CASE REPORT

Frameshift Mutation in a Chinese Patient with Brachydactyly Type C Involving the Third Metacarpal: A Case Report

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Brachydactyly is a common feature of congenital hand anomalies characterized by shortening of the phalanges and/or metacarpals. Mutation of growth differentiation factor-5 (GDF5) may result in loss of appearance and function in brachydactyly type C (BDC). Herein, we describe an 11 year-old Chinese BDC patient with significant shortening of the 1st, 2nd, 3rd, and 5th digits. Notably, according to the analysis of metacarpophalangeal pattern profiles, we do not think the 4th digit appears unaffected as usual. In this patient a novel heterozygous frameshift mutation was identified (c.349delG) causing termination of translation after translating six amino acids from codon 117 (p.A117fs*6). This mutation is located in the propeptide region of GDF5, causing GDF5 haploinsufficiency in BDC. Considering our results expanding the genetic spectrum of BDC-causing mutations, further molecular analysis to diagnose and reclassify isolated brachydactyly on the basis of genotype rather than phenotype is warranted.

Key words: brachydactyly type C; congenital hand anomaly; digital shortening; growth differentiation factor-5

Introduction

Brachydactyly is a common feature of congenital hand anomalies, which may present as an isolated feature or as part of a complex malformation syndrome.[1] The magnitude of digital shortening is variable and involves shortening of the phalanges and/or metacarpals.[2] The anatomic and genetic basis of isolated brachydactyly was classified by Bell in 1951.[1] An extended classification (five groups, A–E) that considers phenotypic complexity was proposed in 1979.[3] Among the different groups, brachydactyly type C (BDC) shows an autosomal dominant pathology characterized by brachymesophalangy of the index, middle, and little digits with possible hyperphalangy of the index and middle digits.[3] Typically, the ring finger appears unaffected and is the longest finger in people with BDC.[2] In addition to the characteristic features of brachydactyly, retarded carpal bone,[4] short stature,[5] broad and/or elongated toes,[5] positional dental abnormality,[6,7] and severe shortening of the forearms and forelegs[8] are also observed. Growth differentiation factor-5 (GDF5) is the only gene known to be associated with BDC.[3]

GDF5, also known as cartilage-derived morphogenetic protein-1, is encoded at 20q11.2.[9] It is synthesized as a large precursor molecule binding to bone morphogenetic protein receptor type 1B (BMPR1B), which belongs to the transforming growth factor (TGF)-β superfamily regulating cartilage and bone formation.[9] Mutations in GDF5 also cause Hunter-Thompson type, Grebe type chondrodysplasia, and recessive acromegaly abnormalities in Du Pan syndrome.[4] To date, the ClinVar database includes 125 reported mutation types in GDF5, seven of which are known to be associated with BDC (http://www.ncbi.nlm.nih.gov/clinvar/?term=gdf5%5Bgene%5D). There are also some other mutation types associated with BDC showing complex clinical manifestations and variable phenotypes (Table 1). Notably, most of these alterations are missense and frameshift mutations.[4,5,7,10–13] Determining the genetic origin of changes in the GDF5 gene is important for understanding its role in cartilage and bone formation and the genetic diagnosis of isolated BDC.

Here, we present a Chinese patient with BDC linked to an unreported frameshift mutation with relevant clinical data.

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Received 29 August 2021; accepted 4 June 2022

Orthopaedic Surgery 2022;14:2386–2390 • DOI: 10.1111/os.13383

TABLE 1 Mutations reported in the GDF5 gene associated with BDC

Author(year)	Varient	Location	Mutation type	Zygosity	References
Polinkovsky *et al*. (1997)	c.901C>T	Prodomain	Missense	Heterozygote	12
Polinkovsky *et al*. (1997)	c.121delG	Prodomain	Frameshift	Heterozygote	12,18
Galjaard *et al*. (2001)					
Galjaard *et al*. (2001)	c.1493G>C	Active signaling domain	Missense	Heterozygote	18
	c.493delC	Prodomain	Frameshift	Heterozygote	
	c.759delG	Prodomain	Frameshift	Heterozygote	
	c.901C>T	Prodomain	Nonsense	Heterozygote	
Galjaard *et al*. (2001)	c.206insG	Prodomain	Frameshift	Heterozygote	18–20
Everman *et al*. (2002)					
Savarirayan *et al*. (2003)					
Everman *et al*. (2002)	c.158delT	Prodomain	Frameshift	Heterozygote	19
	c.612C>A	Prodomain	Missense	Heterozygote	
	c.811ins23	Prodomain	Frameshift	Heterozygote	
	c.830delT	Prodomain	Frameshift	Heterozygote	
Everman *et al*. (2002)	c.1312C>T	Active signaling domain	Missense	Heterozygote	4,19
Seo *et al*. (2013)					
Everman *et al*. (2002)	c.158insC	Prodomain	Frameshift	Heterozygote	17,19
Genovesi *et al*. (2021)					
Holder-Espinasse *et al*. (2004)	c.498insC	Prodomain	Frameshift	Heterozygote	6
Schwabe et at. (2004)	c.517A>G	Prodomain	Missense	Homozygote	5
Yang *et al*. (2008)	c.1118T>G	Prodomain	Missense	Heterozygote	10
	c.1461T>G	Active signaling domain	Missense	Heterozygote	
Gutiérrez-Amavizca *et al*. (2012)	c.404delC	Prodomain	Frameshift	Heterozygote	7
Stange *et al*. (2014)	c.601A>C	Prodomain	Missense	Heterozygote	8
	c.788T>C	Prodomain	Missense	Heterozygote	
Uyguner *et al*. (2014)	c.803_827del25ins25	Prodomain	Indel	Heterozygote	16
Unpublished article (2016)	c.1397G>A	Active signaling domain	Missense	Not known	21
Li *et al*. (this patient)	c.349delG	Prodomain	Frameshift	Heterozygote	

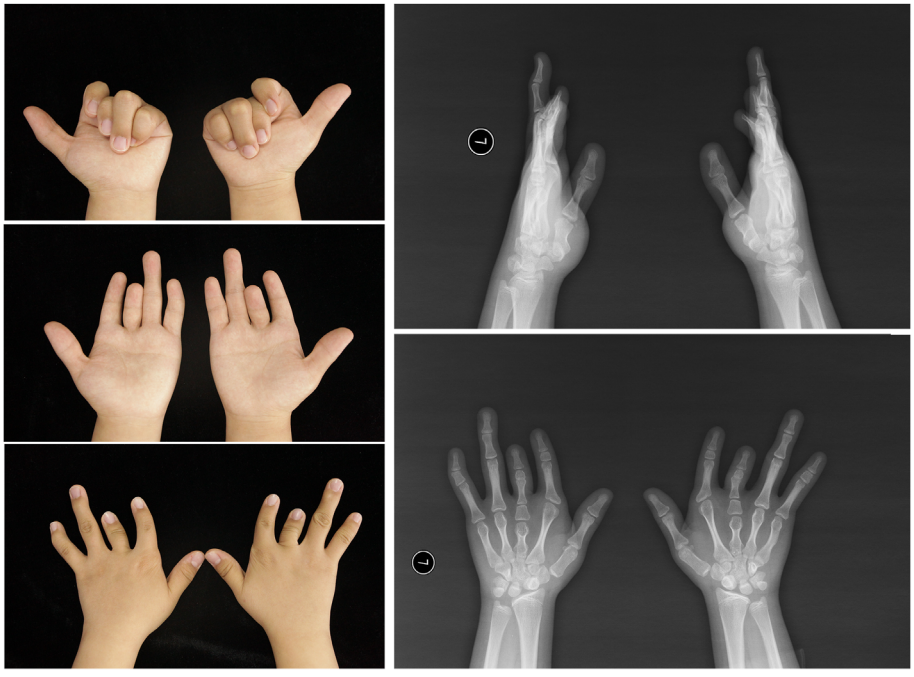

Fig. 1 Both hands and radiographic findings at age 11 years and 10 months. The 1st, 2nd, 3rd, and 5th digits were shortened, whereas the 4th digit was the longest. Bilateral ulnar deviation was detected on the 2nd and 3rd digits, with radial deviation of the distal 5th digit on the left. Radiographs show shortening of the 1st and 3rd metacarpals, 2nd and 5th middle phalanges, and 3rd proximal phalanges on both sides. There may be fibrous connections in the 1st metacarpophalangeal joint. The 3rd middle phalanx and a cornlike element may also connect with fibrocartilage.

Case Report

Clinical Presentation

An 11-year-old girl was admitted with shortening of the index, middle, and little digits on both hands. She had a normal stature and development compared to general Chinese standards. She had no abnormal prenatal or birth history. A family history of shortened digits was not reported. Hand examination revealed that her thumb, index, middle, and little digits were short, whereas the ring digit was the

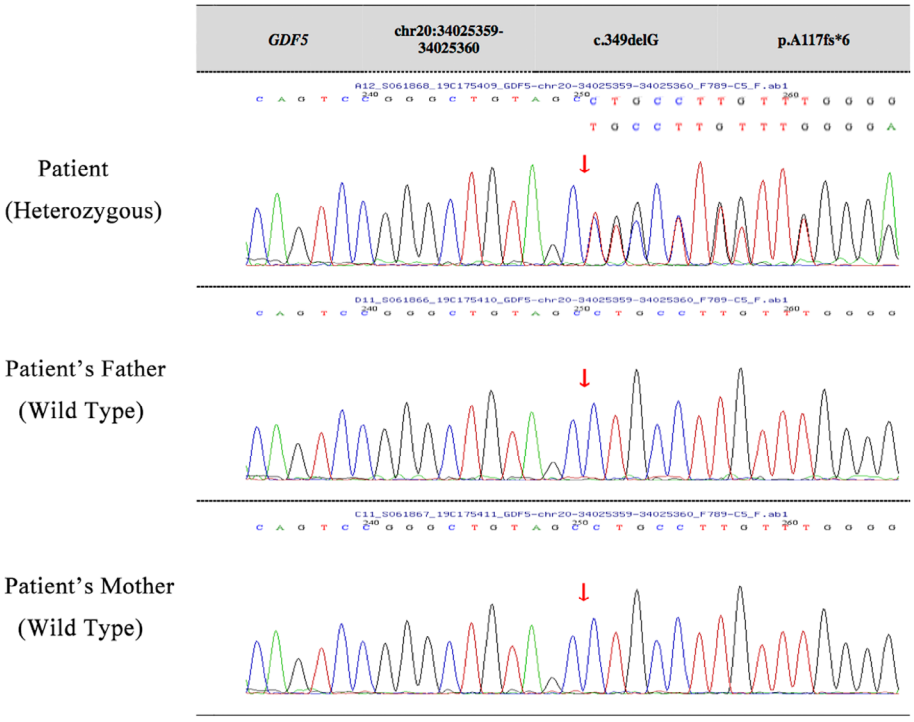

Fig. 2 Reverse Sanger sequencing analysis of GDF5 revealed the heterozygous mutation c.349delG in exon 1.

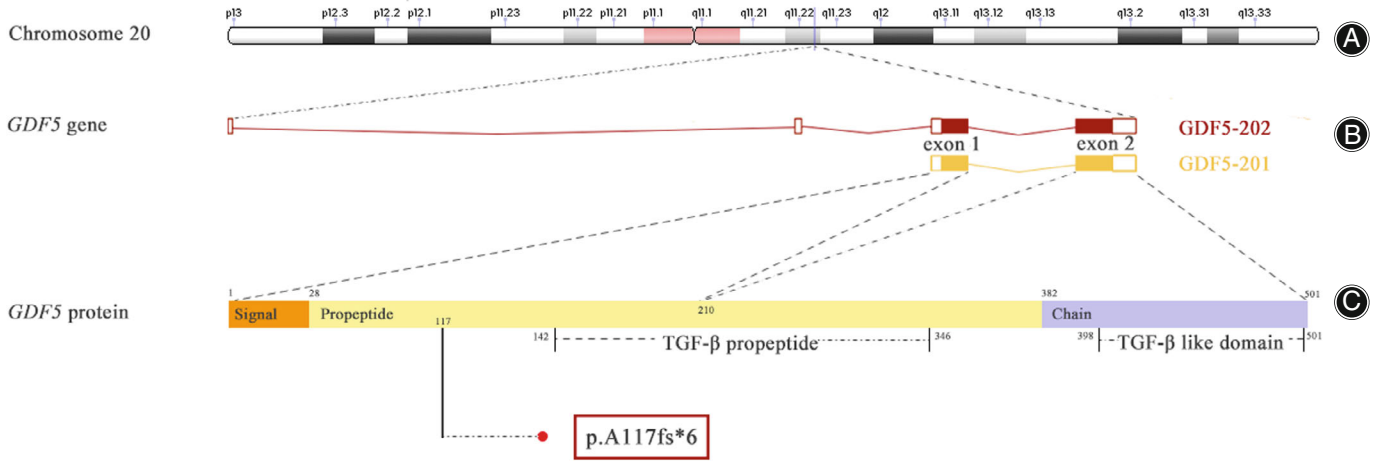

Fig. 3 A GDF5 located on 20q11.2, as displayed in the NCBI Genome database (https://www.ncbi.nlm.nih.gov/genome/gdv/browser/gene/?id=8200). B Genomic layout of GDF5 in human (http://asia.ensembl.org/Homo_sapiens/Gene/Summary?db=core;g=ENSG00000125965;r=20:35433347- 35,454,746). C Region of GDF5 protein and its domains. (https://www.uniprot.org/uniprot/P43026, http://pfam.xfam.org/protein/P43026). The mutation identified is indicated in the box at codon 117.

longest and had a normal appearance. The proximal phalanx of the bilateral index and middle digits were deviated to the ulnar sides, and the distal phalanx of the left little digit was deviated to the radial side. Radiographs showed shortening of the 1st and 3rd metacarpals, 2nd and 5th middle phalanges, and 3rd proximal phalanges on both sides. Fibrous connections may be observed in the 1st metacarpophalangeal joint and between the 3rd middle phalanx and a corn-like element (Figure 1). The patient showed a slightly shortened 1st metacarpal, the length ratio of which to the 4th metacarpal was 0.74 (less than the average ratio of 0.80), and the 4th metacarpal was shorter than its

predicted length (4th:2nd = 0.852 for normal peers, 0.804 for this patient) in her Asian peers.[14] Her feet were unaffected. The range of motion of individual joints was normal, and no other skeletal or non-skeletal dysmorphisms were found.

Molecular Analysis

The patient and her parents provided written informed consent for the publication of this manuscript and any identifying image or data. Whole blood was collected from the patient in blood collection tubes containing EDTA. Genomic DNA was extracted using QIAamp DNA Mini Kit (Qiagen) for DNA library preparation as recommended by Illumina protocols, which included end repair, adapter ligation, and polymerase chain reaction (PCR) enrichment. The amplified DNA was then captured by using a whole-exome capture kit (MyGenostics GenCap Enrichment Technologies). Biotinylated capture probes were designed to tile all exons without repeated regions. The captured DNA was eluted and amplified, and the PCR products were purified using SPRI beads (Beckman). The enriched libraries were sequenced for 150-bp paired-end reads on an Illumina NovaSeq6000 platform. Gene sequencing confirmed a gene mutation in the region coding the potential propeptide domain of the GDF5 protein, with deletion of one base in the coding region 349G (c.349delG) on chromosome 20 (Figure 2). This mutation resulted in termination of translation after translating six amino acids from codon 117 (p.A117fs*6) (Figure 3).

Discussion

After excluding possible syndromic brachydactyly forms, detailed examination of the radiograph and gene analysis report confirmed BDC in this patient, according to the Temtamy and McKusick classification. The patient showed a slightly shortened 1st metacarpal, the length ratio of which to the 4th metacarpal was shorter than other healthy 11-year-old Asian girls.[14] Notably, the 4th finger is generally not affected, and thus it becomes the longest finger.[3] However, in this patient, the 4th metacarpal was shorter than its predicted length, suggesting that the 4th finger was not unaffected but less affected. Since the literature[14] did not list the original Japanese data, we can only use the mean to make a rough comparison. As this disorder shows variable phenotypes even within individuals possessing the same gene mutation, it is particularly important to study the genetic background of BDCs.

This is the first report of this mutation in a Chinese individual, and it has not been recorded in the ClinVar database. GDF5 is a predecessor polypeptide composed of 501 amino acids and plays an important role in skeletal and joint development.[15] Abnormalities in GDF5 can result in various skeletal malformations, including BDC.[16] BMPR1B, the receptor for GDF5, is associated with the development of the proximo-distal trend and joint formation. If the mutation decreases the expression of GDF5 protein or blocks the binding of GDF5 to the TGF-β receptor structural domain of BMPR1B, the related signaling pathway is downregulated, resulting in the development of short fingers; if the mutation increases the affinity of GDF5 for BMPR1B, symphalangism can occur.[9,17] In this patient, we detected the heterozygous mutation c.349delG in exon 1 of GDF5. As a result, the propeptide after codon 117 could not be translated correctly and was terminated after six amino acids (p.A117fs*6), causing GDF5 haploinsufficiency. Therefore, the frameshift alteration in GDF5 is the causative mutation in our patient with BDC. According to embryonic development of hand, why BDC skips the fourth finger is still unclear. For the affected fourth digit, existing studies cannot explain its unusual manifestation. Further cases or research models for subsequent research are needed to improve the understanding of the molecular pathogenesis of this mutation, which will be helpful to reclassify isolated brachydactyly at the molecular genetics level rather than clinical features.

Author Contributions

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors. All authors are in agreement with the manuscript.

Acknowledgements

This study was supported by the Natural Science Foundation of Beijing, China (No. L192052).

Conflict of Interest

All authors declare no conflicts of interest.

Ethical Approval

The patient and her parents provided written informed consent for the publication of this manuscript and any identifying image or data.

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