Pallister-Hall/Greig Cephalopolysyndactyly Syndromes

Indications for Ordering

- Individuals with clinical features that are suggestive of Pallister-Hall syndrome (PHS) or Greig cephalopolysyndactyly syndrome (GCPS)
- Individuals with a first-degree relative with PHS or GCPS

Test Description

- Bidirectional sequencing of the entire coding region and intron/exon boundaries of the *GLI3* gene
- Multiplex ligation-dependent probe amplification (MLPA) to detect large exonic *GLI3* deletions and duplications

Tests to Consider

Primary tests

GLI3-Related Disorders (*GLI3*) Sequencing and Deletion/Duplication 2011465

- Most comprehensive test to confirm a clinical diagnosis of PHS or GCPS

GLI3-Related Disorders (*GLI3*) Sequencing 2011470

- Appropriate first-tier test to confirm a clinical diagnosis of PHS or GCPS
  - Detects majority of variants

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence – rare

Symptoms

PHS

- Severity ranges from mild disease to fetal death
- Hypothalamic hamartoma
  - Seizures may occur (gelastic epilepsy)
  - Pituitary insufficiency sometimes occurs
- Postaxial/central polydactyly
- Bifid epiglottis
- Less common
  - Imperforate anus
  - Renal/genitourinary abnormalities
  - Pulmonary segmentation anomalies
  - Nonpolydactyly skeletal anomalies

GCPS

- Severity ranges from isolated polysyndactyly to seizures, hydrocephalus, and intellectual disability
- Preaxial polysyndactyly of hands and feet
- Craniofacial features
  - Hypertelorism
  - Macrocephaly with frontal bossing

Genetics

Gene – *GLI3*

Inheritance – autosomal dominant

Penetrance – rarely nonpenetrant

De novo variants

- PHS – 25%

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
  - PHS
    - Sequencing – ~90%
    - Deletion/duplication – unknown
  - GCPS
    - Sequencing – 70%
    - Deletion/duplication – 5-10%
- Analytical sensitivity – >98%
- Analytical specificity – >99%

Results

- Positive result – one pathogenic *GLI3* variant detected
  - Causative for PHS or GCPS
- Negative result – no pathogenic *GLI3* variants detected
  - Likelihood of PHS/GCPS significantly reduced, but not excluded
- Inconclusive result – variant(s) of uncertain clinical significance detected

Limitations

- Not detected
  - Regulatory region and deep intronic variants
  - Large deletions/duplications
  - Variants in genes other than *GL13*
- Diagnostic errors can occur due to rare sequence variations
- Deletion/duplication breakpoints will not be determined
- Exon 1 is noncoding and will not be reported

References

- Biesecker LG. Pallister-Hall Syndrome. 2000 May 25 [Updated 2014 Dec 18]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016 (www.ncbi.nlm.nih.gov/books/NBK1465/)
- Biesecker LG. Greig Cephalopolysyndactyly Syndrome. 2001 Jul 9 [Updated 2014 Jun 19]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016 (www.ncbi.nlm.nih.gov/books/NBK1446/)