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GLI3-Related Pallister-Hall Syndrome

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Summary

Clinical characteristics

GLI3-related Pallister-Hall syndrome (*GLI3*-PHS) 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 *GLI3*-PHS may be incorrectly diagnosed as having isolated postaxial polydactyly type A. Individuals with *GLI3*-PHS can have pituitary insufficiency and may die as neonates from undiagnosed and untreated adrenal insufficiency.

Diagnosis/testing

The diagnosis of *GLI3*-PHS 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; symptomatic treatment of seizures; elective repair of polydactyly. 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. Treatment of behavioral issues per psychologist &/or psychiatrist; seizures may begin or worsen with use of stimulants for attention-deficit disorder; developmental intervention and/or special education for developmental delays; standard treatment of anal atresia or stenosis.

Surveillance: Annually during childhood: assess growth, monitor for signs of precocious puberty, and assess developmental progress, educational needs, and behavioral issues.

Agents/circumstances to avoid: Biopsy or resection of hypothalamic hamartoma may result in complications and lifelong need for hormone replacement. Some stimulants used for attention-deficit/hyperactivity disorder may exacerbate seizures.

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Genetic counseling

GLI3-PHS is inherited in an autosomal dominant manner. Individuals with *GLI3*-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 *GLI3*-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.

Diagnosis

Consensus clinical diagnostic criteria for *GLI3*-related Pallister-Hall syndrome (*GLI3*-PHS) have been published [Johnston et al 2010].

Suggestive Findings

GLI3-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-weighted 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

  Bifid epiglottis is a useful feature for clinical diagnosis because it appears to be very rare in syndromes other than *GLI3*-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 nonpolydactyly skeletal anomalies including short limbs

- **Family history consistent with autosomal dominant inheritance** (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The clinical diagnosis of *GLI3*-PHS can be **established** in a proband with BOTH hypothalamic hamartoma and mesoaxial polydactyly, or the clinico-molecular diagnosis can be established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *GLI3* identified by molecular genetic testing (see Table 1) [Johnston et al 2010].

Note: (1) Per ACMG/AMP variant classification guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are handled similarly in a diagnostic testing clinical setting, meaning that both can lead to a clinico-molecular diagnosis [Katz et al 2020]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any pathogenic or likely pathogenic variants. (2) Identification of a heterozygous *GLI3* variant of uncertain significance does not establish or rule out the diagnosis. (3) Molecular testing can often identify novel frameshift and nonsense variants in *GLI3* in individuals with *GLI3*-PHS and related phenotypes. Because they are novel, there is often a dearth of clinical and molecular data that can be used to classify the variant. Given that the mechanism of disease does not involve nonsense-mediated decay of the mRNA in these cases, current ACMG/AMP interpretations, with the ClinGen PVS1 criterion specification, may commonly lead to a classification of such a variant as a variant of uncertain significance. It is recommended that an expert with experience in the clinico-molecular diagnosis of this disorder be consulted in this scenario [Lo-Ciganic et al 2019].

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *GLI3*-PHS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *GLI3* to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: To date, large exon or multiexon deletions or duplications have not been reported in individuals with *GLI3*-PHS.

A multigene panel that includes *GLI3* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition. 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*. (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.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 *GLI3*-Related Pallister-Hall Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
GLI3	Sequence analysis [3]	~95% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]
Unknown [7]	NA	~5%

NA = not applicable
1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; 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. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. To date, no large exon or multiexon deletions or duplications have been reported in individuals with *GLI3*-related Pallister-Hall syndrome. Large deletions and duplications of *GLI3* have been reported in individuals with Greig cephalopolysyndactyly syndrome (see Genetically Related Disorders).
7. In 5% of individuals with clinical features of PHS, no pathogenic variant in *GLI3* was found, suggesting that variants in at least one additional gene locus [Démurger et al 2015, Rubino et al 2018] or unidentified cryptic variants in *GLI3* (including deep intronic or mosaic pathogenic variants) are causative of PHS.

Clinical Characteristics

Clinical Description

GLI3-related Pallister-Hall syndrome (*GLI3*-PHS) displays a wide range of severity. The literature frequently reflects the assumption that *GLI3*-PHS is severe and Greig cephalopolysyndactyly syndrome (GCPS) is mild. This assumption is incorrect, as a minority of individuals with *GLI3*-PHS show multiple severe anomalies and most individuals with *GLI3*-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).

Table 2. *GLI3*-Related Pallister-Hall Syndrome: Frequency of Select Features

Feature	Frequency of Feature [1]	Comment
Hypothalamic hamartoma	+++	
Polydactyly	+++	Postaxial or mesoaxial
Epiglottis abnormalities	++	
Behavioral manifestations	+	
Genitourinary anomalies	+	
Pulmonary segmentation anomalies	+	
Imperforate anus	+	

Table 2. continued from previous page.

Feature	Frequency of Feature [1]	Comment
Oligodactyly	+	

+++ = common; ++ = seen in many affected persons; + = seen in some or a few affected persons

1. Even these coarse estimates of the frequency of specific features are likely to be heavily skewed by phenotypic ascertainment bias. It is likely that the overwhelming majority of diagnosed individuals were ascertained because they had a hypothalamic hamartoma and polydactyly. Therefore, to assert that these malformations are common in *GLI3*-PHS is circular reasoning. This bias can only be resolved by studies using broad-based exome or genome testing of individuals with a wide range of features.

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 panhypopituitarism, which can be life threatening. Cortisol deficiency can occur in individuals with nonfamilial *GLI3*-PHS but appears to be rare in those with familial *GLI3*-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 *GLI3*-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 *GLI3*-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 *GLI3*-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 *GLI3*-PHS can cause severe airway symptoms. Posterior laryngeal clefts can be fatal.

Psychiatric and neuropsychological findings. Some individuals with *GLI3*-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, small kidneys, 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 nonpolydactyly skeletal anomalies including short limbs.

Prognosis for an individual with *GLI3*-PHS and no known family history of *GLI3*-PHS is based on the malformations present in the individual. Literature surveys are not useful for the purpose of establishing the prognosis because there is a large degree of inter-individual heterogeneity and publications tend to show bias of ascertainment to more severe involvement. Although *GLI3*-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. The CAVE descriptor should be discouraged. Early lethality in *GLI3*-PHS is most likely attributable to panhypopituitarism 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 *GLI3*-PHS. For individuals with a family history of affected family members, the prognosis is based on the degree of severity present in the family.

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

Sub-PHS. A previous publication suggested the term sub-PHS as a descriptor for those individuals who did not meet the above-specified clinical diagnostic criteria for *GLI3*-PHS but had some overlapping features and a pathogenic *GLI3* variant consistent with the PHS pathogenetic mechanism (see Nomenclature).

Genotype-Phenotype Correlations

The mutational spectra of GCPS and *GLI3*-PHS are mostly distinct (see Figure 1). GCPS is caused by pathogenic variants of all types, whereas *GLI3*-PHS is overwhelmingly caused by truncating variants that generate 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 GCPS, whereas the majority of pathogenic variants that cause the allelic disorder *GLI3*-PHS are frameshift variants. Haploinsufficiency for *GLI3* causes GCPS, whereas truncating variants 3' of the zinc finger domain of *GLI3* generally cause *GLI3*-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 *GLI3*-PHS and (uncommonly) GCPS. Frameshift variants in the final third of the gene cause GCPS. No apparent correlation exists between the variant position within each of the three regions and the severity of the corresponding phenotypes.

  Note: A single truncating variant in the *GLI3*-PHS region, c.2374C>T (p.Arg792Ter), can cause GCPS and has been observed in six apparently unrelated families [Johnston et al 2005].

Two splice variants have been associated with *GLI3*-PHS, both presumably causing retention of intron 14, which is also predicted to cause a similarly truncated protein [Al-Qattan et al 2017].

Penetrance

No instances of incomplete penetrance of *GLI3*-PHS have been published.

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

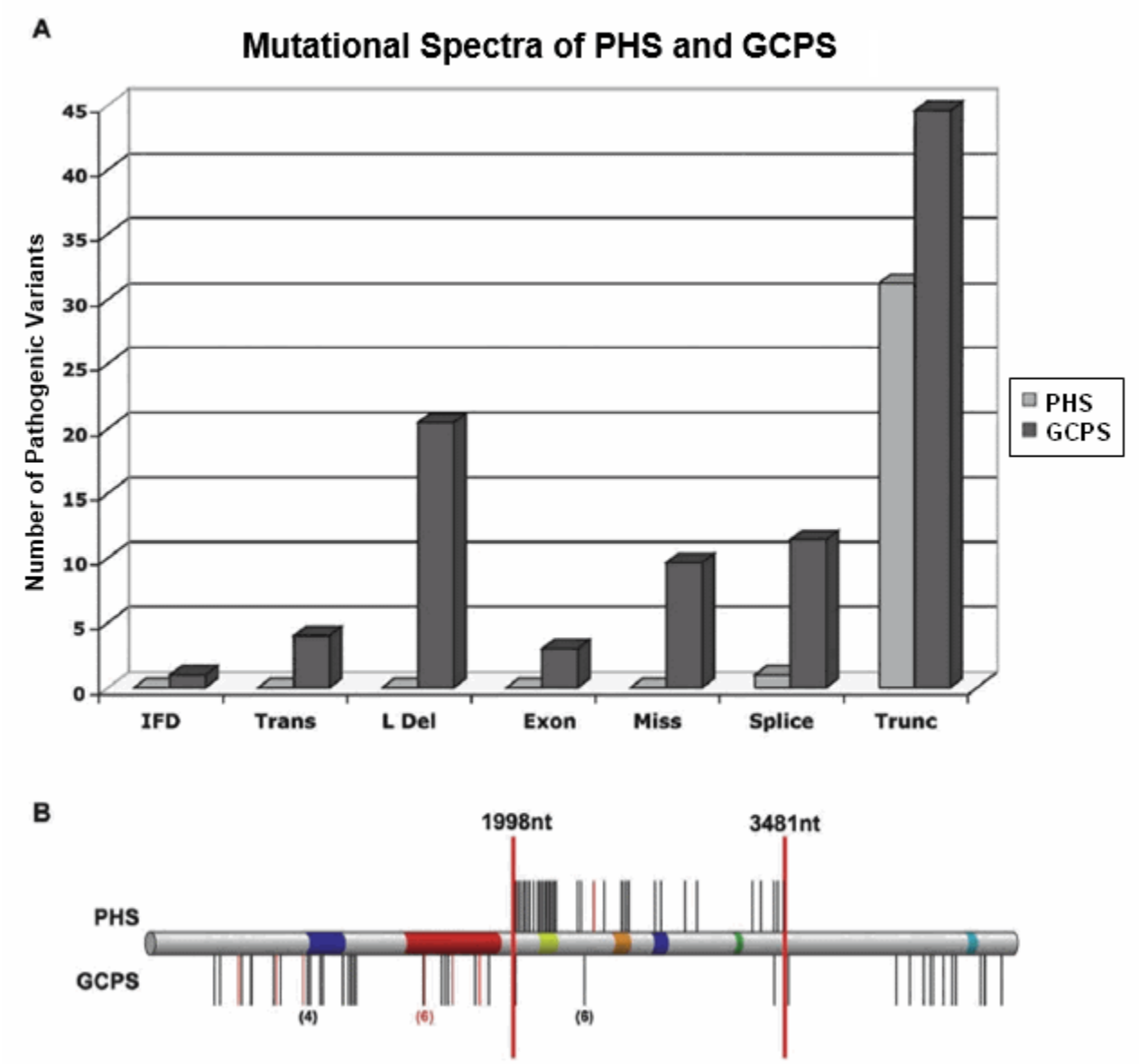

Figure 1. The mutational spectra of *GLI3*-PHS and GCPS are mostly distinct.

Nomenclature

Other descriptors used include the following:

- **Hypothalamic hamartoblastoma syndrome.** This is incorrect; "blastoma" refers to tissues in which the neural elements of hamartomas are immature, it does not reflect the syndromic nature of the phenotype, and it 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.
- **Sub-PHS.** This designation refers to individuals who do not meet the clinical diagnostic criteria for *GLI3*-PHS but have some features of PHS and a pathogenic *GLI3* variant consistent with the PHS pathogenetic mechanism. However, sub-PHS is probably not a useful term and these individuals should instead be considered to have a mild form of PHS.
- **Hall-Pallister syndrome**

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

Prevalence

GLI3-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.

Genetically Related (Allelic) Disorders

Other phenotypes known to be associated with germline pathogenic variants in *GLI3* are summarized in Table 3.

Note: Haploinsufficiency for *GLI3* causes Greig cephalopolysyndactyly syndrome (GCPS), whereas truncating variants in the middle third of the gene, 3' of the zinc finger domain of *GLI3*, generally cause *GLI3*-related Pallister-Hall syndrome (*GLI3*-PHS) [Johnston et al 2005].

Table 3. *GLI3* Allelic Disorders

Disorder	MOI	Clinical Features	Comment
Greig cephalopolysyndactyly syndrome (GCPS)	AD	Polydactyly (commonly preaxial, may be postaxial); commonly assoc w/ cutaneous syndactyly. Craniofacial features incl widely spaced eyes, broad forehead, & macrocephaly. Mesoaxial polydactyly & osseous syndactyly of metacarpals are not part of GCPS.	It is often wrongly assumed that *GLI3*-PHS is severe & GCPS is mild; most persons w/PHS are mildly affected, w/polydactyly, asymptomatic bifid epiglottis, & HH.
Postaxial polydactyly type A (PAP-A) (OMIM 174200)	AD	Limb malformation limited to presence of a single, well-formed supernumerary postaxial digit on 1 or both hands & feet	There is some controversy as to whether PAP-A is distinct from *GLI3*-PHS or is instead a variant of *GLI3*-PHS w/mild, subtle, & asymptomatic bifid epiglottis, HH, anal stenosis, & other signs.
Preaxial polydactyly type IV (PPD-IV) (OMIM 174700)	AD	Preaxial polydactyly of hands &/or feet w/o other malformations (typically same pattern of syndactyly in hands & feet as those w/GCPS). Severity is highly variable. [1]	PPD-IV is essentially GCPS w/o craniofacial manifestations. Because macrocephaly occurs in general population & is common in GCPS, presence of macrocephaly in persons w/ apparently isolated PPD-IV may be difficult to interpret.
Acrocallosal syndrome	AD	Postaxial polydactyly, macrocephaly, agenesis of corpus callosum, & severe DD	2 persons diagnosed w/acrocallosal syndrome have been reported w/missense variants in *GLI3*. [2]
Oral-facial-digital syndrome	AD	Various forms of polydactyly assoc w/ gingival clefts & frenula & cleft palate, some w/HH [3]	This is not a well-defined phenotypic entity & is extremely rare. This phenotype may be considered to be atypical PHS.
Nonsyndromic neuronal migration abnormalities	AD	Non-HH brain anomalies, hypotonia, DD w/o extracranial anomalies	*GLI3* variants have been reported in 2 persons w/these findings. It is not clear that these variants are pathogenic or causative & this entity requires validation. [4]

Table 3. continued from previous page.

Disorder	MOI	Clinical Features	Comment
AR polydactyly syndrome	AR	Postaxial or mesoaxial polydactyly, cutaneous syndactyly, DD, & multiple malformations	Observed in 3 consanguineous families. The parents were apparently unaffected; however, thorough eval for subtle anomalies (e.g., cranial MRI) in parents was not performed. [5]

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; GCPS = Greig cephalopolysyndactyly syndrome; HH = hypothalamic hamartoma; MOI = mode of inheritance
1. Everman [2006]
2. Elson et al [2002], Speksnijder et al [2013]
3. Johnston et al [2010]
4. Siafa et al [2022]
5. El Mouatani et al [2021]

Somatic *GLI3* pathogenic variants have been identified in individuals with nonsyndromic hypothalamic hamartomas [Wallace et al 2008]. Note: The pathogenicity of a subset of the somatic *GLI3* variants reported to be associated with nonsyndromic hypothalamic hamartomas is questioned, as these variants appear to violate the known mechanism of *GLI3* pathogenesis.

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, and heart defect.

Postaxial polydactyly. See Table 4.

Table 4. Disorders Associated with Postaxial Polydactyly in the Differential Diagnosis of *GLI3*-Related Pallister-Hall Syndrome

Gene	Disorder	MOI	Clinical Features	Comment
≥26 genes incl: *ARL6* *BBS1* *BBS2* *BBS4* *BBS5* *BBS7* *BBS9* *BBS10* *BBS12* *CEP290* *CFAP418* *MKKS* *SDCCAG8* *TTC8*	Bardet-Biedl syndrome (BBS)	AR [1]	Primarily characterized by retinal cone-rod dystrophy, obesity & related complications, postaxial polydactyly, cognitive impairment, hypogonadotropic hypogonadism &/or genitourinary malformations, & renal malformations &/or renal parenchymal disease	Overall, BBS is much more common than PHS. It is possible that atypical BBS that resembles PHS may be more common than *GLI3*-related PHS. BBS-related genes should be evaluated in persons w/ overlapping findings.
DHCR7	Smith-Lemli-Opitz syndrome (SLOS)	AR	Characterized by prenatal & postnatal growth restriction, microcephaly, moderate-to-severe ID, & multiple major & minor malformations (incl postaxial polydactyly & 2-3 syndactyly of toes). SLOS is caused by an abnormality in cholesterol metabolism.	

Table 4. continued from previous page.

Gene	Disorder	MOI	Clinical Features	Comment
MKKS	McKusick-Kaufman syndrome (MKS)	AR	Triad of hydrometrocolpos in females & genital malformations in males, PAP or central polydactyly, & CHD	Most non-Amish persons w/MKS evolve into the BBS phenotype in older childhood or adulthood.
SMO	*SMO*-related hypothalamic hamartoma-polydactyly (OMIM 241800)	AR	Hypothalamic hamartomas w/variable degrees & types of polydactyly	Some persons w/this disorder may be properly considered to have *SMO*-related PHS.
TBX5	Holt-Oram syndrome (HOS)	AD	Upper-limb defects, CHD, & cardiac conduction disease. Upper-limb malformations may be unilateral, bilateral/symmetric, or bilateral/asymmetric & range from triphalangeal or absent thumb(s) to phocomelia.	

AD = autosomal dominant; AR = autosomal recessive; CHD = congenital heart disease; ID = intellectual disability; MOI = mode of inheritance; PAP = postaxial polydactyly; PHS = Pallister-Hall syndrome
1. Bardet-Biedl syndrome (BBS) is typically inherited in an autosomal recessive manner.

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 [Cohen et al 2021]. Somatic *GLI3* pathogenic variants have been identified in nonsyndromic hypothalamic hamartomas (see Genetically Related Disorders) [Wallace et al 2008].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *GLI3*-related Pallister-Hall syndrome (*GLI3*-PHS), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with *GLI3*-Related Pallister-Hall Syndrome

System/Concern	Evaluation	Comment
Endocrine	• Assessment for cortisol deficiency • Consultation by endocrinologist, incl eval of growth hormone secretion, FSH & LH secretion, & serum concentration of thyroid hormone in early infancy after eval for & treatment of ACTH deficiency	• Assessment for cortisol deficiency must be performed urgently in persons w/no family history of *GLI3*-PHS & in persons who have family members w/*GLI3*-PHS & cortisol deficiency. • Adrenal crisis can be lethal in infants who have not undergone proper eval & treatment for adrenal insufficiency.
Neurologic	• Cranial MRI to establish location & extent of hamartoma • Neurologic exam to excl signs of intracranial hypertension, which is not typical of hypothalamic hamartomas	Surgical removal of hamartoma is generally contraindicated.
Polydactyly	• Limb radiographs to distinguish postaxial polydactyly from central polydactyly • Eval by hand surgeon to assess timing & surgical approach to correct polydactyly	Surgical correction of mesoaxial polydactyly is typically more complex than that of postaxial polydactyly & should be undertaken by an expert surgeon.

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Epiglottal abnormalities	• Visualization of epiglottis by laryngoscopy • Urgent eval by otolaryngologist for laryngotracheal cleft when signs or symptoms of aspiration are present; elective eval by otolaryngologist in asymptomatic persons	
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Genitourinary anomalies	Renal ultrasonography to evaluate for renal anomalies	
Imperforate anus	Surgical consultation for imperforate anus or anal stenosis if present	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *GLI3*-PHS to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ACTH = adrenocorticotropic hormone; ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MOI = mode of inheritance; *GLI3*-PHS = *GLI3*-related Pallister-Hall syndrome

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with *GLI3*-Related Pallister-Hall Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Endocrine	Endocrine abnormalities are treated as in general population, w/treatment for cortisol deficiency being most urgent.	
Neurologic	Only under most unusual circumstances should HH be removed or even biopsied because complications of surgery & need for lifelong hormone supplements postoperatively generally outweigh benefits.	
	Seizures are treated symptomatically.	Seizures assoc w/*GLI3*-PHS are commonly responsive to ASM; seizures assoc w/ nonsyndromic HH are more commonly refractory to ASM.

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Polydactyly	• OT for manual dexterity of hands may be needed as some persons w/mesoaxial polydactyly have digital malalignment. • Repair of polydactyly should be undertaken on elective basis.	
Epiglottal abnormalities	Standard treatment for epiglottic abnormalities	• Mgmt of epiglottal abnormalities depends on type of abnormality & extent of respiratory compromise. • Bifid epiglottis is often asymptomatic & most do not require treatment, unless accompanied by clear evidence of obstruction or assoc w/other anomalies, such as tracheal stenosis.
Psychiatric/ Behavioral	Treatment per psychologist &/or psychiatrist	Use of stimulants for ADHD should be considered carefully in persons w/CNS lesion that predisposes to seizures (e.g., hypothalamic hamartoma).
DD/ID	Developmental services &/or educational intervention as needed	
Genitourinary anomalies	Treatment per nephrologist &/or urologist	
Imperforate anus	Anal atresia or stenosis treated in standard fashion	

ADHD = attention-deficit/hyperactivity disorder; ASM = anti-seizure medication; CNS = central nervous system; DD/ID = developmental delay / intellectual disability; HH = hypothalamic hamartomas; OT = occupational therapy

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the following evaluations are recommended.

Table 7. Recommended Surveillance for Individuals with *GLI3*-Related Pallister-Hall Syndrome

System/Concern	Evaluation	Frequency
Endocrine	• Assess growth. • Monitor for signs of precocious puberty.	Annually throughout childhood
Development	Monitor developmental progress & educational needs.	
Psychiatric/Behavioral	Behavioral assessment	

Agents/Circumstances to Avoid

Biopsy or resection of hypothalamic hamartoma may result in complications and lifelong need for hormone replacement.

Some stimulants (commonly used for attention-deficit/hyperactivity disorder) may exacerbate seizures.

Evaluation of Relatives at Risk

Prenatal testing of a fetus at risk. Once the *GLI3* pathogenic variant has been identified in an affected family member, prenatal molecular genetic testing may be performed on pregnancies at risk in order to facilitate

prompt postnatal treatment of adrenal insufficiency. Adrenal crisis can be lethal in affected infants who have not undergone proper evaluation and treatment for adrenal insufficiency.

Other family members. It is appropriate to evaluate relatives at risk to identify as early as possible those who would benefit from initiation of treatment and preventive measures. Evaluations include:

- Molecular genetic testing for the *GLI3* pathogenic variant identified in the proband;
- Clinical examination for polydactyly, laryngoscopy for bifid epiglottis, or MRI for hypothalamic hamartoma. The first-degree relative of a proband is considered affected if hypothalamic hamartoma or central or postaxial polydactyly (PAP) is present in the relative. (PAP type B can be used as a diagnostic criterion for first-degree relatives only in persons who are not of central African descent.)

Note: Assessment for cortisol deficiency must be performed urgently in individuals who have family members with *GLI3*-PHS and cortisol deficiency.

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

Pregnancy Management

Pregnancy management of a woman with *GLI3*-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 *GLI3*-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 anti-seizure medication (ASM) during pregnancy reduces this risk. However, exposure to ASM 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 ASM exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of ASM to treat a maternal seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given ASM 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 *GLI3*-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, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

GLI3-related Pallister-Hall syndrome (*GLI3*-PHS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 75% of individuals diagnosed with *GLI3*-PHS have an affected parent.
- Approximately 25% of individuals diagnosed with *GLI3*-PHS have the disorder as the result of a *de novo* *GLI3* pathogenic variant. (Individuals with a *de novo* *GLI3* pathogenic variant are generally more severely affected than individuals with a family history of *GLI3*-PHS [JJ Johnston, unpublished data].)
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a d*e novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

      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.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents.

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Because intrafamilial variability appears to be low, affected sibs would be expected to have clinical findings similar to those of the proband.
- If the *GLI3* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. One instance of parental mosaicism has been reported [Ng et al 2004].
- If the parents are clinically unaffected but their genetic status is unknown, 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 parental germline mosaicism. 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 *GLI3*-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 heterozygous and nonpenetrant or mosaic is low.

Offspring of a proband. Each child of an individual with *GLI3*-PHS has a 50% chance of inheriting the *GLI3* pathogenic variant.

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, the parent's family members may be 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.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *GLI3* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for *GLI3*-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 *GLI3*-PHS in the fetus.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **MedlinePlus**
  Pallister-Hall syndrome
- **American Epilepsy Society**
  www.aesnet.org
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  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. GLI3-Related Pallister-Hall Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

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 GLI3-Related Pallister-Hall Syndrome (View All in OMIM)

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

Molecular Pathogenesis

GLI3 encodes a zinc finger transcription factor that is downstream of sonic hedgehog in the SHH pathway (SHH-PTCH1-SMO-GLI1, GLI2, GLI3) [Villavicencio et al 2000]. The various GLI proteins in turn transcriptionally regulate genes further downstream in the SHH pathway, including *HNF3β*, bone morphogenetic proteins, and other as-yet-unknown targets. The human gene is similar to the mouse paralog *Gli3* and the vertebrate *GLI* gene family is homologous to the *Drosophila melanogaster* gene cubitus interruptus (ci).

Mechanism of disease causation. It has been shown that the truncated forms of the GLI3 protein associated with *GLI3*-PHS repress transcription [Blake et al 2016]. This explains the relatively specific variant-phenotype association because only a subset of variants can trigger this effect. The variants must truncate the protein without engendering nonsense-mediated decay (which would instead cause the GCPS phenotype).

***GLI3*-specific laboratory technical considerations.** 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.

Chapter Notes

Author Notes

Author's web page

The author is a board-certified clinical geneticist and pediatrician. He performs clinical and molecular research on genetic disorders at the National Institutes of Health.

Dr Biesecker is interested in hearing from clinicians treating families affected by *GLI3*-related PHS who have atypical manifestations or those in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders. He is also willing to consult on *GLI3* variant pathogenicity classifications when the variant or presenting phenotypes are atypical.

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Revision History

- 22 February 2024 (aa) Revision: information about *GLI3* pathogenic variant c.2374C>T (p.Arg792Ter) added to Genotype-Phenotype Correlations

- 18 August 2022 (sw) Comprehensive update posted live
- 18 May 2017 (sw) Comprehensive update posted live
- 18 December 2014 (me) Comprehensive update posted live
- 13 September 2012 (me) Comprehensive update posted live
- 18 March 2008 (me) Comprehensive update posted live
- 6 June 2005 (me) Comprehensive update posted live
- 1 May 2003 (me) Comprehensive update posted live
- 25 May 2000 (me) Review posted live
- 20 January 2000 (lb) Original submission

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