

## CLINICAL REPORT

# Whole genome sequencing reveals translocation breakpoints disrupting *TP63* gene underlying split hand/foot malformation in a Chinese family

Ying Peng<sup>1</sup>  | Shuting Yang<sup>1</sup> | Hui Xi<sup>1</sup> | Jiancheng Hu<sup>1</sup> | Zhengjun Jia<sup>1</sup> | Jialun Pang<sup>1</sup> | Jing Liu<sup>1</sup> | Wenxian Yu<sup>1</sup> | Chengyuan Tang<sup>2</sup> | Hua Wang<sup>1</sup>

<sup>1</sup>Department of Medical Genetics, National Health Commission Key Laboratory of Birth Defects Research, Hunan Provincial Maternal and Child Health Care Hospital, Changsha, China

<sup>2</sup>Department of Nephrology, Hunan Key Laboratory of Kidney Disease and Blood Purification, The Second Xiangya Hospital, Central South University, Changsha, China

## Correspondence

Chengyuan Tang, Department of Nephrology, Hunan Key Laboratory of Kidney Disease and Blood Purification, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China.

Email: tangchengyuan@csu.edu.cn

Hua Wang, Hunan Provincial Maternal and Child Health Care Hospital, Changsha, Hunan 410008, China.

Email: wanghua213@aliyun.com

## Funding information

National Natural Science Foundation of China, Grant/Award Number: 81870474, 31601035; Major Scientific and Technological Projects for Collaborative Prevention and Control of Birth Defects in Hunan Province, Grant/Award Number: 2019SK1013; Natural Science Foundation of Hunan Province, Grant/Award Number: 2019JJ40415 and 2018JJ3274

## Abstract

**Background:** Split hand/foot malformation (SHFM) is a congenital limb developmental disorder, which impairs the fine activities of hand/foot in the affected individuals seriously. SHFM is commonly inherited as an autosomal dominant disease with incomplete penetrance. Chromosomal aberrations such as copy number variations and translocations have been linked to SHFM. This study aimed to identify the genetic cause for three patients with bilateral hand and foot malformation in a Chinese family.

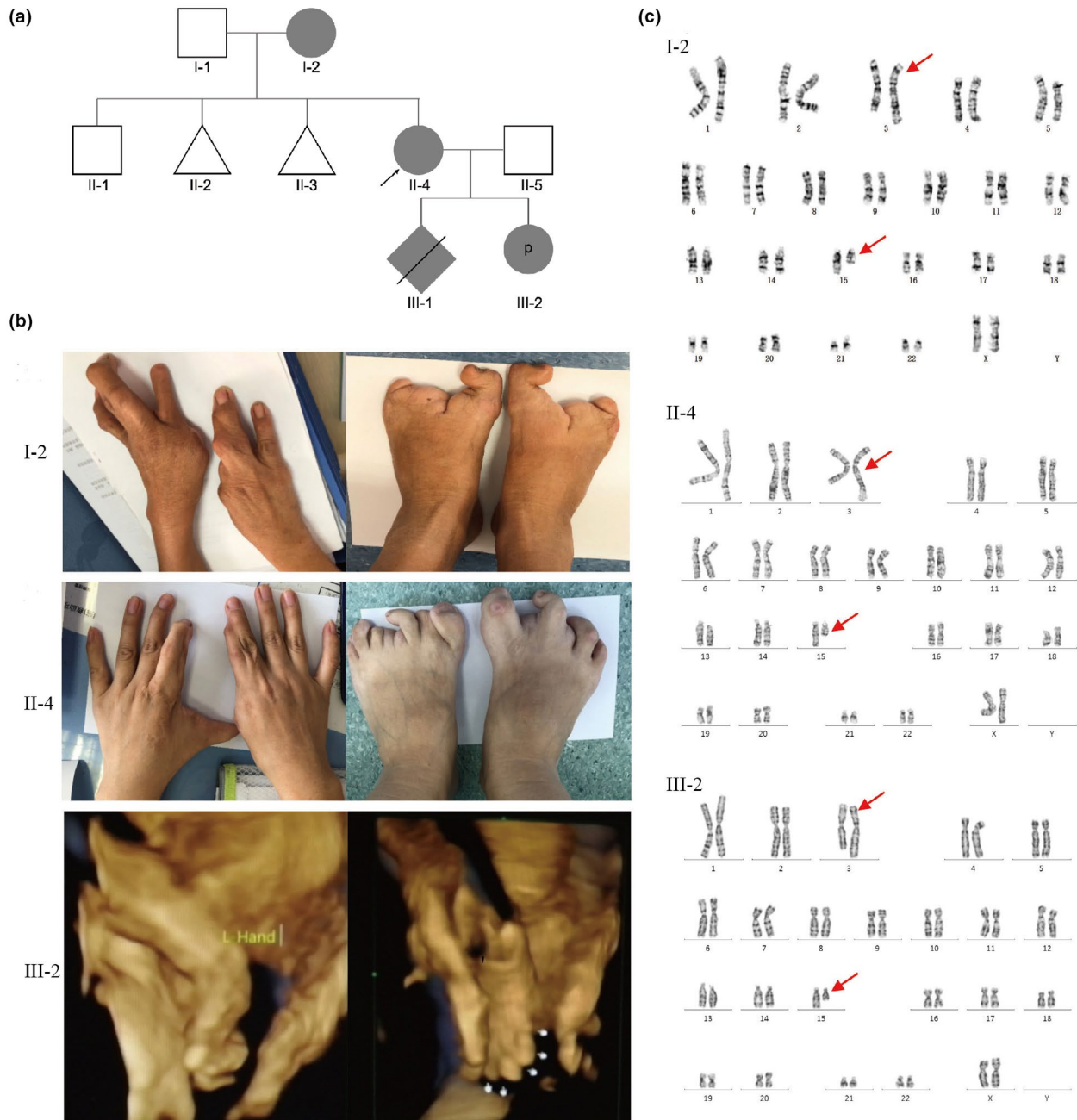
**Methods:** Karyotyping, single-nucleotide polymorphism (SNP) array, whole exome sequencing, whole genome sequencing, and Sanger sequencing were applied to identify the pathogenic variant.

**Results:** Karyotyping revealed that the three patients had balanced reciprocal translocation, 46, XX, t(3;15) (q29;q22). SNP array identified no pathogenic copy number variation in the proband. Trio-WES (fetus–mother–father) sequencing results revealed no pathogenic variants in the genes related to SHFM. Whole-genome low-coverage mate-pair sequencing (WGL-MPS), breakpoint PCR, and Sanger sequencing identified the breakpoints disrupting *TP63* in the patients, but not in healthy family members.

**Conclusion:** This study firstly reports that a translocation breakpoint disrupting *TP63* contributes to the SHFM in a Chinese family, which expands our knowledge of genetic risk and counseling underlying SHFM. It provides a basis for genetic counseling and prenatal diagnosis (preimplantation genetic diagnosis) for this family.

## KEYWORDS

chromosome translocation, split hand/foot malformation, *TP63*, whole genome sequencing



**FIGURE 1** Family pedigree, clinical phenotype and karyotype analysis results of affected persons. (a) A consanguineous pedigree showing four affected members (I-2, II-4, III-1 and III-2) in the three-generation family. (b) Clinical features of the affected individuals, I-2, II-4 and III-2. (c) the karyotype analysis of I-2, II-4 and III-2. Red arrow indicated the translocation between chromosome 3 and chromosome 15

## 1 | INTRODUCTION

Split hand/foot malformation (SHFM OMIM # 605289) is a genetically congenital heterogeneous syndrome with highly variable and asymmetrical clinical features ranging from mild defects such as hypoplasia of a single phalanx or syndactyly to aplasia of one or more digits (Patel et al., 2014). It is estimated that the prevalence of SHFM is around 1/100,000 births (Miyake et al., 2016). Till now, it has demonstrated that the mutations in SHFM pathogenesis

involved single gene point variants, copy number variation, and chromosomal rearrangements. SHFM is a heterogeneous condition caused by multiple loci, including SHFM1 (7q21-q22), SHFM2 (Xq26), SHFM3 (10q24), SHFM4 (3q27), and SHFM5 (2q31). Previous studies demonstrated that the genes involved in SHFM partly include *TP63* (Simonazzi et al., 2012), *DLX5* (OMIM \*600028), *DLX6* (OMIM \*600030), *FGF1* (OMIM \*131220), *FGF8* (OMIM \*600483), *WNT10B* (OMIM \*601906), and *BHLHA9* (OMIM \*615416). The causes of most SHFM cases remain unknown.

Mutations in *TP63* at the SHFM4 locus (mainly including point mutations) are known to underlie both syndromic and non-syndromic forms of SHFM. As a transcription factor of p53 family, TP63 is encoded by *TP63* locating on 3q28 and is homologous to TP53 and *TP73* and plays an essential role in regulating epithelial, limb, and craniofacial development (Yang et al., 1999). It is described that *TP63* acts as one of the most frequently mutant gene which accounts for about 10% of SHFM (Yang et al., 2018). As of now, 148 *TP63* mutations have been identified, including 115 missense/nonsense mutations, five mutations in regulatory sequence, five splicing substitutions, 13 small deletions, five small insertions, one small indels, two gross deletions, and two gross insertions. There is no report of disruption of *TP63* gene caused by complex rearrangements in SHFM cases.

Here, we firstly reported three patients with clinically typical SHFM4 with 46, XX, t(3;15) (q29;q22). We determined the translocation breakpoint sequences by whole-genome low-coverage mate-pair sequencing (WGL-MPS) and identified *TP63* gene disruption in the proband and the affected family members. Meanwhile, we also described the phenotype of this family in brief. This study will expand our knowledge of SHFM and shed light on the genetic diagnosis.

## 2 | MATERIALS AND METHODS

### 2.1 | Patient data

We identified a family with SHFM from Maternal and Child Health hospital in Hunan province, China. This family has eight members across three generations in this genetic disease study (Figure 1a).

The proband (II-4) was a 29-year-old, gravida 2, para 0 woman who had severe limb malformation involving missing thumb of the right hand, “lobster-claw” malformations of the left hand, and syndactyly of the bilateral feet (Figure 1b). Mental retardation, ectodermal findings, and orofacial clefting were not observed.

The proband (II-4) visited the clinical genetics laboratory because the prenatal ultrasound demonstrated that her second fetus (III-2) had SHFM at 21 weeks of gestation (Figure 1b). The first pregnancy (III-1) of this woman was terminated because of SHFM, and no genetic testing was performed for this fetus. The mother (I-2) of the proband had similar split hand/foot features, manifested as absence of the thumbs and second phalanges on the hand, and “lobster-claw” malformations of the bilateral feet (Figure 1b). The mother (I-2) of the proband had two spontaneous abortions.

Following written informed consents, amniocentesis cells were collected for molecular genetic analysis for the fetus (III-2) of the proband, and peripheral blood was collected

from the family members, in compliance with the ethical guidelines in Maternal and Child Health hospital.

### 2.2 | Karyotype analysis

Routine chromosome G-banded (320–400 bands) karyotyping analyses were performed on metaphase cells according to standard protocols (Peng et al., 2020).

### 2.3 | Single-nucleotide polymorphism (SNP) array

Genomic DNA was extracted from the amino fluid cells and peripheral blood lymphocytes using DNA Isolation Kit for Cells and Tissues and QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany), respectively. SNP array analysis was conducted using Affymetrix CytoScan® 750 K Array (Affymetrix Inc, CA, USA) according to the manufacturer's instruction. Data from SNP array analysis were analyzed using Chromosome Analysis Suite (ChAS; version 2.1).

### 2.4 | Whole exome sequencing data analysis

WES library preparation was captured with a biotinylated oligonucleotide probe library (Agilent SureSelect Human All Exon v.6, Agilent), subsequently sequenced by Illumina HiSeq X-Ten (Illumina Inc, San Diego, CA, USA). The adapter sequence and low-quality reads of the sequencing raw data were filtered. The filtered data were aligned to the human genome reference assembly with the Burrows–Wheeler Aligner, and the variants were called using GATK. All variants were annotated by ANNOVAR with database information.

### 2.5 | Whole genome sequencing data analysis

Genomic DNA was extracted from peripheral blood with Qiagen DNA extraction kit and then used to construct a non-size selected mate-pair library and then subjected to 50-bp-end multiplex sequencing by BGISEq-500. After removing reads containing sequencing adapters and low-quality reads, the high-quality pair-end reads were aligned to the NCBI human reference genome (hg19, GRCh37.1) by SOAP2. Then, we retained the uniquely mapped reads for the subsequent analysis and the specific analysis method has been previously described in detail (Dong et al., 2014; Li et al., 2014). Using this specific analysis method, we could take advantage of uniquely paired reads to find all chromosome number and

structure variations, and the corresponding breakpoints on the whole genome, and the accuracy of the breakpoints could be accurate to 1 Kbp. Finally, the breakpoints were validated precisely by Sanger sequencing and PCR.

## 2.6 | Sanger sequencing and PCR

We designed primers for the 500 bp upstream and 500 bp downstream of the breakpoint region, respectively, to verify the breakpoints. By aligning the final PCR product sequences, which crossed the breakpoint, to the human reference genome, we got precise breakpoints. If the aligned sequence did not contain breakpoints, we could adjust the primers to change product sequence interval and verified again according to the above experimental method until a verification sequence that crossed the breakpoint was obtained.

Oligonucleotide primer pairs of the translocation were designed with Gene Runner software (version 5.0.69 Beta; Hastings Software). Forward primer: TAACTTAGGAGAATATCTTTGTGGT; Reverse primer: CCCCAGACCCTTACAATATG. The PCR was amplified in 20  $\mu$ l reaction volume with 10 pMol of each primer pair and sequenced by Sanger methods after purification in CheerLand Precision Biomed Co., Ltd.

## 3 | RESULTS

First, we performed karyotype analysis for these three affected individuals, and the results revealed that their karyotypes are 46, XX, t(3:15) (q29;q22) (Figure 1c).

SNP array analyses showed that fetus had no pathogenic or likely pathogenic copy number variations. In order to exclude single-site variation leading to SHFM, Trio (fetus–mother–father) WES was performed and no SHFM-related pathogenic variants were detected.

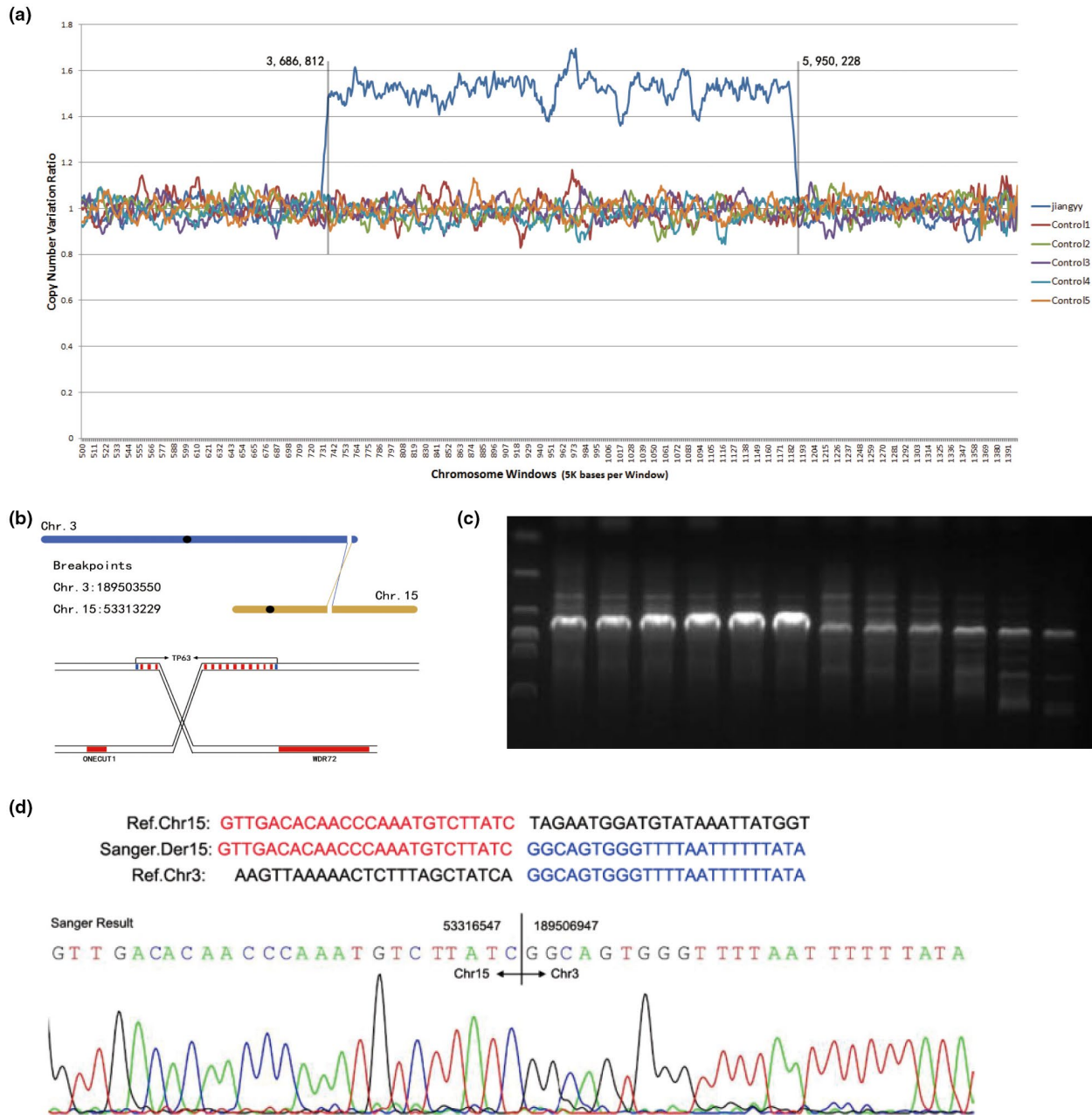
We highly suspected that the SHFM was caused by chromosomal translocation. WGS testing was performed on the peripheral blood samples from the proband. Using the specific analysis method described above, we could find all chromosome number and structure variations, and the corresponding breakpoints on the whole genome by uniquely mapped paired reads, and can also define the true breakpoint within 1 Kbp. We screened the detected chromosomal mutation results, and designed primers for the sequence of 500 bp upstream and 500 bp downstream of the breakpoint region to verify the breakpoints. The PCR product sequences which cover the breakpoint were aligned to the human reference genome, and the precise breakpoint was mapped. We found a translocation mutation in *TP63* gene of which the breakpoints were chr3:189,506,947 and chr15:53,316,547. The breakpoint on *TP63* gene was in intron 3 located in 3q28 and link to the intergenic

region (between *ONECUT1* and *WDR72* gene) in 15q21.3. Verification by PCR and Sanger sequencing showed that the three affected individuals all carried the same translocation mutation in *TP63* gene (Figure 2b-d). In addition, the proband (II-4) also carried an interstitial duplication of 8p 23.2 (3,686,812–5,950,228) (Figure 2a).

## 4 | DISCUSSION

Balanced reciprocal translocations cause no loss of genetic material and generally no special clinical phenotypes. However, 6% of balanced translocation carriers show clinical symptoms, and the potential pathogenic mechanism lies in that key genes are interrupted, fusion genes are formed, or regulatory regions of key genes are affected (Warburton, 1991). Here, we reported three SHFM patients with a balanced reciprocal translocation, t(3:15) (q29;q22). We determined the translocation breakpoint at the nucleotide level, and found that it did disrupt the *TP63* gene. Among previously reported patients with SHFM, chromosomal structural rearrangements are very rare. Christian Babbs et al. reported a sporadic SHFM patient with long bone deficiency who carried a de novo chromosomal translocation t(2;18) (q14.2;p11.2) (Babbs et al., 2007). Klar et al. reported a SHFM1 case who carried a translocation t(7q11.21;9p12) (Klar, 2016). To date, there was no report of SHFM cases that carried a balanced translocation involving chromosome 3. The three patients in this study carried chromosomal translocation t(3:15) (q29;q22), which leads to the disruption of *TP63* and consequently the SHFM4 disorder.

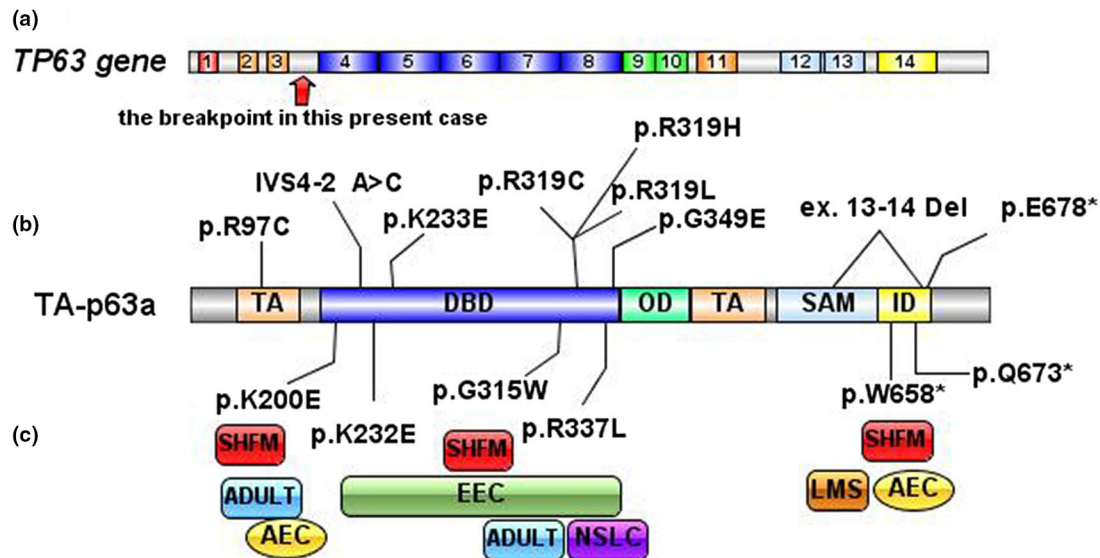
Yang et al. first described the cloning of tumor protein p63 (Yang et al., 1998). The p63 gene generates six isoforms (Di Iorio et al., 2005). The N-terminally truncated ( $\delta$ -N) isoforms without the transactivation domain are generated from a downstream intronic promoter, while the transactivating isoforms are produced by the activity of an upstream promoter. Alternative splicing results in three different C termini, designated  $\alpha$ ,  $\beta$ , and  $\gamma$  for both transcripts. Full-length TAp63- $\alpha$  contains an N-terminal transactivation domain, followed by a DNA-binding domain, an oligomerization domain, a sterile- $\alpha$  motif (SAM) domain, and a C-terminal transactivation inhibitory (TI) domain (Deutsch et al., 2011). The TP63-related genetic diseases include six clinical phenotypes: ectrodactyly-ectodermal dysplasia-cleft lip/palate syndrome 3 (EEC syndrome 3), ankyloblepharon-ectodermal defects-cleft lip/palate syndrome (AEC syndrome), acro-dermato-ungual-lacrima-tooth syndrome (ADULT syndrome), limb-mammary syndrome (LMS), Rapp-Hodgkin syndrome (RHS), and SHFM4 (Sutton & van Bokhoven, 1993). One hundred and forty-eight *TP63* mutations have been identified, and more than 110 mutations in *TP63* are related with EEC and ACE syndrome



**FIGURE 2** Germline Mutations in affected individual II-4 detected by whole genome sequencing. (a) Copy number variation in Chromosome 8 (chr8: 3,686,812–5,950,228) in the affected individual II-4. The copy number variation ratio is between 0.8–1.2 for the five control while it's between 1.4–1.6 for the affected individual II-4. (b) Whole genome sequencing revealed that a translocation occurred in intron 3 of *TP63* gene, located in chr3:189,506,947 and chr15:53,316,547 which was between *ONECUT1* (about 234,338 bp downstream) and *WDR72* (about upstream 489,391 bp) gene in affected individual II-4 and confirmed by sanger sequencing. (c) Sequence chromatogram of the *TP63* translocation in affected individual II-4. The left side of the picture is the II-4 sample, the right side is the control sample, and 6 experimental temperature gradients are set. (d) Sanger original sequence diagram. The two diagrams represent the breakpoint marks of F primer and R primer products respectively

(Kantaputra & Carlson, 2019). Only 15 mutations in *TP63* have been implicated to be involved in SHFM (Figure 3b). Tang JY et al. reported a novel missense mutation of *TP63* (c.1010G>T; R337L) in a SHFM family with hypodontia (Jin et al., 2019). Mutchinick O. M et al. reported R97C in the DNA-binding domain of *TP63* in Mexican patients with isolated SHFM (Zenteno et al., 2005). Lin G et al. reported that

c.728G>A (p.Arg243Gln) in the *TP63* gene was associated with SHFM (Yang et al., 2018). There is no report that *TP63* translocation causes SHFM. In this study, *TP63* was broken in the third intron region and reconnected to 15q21.3, which severely damaged the gene structure of *TP63*, and affected all the amino acids encoded after p.108 that included most of the mutation sites mentioned above.



**FIGURE 3** Schematic diagram of TP63 gene and TA-63a protein structure. (a) Human p63 gene structure. The gene can generate 6 different transcripts due to different promoter sequences at the N-terminal and C-terminal. The red arrow indicates the break point of the study case. (b) Schematic diagram of TA-p63a protein structure. Full-length TAp63-alpha contains an N-terminal transactivation domain, followed by a DNA-binding domain (DBD), an oligomerization domain (OD), a sterile-alpha motif (SAM) domain, and a C-terminal transactivation inhibitory (TI) domain. 15 reported TP63 pathogenic variants identified for SHFM4. (c) 6 diseases related to TP63 mutation. TP63 mutations in different domains are related to different diseases

In addition, we detected that the proband (II-4) had 2.3 Mb interstitial duplication of 8p23.2. Duplications of distal 8p with and without significant clinical phenotypes have been reported, and are often associated with an unusual degree of structural complexity (Harada et al., 2002). Mary Glancy et al. had reported that transmitted duplication of 8p23.1–8p23.2 was associated with speech delay, autism, and learning difficulties (Glancy et al., 2009). In this study, the proband carried the duplication of chromosome 8p23.2 (chr8: 3,686,812–5,950,228), and the duplication interval contained six OMIM genes that were not clearly related to genetic diseases. According to the technical standards for the interruption of CNV (Riggs et al., 2020), the clinical significance of the duplication was unknown. Combining the reported results of these two mutations, we inferred that the break site of the balanced translocation was in the *TP63* gene, which resulted in SHFM4.

In brief, the present study has identified a novel translocation breakpoint disrupting *TP63* in a Chinese family with SHFM, and which was the potential genetic cause of cleft hands and feet for the affected individuals. These findings provide further evidence supporting that *TP63* is critical for normal limb development, expand the genetic spectrum of SHFM, and may contribute to novel approaches to the genetic counseling and diagnosis of SHFM.

#### ACKNOWLEDGMENTS

We thank the family of the proband for their cooperation with this study.

#### CONFLICT OF INTEREST

All authors declare that they have no commercial or other conflicting interests.

#### AUTHOR CONTRIBUTIONS

Y. Peng and H. Wang designed the study. Y. Peng and C. Tang prepared the manuscript. Y. Peng and H. Xi obtained the clinical information. J. Pang and J. Liu performed the SNP array analysis. Y. Peng and S. Yang interpreted the data of SNP array analysis and qPCR. J. Hu and Z. Jia analyzed the karyotype study and WES. W. Yu performed the prenatal ultrasound testing.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

#### ORCID

Ying Peng  <https://orcid.org/0000-0002-0602-6063>

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**How to cite this article:** Peng Y, Yang S, Xi H, et al. Whole genome sequencing reveals translocation breakpoints disrupting TP63 gene underlying split hand/foot malformation in a Chinese family. *Mol Genet Genomic Med*. 2021;9:e1604. <https://doi.org/10.1002/mgg3.1604>