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50 Years Ago in *The Journal of Pediatrics*

Spectrum of *GLI3* Mutations

Marshall RE, Smith DW. Frontodigital syndrome: a dominantly inherited disorder with normal intelligence. J Pediatr 1970; 77:129-33.

Marshall and Smith described a family in which affected members had craniofacial abnormalities, including a prominent forehead, hypertelorism, and polysyndactyly, with apparent autosomal-dominant inheritance. Affected individuals had normal intelligence. The clinical features of affected family members had overlapping features of Pfeiffer, Apert, Carpenter, Rubinstein Taybi, and Leri pleonosteosis syndromes, but lacked ocular, genital, growth, obesity, and cognitive deficits. Phenotypic features in this family were consistent with a syndrome characterized by polysyndactyly and craniofacial features originally described by Greig.[1] As more cases were reported cognitive deficits were subsequently added to the clinical spectrum of what is now known as Greig cephalopolysndactyly syndrome (GCPS).

Mutations in a zinc finger transcription factor, *GLI3*, are associated with phenotypically overlapping but distinct conditions which include GCPS, Pallister-Hall syndrome (PHS, hypothalamic hamartomas, polysyndactyly, other malformations), and acrocallosal syndromes (partial or total absence of the corpus callosum, craniofacial features, and polydactyly) and nonsyndromic polydactyly. Some fairly robust genotype–phenotype correlations have been made for *GLI3* mutations.[2] Mutations in the middle third of *GLI3* that are truncating are null mutations, causing loss of the zinc finger binding domain resulting in PHS. As a result of these truncations, a constitutive GLI3 repressor protein is formed, which affects sonic hedgehog signaling. GCPS is caused by large deletions/duplications, translocations, and a variety of point mutations encompassing nonsense, missense, in-frame deletions, splice and frameshift mutations, or truncating mutations in the amino or carboxy terminus of *GLI3*.

Because the phenotypic expression of *GLI3* mutations is broad, genetic testing for *GLI3* mutations should be considered in individuals with component clinical features of GCPS and PHS that may not meet criterion for clinical diagnosis.

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