyly, and isolated postaxial polydactyly (Ming *et al*., 1998). Thus, it is highly plausible that hedgehog signaling may be involved in HPS despite the fact that mutations in the *SHH* gene itself have not yet been identified in patients with HPS.

Nonetheless, it is likely that HPS is a heterogeneous disorder, as shown by theories of HPS inheritance. Among the cases in Table 1, 28% describe parental consanguinity, leading to the suspicion of autosomal recessive inheritance in some cases (Ramaekers *et al*., 1989;

Bachman *et al*., 1990; Brown *et al*., 1993; Ahmet *et al*., 2006; Marquis-Nicholson *et al*., 2011). Eighteen percent of cases were found to have an affected sibling with HPS. However, the possibility of an X-linked or an autosomal dominant mode of inheritance cannot be ruled out (Atkin, 1988; Seller *et al*., 1993). Although more males overall (45%) are reported than females (28%), both sexes are significantly represented. Finally, germline mosaicism is well described in isolated HPE, and must not be ignored when discussing possible inheritance patterns (Ramaekers *et al*., 1989; Solomon *et al*., 2010).

Differential diagnosis

With the broader inclusion criteria described above, some cases significantly overlap with other disorders, which may lead to difficulties in establishing a diagnosis. Conditions that share common characteristics with HPS include hydrolethalus syndrome and trisomy 13. Other conditions may have overlapping features, such as Smith–Lemli–Opitz syndrome, Meckel syndrome, and Pallister–Hall syndrome, necessitating a full clinical genetic consultation to help determine whether or not these other diagnoses should be pursued by targeted testing.

Genetic evaluation in a few recent cases of HPS ruled out some of these disorders in at least the tested individuals (Cordero *et al*., 2008; Zechi-Ceide *et al*., 2009). However, it must be stated that with many of the patients described in our analysis, it is difficult to exclude all overlapping conditions, as not all have had the same clinical diagnostic work-up or extensive molecular testing. In fact, it may well be that patients diagnosed with HPS represent a causally heterogeneous group of patients. As molecular understanding of diseases advances, the aggregate diagnosis of HPS may dissolve into separate conditions.

Materials and methods

We report on two patients who participated in our National Human Genome Research Institute Institutional Review Board approved protocol on HPE, with appropriate consent obtained from participating families. Samples and available clinical information were sent to our lab from referring clinicians, and sequencing of HPE-associated genes was performed through standard dideoxynucleotide sequencing (methods described in detail in Pineda-Alvarez *et al*., 2010).

We analyzed findings in 38 additional previously reported patients with apparent HPS using Pubmed and Medline as search mechanisms with the search terms including ‘holoprosencephaly’, ‘HPE’, ‘pseudotrisomy’, ‘pseudotrisomy 13’, and ‘holoprosencephaly and polydactyly’.

Results

New patient reports

Patient 39 was a 1-year-old male first child of nonconsanguineous parents of western European descent who had an unremarkable family history. Neuroimaging during gestation showed a partial fusion in the rostral basal ganglia believed to represent mild HPE, as well as a lipoma of the corpus callosum. Postnatal MRI confirmed these findings, and indicated

that a single maxillary central incisor was not present. Birth measurements showed that head circumference, height, and weight were all below the third centile for gestational age; measurements at 12 months of age showed a weight between the 10th and the 25th centile, body length between the 50th and the 75th centile, and microcephaly, with occipito-frontal head circumference less than the third centile. Facial features were consistent with HPE, with marked midface hypoplasia, a flattened nasal bridge, and a midline cleft lip and palate. Limb anomalies included left upper extremity radial deviation and thumb hypoplasia and evidence of right upper extremity preaxial hexadactyly (status-post surgical correction at the time of examination). Additional anomalies included tetralogy of Fallot, multiple fused and hemivertebrae resulting in scoliosis, hypospadias, and micropenis. The patient showed generalized hypotonia and severe motor delay. Laboratory analysis indicated evidence of diabetes insipidus, but no other endocrinological abnormalities. Karyotype analysis, fluorescence in-situ hybridization for 7q36 and 22q11.2, as well as quantitative cholesterol levels were all normal. Sequence analysis of *SHH*, *ZIC2*, *SIX3*, and *TGIF* indicated no mutations. An oligonucleotide array CGH (Signature) was not performed.

Patient 40 was diagnosed *in utero* with HPS. Imaging indicated neuroanatomical anomalies consistent with severe HPE, as well as the presence of a proboscis, polydactyly, cardiac defects, and hemivertebrae. Full autopsy was not performed and further data are not available. Karyotype analysis and oligonucleotide array CGH (Signature) showed no abnormalities. Sequence analysis of *SHH*, *ZIC2*, *SIX3*, *TGIF*, and *GLI2* indicated no mutations.

Combined findings

Patients diagnosed with HPS are presented in Table 1. The availability of clinical details was variable. Slightly less than 80% of patients were described as having classic HPE and 92% overall were found to have some type of central nervous system defect. Brain anomalies were not recorded in 8% of the patients; however, facial features in these cases were consistent with a diagnosis of HPE. These features include eye abnormalities, such as hypotelorism (70%), cleft lip and/or palate (53%), nose anomalies consistent with HPE (28%), and, separately, proboscis (10%). In patients in whom the HPE type was described, there was a skewing toward severe forms. Thirty-three percent of the patients had alobar, 25% had semilobar, and 5% had lobar HPE.

Polydactyly was described in 80% of patients, whereas 93% had some type of limb abnormality, including polydactyly. At least 95% of patients with polydactyly had postaxial polydactyly. Although organ system defects are not believed to be essential to the diagnosis of HPS, there was a high prevalence of cardiac (58%), genitourinary (35%), gastrointestinal (20%), pulmonary (15%), adrenal (10%), skeletal (10%), and renal (8%) abnormalities (for a more detailed description of the patients, please refer to Table 1).

Discussion

Although first described over two decades ago, the definitive diagnosis of HPS remains a challenge. First, the criteria of HPE, polydactyly, and normal chromosomal analysis have served as a guideline for the diagnosis of the syndrome. A broadened list of criteria was

subsequently created (Lurie and Wulfsberg, 1993). Since these criteria were established, more extensive cytogenetic methodologies have become available, leading to the discovery of distinct anomalies found on several chromosomes that may be linked to causes of HPS. Our data suggest that normal chromosomes were found in most but not all cases of HPS. Further, sequencing results from the new patients reported here lend support to the hypothesis that mutations in known and well-characterized HPE-associated genes are not common causes of HPS. With the increased use of newer genomic diagnostic techniques such as high-density microarrays and high-throughput sequencing, smaller regions of genomic variance and individual exonic mutations may be better appreciated, and may possibly lead to an improved understanding of the complex etiology of the condition. It is entirely possible that HPS will remain a unifying clinical diagnosis that can result from many possible genetic and environmental causes, as has been well described for HPE in general (Solomon *et al*., 2010). When a clinician considers a diagnosis of HPS, genetic studies on both a clinical and a research basis should be pursued to further understand the condition, as well as to improve the management of these patients.

Second, our data highlight a high prevalence of a variety of visceral anomalies, most significantly involving the cardiac and genitourinary systems, in patients with HPS. This prevalence of visceral anomalies in HPS appears overall higher than in HPE more generally. In a recent and impressively large study describing a cohort of over 600 European patients with HPE, 27% were found to have visceral anomalies (Mercier *et al*., 2011). Although perhaps not essential for the identification of HPS, clinicians should be aware of the presence of such characteristics in these patients. These findings may also point to potential causes. For example, the neuroanatomical anomalies of HPE can naturally lead to a variety of endocrinologic disturbances, but adrenal cortical development appears to be directly linked to the SHH signaling pathway (Ching and Vilain, 2009; King *et al*., 2009; Huang *et al*., 2010), implying a role for this pathway in at least some patients.

Finally, along these lines, we suggest the following for work-up of a patient in whom a clinician is considering a diagnosis of HPS: detailed clinical exam by a geneticist to assess for polydactyly and other anomalies, with further studies as indicated; neuroimaging (MRI is preferred) to establish the presence and type of HPE as well as other central nervous system anomalies; echocardiogram; renal ultrasound; conventional karyotype, with reflex microarray if the karyotype is negative; further targeted genetic testing if other conditions in the differential diagnosis appear likely; as well as consideration of research participation.

Acknowledgments

The authors would like to thank all the patients who participated in these studies. This research was supported by the Division of Intramural Research, National Human Genome Research Institute, National Institutes of Health, Department of Health and Human Services, USA.

References

Ahmet D, Bahri E, Mustafa A, Varim N, Tunc T. Pseudotrisomy 13 syndrome: a case with left ventricular hypoplasia and duodenal stenosis. Clin Dysmorphol. 2006; 15:41–42. [PubMed: 16317308]

Atkin JF. A new syndrome with cyclopia and trisomy 13 features. Am J Hum Genet. 1988; 43:A36.

Bachman H, Clark RD, Salahi W. Holoprosencephaly and polydactyly: a possible expression of the hydrolethalus syndrome. J Med Genet. 1990; 27:50–52. [PubMed: 2407847]

Bendavid C, Dupe V, Rochard L, Gicquel I, Dubourd C, David V. Holoprosencephaly: an update of cytogenetic abnormalities. Am J Hum Genet. 2010; 154C:86–92.

Boles RG, Teebi AS, Neilson KA, Meyn MS. Pseudo-trisomy 13 syndrome with upper limb shortness and radial hypoplasia. Am J Med Genet. 1992; 44:638–640. [PubMed: 1481825]

Brown S, Gersen S, Anyane-Yeboa K, Warbuton D. Preliminary definition of a 'critical region' of chromosome 13 in q32: report of 14 cases with 13q deletion and review of the literature. Am J Med Genet. 1993; 45:52–59. [PubMed: 8418661]

Cakir M, Mungan I, Makuloglu M, Okten A. Hydrocephalus with cleft lip and palate: an overlap between midline malformation syndromes. Indian J Pediatr. 2006; 73:731–733. [PubMed: 16936370]

Chang L. Alobar holoprosencephaly: report of two cases with unusual findings. Chang Gung Med J. 2003; 26:700–706. [PubMed: 14651170]

Chen C, Chern S, Lee C, Chen L, Chuang C, Chen M. Prenatal diagnosis of *de novo* isochromosome 13q associated with microcephaly, alobar holoprosencephaly and cebocephaly in a fetus. Prenat Diagn. 1998; 18:393–398. [PubMed: 9602489]

Chen C, Chern S, Hsu C, Lee C, Lee M, Wang W. Prenatal diagnosis of *de novo* partial trisomy 13q (13q22→qter) and partial monosomy 8p (8p23.3→pter) associated with holoprosencephaly, premaxillary agenesis, hexadactyly, and a hypoplastic left heart. Prenat Diagn. 2005; 25:331–337. [PubMed: 15849790]

Ching S, Vilain E. Targeted disruption of sonic hedgehog in the mouse adrenal leads to adrenocortical hypoplasia. Genesis. 2009; 47:628–637. [PubMed: 19536807]

Clark RM, Marker PC, Roessler E, Dutra A, Schimenti JC, Muenke M, Kingsley DM. Reciprocal mouse and human limb phenotypes caused by gain- and loss-of-function mutations affecting Lmbr1. Genetics. 2001; 159:715–726. [PubMed: 11606546]

Cohen MM Jr. Perspectives on holoprosencephaly. Part I. Epidemiology, genetics, and syndromology of holoprosencephaly. Teratology. 1989a; 40:211–235. [PubMed: 2688166]

Cohen MM Jr. Holoprosencephaly and cytogenetic finding: further information. Am J Med Genet. 1989b; 34:265. [PubMed: 2817008]

Cohen MM Jr. Perspectives on holoprosencephaly. Part III. Spectra, distinctions, continuities, and discontinuities. Am J Med Genet. 1989c; 34:271–288. [PubMed: 2683788]

Cohen MM Jr, Gorlin RJ. Pseudo-trisomy 13 syndrome. Am J Med Genet. 1991; 39:332–335. [PubMed: 1867286]

Cohen MM Jr, Gorlin RJ. Problems in the delineation of pseudotrisomy syndrome: reply to Drs. Norman, Donnai, Martínez-Frías, Urioste, Martín, and Frías. Am J Med Genet. 1992; 43:636–638.

Cordero DR, Bendavid C, Shanske AL, Haddad BR, Muenke M. Holoprosencephaly-polydactyly syndrome: in search of an etiology. Eur J Med Genet. 2008; 51:106–112. [PubMed: 18178536]

Donnai D. Unknown case: stillborn white male-30 weeks. Proc Gr Genet Center. 1988; 7:64–65.

Edison RJ, Muenke M. Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins. Am J Med Genet. 2004; 131:287–298. [PubMed: 15546153]

Grote W, Rehder H, Weisner D, Wiedemann HR. Prenatal diagnosis of a probably hereditary syndrome with holoprosencephaly, hydrocephaly, octodactyly, and cardiac malformations. Eur J Pediatr. 1984; 143:155–157. [PubMed: 6394337]

Hahn JS, Barnes PD. Neuroimaging advances in holoprosencephaly: refining the spectrum of the midline malformation. Am J Med Genet C Semin Med Genet. 2010; 154C:120–132. [PubMed: 20104607]

Hennekam RC, Van Noort G, De La Fuente AA. Familial holoprosencephaly, heart defects, and polydactyly. Am J Med Genet. 1991; 41:258–262. [PubMed: 1785646]

Hewitt BG, Seller MJ, Bennett CP, Maxwell DM. Holoprosencephaly, polydactyly and normal chromosomes: pseudo-trisomy 13? Clin Genet. 1989; 36:141–143. [PubMed: 2766571]

Higgins JV, Minnick MA. Pseudo-trisomy 13 syndrome: prenatal findings in a family with two affected siblings. Am J Hum Genet. 1992; 51:257.

Huang CJ, Miyagawa S, Matsumaru D, Parker KL, Yao HH. Progenitor cell expansion and organ size of mouse adrenal is regulated by sonic hedgehog. Endocrinology. 2010; 151:1119–11128. [PubMed: 20118198]

King P, Paul A, Lauger E. Shh signaling regulates adrenocortical development and identifies progenitors of steroidogenic lineages. PNAS. 2009; 106:21185–21190. [PubMed: 19955443]

Koolen DA, Herbergs J, Veltman JA, Pfundt R, van Bokhoven H, Stroink H, et al. Holoprosencephaly and preaxial polydactyly associated with a 1.24 Mb duplication encompassing *FBXW11* at 5q35.1. J Hum Genet. 2006; 51:721–726. [PubMed: 16865294]

Lanoue L, Dehart DB, Hinsdale ME, Maeda N, Tint GS, Sulik KK. Limb, genital, CNS, and facial malformations result from gene/environment-induced cholesterol deficiency: further evidence for a link to sonic hedgehog. Am J Med Genet. 1997; 73:24–31. [PubMed: 9375918]

Li YX, Yang HT, Zdanowicz M, Sicklick JK, Qi Y, Camp TJ, Diehl AM. Fetal alcohol exposure impairs hedgehog cholesterol modification and signaling. Lab Invest. 2007; 87:231–240. [PubMed: 17237799]

Lurie IW, Wulfsberg EA. 'Holoprosencephaly-polydactyly' (pseudotrisomy 13) syndrome: expansion of the phenotypic spectrum. Am J Med Genet. 1993; 47:405–409. [PubMed: 8135289]

Marquis-Nicholson R, Aftimos S, Ashton F, Love JM, Stone P, McFarlane J, et al. Pseudotrisomy 13 syndrome: use of homozygosity mapping to target candidate genes. Gene. 2011; 486:37–40. [PubMed: 21756987]

Meinecke P. Letter to the editor: holoprosencephaly, polydactyly and a lethal outcome-another observation. Proc Gr Genet Center. 1989; 8:78–79.

Mercier S, Dubourg C, Garcelon N, Campillo-Gimenez B, Gicquel I, Belleguic M, et al. New findings for phenotype-genotype correlations in a large European series of holoprosencephaly cases. J Med Genet. 2011; 48:752–760. [PubMed: 21940735]

Ming JE, Roessler E, Muenke M. Human developmental disorders and the sonic hedgehog pathway. Mol Med Today. 1998; 4:343–349. [PubMed: 9755453]

Moerman P, Fryns JP. Holoprosencephaly and postaxial polydactyly: another observation. J Med Genet. 1988; 25:501–504. [PubMed: 3172147]

Orioli IM, Castilla EE. Epidemiology of holoprosencephaly: prevalence and risk factors. Am J Med Genet C Semin Med Genet. 2010; 154C:13–21. [PubMed: 20104599]

Pineda-Alvarez DE, Dubourg C, David V, Roessler E, Muenke M. Current recommendations for the molecular evaluation of newly diagnosed holoprosencephaly patients. Am J Med Genet C Semin Med Genet. 2010; 154C:93–101. [PubMed: 20104604]

Ramaekers PR, Legius E, Verloes A, Gillerot Y, Vandenberghe K, Fryns JP. Holoprosencephaly and postaxial polydactyly with normal chromosomes. Another observation of a new malformation syndrome; a case report. Eur J Obstet Gynecol Reprod Biol. 1989; 36:161–165. [PubMed: 2365121]

Ramos-Arroyo MA, de Miguel C, Valiente A, Moreno-Languna S. Further delineation of pseudotrisomy 13 syndrome: a case without polydactyly. Am J Med Genet. 1994; 50:177–179. [PubMed: 8010349]

Seller MJ, Chitty LS, Dunbar H. Pseudotrisomy 13 and autosomal recessive holoprocencephaly. J Med Genet. 1993; 30:970–971. [PubMed: 8301659]

Shiota K, Tanimura T. Letter to the editor: holoprosencephaly, ventricular septal defect and postaxial polydactyly in a human embryo. J Med Genet. 1988; 25:502–503. [PubMed: 3172148]

Solomon BD, Mercier S, Vélez JI, Pineda-Alvarez DE, Wyllie A, Zhou N, et al. Analysis of genotype-phenotyp correlations in human holoprosencephaly. Am J Med Genet C Semin Med Genet. 2010; 154C:133–141. [PubMed: 20104608]

Utine GE, Alanay Y, Aktas D, Talim B, Kale G, Tuncbilek E. Pseudo-trisomy 13 in a fetus: further support for autosomal recessive inheritance. Turk J Pediatr. 2008; 50:287–290. [PubMed: 18773678]

Verloes A, Ayme S, Gambarelli D, Gonzales M, Le Merrer M, Mulliez N, et al. Holoprosencephaly-polydactyly ('pseudotrisomy 13') syndrome: a syndrome with features of hydrolethalus and

Smith–Lemli–Opitz syndrome: a collaborative multicenter study. J Med Genet. 1991; 28:297–303. [PubMed: 1865466]

Young ID, Madders DJ. Unknown syndrome: holoprosencephaly, congenital heart defects, and polydactyly. J Med Genet. 1987; 24:714–716. [PubMed: 3430550]

Zechi-Ceide RM, Ribeiro LA, Raskin S, Pereira Bertolacini CD, Guion-Almeida ML, Richieri-Costa A. Holoprosencephaly, ectrodactyly, and bilateral cleft of lip and palate: exclusion of SHH, TGIF, SIX3, GLI2, TP73L, and DHCR7 as candidate genes. Am J Med Genet. 2009; 149A:1277–1279. [PubMed: 19449411]

Table 1

Cases of holoprosencephaly–polydactyly syndrome/pseudotrisomy 13

Patient	Craniofacial features	Neuroanatomical description	Limb features	Genetic testing[a]	Other abnormal features	Specifics of other abnormal features	References
1	Microphthalmia, facial cleft	Hydrocephalus, HPE, ACC	Peripheral hypoplasia of left arm, tetramelic octodactyly	NS	Cardiac	Consanguinity, cardiac defects	Grote *et al*. (1984)
2	Maxillary agenesis, cleft palate	Alobar HPE, hydrocephalus	Bilateral upper limb postaxial polydactyly, club foot	46,XY	Cardiac, genitourinary	ASD, VSD, cardiac valve abnormalities, microphallus, cryptorchidism	Young and Madders (1987)
3	Hypotelorism, malformed ears	Hydrocephalus	Bilateral 2–3 toe syndactyly, right hand postaxial polydactyly, club foot	46,XY	Genitourinary	Ambiguous genitalia, imperforate anus	Atkin (1988)
4	Cyclopia, proboscis	Alobar HPE	Left foot postaxial polydactyly	46,XY	Genitourinary	Ambiguous genitalia	Atkin (1988)
5	Anophthalmia	Alobar HPE, hydrocephalus, occipital encephalocele, hypoplastic cerebellum and vermis	Postaxial polydactyly of the hands	46,XY	Pulmonary	Consanguinity, bilobed lungs	Donnai (1988)
6	Hypotelorism, suborbital proboscis	Alobar HPE, hydrocephalus, hypoplasia of the pituitary/thyroid glands	Bilateral upper limb postaxial polydactyly	46,XX	Renal	Renal dysplasia, hirtsutism	Moerman and Fryns (1988)
7	NS	HPE	Bilateral postaxial hexadactyly	NS	Other	Affected sibling	Moerman and Fryns (1988)
8	Proboscis, hypotelorism	Alobar HPE	Postaxial polydactyly	NS	Cardiac, genitourinary	Ambiguous genitalia, two vessel cord, VSD, affected sibling	Moerman and Fryns (1988)
9	Cyclopia	Alobar HPE	Bilateral postaxial polydactyly of upper and lower limbs	NS	Cardiac	VSD, two vessel cord	Shiota and Tanimura (1988)
10	Hypotelorism, absent nose, cleft lip/palate	Hydrocephalus, semilobar HPE, absent olfactory/chiasm/pituitary glands	Postaxial polydactyly in all extremities	46,XY	Cardiac, gastrointestinal, adrenal	Consanguinity, adrenal agenesis, splenomegaly, heart defects, affected sibling	Hewitt *et al*. (1989)
11	Microphthalmia, cleft lip, low-set ears	Alobar HPE, occipital encephalocele, hydrocephalus	Postaxial polydactyly of the hands	46,XX	Pulmonary	Lung abnormalities	Meinecke (1989)
12	Hypotelorism, microphthalmia	Hydrocephalus, absent frontal bone, lobar HPE, dysplastic basal ganglia, absent olfactory gland, corpus callosum, hippocampus, cerebellum	Postaxial polydactyly in the left hand and foot	46,XY	Gastrointestinal	Consanguinity, omphalocele, affected sibling	Bachman *et al*. (1990)
13	Microphthalmia, maxillary agenesis	Agenesis of brain structures, hydrocephalus	Postaxial polydactyly of both the hands and the left foot	NS	Other	Consanguinity	Bachman *et al*. (1990)
14	Microcephaly, large anterior fontanelle, low-set ears, hooked nose, microretrognathia, hypertelorism	Enlarged cisterna magna, fused lateral ventricles suggestive of semilobar HPE	Hypoplasia of the first phalanx, left club foot, right hip dislocation	46,XX; patient's father was mosaic 46XY/46XY (2;13)(2q24;13q33)	Cardiac, skeletal	Suggestive of consanguinity, 13 pairs of ribs, VSD, single palmar creases	Verloes *et al*. (1991)
15	Single nostril, median pseudocleft lip,	Semilobar HPE, ACC, agenesis of septum pellucidum and falx cerebri	Postaxial polydactyly of the hands and feet	46,XY	Gastrointestinal, genitourinary	Hypogenitalism, microphallus, Hirschsprung's disease,	Ramaekers *et al*. (1989)

Patient	Craniofacial features	Neuroanatomical description	Limb features	Genetic testing[a]	Other abnormal features	Specifics of other abnormal features	References
	hypotelorism, microphthalmia					thermoregulatory instability, electrolyte and thyroid hormone abnormalities	
16	Hypotelorism, microcephaly, hypoplastic nose, cleft palate	Dysplastic vermis and cerebellar foci, absent olfactory bulbs/tracts	Unilateral postaxial polydactyly (postminimus) of the left foot	NS	Cardiac	Consanguinity, IUGR, single palmer creases, VSD, ASD, affected sibling	Hennekam *et al*. (1991)
17	Microcephaly, hypotelorism, microphthalmia, flat rudimentary nose, bilateral cleft lip/palate, low-set ears	Midline continuity of corpus striatum and thalamus suggestive of semilobar HPE	Not present	46,XY	Genitourinary	Consanguinity, microphallus, cryptorchidism, affected sibling	Hennekam *et al*. (1991)
18	Microphthalmia, cleft lip	Seizures	Postaxial hexadactyly of the hands	Normal karyotype, NS	Other	Consanguinity, apnea	Cohen and Gorlin (1991)
19	Porboscus, cyclopia, microstomia, dysplastic ears	Hydramnios, holosphere	Bilateral postaxial polydactyly of the upper limbs	46,XY	Cardiac, adrenal	ASD, hypoplastic adrenals	Verloes *et al.* (1991)
20	Cleft palate, premaxillary agenesis	NS	Bilateral postaxial polydactyly of the upper limbs	46,XX	Cardiac, gastrointestinal	Cardiomegaly, TOGV, malrotated gut	Verloes *et al.* (1991)
21	Labiopalatine cleft	Hydrocephalus, macroopthalmia, semilobar HPE, aplasia of olfactory gland	Bilateral postaxial polydactyly of the upper limbs	46,XY	Cardiac, gastrointestinal, genitourinary, pulmonary, skeletal	Penile hypoplasia, aplasia of heart, lungs, gallbladder, testes, vertebral anomalies	Verloes *et al.* (1991)
22	NS	Hydrocephalus, alobar HPE, abnormal gyration	Bilateral postaxial polydactyly of the upper and lower limbs	46,XY	Other	Consanguinity	Verloes *et al.* (1991)
23	Absent ocular globes, single nostril	NS	Bilateral postaxial polydactyly	46,XY	Cardiac, genitourinary, adrenal	Ambiguous genitalia, VSD, hypoplastic adrenal glands	Verloes *et al.* (1991)
24	Cleft lip, hypotelerism, flat nose, absence of premaxilla, low-set ears, micrognathia	Semilobar HPE	Right hand postaxial polydactyly, upper limb shortness, radial hypoplasia, bilateral partial 2–3 syndactyly of the toes	46,XX	Cardiac, genitourinary	AV canal defect, lung abnormalities, bicornuate uterus	Boles *et al*. (1992)
25	Micro/anophthalmia	HPE	Postaxial polydactyly	Normal karyotype, NS	Cardiac, renal	Heart defects, renal hypoplasia, ambiguous genitalia	Higgins and Minnick (1992)
26	Cleft lip/palate	HPE	Postaxial polydactyly	Normal karyotype, NS	Cardiac, renal	Heart defects, renal hypoplasia	Higgins and Minnick (1992)
27	Cleft lip/palate, hypotelorism, absent nose	Semilobar HPE, absent olfactory lobes and optic nerves	Not present	46,XY; mother mosaic 45,X/46,XX/47,XXX/48,XXXX	Other	Sibling with poly/hexadactyly	Seller *et al*. (1993)
28	Microcephaly, upslanted fissure, exophthalmos, hypotelorism, cleft lip/palate, abnormal ears	Alobar HPE, seizures	Not present	46,XX	Cardiac, genitourinary	Heart anomalies, uterine duplication	Ramos-Arroyo *et al.* (1994)

Patient	Craniofacial features	Neuroanatomical description	Limb features	Genetic testing[a]	Other abnormal features	Specifics of other abnormal features	References
29	Microcephalic, microphthalmia, hypotelorism, cebocephalus, pseudocleft palate	Alobar HPE, absent olfactory and optic nerves, dysgenesis of hypopituitary,	NS	46,XX	Gastrointestinal, pulmonary, adrenal	Acrocyanosis, choanal atresia, lung and spleen abnormalities, dysgenesis of thyroid and adrenal glands	Koolen *et al.* (2006)
30	Hypotelorism, pseudocleft palate	Alobar HPE with fused thalamus, absent olfactory and optic nerves, dysgenesis of hypopituitary	Preaxial polydactyly of the left hand	46,XX	Gastrointestinal, adrenal	Choanal atresia, dysgenesis of thyroid and adrenal glands	Koolen *et al.* (2006)
31	Hypotelorism, nasal hypoplasia, midface cleft, premaxillary agenesis, low-set ears	Alobar HPE, absent olfactory and optic nerves	Postaxial polydactyly of the right hand	46,XX, partial trisomy 13q (13q22→qter) and partial monosomy 8p (8p23.3→pter)	Cardiac	Hypoplastic left heart	Chang (2003)
32	Macrocephaly, microagnathia, cleft lip/palate, hypertelorism, low-set ears, broad nose	Hydrocephalus, midline brain defect NS	Club foot	46,XY	Cardiac	Laryngeal stenosis, ASD	Cakir *et al*. (2006)
33	Microcephaly, hypotelorism, flat rudimentary nose, single nasal opening, high palate, dysplastic low-set ears	Alobar HPE	Postaxial polydactyly of the upper limbs	46,XX	Cardiac, gastrointestinal, genitourinary	Single creases, ASD, ventricular hypoplasia, duodenal stenosis	Ahmet *et al*. (2006)
34	Facial dysmorphic features, NS	Lobar HPE, seizures	Right preaxial polydactyly	dup5q35.1	Cardiac, genitourinary	Vesicoureteral reflux, VSD	Chen *et al.* (2005)
35	Hypotelorism, cleft lip, flat nose, single nostril, low-set ears	Semilobar HPE, hydrocephalus	Postaxial polydactyly in all extremities	46,XY	Cardiac, pulmonary	Consanguinity, lung abnormalities, VSD	Utine *et al*. (2008)
36	Macrocephalic, extropia, hypoplastic ala nasae	Semilobar HPE, hydrocephalus	Polysyndactyly in all extremities	46,XY; negative for mutations in *SHH, ZIC2, SIX3, TGIF, GLI3, FBXWII, DISP1*. Normal DHCR7	Other	Hemangioma, hypotonia, motor delay	Cordero *et al*. (2008)
37	Cleft lip/palate	Semilobar HPE	Bilateral syndactyly and hypoplasia of the toes	46XY, negative for mutations in *SHH, TGIF, SIX3, GLI2, TIP73L, DHCR7*	Genitourinary	Ectopic testes, microphallus	Zechi-Ceide *et al.* (2009)
38	Hypotelorism, cleft lip/palate, brachycephalic contour of the skull, flat nose with midline groove and shallow dimples in place of the nostrils, low-set ears	HPE, rudimentary falx and cerebral hemispheres replaced by a holosphere, interhemispheric fissure	Postaxial polydactyly, partial syndactyly	46,XX, with 21 noted LCSHs	Cardiac, pulmonary, adrenal	VSD, incomplete lobation of the right lung with rudimentary horizontal and oblique fissures, adrenal hypoplasia, possible affected siblings	Marquis-Nicholson *et al*. (2011)
39	Cleft lip/palate, flat nose	HPE	Hexadactyly, thumb hypoplasia, right radial deviation	46,XY, no deletion of 7q36 or	Cardiac, genitourinary, skeletal	Tetralogy of Fallot, hypospadias, vertebral anomalies, hypotonia	This report

Patient	Craniofacial features	Neuroanatomical description	Limb features	Genetic testing[a]	Other abnormal features	Specifics of other abnormal features	References
				22q11.2, no cholesterol abnormalities, negative *SHH*, *ZIC2*, *SIX3*, *TGIF*			
40	Proboscis	HPE	Polydactyly, NS	Normal karyotype, negative for mutations in *SHH*, *ZIC2*, *SIX3*, *TGIF*, *GLI2*, and normal oligonucleotide array CGH (Signature)	Cardiac, skeletal	Cardiac and vertebral anomalies	This report

The amount of information was variable for patients, and details are given as specified in the original sources; hence, the terminology may differ slightly between patients so as not to alter data through misinterpretation. ACC, agenesis of the corpus callosum; ASD, atrial septal defect; AV, atrioventricular; HPE, holoprosencephaly; IUGR, intrauterine growth restriction; LCSHs, long contiguous stretches of homozygosity; NS, not specified; TOGV, transposition of the great vessels; VSD, ventricular septal defect.

[a]By conventional chromosome analysis (karyotype) unless otherwise noted.