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Trichorhinophalangeal Syndrome

Synonym: Tricho-Rhino-Phalangeal Syndrome (TRPS)

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Summary

Clinical characteristics

Trichorhinophalangeal syndrome (TRPS) comprises TRPS I (caused by a heterozygous pathogenic variant in *TRPS1*) and TRPS II (caused by a contiguous gene deletion of *TRPS1*, *RAD21*, and *EXT1*). Both TRPS types are characterized by distinctive facial features (large nose with broad nasal ridge and tip and underdeveloped alae; thick and broad medial eyebrows; long philtrum; thin vermilion of the upper lip; and large prominent ears); ectodermal features (fine, sparse, depigmented, and slow-growing hair and dystrophic nails); and skeletal findings (short stature, brachydactyly with ulnar or radial deviation of the fingers, short feet, and early, marked hip dysplasia). TRPS II is additionally characterized by multiple osteochondromas and an increased risk of mild-to-moderate intellectual disability.

Diagnosis/testing

The clinical diagnosis of TRPS can be established in a proband with characteristic facial features, ectodermal and joint manifestations, and skeletal findings of cone-shaped epiphyses. The molecular diagnosis of TRPS I is established in an individual with suggestive findings and identification of a heterozygous pathogenic variant in *TRPS1*; the molecular diagnosis of TRPS II is established in an individual with suggestive findings and a contiguous 8q23.3-q24.11 deletion that includes *TRPS1*, *RAD21*, and *EXT1*.

Management

Treatment of manifestations: Management of TRPS is principally supportive. Practical advice on hair care and use of wigs; consider extraction of supernumerary teeth; consider growth hormone (GH) therapy in those with short stature and GH deficiency; occupational therapy can benefit fine motor skills; analgesics (e.g., NSAIDs or other non-opiods) for joint pain; physiotherapy may relieve pain and aid mobility; encourage regular exercise; support with mobility at school and work as needed; consider prosthetic hip implantation in those with severe hip dysplasia; sunlight exposure, adequate dietary intake of calcium and vitamin D, and/or calcium and vitamin D

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supplementation; modify activities to prevent fractures; consider bisphosphonates in those with osteopenia; treatment of cardiac anomalies per cardiologist; peer support and psychological counseling if indicated. In those with TRPS II, consider resection of symptomatic osteochondromas; developmental and educational support.

Surveillance: Monitor linear growth and assess for joint manifestations at each visit throughout childhood; assess for frequent fractures at each visit; DXA scan as needed in those with suspected osteopenia. In those with TRPS II, radiographs of osteochondromas when symptomatic and at the end of puberty. In those with a clinical diagnosis of TRPS (of unknown molecular cause) and those with TRPS II, developmental assessment annually throughout childhood.

Agents/circumstances to avoid: High-impact or contact sports may pose a risk to those with impaired mobility.

Genetic counseling

TRPS is inherited in an autosomal dominant manner. Many individuals with TRPS I have an affected parent; about one third of affected individuals have the disorder as the result of a *de novo* pathogenic variant. Most individuals with TRPS II whose parents have undergone genetic testing have the disorder as the result of a *de novo* contiguous 8q23.3-q24.11 deletion. Each child of an individual with TRPS has a 50% chance of inheriting the TRPS-related genetic alteration. Once the TRPS-related genetic alteration has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

Trichorhinophalangeal Syndrome: Included Phenotypes
• Trichorhinophalangeal dysplasia type I • Trichorhinophalangeal dysplasia type II (Langer-Giedion syndrome)

For synonyms and outdated names see Nomenclature.

Diagnosis

No consensus diagnostic criteria for trichorhinophalangeal syndrome (TRPS) have been published.

TRPS includes TRPS I (caused by a heterozygous pathogenic variant in *TRPS1*) and TRPS II (caused by deletion of the contiguous genes *TRPS1*, *RAD21*, and *EXT1*).

Suggestive Findings

TRPS should be suspected in individuals with the following clinical, radiographic, and family history findings.

Clinical Findings

TRPS I and TRPS II

- **Characteristic facial features.** Most distinctive (and possibly unique) is the large nose with broad nasal ridge and tip, underdeveloped alae, and (on occasion) a broad nasal septum. Other findings include thick and broad medial eyebrows, long philtrum, thin vermilion of the upper lip, and large prominent ears (see Figure 1A and 1B).
- **Ectodermal features** are fine, sparse, depigmented, and slow-growing hair, dystrophic nails, and small breasts (see Figure 1B).
- **Skeletal findings** include short stature, brachydactyly with ulnar or radial deviation of the fingers (see Figure 2), short feet, and early, marked hip dysplasia.

TRPS II only

- **Multiple osteochondromas** are typically first observed clinically on the scapulae and around the elbows and knees between ages one month and six years (see Figure 1C).
- **Intellectual disability,** if present, is typically mild to moderate.

Radiographic Findings

TRPS I and TRPS II

- **Cone-shaped epiphyses** are present in almost all individuals with TRPS; detectable at an early age (typically after age two years) when the epiphyses are just forming, and most frequently occurring in the middle phalanges, although they may occur in any phalanx of the hands and feet (see Figure 3 and Figure 4) [Vaccaro et al 2005].
- In individuals with **hip dysplasia**, Perthes-like lesions such as flat (coxa plana) or irregular femoral head, as well as narrowing of the joint space and subchondral sclerosis (See Figure 5.)
- **Secondary joint degeneration,** characterized by narrowing of the joint space and subchondral sclerosis; in addition to the hip, the fingers and very rarely other joints may also be affected [Maas et al 2015, de Barros & Kakehasi 2016, Güneş et al 2023].

TRPS II only

- **Multiple osteochondromas.** Exostoses arising from the metaphyses of long bones that may be sessile (flat) or pedunculated and directed away from the joint; most common around the elbows and knees, but other joints can be involved; commonly observed on the scapulae (See Figure 6.)

Family History

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

Clinical diagnosis. The clinical diagnosis of TRPS can be established in a proband with typical clinical findings including characteristic facial features, ectodermal manifestations, and skeletal findings including cone-shaped epiphyses.

Molecular diagnosis. The diagnosis of TRPS **is established** in a proband with suggestive findings who has **one of the following** on molecular genetic testing (see Table 1):

- **TRPS I.** A heterozygous pathogenic (or likely pathogenic) variant in *TRPS1*
- **TRPS II.** A heterozygous deletion of 8q23.3-q24.11 that spans the *TRPS1-EXT1* interval

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *TRPS1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **single-gene testing** or **chromosomal microarray analysis (CMA)** depending on the phenotype.

TRPS I

- **Single-gene testing.** Sequence analysis of *TRPS1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is

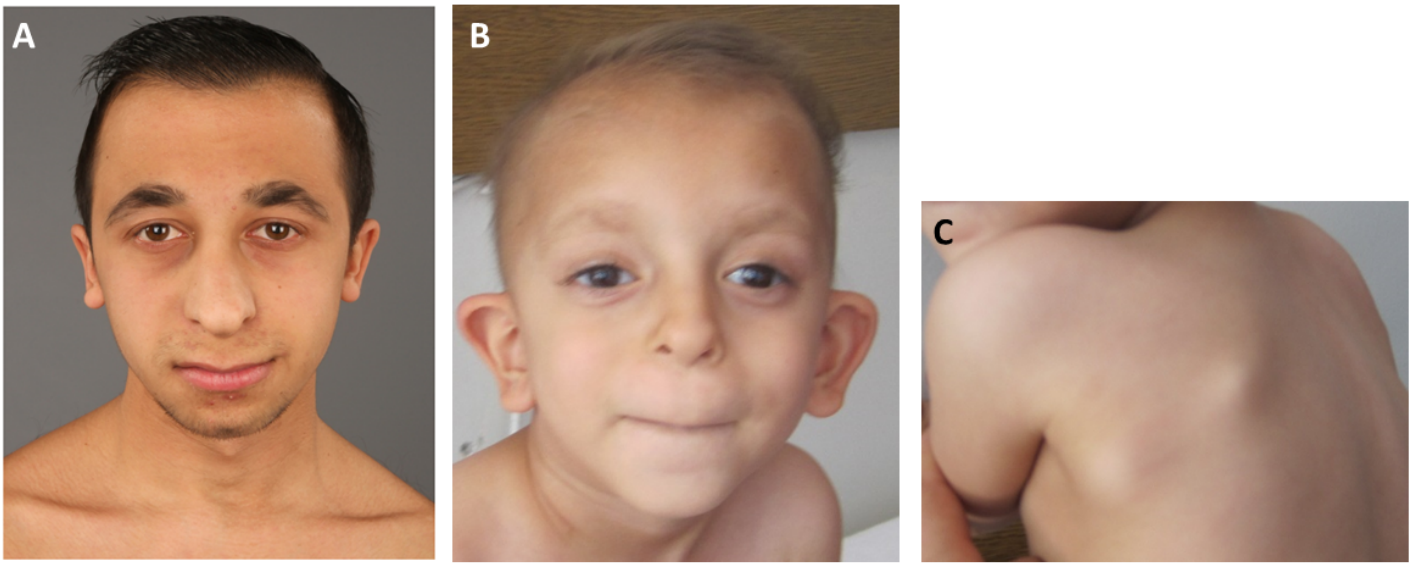

Figure 1. Clinical features of TRPS I and TRPS II

A. Facial features of a male age 16 years with TRPS I. Note the broad nasal ridge and nasal tip without a broad nasal bridge; underdeveloped alae nasi; wide and low-hanging columella; long philtrum; and medial flaring of the eyebrows.

B. Facial features of a boy (at age six years) with TRPS II. Note the sparse, light-colored, and broad medial eyebrows; sparse and thin hair; broad nasal tip; broad columella; long philtrum; thin vermilion of the upper lip; and large, prominent ears.

C. Exostoses on the shoulder

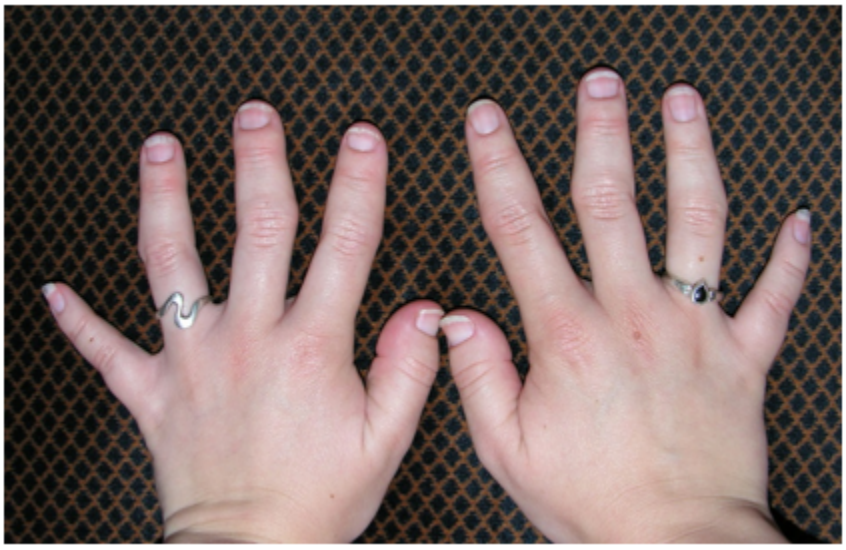

Figure 2. Hands of a woman age 21 years with TRPS

Note metacarpal shortening, ulnar deviation of the third fingers, radial deviation of the fourth fingers, and short thumbs.

detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

- **Karyotype** may be considered to detect an apparently balanced translocation or inversion involving 8q24.

TRPS II

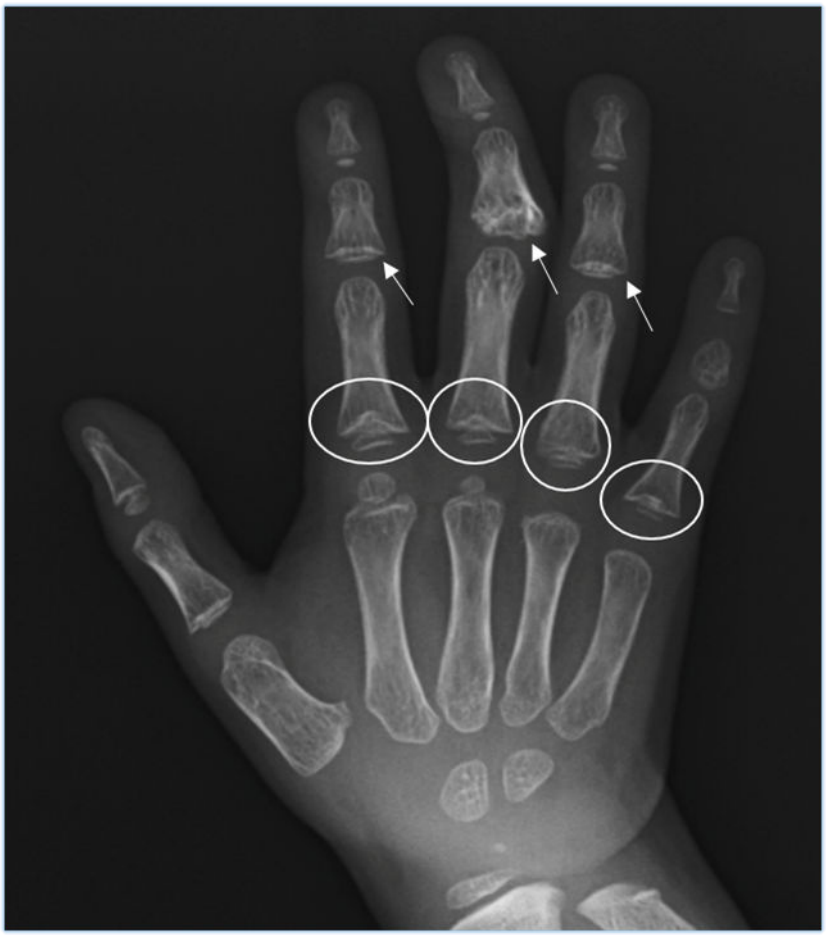

Figure 3. AP radiograph of the hand of a boy age four years with TRPS

Note cone-shaped epiphyses of the second to fifth proximal phalanges (circles) and more subtle, partially fused cone-shaped epiphyses of the second to fourth middle phalanges (arrows).

- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *TRPS1*, *RAD21*, *EXT1*) that cannot be detected by sequence analysis.

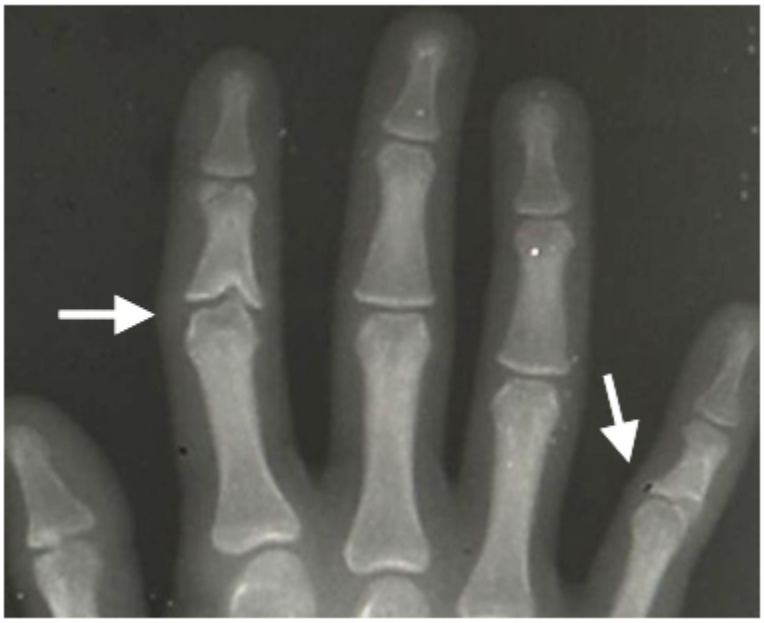

Figure 4. Residual angulated deformity of the proximal aspects of the second and fifth middle phalanges (arrows) related to fusion of prior cone-shaped epiphyses

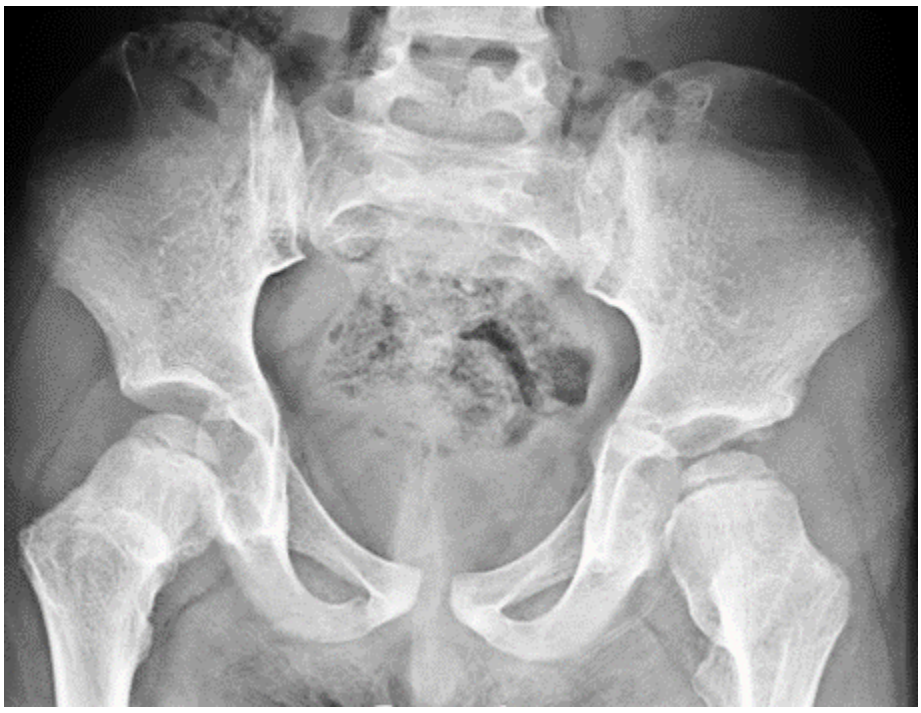

Figure 5. Flattened capital femoral epiphyses (coxa plana) and broad femoral neck in a boy with TRPS II (age six years)

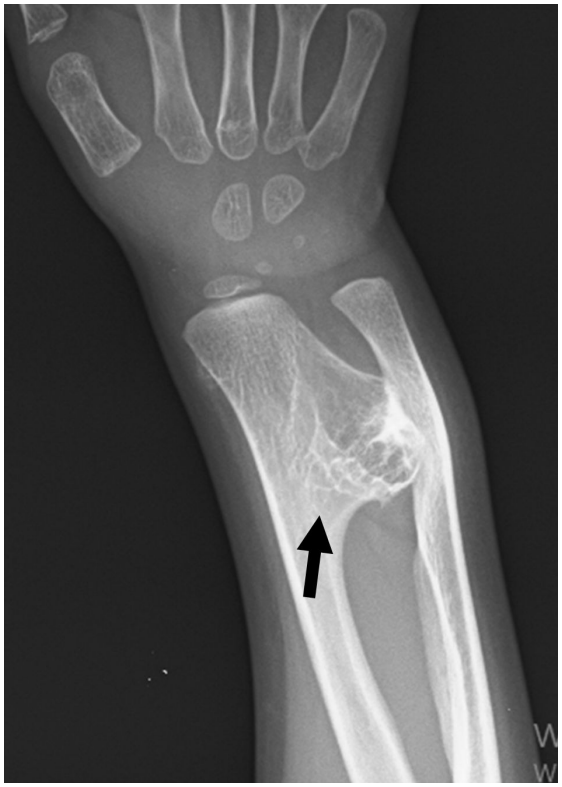

Figure 6. Exostosis of the radius (arrow)

Table 1. Molecular Genetic Testing Used in Trichorhinophalangeal Syndrome

Gene [1]	Phenotype	Method	Proportion of Pathogenic Variants [2] Identified by Method
TRPS1	TRPS I	Sequence analysis [3]	~81% [4]
		Gene-targeted deletion/ duplication analysis [5]	~7% [4]
		Karyotype (to detect structural variants)	~3% [4, 6]
	TRPS II	CMA [7]	~9% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Lüdecke et al [2001], Chen et al [2010], Maas et al [2015], Solc et al [2017], Wang et al [2020], Güneş et al [2023], and Öztürk et al [2023]. Data may be biased toward inclusion of more severely affected individuals (n=206).
5. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., contiguous deletion of *TRPS1*, *RAD21*, *EXT1*) may not be detected by these methods.
6. Chromosome 8 inversions have been reported in two individuals with TRPS I, inv(8)(q13:q24.1) and inv(8)(q21.1:q24.1) [Maas et al 2015]. Other inversions and translocations involving this region of chromosome 8 have also been reported [Lüdecke et al 2001, David et al 2013, Crippa et al 2014, Lei et al 2020].
7. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *TRPS1*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 8q24 region. CMA designs in current clinical use target the 8q24 region.

Clinical Characteristics

Clinical Description

Trichorhinophalangeal syndrome (TRPS) comprises TRPS I (caused by a heterozygous pathogenic variant in *TRPS1*) and TRPS II (caused by contiguous gene deletion of *TRPS1*, *RAD21*, and *EXT1*). Both types of TRPS are characterized by distinctive facial features, ectodermal features (fine, sparse, depigmented, and slow-growing hair, dystrophic nails, and small breasts), and skeletal findings (short stature, short feet, brachydactyly with ulnar or radial deviation of the fingers, and early, marked hip dysplasia). TRPS II is additionally characterized by multiple osteochondromas (typically first observed clinically on the scapulae and around the elbows and knees between ages one month and six years) and an increased risk of mild-to-moderate intellectual disability (see Table 2).

The largest cohort of individuals with TRPS reported to date includes 103 affected individuals from a large European collaborative study [Maas et al 2015]. This study and other studies [Giedion et al 1973, Lüdecke et al 2001, Güneş et al 2023] demonstrate that the phenotype of TRPS I within a family can vary markedly, and variability can be seen in all clinical and radiographic features.

Table 2. Trichorhinophalangeal Syndrome: Frequency of Select Features

Feature		% of Persons w/Feature [1]		
		TRPS I (n=133)	TRPS II (n=22)	Both TRPS I & II (n=155)
Characteristic facial features		~100%	~100%	~100%
Ectodermal features	**Sparse hair**	>85%	70%-80%	>85%
	Abnormal nails	40%-50%	~50%	40%-50%
Skeletal features	**Short stature**	40%-50%	~80%	50%-60%
	Cone-shaped epiphyses	>95%	~90%	>95%
	Brachydactyly	70%-80%	~60%	70%-80%
	Short metacarpals	>65%	~70%	>65%
	Hip dysplasia	~25%	~60%	~30%
	Osteopenia	~20%	25%-30%	~20%
	Osteochondromas	~0%	>85% [2]	~10%
Other	**Intellectual disability**	~10%	50%-60%	~15% [3]
	Microcephaly	<10%	50%-60%	10%-20% [3]
	Cardiac anomalies	~10%	~20%	~10%

1. Chen et al [2010], Maas et al [2015], Solc et al [2017], Wang et al [2020], Güneş et al [2023], Öztürk et al [2023]
2. Only occurs in TRPS II; due to *EXT1* deletion in those with TRPS II
3. Significantly more common in those with TRPS II

Facial Features

Characteristic facial features that are similar in both TRPS I and TRPS II include a large nose, broad nasal ridge and tip, underdeveloped alae, long philtrum, thin vermilion of the upper lip, and large, prominent ears. Other craniofacial features include a high forehead, a broad nasal septum, a horizontal smile, narrow, high-arched palate, micrognathia, and a horizontal chin furrow. Clear differences can be observed in the parts of the

eyebrow: the medial eyebrow is almost always denser and wider than the lateral eyebrow [Lüdecke et al 2001, Vaccaro et al 2005, Maas et al 2015, Güneş et al 2023].

Ectodermal Features

Scalp hair. Almost all affected individuals have fine and sparse hair from a young age, particularly marked in the frontotemporal region [Jeon et al 2014, Wang et al 2020]. Scalp hair is typically slow growing and brittle. Hair color is frequently light, although it is not known if this is an associated finding.

One third of males lose their hair completely or almost completely within a few years of puberty. Women typically have more hair, but a high anterior hairline is common.

Variability exists and some individuals have near-normal scalp hair, and in some individuals the thickness and quality of hair improves with time.

Nails are thin and dystrophic in about half of individuals with TRPS; nail changes are more notable in the feet than the hands.

Teeth. Supernumerary teeth and malocclusion may be present. In addition, delayed eruption of the primary dentition and microdontia have been reported in a few individuals [Maas et al 2015].

Small breasts. Small breasts were found in four of 15 females (36%) [Maas et al 2015].

Skeletal Features

Short stature. Reduced linear growth is common in individuals with TRPS and is progressive [Lüdecke et al 2001, Maas et al 2015]. Lüdecke et al [2001] reported that birth length in 16 individuals was within the normal range, and the height z score of 28 adults with TRPS I was lower (-1.29) than that of 34 children (-0.96). Short stature was reported in 40%-50% of individuals with TRPS I and in 80% of individuals with TRPS II [Maas et al 2015, Güneş et al 2023, Öztürk et al 2023]. In individuals with a *TRPS1* pathogenic variant reported between 1999 and 2023, 45.3% had short stature. The height z score for those with short stature was -3.27, compared to -0.87 for individuals without short stature.

There are a few reports of growth hormone deficiency in individuals with TRPS [Levy-Shraga et al 2020, Huang et al 2022a].

Joint manifestations. Short hands and feet are common in both TRPS I and TRPS II, typically with uneven shortening of one or more metacarpals or metatarsals and swelling of the proximal interphalangeal joints resulting in characteristic clinobrachydactyly [Lüdecke et al 2001]. Deviation of the phalanges and limited mobility of the small joints, which can be confused with rheumatoid arthritis, is very common [Maas et al 2015, Solc et al 2017, Öztürk et al 2023].

Hip dysplasia occurs especially in individuals with TRPS II, typically in pre-adolescence and early adulthood [Maas et al 2015, Grace & Ashby 2023]. By age 30 years, implantation of a prosthetic hip may be necessary. Degenerative skeletal changes can also be present in the cervical spine, knees, and ankles [Izumi et al 2010].

Delayed skeletal maturation has also been described [de Barros & Kakehasi 2016]. Note: Even in individuals with marked epiphyseal involvement, bone age can usually be determined reliably using the large number of unaffected epiphyses to assess skeletal maturation.

Osteopenia may be present in individuals with TRPS I and TRPS II but is likely more common in those with TRPS II. Reduced bone mass was described in two individuals with TRPS I [Stagi et al 2008]. Severe osteoporosis is reported in some affected individuals [Shao et al 2011, Macchiaiolo et al 2014].

Multiple osteochondromas occur only in individuals with TRPS II due to the deletion of *EXT1*. Osteochondromas usually occur between age one month and six years. They first appear clinically on the shoulder blades and around the elbows and knees. The reported incidence of osteochondromas (85% in those with TRPS II) may be biased by the inclusion of very young individuals [Maas et al 2015]. The natural history is the same as seen in hereditary multiple osteochondromas [Hennekam 1991].

Psychomotor Development

The proportion of individuals with TRPS I with mild intellectual disability is reported to be slightly higher than in the general population. However, more than half of individuals with TRPS II have mild-to-moderate intellectual disability [Maas et al 2015, Güneş et al 2023]. Delays in motor development are usually associated with hip dysplasia and are therefore likely to be secondary [Maas et al 2015].

Other

Body weight is usually normal in relation to height.

Head circumference is typically normal throughout life in individuals with TRPS I. In those with TRPS II, 50%-60% of individuals have a head circumference below the 3rd centile [Lüdecke et al 2001, Maas et al 2015, Güneş et al 2023, Öztürk et al 2023].

Cardiac abnormalities vary from minor anomalies (persistent ductus arteriosus, persistent foramen ovale, bicuspid aortic valves, mitral valve regurgitation) to significant problems (aortic stenosis, anomalous venous return). Cardiac rhythm disturbances are rare.

Genotype-Phenotype Correlations

There is no clear genotype-phenotype correlation in TRPS I. However, missense variants have been reported to be associated with a more severe phenotype such as significant brachydactyly and severe short stature [Lüdecke et al 2001, Maas et al 2015, Wang et al 2020, Güneş et al 2023, Öztürk et al 2023]. Phenotypic variability is also observed within and between families with the same *TRPS1* pathogenic variant [Giedion et al 1973, Lüdecke et al 2001, Maas et al 2015].

The size of the minimal critical region responsible for the phenotypic features of TRPS II has been reported to be around 3 Mb [Favilla et al 2022, Güneş et al 2023]. In TRPS II, no correlation was found between the size of the deleted segment and the severity of intellectual disability [Favilla et al 2022].

Penetrance

No instances of reduced penetrance have been reported; thus, penetrance is believed to be 100% [Lüdecke et al 2001].

Nomenclature

It has been suggested that individuals with severe short stature and brachydactyly may have a distinguishable phenotype called TRPS III [Lüdecke et al 2001]. However, this term is no longer in use as this phenotype is now considered to be within the spectrum of TRPS I [Maas et al 2015].

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], TRPS caused by a heterozygous pathogenic variant in *TRPS1* is referred to as trichorhinophalangeal dysplasia types 1/3. TRPS caused by a contiguous 8q23.3-q24.11 deletion spanning the *TRPS1-EXT1* interval is referred to as Langer-Giedion syndrome (trichorhinophalangeal dysplasia type 2).

Prevalence

There are no population-based estimates of the prevalence of TRPS. To date, 350 affected individuals have been reported [Orphanet Report Series 2023]. However, since most individuals with TRPS I do not have intellectual disability or short stature, the prevalence of TRPS I may be higher than assumed because some individuals remain undiagnosed.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TRPS1*.

Phenotypes associated with germline pathogenic variants in *EXT1* or *RAD21* are summarized in Table 3.

Table 3. Genetically Related (Allelic) Disorders

Gene	Disorder	Comment
EXT1	Hereditary multiple osteochondromas (HMO)	*EXT1*-related HMO is not assoc w/ID or the characteristic craniofacial, ectodermal, & digital manifestations seen in TRPS.
RAD21	Cornelia de Lange syndrome (CdLS)	Persons w/*RAD21*-related CdLS often display growth restriction & minor skeletal anomalies that overlap w/TRPS. *RAD21*-related CdLS is not assoc w/the characteristic craniofacial, ectodermal, & joint manifestations of TRPS.

ID = intellectual disability; TRPS = trichorhinophalangeal syndrome

Differential Diagnosis

Trichorhinophalangeal syndrome (TRPS) is often considered in the differential diagnosis of disorders with abnormalities of the hair, nose, and limbs (see Table 4).

Table 4. Disorders of Interest in the Differential Diagnosis of Trichorhinophalangeal Syndrome

Gene / Genetic Mechanism	Disorder	MOI	Features of Disorder:	
			Overlapping w/TRPS	Distinguishing from TRPS
DYNC2H1 *DYNC2LI1* *EVC* *EVC2* *GLI* *PRKACA* *PRKACB* *SMO* *WDR35*	Ellis-van Creveld syndrome	AR AD [1]	• Short stature • Brachydactyly	• Nasal shape • Oral frenula • Polydactyly
EXT1 *EXT2*	Hereditary multiple osteochondromas	AD	Multiple osteochondromas	• Absence of ID • Absence of characteristic craniofacial & digital anomalies assoc w/TRPS II.
FBN1	Acromicric dysplasia (OMIM 102370)	AD	• Short stature • Brachydactyly • Cone-shaped epiphyses	• Round face • Long eyelashes • Anteverted nostrils • Thickened skin • Absence of sparse hair

Table 4. continued from previous page.

Gene / Genetic Mechanism	Disorder	MOI	Features of Disorder:	
			Overlapping w/TRPS	Distinguishing from TRPS
GJA1	Oculodentodigital syndrome (OMIM 164200 & 257850)	AD AR	• Slow-growing, dry hair • Underdeveloped alae nasi • Long philtrum	• Ocular manifestations • Distinct dental anomalies: enamel hypoplasia, tooth agenesis, microdontia
GNAS	Pseudohypoparathyroidism (See Disorders of *GNAS* Inactivation.)	AD	• Short stature • Brachydactyly • Cone-shaped epiphyses • ID	• Ectopic ossifications • ↑ serum PTH level, hypocalcemia, hyperphosphatemia
POC1A	Short stature, onychodysplasia, facial dysmorphism, & hypotrichosis (SOFT) syndrome (OMIM 614813)	AR	• Short stature • Brachydactyly • Prominent nose • Cone-shaped epiphyses • Sparse hair • Dental anomalies	• Intrauterine growth restriction • Long, triangular face
PPP2R3C	Myoectodermal gonadal dysgenesis syndrome (OMIM 618419)	AR	• Short stature • Thick eyebrows • Large nose • Hypoplastic alae nasi • Long philtrum • Prominent ears	• Gonadal dysgenesis • Wide nasal bridge
RMRP	Cartilage-hair hypoplasia – anauxetic dysplasia spectrum disorders	AR	• Fine hair • Cone-shaped epiphyses • Short stature	• Nasal shape • Immunodeficiency

AD = autosomal dominant; AR = autosomal recessive; ID = intellectual disability; MOI = mode of inheritance; PTH = parathyroid hormone; TRPS = trichorhinophalangeal syndrome

1. Ellis-van Creveld (EVC) syndrome caused by pathogenic variants in *DYNC2H1*, *DYNC2LI1*, *EVC*, *EVC2*, *GLI*, *SMO*, or *WDR35* is inherited in an autosomal recessive manner. EVC syndrome caused by pathogenic variants in *PRKACA* or *PRKACB* (accounting for 2% of affected individuals) is inherited in an autosomal dominant manner.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and support needs of an individual diagnosed with trichorhinophalangeal syndrome (TRPS), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Trichorhinophalangeal Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Ectodermal	Dental exam for supernumerary teeth	
Skeletal	• Measurement of height • Radiographs of hands, feet, pelvis, & hips, if joint pain, swelling, &/or limited mobility are present	In those w/osteopenia on radiographs, further investigation for low bone mineral density may be warranted (e.g., DXA scan, serum calcium, phosphorus, magnesium, & referral to endocrinologist for mgmt of bone health)
	Assessment of osteochondromas by orthopedic specialist for evidence of functional limitation	In those w/TRPS II

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Development	Developmental assessment	In younger persons w/clinical diagnosis of TRPS (of unknown molecular cause) & in all children w/TRPS II
Endocrinologic	Eval for GH deficiency	In those w/short stature
Cardiac	Cardiac eval incl echocardiogram	At diagnosis
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of TRPS to facilitate medical & personal decision making

DXA = dual-energy x-ray absorptiometry; GH = growth hormone; MOI = mode of inheritance; TRPS = trichorhinophalangeal syndrome
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management of TRPS is principally supportive (see Table 6).

Table 6. Trichorhinophalangeal Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Sparse hair	• Practical advice on hair care & use of wigs • Topical minoxidil treatment & hair transplantation may be useful. [1]	
Dental	Extraction of supernumerary teeth can be considered.	
Short stature	Human GH therapy may be considered in those w/ short stature & proven GH deficiency. [2]	Results of treatment vary. Although some persons have accelerated growth w/GH treatment, some do not show ↑ growth velocity despite GH treatment.
Limited mobility of digits	• OT can be beneficial for fine motor impairment. • Mechanical aids such as electric can openers may ameliorate problems caused by joint anomalies.	In a single report resection arthrodesis w/ tension band osteosynthesis stabilized painful ulnar dislocation of the proximal interphalangeal joints in digits w/cone-shaped epiphyses. [3] Of note, no follow-up or other similar reports are available.

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Hip dysplasia	• Analgesics (e.g., NSAIDs or other non-opioids) • Physiotherapy can help relieve pain & maintain hip range of motion. • Encourage regular exercise. • Support w/mobility at school & work as needed	High-impact or contact sports may pose a risk to those w/impaired mobility.
	Prosthetic hip implantation should be considered in those w/severe hip dysplasia.	Prosthetic hip implantation may be required as early as age 30 yrs. Such prostheses may require multiple revisions due to their limited life span. Obtaining functional improvement through prosthetic joint surgery can be challenging given the presence of damage to other joints, either in the form of TRPS-related osteoarthritis-like changes or secondary to long-term compensatory stress.
Osteopenia	• Recommendations for sunlight exposure • Ensure adequate dietary intake of calcium & vitamin D &/or calcium & vitamin D supplementation. • Modify activities to prevent fractures. • Consider bisphosphonates.	
Osteochondromas (assoc w/ TRPS II)	For osteochondromas assoc w/pain, restricted range of motion, or nerve compression, resection should be considered.	See Hereditary Multiple Osteochondromas.
Intellectual disability (assoc w/ TRPS II)	Developmental support & educational services	
Cardiac anomalies	Treatment per cardiologist	
Psychosocial	Peer support & (if indicated) psychological counseling for persons who are self-conscious about their physical differences	

GH = growth hormone; NSAIDs = nonsteroidal anti-inflammatory drugs; OT = occupational therapy; TRPS = trichorhinophalangeal syndrome

1. Topical minoxidil treatment was reported to improve hair density and length in one individual with TRPS [Choi et al 2024]; however, generalized hypertrichosis was also reported in one individual after nine months of minoxidil treatment [Shin et al 2023]. Hair transplantation was performed successfully in one individual [Choi et al 2018].

2. When the growth pattern of a child with TRPS is below the normal range for age and sex and is of concern to the family, growth hormone (GH) stimulation tests can be performed. If the result is subnormal, GH therapy may be considered [Marques et al 2015, Huang et al 2022a] despite reported variable results.

3. Brenner et al [2004]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended.

Table 7. Trichorhinophalangeal Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Skeletal	• Monitor linear growth. • Assess for joint manifestations.	At each visit throughout childhood
	Assess for frequent fractures.	At each visit
	DXA scan	As needed in those w/suspected osteopenia
	Radiographs of symptomatic osteochondromas	In those w/TRPS II when symptomatic & at the end of puberty (when normal growth of osteochondromas has ceased) to provide a baseline for any future changes.
Development	Developmental assessment	Annually throughout childhood in persons w/clinical diagnosis of TRPS (of unknown molecular cause) & in all children w/TRPS II

DXA = dual-energy x-ray absorptiometry; TRPS = trichorhinophalangeal syndrome

Agents/Circumstances to Avoid

High-impact or contact sports may pose a risk to those with impaired mobility.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. To date, there are no therapies under investigation.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Trichorhinophalangeal syndrome (TRPS) is inherited in an autosomal dominant manner.

- TRPS I is caused by a heterozygous pathogenic variant in *TRPS1*.
- TRPS II is caused by a contiguous 8q23.3-q24.11 deletion that spans the *TRPS1-EXT1* interval.

Risk to Family Members – TRPS I

Parents of a proband

- Many individuals diagnosed with TRPS I have an affected parent. Although the TRPS I phenotype can vary markedly within a family [Giedion et al 1973, Lüdecke et al 2001, Maas et al 2015], a clinical diagnosis is usually possible in affected individuals (see Clinical Description).
- Approximately one third of individuals diagnosed with TRPS I have the disorder as the result of a *de novo* pathogenic variant.

- If the proband appears to be the only affected family member (i.e., a simplex case), recommendations for the evaluation of parents of a proband include complete physical examination, radiologic studies of hands and feet, and molecular genetic testing to evaluate the genetic status of the parents and inform recurrence risk assessment.

  Note: If the proband has a structural variant involving *TRPS1* (e.g., a chromosome 8 inversion), chromosome analysis of the parents is recommended.

- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism [Corsini et al 2014]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

- The family history of some individuals diagnosed with TRPS I may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing have been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%. The phenotype of TRPS I can vary markedly among affected family members, and variability can be seen in all clinical and radiographic features [Lüdecke et al 2001, Maas et al 2015, Güneş et al 2023, Öztürk et al 2023].
- If a parent has a structural chromosome rearrangement involving the 8q23.3 region, the risk to sibs is increased. The estimated risk depends on the specific chromosome rearrangement.
- If the *TRPS1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. Somatic and germline mosaicism in an unaffected parent has been reported [Corsini et al 2014].
- If the parents have not been tested for the *TRPS1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low but still increased over that of that of the general population because of the possibility of parental germline mosaicism [Corsini et al 2014].

Offspring of a proband. Each child of an individual with TRPS I has a 50% chance of inheriting the *TRPS1* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *TRPS1* pathogenic variant, the parent's family members may be at risk.

Risk to Family Members – TRPS II

Parents of a proband

- To date, most individuals diagnosed with TRPS II whose parents have undergone genetic testing have the disorder as the result of a *de novo* contiguous 8q23.3-q24.11 deletion.
- Some individuals diagnosed with TRPS II have an affected parent. The phenotype within a family can vary but only to a limited extent; however, a clinical diagnosis of TRPS II is usually possible in affected individuals (see Clinical Description).

- Evaluation of the parents by genomic testing that will detect the deletion present in the proband is recommended to confirm their genetic status and to allow reliable recurrence risk counseling. Testing for a balanced chromosome rearrangement in the parents is also recommended.
- If the deletion identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* deletion.
  - The proband inherited a deletion from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a deletion that is present in the germ (gonadal) cells only.
- The family history of some individuals diagnosed with TRPS II may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or genomic testing have been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or has the genetic alteration identified in the proband, the risk to the sibs is 50%. The TRPS II phenotype within a family can vary but only to a limited extent.
- If a parent has a balanced structural chromosome rearrangement, the risk to sibs is increased and depends on the specific chromosome rearrangement and the possibility of other variables.
- If neither parent is found to have the deletion identified in the proband and parental chromosome analysis is normal, the recurrence risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the possibility of parental germline mosaicism. To date this has not been reported.
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but greater than that of the general population because of the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with TRPS II has a 50% chance of inheriting the 8q23.3-q24.11 deletion.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has an TRPS-related genetic alteration or chromosome rearrangement, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of having a child with TRPS.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022b].

Prenatal Testing and Preimplantation Genetic Testing

Once the TRPS-related genetic alteration has been identified in an affected family member, prenatal and preimplantation genetic testing (PGT) are possible. Note: While prenatal testing and PGT can be used to detect a

familial genetic alteration associated with TRPS, the severity of the TRPS I or TRPS II phenotype cannot be predicted on the basis of test results.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, a discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Trichorhinophalangeal syndrome type I
- **MedlinePlus**
  Trichorhinophalangeal syndrome type II

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Trichorhinophalangeal Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
EXT1	8q24.11	Exostosin-1	EXT1 gene database	EXT1	EXT1
RAD21	8q24.11	Double-strand-break repair protein rad21 homolog	RAD21 database	RAD21	RAD21
TRPS1	8q23.3	Zinc finger transcription factor Trps1	TRPS1 database	TRPS1	TRPS1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Trichorhinophalangeal Syndrome (View All in OMIM)

150230	TRICHORHINOPHALANGEAL SYNDROME, TYPE II; TRPS2
190350	TRICHORHINOPHALANGEAL SYNDROME, TYPE I; TRPS1
604386	TRANSCRIPTIONAL REPRESSOR, GATA-BINDING 1; TRPS1
606462	RAD21 COHESIN COMPLEX COMPONENT; RAD21
608177	EXOSTOSIN GLYCOSYLTRANSFERASE 1; EXT1

Molecular Pathogenesis

TRPS1 encodes the zinc finger transcription factor Trps1 (TRPS1), which represses GATA-regulated genes and binds to a dynein light chain protein. TRPS1 consists of nine zinc finger domains, seven classic and two Ikaros-like zinc finger domains, as well as a cysteine-rich and a GATA-like zinc finger region. Binding of the encoded

protein to the dynein light chain protein impairs binding to GATA consensus sequences and represses its transcriptional activity. In addition, TRPS1 can also activate the transcription of target genes by binding to promoters [Yang et al 2022]. TRPS1 plays a role in various cellular processes such as bone mineralization, chondrocyte differentiation, and hair follicle development by mediating various signaling pathways such as osteocalcin, PTHrP, and Sox9/STAT3/Wnt/β-catenin.

TRPS1, *RAD21*, and *EXT1* are located on chromosomes 8q23.3-q24.11 (within ~2.8 Mb). While loss-of-function variants in *TRPS1* lead to TRPS I, the contiguous gene deletion of *TRPS1*, *RAD21*, and *EXT1* causes TRPS II.

To date, 166 different *TRPS1* pathogenic variants associated with TRPS have been reported in the Human Gene Mutation Database (HGMD). Of these pathogenic variants, 94 (56.6%) are truncating variants (including nonsense [21.7%], frameshift [32.5%], and splice variants [2.4%]), 31 (18.7%) are missense variants, 30 (18.1%) are gross deletions, two are gross insertions, and nine are complex rearrangements. With the exception of four missense variants, all missense variants are located in exons 6 and 7. Missense variants in *TRPS1* are associated with more severe phenotypes, including pronounced short stature and brachydactyly [Lüdecke et al 2001, Maas et al 2015, Wang et al 2020, Güneş et al 2023, Öztürk et al 2023].

Most phenotypic features of TRPS II are explained by the deletion of *TRPS1* and *EXT1*. The minimal critical region responsible for TRPS II spans approximately 3.2 Mb encompassing the *TRPS1-EXT1* interval [Favilla et al 2022]. However, the larger the deletion and the greater the number of genes deleted outside the minimal critical region, the more likely additional features (e.g., cognitive dysfunction, epilepsy) will occur [Chen et al 2013, Maas et al 2015]. Haploinsufficiency of *RAD21*, which lies between *TRPS1* and *EXT1*, may contribute to more severe manifestations, particularly cognitive impairment. The features of isolated *RAD21* deletions have not been identified in individuals with TRPS II and are therefore likely to be very limited.

Mechanism of disease causation. Loss of function (haploinsufficiency)

Note: Missense variants are predicted to exhibit a dominant-negative effect as a part of a multimeric protein complex, unlike the haploinsufficiency (loss of function) associated with truncating variants [Lüdecke et al 2001].

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