Pallister-Hall/Greig Cephalopolysyndactyly Syndromes Testing

Pallister–Hall syndrome (PHS) and Greig cephalopolysyndactyly syndrome (GCPS) are autosomal dominant pleiotropic syndromes caused by pathogenic variants in the GLI3 gene. Typical GCPS is characterized by preaxial polydactyly or mixed pre- and postaxial polydactyly, wide-spaced eyes, and macrocephaly. Individuals with mild GCPS may have subtle craniofacial findings. Mild GCPS spectrum is a continuum with preaxial polysyndactyly type IV (polydactyly without any craniofacial manifestation) and crossed polydactyly (preaxial polydactyly of the feet and postaxial polydactyly of the hands plus syndactyly of the third/fourth fingers and first/third toes). Severe GCPS symptoms include seizures, hydrocephalus, and intellectual disability. GLI3 is the only gene known to be associated with GCPS; however, some affected individuals may have a chromosomal deletion of chromosome 7p13 region that includes the GLI3 gene.¹ Pallister-Hall syndrome (PHS) is a rare condition associated with polydactyly and hypothalamic hamartoma. The majority of PHS cases are identified during childhood; however, rare cases have been reported with diagnoses during adulthood.² PHS is caused predominantly by frameshift or nonsense pathogenic variants in the GLI3 gene. Other syndromes involving polydactyly are also caused by GLI3 pathogenic variants, including polydactyly syndromes postaxial polydactyly type A, autosomal dominant preaxial polydactyly type IV, and postaxial polydactyly type A/B.³

Disease Overview

Prevalence

Rare

Symptoms

Greig Cephalopolysyndactyly Syndrome

- Variable clinical presentation; ranges from isolated polysyndactyly to seizures, hydrocephalus, and intellectual disability
- Preaxial polysyndactyly of hands and feet
- Craniofacial features:
  - Hypertelorism
  - Macrocephaly with frontal bossing
Pallister-Hall Syndrome

- Severity ranges from mild disease to death in the neonatal period, depending on the presence of life-threatening malformations and/or disease severity in other affected relatives
- Hypothalamic hamartoma (abnormal growth in the brain)
- Postaxial/central polydactyly
- Bifid epiglottis (airway malformation that does not require treatment)
- Seizures, pituitary insufficiency may occur in some patients
- Less common:
  - Renal/genitourinary abnormalities
  - Pulmonary segmentation anomalies
  - Nonpolydactyly skeletal anomalies

Genetics

Gene

GLI3

Inheritance

Autosomal dominant

Penetrance

Complete penetrance, with rare exceptions

De novo Variants

PHS: 25%\(^4\)

GCPS: unknown\(^1\)

Test Interpretation

Clinical Sensitivity

Pallister-Hall Syndrome

- Sequencing: ~90%
  - Frameshift or nonsense pathogenic variants account for the majority of cases
- Deletion/duplication: unknown

Greig Cephalopolysyndactyly Syndrome

- Sequencing: 70%
- Deletion/duplication: 5-10%
Analytical Sensitivity/Sensitivity

>98%/>99%

Results

- Positive: one pathogenic GLI3 variant detected
  - Confirms diagnosis of PHS or GCPS
- Negative: no pathogenic GLI3 variants detected
  - Likelihood of PHS/GCPS significantly reduced, but not excluded
- Uncertain: variant(s) of uncertain clinical significance detected
  - Unknown if variant is disease-causing or benign

Limitations

- Diagnostic errors can occur due to rare sequence variations or repeat element insertions
- Breakpoints of large deletions/duplications and regulatory region and deep intronic variants are not detected
- Exon 1 is noncoding and will not be reported
- Single exon deletion/duplications may not be detected due to probe location

References


