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

Xiaokai Fang1,2, Qing Yang2,3

1Department of Dermatology, Shandong Provincial Hospital for Skin Diseases, Cheeoloo College of Medicine, Shandong University, 2Department of Dermatology, Shandong Provincial Hospital for Skin Diseases, Shandong First Medical University, 3Shandong Provincial Institute of Dermatology and Venereology, Jinan, China

INTRODUCTION

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, TRPS1

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-
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.

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 sites³. 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.
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 from 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.

ACKNOWLEDGMENT

I gratefully acknowledge the patients for their participation in the study and for consenting the publication of clinical data and photos.

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.

FUNDING SOURCE

None.

ORCID

Xiaokai Fang, https://orcid.org/0000-0003-4423-8873
Qing Yang, https://orcid.org/0000-0002-7867-8845

REFERENCES

1. Lüdecke HJ, Schaper J, Meinecke P, Momeni P, Gross S, von Holtum D, et al. Genotypic and phenotypic spectrum in tricho-rhino-phalangeal syndrome types I and III. Am J Hum Genet 2001;68:81-91.
2. Ullah A, Umair M, Hussain S, Jan A, Ahmad W. Sequence variants in GDF5 and TRPS1 underlie brachydactyly and tricho-rhino-phalangeal syndrome type III. Pediatr Int 2018;60:304-306.
3. Schwarz JM, Cooper DN, Schuelle M, Seelow D. MutationTaster2: mutation prediction for the deep-sequencing age. Nat Methods 2014;11:361-362.
4. Waterhouse A, Bertoni M, Bienert S, Studer G, Tauriello G, Gummy R, et al. SWISS-MODEL: homology modelling of protein structures and complexes. Nucleic Acids Res 2018;46:W296-W303.
5. Itoh M, Kittaka Y, Nida Y, Saikawa Y. A novel frameshift mutation in the TRPS1 gene caused Tricho-rhino-phalangeal syndrome type I and III in a Japanese family. Clin Pediad Enocrinol 2016;25:115-118.
6. Maas SM, Shaw AC, Bikker H, Lüdecke HJ, van der Tuin K, Badura-Stronka M, et al. Phenotype and genotype in 103 patients with tricho-rhino-phalangeal syndrome. Eur J Med Genet 2015;58:279-292.
7. Su W, Shi X, Lin M, Huang C, Wang L, Song H, et al. Non-ossifying fibroma with a pathologic fracture in a 12-year-old girl with tricho-rhino-phalangeal syndrome: a case report. BMC Med Genet 2018;19:211.
8. Izumi K, Takagi M, Parikh AS, Hahn A, Miskovsky SN, Nishimura G, et al. Late manifestations of tricho-rhino-phalangeal syndrome in a patient: expanded skeletal phenotype in adulthood. Am J Med Genet A 2010;152A:2115-2119.
9. Suemoto H, Muragaki Y, Nishioka K, Sato M, Ooshima A, Itoh S, et al. Trps1 regulates proliferation and apoptosis of chondrocytes through Stat3 signaling. Dev Biol 2007;312:572-581.
10. Saadi A, Dang J, Shan S, Ladjouze-Rezig A, Lefkir-Tafiani S, Gong Y, et al. Ankylosing spondylitis: analysis of gene-gene interactions between IL-12β, JAK2, and STAT3 in Han Chinese and Algerian cohorts. Cent Eur J Immunol 2019;44:65-74.
11. Fantauzzo KA, Kurban M, Levy B, Christiano AM. Trps1 and its target gene Sox9 regulate epithelial proliferation in the developing hair follicle and are associated with hypertrichosis. PLoS Genet 2012;8:e1003002.
12. Bleil J, Sieper J, Maier R, Schlichting U, Hempfing A, Syrbe U, et al. Cartilage in facet joints of patients with ankylosing spondylitis (AS) shows signs of cartilage degeneration rather than chondrocyte hypertrophy: implications for joint remodeling in AS. Arthritis Res Ther 2015;17:170.
13. Jo S, Han J, Lee YL, Yoon S, Lee J, Wang SE, et al. Regulation of osteoblasts by alkaline phosphatase in ankylosing spondylitis. Int J Rheum Dis 2019;22:252-261.
14. Napierala D, Garcia-Rojas X, Sam K, Wakui K, Chen C, Mendoza-Londono R, et al. Mutations and promoter SNPs in RUNX2, a transcriptional regulator of bone formation. Mol Genet Metab 2005;86:257-268.
15. Wuelling M, Schneider S, Schröther VA, Waterkamp C, Hoffmann D, Vortkamp A. Wnt5a is a transcriptional target of Gli3 and Trps1 at the onset of chondrocyte hypertrophy. Dev Biol 2020;457:104-
16. Briolay A, Lencel P, Bessueille L, Caverzasio J, Buchet R, Magne D. Autocrine stimulation of osteoblast activity by Wnt5a in response to TNF-α in human mesenchymal stem cells. Biochem Biophys Res Commun 2013;430:1072-1077.

17. Merjaneh L, Parks JS, Muir AB, Fadoju D. A novel TRPS1 gene mutation causing trichorhinophalangeal syndrome with growth hormone responsive short stature: a case report and review of the literature. Int J Pediatr Endocrinol 2014;2014:16.