Letter to the Editor

A novel frameshift mutation of the GLI3 gene in a family with broad thumbs with/without big toes, postaxial polydactyly and variable syndactyly of the hands/feet

To the Editor:

Mutations of the GLI3 gene lead to a wide variety of phenotypes such as Greig cephalopolysyndactyly (GCP), Pallister–Hall syndrome (PHS), postaxial polydactyly (PAP) types A/B, and preaxial polysyndactyly (PPD) type IV (1–7). The main clinical features of these phenotypes are summarized in Table 1.

The GLI3 protein may be divided into three parts (Fig. 1). The part towards the N-terminal contains the zinc finger domain (ZFD). Mutations that predict truncation before or within the ZFD result in GCP. These are considered as null mutations (haploinsufficiency) caused by loss of the zinc finger DNA-binding domain (1, 2). Patients with PHS have protein truncation after the ZFD but before domain 3. Truncations in this middle part of the protein results in abundance of a constitutive, repressor form of GLI. This skews the balance of activator (GLI3A) vs repressor (GLI3R) forms of GLI3 in the limb bud. Mutations that predict truncations in the carboxy terminal part of the GLI3 protein cause a variable degree of loss of the transactivation domain of GLI3, and this result in a variable phenotype including GCP, PAP types A and B, and PPD type IV (1–7).

We report on a family with a novel frameshift mutation of the GLI3 gene which predicts truncation in the N-terminal third of the protein. However, none of the affected family members had craniofacial symptoms. Instead, all affected members had broad thumbs with/without big toes, PAP of the hands with/without feet, and variable simple (cutaneous) syndactyly of the hands and feet.

A 3-year-old boy (Fig. 2) presented with rudimentary PAP of the hands, broad thumbs, broad mildly deviated big toes, and simple syndactyly of the left hand and both feet. There were no craniofacial or systemic abnormalities. The left leg had a small venous malformation. His father and four other family members also had similar limb features with no craniofacial or systemic abnormalities (Fig. 3). All members had PAP of the hands with/without feet, broad thumbs with/without big toes, and variable simple syndactyly of the hands/feet. The PAP was rudimentary in all but

<table>
<thead>
<tr>
<th>Name</th>
<th>Main clinical features</th>
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<tr>
<td>GCS</td>
<td>Frontal bossing; craniosynostosis; hypertelorism; broad thumbs/big toes; pre- and post-axial polydactyly of the hands and feet; syndactyly.</td>
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<tr>
<td>PHS</td>
<td>Hypothalamic hamartoma, hypopituitarism, short midface with anteverted nostrils, laryngeal cleft, central or PAP of the hands, syndactyly.</td>
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<tr>
<td>PAP</td>
<td>Little finger polydactyly. The extra finger can be well formed (type A) or rudimentary (type B). Familial PAP is associated with many different gene mutations. Cases associated with GLI3 mutations may also show concurrent syndactyly.</td>
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<tr>
<td>Preaxial polydactyly type IV</td>
<td>Preaxial polysyndactyly of the hands/feet with simple syndactyly of the other digits.</td>
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GCS, Greig cephalopolysyndactyly syndrome; PAP, postaxial polydactyly; PHS, Pallister–Hall syndrome.
Fig. 2. The index case: (a) clinical appearance of the hands; (b) X-ray of the right hand; (c) X-ray of the left hand; (d) clinical appearance of the feet; (e) X-ray of the feet.
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Fig. 3. The family pedigree. Inheritance is autosomal dominant.

one member in whom there was bilateral PAP type A of both feet. None of the other family members had vascular malformations or other concurrent anomalies. Intelligence was normal. All coding exons as well as the flanking non-coding sequences of the GLI3 gene were amplified and sequenced. The family was found to be heterozygous in exon 10 of the GLI3 gene for a double-nucleotide deletion defined as C.1615_1616 del GA, which is predicted to result in a frameshift mutation, leading to a premature protein termination P. Arg 539 Thr fs x 12.

To our knowledge, the deletion described in our family has not been previously reported. This frameshift mutation predicts truncation in the N-terminal part of the gene and a GCPS phenotype is expected (1–7). However, none of the family members had craniofacial features. One might argue that the apparent absence of craniofacial symptoms in this family could be explained by the reduced expressivity resulting in a very mild degree of craniofacial abnormalities; and this was previously suggested by Johnston et al. (2). Another argument is that the truncation site in our case represents a unique entity of isolated familial digital anomalies; and Fujioka et al. (7) favoured this argument. Several families have been reported with isolated polydactyly/syndactyly and truncations at different points within the C-terminal part of the GLI protein (2, 6, 7). Documentation of these mutations is important for future case reports to investigate if similar truncation points will result in isolated polydactyly/syndactyly phenotypes without any craniofacial symptoms.

Acknowledgement
The work was funded by the College of Medicine Research Center, Deanship of Scientific Research, King Saud University, Saudi Arabia.

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References

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