



Trichorhinophalangeal Syndrome

Synonym: Tricho-Rhino-Phalangeal Syndrome (TRPS)

Saskia Maas, MD,¹ Adam Shaw, BM, MD,² Hennie Bikker, PhD,³ and Raoul CM Hennekam, PhD, MD⁴

Created: April 20, 2017.

Summary

Clinical characteristics

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 characterized by multiple osteochondromas (typically first observed clinically on the scapulae and around the elbows and knees between ages 1 month and 6 years) and an increased risk of mild-to-moderate intellectual disability.

Diagnosis/testing

The diagnosis of TRPS is established in a proband with one of the following:

- Typical clinical findings including facial features, ectodermal manifestations, and distal limb anomalies and radiographic findings of cone-shaped epiphyses
- Suggestive findings of TRPS I and identification of a heterozygous pathogenic variant in *TRPS1*
- Suggestive findings of TRPS II and a contiguous 8q23.3-q24.11 deletion that includes *TRPS1*, *RAD21*, and *EXT1*

Management

Treatment of manifestations: Management is principally supportive. Ectodermal issues: advice about hair care and use of wigs; extraction of supernumerary teeth can be considered. Skeletal issues: in those with short stature with and without proven growth hormone deficiency, use of human growth hormone therapy has had variable results; the mainstay treatment of joint pain is use of analgesics (e.g., NSAIDs or other non-opiates);

Author Affiliations: 1 Departments of Clinical Genetics and Pediatrics, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; Email: s.m.maas@amc.uva.nl. 2 Guy's & Saint Thomas' Hospitals London, United Kingdom; Email: adam.shaw@gstt.nhs.uk. 3 Department of Clinical Genetics, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; Email: h.bikker@amc.uva.nl. 4 Department of Pediatrics, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; Email: r.c.hennekam@amc.uva.nl.

physiotherapy may aid mobility; occupational therapy can benefit fine motor skills/tasks; prosthetic hip implantation should be considered in those with severe hip dysplasia.

Surveillance: For TRPS I and TRPS II: routine monitoring of linear growth and psychomotor developmental in childhood. For TRPS II only: x-ray evaluation of osteochondromas when symptomatic and at the end of puberty (when normal growth of osteochondromas has ceased) to provide a baseline for comparison with any future enlargement

Genetic counseling

TRPS is inherited in an autosomal dominant manner.

- TRPS I. Many individuals with TRPS I have an affected parent; the exact proportion of TRPS I caused by a *de novo* pathogenic variant is unknown. Each child of an individual with TRPS I has a 50% chance of inheriting the *TRPS1* pathogenic variant.
- TRPS II. Most individuals with TRPS II have the disorder as the result of a *de novo* contiguous gene deletion of *TRPS1*, *RAD21*, and *EXT1*. Each child of an individual with TRPS II has a 50% chance of inheriting the contiguous gene deletion.
- TRPS I and TRPS II. Once the genetic alteration causative of TRPS has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

Trichorhinophalangeal Syndrome: Included Phenotypes
<ul style="list-style-type: none"> • Trichorhinophalangeal syndrome I • Trichorhinophalangeal syndrome 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 and radiographic findings.

Clinical

TRPS I and TRPS II

- **Characteristic facial features.** Most distinctive (and possibly unique) is the large nose with a broad ridge and tip, underdeveloped alae, and (on occasion) a broad septum. Other findings are: thick and broad eyebrows, a long philtrum with thin upper vermilion, and large prominent ears (see Figure 1).
- **Ectodermal features** include fine, sparse, depigmented, and slow-growing hair; dystrophic nails; and small breasts.
- **Skeletal findings** include short stature; short feet; brachydactyly with ulnar or radial deviation of the fingers (see Figure 2); 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.
- **Intellectual disability**, if present, is typically mild to moderate.

Radiographic

TRPS I and TRPS II

- Cone-shaped epiphyses. Present in almost all individuals with TRPS; detectable at an early age (typically after age 2 years) when 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, Figure 4) [Vaccaro et al 2005]
- Hip deformities such as coxa vara, coxa plana, and coxa magna
- Secondary joint degeneration, characterized by joint space narrowing and subchondral sclerosis; involving hips more commonly than fingers but may be found in almost any joint [de Barros & Kakehasi 2016]

TRPS II only

- Multiple osteochondromas. Exostoses arising from the metaphyses of long bones which 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 5)

Establishing the Diagnosis

The diagnosis of TRPS is **established** in a proband with:

- Typical clinical findings including facial features, ectodermal manifestations, and distal limb anomalies, and radiographic findings of cone-shaped epiphyses; OR
- Suggestive findings of TRPS I and identification of a heterozygous pathogenic variant in *TRPS1* (see Table 1); OR
- Suggestive findings of TRPS II and a contiguous 8q23.3q24.11 deletion that spans the *TRPS1-EXT1* interval (see Table 1).

Molecular genetic testing is often not required to make the diagnosis, as the phenotype is often marked and distinct. When the clinical presentation is mild or atypical, molecular confirmation can be helpful.

If molecular genetic testing is indicated, the approaches vary by phenotype:

- **TRPS I: single-gene testing.** Sequence analysis of *TRPS1* is performed first. If no pathogenic variant is detected, either chromosomal microarray analysis (CMA) or gene-targeted deletion/duplication analysis is indicated to determine if the clinical findings are caused by a mild presentation of TRPS II. If no pathogenic variant is identified, karyotype may be considered to detect an apparently balanced translocation or inversion involving 8q24.
- **TRPS II: chromosomal microarray analysis (CMA)** using either array comparative genomic hybridization or SNP arrays

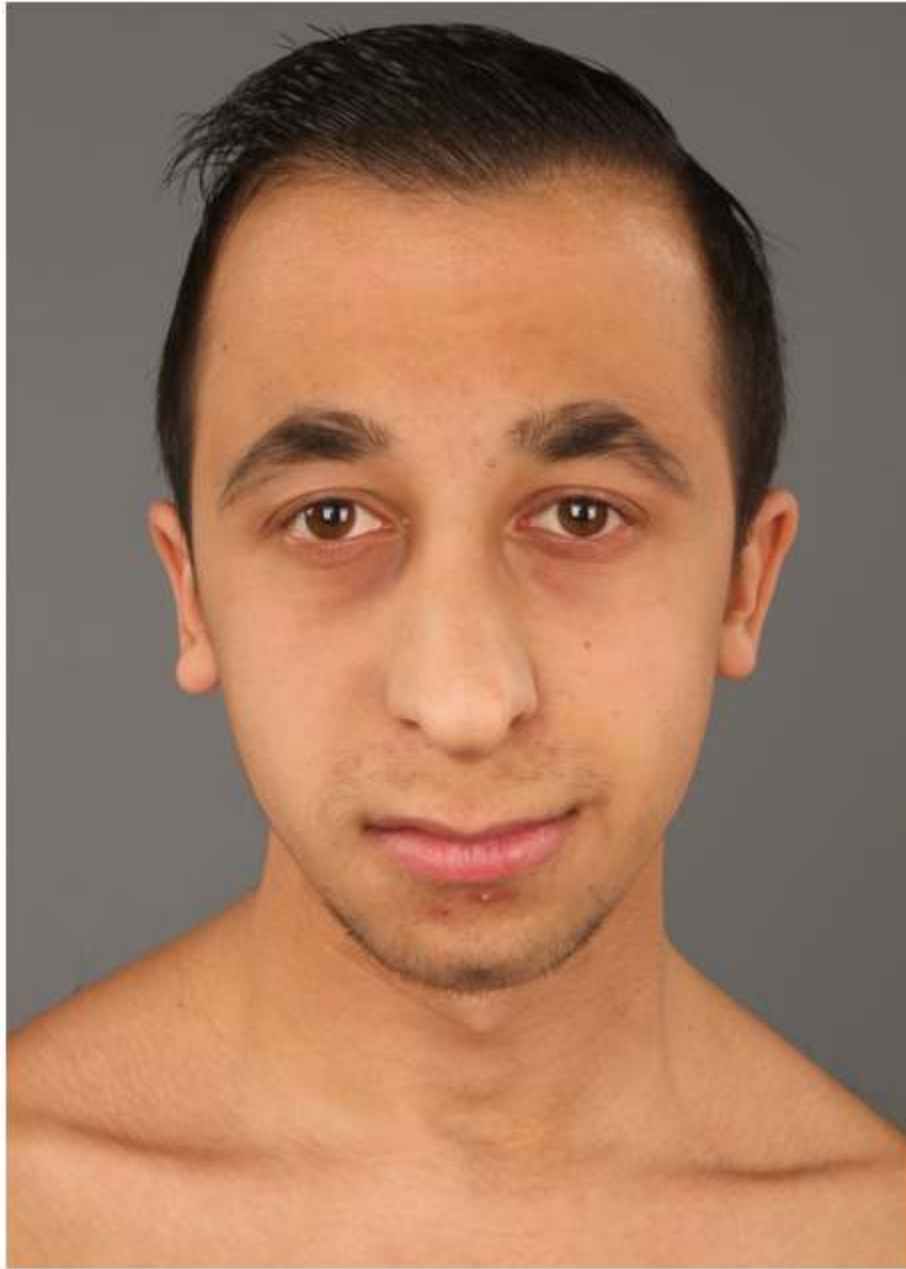


Figure 1. Facial features of a male age 16 years. Note the broad nasal ridge and tip without broadening of the nasal bridge. The alae nasi are underdeveloped; the columella is wide and low hanging; the philtrum is smooth. Some medial flaring of the eyebrows.



Figure 2. Hands of a woman age 21 years. Note metacarpal shortening and ulnar deviation of the third fingers, radial deviation of the fourth fingers, and short thumbs.



Figure 3. Frontal radiograph of the hand of a male age four years. Note the coned epiphyses of the third to fifth proximal phalanges (circles), and more subtle, partially fused coned epiphyses of the second to fourth middle phalanges (arrows).



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. Exostosis of the humerus (arrow)

Table 1. Molecular Genetic Testing Used in Trichorhinophalangeal Syndrome

Gene ¹	Phenotype	Method	Proportion of Probands with a Pathogenic Variant ^{2, 3} Detectable by Method
<i>TRPS1</i>	TRPS I	Sequence analysis ⁴	83/103 ⁵
		Gene-targeted deletion/duplication analysis ⁶	4/103 ⁵
		Karyotype (to detect structural variants)	2/103 ^{5, 7}
	TRPS II	CMA ⁸	14/103 ⁵

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic variants detected in this gene.

3. Note: The total number of individuals with TRPS reported is relatively small and may represent the severe end of the clinical spectrum. The estimated proportion of pathogenic variants detected by each method may change over time.

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

5. Maas et al [2015]. These data are similar to those of a different, earlier study of 51 affected individuals [Lüdecke et al 2001]; however, both series are likely biased toward inclusion of more severely affected individuals.

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

7. Two individuals with chromosome 8 inversions – inv(8) (q13q24.1) and inv(8) (q21.1q24.1) – were detected. Other inversions and balanced translocations involving this region of chromosome 8 have also been reported [Lüdecke et al 2001, David et al 2013, Crippa et al 2014].

8. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 8q24 region. Note: The 8q24 deletion may not have been detectable by older oligonucleotide or BAC platforms.

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 characterized by multiple osteochondromas (typically first observed clinically on the scapulae and around the elbows and knees between ages 1 month and 6 years) and an increased risk of mild-to-moderate intellectual disability.

The largest cohort of individuals with TRPS reported to date is the 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] demonstrate that the phenotype of TRPS I within a family can vary markedly. The variability is present in all findings: face morphology, ectodermal signs, growth, and clinical and radiographic findings.

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]. 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 hair line is usual.

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

Eyebrows. The eyebrows are typically densely implanted (thick) and broad nasally, particularly in TRPS II. Marked differences can be observed within the various parts of an eyebrow: the medial part is almost invariably more densely implanted and broader than the middle or lateral parts.

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 can be present.

Skeletal Features

Short stature. Reduced linear growth is common in TRPS, especially in those with TRPS II. It is more marked postnatally than prenatally.

Short hands and feet are common in both TRPS I and TRPS II, with typically uneven shortening of one or more metacarpal/tarsals and swelling of the proximal interphalangeal joints resulting in a characteristic clinobrachydactyly [Lüdecke et al 2001]. Impaired small joint mobility, which may be mistaken for rheumatoid arthritis, is very common in individuals over age 40 years.

The main long-term morbidity associated with TRPS is the early osteoarthritis-like changes affecting the large joints, especially the hips, leading to pain and decreased mobility from adolescence or early adulthood [Rué et al 2011, Maas et al 2015]. Degenerative skeletal changes can also be present in the cervical spine, knees, and ankles [Izumi et al 2010].

Delayed skeletal maturation is also 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 both TRPS types, but is likely more common in 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 (i.e., those with a deletion encompassing *EXT1*). They usually present between ages one month and six years; the natural history is the same as seen in [multiple osteochondromas](#) [Hennekam 1991].

Psychomotor Development

The proportion of individuals with TRPS I with intellectual disability is similar to that in the general population; in contrast, two thirds of individuals with TRPS II have mild-to-moderate intellectual disability.

Delay in motor development is usually associated with hip dysplasia and, 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 except for those with TRPS II, one third of whom have a head circumference below the 3rd centile [Lüdecke et al 2001].

Cardiac abnormalities, present in 15% of individuals with TRPS, 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

No genotype-phenotype correlations are evident in TRPS I. Marked variability is observed within and among families with the same *TRPS1* pathogenic variant [Giedion et al 1973, Lüdecke et al 2001, Maas et al 2015].

Four of the five missense pathogenic variants identified by Lüdecke et al [2001] altered the GATA DNA-binding zinc finger, and six of the seven unrelated individuals with these pathogenic variants had more marked short stature in what appeared to be a distinguishable phenotype, which was designated TRPS III. However, this term is no longer in use as this phenotype is now considered to be within the spectrum of TRPS I [Lüdecke et al 2001, Maas et al 2015].

Penetrance

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

Nomenclature

Individuals with sparse hair, unusual facial features (predominantly in the shape of the nose), and anomalies of the distal limbs were first described by the Dutch physician Van der Werff ten Bosch [1959].

Giedion suggested the name tricho-rhino-phalangeal syndrome because of the triad of most prominent features [Giedion 1966].

Affected individuals who also had developmental delay and multiple osteochondromas were described almost simultaneously by Langer [1969] and Gorlin et al [1969].

Hall et al [1974] suggested subdivision of TRPS into TRPS I for individuals with normal development and absent osteochondromas, and TRPS II or Langer-Giedion syndrome for those with intellectual disability and multiple osteochondromas.

TRPS III, a term coined by Niikawa & Kamei [1986] to describe what appeared to be a TRPS phenotype characterized by marked short stature, is no longer in use as this finding is now considered to be within the phenotypic spectrum of TRPS I.

Prevalence

Unbiased population-based estimates of the prevalence of TRPS are not available. TRPS may frequently remain undiagnosed. Nonetheless, the condition is probably rare, with a prevalence of 0.2-1 per 100,000.

TRPS is seen in all ethnic groups.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *TRPS1* or contiguous gene deletions that include *TRPS1*.

When *RAD21* (which is upstream of *EXT1*) is deleted the phenotype can resemble [Cornelia de Lange syndrome](#) [Deardorff et al 2012, Chen et al 2013, Ansari et al 2014].

In TRPS II the phenotype is typically dominated by the deletion of *TRPS1* and *EXT1*; the external phenotypic characteristics that occur with isolated *RAD21* deletions are not clearly observed in TRPS II; however, some contribution cannot be excluded at present.

Differential Diagnosis

TRPS is often considered in the differential diagnosis of disorders with abnormalities of the hair, nose, and limbs.

Table 2. Disorders to Consider in the Differential Diagnosis of Trichorhinophalangeal Syndrome

Disorder	Gene(s)	MOI	Clinical Features of the Differential Disorder	
			Overlapping w/TRPS	Distinguishing from TRPS
Oculo-dento-digital syndrome	<i>GJA1</i>	AD	<ul style="list-style-type: none"> • Slow-growing, dry hair • Underdeveloped alae nasi • Long philtrum 	<ul style="list-style-type: none"> • Eye signs • Dental signs more expressed
Cartilage-hair syndrome	<i>RMRP</i>	AR	<ul style="list-style-type: none"> • Short stature • Fine hair • Cone-shaped epiphyses 	<ul style="list-style-type: none"> • Nasal shape • Immunodeficiency
Ellis-Van Creveld syndrome	<i>EVC</i> <i>EVC2</i>	AR	<ul style="list-style-type: none"> • Short stature • Brachydactyly 	<ul style="list-style-type: none"> • Nasal shape • Oral frenula • Polydactyly

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and support needs of an individual diagnosed with trichorhinophalangeal syndrome (TRPS), the following should be evaluated.

For TRPS I and TRPS II

- Measurement of height
- Developmental assessment, at younger age for both TRPS I and TRPS II as the distinction may clinically not yet be possible. At an older age, only for TRPS II
- X-rays of hands, feet, pelvis, and hip, if symptomatic
- If evidence of osteopenia on x-ray, further investigation of bone mineral density and metabolism may be warranted
- Dental examination for supernumerary teeth
- Cardiac evaluation (once)
- Consultation with a clinical geneticist and/or genetic counselor

For TRPS II only

- Review of osteochondromas by an orthopedic specialist for evidence of functional limitation
- Evaluation of vision and hearing as is recommended in all persons with intellectual disability of any cause

Treatment of Manifestations

Management of TRPS is principally supportive.

Ectodermal Features

Hair. Practical advice on hair care and the use of wigs can be beneficial.

Dental. Extraction of supernumerary teeth can be considered [Kantaputra et al 2008, Lubinsky & Kantaputra 2016].

Skeletal

Short stature. In those with short stature and proven growth hormone deficiency, human growth hormone therapy may be considered; however, reported results vary. Treatment has infrequently led to an increase in growth velocity [Riedl et al 2004, Stagi et al 2008, Sarafoglou et al 2010, Sohn et al 2012].

Note: 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 stimulation tests can be performed. If the result is subnormal, GH therapy may be considered [Marques et al 2015] despite reported variable results.

Hands. In a single report resection arthrodesis with tension band osteosynthesis stabilized painful ulnar dislocation of the proximal interphalangeal (PIP) joints in digits with cone-shaped epiphyses [Brenner et al 2004]. Of note, no follow-up or other similar reports are available.

Joint pain. Regular simple analgesia (e.g., NSAID or other non-opiates) is the mainstay treatment for joint pain.

Physiotherapy may aid mobility. Exercise is to be encouraged, but high-impact or contact sports may pose a risk to those with already impaired mobility. Patients may require support with mobility at school and work.

Occupational therapy can benefit many fine-motor tasks and mechanical aids such as electric can openers may ameliorate problems caused by joint anomalies.

Prosthetic hip implantation should be considered in those with severe hip dysplasia. Prosthetic hip implantation may be required as early as age 30 years. 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. Bisphosphonates can be considered in individuals with TRPS I and bone fragility [Macchiaiolo et al 2014].

Other. Peer support and (if indicated) psychological counseling can be beneficial for individuals who are self-conscious about their physical differences.

For TRPS II Only

Exostoses. In case of clinical problems such as pain, restricted range of motion, or nerve compression, resection of exostoses should be considered [Payne et al 2016]. See [Hereditary Multiple Osteochondromas](#).

Surveillance

For TRPS I and TRPS II

- Monitor linear growth in childhood
- Routine developmental assessments in childhood

For TRPS II only. X-ray evaluation of osteochondromas when symptomatic and at the end of puberty (when normal growth of osteochondromas has ceased) to provide a baseline for comparison with any future enlargement

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](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face 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 deletion of the contiguous genes *TRPS1*, *RAD21*, and *EXT1* on chromosome 8.

Risk to Family Members – TRPS I

Parents of a proband

- Many individuals diagnosed with TRPS I have an affected parent. Although the 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 each affected individual (see Clinical Description).
- Because simplex cases (i.e., a single occurrence in a family) have not been evaluated sufficiently to determine if the *TRPS1* pathogenic variant occurred *de novo*, the exact proportion of TRPS I caused by a *de novo* pathogenic variant is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant (i.e., neither parent is known to be affected) include molecular genetic testing for the pathogenic variant identified in the proband, complete physical examination, and radiologic studies of hands and feet.
- If the *TRPS1* pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or parental mosaicism. Somatic and germline mosaicism in an unaffected parent has been reported [Corsini et al 2014]. A reliable estimate of the frequency is not available; based on the authors' experience, the frequency is low (<2%).
- The family history of some individuals with TRPS I may appear to be negative because of failure to recognize the disorder clinically in family members or early death of the parent before clinical findings are recognized. 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 genetic status of the proband's parents:

- If a parent of the proband is affected, the risk to the sibs is 50%. The phenotype within a family can vary markedly [Giedion et al 1973, Lüdecke et al 2001, Maas et al 2015].
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.

- If the *TRPS1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is greater than 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 is affected, his or her family members may be at risk.

Risk to Family Members – TRPS II

Parents of a proband

- Most individuals diagnosed with TRPS II have the disorder as the result of a *de novo* contiguous gene deletion of *TRPS1*, *RAD21*, and *EXT1*. Because simplex cases (i.e., a single occurrence in a family) have not been evaluated sufficiently to determine if the deletion occurred *de novo*, the exact proportion of TRPS II caused by a *de novo* deletion is unknown.
- 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 is usually possible in each affected individual (see Clinical Description).
- Evaluation of the parents by genomic testing that will detect the deletion present in the proband is recommended.
- If the deletion found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* deletion in the proband or germline mosaicism in a parent. Although no instances of parental germline mosaicism have been reported, it remains a theoretic possibility.
- 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.
- Note: If the parent is the individual in whom the deletion first occurred, s/he may have somatic mosaicism for the deletion and may be mildly/minimally affected. To date only one instance of somatic mosaicism has been reported in an individual with a molecularly confirmed diagnosis [Shanske et al 2008].

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, the risk to the sibs is 50%. The phenotype within a family can vary but only to a limited extent.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the deletion found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism. To date this has not been reported.

Offspring of a proband. Each child of an individual with TRPS II has a 50% chance of inheriting the contiguous gene deletion of *TRPS1*, *RAD21*, and *EXT1*.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, his or her family members may be at risk.

Related Genetic Counseling Issues

Prediction of phenotype. Because of intrafamilial clinical variability, it is not possible to predict the severity of the phenotype in family members who have inherited a *TRPS1* pathogenic variant or deletion that includes

TRPS1 (except that all individuals with a deletion that includes *EXT1* as well will develop multiple exostoses, i.e., TRPS type II).

Considerations in families with an apparent *de novo* genetic alteration. When neither parent of a proband with an autosomal dominant condition has the genetic alteration identified in the proband or clinical evidence of the disorder, the genetic alteration is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

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 is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the genetic alteration causative of TRPS 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, 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, 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](#).

- **National Library of Medicine Genetics Home Reference**
[Langer-Giedion syndrome](#)

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
<i>EXT1</i>	8q24.11	Exostosin-1	EXT1 gene database	EXT1	EXT1
<i>RAD21</i>	8q24.11	Double-strand-break repair protein rad21 homolog		RAD21	RAD21

Table A. continued from previous page.

<i>TRPS1</i>	8q23.3	Zinc finger transcription factor Trps1	TRPS1 homepage - LOVD - Australian Human Variome Project	<i>TRPS1</i>	<i>TRPS1</i>
--------------	--------	--	--	--------------	--------------

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	ZINC FINGER TRANSCRIPTION FACTOR TRPS1; TRPS1
606462	RAD21 COHESIN COMPLEX COMPONENT; RAD21
608177	EXOSTOSIN GLYCOSYLTRANSFERASE 1; EXT1

Molecular Pathogenesis

TRPS1, *RAD21*, and *EXT1* are located on chromosome 8q23.3-8q24.11 (within ~2.8 Mb). Single-nucleotide variants (missense, nonsense, small deletions) in *TRPS1* cause trichorhinophalangeal syndrome type I (TRPS I), while larger deletions that include *TRPS1*, *RAD21*, and *EXT1* cause TRPS II. Most of the phenotypic features of TRPS II are explained by deletion of *TRPS1* and *EXT1*. However, the larger the deletion and the more genes that are deleted outside the interval *TRPS1* – *EXT1*, the more likely that additional features (e.g., disturbance of cognitive functions) will be present [Lüdecke et al 1999]. Haploinsufficiency of *RAD21*, located between *TRPS1* and *EXT1*, may contribute to more severe features, especially disturbed cognitive functioning. Characteristics of isolated *RAD21* deletions are not identified in the physical appearance of individuals with TRPS II and, thus, are likely very limited.

TRPS1

Gene structure. *TRPS1* spans approximately 260 kb and contains seven exons, of which six are coding exons.

Pathogenic variants. More than 130 pathogenic variants in *TRPS1* have been reported. A list of *TRPS1* pathogenic variants can be found in Maas et al [2015]. The number of recurrent pathogenic variants is low.

Identified pathogenic variants include heterozygous missense variants in exons 6 and 7 of *TRPS1*.

The other pathogenic variants are nonsense variants (small deletions/duplications, premature stop codons, splice variants) located anywhere in the coding sequences.

Whole-gene deletions are common; breakpoints can be variable

Table 3. *TRPS1* Pathogenic Variants Discussed in This GeneReview

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1010_1014dup	p.(Cys339GlnfsTer27)	NM_014112.4 NP_054831.2
c.1093C>T	p.Gln365Ter	
c.1105C>T	p.Gln369Ter	
c.1176dup	p.Asn393Ter	
c.1231dup	p.(Gln411ProfsTer11)	

Table 3. continued from previous page.

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1460del	p.(Lys487SerfsTer13)	
c.1630C>T	p.Arg544Ter	
c.1870C>T	p.Arg624Ter	
c.1882C>T	p.Gln628Ter	
c.2094C>A	p.Tyr698Ter	
c.(2096+1_2097-1)_(2700+1_2701-1)dup	?	
c.(2096+1_2097-1)_(2700+1_2701-1)del	?	
c.2179_2180del	p.(Val727SerfsTer29)	
c.2355_2356del	p.(Lys786GlyfsTer14)	
c.2394dup	p.(Ser799GlnfsTer2)	
c.2557C>T	p.Arg853Ter	
c.(2700+1_2701-1)_(*_?)del	?	
c.2731A>T	p.(Asn911Tyr)	
c.2732A>G	p.(Asn911Ser)	
c.2756T>C	p.(Leu919Pro)	
c.2761C>T	p.Arg921Ter	
c.2762G>C	p.(Arg921Pro)	
c.2762G>A	p.(Arg921Gln)	
c.2783_2784insC	p.(Val929CysfsTer22)	
c.2794G>A	p.(Ala932Thr)	
c.2795C>T	p.(Ala932Val)	
c.2801G>T	p.(Gly934Val)	
c.2823+1G>T	?	
c.2824-23T>G	?	
c.(2823+1_2824-1)_(*1_?)del	?	
c.2852_2859dup	p.(Gly954LysfsTer43)	
c.2981_2984del	p.(Glu994GlyfsTer7)	
c.2893C>T	p.(Arg965Cys)	
c.2894G>A	p.(Arg965His)	
c.3077del	p.(Ser1026ThrfsTer27)	
c.3140del	p.(Pro1047LeufsTer6)	
c.3424del	p.(Ser1142ValfsTer36)	
inv(8)(q13q24.1)	?	
Inv(8)(q21.1q24.1)	?	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

Normal gene product. *TRPS1* encodes a 1294-amino acid transcription factor that represses GATA-regulated genes and binds to a dynein light chain protein. Binding of the encoded protein to the dynein light chain protein affects binding to GATA consensus sequences and suppresses its transcriptional activity.

Abnormal gene product. Heterozygous *TRPS1* pathogenic variants cause trichorhinophalangeal syndrome type I (TRPS I).

EXT1

Gene structure. *EXT1* spans about 312 kb and has 11 coding exons that together encode a protein of 746 amino acids. One transcript is known; [NM_000127.2](#) (2241 nucleotides). *EXT1* is located distal to *TRPS1* and large deletions involving *TRPS1* and *EXT1* cause TRPS II.

Abnormal gene product. The role of *EXT1* in individuals with hereditary multiple osteochondromas, is also discussed in the *GeneReview* on [hereditary multiple osteochondromas](#) (previously called hereditary multiple exostoses).

RAD21

Gene structure. *RAD21* spans about 29 kb, has 14 (13 coding and 1 noncoding) exons that together encode a protein of 631 amino acids. One transcript is known; [NM_006265.2](#) (1896 nucleotides). *RAD21* is located between *TRPS1* and *EXT1*.

Abnormal gene product. Heterozygous pathogenic variants in *RAD21* cause Cornelia de Lange syndrome-4 (CDLS4). Dominant missense variants in *RAD21* result in more severe functional defects and more severe clinical features than loss-of-function variants or deletions. Only whole-gene deletions are relevant in the scope of TRPS.

References

Literature Cited

- Ansari M, Poke G, Ferry Q, Williamson K, Aldridge R, Meynert AM, Bengani H, Chan CY, Kayserili H, Avci S, Hennekam RC, Lampe AK, Redeker E, Homfray T, Ross A, Falkenberg Smeland M, Mansour S, Parker MJ, Cook JA, Splitt M, Fisher RB, Fryer A, Magee AC, Wilkie A, Barnicoat A, Brady AF, Cooper NS, Mercer C, Deshpande C, Bennett CP, Pilz DT, Ruddy D, Cilliers D, Johnson DS, Josifova D, Rosser E, Thompson EM, Wakeling E, Kinning E, Stewart F, Flinter F, Girisha KM, Cox H, Firth HV, Kingston H, Wee JS, Hurst JA, Clayton-Smith J, Tolmie J, Vogt J, Tatton-Brown K, Chandler K, Prescott K, Wilson L, Behnam M, McEntagart M, Davidson R, Lynch SA, Sisodiya S, Mehta SG, McKee SA, Mohammed S, Holden S, Park SM, Holder SE, Harrison V, McConnell V, Lam WK, Green AJ, Donnai D, Bitner-Glindzicz M, Donnelly DE, Nellåker C, Taylor MS, FitzPatrick DR. Genetic heterogeneity in Cornelia de Lange syndrome (CdLS) and CdLS-like phenotypes with observed and predicted levels of mosaicism. *J Med Genet.* 2014;51:659–68. PubMed PMID: 25125236.
- Brenner P, Hinkel GK, Krause-Bergmann A. Surgical therapy of cone-shaped epiphyses of the proximal interphalangeal joints in tricho-rhino-phalangeal syndrome type I: a survey among three successive generations of a single family. *Zentralbl Chir.* 2004;129:460–9. PubMed PMID: 15616909.
- Chen CP, Lin SP, Liu YP, Chern SR, Wu PS, Su JW, Chen YT, Lee CC, Wang W. An interstitial deletion of 8q23.3-q24.22 associated with Langer-Giedion syndrome, Cornelia de Lange syndrome and epilepsy. *Gene.* 2013;529:176–80. PubMed PMID: 23933416.
- Corsini C, Gencik M, Willems M, Decker E, Sanchez E, Puechberty J, Schneider A, Girard M, Edery P, Bretonnes P, Cottalorda J, Lefort G, Jeandel C, Sarda P, Genevieve D. Somatic mosaicism in

- trichorhinophalangeal syndrome: a lesson for genetic counseling. *Eur J Hum Genet.* 2014;22:136–9. PubMed PMID: 23572024.
- Crippa M, Bestetti I, Perotti M, Castronovo C, Tabano S, Picinelli C, Grassi G, Larizza L, Pincelli AI, Finelli P. New case of trichorhinophalangeal syndrome-like phenotype with a de novo t(2;8)(p16.1;q23.3) translocation which does not disrupt the TRPS1 gene. *BMC Med Genet.* 2014;15:52. PubMed PMID: 24886451.
- David D, Marques B, Ferreira C, Araújo C, Vieira L, Soares G, Dias C, Pinto M. Co-segregation of trichorhinophalangeal syndrome with a t(8;13)(q23.3;q21.31) familial translocation that appears to increase TRPS1 gene expression. *Hum Genet.* 2013;132:1287–99. PubMed PMID: 23835950.
- Deardorff MA, Wilde JJ, Albrecht M, Dickinson E, Tennstedt S, Braunholz D, Mönnich M, Yan Y, Xu W, Gil-Rodríguez MC, Clark D, Hakonarson H, Halbach S, Michelis LD, Rampuria A, Rossier E, Spranger S, Van Maldergem L, Lynch SA, Gillissen-Kaesbach G, Lüdecke HJ, Ramsay RG, McKay MJ, Krantz ID, Xu H, Horsfield JA, Kaiser FJ. RAD21 mutations cause a human cohesinopathy. *Am J Hum Genet.* 2012;90:1014–27. PubMed PMID: 22633399.
- de Barros GM, Kakehasi AM. Skeletal abnormalities of tricho-rhino-phalangeal syndrome type I. *Rev Bras Reumatol Engl Ed.* 2016;56:86–9. PubMed PMID: 27267340.
- Giedion A. Das tricho-rhino-phalangeale Syndrom. *Helv Paediatr Acta.* 1966;21:475–85. PubMed PMID: 5991804.
- Giedion A, Burdea M, Fruchter Z, Meloni T, Trosc V. Autosomal-dominant transmission of the tricho-rhino-phalangeal syndrome. Report of 4 unrelated families, review of 60 cases. *Helv Paediatr Acta.* 1973;28:249–59. PubMed PMID: 4723882.
- Gorlin RJ, Cohen MM Jr, Wolfson J. Tricho-rhino-phalangeal syndrome. *Am J Dis Child.* 1969;118:595–9. PubMed PMID: 5820605.
- Hall BD, Langer LO, Giedion A, Smith DW, Cohen MM Jr, Beals RK, Brandner M. Langer-Giedion syndrome. *Birth Defects Orig Artic Ser.* 1974;10:147–64.
- Hennekam RC. Hereditary multiple exostoses. *J Med Genet.* 1991;28:262–6. PubMed PMID: 1856833.
- Izumi K, Takagi M, Parikh AS, Hahn A, Miskovsky SN, Nishimura G, Torii C, Kosaki K, Hasegawa T, Neilson D. Late manifestations of tricho-rhino-phalangeal syndrome in a patient: expanded skeletal phenotype in adulthood. *Am J Med Genet.* 2010;152A:2115–9. PubMed PMID: 20635356.
- Jeon J, Kim JH, Oh CH. Trichorhinophalangeal syndrome type I--clinical, microscopic, and molecular features. *Indian J Dermatol Venereol Leprol.* 2014;80:54–7. PubMed PMID: 24448126.
- Kantaputra P, Miletich I, Lüdecke HJ, Suzuki EY, Praphanphoj V, Shivdasani R, Wuelling M, Vortkamp A, Napierala D, Sharpe PT. Tricho-rhino-phalangeal syndrome with supernumerary teeth. *J Dent Res.* 2008;87:1027–31. PubMed PMID: 18946009.
- Langer LO Jr. The thoracic-pelvic-phalangeal dystrophy. *Birth Defects Orig Artic Ser.* 1969;5:55–64.
- Lubinsky M, Kantaputra PN. Syndromes with supernumerary teeth. *Am J Med Genet A.* 2016;170:2611–6. PubMed PMID: 27250821.
- Lüdecke HJ, Schaper J, Meinecke P, Momeni P, Gross S, von Holtum D, Hirche H, Abramowicz MJ, Albrecht B, Apacik C, Christen HJ, Claussen U, Devriendt K, Fastnacht E, Forderer A, Friedrich U, Goodship TH, Greiwe M, Hamm H, Hennekam RC, Hinkel GK, Hoeltzenbein M, Kayserili H, Majewski F, Mathieu M, McLeod R, Midro AT, Moog U, Nagai T, Niikawa N, Orstavik KH, Plöchl E, Seitz C, Schmidtke J, Tranebjaerg L, Tsukahara M, Wittwer B, Zabel B, Gillissen-Kaesbach G, Horsthemke B. Genotypic and phenotypic spectrum in tricho-rhino-phalangeal syndrome types I and III. *Am J Hum Genet.* 2001;68:81–91. PubMed PMID: 11112658.

- Lüdecke H-J, Schmidt O, Nardmann J, von Holtum D, Meinecke P, Münke M, Horsthemke B. Genes and chromosomal breakpoints in the Langer-Giedion syndrome region on human chromosome 8. *Hum Genet.* 1999;105:619–28. PubMed PMID: 10647898.
- Maas SM, Shaw AC, Bikker H, Lüdecke HJ, van der Tuin K, Badura-Stronka M, Belligni E, Biamino E, Bonati MT, Carvalho DR, Cobben J, de Man SA, Den Hollander NS, Di Donato N, Garavelli L, Grønberg S, Herkert JC, Hoogeboom AJ, Jamsheer A, Latos-Bielenska A, Maat-Kievit A, Magnani C, Marcelis C, Mathijssen IB, Nielsen M, Otten E, Ousager LB, Pilch J, Plomp A, Poke G, Poluha A, Posmyk R, Rieubland C, Silengo M, Simon M, Steichen E, Stumpel C, Szakszon K, Polonkai E, van den Ende J, van der Steen A, van Essen T, van Haeringen A, van Hagen JM, Verheij JB, Mannens MM, Hennekam RC. Phenotype and genotype in 103 patients with tricho-rhino-phalangeal syndrome. *Eur J Med Genet.* 2015;58:279–92. PubMed PMID: 25792522.
- Macchiaiolo M, Mennini M, Digilio MC, Buonuomo PS, Lepri FR, Gnazzo M, Grandin A, Angioni A, Bartuli A. Tricho-rhino-phalangeal syndrome and severe osteoporosis: a rare association or a feature? An effective therapeutic approach with bisphosphonates. *Am J Med Genet A.* 2014;164A:760–3. PubMed PMID: 24357341.
- Marques JS, Maia C, Almeida R, Isidoro L, Dias C. Should patients with trichorhinophalangeal syndrome be tested for growth hormone deficiency? *Pediatr Endocrinol Rev.* 2015;13:465–7. PubMed PMID: 26540763.
- Niikawa N, Kamei T. Letter to the Editor: The Sugio-Kajii syndrome, proposed tricho-rhino-phalangeal syndrome type III. *Am J Med Genet* 1986; 24:759-60.
- Payne R, Sieg E, Fox E, Harbaugh K, Rizk E. Management of nerve compression in multiple hereditary exostoses: a report of two cases and review of the literature. *Childs Nerv Syst.* 2016;32:2453–58. PubMed PMID: 27444292.
- Riedl S, Giedion A, Schweizer K, Müllner-Eidenbröck A, Grill F, Lüdecke HJ. 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 Part A.* 2004;131:200–3. PubMed PMID: 15523607.
- Rué M, Lüdecke H-J, Sibon I, Richez C, Taine L, Foubert-Samier A, Arveiler B, Schaefferbeke T, Lacombe D, Tison F, Goizet C. Rheumatologic and neurological events in an elderly patient with tricho-rhino-phalangeal syndrome type I. *Eur J Med Genet.* 2011;54:e405–8. PubMed PMID: 21524721.
- Sarafoglou K, Moassesfar S, Miller BS. Improved growth and bone mineral density in type I trichorhinophalangeal syndrome in response to growth hormone therapy. *Clin Genet.* 2010;78:591–3. PubMed PMID: 20569260.
- Shanske AL, Patel A, Saukam S, Levy B, Lüdecke H-J. Clinical and molecular characterization of a patient with Langer-Giedion Syndrome and mosaic del(8)(q22.3q24.13). *Am J Med Genet A.* 2008;146A:3211–16. PubMed PMID: 19012352.
- Shao C, Tian J, Shi DH, Yu CX, Xu C, Wang LC, Gao L, Zhao JJ. A novel mutation in TPRS1 gene caused tricho-rhino-phalangeal syndrome in a Chinese patient with severe osteoporosis. *Chin Med J (Engl).* 2011;124:1583–5. PubMed PMID: 21740822.
- Sohn YB, Ki CS, Park SW, Cho SY, Ko AR, Kwon MJ, Kim JY, Park HD, Kim OH, Jin DK. Clinical, biochemical, and genetic analysis of two Korean patients with trichorhinophalangeal syndrome type I and growth hormone deficiency. *Ann Clin Lab Sci.* 2012;42:307–12. PubMed PMID: 22964620.
- Stagi S, Bindi G, Galluzzi F, Lapi E, Salti R, Chiarelli F. Partial growth hormone deficiency and changed bone quality and mass in type I trichorhinophalangeal syndrome. *Am J Med Genet A.* 2008;146A:1598–604. PubMed PMID: 18478599.
- Vaccaro M, Guarneri C, Blandino A. Trichorhinophalangeal syndrome. *J Am Acad Dermatol.* 2005;53:858–60. PubMed PMID: 16243138.

Van der Werff ten Bosch JJ. The syndrome of brachymetacarpal dwarfism [“pseudo-pseudo-hypoparathyroidism”] with and without gonadal dysgenesis. *Lancet*. 1959;1:69–71. PubMed PMID: 13621640.

Chapter Notes

Revision History

- 20 April 2017 (bp) Review posted live
- 20 September 2016 (rh) Original submission

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (<http://www.genereviews.org/>) and copyright (© 1993-2020 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the [GeneReviews® Copyright Notice and Usage Disclaimer](#). No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the [GeneReviews® Copyright Notice and Usage Disclaimer](#).

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.