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Mutation-in-Brief

A novel frameshift mutation in the *TRPS1* gene caused Tricho-rhino-phalangeal syndrome type I and III in a Japanese family

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Introduction

Tricho-rhino-phalangeal syndrome (TRPS) is a heritable congenital syndrome characterized by craniofacial and skeletal abnormalities. TRPS is an autosomal dominant syndrome with high penetrance and wide phenotypic variability. TRPS is classified into three subtypes; TRPS types I (TRPS I; OMIM 190350) and III (TRPS III; OMIM 190351) have distinct clinical manifestations that often correspond to distinct mutations in the *TRPS1* gene. Patients with either TRPS I or III have sparse scalp hair, a nose with a bulbous tip, and skeletal abnormalities including cone-shaped epiphyses at the phalanges and short stature (1). Skeletal malformations in patients with TRPS III are more severe than that in patients with TRPS I (2). TRPS type II (TRPS II; OMIM 150230) is caused by a contiguous gene deletion involving *TRPS1* and *EXT1*. Several genotype-phenotype relationship studies on TRPS indicate that TRPS III is at the most severe end of the TRPS clinical spectrum and TRPS I is at the least severe end (3).

Here, we describe a Japanese family with two TRPS cases with intra-familial phenotypic variability (TRPS I and TRPS III). Both cases were associated with a single newly described frameshift mutation in *TRPS1*.

Case Report

Patient 1: A 20-yr-old Japanese woman was referred for evaluation of short stature. She weighed 43 kg (–1.5 SD) with a height of 140.0 cm (–3.4 SD) (Fig. 1a). Pubertal development was normal. She had characteristic features of TRPS including sparse scalp hair, a nose with a bulbous tip, and severe brachydactyly manifested by cone-shaped epiphyses at the phalanges and shortness of all phalanges (< –4 SD score for age) (Fig. 1b). Laboratory tests showed that serum levels of calcium, inorganic phosphate, alkaline phosphatase, free T4, TSH, PTH, and IGF I were normal. The karyotype was 46,XX. Phenotypic features of the patient with severe short stature were compatible with TRPS III. Her father's height was 160 cm (–1.9 SD) and her maternal grandmother had short stature

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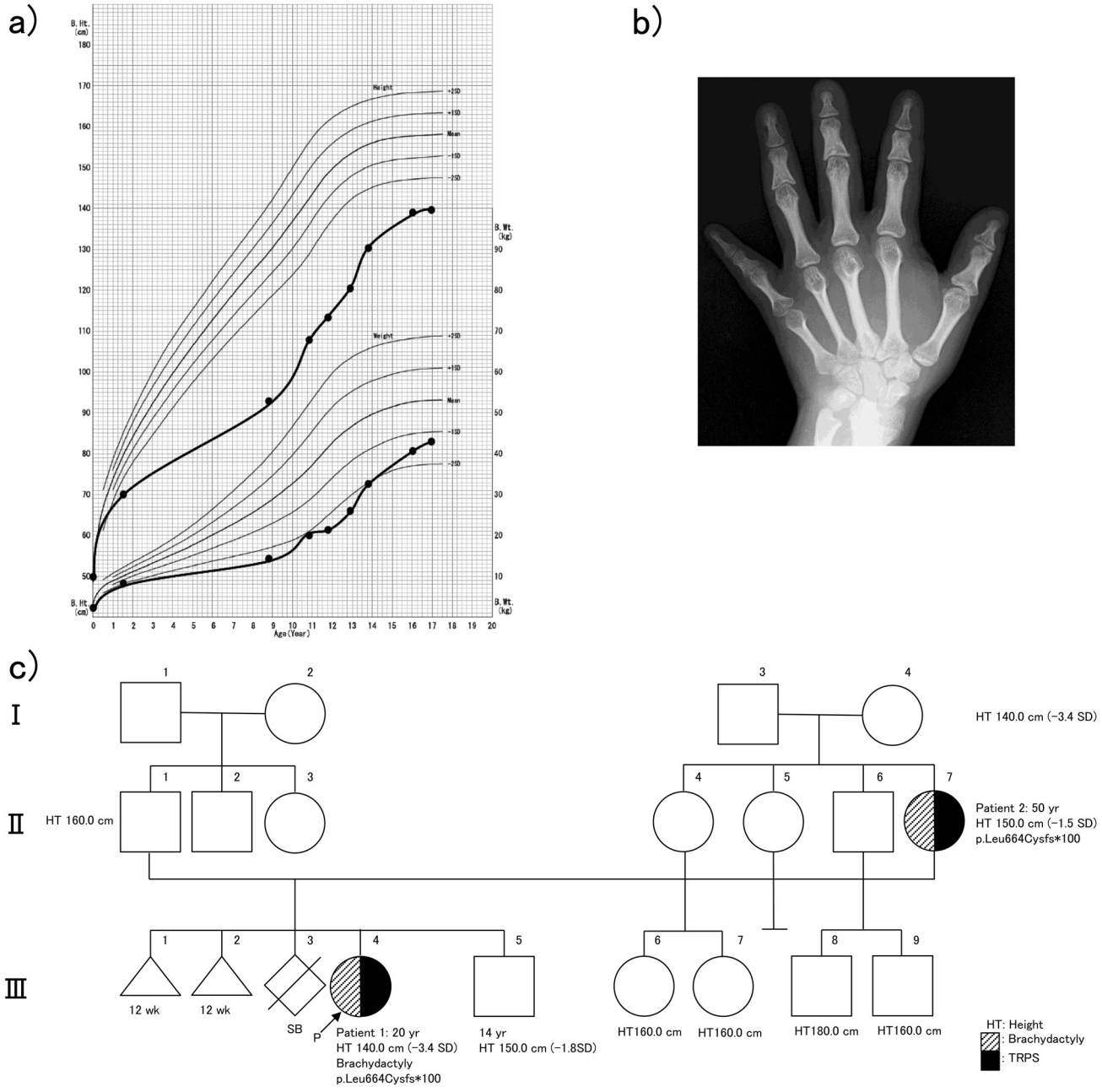

Fig. 1. a: A growth curve for patient 1 shows severe growth failure during childhood. b: A hand X-ray for patient 1 demonstrates cone-shaped epiphyses and shortness of all phalanges (< –4 SD score for age). c: Pedigree tree for three generations of a Japanese family. The proband (Patient 1) is III-4. Patient 1 and 2 (II-7) had brachydactyly, and Patient 1 and maternal grandmother (I-4) had short stature.

(140 cm, –3.4 SD) (Fig. 1c).

Patient 2: The patient was a 54-yr–old Japanese woman, and the mother of Patient 1. She weighed 56 kg (+0.4 SD) with a height of 150.0 cm (–1.5 SD). She had sparse scalp hair, a nose with a bulbous tip, and brachydactyly (< –2 SD for age).

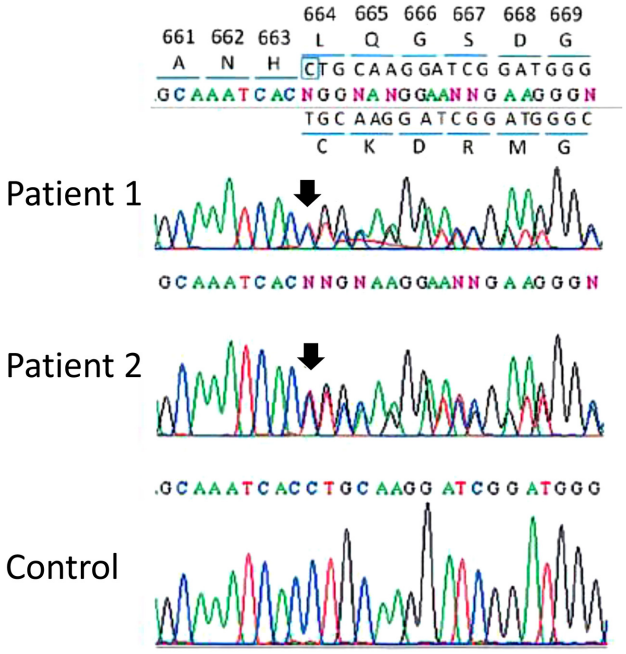

Fig. 2. Identification of a novel mutation in the *TRPS 1* gene. A heterozygous frameshift mutation c.1990delC (p.Leu664Cysfs*100) was identified in exon 4 of *TRPS 1* in both patients.

Mutation Analysis of the *TRPS1* Gene

Informed consent for mutation analysis was obtained from Patient 1 and Patient 2. The ethics committee of the Kanazawa Medical University approved this study. Genomic DNA was extracted from white blood cells of the indicated family members. PCR and direct sequencing were performed via standard methods. Analysis of *TRPS1* revealed a novel mutation, c.1990delC (p.Leu664Cysfs*100) in exon 4 of both patients (Fig. 2).

Discussion

We present a Japanese TRPS family with intra-familial phenotypic variability. Patient 2 had TRPS I, and Patient 1 had TRPS III. The observed phenotypic variability was associated with identical *TRPS1* mutations. Patient 1 was assessed as having TRPS III because she had severe brachydactyly, due to generalized shortness of all phalanges, and severe short stature; her final height was below the target height range (140.5–156.5 cm). On the other hand, we assessed Patient 2 as TRPS I because she had the typical features without severe short stature. The *TRPS1* gene maps to 8q24 and encodes a transcription factor comprising nine zinc-finger domains, including a single GATA-type DNA binding motif. The c.1990delC (p.Leu664Cysfs*100) frameshift mutation identified here is not listed in the database of multiple small-scale variations that include insertions/deletions, microsatellites, and non-polymorphic variants (dbSNP; www.ncbi.nlm.nih.gov/snp/). Therefore, it would be a newly described pathogenic mutation.

Previous studies have shown that most patients with nonsense *TRPS* mutations have the less severe TRPS I phenotype (3), whereas patients with missense mutations in the GATA-type zinc finger motif have the more severe TRPS III phenotype (4). Mechanisms to account for these observations have been proposed. Hypothetically, nonsense mutations can reduce the number of functional *TRPS I* gene copies (haploinsufficiency), leading to a TRPS I phenotype. In contrast, missense mutations in the GATA-type motif can cause a dominant-negative effect on transcriptional regulation, leading to a more severe TRPS III phenotype (3). However, the molecular basis underlying the phenotypic variation has not been elucidated. This is highlighted by the frameshift mutation detected in our patients being responsible for both a TRPS I phenotype (Patient 2) and a TRPS III phenotype (Patient 1). Discovery of more mutations, along with associated functional analyses, could more definitively establish genotype-phenotype correlations for *TRPS1* and define the TRPS clinical spectrum.

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