Received: 16 October 2018 | Revised: 26 February 2019 | Accepted: 6 March 2019

DOI: 10.1002/mgg3.690

ORIGINAL ARTICLE

Molecular Genetics & Genomic Medicine Open Access WILEY

Identification of novel mutations in preaxial polydactyly patients through whole-exome sequencing

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Abstract

Background: Polydactyly is one of the most common hereditary limb malformation characterized by additional digits in hands and/or feet. With extra fingers/toes, which could be very problematic, polydactyly patients are usually treated in early childhood by removing of extra digits with surgery. Genetically, polydactyly is caused by mutations of genes that involve in digit formation.

Methods: In the current report, we performed genetic analysis for polydactyly using DNA samples from a cohort of 20 Chinese patients. All patients show preaxial polydactyly in one of their hands.

Results: With whole-exome sequencing (WES), we have identified two novel heterozygous mutations c.G2844A in *GLI3* gene (OMIM 165240) and c.1409_1410del in *EVC* gene (OMIM 604831). Compound heterozygous mutations that affect *KIAA0586* gene (OMIM 610178) are also detected. Proteins encoded by the genes have important roles in primary cilia and regulate sonic hedgehog signaling pathway.

Conclusion: Our study highlights the important roles of primary cilia in limb development, and helps to further understand the molecular mechanisms for polydactyly formation.

KEYWORDS

cilia, ciliopathies, limb malformation, polydactyly, sonic hedgehog signaling pathway

1 | INTRODUCTION

Polydactyly refers to a situation of having an extra finger or toe. Based on the position of the extra digit, it can be classified as preaxial polydactyly, postaxial polydactyly, and central polydactyly (Biesecker, 2010; Faust, Kimbrough, Oakes, Edmunds, & Faust, 2015; Goldfarb, 2010). Preaxial polydactyly is the most common situation, in which an extra digit(s) is on the side of the thumb or big toe (radial side of the hand/toe). The clinical features of preaxial polydactyly are diverse, which vary from a barely visible broadening of the distal phalanx to complete duplication of the thumb including the first metacarpal. Preaxial polydactyly can be further classified into seven groups (type I–VII) based on the level of the bifurcation by Wassel's classification (Wassel, 1969). Postaxial polydactyly is defined as an extra digit on the side of the little finger/toe (ulnar or fibular side of the hand/foot). The extra digit is underdeveloped in many cases, consisting of an end phalanx with a nail and connected to the hand/foot with a small stalk of tissue. A fully developed extra digit with bone, muscle, nerves, and blood vessels has been seen in some cases while a triplication of the little digit is very

TABLE 1 PCR primer sequences

Sample ID	CHROM	POS	dbSNP ID	Variant	Forward primer	Reverse primer
S4	14	58896083	rs147119902	KIAA0586:NM_014749.3:exon2:c.T202A:p.S68T	ATTCCTTTGTTTTGTTAGGT	CATCAGACTTAACTTCTGCT
S4	14	58941425	rs139493302	KIAA0586:NM_014749.3:exon18:c.C2507T:p.P836L	ATATAATGGTCCTCCATTTC	GCCAGTTGCTTCTACTTTTC
S7	7	42005827	—	GLI3:NM_000168.5:exon15:c.G2844A:p.M948I	CCGACGCCCCTGCCCAACAT	GAGAGGATGAGCCTGAAGAC
S20	4	5755604	—	EVC:NM_001306090.1:exon10:c.1409_1410del:p.Q470fs	GCTGGCCCAAGAGGAGGAAC	AGAAGCTTCCTGGCTGAGGC

rare. Central polydactyly is a very rare situation, in which the index, middle, or ring finger is duplicated (Faust et al., 2015; Malik, 2014; Wyhe, Trost, Koshy, & Pederson, 2016).

Polydactyly is caused by abnormal anterior-posterior pattern formation during limb development (Faust et al., 2015). Limb bud formation starts between 26 and 28 days after fertilization and grows in three dimensions, proximal to distal, dorsal to ventral, and anterior to posterior. There are three major signaling pathways that control the growth of the limb in a three-dimensional axis: the apical ectodermal ridge controls proximal to distal orientation, the zone of polarizing activity controls anterior to posterior orientation, and the wingless type signaling pathway controls dorsal ventral orientation. The whole process involves in multiple signaling pathways, transcription factors, and secreted proteins. Many of the genes are related to structure and functions of cilia, and participate in sonic hedgehog pathway. Since interference of gene functions by genetic mutations leads to limb abnormalities (Biesecker, 2010; Verma & El-Harouni, 2015), discovery of gene lesion would benefit patients and their families, and promote the research of limb abnormalities. In this study, we performed whole-exome sequencing (WES) using polydactyly patient DNA to identify novel gene mutations that cause polydactyly.

2 | MATERIALS AND METHODS

2.1 | Patients

All patient samples were obtained through the First Hospital of Jilin University, China. Written informed consent under an approved Institutional Review Board protocol was provided by all subjects. Genomic DNA was isolated from patient blood and quantified with Qubit (Thermo Fisher Scientific) and Nanodrop (Thermo Fisher Scientific). The A260/A280 for all DNA samples is between 1.8 and 2.0.

2.2 | Exome Sequencing and variant detection

WES was conducted at Novogene Corporation. Sequencing libraries were prepared using patient genomic DNA. Exome capture was performed with SureSelect Human All ExonV6 kit (Agilent) according to the manufacturer's instructions. 150 bp paired-end sequencing was performed on HiSeq 4000 (Illumina). Sequencing reads were aligned to the human hg19 reference genome using the Burrows Wheelers Aligner MEM algorithm (Li & Durbin, 2009). Duplicated reads were marked by Picard (http://broadinstitute.github.io/picard) and excluded from downstream analysis. Variant calling was performed using SAMtools (Li et al., 2009). Copy number variation (CNV) is measured with coNIFER software (Krumm et al., 2012). Variants were annotated with the software developed by Novogene Corporation.

2.3 | Variant filtering

Since polydactyly is a rare human disease, SNP/Indel variants with minor allele frequency (MAF) less than 0.01 in 1,000 genome project (Adam et al., 2015) were kept for downstream analysis. Synonymous variants and the variants in deep intron regions were filtered. Functional effects of the variants were predicted with SIFT, PolyPhen2, MutationTaster, and CADD algorithms (Adzhubei et al., 2010; Jana Marie, Cooper, Markus, & Dominik, 2014; Martin et al., 2014; Prateek, Steven, & Ng, 2009). Variants that are predicted to be deleterious by at least two algorithms were kept for further analysis.

2.4 | Sanger sequencing

PCR primers targeting the variants were designed using Primer3 (Table 1). Genomic DNA from each sample was amplified by PCR reactions. Sanger sequencing was performed at Genesky Biotechnologies Inc. on the 3730 DNA Analyzer (Thermo Fisher Scientific).

2.5 | Protein sequence alignment

Protein sequences were downloaded from NCBI database. Multiple sequence alignment was performed with EMBL-EBI Clustal Omega program (https://www.ebi.ac.uk/Tools/msa/clustalo/) using default settings.

3 | RESULTS

There are total 20 Chinese patients involved in this study. All cases showed preaxial polydactyly and were sporadic. The cases were classified using Wassel's classification method and Temtemy–McKusick scheme, respectively (Table 2). Polydactyly was seen in only one hand for all patients. Other abnormalities had not been seen in most of patients, except for patient S5, who showed ptosis and a relatively small buttock, suggesting not all cases were isolated. It could be that all patients were infants so abnormalities such as delayed development were not prominent.

To identify mutations that lead to polydactyly, WES was performed using genomic DNA isolated from patient blood. Sequencing reads were aligned to human reference genome, and variants were called by SAMtools. We have identified gene mutations in three patients S4, S7, and S20 (Table 3). Patient S4 carries *KIAA0586* (NM_014749.3) compound heterozygous point mutations p.S68T (dbSNP ID: rs147119902) and p.P772L (rs139493302). Both rs147119902 and rs139493302 have been found in east and south Asian, and Non-Finnish

TABLE 2 Patient summary

Patient	Age	Gender	Preaxial polydactyly	Wassel classification	Temtamy-McKusick classification	OMIM
S1	6 months	Male	Right hand	VI	PPD1	174400
S2	12 months	Female	Right hand	VII	PPD2	174500
S3	15 months	Male	Right hand	IV	PPD1	174400
S4	11 months	Female	Left hand	VII	PPD2	174500
S5	1 year	Male	Right hand	V	PPD1	174400
S6	8 months	Female	Left hand	IV	PPD1	174400
S7	7 months	Female	Right hand	V	PPD1	174400
S8	6 years	Female	Left hand	VI	PPD1	174400
S9	11 months	Male	Left hand	III	PPD1	174400
S10	8 months	Male	Right hand	IV	PPD1	174400
S11	11 months	Male	Left hand	IV	PPD1	174400
S12	14 months	Male	Left hand	IV	PPD1	174400
S13	16 months	Male	Left hand	III	PPD1	174400
S14	1 year	Female	Left hand	II	PPD1	174400
S15	15 months	Male	Right hand	V	PPD1	174400
S16	9 months	Female	Right hand	IV	PPD1	174400
S17	11 months	Male	Right hand	IV	PPD1	174400
S18	1 year	Male	Right hand	VII	PPD2	174500
S19	7 months	Male	Left hand	VI	PPD1	174400
S20	10 months	Male	Left hand	IV	PPD1	174400

TABLE 3 Summary of gene mutations in the study

Sample ID	Inheritance mode	CHROM	POS	dbSNP ID	REF	ALT	GeneName	Description	Func	ExonicFunc
S4	AR	14	58896083	rs147119902	T	A	KIAA0586	KIAA0586	exonic	missense SNV
S4	AR	14	58941425	rs139493302	C	T	KIAA0586	KIAA0586	exonic	missense SNV
S7	AD	7	42005827	—	C	T	GLI3	GLI family zinc finger 3	exonic	missense SNV
S20	AD	4	5755604	—	CAG	C	EVC	Ellis van Creveld protein	exonic	frameshift deletion

Note. NA: variant not reported in database

European with allele frequency <0.01 in the EXAC database (http://exac.broadinstitute.org). Patient S7 carries a heterozygous mutation p.M948I in *GLI3* gene (NM_000168.5). Patient S20 carries a 2-bp heterozygous deletion in *EVC* gene, which leads to a frameshift (p.Q470fs) and early termination of *EVC* protein translation. All variants have low MAF (less than 1%) or not been reported in public databases including 1,000 Genomes (www.internationalgenome.org), ESP (evs.gs.washington.edu/EVS/), and ExAc (exac.broadinstitute.org), further supporting they are rare in human populations (Table 3).

We next compared genotypes between patients and an unaffected person, who was used as a normal control. We were able to confirm all the mutations by Sanger sequencing (Figure 1). To evaluate the impact of missense mutations at protein level, the protein conservation was analyzed in seven species. The data revealed the missense mutations in KIAA0586 and GLI3 affect highly conserved amino acids (Figure 2), suggesting mutated sites are crucial for protein functions.

In addition to above mutations, it is possible that pathogenic variants are detected by WES in other patients but are not identified in this study. As a reference, exonic nonsynonymous single-nucleotide variants (SNVs) and small insertions/deletions (indels) in polydactyly-related genes including GLI1, IQCE, and ZNF141 in all patients detected by WES are listed in Supplementary Table S1.

4 | DISCUSSION

Polydactyly is a common congenital hand abnormality with high diversities in clinical, ranging from a rudimentary floating type to complex manifestations. It is a genetically heterogeneous disorder, which can be caused by mutations of a broad spectrum of genes. Both autosomal dominant form and autosomal recessive form have been reported. There are at least 310 entries of disorders that have polydactyly phenotype (Biesecker, 2010).

In this study, we have identified mutations in polydactyly patients that include *EVC*, *GLI3*, and *KIAA0586* genes. EVC protein contains a leucine zipper and a transmembrane domain and is localized in cilia. It mediates transduction of extracellular signals to the nucleus through the hedgehog pathway (Caparrós-Martín et al., 2013; Victor L Ruiz-Perez et al., 2007). Autosomal dominant mutations of *EVC* gene have been shown to cause Weyers acrofacial dysostosis (OMIM 193530), which is featured by dental anomalies, nail dystrophy, postaxial polydactyly, and mild short stature (Ruiz-Perez et al., 2000).

GLI3 protein is a member of GLI family, which are transcription factors that mediate the Sonic hedgehog signaling pathway. GLI3 localizes to the tips of primary cilia in a hedgehog-dependent manner (Goetz & Anderson, 2010; Xiaohui et al., 2010). Autosomal dominant mutations for *GLI3* gene have been seen in several skeletal dysplasias including Greig cephalopolysyndactyly syndrome (OMIM 175700), Pallister-Hall syndrome (OMIM 146510), Polydactyly, postaxial, types A1 and B (OMIM 174200), and Polydactyly, preaxial, type IV (OMIM 174700) (Fujioka et al., 2010; Kini et al., 2010; Mcdonald-Mcginn et al., 2010; Radhakrishna et al., 1997).

KIAA0586 gene encodes a centrosomal protein, which is essential for primary cilia formation and hedgehog signaling (Stephen et al., 2013; Tetsuo, Sehyun, Yu-Chun, Takanari, & Brian David, 2014; Yin et al., 2009). Depletion of *KIAA0586* in mice and chicken leads to typical ciliopathy phenotypes including face and neural tube defects,

Variant	cyto-Band	OMIM	1,000 Genomes	ESP	ExAC
KIAA0586:NM_014749.3:exon2:c.T202A:p.S68T	14q23.1	Joubert syndrome 23, OMIM 616490; Short-rib thoracic dysplasia 14 with polydactyly, OMIM 616546	0.005	NA	0.002
KIAA0586:NM_014749.3:exon18:c.C2507T:p.P836L	14q23.1	Joubert syndrome 23, OMIM 616490; Short-rib thoracic dysplasia 14 with polydactyly, OMIM 616546	0.003	NA	0.001
GLI3:NM_000168.5:exon15:c.G2844A:p.M948I	7p14.1	Greig cephalopolysyndactyly syndrome, OMIM 175700; Pallister-Hall syndrome, OMIM 146510; Polydactyly, preaxial, type IV, OMIM 174700; Polydactyly, postaxial, types A1 and B, OMIM 174200; Hypothalamic hamartomas, somatic, OMIM 241800	NA	NA	NA
EVC:NM_001306090.1:exon10:c.1409_1410del:p.Q470fs	4p16.2	Ellis-van Creveld syndrome, OMIM 225500; Weyers acrodental dysostosis, OMIM 193530	NA	NA	NA

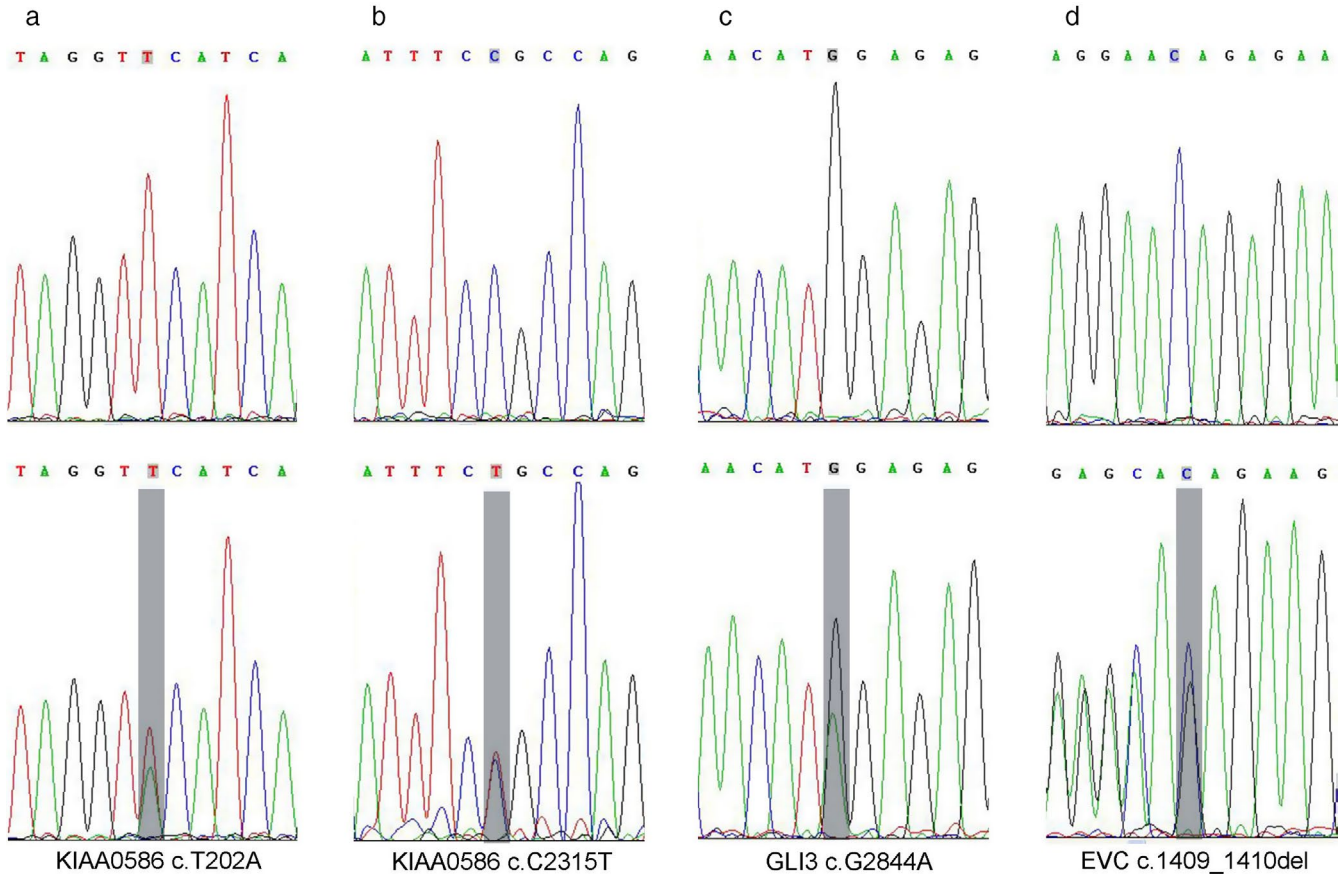

FIGURE 1 Confirmation of gene mutations by Sanger Sequencing. Chromatograms illustrating mutations in (a and b) *KIAA0586*, (c) *GLI3*, and (d) *EVC* genes detected by Sanger sequencing. Sequencing results from an unaffected person are shown on top panels, and results from the patients are shown on the bottom panels. Mutation sites are shaded with grey boxes

polydactyly, and cystic kidney disease (Davey et al., 2006; Fiona et al., 2011). Autosomal recessive mutations for *KIAA0586* cause Short-rib thoracic dysplasia 14 (SRTD14) with polydactyly (OMIM 616546) and Joubert syndrome 23 (OMIM 616490) (Caroline et al., 2015; Bachmann-Gagescu et al., 2015).

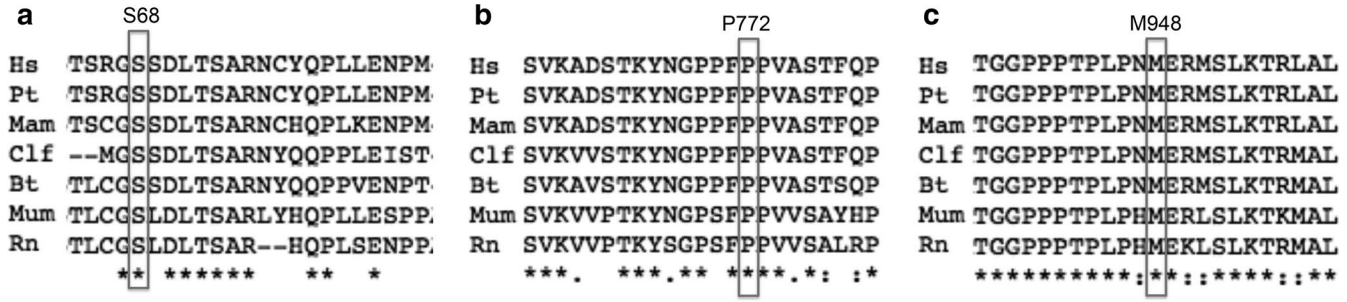

FIGURE 2 Protein sites with amino acid substitutions are evolutionarily conserved among seven species. Protein multiple sequence alignment for (a) KIAA0586 S68, (b) KIAA0586 P772, and (c) GLI3 M948. Protein sites with mutations are highlighted with grey boxes. Asterisks indicate protein positions as fully conserved. Dots indicate positions with similar amino acid residues. Hs, Homo sapiens; Pt, Pan troglodytes; Mam, Macaca mulatta; Clf, Canis lupus familiaris; Bt, Bos Taurus; Mum, Mus musculus; Rn, Rattus norvegicus

Polydactyly is caused by abnormal anterior-posterior patterning formation. It may associate with other clinical phenotypes as part of a syndrome. The genetics of polydacyly is highly complex, with mutations identified in a broad spectrum of genes (Biesecker, 2011). While many of the genes are involved in sonic hedgehog signaling pathway and function of primary cilia, mutation of the genes leads to clinically distinct phenotypes. In this study, we reported mutations in cilia genes in polydactyly patients, highlighting the important roles of primary cilia in limb patterning formation. WES is a valuable diagnostic tool for identifying gene mutations in disorders with high genetic heterogeneity such as polydactyly.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was given by the Ethics Committee of the First Hospital of Jilin University, Changchun, China. All patients gave their written information consent.

AVAILABILITY OF DATA AND MATERIAL

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

All the authors declare that they have no conflict of interest.

AUTHOR' S CONTRIBUTIONS

LL and TW contributed to the study design. TW, ZX, YD, YL, YF, and JR collected the data and performed the data analysis. All authors prepared the manuscript. TW and ZX amended the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Wang T, Xuan Z, Dou Y, et al. Identification of novel mutations in preaxial polydactyly patients through whole-exome sequencing. *Mol Genet Genomic Med*. 2019;7:e690. https://doi.org/10.1002/mgg3.690