The Turkish Journal of Pediatrics 2023; 65: 81-95
https://doi.org/10.24953/turkjped.2022.793

Original Article

Expanding the clinical and molecular features of tricho-rhino-phalangeal syndrome with a novel variant

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ABSTRACT

Background. Tricho-rhino-phalangeal syndrome (TRPS) is a rare, autosomal dominant disorder characterized by typical craniofacial features, ectodermal and skeletal findings. TRPS type 1 (TRPS1) is caused by pathogenic variations in the *TRPS1* gene, which relates to the vast majority of cases. TRPS type 2 (TRPS2) is a contiguous gene deletion syndrome involving loss of functional copies of the *TRPS1, RAD21,* and *EXT1*. Herein, we reported the clinical and genetic spectrum of seven TRPS patients with a novel variant. We also reviewed the musculoskeletal and radiological findings in the literature.

Methods. Seven Turkish patients (three female, four male) from five unrelated families aged between 7 to 48 years were evaluated. The clinical diagnosis was confirmed by either molecular karyotyping or *TRPS1* sequencing analysis via next-generation sequencing.

Results. Both TRPS1 and TRPS2 patients had some common distinctive facial features and skeletal findings. All patients had a bulbous nose with hypoplastic alae nasi, brachydactyly, short metacarpals and phalanges in variable stages. Low bone mineral density (BMD) was identified in two TRPS2 family members presenting with bone fracture, and growth hormone deficiency was detected in two patients. Skeletal X-ray imaging revealed cone-shaped epiphysis of the phalanges in all, and multiple exostoses were present in three patients. Cerebral hamartoma, menometrorrhagia and long bone cysts were among the new/rare conditions. Three pathogenic variants in TRPS1 were identified in four patients from three families, including a frameshift (c.2445dup, p.Ser816GlufsTer28), one missense (c.2762G>A), and a novel splice site variant (c.2700+3A>G). We also reported a familial inheritance in TRPS2 which is known to be very rare.

Conclusions. Our study contributes to the clinical and genetic spectrum of patients with TRPS while also providing a review by comparing with previous cohort studies.

Key words: Tricho-rhino-phalangeal syndrome, *TRPS1* gene, multiple exostoses, novel mutation, TRPS2.

Tricho-rhino-phalangeal syndrome (TRPS) is a rare autosomal dominant disorder characterized by typical craniofacial features, ectodermal (hair, nail, skin, teeth), and skeletal anomalies. The exact prevalence of TRPS is unknown; the estimated prevalence is 0.2-1/100,000.[1,2] It was first described in 1966 by Giedion, and less than 250 TRPS patients have been reported.[3,4] There are two clinical subtypes of TRPS; one of them is TRPS type 1 (TRPS1) (OMIM #190350) caused by pathogenic variants in the *TRPS1* gene located on chromosome 8q23.3, and the other one is TRPS type 2 (Langer–Giedion syndrome, LGS), (OMIM #150230), a contiguous gene deletion syndrome is caused by submicroscopic deletion of the chromosomal segment 8q23.3-8q24.11, containing *TRPS1, RAD21,* and *EXT1*. Although both subtypes have similar clinical manifestations, TRPS2 is differentiated by multiple cartilaginous exostoses and intellectual

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Received 17th August 2022, revised 4th November 2022, acceted 20th November 2022.

disability. A different subtype of TRPS has also been described; however, TRPS type 3 is now accepted within the spectrum of TRPS1 with more severe brachydactyly and short stature.[2,5]

TRPS1 gene is a zinc finger transcription factor expressed in cartilage, kidneys, and hair follicles that represses GATA-regulated genes and regulates bone perichondrium mineralization, chondrocyte proliferation, differentiation, and apoptosis.[6,7] TRPS1 has high penetrance and wide phenotypic variability. More than 130 pathogenic variants have been described in the *TRPS1* gene. TRPS2 is usually sporadic, although a few familial cases have been reported.[1,8-10]

In our study, we aimed to reveal the clinical and molecular spectrum of patients with TRPS and provide a review by comparing them with previous cohort studies.

Material and Methods

Ethical compliance

Ethical approval was obtained from the Ethical Committee of Akdeniz University (Project no: 20.07.2022/KAEK-484).

Written informed consent was obtained from patients older than 18 years and the parents of all children.

Patients and clinical evaluation

Seven TRPS (type 1 and 2) patients from five unrelated families were included in this study. Clinical and molecular diagnosis of the patients were performed at two tertiary centers; Akdeniz University and Ankara University, between the years 2017-2021. The patients whose diagnoses were not confirmed via genetic analysis and, who did not have regular follow-ups, were excluded.

Demographic, laboratory, and radiological data were obtained from the hospital records. Prematurity was defined as <37 weeks due to gestational age. Birth weights greater than the 90th percentile for their gestational age were described as large for gestational age (LGA). The anthropometric measurement values were evaluated according to the national reference data for Turkish children by Neyzi et al.[11] Weight of standard deviation score (SDS) < -2 was described as underweight, height SDS < -2 was described as short stature, and head circumference SDS < -2 was described as microcephaly. Ankara Developmental Screening Inventory (AGTE) and Wechsler Intelligence Scale for Children-R (WISC-R) tests were used to evaluate the mental status. Intelligence quotient (IQ) values were described as mild intellectual disability (ID) (IQ score: 55-70), moderate ID (IQ score: 40-54), and severe ID (IQ score: 25-39).

Molecular Analysis

Molecular karyotyping was performed using the DNA samples of patients obtained from peripheral whole blood. Methods used for molecular karyotyping were either single nucleotide polymorphism (SNP) array (Affymetrix, Illumina) or array comparative genomic hybridization (aCGH) (Agilent) depending on the laboratory the sample was sent and the procedures were followed according to the manufacturers' instructions. All the coding exons and the intronic–exonic boundary regions of the *TRPS1* gene were sequenced by the next-generation sequencing (NGS) method (Miseq-Illumina) after extracting genomic DNA from whole blood samples. Variants were described using the Human Genome Variation Society nomenclature guidelines and were checked against those available in 1000 Genomes, dbSNP, ClinVar, and Human Genome Mutation Database. American College of Medical Genetics and Genomics Standards and Guidelines were used to determine variant pathogenicity.[12]

Statistical analyzes were performed with the SPSS 23.0 package program. Descriptive statistics were presented as n (%) and mean±standard deviation and median (min-max) values.

Results

Clinical features, dysmorphic facial features and growth parameters

Our study included seven patients (three females, four males) from five unrelated families. The median age of the patients was 15 years (min 7 - max 48 years). The median age at molecular diagnosis was 12 years (min 7 - max 45 years). Diagnostic delay between initial examination and diagnosis ranged from 2 months to 5 years. A mother had gestational diabetes, while the others' prenatal screening tests were normal. Five patients had term delivery. The median birth weight was 3350 grams (min 2800 - max 4500 grams), and two patients (P2, P5) were LGA. One patient (P2) had hypotonia and feeding problems in infancy. Five patients had microcephaly. Short stature was present in five patients. At the last visit, the median height SDS was -2.68 SDS (min -4.66 - max -0.6 SDS). Height SDS was normal in P1 and P6; P1 had decreased growth velocity (3 cm/year). Anthropometric measurements and clinical features of TRPS patients are summarized in Table I.

All patients had a bulbous nose with hypoplastic alae nasi, and all patients except one (P3) had a large nose. The characteristic facial features of the patients are shown in Fig. 1. Only P3 had normal scalp hair. Three patients (P1, P2, P5) had blond hair. One patient (P3) had synophrys, and laterally thin eyebrows were seen in five patients.

Two patients (P2, P6) had mild intellectual disability. Neuromotor developmental delay was seen only in one patient (P2), and diffuse cerebral atrophy was revealed in her cranial MRI. Millimetric T2, FLAIR hyperintense nodular appearance in the left globus pallidus (hamartoma) was detected in P3.

Skeletal findings

The bone age was delayed in five prepubertal patients. Low BMD was detected in one older TRPS2 patient (P4) and his son (P3) [P4; lumbar z score -2, hip z score -2,9, P3; lumbar z score -4,6, hip z score -3,4 (low z-score for age <-2)]. A history of bone fracture was noted in one patient (P3). Two patients had chronic joint pain.

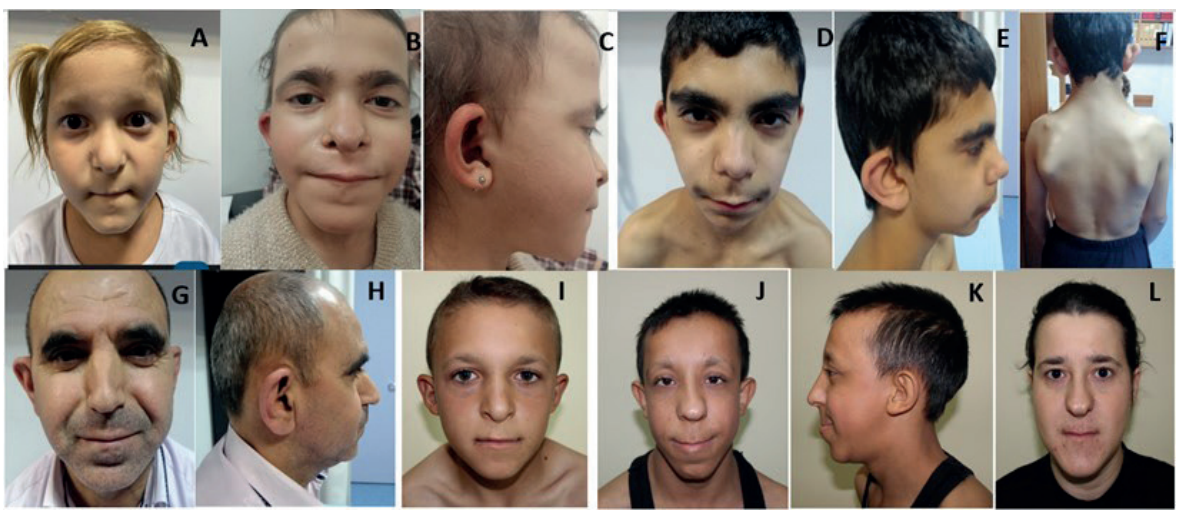

Fig. 1. Clinical photographs of 7 patients with TRPS. All patients had bulbous nasal tip, large nose except for Patient 3, triangular face, low-set anteverted ears, underdeveloped alae nasi, wide columella, long-smooth philtrum, thin upper lip, horizontal groove on chin, sparse hair except for Patient 3, medial/total thick eyebrows. Sparseness of the lateral part of the eyebrows were seen in some patients. Patient 3 had winged scapula (F).

A. Patient 1, 7-year-old girl with TRPS1; B and C. Patient 2, 11-year-old girl with TRPS2; D, E and F. Patient 3, 15-year-old boy with TRPS2; G and H. Patient 4, 48-year-old man with TRPS2; I. Patient 5, 12-year-old boy with TRPS1; J and K. Patient 6, 16-year-old boy with TRPS1; L. Patient 7, 19-year-old girl with TRPS1.

Table I. Anthropometric measurements and clinical features of TRPS patients.

Family	F1	F2	F3		F4	F5		Total (n=7)
Patient	P1	P2	P3	P4	P5	P6	P7	
Gender	Female	Female	Male	Male	Male	Male	Female	4M/3F
Age	7.5y	11y	15y	48y	15y	20y/4m	22y/5m	Mean 19.8±13.3 y
								Median 15 y (7,5-48)*
Clinical type	TRPS 1	TRPS 2	TRPS 2	TRPS 2	TRPS 1	TRPS 1	TRPS 1	
Genetic origin	De novo	De novo	Paternal	De novo	De novo	Paternal	Paternal	
Age at diagnosis	7y	7y	12y	45y	11y/9m	15y/8m	19y	Mean 16.7±13.1 y
								Median 12 y (7-45)*
Birth age	Term	Preterm	Term	Term	Term	Postterm	Term	
Weight (birth)	3300 gr	3400 gr	2800 gr	NA	4500 gr	NA	NA	
Weight (last examination)	21.5 kg	39.9 kg	32 kg	54 kg	30.5 kg	42.6 kg	65 kg	Mean 40.6±14.8 kg
	(-0.38 SDS)	(-0.16 SDS)	(-4.56 SDS)		(-1.64 SDS)	(-2.6 SDS)		Median 39.9 kg (21.5-65)*
Height (last examination)	113.9 cm	129.9 cm	140 cm	144.8 cm	131.5 cm	145 cm	159 cm	Mean 137±14.3 cm
	(-1.45 SDS)	(-2.54 SDS)	(-4.66 SDS)		(-2.68 SDS)	(-3.93 SDS)		Median 131 cm (113.9-159)*
Head circumference	51 cm	53 cm	52 cm	52.5 cm	51 cm	52.5 cm	52 cm	Mean 52±0.7 cm
	(-0.13 SDS)	(-0.36 SDS)	(-2.5 SDS)		(-2.3 SDS)	(-3.09 SDS)		Median 52 cm (51-53)*
Craniofacial features								
Face								
Prominent, long philtrum	+	+	+	+	+	+	+	7/7
Horizontal groove on chin	+	+	+	+	-	+	-	5/7
Ears								
Large, prominent ear	-	-	+	+	-	-	-	2/7
Low set ears	+	+	+	+	+	+	+	7/7
Anteverted ears	+	+	+	+	+	+	+	7/7
Overfolded helices	+	+	-	-	-	-	-	2/7

ASD: atrial septal defect, BMD: bone mineral density, GH: growth hormone, LT4: levothyroxine, MRI: magnetic resonance imaging, NA: not applicable, PS: pulmonary stenosis, SDS: standard deviation score, TRPS1: tricho-rhino-phalangeal syndrome 1, TRPS2: tricho-rhino-phalangeal syndrome 2, VSD: ventricular septal defect, VUR: vesicoureteral reflux. *Median (min-max).

Table I. Continued.

Eyes								
Thin eyebrows (laterally)	+	+	-	-	+	+	+	5/7
Thick eyebrows (medially)	+	+	+	+	+	+	+	7/7
Synophrys	-	-	+	-	-	-	-	1/7
Nose								
Large nose	+	+	-	+	+	+	+	6/7
Bulbous nose tip	+	+	+	+	+	+	+	7/7
Short nose	-	-	+	-	-	-	-	1/7
Anteverted nares	-	-	+	-	-	-	-	1/7
Hypoplastic alae nasi	+	+	+	+	+	+	+	7/7
Mouth								
Narrow palate	+	+	+	+	-	+	-	5/7
Thin upper lip	+	+	+	+	+	+	+	7/7
Teeth								
Small teeth	+	+	-	+	+	-	-	4/7
Carious teeth	+	+	+	+	+	+	+	7/7
Dental malocclusion	+	-	+	+	+	+	+	6/7
Crowded teeth	+	-	+	+	-	+	-	4/7
Skeletal findings								
Chest								
Rib exostoses	-	+	+	+	-	-	-	3/7
Scapulae exostoses	-	+	+	-	-	-	-	2/7
Winged scapulae	-	-	+	-	-	-	-	1/7
Osteoarthritis (late-onset)	-	-	-	+	-	-	-	1/7
Joint pain	-	+	-	+	-	-	-	2/7
Scoliosis/ Lordosis	-	Scoliosis	Scoliosis/ Lordosis	Scoliosis	Scoliosis	-	-	4/7

ASD: atrial septal defect, BMD: bone mineral density, GH: growth hormone, LT4: levothyroxine, MRI: magnetic resonance imaging, NA: not applicable, PS: pulmonary stenosis, SDS: standard deviation score, TRPS1: tricho-rhino-phalangeal syndrome 1, TRPS2: tricho-rhino-phalangeal syndrome 2, VSD: ventricular septal defect, VUR: vesicoureteral reflux. *Median (min-max).

Table I. Continued.

Low BMD	-	-	+	+	-	-	-	2/7
Pelvis								
Hip dysplasia	-	Narrow joint space	Narrow joint space	Narrow joint space	-	Unilateral coxa magna	-	4/7
Limbs								
Multiple exostoses	-	+	+	+	-	-	-	3/7
Hyper extensible joints	+	+	+	-	-	-	-	3/7
Fracture history	-	-	+	-	-	-	-	1/7
Hands								
Short hands	+	+	+	+	+	+	+	7/7
Short metacarpals	+	+	+	+	+	-	+	6/7
Short phalanges	+	+	+	+	+	+	+	7/7
Swelling of proximal interphalangeal joints	+	+	+	+	+	+	+	7/7
Cone-shaped epiphyses	+	+	+	+	+	+	+	7/7
Feet								
Short metatarsals	-	+	+	+	+	+	+	6/7
Short feet	-	+	+	+	+	+	+	6/7
Pes planus	-	+	-	-	-	+	+	3/7

ASD: atrial septal defect, BMD: bone mineral density, GH: growth hormone, LT4: levothyroxine, MRI: magnetic resonance imaging, NA: not applicable, PS: pulmonary stenosis, SDS: standard deviation score, TRPS1: tricho-rhino-phalangeal syndrome 1, TRPS2: tricho-rhino-phalangeal syndrome 2, VSD: ventricular septal defect, VUR: vesicoureteral reflux. *Median (min-max).

Table I. Continued.

Ectodermal findings								
Skin								
Dry skin	+	+	+	+	+	+	+	7/7
Hair								
Sparse, thin hair	+	+	-	+	+	+	+	6/7
Temporal baldness	+	+	-	+	+	+	+	6/7
Fine,blonde scalp hair	+	+	-	-	+	-	-	3/7
Nails								
Thin nails	-	+	+	+	+	+	+	6/7
Brittle nails	-	+	+	+	+	+	-	5/7
Neurological abnormalities								
Hypotonia	-	+	-	-	-	-	-	1/7
Intellectual disability	-	Mild	-	-	-	Mild	-	2/7
Developmental delay	-	+	-	-	-	-	-	1/7
Cranial MRI	-	Diffuse cerebral atrophy	Nodular appearance in the left globus pallidus (hamartoma)	-	-	-	-	2/7
Other findings	-	Hypothyroidism, thyroid hypoplasia, left renal focal caliectasis, Mild hearing loss, GH deficiency, strabismus	VSD, PS, ASD-Myopia		Mild hearing loss, inguinal hernia	Bicuspid aortic valve, bilateral VUR, nephrocalcinosis, Left atrophic kidney, GH deficiency, Mild hearing loss	Menometrorrhagia	
Therapies	-	GH, LT4	-	-	-	-	-	

ASD: atrial septal defect, BMD: bone mineral density, GH: growth hormone, LT4: levothyroxine, MRI: magnetic resonance imaging, NA: not applicable, PS: pulmonary stenosis, SDS: standard deviation score, TRPS1: tricho-rhino-phalangeal syndrome 1, TRPS2: tricho-rhino-phalangeal syndrome 2, VSD: ventricular septal defect, VUR: vesicoureteral reflux. *Median (min-max).

Three patients had hyperextensible joints, and four patients developed scoliosis. Three patients had pes planus, and one patient (P3) had winged scapulae. All patients had brachydactyly, short metacarpals and phalanges in variable stages. Swelling of proximal interphalangeal joints and deviation of the fingers were also detected in all patients. Short feet and short metatarsals were seen in six patients. Hand and feet photography of the patients are shown in Fig. 2.

Skeletal X-ray imaging revealed cone-shaped epiphysis at the phalanges in all patients. Multiple exostoses (at the rib, scapula, knee and ankle joints, bilateral femur, tibia, fibula, humerus, radius, ulna metaphyseal, and diaphyseal segments) were present in three patients. One patient (P6) had unilateral coxa magna, three patients had hip joint space narrowing, and one patient (P3) had a cystic lesion in the femur. P4 had a subluxation in the radiocarpal joint of the left wrist and a fusion of the C2-C3 cervical vertebrae spinous processes. The radiological findings of the patients are shown in Fig. 3 and 4.

Other findings

Endocrinologic evaluation revealed hypothyroidism and hypoplasia of thyroid gland in P2. P7 was followed-up due to menometrorrhagia. Growth hormone deficiency was detected in P2 and P6.

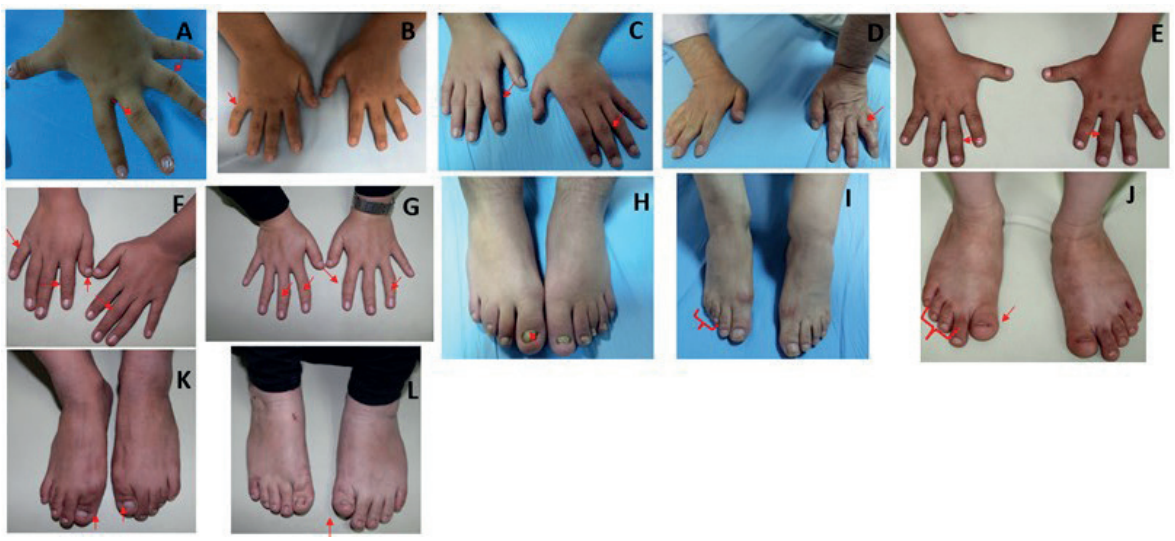

Fig. 2. Photographs of hands and feet of the patients.

A. Patient 1, 7-year-old girl with TRPS1. Note radial and ulnar deviation of the phalanges and swelling of proximal interphalangeal joints.

B. Patient 2, 11-year-old girl with TRPS2. Note brachydactyly and clinodactyly.

C and H. Patient 3, 15-year-old boy with TRPS2. Note brachydactyly, swelling of interphalangeal joints, short feet, metatarsal shortening and dystrophic nails.

D and I. Patient 4, 48-year-old man with TRPS2. Note short left hand, deformities of the phalanges, short feet and metatarsal shortening.

E and J. Patient 5, 12-year-old boy with TRPS1. Note brachydactyly, metacarpal shortening, swelling of interphalangeal joints, metatarsal shortening except for second metatarsal.

F and K. Patient 6, 16-year-old boy with TRPS1. Note the swelling of the interphalangeal joints, deviation of the phalanges, short feet, and shortening of the first metatarsals.

G and L. Patient 7, 19-year-old girl with TRPS1. Note radial and ulnar deviation of the phalanges, metacarpal shortening, short feet and metatarsals.

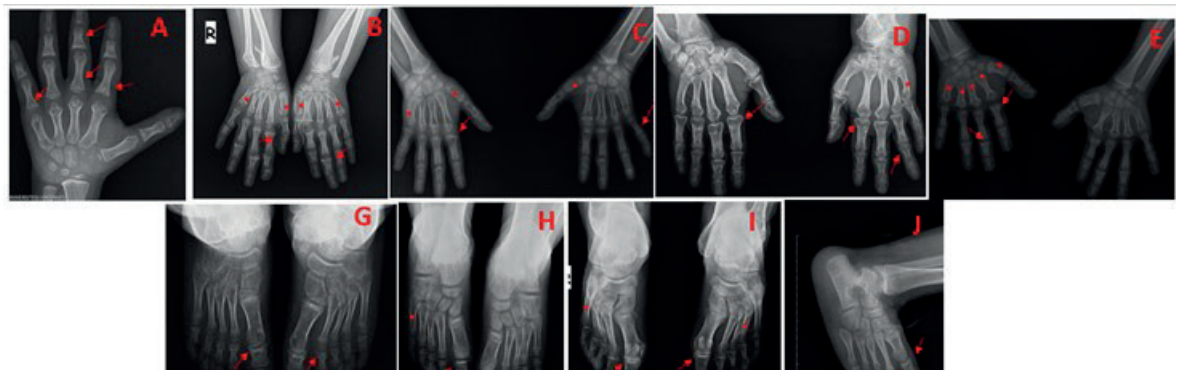

Fig. 3. X-ray imaging of the hands and feet shows cone-shaped epiphyses at the phalanges and metacarpal and metatarsal shortening. Note variably shortening of metatarsals and metacarpals. Patient 5 had a more severe shortening of the metacarpals.

A. Patient 1, 7-year-old girl with TRPS1; B and G. Patient 2, 11-year-old girl with TRPS2; C and H. Patient 3, 15-year-old boy with TRPS2; D and I. Patient 4, 48-year-old man with TRPS2; E and J. Patient 5, 12-year-old boy with TRPS1; F. Patient 6, 16-year-old boy with TRPS1.

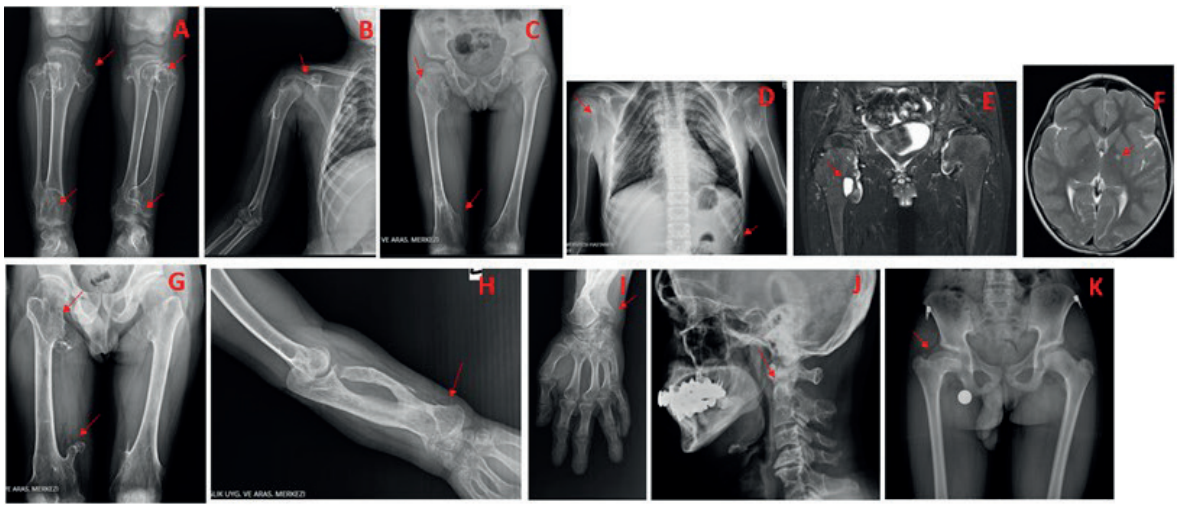

Fig. 4. Radiological findings of the patients

A and B. Patient 2 at the age of 7 years and 2 months, X-ray showed exostoses on the scapulae and around the knees and ankles.

C, D, E, and F. Patient 3 at the age of 12 years, X-ray showed exostoses at long bones, rib, scapula. Pelvic MRI showed a cystic lesion in the femur. Cranial MRI showed millimetric T2 FLAIR hyperintense nodular appearance in the left globus pallidus (hamartoma).

G, H, I and J. Patient 4 at the age of 45 years, skeletal X-Ray showed exostoses at long bones, subluxation in the radiocarpal joint, and fusion of the C2-C3 cervical vertebrae spinous processes, respectively.

K. Patient 6 with TRPS1 at the age of 16 years, pelvic X-Ray shows coxa magna.

Genitourinary anomalies such as unilateral focal caliectasic areas in renal collecting system, bilateral vesicoureteral reflux, nephrocalcinosis, and unilateral atrophic kidney were detected in renal ultrasonography of P2 and P6. One patient (P5) underwent surgery due to unilateral inguinal hernia.

Cardiovascular defects were presented in two patients (P3, P6). Echocardiographic examination revealed ventricular septal defect, pulmonary stenosis, and right arcus aorta, a bicuspid aortic valve. P3 was operated on due to pulmonary stenosis at the age of ten months.

Three patients (P2, P5, P6) had mild conductive hearing loss. One patient (P3) had myopia, and P2 underwent surgery due to strabismus.

Molecular Results

The clinical diagnosis was confirmed by either molecular karyotyping or *TRPS1* sequencing analysis via next-generation sequencing. *De novo* variants were identified in four patients, while three had paternal inheritance. SNP array analysis revealed a deletion in the q23.3q24.11 band region of chromosome 8 in three TRPS2 patients. P2 had the 2.619 kb deleted region, including *TRPS1, EIP3H, RAD21, SCL30AB, MED30*, and *EXT1*. P3 and P4 had a 3.488 kb deleted region, including *EIF3H, RAD21, SLC30A8, MED30, EXT1, TNFRSF11B, COLEC10, MAL2, NOV*, and *ENPP2*.

Three different pathogenic variants in *TRPS1* gene were identified in four patients from three families, including a frameshift (c.2445dup, p.Ser816GlufsTer28) in the exon 5, one missense (c.2762G>A), and a novel splice region variant (c.2700+3A>G). The results of the genetic analysis are presented in Table II.

Discussion

Phenotypical Features and Ectodermal Findings

Tricho-Rhino-Phalangeal Syndrome has a broad phenotypic spectrum. Short stature, sparse hair and prominent nose with bulbous tip represent the clinical hallmarks of the disease. Maas et al.[1] reported similar facial features in TRPS patients either with microdeletion or *TRPS1* variants; besides broad eyebrows are more common in TRPS2. Ectodermal findings including dry skin, sparse hair, dystrophic nails, oligodontia, dental malocclusion, and carious teeth are the other common features of the syndrome.[1,2,8,13] In our study, a large nose with bulbous nasal tip, hypoplastic alae nasi, prominent long philtrum and anteverted ears appear as the most recognizable facial findings both in childhood and adults. Sparse and slow-growing hair was seen in almost all our patients, but P3 had some facial and ectodermal features of Cornelia de Lange syndrome (CdLS) such as a small, upturned nose, thick eyebrows, synophrys,

Table II. The results of the genetic analysis.

	Patient no	Exon/ Intron	Nucleotide change	Protein Change	Coding impact	ACMG classification[12]	Reference
TRPS1 Sequence analysis	1	Exon 5	c.2445dup	p.S816EfsTer28	Nonsense	Likely Pathogenic	Momeni et al.[6]
	5	Exon 6	c.2762G>A	p.R921Q	Missense	Pathogenic	Maas et al.[1]
	6	Intron 5	c.2700+3A>G		Splice site	Likely Pathogenic	NR
	7	Intron 5	c.2700+3A>G		Splice site	Likely Pathogenic	NR
	Patient no	Deletion size	Deleted genes				
Chromosomal microarray analysis	2	2.619 kb	*TRPS 1, EIP3H, RAD21, SCL30AB, MED30, EXT1*				
	3	3.488 kb	*EIF3H, RAD21, SLC30A8, MED30, EXT1, TNFRSF11B, COLEC10, MAL2, NOV, ENPP2*				
	4	3.488 kb	*EIF3H, RAD21, SLC30A8, MED30, EXT1, TNFRSF11B, COLEC10, MAL2, NOV, ENPP2*				

NR: not reported.

and hirsutism. He had a 3.48 kb deletion in chromosome 8q23.3q24.11 containing *RAD21* and *EXT1* genes. Herrero-García A. et al.[14] reported a mixed phenotype of TRPS2 and CdLS in an 8q23.3-q24.1 microdeletion and they hypothesized the *RAD21* gene deletion has a mixed phenotype of TRPS2 and CdLS, similar to P3.

Anthropometric Measurement and Growth

The growth parameters such as weight and head circumference are usually normal in TRPS1; however, microcephaly can be seen in one-third of TRPS2. Recently, Maas et al.[1] reported six patients with microcephaly; three had TRPS2, and two had *TRPS1* missense mutation. Consistent to the report, two of our TRPS patients with microcephaly had TRPS2, one had *TRPS1* missense mutation, and two had *TRPS1* splice site mutation.

Linear growth is reduced in almost all TRPS patients, more marked in TRPS2. Lüdecke et al.[5] reported the average height of 75 TRPS patients was -1.41±1.15 SDS; besides, patients with *TRPS1* missense mutations are shorter than those with nonsense mutations.[1,5,15] Growth hormone (GH) deficiency or insensitivity are described in some TRPS patients, but the results of GH treatment were variable.[16] In our study, the average height SDS was -2.88. Short stature was more significant in TRPS2, and similar to the literature, the patient with missense mutation was shorter than the patient with nonsense mutation. Only one patient (P2) had started to receive GH treatment at the age of four years and for longer duration, resulting in an increase in height SDS from −4.1 SDS to −2.3 SDS. Growth responds consistently to GH therapy; however, further studies and larger cohort of patients are required for the determination of efficiency.

Musculoskeletal and Radiologic Features

Deformities of the hands and feet are seen frequently, like brachydactyly, ulnar or radial deviation of fingers, metacarpal or metatarsal shortening, and short feet. The fourth and fifth metacarpals or metatarsals are the most commonly affected ones.[1,5] Other skeletal findings include winged scapula, scoliosis, pectus carinatum/excavatum, and joint hypermobility.[1,2,17] Low BMD is usually detected in adults, except in two reported children, and it may rarely present in TRPS1, but is more common in TRPS2.[1,18-20] Osteoarthritis-like changes, joint pain, and decreased mobility affect the small/large joints, and hips, which can be related to long-term morbidity. These complaints can be mistakenly interpreted as rheumatoid arthritis.[1,18] Hip dysplasia such as coxa vara, coxa plana, joint space narrowing, and Perthes-like femoral head changes are present in 47-70% of patients.[1,8,17,18] Hemivertebrae, long bone cysts, non-ossifying fibroma, tibial hemimelia, and duplicated thumb have been rarely reported.[1,21-23]

The most typical radiographic feature in TRPS is cone-shaped epiphyses, which are usually present in the second finger's middle phalanx. They are detectable typically after two years of age and can cause ulnar or radial deviation.[1,24] Exostoses usually occur around the elbows, knees, and scapula in TRPS2 from the newborn period, and do not progress after puberty. Malignant transformation of osteochondromas in TRPS2 has not been reported, but the risk cannot be excluded.[1,25-27] The comparison of musculoskeletal and radiological findings of TRPS via literature is presented in Table III.

In our study, all patients had brachydactyly, interphalangeal joint deformity, cone-shaped epiphysis, and limb deformities. Hands were more affected than the feet. Scoliosis, short metacarpals and metatarsals were seen in more than half of TRPS patients. Exostoses were seen at the rib, scapula, long bones, and joints in three patients. The mobility decreased only in a patient due to joint pain and knee exostoses at the age of 11 years. No malignant transformation was observed, and one of them had exostosis excision on his left arm due to pain, limitation of movement, and nerve compression. In TRPS2 family members (P3, P4), low BMD and vitamin D deficiency were detected, and P3 had

osteoporosis presenting with an ulnar fracture at the age of 15 years. In TRPS, low BMD can be a risk in adolescents and we should recommend checks on vitamin D and dual energy X-ray absorptiometry (DEXA) scans at appropriate intervals to assess bone loss and fracture risk.

Table III. Comparison of musculoskeletal and radiological findings of TRPS in literature.

	Maas et al. 2015[1]	Lüdecke et al. 2001[5]	Wang et al. 2020[27]	Schinzel et al. 2013[25]	de Barros et al. 2014[17]	Present study
	n=103 (%)	n=51 (%)	n=5 (%)	n=4 (%)	n=1 (%)	n=7 (%)
Musculoskeletal findings						
Short stature	37/66 (56%)	24/75 (32%)	4/5 (80%)	4/4 (100%)	1/1 (100%)	5/7 (71%)
Brachydactyly	65/99 (66%)	29/45 (64%)	5/5 (100%)	4/4 (100%)	1/1 (100%)	7/7 (100%)
Deformity in interphalangeal joints	NA	NA	NA	NA	1/1 (100%)	7/7 (100%)
Polydactyly	1/99 (1%)	NA	NA	0/4 (0%)	0/1 (0%)	0/7 (0%)
Oligodactly	0/0 (0%)	NA	NA	1/4 (25%)	0/1 (0%)	0/7 (0%)
Syndactyly	NA	NA	NA	1/4 (25%)	0/1 (0%)	0/7 (0%)
Short feet	38/65 (58%)	NA	NA	1/4	NA	6/7 (85%)
Hyperextensible joints	38/63 (60%)	NA	NA	2/4 (50%)	NA	3/7 (43%)
Scoliosis/kyposis	30/93 (32%)	NA	4/5 (80%)	4/4 (100%)	NA	4/7 (57%)
Winged scapulae	17/58 (32%)	NA	NA	2/4 (50%)	-	1/7 (14%)
Chest deformity	NA	NA	NA	2/4 (50%)	NA	0/7 (0%)
Pes planus	NA	NA	NA	NA	NA	3/7 (43%)
Fractures	20/87 (23%)	NA	NA	2/4 (50%)	0/1 (0%)	1/7 (14%)
Joint pains	22/34 (65%)	NA	NA	1/4 (25%)	1/1 (100%)	2/7 (28%)
Limb length discrepancy	10/45 (22%)	NA	NA	2/4 (25%)	0/1 (0%)	1/7 (14%)
Hip surgery	7/65 (11%)	NA	NA	0/4 (0%)	0/1 (0%)	0/7 (0%)
Other ortopedic surgery	18/93 (19%)	NA	NA	2/4 (50%)	0/1 (0%)	1/7 (14%)
Radiological Findings						
Cone shaped epiphysis	58/60 (97%)	NA	5/5 (100%)	4/4 (100%)	1/1 (100%)	7/7 (100%)
Short metacarpals	58/93 (62%)	NA	NA	2/4 (50%)	0/1 (0%)	6/7 (86%)
Short metatarsals	34/58 (59%)	NA	NA	NA	NA	6/7 (86%)
Delayed bone age before puberty	NA	20/21 (%95)	NA	NA	1/1 (100%)	5/5 (100%)
Accelerated bone age after puberty	NA	4/5 (%80)	NA	1/4 (25%)	NA	0/3 (0%)
Coxa plana	8/15 (%53)	NA	NA	NA	1/1 (100%)	0/7 (0%)
Coxa magna	NA	NA	NA	NA	0/1 (0%)	1/7 (14%)
Perthes-like changes/hip dysplasia	18/38 (%47)	NA	NA	1/4 (25%)	1/1 (100%)	0/7 (0%)
Dislocated patellae	9/64 (%14)	NA	NA	NA	NA	0/7 (0%)
Subluxation in other joints	NA	NA	NA	2/4 (50%)	NA	2/7 (28%)
Osteopenia	11/44 (%25)	NA	NA	1/4 (25%)	1/1 (100%)	2/7 (28%)
Osteoarthritis	NA	NA	NA	NA	1/1 (100%)	2/7 (28%)
Exostoses	12/85 (%14)	NA	1/5 (%20)	4/4 (100%)	0/1(0%)	3/7 (43%)

NA: not available, TRPS: tricho-rhino-phalangeal syndrome.

Other findings

Intellectual disability in TRPS1 is similar to the general population; however, mild to moderate intellectual disability occurs in two-thirds of the TRPS2. Language development is better than motor skills, and practical skills are better than IQ scores in some TRPS2 patients. Neuromotor delay may occur secondary to hip dysplasia. Seizures, neurologic abnormalities, and cranial MRI findings such as polymicrogyria, hydrocephalus, and Chiari malformation have also been reported.[1,25,27] In our study, mild intellectual disability was revealed in two patients. One of them was TRPS1 (P6), and the other was TRPS2 (P2), who had a neuromotor delay in infancy and cerebral atrophy. None of patients had seizures. Hamartoma at globus pallidus in P3 has been considered a new condition that may accompany TRPS2, which has not been defined in the literature. Intracranial hamartoma which is located in a different region from the hypothalamus is also extremely rare.[28]

Urogenital anomalies include unilateral kidney, ureter-bladder junction stenosis, vesicoureteral reflux, renal cysts, hydrometrocolpos, vaginal atresia, and persistent cloaca. Endocrinologic abnormalities such as hypothyroidism and idiopathic hypoglycemia have been reported.[1,8] Cardiovascular defects were reported in a minority (15%) of TRPS patients, and usually not severe and life-threatening. Persistent ductus arteriosus, patent foramen ovale, bicuspid aortic valves, mitral valve regurgitation, aortic stenosis, and anomalous venous return have been reported.[2] Hearing impairment was detected in 11% and ocular findings like myopia, hypermetropia, astigmatism, optic disc atrophy, and strabismus have been reported.[1]

In our study, focal caliectasis, bilateral vesicoureteral reflux, nephrocalcinosis, and left atrophic kidney were detected. Recently, a study mentioned menorrhagia and metrorrhagia in TRPS1 females above 16 years.[1] Similarly, our TRPS1 patient (P7) was followed-up long term due to menometrorrhagia. Cardiovascular defects were seen in two patients, and one of them underwent surgery due to pulmonary stenosis. There was a conductive hearing loss in three patients especially secondary to recurrent otitis media. Both TRPS1 and TRPS2 patients should be evaluated in terms of endocrinological, genitourinary, cardiological, audiological, and ophthalmological system. Menstrual irregularities should be assessed at the diagnosis or follow-up in TRPS females.

Genotype

No exact genotype–phenotype correlation in TRPS has yet been identified, except for TRPS2, which was associated with multiple exostoses and more marked intellectual disability. Nonsense and frameshift variants are the most common pathogenic variants in *TRPS1*. Missense variants clustering in exon six and intragenic and whole gene deletions with variable breakpoints have also been reported.[1,29,30] Lüdecke et al.[5] showed that most patients with nonsense *TRPS1* mutations have the less severe phenotype, whereas patients with missense mutations in the GATA-type zinc finger domain have more severe phenotype. Mutations in exon six might have more marked facial characteristics and shortening of hands and feet.[5] Consistent with the literature, P5 who had missense mutation in the GATA-type zinc finger domain had more severe brachydactyly. We observed that marked variability can be seen even in families with the same pathogenic variant. In familial TRPS1 patients (P6, P7) with a novel splice site mutation an intrafamilial clinical variability was observed. While P6 had severe short stature, his sister's (P7) height was normal. In addition, only a few TRPS2 patients without deletion of *TRPS1* gene have been reported, like our patients P3 and P4. It may be related to the proximal breakpoint being close to the *TRPS1* gene and the alteration of gene expression even if undamaged.[31]

In conclusion, a detailed clinical and radiological evaluation should be obtained in patients presenting with short stature, typical facial and skeletal findings, TRPS syndrome

should be considered. Genetic tests are needed to confirm the clinical diagnosis. Imagings of the central nervous system, and follow-ups of skeletal system are also recommended. Further research will help outlining the comorbidities and genotypic spectrum of patients.

Acknowledgement

The authors thank the Pamukkale University Hospital Medical Genetics Laboratory, and Intergen Genetics Center for performing the genetic analyses of the patients.

Ethical approval

This study was approved by the Ethics Committee of Akdeniz University (20.07.2022/KAEK-484).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: NÖ, BN; data collection: BN, HM, ÖYB, EM; analysis and interpretation of results: NÖ, BN, HM, GK, GOÇ; draft manuscript preparation: NÖ, BN, HM. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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