

Cancer Prone Disease Section

Mini Review

Pallister Hall syndrome (PHS)

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Identity

Inheritance: Autosomal dominant; rare with unknown incidence.

Clinics

Phenotype and clinics

- Major findings: Hypothalamic hamartoma: a non-enhancing mass in the floor of the third ventricle posterior to the optic chiasm that is isointense to grey matter on T1 and T2 pulse sequences of an MRI, but may have distinct intensity on FLAIR. (Neither cranial CT examination nor cranial ultrasound examination is adequate for diagnosis of hypothalamic hamartoma).
- Central polydactyly: The presence of six or more well-formed digits with a 'Y' shaped metacarpal or metatarsal bone.
- Postaxial polydactyly: Can be either PAP-A with a well shaped digit on the ulnar or fibular aspect of the limb, or PAP-B with a rudimentary digit or nubbin in the same position.
- 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, and pulmonary segmentation anomalies such as bilateral bilobed lungs.

Neoplastic risk

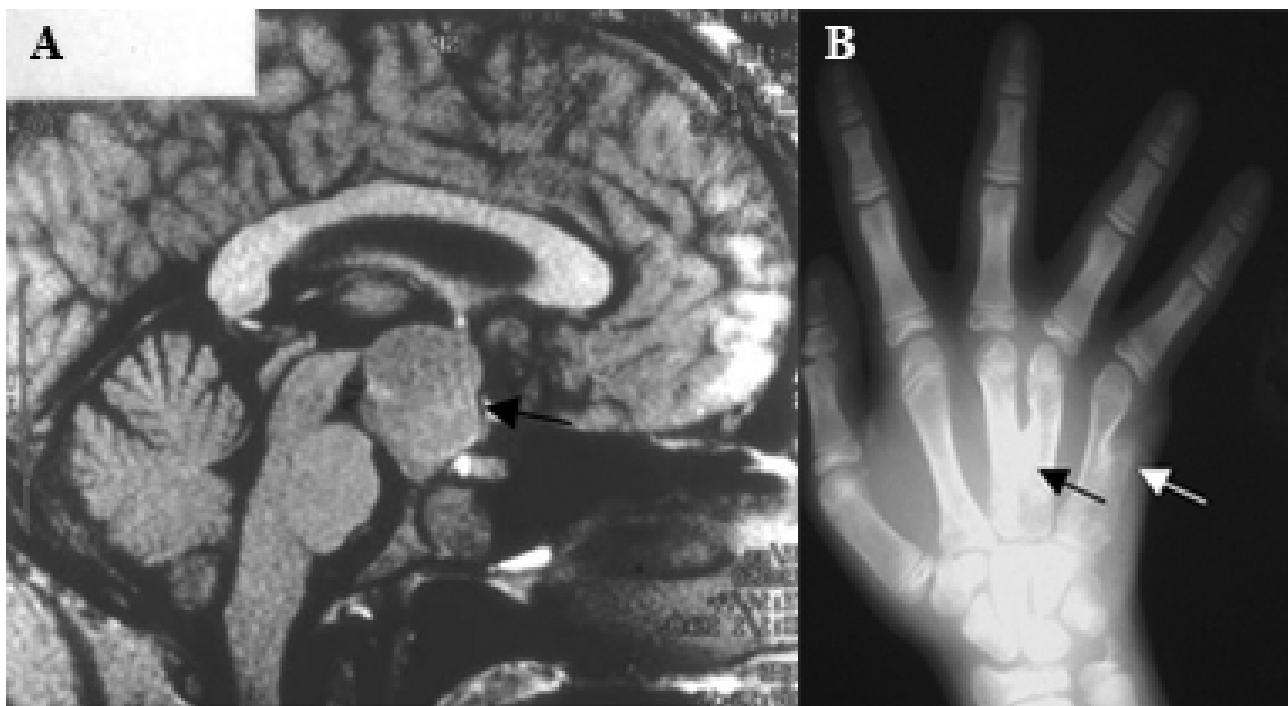
No increased risk of cancer has been reported for individuals with PHS. Hypothalamic hamartomas, a benign growth, are found in a majority of patients.

Treatment

Treatment of individuals with PHS depends on their individual manifestations. Management of epiglottic abnormalities depends on the type of abnormality and extent of respiratory compromise. Seizures are treated symptomatically. Treatment for endocrine abnormalities, especially for cortisol deficiency, is urgent. Repair of polydactyly can be undertaken on an elective basis and anal atresia or stenosis treated in the standard manner. Hypothalamic hamartomas should not be removed or biopsied because of the risk of surgical complications and need for hormone supplements during the individual's remaining life.

Prognosis

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 this purpose because reported cases tend to show bias of ascertainment to more severe involvement. Although PHS has been categorized as a member of the CAVE (cerebro-acro-visceral early lethality) group of disorders, few affected individuals have an early lethality phenotype. This early lethality 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 excellent 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. Several large families have been reported as having a mild form of PHS with excellent general health and normal longevity.



A : MRI showing hypothalamic hamartoma in PHS patient.
 B : Hand film showing central polydactyly, note 'Y' shaped metacarpal.

Genes involved and Proteins

GLI3

Location: 7p14

DNA/RNA

Description: GLI3 has 15 exons, 14 of which are coding exons, and extends over approximately 300 kb of genomic DNA.

Protein

Description: 1580 amino acids; GLI3 contains a C2H2 zinc finger and six additional domains conserved between GLI family members.

Function: GLI3 functions as both an activator and repressor of transcription, playing a central role in the Sonic Hedgehog pathway. In the presence of Sonic Hedgehog GLI3 enters the nucleus and activates transcription of downstream genes. In the absence of

Sonic Hedgehog full length GLI3 is retained in the cytoplasm where it is cleaved into a repressor form. The repressor form is free to move into the nucleus and downregulate transcription.

Homology: GLI family of transcription factors, C2H2 zinc finger domain.

Mutations

Germinal: Over 36 mutations have been identified in individuals with PHS. All mutations identified to date predict a truncated protein.

Mutations that cause PHS are thought to result in the production of a constitutive repressor protein. The majority of truncating mutations in the middle third of the protein cause PHS. These mutations retain the C2H2 zinc finger but are missing the last third of the protein.



Schematic of GLI3 protein showing seven conserved domains between the GLI family members, the C2H2 zinc finger is shown in red. Positions of thirty distinct PHS mutations are marked by lines above the protein.

References

- Ruppert JM, Vogelstein B, Arheden K, Kinzler KW. GLI3 encodes a 190-kilodalton protein with multiple regions of GLI similarity. *Mol Cell Biol* 1990;10:5408-5415.
- Löw M, Moringlane JR, Reif J, Barbier D, Beige G, Kolles H, Kujat C, Zang KD, Henn W. Polysyndactyly and asymptomatic hypothalamic hamartoma in mother and son: A variant of Pallister-Hall syndrome. *Clin Genet* 1995;48:209-212.
- Verloes A, David A, Ngô L, Bottani A. Stringent delineation of Pallister-Hall syndrome in two long surviving patients: Importance of radiological anomalies of the hands. *J Med Genet* 1995;32:605-611.
- Kang S, Allen J, Graham JM, Jr., Grebe T, Clericuzio C, Patronas N, Ondrey F, Green E, Schäffer A, Abbott M, Biesecker LG. Linkage mapping and phenotypic analysis of autosomal dominant Pallister-Hall syndrome. *J Med Genet* 1997a;34:441-446.
- Kang S, Graham JM, Jr., Olney AH, Biesecker LG. GLI3 frameshift mutations cause autosomal dominant Pallister-Hall syndrome. *Nat Genet* 1997b;15:266-268.
- Ondrey F, Griffith A, Van Waes C, Rudy S, Peters K, McCullagh L, Biesecker LG. Asymptomatic laryngeal malformations are common in patients with Pallister-Hall syndrome. *Am J Med Genet* 2000;94:64-67.
- Killoran CE, Abbott M, McKusick VA, Biesecker LG. Overlap of PIV syndrome, VACTERL and Pallister-Hall syndrome: Clinical and molecular analysis. *Clin Genet* 2000;58:28-30.
- Galasso C, Scirè G, Fabbri F, Spadoni GL, Killoran CE, Biesecker LG, Boscherini B. Long-term treatment with growth hormone improves final height in a patient with Pallister-Hall syndrome. *Am J Med Genet* 2001;99:128-131.
- Haynes JH, Bagwell CE. Hirschprung's disease and imperforate anus in Pallister-Hall syndrome: A new association. *J Pediatr Surg* 2003;38:1411-1412.
- Kremer S, Minotti L, Thiriaux A, Grand S, Satre V, Le Bas JF, Kahane P. Epilepsy and hypothalamic hamartoma: Look at the hand Pallister-Hall syndrome. *Epileptic Disord* 2003;5:27-30.
- Ng D, Johnston JJ, Turner JT, Boudreau EA, Wiggs EA, Theodore WH, Biesecker LG. Gonadal mosaicism in severe Pallister-Hall syndrome. *Am J Med Genet* 2004;124A:296-302.
- Boudreau EA, Liow K, Frattali CM, Wiggs E, Turner JT, Feuillan P, Sato S, Patsalides A, Patronas N, Biesecker LG, Theodore WH. Hypothalamic hamartomas and seizures: distinct natural history of isolated and Pallister-Hall syndrome cases. *Epilepsia* 2005;46(1):42-47.
- Johnston JJ, Olivos-Glander I, Killoran C, Elson E, Turner JT, Peters KF, Abbott MH, Aughton DJ, Aylsworth AS, Bamshad MJ, Booth C, Curry CJ, David A, Dinulos MB, Flannery DB, Fox MA, Graham JM, Jr., Grange K, Guttmacher AE, Hannibal MC, Henn W, Hennekam RCM, Holmes LB, Hoyme HE, Leppig KA, Lin AE, MacLeod P, Manchester DK, Marcelis C, Mazzanti L, McCann E, McDonald MM, Mendelsohn NJ, Moeschler JB, Moghaddam B, Neri G, Newbury-Ecob R, Pagon RA, Phillips J, III, Sadler LS, Stoler JM, Tilstra D, Walsh Vockley CM, Zackai EH, Zadeh TM, Brueton L, Black GCM, Biesecker LG. Molecular and clinical analyses of Greig cephalopolysyndactyly and Pallister-Hall syndromes: Robust phenotype prediction from the type and position of GLI3 mutations. *Am. J. Hum. Genet* 2005;76:609-622.
- McCann E, Fryer AE, Craigie R, Baillie C, Ba'ath ME, Selby A, Biesecker LG. Genitourinary malformations as a feature of the Pallister-Hall syndrome. *Clin Dysmorphol* 2006;15(2):75-79.

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