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Genetics Corner: A Consultation for Familial Polysyndactyly

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Clinical Summary:

A 7-month-old female was referred to Pediatric Genetics for preaxial polydactyly and syndactyly of both hands and feet (Figure 1a–c) and a positive family history of a similarly affected father. She was normocephalic (OFC at nine mos Z-score 1.05) with bilateral epicanthal folds and telecanthus. Her pediatrician had prescribed a helmet for plagiocephaly, which had resolved by the time of the visit. The exam and visit were completed by telehealth (video).

Imaging studies on the infant showed preaxial polydactyly of both feet. The first metatarsal of the left foot was associated with two sets of proximal and distal phalanges. The distal phalanx of the second digit was bifid with partial soft tissue fusion of the first and second digits and, possibly, third digits on the left and partial soft tissue fusion of the first, second, and third digits on the right.

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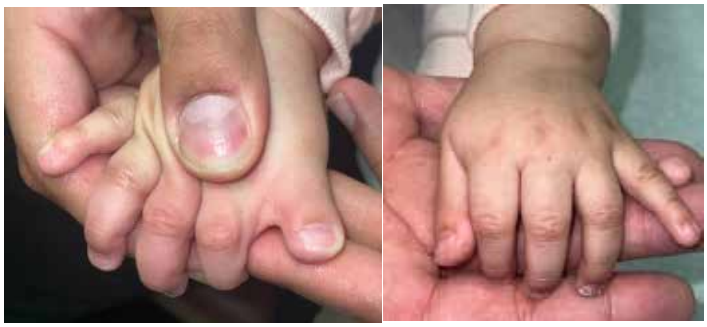
X-rays also showed preaxial polydactyly of both hands with bif first digits as well as soft tissue mass with punctate calcification arising off the fifth digit at the level of the proximal interphalangeal joint (postaxial polydactyly) on the left. There was partial soft tissue fusion of the first and second digits.

The infant was otherwise healthy, feeding well with normal stooling and voiding. No hearing or vision concerns were identified. She was developmentally on target.

The family history was significant for her father with similar pre- and postaxial polydactyly with broad thumbs, broad toes, and preaxial polydactyly of the right foot with syndactyly. He had prominent supraorbital ridges, downslanting palpebral fissures, and hypertelorism. While the paternal grandmother was reported to be asymptomatic, at least one of her family members had digit anomalies. Parents were of Hispanic ancestry; parental consanguinity was denied.

Figure 1a: Bilateral preaxial polydactyly/ syndactyly of the feet

Figure 1b and 1c: Preaxial polydactyly of hands bilaterally; postaxial polydactyly of left hand



The clinical features in the patient and her father—polydactyly and craniofacial dysmorphisms—were suggestive of Greig cephalopolysyndactyly syndrome (GCPS), inherited in an autosomal dominant manner due to pathogenic variants (mutations) in the *GLI3* gene. Molecular genetic testing confirmed the diagnosis and detected a pathogenic variant in *GLI3,* a deletion of exon 4, in our patient.

Discussion:

Polydactyly is the most common hereditary limb malformation, characterized by supernumerary fingers or toes. The estimated prevalence is 1/630 and 1/3300 among Caucasians and between 1/100 and 1/300 in African Americans. (1) While non-syndromic polydactyly can be multifactorial or inherited in an autosomal dominant manner, over 100 syndromes have also been associated with this birth defect.

"The two most common types are postaxial polydactyly (PAP), with the extra digit at the fifth finger or toe (on the ulnar/ peroneal side), and preaxial polydactyly (PPD), having the extra digit attached on the greater toe or thumb side (radial/ medial). Isolated postaxial polydactyly is ten times more common in African Americans and is more common in males. Preaxial polydactyly is 3–4 times more common in Native Americans than in Caucasians or African Americans. It is more often unilateral and more common in females. It may be seen with other anomalies in infants of diabetic mothers. Mesoaxial (central) polydactyly, when there is duplication of the second, third, or fourth digits of the hands or feet, is very rare"

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The limb buds appear at week 4, and the basic structures of the limbs (bones, muscle groups) are established by week 8 of gestation. The limbs' patterning, growth, and maturation occur along proximal-distal, anterior (rostral)-posterior (caudal), and dorsal-ventral axes of the developing embryo. Anterior-posterior patterning is determined by the Shh (Sonic Hedgehog) signaling. This protein is a well-studied morphogen that specifies digit identity by dose-dependent activation of target genes. *GLI3* encodes a zinc finger transcription factor that negatively regulates both the expression of *SHH* and its target genes and restricts the potential of a polydactylous limb to pentadactyly (Figure 2). (3, 4)

Pathogenic variants (mutations) in *GLI3* are associated with both non-syndromic and syndromic polydactyly: Grieg cephalopolysyndactyly syndrome (GCPS), Pallister-Hall syndrome, as well as isolated polydactyly classified as postaxial polydactyly types A1 and B and preaxial polydactyly, type IV. All of these are inherited in an autosomal dominant manner.

There are known genotype-phenotype correlations in *GLI3* (Figure 3). GCPS is caused by truncating mutations upstream or within of the zinc finger domain (ZFD) as well as missense and nonsense variants in other parts of the gene that result in haploinsufficiency of the gene. (5) A small proportion of GCPS is associated with the deletion of the *GLI3* gene as part of a contiguous gene deletion on chromosome 7p14. (6)

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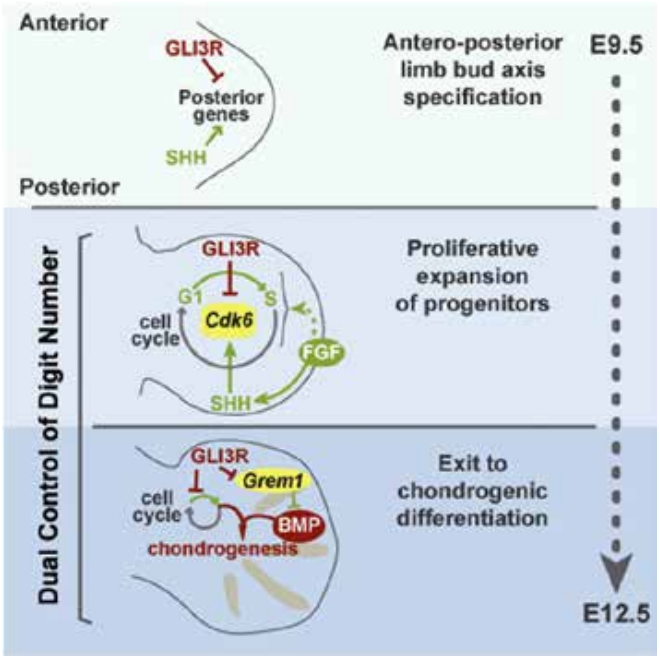
Figure 2: (Creative Commons License) graphical representation of GLI3 signaling and constraint of digit number in mice. (4)

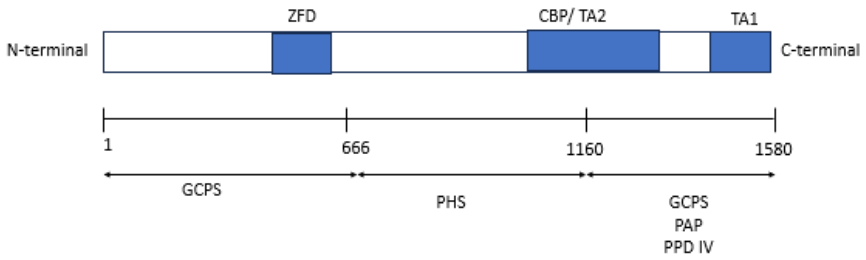


The exon 4 deletion in our patient is upstream of the ZFD in exon 12.

Pallister-Hall syndrome is caused by frameshift, nonsense, and splicing mutations in the middle third of the *GLI3* gene, corresponding to exon 14 and parts of exons 13 and 15.

GCPS is characterized by craniofacial features (Table 1), including macrocephaly, frontal bossing, prominent forehead, scaphocephaly, and hypertelorism associated with pre- and postaxial polydactyly. There may be broad or duplicated thumbs, broad or duplicated halluces, and cutaneous syndactyly of the fingers and toes. It is highly penetrant, meaning that those with mutations in the gene express clinical features in a family, but there can be inter- and intrafamilial phenotypic variability. (7) Less frequently, it can also include craniosynostosis, typically midline: metopic or

Figure 3: *GLI3* genotype-phenotype correlations (adapted from Al-Qattan MM *et al.,* 2017).



GLI3 protein domains and known genotype–phenotype correlations. ZFD, zinc finger domain; CBPD: cyclic AMP-binding protein-binding domain; TA 1 and 2, transactivation domain 1 and 2;
GCPS: Greig cephalopolysyndactyly syndrome; PHS: Pallister–Hall syndrome; PAP: postaxial polydactyly A/B;
PPD IV: preaxial polydactyly type IV.

sagittal. (8)

Developmental delay, intellectual disability, or seizures appear to be uncommon manifestations (~<10%) of GCPS and may be more common in individuals with large (>300-kb) deletions that encompass *GLI3*. Approximately 20% of individuals with GCPS have hypoplasia or agenesis of the corpus callosum.

Surveillance primarily involves reviewing head growth in infants and children; if faster than normal or neurologic concerns arise, a brain MRI is indicated.

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Practical Applications:

1. Evaluate for craniosynostosis when you suspect GCPS or syndromic polydactyly when there is complex polydactyly or syndactyly.
2. Suspect a genetic etiology when there is a positive family history of polydactyly, even when isolated.
3. Order chromosome microarray analysis if there are other anomalies and/or growth or developmental concerns to evaluate for a contiguous gene deletion syndrome
4. Genotype-phenotype correlations in GLI3-associated polydactyly help distinguish diagnoses with overlapping clinical features and help guide clinical management.
5. Understand the differences in the incidence of polydactyly based on ancestry: isolated postaxial polydactyly is quite common in African Americans, while preaxial polydactyly is common in Native Americans.
6. Isolated polydactyly can be sporadic and multifactorial. Postaxial polydactyly is seen more commonly in males.
7. Preaxial polydactyly is less common, and mesoaxial polydactyly is the least common.

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Table 1: Select Features of Greig Cephalopolysyndactyly Syndrome (9)

Feature	% of patients with feature	Comment
Macrocephaly	50	
Widely-spaced eyes	50	
Preaxial polydactyly	90	More common in the feet
Markedly broad hallux	25	
Markedly broad thumb	30	
Postaxial polydactyly	50	More common in hands
Cutaneous syndactyly	75	

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Disclosure: There are no reported conflicts.

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