GLI3 Gene Analysis in Greig Cephalopolysyndactyly Syndrome and Pallister Hall Syndrome

Clinical Features:
Grieg cephalopolysyndactyly syndrome (GCPS) is typically characterized by macrocephaly (>97th percentile), prominent forehead, hypertelorism, pre- or postaxial polydactyly (typically preaxial polydactyly of feet and postaxial polydactyly of hands), and syndactyly. Developmental delay, mental retardation, and seizures have been reported in a minority of cases (<10%); severely affected individuals are more likely to have a contiguous gene deletion syndrome that includes the GLI3 gene.[8] A "presumptive diagnosis" of GCPS can be made in a proband with preaxial polydactyly, syndactyly of toes 1-3 or fingers 3-4, hypertelorism, and macrocephaly. A firm diagnosis of GCPS can be made when a first degree relative has a diagnosis of GCPS or in an individual with GCPS phenotype and a variant in the GLI3 gene.[2]

Pallister Hall syndrome (PHS) is a clinically distinct syndrome from GCPS. The hallmark features of PHS include hypothalamic hamartoma, central polydactyly, postaxial polydactyly type A or B, bifid epiglottis or laryngeal cleft, imperforate anus, renal malformations, genitourinary abnormalities, pulmonary segmentation, and short limbs. A diagnosis can be made in a proband with central polydactyly and hypothalamic hamartoma or when a first degree relative of a proband has hypothalamic hamartoma or central or postaxial polydactyly.[3]

Additionally, variants in GLI3 have been identified in families with isolated postaxial polydactyly type A/B (PAP-A/B) and preaxial polydactyly type IV (PPDIV).[13,14] Reports have also identified GLI3 variants in individuals with metopic craniosynostosis and polysyndactyly,[7,11] polydactyly and overlapping features of oral-facial-digital syndrome (OFDS),[10] and one case report of an individual with acrocallosal syndrome (ACS),[5] although the vast majority of individuals with ACS do not have variants in GLI3.

Inheritance Pattern/Genetics:
Autosomal dominant with variable expressivity. Non-penetrance in GCPS syndrome has been reported in one family.[4] Germline mosaicism has been hypothesized in one family with PHS.[12]

Test Methods:
For those individuals with a presumptive diagnosis of GCPS, bi-directional DNA sequence is obtained and analyzed for all coding exons (2-15) and splice sites of the GLI3 gene. Concurrently, targeted array comparative genomic hybridization (aCGH) analysis with exon-level resolution (ExonArrayDx) is performed to evaluate for a deletion or duplication of one or more exons of the GLI3 gene. This method is also recommended for those individuals with polydactyly and metopic craniosynostosis/polysyndactyly. GenomeDx (whole genome aCGH)

may be considered in individuals with GCPS to exclude the possibility of an unbalanced translocation or a large contiguous gene deletion syndrome.

For those individuals suspected of having PHS, bi-directional sequence analysis of exons 13-15 and their splice sites is obtained and analyzed. This method is also recommended for those individuals with overlapping features of OFDS. If no variant is identified in these three exons, sequencing of the remainder of the GLI3 gene and deletion/duplication analysis (ExonArrayDx) can be performed upon request.

Variants/deletions found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, qPCR, or other appropriate method.

Test Sensitivity:
Variants are identified in approximately 68% (39/57) of individuals with a clinical diagnosis of GCPS using a combination of sequence and deletion/duplication analysis of the GLI3 gene.[9,10] In individuals with a clinical diagnosis of PHS, sequence analysis of the GLI3 gene will identify a variant in approximately 91% (20/22) of affected individuals.[9,10] In individuals not meeting strict clinical criteria for GCPS or PHS, variants were identified in 29% and 50% of affected individuals respectively.[10] One study examined the presence of GLI3 gene variants by sequence and deletion/duplication analysis in a population of individuals with congenital limb malformations; 2.5% (5/202) of individuals with congenital limb malformations had a variant in the GLI3 gene.[6] Additionally, variants in the GLI3 gene have been identified in 29% of individuals with overlapping features of GCPS or PHS and OFDS.[10]

The GLI3 (GLI-Kruppel Family Member 3) gene is located on chromosome 7p13 and codes for a zinc finger transcription factor expressed early in development. GLI3 is a bifunctional mediator of the Sonic Hedgehog (SHH) pathway, activating or repressing the transcription of downstream genes.[1] PHS variants are all frameshift and nonsense variants, with one reported splice-site variant, resulting in protein truncation. All reports of individuals with PHS have variants occurring within a central domain spanning nucleotides 1998-3481 (exons 13-15). In contrast, GCPS is typically caused by translocations involving the GLI3 gene, large deletions, frameshift, missense, and splice-site variants. These variants typically occur in the first and last third of the gene. Variants resulting in haploinsufficiency of GLI3 result in the GCPS phenotype.

References:

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