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Pallister-Hall Syndrome

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Summary

Clinical characteristics

Pallister-Hall syndrome (referred to as PHS in this entry) is characterized by a spectrum of anomalies ranging from polydactyly, asymptomatic bifid epiglottis, and hypothalamic hamartoma at the mild end to laryngotracheal cleft with neonatal lethality at the severe end. Individuals with mild PHS may be incorrectly diagnosed as having isolated postaxial polydactyly type A. Individuals with PHS can have pituitary insufficiency and may die as neonates from undiagnosed and untreated adrenal insufficiency.

Diagnosis/testing

The diagnosis of Pallister-Hall syndrome can be established in a proband with both hypothalamic hamartoma and mesoaxial polydactyly. Identification of a heterozygous pathogenic variant in *GLI3* confirms the diagnosis.

Management

Treatment of manifestations: Urgent treatment for endocrine abnormalities, especially cortisol deficiency; management of epiglottic abnormalities depending on the abnormality and the extent of respiratory compromise. Bifid epiglottis, the most common abnormality, typically does not need treatment. Standard treatment of anal atresia or stenosis; symptomatic treatment of seizures; elective repair of polydactyly; developmental intervention or special education for developmental delays.

Prevention of secondary complications: Biopsy or resection of hypothalamic hamartoma may result in complications and lifelong need for hormone replacement; seizures may begin or worsen with use of stimulants for attention deficit disorder.

Surveillance: During childhood, annual developmental assessment and annual medical evaluation to assess growth and monitor for signs of precocious puberty.

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Genetic counseling

Pallister-Hall syndrome is inherited in an autosomal dominant manner. Individuals with PHS may have an affected parent or may have the disorder as the result of a *de novo* pathogenic variant. About 25% of individuals have a *de novo* pathogenic variant. Persons with a *de novo* pathogenic variant are generally more severely affected than those with a family history of PHS. The risk to offspring of an affected individual is 50%. Prenatal testing for pregnancies at increased risk is possible if the pathogenic variant in the family is known. The reliability of ultrasound examination for prenatal diagnosis is unknown.

GeneReview Scope

Included Phenotypes
• Pallister-Hall syndrome (PHS) • Sub-Pallister-Hall syndrome (Sub-PHS)

For synonyms and outdated names see Nomenclature.

Diagnosis

Suggestive Findings

Pallister-Hall syndrome (PHS) **should be suspected** in individuals with the following features:

- **Hypothalamic hamartoma,** a non-enhancing mass in the floor of the third ventricle posterior to the optic chiasm that is isointense to gray matter on T_1 and T_2 pulse sequences of an MRI, but may have distinct intensity on FLAIR

  Note: Neither cranial CT examination nor cranial ultrasound examination is adequate for diagnosis of hypothalamic hamartoma.

- **Mesoaxial (i.e., insertional or central) polydactyly,** the presence of six or more well-formed digits with a Y-shaped metacarpal or metatarsal

- **Postaxial polydactyly (PAP) types A and B.** PAP-A is the presence of a well-formed digit on the ulnar or fibular aspect of the limb. PAP-B is the presence of a rudimentary digit or nubbin in the same location. Postaxial polydactyly is probably more common than mesoaxial polydactyly; however, the nonspecificity of postaxial polydactyly and the high frequency of postaxial polydactyly type B in persons of central African descent require caution in its use as a diagnostic feature.

- **Bifid epiglottis,** a midline anterior-posterior cleft of the epiglottis that involves at least two thirds of the epiglottic leaf. It is a useful feature for clinical diagnosis because it appears to be very rare in syndromes other than PHS and is also rare as an isolated malformation.

- **Other.** Imperforate anus, renal abnormalities including cystic malformations, renal hypoplasia, ectopic ureteral implantation, genitourinary anomalies including hydrometrocolpos, pulmonary segmentation anomalies including bilateral bilobed lungs, and non-polydactyly skeletal anomalies including short limbs

Establishing the Diagnosis

The clinical diagnosis of **PHS is established** in a proband with BOTH hypothalamic hamartoma and mesoaxial polydactyly.

Identification of a heterozygous pathogenic variant in *GLI3* by molecular genetic testing confirms the diagnosis of PHS (see Table 1).

The clinical diagnosis of **sub-PHS is established** in a proband with:

- One of the following:
  - Mesoaxial polydactyly
  - Hypothalamic hamartoma
  - Oligodactyly
  - Postaxial polydactyly; AND
- One of the following:
  - Bifid epiglottis
  - Imperforate anus
  - Small nails
  - Hypopituitarism
  - Growth hormone deficiency
  - Genital hypoplasia

Identification of a heterozygous pathogenic variant in *GLI3* by molecular genetic testing confirms the diagnosis of sub-PHS (see Table 1).

Note: Several individuals with nonsyndromic hypothalamic hamartomas and somatic mosaicism for *GLI3* pathogenic variants in the hamartoma have been reported [Wallace et al 2008]. While these individuals do not meet the clinical diagnostic criteria for PHS *sensu stricto*, they may be considered to have a partial form of PHS and consideration should be given to evaluating such individuals for other manifestations of the disorder.

Molecular Genetic Testing

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *GLI3* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- **A multigene panel** that includes *GLI3* and other genes of interest (see Differential Diagnosis) may be considered 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Pallister-Hall Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
GLI3	Sequence analysis [3]	20/22 [4, 5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]
Unknown [8]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Combined data from Johnston et al [2005], Johnston et al [2010], and Démurger et al [2015]
5. In eight (40%) of 20 persons with sub-PHS a *GLI3* pathogenic variant was identified; the pathogenic variants were similar to those identified in individuals with PHS [Johnston et al 2010].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.
8. In 5% of individuals with clinical features of PHS, no pathogenic variant in *GLI3* was found, suggesting at least one additional gene locus [Démurger et al 2015] or cryptic variants in *GLI3* (including deep intronic or mosaic pathogenic variants).

Clinical Characteristics

Clinical Description

Pallister-Hall syndrome (PHS) displays a wide range of severity. The literature frequently reflects the assumption that PHS is severe and Greig cephalopolysyndactyly syndrome is mild. This is clearly incorrect, as a minority of individuals with PHS show multiple severe anomalies and most individuals with PHS are mildly affected with polydactyly, asymptomatic bifid epiglottis, and hypothalamic hamartoma. Without careful clinical evaluation, these individuals may be incorrectly diagnosed with postaxial polydactyly type A (PAP-A).

Hypothalamic hamartoma. Hypothalamic hamartoma is a malformation, not a tumor. Hypothalamic hamartomas grow at the rate of – or more slowly than – the surrounding brain tissue. Hypothalamic hamartomas may be large (≤4 cm in greatest dimension); little correlation exists between the size of the hypothalamic hamartoma and presence or severity of symptoms. Individuals with hypothalamic hamartomas may have neurologic symptoms, although most are asymptomatic. Removal of the hypothalamic hamartoma is not indicated and often results in iatrogenic pituitary insufficiency or other complications.

Endocrine manifestations. The endocrine manifestations of a hypothalamic hamartoma range from isolated growth hormone deficiency or isolated precocious puberty to pan hypopituitarism, which can be life threatening. Cortisol deficiency can occur in individuals with nonfamilial PHS, but appears to be rare in those with familial PHS.

Neurologic findings. The best-described neurologic complication of hypothalamic hamartoma is gelastic epilepsy, a partial complex seizure manifest by clonic movements of the chest and diaphragm that simulate laughing. Other types of seizures may be caused by hypothalamic hamartoma. Seizures associated with hypothalamic hamartoma in individuals with PHS are generally milder and are responsive to treatment, in contrast to individuals with nonsyndromic hypothalamic hamartoma, who often have refractory seizures [Boudreau et al 2005]. No individual with PHS has been shown to have visual field loss even with a hypothalamic hamartoma near the optic chiasm.

Polydactyly. Postaxial polydactyly may be more common than mesoaxial polydactyly in individuals with PHS. Postaxial polydactyly (PAP) type A is the presence of a well-formed digit on the ulnar or fibular aspect of the limb. PAP type B is the presence of a rudimentary digit or nubbin in the same location. Mesoaxial (i.e., insertional or central) polydactyly is the presence of six or more well-formed digits with a Y-shaped metacarpal or metatarsal.

Note: The nonspecificity of postaxial polydactyly and the high frequency of PAP type B in persons of central African descent require caution in its use as a diagnostic feature.

Epiglottic abnormalities. Bifid epiglottis is nearly always asymptomatic; however, the more severe clefts of the larynx reported in individuals with PHS can cause severe airway symptoms. Posterior laryngeal clefts can be fatal.

Psychiatric and neuropsychological findings. Some individuals with PHS have behavioral manifestations including a few with severe intellectual disability and behavioral disturbances [Ng et al 2004]. A larger study of behavioral manifestations of this disorder was inconclusive, reflecting the difficulty of assessing mild behavioral phenotypes in rare disorders [Azzam et al 2005].

Genitourinary anomalies. Renal abnormalities include cystic malformations, renal hypoplasia, and ectopic ureteral implantation; genitourinary anomalies include hydrometrocolpos. The pathogenetic mechanism of the genitourinary anomalies has been delineated [Blake et al 2016].

Other findings include imperforate anus, pulmonary segmentation anomalies including bilateral bilobed lungs, and non-polydactyly skeletal anomalies including short limbs.

The prognosis for an individual with PHS and no known family history of PHS is based on the malformations present in the individual. Literature surveys are not useful for the purpose of establishing the prognosis because reported persons tend to show bias of ascertainment to more severe involvement. Although PHS has been categorized as a member of the CAVE (*c*erebro*a*cro*v*isceral *e*arly lethality) group of disorders, few affected individuals have an early lethality phenotype. This early lethality is most likely attributable to pan hypopituitarism that is caused by pituitary or hypothalamic dysplasia or severe airway malformations such as laryngotracheal clefts. In addition, imperforate anus can cause serious complications if not recognized promptly. Thus, in the absence of life-threatening malformations, the prognosis should be assumed to be good for individuals with the nonfamilial occurrence of PHS. For individuals with a family history of affected family members, the prognosis is based on the degree of severity present in the family.

Sub-PHS

Sub-PHS is a descriptor applied to individuals who have features of PHS but do not meet the clinical criteria for diagnosis of PHS (see Establishing the Diagnosis). In one study, eight (40%) of 20 persons affected with sub-PHS had pathogenic variants in *GLI3* that were similar to the pathogenic variants in individuals with PHS [Johnston et al 2010].

Genotype-Phenotype Correlations

See Figure 1. The mutational spectra of GCPS and PHS are mostly distinct. GCPS is caused by pathogenic variants of all types, whereas PHS is only caused by truncating variants and one splice variant that generates a frameshift and a truncation. Within the frameshift variant category, a genotype-phenotype correlation has been demonstrated on two levels:

- **Class of variant.** Pathogenic variants of all classes can cause Greig cephalopolysyndactyly syndrome (GCPS), whereas the majority of pathogenic variants that cause the allelic disorder PHS are frameshift

variants. Haploinsufficiency for GLI3 causes GCPS, whereas truncating variants 3' of the zinc finger domain of *GLI3* generally cause PHS [Kang et al 1997] (Figure 1A).

- **Variant position.** Among all frameshift variants in *GLI3*, variants in the first third of the gene are only known to cause GCPS (Figure 1B). Frameshift variants in the middle third of the gene cause PHS and (uncommonly) GCPS. Frameshift variants in the final third of the gene cause GCPS. There is no apparent correlation of the variant position within each of the three regions and the severity of the corresponding phenotypes.

Penetrance

No instances of incomplete penetrance of PHS have been published.

Ng et al [2004] reported one individual with apparent germline mosaicism without evident clinical features.

Nomenclature

Other descriptors used include the following:

- **Hypothalamic hamartoblastoma syndrome.** This is incorrect as "blastoma" refers to tissues in which the neural elements of hamartomas are immature, and is also incorrect as it does not reflect the syndromic nature of the phenotype and may be confused with isolated hamartomas.
- **CAVE (*c*erebro*a*cro*v*isceral *e*arly lethality) complex.** This designation is inappropriate as most individuals are mildly affected and do not manifest early lethality.
- **Hall-Pallister syndrome**

Note: The abbreviation "HPS" is used for the Hermansky-Pudlak syndrome.

Prevalence

PHS is rare. The prevalence is unknown. More than 100 affected persons are known to the author [Biesecker, personal observation] and a number of additional individuals have been reported (see, e.g., Démurger et al [2015]). It is suspected that many individuals with postaxial polydactyly and asymptomatic hypothalamic hamartoma or bifid epiglottis may be misdiagnosed as having nonsyndromic PAP-A.

PHS is pan ethnic.

Genetically Related (Allelic) Disorders

GLI3. Other phenotypes are associated with pathogenic variants in *GLI3*.

Greig cephalopolysyndactyly syndrome (GCPS) includes polydactyly that is commonly preaxial and may also be postaxial. The polydactyly is commonly associated with cutaneous syndactyly. Craniofacial features seen in GCPS include widely spaced eyes, broad forehead, and macrocephaly. Mesoaxial polydactyly and osseous syndactyly of the metacarpals are not part of GCPS.

Most individuals with GCPS have pathogenic variants that cause haploinsufficiency of GLI3, although a few individuals with a single-nucleotide variant (SNV) have been described. However, it has not been demonstrated that these SNVs have stable mRNA or protein. If the stability of these molecules were reduced, the SNVs would result in functional haploinsufficiency. At least one individual with preaxial polydactyly type IV (PPDIV) has been reported to have a *GLI3* pathogenic variant [Radhakrishna et al 1999] – a finding consistent with clinical suspicion that PPDIV is a mild form of GCPS, in which the limb findings occur without the craniofacial features. However, the craniofacial findings are subtle and controversy exists as to the distinction between nonsyndromic PPDIV and mild GCPS [Biesecker 2006].

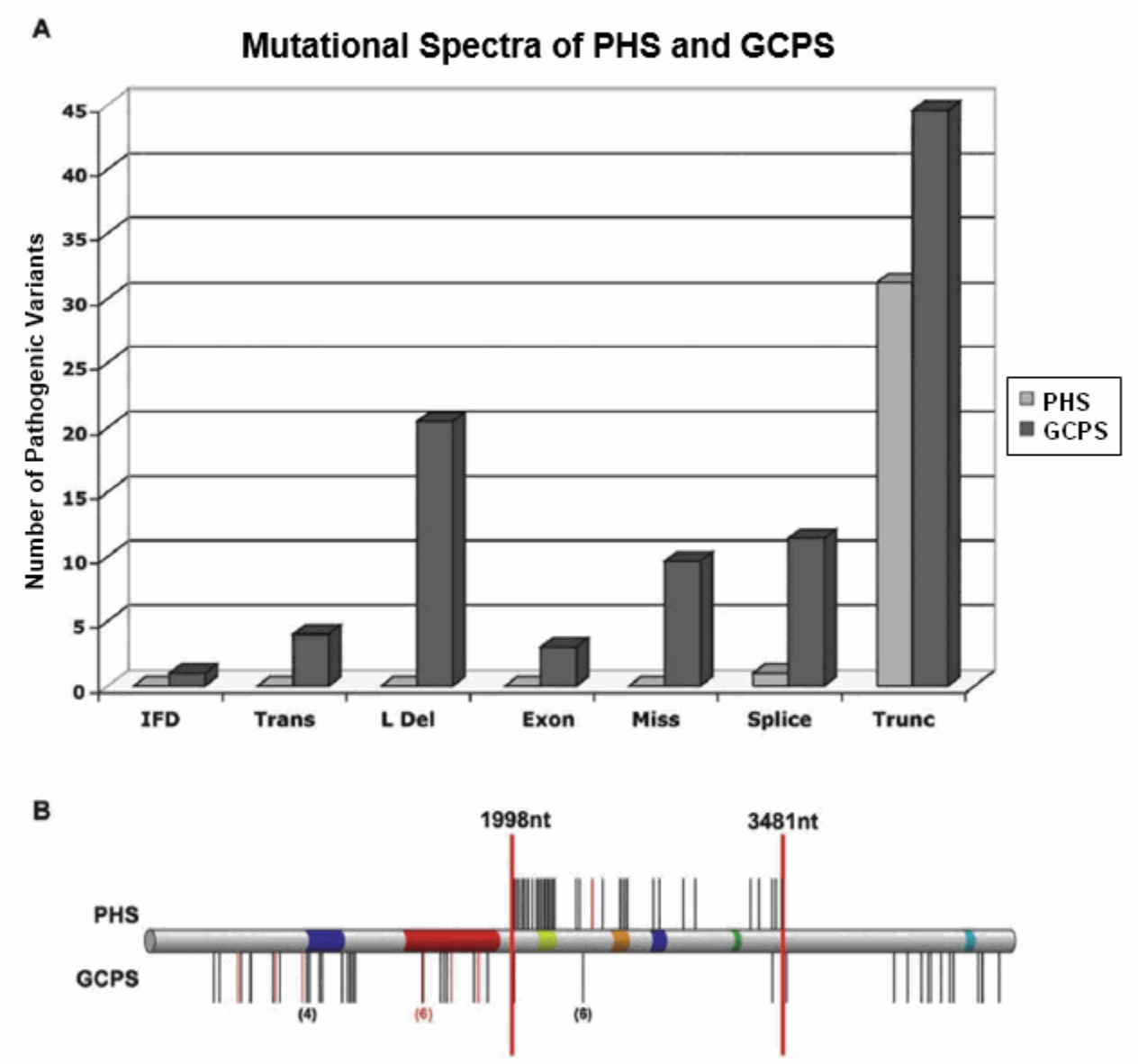

Figure 1. The mutational spectra of PHS and GCPS are mostly distinct.

Sub-GCPS is a descriptor applied to individuals who have features of GCPS, but do not meet clinical criteria for a diagnosis of GCPS. The clinical criteria for sub-GCPS include:

- One of the following:
  - Preaxial polydactyly
  - Broad thumbs or great toes
  - Cutaneous syndactyly
  - Macrocephaly
  - Widely spaced eyes;

  OR
- Both of the following:
  - Postaxial polydactyly
  - Hypoplasia of the corpus callosum

In one study, eight (29%) of 28 individuals who met these criteria had pathogenic variants in *GLI3* [Johnston et al 2010].

Isolated postaxial polydactyly type A (PAP-A). Pathogenic variants in *GLI3* have been identified in individuals with PAP-A [Radhakrishna et al 1999]. The PAP-A phenotype has also been shown to result from pathogenic variants in other genes.

Isolated preaxial polydactyly type IV (PPDIV) comprises preaxial polydactyly of the hands and/or feet in the absence of other malformations. The severity of the PPDIV is highly variable [Everman 2006]. Because macrocephaly occurs in the general population and is common in GCPS, the presence of macrocephaly in a person with apparently isolated PPDIV is difficult to interpret.

Oral-facial-digital overlap syndrome is a descriptor used for individuals who have features that overlap with OFD and PHS. The criteria for this disorder:

- Polydactyly; AND
- One of the following:
  - Oral frenula
  - Oral hamartoma
  - Cleft lip
  - Cleft palate
  - Cerebellar vermis hypoplasia
  - Tibial hypoplasia

In one study, six (29%) of 21 individuals in this category had a pathogenic variant in *GLI3* [Johnston et al 2010].

Differential Diagnosis

Central polydactyly

- **Oral-facial-digital syndrome type 6** (OMIM 277170), caused by biallelic pathogenic variants in *CPLANE1*, includes central polydactyly with hypoplasia of the cerebellar vermis. Renal agenesis and dysplasia have been described.
- **Holzgreve syndrome** (OMIM 236110) includes central polydactyly, cleft palate, heart defect.

Postaxial polydactyly

- **McKusick-Kaufman syndrome(MKS)** is characterized by the triad of hydrometrocolpos in females and genital malformations in males, postaxial polydactyly (PAP) or central polydactyly, and congenital heart disease (CHD). Pathogenic variants in *MKKS* have been found in individuals with MKS within the Amish population. Inheritance is autosomal recessive.
- **Bardet-Biedl syndrome(BBS)** is characterized by rod-cone dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotropic hypogonadism, complex female genitourinary malformations, and renal dysfunction, which is a major cause of morbidity and mortality. Hypothalamic hamartoma and bifid epiglottis are rare manifestations of BBS [Stevens & Ledbetter 2005]. At least 19 genes are associated with BBS: *BBS1*, *BBS2*, *ARL6*, *BBS4*, *BBS5*, *MKKS*, *BBS7*, *TTC8*, *BBS9*, *BBS10*, *TRIM32*, *BBS12, MKS1*, *CEP290*, *WDPCP*, *SDCCAG8*, *LZTFL1*, *BBIP1*, and *IFT27*. Inheritance is typically autosomal recessive.
- **Holt-Oram syndrome(HOS)** is characterized by: upper-extremity malformations involving radial, thenar, or carpal bones; a personal and/or family history of congenital heart malformation (most commonly ostium secundum atrial septal defect and ventricular septal defect, especially those occurring in the muscular trabeculated septum); and/or cardiac conduction disease. *TBX5* pathogenic variants are found

in more than 70% of individuals who meet strict diagnostic criteria for HOS. Inheritance is autosomal dominant.

- **Smith-Lemli-Opitz syndrome (SLOS)** is a congenital multiple anomaly syndrome caused by an abnormality in cholesterol metabolism resulting from deficiency of the enzyme 7-dehydrocholesterol reductase. It is characterized by prenatal and postnatal growth retardation, microcephaly, moderate-to-severe intellectual disability, and multiple major and minor malformations including postaxial polydactyly. *DHCR7* is the only gene known to be associated with SLOS. Inheritance is autosomal recessive.

Hypothalamic hamartoma. Nonsyndromic or isolated hypothalamic hamartomas may cause either endocrine disturbance (most commonly, growth hormone deficiency or precocious puberty) or a severe neurologic picture of refractory seizures, behavior problems, and cognitive decline. Gelastic epilepsy may be associated. Somatic *GLI3* pathogenic variants have been identified in nonsyndromic hypothalamic hamartomas [Wallace et al 2008].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Pallister-Hall syndrome (PHS), the following evaluations are recommended if they have not already been completed:

- Assessment for cortisol deficiency. This must be performed urgently in individuals who have no family history of PHS and in individuals who have family members with PHS and cortisol deficiency. Of note, adrenal crisis can be lethal in infants who have not undergone proper evaluation and treatment for adrenal insufficiency.
- Consultation by an endocrinologist, including evaluation of growth hormone secretion, FSH and LH secretion, and serum concentration of thyroid hormone in early infancy after evaluation for and treatment of ACTH deficiency
- Cranial MRI to establish the location and extent of hamartoma
- Neurologic examination to exclude signs of intracranial hypertension, which is not typical of hypothalamic hamartomas
- Visualization of the epiglottis by laryngoscopy; urgent evaluation by an otolaryngologist for laryngotracheal cleft when signs or symptoms of aspiration are present; elective evaluation by an otolaryngologist in asymptomatic individuals for the purpose of establishing the diagnosis or establishing the extent of anomalies
- Limb radiographs to distinguish postaxial polydactyly from central polydactyly
- Evaluation by a hand surgeon to assess the timing and surgical approach to correct the polydactyly. Note that the surgical correction of mesoaxial polydactyly is typically more complex than for postaxial polydactyly and should be undertaken by an expert surgeon.
- Renal ultrasonography to evaluate for renal anomalies
- Surgical consultation for imperforate anus or anal stenosis if present
- Developmental assessment
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Endocrine abnormalities are treated as in the general population, with treatment for cortisol deficiency being the most urgent.

Anal atresia or stenosis should be treated in standard fashion.

Management of epiglottic abnormalities depends on the type of abnormality and extent of respiratory compromise and is the same as in the general population. Bifid epiglottis is commonly asymptomatic and most do not require treatment, unless accompanied by clear evidence of obstruction or associated with other anomalies, such as tracheal stenosis.

Seizures are treated symptomatically. Seizures associated with PHS are commonly responsive to antiepileptic drugs (AEDs), whereas seizures associated with nonsyndromic hypothalamic hamartomas are more commonly refractory to AEDs.

Repair of polydactyly should be undertaken on an elective basis.

If developmental delays are detected, intervention and/or special education are indicated.

Occupational therapy for manual dexterity of the hands may be necessary as some individuals with mesoaxial polydactyly have digital malalignment.

Prevention of Secondary Complications

Only under the most unusual circumstances should a hypothalamic hamartoma be removed or even biopsied because the complications of surgery and the need for lifelong hormone supplements postoperatively generally outweigh the benefits.

Use of stimulants for attention deficit disorder should be considered carefully in persons with a CNS lesion that predisposes to seizures (e.g., hypothalamic hamartoma).

Surveillance

During childhood:

- Annual medical evaluations to assess growth and monitor for signs of precocious puberty
- Annual screening for developmental delay or learning disorders

Agents/Circumstances to Avoid

As noted in Prevention of Secondary Complications, some stimulants (commonly used for attention deficit and hyperactivity disorders) may exacerbate seizures.

Evaluation of Relatives at Risk

It is appropriate to evaluate relatives at risk in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures.

- If the pathogenic variant in the family is known, molecular genetic testing can be used to clarify the genetic status of at-risk relatives.
- If the pathogenic variant in the family is not known, clinical examination for polydactyly, laryngoscopy for bifid epiglottis, or MRI for hypothalamic hamartoma can be used to clarify the genetic status of at-risk relatives.
- The first-degree relative of a proband is considered affected if hypothalamic hamartoma or central or postaxial polydactyly are present in the relative. (Postaxial polydactyly type B can be used as a diagnostic criterion for first-degree relatives only in persons who are not of central African descent.)

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnancy management of a woman affected with PHS should be attuned to guidelines for the specific manifestations of the disorder. For example, the management of pregnant women with gelastic epilepsy who need to take anticonvulsants is challenging. As there are no guidelines specific to PHS, the author recommends following general guidelines for anticonvulsants in pregnancy [Borthen & Gilhus 2012].

In general, women with epilepsy or a seizure disorder from any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of antiepileptic medication during pregnancy reduces this risk. However, exposure to antiepileptic medication may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from antiepileptic medication exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of antiepileptic medication to treat a maternal seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given antiepileptic drug during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

The management of fertility and pregnancy (which is uncommon in individuals with hypopituitarism) in individuals with hypopituitarism caused by PHS is similarly challenging and again, it is recommended that general guidelines be followed [Kübler et al 2009].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Pallister-Hall syndrome (PHS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 75% of individuals diagnosed with PHS have an affected parent.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant (i.e., a proband with no known family history of PHS).
- If the *GLI3* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, two possible explanations are a *de novo* pathogenic variant in the proband or germline mosaicism in a parent.
    - ***De novo* pathogenic variant.** The proportion of probands who have a *de novo GLI3* pathogenic variant is about 25%. Individuals with a *de novoGLI3* pathogenic variant are generally more severely affected than individuals with a family history of PHS [JJ Johnston, unpublished data].

- **Germline mosaicism.** The description of a single parent with germline mosaicism for a *GLI3* pathogenic variant [Ng et al 2004] does not allow for estimation of the frequency of this event for genetic recurrence risk estimates, but it must be considered as a possibility.

- Because there has only been a single occurrence of parental germline mosaicism (and no reports of non-penetrance) reported to date, the parents of a proband with no known family history of PHS should be examined for evidence of extra digits. If there is no evidence of extra digits, it is reasonable to conclude that the probability of the parent being non-penetrant or mosaic is very low.

Sibs of a proband

- The risk to the sibs of a proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low, but greater than that of the general population because of the possibility of germline mosaicism. One instance of parental mosaicism has been reported [Ng et al 2004].
- The risks to sibs of individuals with isolated hypothalamic hamartomas caused by somatic *GLI3* pathogenic variants is unknown.

Offspring of a proband

- Each child of an individual with PHS has a 50% chance of inheriting the *GLI3* pathogenic variant.
- Because intrafamilial variability appears to be low, affected offspring would be expected to have clinical findings similar to those of the parent.
- The risk to offspring of individuals with isolated hypothalamic hamartomas caused by somatic *GLI3* pathogenic variants is unknown.

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 *GLI3* pathogenic variant, his or her family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk family members for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant or clinical evidence of the disorder, it is likely that the proband has a *de novo* pathogenic variant. As noted in Risk to Family Members, **Sibs of a proband**, one instance of germline mosaicism and sib recurrence of PHS has been described. However, the actual risk for this phenomenon cannot be estimated from a single case, though it is clearly not common. Other possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the *GLI3* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for PHS are possible.

Ultrasound examination. In fetuses at 50% risk, prenatal ultrasound examination may detect polydactyly. However, a normal ultrasound examination does not eliminate the possibility of PHS in the fetus.

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.

- **National Library of Medicine Genetics Home Reference**
  Pallister-Hall syndrome
- **American Epilepsy Society (AES)**
  www.aesnet.org
- **Epilepsy Foundation**
  8301 Professional Place East
  Suite 200
  Landover MD 20785-7223
  Phone: 800-332-1000 (toll-free)
  Email: ContactUs@efa.org
  www.epilepsy.com
- **Medline Plus**
  Polydactyly

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Pallister-Hall Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GLI3	7p14.1	Transcriptional activator GLI3	GLI3 @ LOVD	GLI3	GLI3

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Pallister-Hall Syndrome (View All in OMIM)

146510	PALLISTER-HALL SYNDROME; PHS
165240	GLI-KRUPPEL FAMILY MEMBER 3; GLI3

Gene structure. *GLI3* extends over approximately 276 kb and includes 15 exons. The mRNA is approximately 8 kb, the reference cDNA is 8,209 bp (NM_000168.3, NP_000159.3), and the open reading frame is 4,740 bp. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. A number of putative benign variants exist in *GLI3*; see Table 2 (pdf). Most of the variants have been seen in multiple unrelated persons and are not believed to be associated with any phenotypic effects, although they have not been rigorously analyzed for subtle effects. They are included in Table 2 if they lie within an exon or if they are in an intron within 25 bp of an exon. Readers should refer to the dbSNP reference number, Table A (**Locus-Specific Databases**, **HGMD**, and **ClinVar**), and the primary literature for confirmation and for additional data.

Pathogenic variants. Selected pathogenic variants reported in individuals with PHS are in Table 3 (pdf). Multiple *de novo* pathogenic variants have been identified by Johnston et al [2005], Johnston et al [2010], and Démurger et al [2015].

Normal gene product. The gene encodes a protein of 1,580 amino acids.

Note: As the result of a cDNA sequencing error, older citations described a longer open reading frame that predicted a protein of 1,596 amino acids; the error has been corrected in the GenBank entry NM_000168.3.

Abnormal gene product. It has been shown that truncated forms of the GLI3 protein repress transcription [Blake et al 2016].

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Chapter Notes

Author Notes

Author's web page

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Revision History

- 18 May 2017 (sw) Comprehensive update posted live
- 18 December 2014 (me) Comprehensive update posted live
- 13 September 2012 (me) Comprehensive update posted live
- 15 June 2010 (cd) Revision: deletion/duplication analysis no longer available clinically

- 3 February 2009 (cd) Revision: deletion/duplication analysis available clinically
- 18 March 2008 (me) Comprehensive update posted live
- 2 June 2006 (cd) Revision: prenatal diagnosis clinically available
- 6 June 2005 (me) Comprehensive update posted live
- 1 May 2003 (me) Comprehensive update posted live
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- 20 January 2000 (lb) Original submission

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