CASE REPORT

A novel nonsense mutation in the TRPS1 gene in a case of trichorhinophalangeal syndrome type I

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Abstract

The trichorhinophalangeal syndromes are rare malformation syndromes with autosomal dominant inheritance. Diagnostic features include distinctive facial dysmorphisms and various skeletal abnormalities. The affected gene, the TRPS1 on 8q24.1, was first identified in 2000 and more than 50 mutations have been found. We present a patient with a novel nonsense mutation in the TRPS1 gene.

Introduction

The trichorhinophalangeal syndromes (TRPSs Type I, II, and III) are autosomal dominant disorders characterized by craniofacial and skeletal abnormalities. They share common features, such as sparse and slow-growing scalp hair, laterally sparse eyebrows, bulbous pear-shaped nose, elongated and flat philtrum, thin upper lip, and protruding ears. Besides, various skeletal abnormalities are constantly observed, including short stature, shortening of the phalanges and metacarpals, cone-shaped epiphyses, and hip dysplasia. The TRPS1 gene was first identified in 2000 and mapped to 8q24.1. The gene encodes a zinc-finger transcription factor and the mutations in it are responsible for TRPS. In the present report, we describe a TRPS I patient with a novel mutation in the TRPS1 gene.

Case report

A 16-year-old girl was referred to the pediatric rheumatology clinic in our hospital for evaluation of possible juvenile idiopathic arthritis because of the presence of swelling of the interphalangeal joints and clinodactyly of the fingers in 2000. She was further referred to our dermatology clinic for evaluation of the diffuse sparse hair noted for years. Physical examination revealed that she was well developed and nourished. Her intelligence appeared to be normal. Facial dysmorphisms were noted: fine hair with a high hairline, high-bossed forehead, laterally sparse eyebrows, bulbous pear-shaped nose, elongated philtrum, and prognathism (Figure 1). There was absence of protruding ears, horizontal groove on the chin, hypoplastic mandible, supernumerary teeth, dental malocclusion, or any nail changes (thin nails, koilonychia, leukonychia). Brachydactyly of the first toes and clinodactyly of the fingers and toes on both sides were also noted (Figures 2A and 2B). Radiological examination confirmed the presence of brachydactyly and clinodactyly and revealed cone-shaped epiphyses of all middle phalanges of fingers and toes (Figures 3A and 3B). No cartilaginous exostoses were found. There is no evidence of systemic involvement, such as diabetes mellitus, hypothyroidism, growth hormone deficiency, and renal and heart defects. Her parents were not consanguineous and she appeared to be the only affected member in her family. TRPS mutation analysis was performed on her and her parents. As described by Momeni et al., the Exons 3–7 of the TRPS1 gene were amplified. Automatic sequence analysis of the TRPS1 gene revealed a novel nonsense mutation (G2218T) on Exon 5, which results in the amino acid change E740X and a premature stop of the TRPS1 protein (Figure 4). The results of her parents were negative.

Discussion

The TRPS I (Online Mendelian Inheritance in Man [OMIM] 190350), TRPS II (OMIM 150230), and TRPS III (OMIM 190351) are rare autosomal dominant malformation syndromes. Giedion reported
the first case of TRPS in 1966. In 2000, the TRPS1 gene was identified and mapped to chromosomal band 8q24.1 by Momeni et al. Several deletions, nonsense, and missense mutations in the TRPS1 gene leading to TRPS I have been described in the literature. TRPS II is a contiguous gene syndrome whose deletions encompass both the EXT1 and TRPS1 gene. TRPS II differs from TRPS I by the presence of mental retardation and multiple cartilaginous exostoses. TRPS III was suggested to be a subset of TRPS I and it specifically results from missense mutations in the GATA DNA-binding zinc finger of the TRPS1 protein. TRPS III has similar clinical features to TRPS I except that TRPS III presents more severe brachydactyly and growth retardation. The absence of mental retardation, exostoses, and growth retardation classifies our case as TRPS I, which was further confirmed by the mutation analysis.

The differential diagnoses also presenting alopecia and structural abnormalities of the nose and the hands and possibly mimicking TRPS I include the oral-facial-digital syndrome, Larsen’s syndrome, alopecia-onychodysplasia-hypohidrosis-deafness syndrome, trichoonychodental dysplasia, hidrotic ectodermal dysplasia (Clouston’s syndrome), chondroectodermal dysplasia (Ellis-vanCreveld syndrome), and Coffin-Siris syndrome. The correct diagnosis of TRPS can be made based on clinical and radiological findings and genetic analysis.

The TRPS1 gene has 7 exons and encodes a transcription factor composed of 1281 amino acids with 9 putative zinc-finger motifs. It functions as a GATA family sequence-specific transcription repressor. The Ikaros-like sequence consists of the last two motifs.

Figure 1 Characteristic facial dysmorphisms, including fine hair with a high hairline, high-bossed forehead, laterally sparse eyebrows, bulbous pear-shaped nose, elongated philtrum, and prognathism.

Figure 2 (A,B) Brachydactyly of the first toes and clinodactyly of the fingers and toe.

Figure 3 (A,B) Cone-shaped epiphyses of all middle phalanges of fingers and toes.
(Motifs 8 and 9) and mediates the transcription repressive function of the TRPS1 gene. The seventh motif binds to the GATA consensus sequence, which is also indispensable for the repression activity of the gene. The missense mutations located on Exon 6 where the GATA DNA-binding motif is lead to TRPS III. In our case, the nonsense mutation (G2179T) on Exon 5 results in a premature stop codon and an abnormally truncated TRPS1 protein, which lacks the most C-terminal region, including the Ikaros-like sequence and GATA-binding motif. To the best of our knowledge, this is a new mutation in TRPS1 gene.

The TRPS is an autosomal dominant inheritance. In this report, our patient had no family history and mutation analysis of the parents also showed negative result. Review of the literature showed that about 60% (30/51) are sporadic cases.

In conclusion, we present a typical case of TRPS I with a novel nonsense mutation. The patients of TRPS may visit the clinics of dermatology and other specialties. More familiarity is required from the clinician to not overlook the potential patients and the possibility of further genetic counseling.

References