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TRPS1 mutation associated with Trichorhinophalangeal syndrome type I with 15 supernumerary teeth, hypoplastic mandibular condyles with slender condylar necks, and unique hair morphology

REVISION 2

Running title: *TRPS1* mutation and unique hair finding

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Abstract

Trichorhinophalangeal syndrome type 1 (TRPS1; MIM 190350) is an autosomal dominant disorder caused by mutations in *TRPS1*. We report a Thai male affected with TRPS1, who carried a c.1842C>T (p.Arg615Ter) mutation. He had 15 supernumerary teeth, double mental foramina, hypoplastic mandibular condyles with slender condylar necks, and unique ultrastructural hair findings. Body hair was absent. The hair in the area of a congenital melanocytic nevus had a greater number of hair cuticles than normal. Occipital hair had abnormal hair follicles and cuticles. The scale edges of the hair cuticles were detached and rolled up. Hypoplastic mandibular condyles with slender condylar necks, double mental foramina, and the roll-up edges of hair cuticles have not been reported in patients with TRPS1.

Key words: TRPS1, abnormal hair cuticle, abnormal temporomandibular joint, supernumerary teeth, double mental foramina

INTRODUCTION

Trichorhinophalangeal syndrome type I (TRPS1; MIM 190350) is an autosomal dominant disorder caused by mutations in *TRPS1*. Characteristic features of the patients include sparse and slow-growing scalp hair, bulbous tip of nose, short stature, brachydactyly, and cone-shaped epiphyses of the phalanges.[1,2] Here we report a patient with a *TRPS1* mutation who had 15 supernumerary teeth, double mental foramina, hypoplastic mandibular condyles with slender condylar necks, and a unique hair morphology.

CASE REPORT

A 21-year-old Thai man of normal intelligence presented with malocclusion (Fig. 1a). He was the second child of non-consanguineous healthy parents, with a normal sister. His height was 155 cm (<3 centile), and disproportionate short stature was noted (Fig. 1b). He was born with no scalp hair or eyebrows (Fig. 1c). Pubic hair and axillary hair first appeared at age 15 years. At age 21 years he had no body hair including mustache and beard. His scalp hair was fine, sparse and slow-growing, with alopecia in the occipital area (Fig. 1d). There was a large hairy congenital melanocytic nevus (CMN) on his left thigh (Fig. 1e). This CMN was 2 cm in diameter at birth, and it became larger with age. Brachydactyly of hands and feet was noted. Fingernails and toenails were narrow and

slow-growing (Fig. 1f-g). Radiographic examination showed cone-shaped epiphyses of the middle phalanges of fingers, short first metatarsal bones, short middle and distal phalanges of toes, fusion of middle and distal phalanges 3, 4, 5 on the right and left toes, and an unremarkable pelvis (Fig. 2b-d).

Oral examination showed two erupted supernumerary maxillary permanent teeth, severe crowded teeth, and anterior and posterior open bite (Fig. 1h,i). Lateral cephalometric analysis revealed short anterior cranial base length, short mandibular length, and midface hypoplasia. Cone-beam computed tomography and panoramic radiography showed 15 supernumerary teeth, double mental foramina on the right side, and hypoplastic mandibular condyles with slender condylar necks (Fig. 2a,e). The morphology of all extracted supernumerary teeth resembled that of premolars (Fig. 2e,1k). Two nerve bundles came out from double mental foramina (Fig. 1j).

Scanning electron micrographs of his vertex hair showed normal hair follicles and cuticles (Fig. 3a). The occipital hair had hypoplastic and twisted hair follicles. The scale edges of the hair cuticles detached from the inner root sheath and rolled up (Fig. 3b-d). Hair from the CMN had a greater than normal number of cuticles than those of normal hair. The edges of the hair cuticles appeared serrated (Fig. 3e-i). The tip of the hair is comprised of a stack of hair cuticles (Fig. 3h,i). His axillary hair appeared normal (Fig. 3j).

Mutation analysis

Mutation analysis of *TRPS1* showed a *de novo* heterozygous base substitution c.1842C>T (p.Arg615Ter; rs121908431). Another *TRPS1* variant (c.2458C>G; p.Pro820Ala; rs78472570) was found in exon 5. The allele frequency of this variant according to gnomAD was 0.0008516. This rare variant was found in his unaffected father and sister. His mother had none of those variants.

DISCUSSION

We report a man affected with TRPS1 who carried a *de novo* heterozygous base substitution c.1842C>T; p.Arg615Ter in *TRPS1*, which is predicted to cause a stop codon at codon 615 and premature truncation of TRPS1 protein. This variant has previously been reported to cause TRPS1.[1] TRPS1 is a vertebrate transcription activator and repressor.[1,3] The ability to repress or activate the target genes depends on the integrity of the Trps1 GATA-type zinc-finger domain and the C-terminal 119 amino acids of the protein, which contains two Ikaros-like zinc-finger domains.[4] Mutations in the GATA binding sites abolish TRPS1-mediated repression of target gene transcription, and the mutant proteins resulting from missense mutations have been shown to have a decreased affinity to DNA and

function in a dominant-negative manner.[2] The mutation found in our patient is predicted to eliminate half of the DNA-binding domain and the rest of the TRPS1 protein, which has important functions. The other variant (c.2458C>G; p.Pro820Ala) found in the patient was also found in his unaffected father and sister, implying its nonpathogenicity.

Supernumerary teeth have been reported in patients with TRPS1,[5-7] but only three patients were tested to have *TRPS1* mutations.[8,9] The supernumerary teeth found in our patient and the previously reported patients with *TRPS1* mutations had the morphology of premolars. Since the incisors and molars were not formed when the patients were absent of "functional" *TRPS1*, this "suggests" that *TRPS1* is necessary for the formation of incisors and molars. Hypoplastic mandibular condyles with slender condylar necks were likely the results of *TRPS1* mutation because *Trps1* is required for the development of temporomandibular joint.[10]

Hypotrichosis in our patient appeared to be androgenic, similar to that of other patients with TRPS1.[11] The first appearance of the axillary and pubic hair of our patient at puberty supports the influence of androgen. At 21 years his scalp hair was fine, sparse and slow-growing, and more severely affected in the occipital area. During early hair morphogenesis *Trps1* regulates a number of transcription factors, Wnt inhibitors, and extracellular matrix proteins.[3,4] Patients with *TRSP1* mutations or mice lacking Trps1 GATA domain have reduced expression of *TRPS1*[12] and WNT inhibitors, activation of WNT signalling, and subsequent fine hair and fewer hair follicles.[4] The mice lacking Trps1 GATA domain, increased Wnt signaling takes place only in the epithelial placode stage, but not in the later stages.[3] The patients with TRPS1 have less hair because even though *TRPS1* is downregulated, but the WNT signaling is not upregulated in the later stages of hair development to promote hair growth. In addition there is also an evidence showing that hair of the mice lacking GATA domain fail to be activated by a number of Wnt inhibitors in the epithelial placode at the initiation of hair follicle morphogenesis, leading to abnormal hair follicles as also seen in TRPS1 patients.[3] Hair from the top of the head had a normal appearance. However, hair from the occiput had hypoplastic and twisted hair follicles with the roll up of the scale edges of the hair cuticles. Hair in different parts of the scalp of the patients with TRPS1 have been shown to have different gene expression profile.[11]

The roll-up of the scale edges of the hair cuticles has not been reported in patients with TRPS1. This is hypothesized to be due to the abnormal keratin composition of the hair cuticles, since keratins are the most abundant proteins of the hair cuticles and a number of genes related to keratins and hair morphogenesis including *TRPS1* are down-regulated in the balding scalp of patients with TRPS1. One of the genes that are down-

regulated in the hair of patient with TRSP1 is *SOX21*, a target gene of TRPS1.[13] *Sox21* is expressed in the cuticle layer and the progenitor cells of the hair shaft. This gene has a crucial role in hair morphogenesis by regulating the layered differentiation of hair follicles, and absence of *Sox21* leads to hair loss.[13] We hypothesize that the alopecia and the roll-up edges of hair cuticles in our patient are the effects of down-regulation of *SOX21* as a result of *TRPS1* mutation because *Sox21* has important role in the interdigitation between hair cuticles and the inner root sheath.[13]

CMN is known to be the result of postzygotic somatic mutations involving proteins in the mitogen-activated protein kinase pathway, especially *NRAS* and *BRAF*. It is believed that CMN is a coincidence, and not related to *TRPS1* mutation. The absence of body hair but increased number of hair cuticles of hair from CMN would suggest a link between increased melanin biosynthesis and prolonged anagen phase of hair follicles. It is noteworthy that increased melanogenesis in CMN overcomes *TRPS1* mutation-associated hypotrichosis. This link is likely to involve a RET tyrosine kinase activity, since its the role in extending the anagen phase of hair cycle in association with upregulation of melanin production is known.[14] In fact, this is supported by a study showing that transgenic mice with a constitutive activated RET have prolonged anagen phase of hair follicles along with accelerated melanin production in and around hair bulbs.[14] Upregulation of *Shh* and *Edn1* in keratinocytes has been shown to cause hyperpigmentation and hypertrichosis.[15] Therefore, *SHH* and *EDN1* could also play a role in the hypertrichosis reported herein. However, the roll-up of the scale edges of the hair cuticles, double mental foramina, and abnormal condyles have not previously been reported.

CONFLICT OF INTEREST: "Authors declare no conflict of interests for this article"

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Supporting information

Figure 1S. Electropherograms of a *TRPS1* variant. A *de novo* heterozygous base substitution c.1842C>T is predicted to cause a stop codon at codon 615 and premature truncation of TRPS1 protein (p.Arg615Ter).

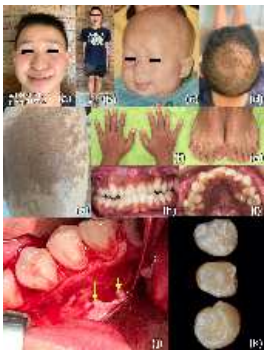
Figure 2S. Electropherograms of a *TRPS1* variant. A heterozygous base substitution (c.2458C>G; p.Pro820Ala) is found in the patient and his unaffected father and sister. His mother has none of those variants.

Figure legends

Figure 1. Patient with TRPS I at age 21 years. A, B) Bulbous tip of nose and thin vermillion border of upper lip. C) Disproportionate short stature. The upper part of the body is longer than the lower part. Brachydactyly of D) hands and E) feet. F) Crowding of teeth with open bite and anterior crossbite. G) Supernumerary teeth have premolar morphology.

Figure 2. Radiographs of patient at age 21 years. A) Cone-beam computed tomography shows double mental foramina on the right side and hypoplastic mandibular condyles with long condylar necks. B) Pelvis is unremarkable. C) Short first metatarsal bones, short middle and distal phalanges of toes, and fusion of middle and distal phalanges 3, 4, 5 on the right and left toes. D) Middle phalanges 2-5 are short. Cone-shaped epiphyses of the middle phalanges of fingers. E) 15 supernumerary teeth with premolar or molar morphology. All are located in the premolar and molar areas.

Figure 3. Scanning electron micrographs of vertex hair A,B) Normal hair follicle with hypoplastic hair cuticles. **Occiput hair** C) Hypoplastic and twisted hair follicles. D-F) Hypoplastic hair cuticles with roll-up of the scale edges.



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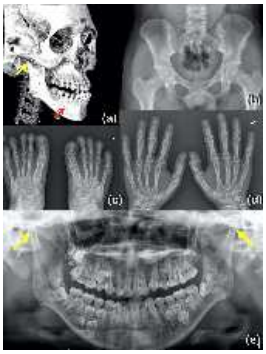

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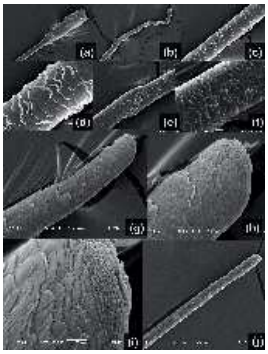

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