

Trichorhinophalangeal syndrome type II presenting with short stature in a child

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ABSTRACT

Trichorhinophalangeal syndrome type II (TRPSII) (synonym: Langer-Giedon syndrome) is a rare autosomal dominant contiguous gene syndrome, resulting from a microdeletion encompassing the *EXT1* and the *TRPS1* gene at 8q24 (MIM#150230). This syndrome combines the clinical features of two autosomal dominant disorders, trichorhinophalangeal syndrome type I (MIM#190350) and hereditary multiple osteochondromas type I (MIM#133700). TRPSII is characterized by sparse scalp hair, a long nose with a bulbous tip, long flat philtrum, cone-shaped epiphyses of the phalanges, retarded bone age in infancy and multiple cartilaginous osteochondromas. We report a Turkish patient who had the clinical features and skeletal signs of TRPSII in whom a 13.8Mb deletion in 8q23.1-8q24.13 was detected.

Key Words: trichorhinophalangeal syndrome type II, chromosome deletion, short height.

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INTRODUCTION

The trichorhinophalangeal syndromes (TRPS) are autosomal dominant disorders which are subclassified into three subtypes (TRPSI, TRPSII and TRPSIII) depending on the pattern of mutation in the *TRPS1* gene.^{1,2} Features common

to all three types are characterized by unique facial features including slowly growing and sparse scalp hair, medially thick and laterally thin eyebrows, bulbous tip of the nose, long flat philtrum, thin upper lip with vermilion border and protruding ears.^{2,3} Additionally, skeletal anomalies including short phalanges and short metacarpals (mild to severe brachydactyly), cone-shaped epiphyses, hip dysplasia, and short stature have been described in TRPS.^{2,3} *TRPS1* gene, which is located on chromosomal band 8q24.1, encodes an atypical member of the GATA type family of transcription factors and represents a candidate gene for bone homeostasis regulation.³ TRPSI is caused by heterozygous mutation or deletion of the *TRPS1* gene, whereas TRPSIII is results from a heterozygous missense mutations of this gene. TRPSII, also known as Langer-Giedon syndrome (MIM #150230), is defined as a contiguous gene disorder caused by loss of functional copies not only of the *TRPS1* gene but also the neighboring *EXT1* gene.⁴ The *EXT1* gene encodes a Golgi localized type 2 transmembrane protein with glycosyltransferase activity. *EXT1* seems to have a regulatory effect on longitudinal bone growth.⁴

We report a Turkish patient with a phenotype overlapping TRPSII with a chromosomal deletion in 8q23.1-8q24.13. Written informed consent by both parents was obtained for publication of this case report.

CASE

Our patient is a 12-years-old boy who was referred because of short stature, dysmorphic facial features and skeletal abnormalities. He was born to non-consanguineous Turkish parents with a birth weight of 3200 g after an uneventful term pregnancy. He had a healthy sister and family history revealed no cases of skeletal abnormalities. He had bilateral talipes calcaneovalgus, bilateral hip dislocation and unilateral inguinal hernia, which were corrected by surgery in the first year of life. Osteochondromas had begun to occur at the age of 2. Therefore, he received multiple orthopedic interventions. He had delayed

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developmental milestones and sat at 1 year, stood at 24 months and walked at 2.5 years. He had moderate mental retardation.

Physical examination revealed a weight of 30 kg (3rd – 10th percentile, -1.70 SDS), a height of 120 cm (< 3rd percentile, -4.12 SDS), a head circumference of 45.6 cm (10th – 25th percentile). His facial features disclosed a widow's peak, sparse-fine hair, heavy eyebrows, low set ears, a bulbous nose with a wide columella, elongated philtrum and large laterally protruding ears. Other features included pectus excavatum, hypermobile joints, genu valgum, multiple osteochondromas and redundant skin (Figure 1).

Laboratory testing including a full blood count, electrolytes, liver enzymes, creatine phosphokinase, calcium, phosphate, alkaline phosphatase, urea, creatinine, thyroid hormones, parathyroid hormone, 25-OH vitamin D, urine and blood amino acid chromatography were normal. Abdominal ultrasonography (USG) and cranial magnetic resonance imaging revealed no abnormalities. Skeletal X-ray showed multiple osteochondromas (at wrist, knee and ankle joints), sclerotic femoral heads, short femoral necks, femoral cortical irregularity and hip joint irregularities (more severe in right hip). The radiographs of the hands showed markedly

delayed bone age, cone-shaped epiphyses at the proximal interphalangeal joints and short phalanges (Figure 2). Fundoscopic examination was normal, as was hearing testing.

Cytogenetic (550 GTG banding) analysis was performed on cultured peripheral blood lymphocytes according to standard cytogenetic techniques. Interstitial deletion in the long arm of chromosome 8 was detected including q23 and q24 (Figure 3A). Deletion of the *EXT1* gene on 8q24 was also confirmed by MLPA (Multiplex Ligation-dependent Probe Amplification) analysis. Further array CGH analysis was performed using Nimble Gene MS200 platform allowing a theoretical CNV (Copy number variant) detection resolution of ≥ 4.7 kb. The technique used allowed fine mapping of the breakpoints of the deletion and confirmed the deletion between the bands 8q23.1 and 8q24.13 (Figure 3B). The deletion occurred between the genomic positions 110,332,662-124,170,948. Cytogenetic analysis of the parents were normal indicating this was a *de novo* deletion.

DISCUSSION

This patient had a deletion at chromosome bands 8q23.1–q24.1 encompassing both *TRPS1* and *EXT1* genes that account for the phenotype.

FIGURE 1: Dysmorphic facial features and skeletal abnormalities



TRPS1 (OMIM 604386), mapped to chromosome 8q23.1-q24.1, is associated with the development and differentiation of the bones, kidneys and hair follicles.^{1,2,5} TRPS1 and TRPSIII results from mutations or haploinsufficiency of TRPS1.^{1-3,5} TRPSI (OMIM 190350) is characterized by sparse scalp hair, bulbous tip of the nose, long philtrum, protruding ears, cone-shaped epiphyses at the phalanges, hip malformations and short stature.⁶ TRPSII is a contiguous gene syndrome

with deletion of both *TRPS1* and *EXT1* that differs from TRPS I by the presence of multiple exostoses and mental retardation.⁷ TRPSIII (OMIM 190351) is similar to TRPSI, but has more severe shortening of all phalanges and metacarpals, severe short stature and severe brachydactyly but no exostoses.³ Most cases of TRPSII are sporadic although there are a few cases which are familial.³

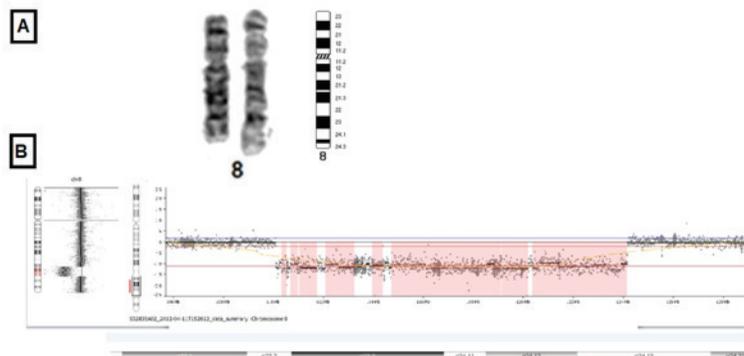
The skeletal findings in TRPSII include cone-shaped epiphysis of the phalanges of the hands leading to deformity of the fingers, delayed bone age, osteochondromas and hip malformations.³ Verheij et al., reported two patients with a deletion in the long arm of chromosome 8.⁸ In one of them the deletion region (q24.1-24.3) included the *TRPS1* and *EXT1* genes. The patient had the facial features of TRPSII, however, he had hand anomalies including the fusion of the third and fourth metatarsals and oligodactyly, a unilateral coloboma of the right iris, pulmonary stenosis, ventricular septal defects. They suggested that other genes which are present in the deleted region may be responsible for these additional features.⁸

Our patient showed the typical facial features and skeletal signs of TRPSII. The clinical findings are strongly associated with TRPSII, 8q24.1 deletion syndrome. The patient has a 13.8 Mb deletion lying through 8q23.1 to 8q24.13, nephroblastoma overexpressed (*NOV*) gene, is located 8q24.1. *NOV* protein is a member of a CCN family (cysteine-rich secreted proteins).^{9,10} The members of the CCN are expressed in extracellular matrix that play critical roles in cell differentiation and function, cardiovascular and skeletal development, injury repair, fibrotic

FIGURE 2: Hands x-ray



FIGURE 3: Interstitial deletion in the long arm of chromosome 8 including q23 and q24



diseases and cancer. Their expression and function in skeletal tissue is partially understood.¹¹ In a study which is revealed *Novdel3* mutant and non-mutant mice, *Novdel3*^{+/-} and *Novdel3*^{-/-} mice exhibited multiple defects in skeletogenesis and joint formation. Skeletal abnormalities include fusion of the tarsal bones in the foot, flattening of the patella, malformation of the wrist, dislocation of the hip, and abnormal articulation of the joints resulting in laxity of the limbs. The authors suggested that a detailed molecular analysis of chondrogenic differentiation in the *Novdel3*^{-/-} embryos will shed further light on the role of NOV in this pathway.¹² We suggest that the deletion of the *NOV* gene may play a role in skeletal anomalies in human.

Radiologically, cone-shaped epiphyses (cone) are found in TRPS as the most consistent finding.¹ Mesophalangeal cones type 12 of Giedion is characteristic, in which the periphery thins towards the base.¹³ The excavation sign is almost always present in type 12 cones, with progressive excavation of the cone's base. Our patient had a type 12A cone, which is occasionally seen in TRPS I and III and almost in all TRPS II.¹³ However, features in hands include triphalangeal thumb which can be associated with polydactyly, shortening of the metacarpals (especially 4th and 5th metacarpals), and shortening of the phalanges in patients with TRPS.¹⁴ Type 12A cones and shortening of the phalanges were seen in our patient. The mechanism underlying association of TRPS II with cone-shaped epiphyses and short bifid first metacarpals of the hand is TRPS1 gene, which is responsible for bone homeostasis regulation. Further studies may help us understand the function of TRPS1 gene in heterogeneity for skeletal signs.

In conclusion, this report of a Turkish patient with TRPS II is important because it is due to large deletion inside 8q23 and q24 which was confirmed by array CGH (Comparative genomic hybridization) analysis. The extensive variation in the size of deletions and the other gene or genes in the deleted regions may be the cause for the additional features in TRPS II patients. ■

REFERENCES

- Lüdecke HJ, Wagner MJ, Nardmann J, La Pillo B, et al. Molecular dissection of a contiguous gene syndrome: localization of the genes involved in the Langer-Giedion syndrome. *Hum Mol Genet* 1995;4(1):31-6.
- Alanay Y, Lachman RS. A review of the principles of radiological assessment of skeletal dysplasias. *J Clin Res Pediatr Endocrinol* 2011;3(4):163-78.
- Lüdecke HJ, Schaper J, Meinecke P, Momeni P, et al. Genotypic and phenotypic spectrum in tricho-rhino-phalangeal syndrome types I and III. *Am J Hum Genet* 2001;68(1):81-91.
- Riedl S, Giedion A, Schweitzer K, Müllner-Eidenböck A, et al. Pronounced short stature in a girl with tricho-rhino-phalangeal syndrome II (TRPS II, Langer-Giedion syndrome) and growth hormone deficiency. *Am J Med Genet A* 2004;131(2):200-3.
- Wells C, Spaggiari E, Malan V, Stirnemann JJ, et al. First fetal case of the 8q24.3 contiguous genes syndrome. *Am J Med Genet A* 2016;170A(1):239-42.
- Momeni P, Glöckner G, Schmidt O, von Holtum D, et al. Mutations in a new gene, encoding a zinc-finger protein, cause tricho-rhino-phalangeal syndrome type I. *Nat Genet* 2000;24(1):71-4.
- Li Q, Zhang Z, Yan Y, Xiao P, et al. Annular pancreas in Trichorhinophalangeal syndrome type II with 8q23.3-q24.12 interstitial deletion. *Mol Cytogenet* 2015;8:95.
- Verheij JB, De Munnik SA, Dijkhuizen T, de Leeuw N, et al. An 8.35 Mb overlapping interstitial deletion of 8q24 in two patients with coloboma, congenital heart defect, limb abnormalities, psychomotor retardation and convulsions. *Eur J Med Genet* 2009;52(5):353-7.
- Chen CP, Lin MH, Chen YY, Chern SR, et al. Prenatal diagnosis and array comparative genomic hybridization characterization of interstitial deletions of 8q23.3-q24.11 and 8q24.13 associated with Langer-Giedion syndrome, Cornelia de Lange syndrome and haploinsufficiency of TRPS1, RAD21 and EXT1. *Taiwan J Obstet Gynecol* 2015;54(5):592-6.
- Selenti N, Tzetzis M, Braoudaki M, Gianikou K, et al. An interstitial deletion at 8q23.1-q24.12 associated with Langer-Giedion syndrome/ Trichorhinophalangeal syndrome (TRPS) type II and Cornelia de Lange syndrome 4. *Mol Cytogenet* 2015;8:64.
- Parisi MS, Gazzo E, Rydzial S, Canalis E. Expression and regulation of CCN genes in murine osteoblasts. *Bone* 2006;38(5):671-7.
- Heath E, Tahri D, Andermarcher E, Schofield P, et al. Abnormal skeletal and cardiac development, cardiomyopathy, muscle atrophy and cataracts in mice with a targeted disruption of the *Nov* (*Ccn3*) gene. *BMC Dev Biol* 2008;8:18.
- Giedion A. Phalangeal cone-shaped epiphyses of the hand: their natural history, diagnostic sensitivity, and specificity in cartilage hair hypoplasia and the trichorhinophalangeal syndromes I and II. *Pediatr Radiol* 1998;28(10):751-8.
- Castriota-Scanderberg A, Dallapiccola B. Abnormal skeletal phenotypes: from simple signs to complex diagnoses. Berlin: Springer; 2005.