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A Missense Mutation in *TRPS1* in a Family with Trichorhinophalangeal Syndrome Type III Accompanied by Ankylosing Spondylitis

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Trichorhinophalangeal syndrome (TRPS) is a rare autosomal dominant genetic disorder characterized by distinctive craniofacial features, skeletal abnormalities and short stature; it is classified into three subtypes according to genetics and clinical manifestations. We report a Han Chinese family with 2 TRPS type III patients, the proband and his mother, with typical clinical presentation. There were also 3 ankylosing spondylitis (AS) patients in this family, the proband's mother and 2 uncles. A missense mutation, c.2762G>A (p.Arg921Gln), in the transcriptional repressor GATA binding 1 (*TRPS1*) gene was detected in the proband and his mother. The association between TRPS and AS and the diagnostic criteria for TRPS are discussed.

Keywords: Chinese Han family, Mutation, missense, Spondylitis, ankylosing, Trichorhinophalangeal syndrome type III, *TRPS*1

INTRODUCTION

Trichorhinophalangeal syndrome (TRPS) is a rare genetic disease with an autosomal dominant inheritance pattern. The main clinical features are craniofacial and bone formation abnormalities. TRPS is classified into three subtypes, TRPS I, II, and III, according to genetic and clinical manifestations[1]. We report a Han Chinese family including 2 TRPS III patients with a missense mutation in the transcriptional repressor GATA binding 1 (*TRPS1*) gene. The family also had 3 ankylosing spondylitis (AS) patients, the proband's mother and 2 uncles, and his mother had both TRPS III and AS.

CASE REPORT

The proband (III:1, Fig. 1) was a 14-year-old male with short, thin hair since birth. His height was 120 centimetres, without cartilaginous exostoses or intellectual disability. He exhibited the typical clinical manifestations of sparse lateral eyebrows; piriform nose; long, flat philtrum; thin upper lip; large, erect ears; brachydactyly; and toe shortening (Fig. 2). Brachydactyly, toe shortening and abnormal epiphyses of the bilateral distal ulna and radius were observed by radiography. Histopathological examination of the scalp revealed epidermal hyperkeratosis and few hair follicles in the dermis (Fig. 3). Systematic laboratory examinations showed normal results.

The proband's mother (II:1), a 38-year-old female, displayed clinical manifestations similar to those of the proband (Supplementary Fig. 1). She had been diagnosed with AS two years earlier. She was hospitalized for lumbago and backache and had a 5-year medical history of morning stiffness with mild remission after activity. Auxiliary examination showed elevated HLA-b27 and bilateral sacroiliac joint inflammation. Two other family members, the proband's 2 uncles (II:3, II:5), also had 12- and 3-year histories of AS, re-

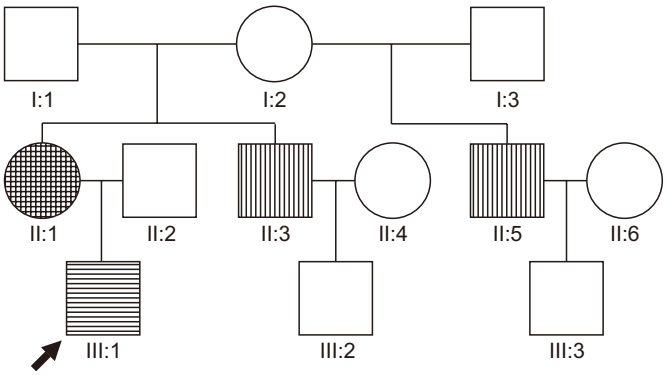

Fig. 1. Family pedigree. Horizontal line: trichorhinophalangeal syndrome (TRPS) patients, vertical bar: ankylosing spondylitis (AS) patients, grid line: patients with both TRPS and AS, arrow: proband.

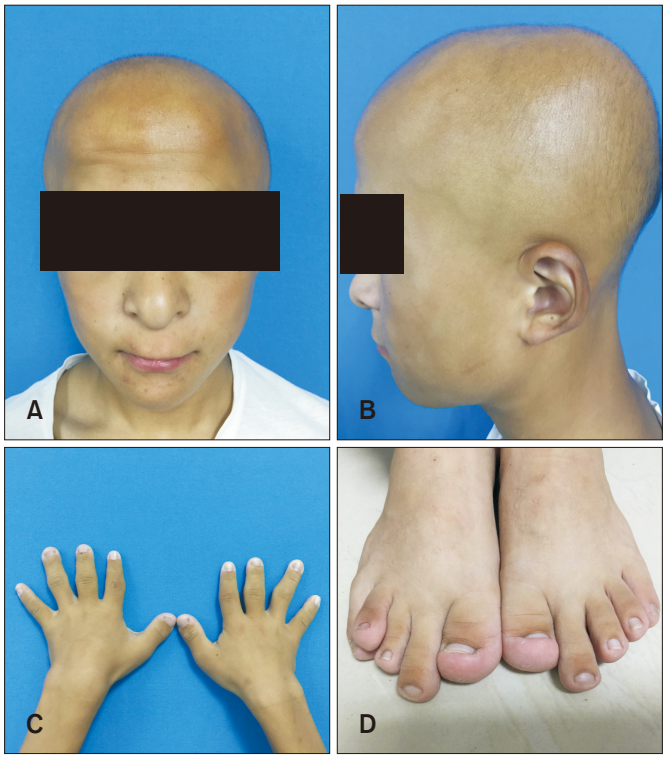

Fig. 2. Clinical features of the proband. Craniofacial features (A, B), brachydactyly (C), and toe shortening (D).

spectively. There was no history of consanguineous marriage or exposure to toxic substances in this family.

This study was approved by the Ethical Committee and was carried out according to the principles of the Declaration of Helsinki (2014-KYKT-23). Nine people (II:1~6; III:1~3) or their legal guardians provided written consent to join the study, including authorization to extract peripheral anticoagulated blood and to publish these case details.

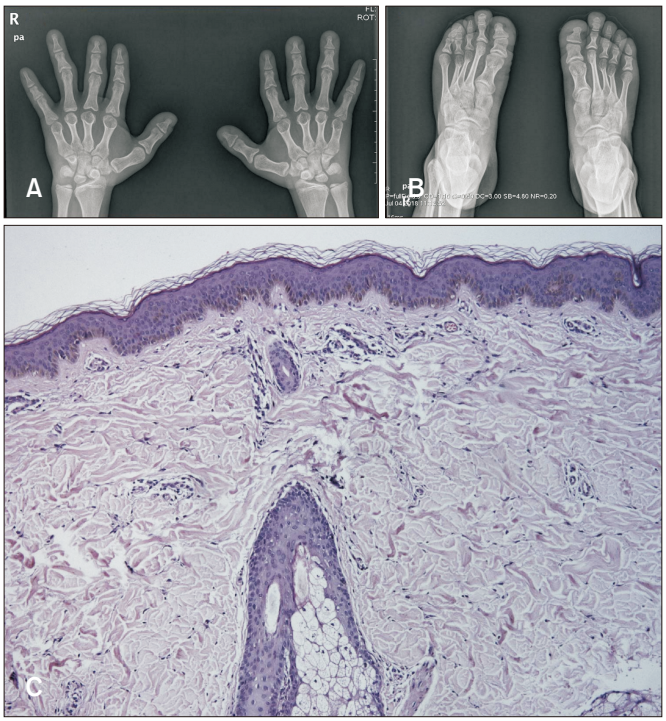

Fig. 3. Brachydactyly, cone-shaped epiphysis of hands (A) and toes shortening (B) on radiology. (C) Histopathological image shows sparse hair (H&E, ×100).

The genomic DNA of the 9 family members (II:1~6; III:1~3) was isolated. Segmented primer sequences for *TRPS1* were designed (Supplementary Table 1), and the DNA of all 9 individuals was analyzed by Sanger sequencing for *TRPS1* using an ABI3500 sequencer (Applied Biosystems, Foster City, CA, USA). A heterozygotic missense mutation in exon 6 of *TRPS1*, c.2762G>A (p.Arg921Gln), was found in the proband and his mother (Fig. 4). This variant was not detected in the other 7 members (II:2~6, III:2, III:3) of this family or in 100 healthy Han Chinese control individuals.

This TRPS pathogenic mutation is recorded in dbSNP (rs121908435), ClinVar (RCV000005919.2) and HGMD (CM010486)[2], and it is predicted by MutationTaster to lead to changes in amino acid sequence, protein features and splice sites[3]. *TRPS1*-encoded protein models exhibit different configurations and complexities between healthy controls and patients with the mutation (Supplementary Fig. 2)[4]. The diagnosis of TRPS III was definitive in this case.

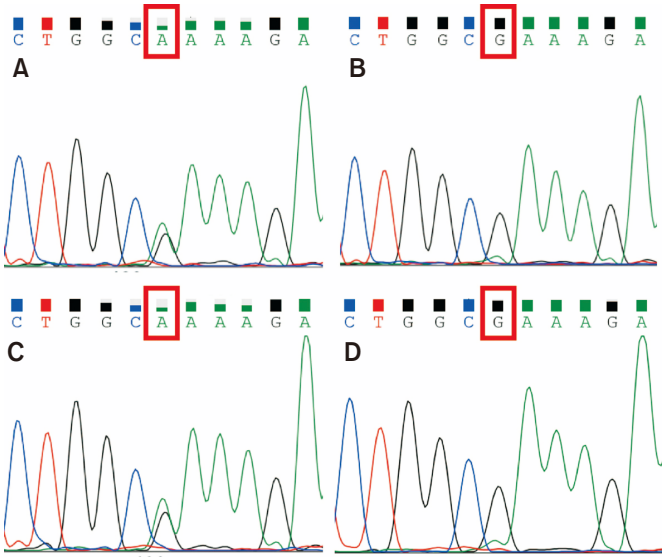

Fig. 4. Sanger sequencing of the mutation site, c.2762G>A (p.Arg921Gln), in the *TRPS1* gene: heterozygous mutations in trichorhinophalangeal syndrome patients (A: II:1, C: III:1); normal control (B: II:2); validation sequencing in other normal controls (D: take II:3 for example).

DISCUSSION

TRPS is a rare genetic disorder in clinical practice, presenting as multisystem involvement. We report a Han Chinese family with proband exhibiting typical clinical features. A missense mutation in exon 6 of *TRPS1*, c.2762G>A (p.Arg921Gln), was verified in the proband and his mother. This variant has been reported in European and South Asian families and leads to a severe TRPS III phenotype[1,2], but it has not yet been reported in Han Chinese people.

TRPS I and III are caused by variants in *TRPS1*, whereas TRPS II is derived from deletion of both *TRPS1* and exostosin glycosyl transferase 1 (*EXT1*)[2]. In general, nonsense or deletion mutations outside the *TRPS1* GATA-binding zinc finger domain lead to TRPS I[1], which has a relatively mild phenotype. Nonsense mutations are theorized to reduce the number of copies of functional *TRPS1*, known as haploinsufficiency, leading to the TRPS I phenotype by reducing nuclear TRPS1 protein concentration. The mutation in our case is located in the GATA-binding zinc finger motif, which is flanked by two potential nuclear localization signals. Based on previous studies, patients with missense mutations in this motif always have a more severe TRPS III phenotype. The mechanism may be related to the dominant-negative effect on transcriptional regulation[5]. Some studies have shown that missense mutations in exon 6 lead to more serious clinical manifestations[6].

Therefore, we suggest that the diagnostic and typing criteria for this rare disease should be improved. In addition to making clear the standard of distinguishing mild from severe clinical manifestations, the position of the variant in *TRPS1* should be included in the criteria.

Complications of TRPS are rarely reported, with only a few cases, such as non-ossifying fibroma with pathological fracture[7]. In our family, the proband's mother had both TRPS III and AS. Clinically, both diseases involved bone and joint. Although TRPS has traditionally been considered dysplastic damage, which was different with the inflammatory lesion in AS patients, adult TRPS patients have also been reported to have osteopenia and severe early-onset osteoarthritis[8].

Genetic analysis may hold the key to further explaining the relationship between these two diseases as several genes have been reported to play a role in both diseases[9-16]. Suemoto et al.[9] revealed that the TRPS1 protein acts as a repressor of signal transducer and activator of transcription 3 (*STAT3*) expressions, in turn controlling the proliferation and survival of chondrocytes; thus, the TRPS1 protein can affect the STAT3 signalling pathway. Furthermore, STAT3 plays an important role in the pathogenesis of AS, especially in the Han Chinese population[10]. *TRPS1* represses expression of SRY-box transcription factor 9 (Sox9), which regulate chondrocyte differentiation and disturb cartilage homeostasis promoting cartilage degeneration in AS[11,12]. Also, the RUNX family transcription factor 2 (RUNX2), which regulate osteoblast differentiation in AS[13], can be repressed by *TRPS1*[14]. And Wnt family member 5A (*WNT5A*), a transcriptional target of *TRPS1* in chondrocytes[15], may be potentially involved in the effects of inflammation on bone formation in AS[16].

Considering that AS is a polygene-related disease with complex pathogenesis, the potential link between TRPS and AS could only be speculated theoretically at present. Further clinical and experimental validation is still needed. In this family, *TRPS1* genotype and AS phenotype did not cosegregate, which may due to the onset of AS is time dependent and regulated by multiple genes.

Merjaneh et al.[17] used growth hormone to treat TRPS patients, and based on limited data, this approach appears to be effective. In our case, we did not give the patient any treatment because of the inaccuracy of the therapeutic method and the

cost of growth hormone.

In summary, we report a family with severe TRPS III accompanied by AS and a mutation site, c.2762G>A (p.Arg921Gln), in *TRPS1*. The association between TRPS and AS needs more exploration. Furthermore, the diagnostic criteria for TRPS need to be improved.

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SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://anndermatol.org/src/sm/ad-34-139-s001.pdf.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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