

ORIGINAL ARTICLE

TRPS1 mutation detection in Chinese patients with Tricho-rhino-phalangeal syndrome and identification of four novel mutations

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Abstract

Background: Tricho-rhino-phalangeal syndrome (TRPS) is a rare autosomal dominant disorder characterized by craniofacial and skeletal malformations including short stature, thin scalp hair, sparse lateral eyebrows, a pear-shaped nose, and cone-shaped epiphyses. This condition is caused by haploinsufficiency or dominant-negative effect of the *TRPS1* gene.

Methods: In this study, we analyzed the clinical and genetic data of five unrelated TRPS patients. They were suspected of having TRPS on the basis of clinical and radiological features including typical hair and facial features, as well as varying degrees of skeletal abnormalities. Next-generation sequencing was performed to identify variants of the *TRPS1* gene in the five patients.

Results: In patient 1, we found a novel mutation at c.1338C>A (p.Tyr446*) (*de novo*). Patient 2 had a novel phenotype of hydrocephaly and Arnold–Chiari syndrome and we also found a maternally inherited novel mutation at c.2657C>A (p.Ser886*). Patient 3 had a *de novo* novel mutation at c.2726G>C (p.Cys909Ser) leading to more severe phenotypes. Patient 4 had a paternally inherited known mutation at c.2762G>A (p.Arg921Gln). Patient 5 with a novel phenotype of hepatopathy had a novel deletion at [GRCh37] del(8)(q23.3-q24.11) chr8:g.116,420,724-119,124,058 (over 2,700 kb). In addition, the patient 3 who harboring missense variants in the GATA binding domain of *TRPS1* showed more severe craniofacial and skeletal phenotypes.

Conclusions: We describe four novel mutations and two novel phenotypes in five patients. The mutational and phenotypic spectrum of TRPS is broadened by our study on *TRPS* mutations. Our results reveal the significance of molecular analysis of *TRPS1* for improving the clinical diagnosis of TRPS.

KEYWORDS

novel mutation, novel phenotype, Tricho-rhino-phalangeal syndrome, *TRPS1*

1 | INTRODUCTION

TRPS is an autosomal dominant malformation syndrome characterized by craniofacial and skeletal abnormalities, including short stature, sparse and slowly growing hair, and distinctive facial features with large prominent ears, rarefaction of lateral eyebrows, pear-shaped nasal tip, a high philtrum, and thin upper lip. In addition, patients also present cone-shaped epiphyses of middle and proximal phalanges and severe generalized shortening of all phalanges, metacarpals, and metatarsal bones (Vacarro, Guarneri, & Blandino, 2005).

TRPS is caused by mutations in the *TRPS1* (# OMIM 604386) gene and there are three subtypes of TRPS. TRPS type I (TRPS I, # OMIM 190350) is characterized by sparse scalp hair, a bulbous nose, protruding ears, a thin upper lip, and mild skeletal dysplasia with cone-shaped epiphyses, short stature, and shortening of phalanges (Ludecke et al., 2001); patients with the TRPS I phenotype mostly possess nonsense mutations. TRPS type II (TRPS II or Langer–Giedion syndrome, # OMIM 150230) is a contiguous gene deletion syndrome involving the loss of the *TRPS1* and the *EXT1* genes, the latter being mutated in multiple exostosis type I (Ludecke et al., 1999). Patients with more severe shortening of all phalanges and metacarpals and growth retardation, described as TRPS type III (TRPS III, # OMIM 190351), have been found to carry missense mutations in the GATA-type DNA-binding zinc finger domain (Ludecke et al., 2001). Several researchers have reported the management of TRPS short stature using growth hormone (GH) supplementation (Merjaneh, Parks, Muir, & Fadoju, 2014; Sohn et al., 2012). However, the available results have been controversial.

To date, although a few hundred cases of TRPS have been described in the literature, many cases probably remain undiagnosed or misdiagnosed. Herein, we present five cases from five unrelated families with TRPS of diverse phenotypes; we detected five mutated genes by next-generation sequencing (NGS).

2 | METHODS

2.1 | Ethical compliance

Ethical approval was obtained from the ethics committee of Shanghai Children's Medical Center affiliated to Shanghai Jiao Tong University School of Medicine (SCMCIRB-K2016013). Written informed consent was obtained from the patient's father.

2.2 | Patients and clinical evaluation

Five patients were suspected of having TRPS on the basis of clinical and radiological features including typical hair and facial features, as well as varying degrees of skeletal abnormalities.

2.3 | Molecular studies

Five probands of these unrelated families were selected for whole-exome sequencing (WES). DNA was extracted from EDTA blood samples of the patients and their parents using the QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany). Then, 3 µg genomic DNA was processed by M220 (Covaris, Woburn, MA, USA) to obtain 150–200 bp DNA fragments. The adapter-ligated library was prepared using the Paired-end Sequencing Library Prep Kit (Agilent Technologies, Santa Clara, CA, USA) and both the coding exons and flanking intronic regions were enriched using the SureSelect XT Human All Exon Kit v6 (Agilent Technologies). Then, clusters were generated by isothermal bridge amplification with an Illumina cBot station and high-throughput sequencing was performed with a HiSeq 2500 System (Illumina, San Diego, CA, USA). The above data were evaluated by the Illumina Sequence Control software and then the data were read using the NextGENe® software (SoftGenetics, State College, PA, USA). The analyzed data included each exon and its intronic region of about 50 bp on both sides. The read data were uploaded to the Ingenuity® Variant Analysis platform (Ingenuity Systems, Redwood City, CA, USA) for bioinformatics analysis. Candidate variants were identified by Sanger sequencing. The DNA of patients' parents was also isolated and subjected to Sanger sequencing in order to confirm the origin of the candidate variants. For pathogenicity analysis, we screened all the identified variants and categorized the pathogenicity of variants according to the American College of Medical Genetics and Genomics guideline (Richards et al., 2015). Copy number variant (CNV) was analyzed using a combination of the current guideline (Kearney, Thorland, Brown, Quintero-Rivera, & South, 2011) and in-house criteria of our laboratory.

3 | RESULTS

In total, five patients (two females and three males) were diagnosed clinically with TRPS. Among all enrolled patients with TRPS, the diagnosis was supported by clinical features, radiological features, and laboratory findings.

3.1 | Clinical features

3.1.1 | Patient 1

Patient 1 was a 4-year-and-9-month-old boy with a short stature for 3 years. Clinical examination found a proportionate short stature (97.2 cm, –3 SD), sparse and thin M-shaped hair-line, sparse eyebrows with lateral rarefaction, a pear-shaped

nose, a long philtrum, a thin upper lip, and low ear position (Figure 1a,b). No intellectual impairment was noticed. Examination of the extremities revealed brachydactyly and hypoplastic nails (Figure 2a). Bone X-rays showed that the bone age was 3 years, his phalanx bones were tapered, and some bones had merged in advance (Figure 2b,c). Laboratory examination revealed no obvious abnormality and there was no similar medical history in the family.

3.1.2 | Patient 2

A 2-year-old boy presented a normal stature (88 cm, 0 SD), scaphocephaly, large head circumference, thin scalp hair, a typical pear-shaped nose, and a long philtrum with a thin upper lip and large malformed ears (Figure 1c,d). He presented brachydactyly in both the hands and feet with hypoplastic nails (Figure 2d). Moreover, computed tomography (CT) revealed that he had moderate bandy-leg (Figure 2e). He also presented apparent premature aging of skin (Figure 2f). Brain magnetic resonance imaging (MRI) revealed that he had hydrocephalus and Chiari malformation, which may be a novel phenotype in TRPS (Figure 2g). His mother had the same distinctive facial features, except the hydrocephalus (Figure 1e,f). She had deformities of the hands and feet (Figure 2h,i). No obvious abnormalities were found in a laboratory test.

3.1.3 | Patient 3

The patient was a 10-year-old girl who presented with a short stature (126.1 cm, $-3SD$) and poor growth, thin sparse slow growing hair, absence of lateral eyebrows, a bulbous nasal tip, and a mandibular malformation (Figure 1g,h). It is possible that temporomandibular joint changes caused the mandibular malformation. She also showed severe brachydactyly with clinodactyly, and deviation of the index finger on both hands (Figure 2j). Through radiological examination, she was diagnosed with congenital epiphyseal dystrophy and conical epiphysis. The metacarpal bone collar was all embedded in the metaphysis and there was a defect present in the proximal metaphysis of the second and third middle phalangeal bone, long femoral neck and enlarged trochanter, 4, 5 lumbar spondylolysis, anterior and lateral position of thoracolumbar spine, and anterior position of the pelvis. Laboratory examination revealed that insulin-like growth factor (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) were within normal limits. Her parents had no related clinical phenotypes.

3.1.4 | Patient 4

The patient was a 10-year-old boy who presented with a normal stature (136 cm, $-1SD$) and poor growth. He had fine and sparse hair, thick and broad eyebrows, especially

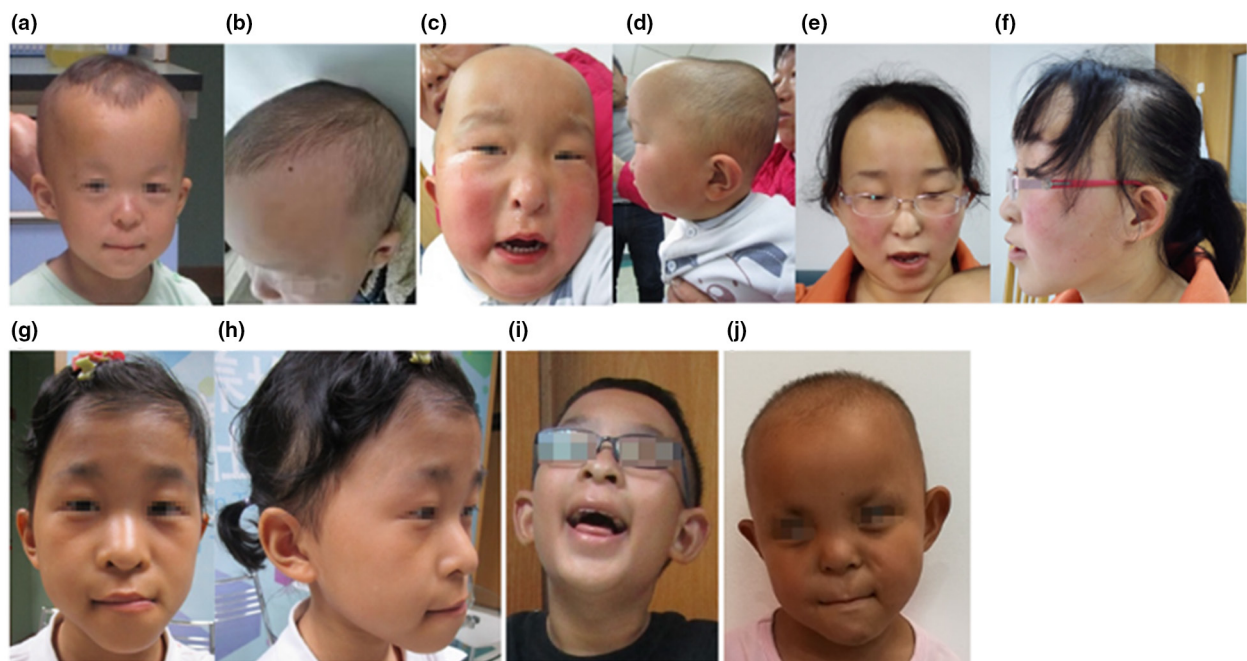


FIGURE 1 Typical dysmorphic features of TRPS in the five patients. They all had sparse hair, thick eyebrows with lateral rarefaction, a characteristic pear-shaped nose, a long-smooth philtrum and thin upper lip, and low ear position. (a, b) Patient 1 showed typical facial features. (c, d) Patient 2 showed hydrocephalus and scaphocephaly. (e, f) The mother of Patient 2 showed typical facial features. (g, h) Patient 3 showed severe mandibular malformation. (i) Patient 4 showed typical facial features. (j) Patient 5 showed typical facial features with a bit of jaundice

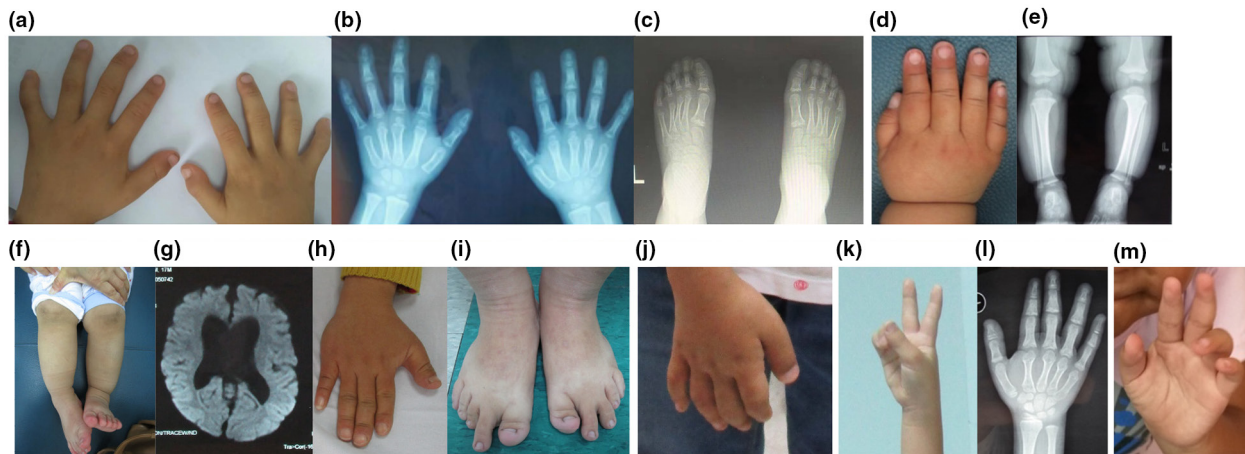


FIGURE 2 Photograph and radiograph of hands, feet, and legs showing brachydactyly. (a, b, c) Patient 1 showed cone-shaped epiphyses in hands and feet. (d, e, f, g) Patient 2 showed hand and feet deformities and an apparent premature aging of skin. He also had a novel phenotype of hydrocephalus and Chiari malformation. (h, i) The mother of Patient 2 presented hand and feet deformities too. (j) Patient 3 showed more severe brachydactyly. (k, l) Patient 4 showed cone-shaped epiphyses in both hands. (m) Patient 5 showed hand deformities. X-rays of cone-shaped epiphyses are not shown for patients 2, 3, and 5

the medial portion, a broad nasal ridge and tip, and a broad columella (Figure 1i). He also presented brachydactyly in both hands (Figure 2k). Radiological examination revealed the presence of epiphyseal closing and cone-shaped epiphyses of the middle phalanx. We found that the ossification center of the metacarpal bone was embedded into the metaphysis and also observed irregular metaphyses of the proximal middle phalanx (Figure 2l). The heights of the mother and father were 156 cm and 153 cm, respectively. In addition, his father had typical facial alterations and brachydactyly. Unfortunately, more clinical information about his father was not available.

3.1.5 | Patient 5

The patient was a 4-year-old girl with hepatomegaly and developmental retardation. She had typical craniofacial abnormalities, including fine and sparse depigmented hair, broad and sparse eyebrows, a pear-shaped nose, long and smooth philtrum, a thin upper lip, prominent ears with an abnormal fold, and some jaundice (Figure 1j). She had a short stature with a short neck, brachydactyly, and scoliosis (Figure 2m). She also had slight mental retardation. X-ray of the right knee revealed a cartilage tumor on the right femur. Clinical experiments showed that there was no obvious abnormality in the content of amino acids and acylcarnitine spectrum (C0–C18). Serum biochemical examination showed abnormal liver function. Indexes of liver function including alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic acid (L-CAC), total bile acid (TBA), urea, lactate dehydrogenase (LDH), hypersensitive c-reactive protein (hs-CRP), and copper blue protein

(CBP) were upregulated; however, prealbumin (PAB) was downregulated.

3.2 | Mutation analysis

The clinical features of our patients supported the suspicion of TRPS and genetic analysis revealed that these five patients were heterozygous mutant for *TRPS1* gene. Patient 1 and patient 2 had the nonsense mutations c.1338C>A (p.Tyr446*) and c.2657C>A (p.Ser886*) in the exons 4 and 5, respectively. Two missense mutations, c.2726G>C (p.Cys909Ser) and c.2762G>A (p.Arg921Gln), were identified in patient 3 and patient 4, respectively, both in the exon 6 (Figure 3). Patient 5 had a gross deletion, seq [GRCh37] del(8)(q23.3-q24.11) chr8:g.116,420,724-119,124,058; this region contains several important OMIM genes such as *TRPS1*, *RAD21*, *EXT1*, etc. We also carried out genetic analysis of their parents and found that the mutation in patient 2 was inherited from his mother, while the mutation in patient 4 was inherited from the father. The parents of the other patients did not harbor any mutations in the *TRPS1* gene, suggesting that these mutations are *de novo*. The identified mutations were interpreted as “pathogenic” according to ACMG guidelines.

4 | DISCUSSION

The *TRPS1* gene encodes a nuclear transcription factor comprising 1,294 amino acids with an unusual combination of different types of 10 zinc finger motifs, including seven zinc finger C₂H₂-type domains that are related to those found in the transcription factor TFIIIA of *Xenopus laevis*, one GATA

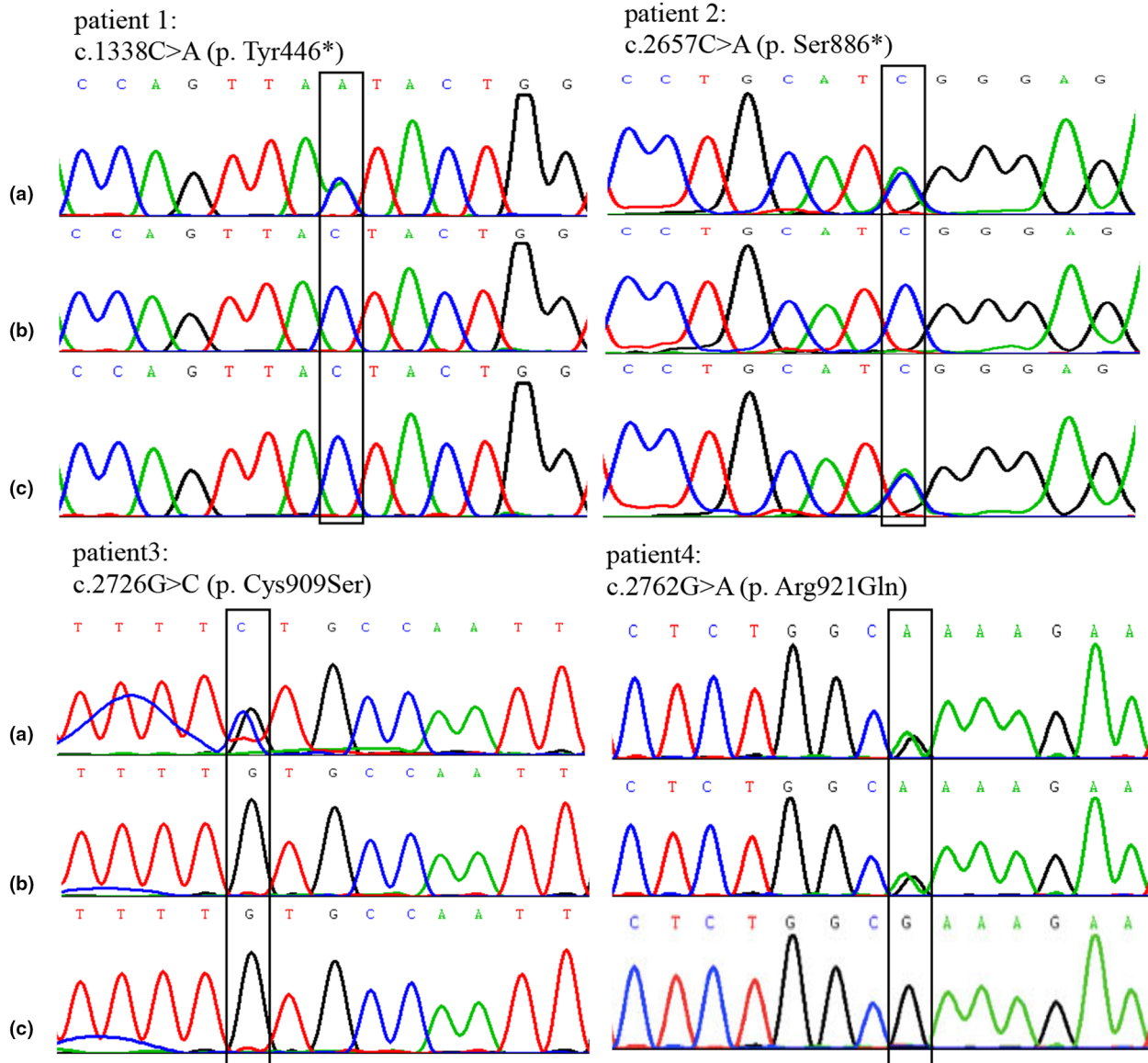


FIGURE 3 Mutation analysis. The figure shows Sanger sequencing of four unrelated families. Patient 1 had c.1338C>A (p.Tyr446*), and patient 2 had c.2657C>A (p.Ser886*), inherited from his mother. Patient 3 had a missense mutation c.2726G>C (p.Cys909Ser), and patient 4 had c.2762G>A (p.Arg921Gln), inherited from his father

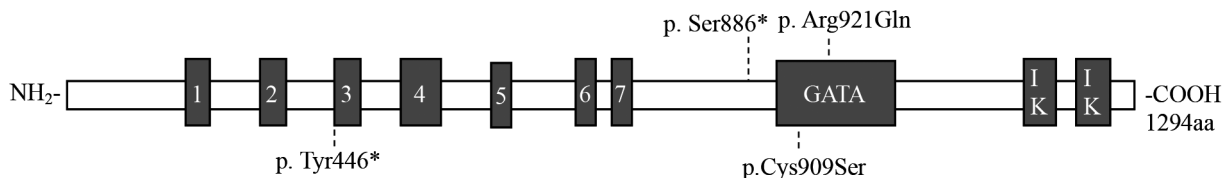


FIGURE 4 Representation of the structure of the TRPS1 protein. Filled squares indicate the zinc finger motifs. The filled squares are 1–7 C₂H₂-type domains, the GATA zinc finger domain, two Ikaros-like C₂H₂-type zinc finger domains at the C-terminal. The dashed lines indicate the position of the mutations p.Tyr446*, p.Ser886*, p.Cys909Ser, and p.Arg921Gln. Annotation according to the reference sequence NM_014112.4

C₄-type domain, and two Ikaros-like C₂H₂-type zinc fingers (http://smart.embl-heidelberg.de/smart/show_motifs.pl?ID=Q9UHF7-2) (Momeni et al., 2000) (Figure 4). The GATA zinc-finger is flanked by two basic nuclear localization signals (NLS1: LRRRRG, 886–891 aa, and NLS2:

RRRTRKR, 946–952 aa), and it has been demonstrated that only the second motif functions as an NLS in TRPS1 (Kaiser et al., 2004), indicating that TRPS1 functions as a nuclear zinc finger protein. As mentioned by Ludecke et al., GATA-type zinc fingers act as sequence-specific transcription

TABLE 1 Genetic and clinical features in TRPS^a cases

Patient	1	2	3	4	5
<i>Diagnosis genotype</i>	TRPS I	TRPS I	TRPS III	TRPS I	TRPS II
Mutation	c.1338C>A, p.Tyr446* (het)	c.2657C>A, p.Ser886* (het)	c.2726G>C, p.Cys909Ser (het)	c.2762G>A, p.Arg921Gln (het)	seq [GRCh37] del(8)(q23.3-q24.11)
Chromosomal location ^b	Chr8: 116,616,858	Chr8: 116,599,271	Chr8: 116,430,655	Chr8: 116,430,619	Chr8: 116,420,724-119,124,058
Exon	4	5	6	6	/
Inheritance	<i>De novo</i>	Maternal	<i>De novo</i>	Paternal	<i>De novo</i>
Evidence level ^c	PVS1+PS2+PM2	PVS1+PM2+PP3	PS2+PM1+PM2+PM5	PM1+PM2+PM5+PP3+PP4+PP5	/
Classification	P	P	P	P	P
Reference (PMID)	/	/	/	11112658; 11807863	/
<i>Phenotype</i>					
<i>Craniofacial</i>					
Sparse hair	+	+	+	+	+
Thick and broad eyebrows	+	+	+	+	+
Bulbous nose	+	+	+	+	+
Long philtrum	+	+	+	+	+
Thin upper vermillion	+	+	+	+	+
Low set ear	+	+	+	+	+
<i>Limbs and trunk</i>					
Cone-shaped epiphyses at phalanges	+	+	+	+	+
Short stature	++	-	++	+	+
Dystrophic nails	+	+	+	+	+
Brachydactyly	+	+	++	++	+
Scoliosis	+	+	+	-	+
<i>Other manifestations</i>	-	Hydrocephaly and Arnold-Chiari syndrome	Mandibular malformation	-	Hepatopathy ; Mental retardation ; Osteochondroma

^aAnnotation according to the reference sequence NM_014112.4.

^bHuman genome version was [GRCh37/hg19].

^cThe evidence level could be classified into several subclasses based on the standard guideline (Richards et al., 2015). PVS, pathogenic very strong. PS, pathogenic strong. PM, pathogenic moderate. PP, pathogenic supporting. -: The patient had no such phenotype; +: The patient had such a phenotype; ++: The patient had a more severe phenotype.

regulators and all mutations within this domain result in a severe phenotype (Ludecke et al., 2001).

GATA transcription factor is a conserved nuclear protein that performs an important function in vertebrate and invertebrate development. This protein represses GATA-regulated genes and binds to a dynein light chain protein, LC8a, which is known to interact with more than 10 different molecules including both proteins and nucleic acids (Kaiser et al., 2003). Binding of the encoded protein to the dynein light chain protein affects binding to GATA consensus sequences and suppresses its transcriptional activity (Kaiser et al., 2003). Defects in this domain are a cause of Tricho-rhino-phalangeal syndrome (TRPS) types I-III.

Recently, the mechanisms underlying the skeletal abnormalities in TRPS have been elucidated in previous studies (Napierala et al., 2008; Nishioka et al., 2008; Wuelling et al., 2009). TRPS1 plays an important role in endochondral ossification and mineralization. These reports suggest that TRPS1 performs specific functions in different zones of epiphyseal cartilage by interacting with different subsets of transcription factors (e.g., RUNX2 and GLI3) or suppressing different target genes (e.g., STAT3 and PTHRP). It has been suggested that TRPS is caused by the deregulation of chondrocyte and perichondrium development due to the loss of TRPS1 function. TRPS1 expression in the mesenchyme surrounding the hair follicle and underlying the epidermis is specific to morphogenesis and is not observed during postnatal hair follicle cycling (Millar, 2002). However, the molecular mechanism by which the loss of TRPS1 affects hair follicle development remains unclear.

Genotypic analysis of patients with TRPS has helped to identify different mutations in the *TRPS1* gene. We present five sporadic monoallelic mutations in five patients with clinical features compatible with different forms of TRPS (Table 1). TRPS type I is always associated with deletions and nonsense mutations in the N-terminal half of a *TRPS1* allele. Patient 1 with TRPS I harbored a novel nonsense mutation in exon 4, c.1338C>A (p.Tyr446*). Meanwhile, the novel mutation c.2657C>A (p.Ser886*) led to a TRPS type I phenotype in patient 2. However, patient 4 had typical TRPS I clinical features without severe brachydactyly and short stature (<-2SD); and the missense mutation of *TRPS1* in exon 6, c.2762G>A (p.Arg921Gln), which has already been described before (Kobayashi et al., 2002; Ludecke et al., 2001). These nonsense and missense mutations may cause haploinsufficiency of TRPS1 due to the loss of a functional copy of the *TRPS1* gene leading to TRPSI. TRPS1 is present in the nucleus in a limited amount and its dysfunction is probably due to an altered stoichiometry of heterodimers (Momeni et al., 2000). In addition, patient 2 had a novel phenotype, hydrocephaly, and Arnold-Chiari syndrome, which has never been reported before. However, the Cys909Ser mutation of *TRPS1* in patient 3 causes the functional modification of

the GATA-type motif. She had severe skeletal deformities and quite severe brachydactyly and jaw deformity. TRPS III has a more severe phenotype than TRPS I, which is associated with missense mutations in the GATA binding domain or the Ikaros-type zinc finger domain, giving rise to alleles that encode an antagonist of the wild-type TRPS1 protein and result in a dominant-negative effect (Ludecke et al., 2001). Therefore, the altered GATA-type zinc finger motif may bind to DNA sequences with much lower affinity or not allow the normal TRPS1 protein to bind the consensus elements. Thus, the mutant Cys909Ser TRPS1 protein might have a dominant-negative effect on the regulation of DNA transcription. The identification of the missense mutation p.Cys909Ser in exon 6 further supports that the mutations in this exon may be related to more pronounced features of the syndrome. But despite having a mutation in exon 6, p.Arg921Gln, patient 4 lacked severe brachydactyly and growth retardation. This might be caused by the racial and/or genetic background. Adequate attention should be paid to the patient's bone throughout the future clinical course. Besides, mutations in the NLS prevent the translocation of TRPS1 into the nucleus, which results in a reduction in the nuclear TRPS1 concentration (Kaiser et al., 2004). A contiguous over 2,700 bp deletion involving chr8(q23.3-q24.11) was detected by CNV analysis using whole-exome sequencing in patient 5. The most distinguishable feature of TRPS II from type I and III is exostoses, which are only present in those individuals with a deletion that extends to *EXT1*. Furthermore, intellectual disability (developmental delay) is present in most but not all TRPS II patients, typically mild to moderate in severity, and does not seem to correlate with the size of the deleted segment. Maas et al. had summarized the information on 103 cytogenetically or molecularly confirmed TRPS individuals and suggested that the size of contiguous gene deletions varies considerably in TRPS II, and there are no common breakpoints (Maas et al., 2015; Selenti et al., 2015). In our patient, CNV analysis revealed the deletion of both *TRPS1* and *RAD21* genes which is in accordance with the dysmorphic facial features. Multiple exostoses strongly support the clinical diagnosis of TRPS II. This can further confirm the relationship between TRPS II and 8q24.1. However, we do not know the reason for the abnormal liver function.

TRPS is a rare disease with no effective treatment. Feeding difficulties, hypozincemia, and insufficient bone mass require nutritional and pediatric follow-up in order to adjust the dietary structure and micronutrient intake. Functional disability or chronic arthralgias may be corrected through orthopedic procedures. Early diagnosis and physical therapy can help in delaying the occurrence of secondary joint degeneration and chronic joint pain. The special facial features and exogenous bone warts of this disease can be improved by surgery and hair transplantation is effective for thinning hair (Choi et al., 2018). Several studies have suggested an

association between TRPS and growth hormone deficiency and other endocrine disturbances. The affected individuals with short stature and low growth rate need the evaluation of the growth hormone axis. It is suggested that GH therapy could improve growth and bone mineral density in children with growth failure (Sarafoglou, Moassesfar, & Miller, 2010; Stagi et al., 2008). Indeed, accurate clinical and genetic diagnosis requires adequate and timely treatment interventions.

5 | CONCLUSION

In summary, our study has expanded the existing knowledge on the phenotypic and genotypic spectrum of *TRPS1*. We report the identification of five different mutations responsible for Tricho-rhino-phalangeal syndrome, type I-III, in five Chinese patients. In addition, hydrocephaly and Arnold-Chiari syndrome in patient 2 as well as the hepatopathy in patient 5 may be considered as novel phenotypes of TRPS and would require more attention. It is essential to perfect a comprehensive clinical examination, collect detailed family history, and make an accurate molecular diagnosis. Early discovery, diagnosis, and proper treatment of the conditions generally increase the chances of improvement of the quality of life for patients.

6 | CONSENT FOR PUBLICATION

Ethical approval was obtained from the ethics committee of Shanghai Children's Medical Center affiliated to Shanghai Jiao Tong University School of Medicine (SCMCIRB-K2016013). Written informed consent was obtained from the patient's father.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

C. Wang critically drafted and revised the manuscript, and reviewed the literature for data on other reported patients suffering from TRPS. X. Wang and Y. Xu assessed the clinical manifestation of the patient and collected the raw data from our hospital work system. J. Wang and R. Yao analyzed data generated by next-generation sequencing, found the variants, and judged the pathogenicity. J. Wang, T. Yu, and N. Li reviewed the manuscript. Y. Qing operated Sanger sequencing to confirm the variants. All authors have read and approved the manuscript.

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