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Autosomal Dominant *TRPV4* Disorders

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Summary

Clinical characteristics

The autosomal dominant *TRPV4* disorders (previously considered to be clinically distinct phenotypes before their molecular basis was discovered) are now grouped into neuromuscular disorders and skeletal dysplasias; however, the overlap within each group is considerable. Affected individuals typically have either neuromuscular or skeletal manifestations alone, and in only rare instances an overlap syndrome has been reported.

The three autosomal dominant neuromuscular disorders (mildest to most severe) are:

- Charcot-Marie-Tooth disease type 2C
- Scapuloperoneal spinal muscular atrophy
- Congenital distal spinal muscular atrophy

The autosomal dominant neuromuscular disorders are characterized by a congenital-onset, static, or later-onset progressive peripheral neuropathy with variable combinations of laryngeal dysfunction (i.e., vocal fold paresis), respiratory dysfunction, and joint contractures.

The six autosomal dominant skeletal dysplasias (mildest to most severe) are:

- Familial digital arthropathy-brachydactyly
- Autosomal dominant brachyolmia
- Spondylometaphyseal dysplasia, Kozlowski type
- Spondyloepiphyseal dysplasia, Maroteaux type
- Parastremmatic dysplasia
- Metatropic dysplasia

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The skeletal dysplasia is characterized by brachydactyly (in all 6); the five that are more severe have short stature that varies from mild to severe with progressive spinal deformity and involvement of the long bones and pelvis. In the mildest of the autosomal dominant *TRPV4* disorders life span is normal; in the most severe it is shortened.

Bilateral progressive sensorineural hearing loss (SNHL) can occur with both autosomal dominant neuromuscular disorders and skeletal dysplasias.

Diagnosis/testing

The diagnosis of an autosomal dominant *TRPV4* disorder is established in a proband with characteristic clinical and neurophysiologic findings, radiographic findings in the skeletal dysplasias, and a heterozygous *TRPV4* pathogenic variant identified on molecular genetic testing.

Management

Treatment of manifestations: Treatment is focused on symptom management. Affected individuals are often evaluated and managed by a multidisciplinary team that may include neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. SNHL is managed by specialists to determine the best management options.

- For neuromuscular disorders, neuropathy and respiratory dysfunction are managed in a routine manner; individuals with laryngeal dysfunction require ENT evaluation that should include speech therapy, laryngoscopy, and, in some instances, surgery.
- For skeletal dysplasias, physical therapy/exercise and heel-cord stretching to maintain function; surgical intervention when kyphoscoliosis compromises pulmonary function and/or causes pain and/or when upper cervical spine instability and/or cervical myelopathy are present.

Surveillance: For neuromuscular disorders, annual neurologic examinations, physical therapy assessments, ENT monitoring of laryngeal function, dynamic breathing chest x-ray, and hearing assessment. For skeletal dysplasias, annual evaluation for joint pain and scoliosis; assessment for odontoid hypoplasia before a child reaches school age and before surgical procedures involving general anesthesia; annual hearing assessment.

Agents/circumstances to avoid: For neuromuscular disorders, obesity, as it makes walking more difficult; diabetes; medications that are toxic or potentially toxic to persons with a peripheral neuropathy. For skeletal dysplasias, extreme neck flexion and extension (in those with odontoid hypoplasia); activities that place undue stress on the spine and weight-bearing joints.

Pregnancy management: Ideally a woman with *TRPV4* disorder would seek consultation from a high-risk OB-GYN or maternal-fetal medicine specialist to evaluate risk associated with pregnancy and delivery.

Genetic counseling

TRPV4 disorders are inherited in an autosomal dominant manner. Most individuals diagnosed with an autosomal dominant *TRPV4* disorder have an affected parent. However, since the most severe skeletal phenotypes can be lethal in childhood (or in utero), children with these phenotypes likely have a *de novo* pathogenic variant and unaffected parents. Each child of an individual with an autosomal dominant *TRPV4* disorder has a 50% chance of inheriting the pathogenic variant. Specific phenotype, age of onset, and disease severity cannot be predicted accurately because of reduced penetrance and variable expressivity. However, in general, a child who inherits a *TRPV4* pathogenic variant associated with neuromuscular disease or skeletal dysplasia from an affected parent is likely to have the same phenotype as the parent. Prenatal and preimplantation genetic testing are possible if the pathogenic variant has been identified in an affected family member.

GeneReview Scope

Autosomal Dominant *TRPV4* Disorders: Included Phenotypes [1]	
Neuromuscular disorders	• Charcot-Marie-Tooth neuropathy type 2C (CMT2C) • Scapuloperoneal spinal muscular atrophy (SPSMA) • Congenital distal spinal muscular atrophy (CDSMA)
Skeletal dysplasias	• Familial digital arthropathy-brachydactyly • Autosomal dominant brachyolmia • Spondylometaphyseal dysplasia, Kozlowski type • Spondyloepiphyseal dysplasia, Maroteaux type • Parastremmatic dysplasia • Metatropic dysplasia

For synonyms and outdated names see Nomenclature.
1. The phenotypes comprising the two groups of autosomal dominant *TRPV4* disorders are listed from mildest to most severe. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Suggestive Findings

Neuromuscular Disorders

An **autosomal dominant *TRPV4* neuromuscular disorder should be suspected** in individuals with the following range of clinical findings (see Table 1).

Charcot-Marie-Tooth disease type 2C (CMT2C)

- A progressive peripheral neuronopathy/neuropathy (primarily motor, rather than sensory) associated with pes cavus, distal amyotrophy, and foot drop
  - Nerve conduction studies [Dyck et al 1994, Zimoń et al 2010] show: (1) reduced compound motor action potential (CMAP) amplitudes with normal velocities (>40-60 m/s), although occasionally they may be mildly abnormal (36-40 m/s); and (2) normal, decreased, or absent distal sensory nerve action potential (SNAP) amplitudes.
  - Electromyography shows predominantly chronic neurogenic changes.
  - Nerve biopsy is infrequently employed, as the findings (loss of myelinated fibers with signs of regeneration, axonal sprouting, and atrophic axons with neurofilaments) do not differentiate between various causes of axonal neuropathy.
- Laryngeal dysfunction (i.e., vocal fold paresis) that may be bilateral and severe (resulting in inspiratory stridor and/or a raspy [hoarse] voice) or asymmetric (often more severe on the left than the right). Mild paresis may be inferred by presence of flaccid dysphonia [Dyck et al 1994]. Laryngoscopy often shows paresis of one or both vocal folds.
- Sensorineural hearing loss (SNHL), which is bilateral and progressive and ranges from mild to moderate. Onset is from childhood to adulthood [Kannu et al 2007, Landouré et al 2010].
- Respiratory dysfunction in some cases including intercostal and diaphragm muscle weakness, which may lead to respiratory insufficiency and/or sleep apnea [Chen et al 2010]. Chest radiograph and pulmonary function tests may demonstrate diaphragm weakness with decreased inspiratory and expiratory pressures [Dyck et al 1994, Donaghy & Kennett 1999].
- Joint contractures (appearing similar to arthrogryposis multiplex congenita [AMC]) and short stature in some cases
- A family history consistent with autosomal dominant inheritance

Scapuloperoneal spinal muscular atrophy (SPSMA)

- Slowly progressive lower motor neuron loss associated with muscle weakness and atrophy proximally in the shoulder girdle region (with characteristic scapular winging) and distally in the peroneal (lower leg) muscles. In severe cases, absence of muscle and weakness are evident at birth [DeLong & Siddique 1992, Auer-Grumbach et al 2010, Deng et al 2010].
- Muscle biopsy (infrequently performed) shows evidence of denervation and renervation [Deng et al 2010, Berciano et al 2011].
- Laryngeal dysfunction (laryngomalacia and vocal fold anomalies as in **CMT2C**), vocal cord paresis, and transient dysphonia [Berciano et al 2011]
- SNHL (as in **CMT2C**)
- Sensory deficits (rare)
- Kyphoscoliosis

Congenital distal spinal muscular atrophy (CDSMA)

- Congenital-onset, non-progressive or slowly progressive lower motor neuron loss associated with muscle weakness and atrophy, predominantly affecting the lower extremities (distal greater than proximal)
- Flexion contractures of the knees and hips often present at birth (i.e., AMC). Severe bilateral clubfoot is also seen.
- MRI of calf and thigh muscles shows a distinct pattern of fatty atrophy with preservation of the biceps femoris in the lateral thighs and of the medial gastrocnemius in the posteromedial calves [Astrea et al 2012].

Table 1. Neurologic Findings by *TRPV4* Neuromuscular Phenotype

Finding	Phenotype		
	CMT2C	SPSMA	CDSMA
Age at onset	Birth – adulthood	Birth – adulthood	Prenatal
Neuropathy	Peripheral, progressive (distal)	Peripheral, progressive (distal > proximal)	Paresis of legs at birth [1]
Vocal cord paralysis	+	+ (transient dysphonia)	±
SNHL	+	+	–
Respiratory dysfunction [2]	+	+	±
Joint contractures	–	–	AMC (mainly involving feet, knees, & hips)
Other	See footnote 3.	See footnote 4.	See footnote 5.

AMC = arthrogryposis multiplex congenita; CMT2C = Charcot-Marie-Tooth disease type 2C; CDSMA = congenital distal spinal muscular atrophy; SNHL= sensorineural hearing loss; SPSMA = scapuloperoneal spinal muscular atrophy

1. More mild manifestation: congenital weakness of the distal part of the lower limbs only. More severe manifestation: weakness of the pelvic girdle and trunk muscles, resulting in scoliosis.

2. Secondary to diaphragmatic and intercostal muscle involvement

3. Cold sensitivity (i.e., worsening of hand weakness in the cold)

4. Rounded shoulders, laterally displaced scapulae

5. Proximal muscle weakness (shoulder girdle, pelvic girdle) later in the disease course

Skeletal Dysplasias

An **autosomal dominant *TRPV4* skeletal dysplasia should be suspected** in individuals with the following skeletal findings:

- Familial digital arthropathy-brachydactyly characterized by the following:
  - Normal hands and feet at birth, then relative shortening of the middle and distal phalanges with swelling and decreased range of motion of the interphalangeal joints in early childhood
  - Progressive arthropathy of the other joints of the hands and feet with pain and deformity
  - No clinical overlap with other *TRPV4* skeletal dysplasias
- The other autosomal dominant *TRPV4* skeletal dysplasias (autosomal dominant brachyolmia; spondylometaphyseal dysplasia, Kozlowski type; spondyloepiphyseal dysplasia, Maroteaux type; parastremmatic dysplasia; and metatropic dysplasia) form a phenotypic continuum of overlapping disorders from mild to severe, each with:
  - Short stature
  - Progressive spinal deformity with scoliosis with or without kyphosis, and radiographic features of platyspondyly and overfaced pedicles
  - At least one additional distinctive feature (See Table 2.)

Table 2. Radiographic and Clinical Features of Autosomal Dominant *TRPV4* Skeletal Dysplasias

Findings	Phenotype					
	Mild	Intermediate			Severe	
	Familial digital arthropathy-brachydactyly	Autosomal dominant brachyolmia	Spondylo-metaphyseal dysplasia, Kozlowski type	Spondylo-epiphyseal dysplasia, Maroteaux type	Parastremmatic dysplasia [1]	Metatropic dysplasia
Hands/ Feet	Normal at birth; progressive swelling & arthropathy (See details.)	Clinodactyly	Brachydactyly; hypoplastic carpal bones w/severe delay in ossification	Brachydactyly	Joint contractures	Brachydactyly w/ delayed carpal ossification
Spine	Normal	± scoliosis, kyphosis; mild platyspondyly	Platyspondyly; overfaced pedicles [2]		Significant kyphoscoliosis; overfaced pedicles [2]	Platyspondyly; overfaced pedicles [2]
Long bones	NA	Minimal metaphyseal changes; short femoral neck w/ irregular proximal femoral metaphyses	± mild metaphyseal changes; genu varum	Mild-to-moderate metaphyseal changes; genu varum	Severe metaphyseal changes w/severe limb deformity; joint contractures; other [3]	Dumbbell-shaped long bones w/ epiphyseal dysplasia & prominent joints; progressive joint contractures; other [4]
Pelvis	Normal	NA	Square, short, flared iliac wings; flat, irregular acetabulae; coxa vara; ± supra-acetabular notches	Champagne-glass configuration of pelvic inlet	Halberd-shaped [5] pelvis; supra-acetabular notches	

Table 2. continued from previous page.

Findings	Phenotype					
	Mild	Intermediate			Severe	
	Familial digital arthropathy-brachydactyly	Autosomal dominant brachyolmia	Spondylo-metaphyseal dysplasia, Kozlowski type	Spondylo-epiphyseal dysplasia, Maroteaux type	Parastremmatic dysplasia [1]	Metatropic dysplasia
Other	Average height; early-childhood onset	Mild short stature; limbs unaffected; good physical function	Short-trunk short-stature dwarfism; broad chest; early-childhood onset w/ waddling gait	Short-trunk short-stature dwarfism	Significant short-trunk short-stature dwarfism	May be lethal prenatally or perinatally; at birth, short-limb short-stature dwarfism [6]

NA = not applicable
1. Rarest *TRPV4*-related skeletal dysplasia
2. Overfaced pedicles = lateral border of the vertebrae appears outside the lateral edge of the pedicles, a characteristic feature of *TRPV4* skeletal dysplasias best viewed on AP x-ray of the spine; images in Nemec et al [2012].
3. Additional findings: hyperplastic femoral trochanters, severe genu valgum, bowing of long bones, legs twisted along the long axis
4. Histologic findings: thin seal of bone at the chondroosseous junction, absent primary metaphyseal spongiosa, abnormal metaphyseal vascular invasion, arrest of endochondral ring structures with persistence of circumferential growth
5. The term "Halberd-shaped pelvis" is derived from the shape of a Swedish battle ax.
6. Progressive kyphoscoliosis and platyspondyly subsequently alter proportions from short-limb to short-trunk dwarfism.

Establishing the Diagnosis

The diagnosis of an **autosomal dominant *TRPV4* disorder is established** in a proband with suggestive findings and a heterozygous pathogenic variant in *TRPV4* identified by molecular genetic testing (see Table 3).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *TRPV4* variant of uncertain significance does not establish or rule out the diagnosis.

Single-gene testing. Sequence analysis of *TRPV4* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: (1) Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. (2) To date, a large *TRPV4* deletion or duplication has not been reported in an individual with an autosomal dominant *TRPV4* disorder.

A multigene panel that includes *TRPV4* and other genes of interest (see Differential Diagnosis) can be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 3. Molecular Genetic Testing Used in Autosomal Dominant *TRPV4* Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TRPV4	Sequence analysis [3]	100% [4]
	Deletion/duplication analysis [5]	See footnote 6.

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. Sequence analysis can detect 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.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. 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.
6. The authors are unaware of a whole-gene or contiguous gene deletion of *TRPV4* causing one of the recognized phenotypes.

Clinical Characteristics

Clinical Description

The two groups of disorders and the phenotypes comprising autosomal dominant *TRPV4* disorders (listed from mildest to most severe) are:

- Neuromuscular disorders (see Table 1):
  - Charcot-Marie-Tooth disease type 2C
  - Scapuloperoneal spinal muscular atrophy
  - Congenital distal spinal muscular atrophy
- Skeletal dysplasias (see Table 2):
  - Familial digital arthropathy-brachydactyly
  - Autosomal dominant brachyolmia
  - Spondylometaphyseal dysplasia, Kozlowski type
  - Spondyloepiphyseal dysplasia, Maroteaux type
  - Parastremmatic dysplasia
  - Metatropic dysplasia

The phenotypic spectra within both neuromuscular and skeletal groups are broad and overlapping, and the phenotypes of both groups can in rare cases overlap as well [Chen et al 2010, Unger et al 2011, Cho et al 2012].

Of note, sensorineural hearing loss (SNHL), which is bilateral and progressive and ranges from mild to moderate, can occur in both phenotypes. Onset is from childhood to adulthood [Kannu et al 2007, Landouré et al 2010].

Neuromuscular Disorders

The autosomal dominant *TRPV4* neuromuscular disorders are peripheral neuropathies/neuronopathies in which motor nerves are more prominently affected than sensory nerves [Landouré et al 2010].

Clinical findings and age of onset can be extremely variable in *TRPV4* neuromuscular disorders both between and within families [Dyck et al 1994, Donaghy & Kennett 1999, Zimoń et al 2010, Echaniz-Laguna et al 2014]. Affected individuals usually become symptomatic between early childhood and age 25 years; however, disease onset can range from birth, with breathing difficulties and delayed walking, to after the eighth decade [Zimoń et

al 2010, Echaniz-Laguna et al 2014]. In some, the manifestations can be so mild as to go unrecognized by the affected individual and physicians.

Affected individuals typically demonstrate progressive weakness and atrophy of distal muscles in the feet and/or hands, usually associated with depressed tendon reflexes and mild or no sensory loss. However, the congenital phenotypes, scapuloperoneal spinal muscular atrophy (SPSMA) and congenital distal spinal muscular atrophy (CDSMA), are characterized by long plateau periods without obvious deterioration [Vlam et al 2012]. Atrophy of the intrinsic hand muscles is common, but tendon reflexes may be intact in the arms. Proximal limb muscles may be involved, particularly in SPSMA. The pattern of muscle involvement in SPSMA includes progressive shoulder girdle atrophy and weakness leading to scapular winging (scapula alata) and involvement of the two muscle groups below the knee (peroneal distribution) [DeLong & Siddique 1992]. Mild sensory deficits of position, vibration, and pain/temperature may occur in the feet or sensation may be intact.

Laryngeal dysfunction is a hallmark of Charcot-Marie-Tooth disease type 2C (CMT2C) and is often observed in individuals with SPSMA and CDSMA [Auer-Grumbach et al 2010, Deng et al 2010, Landouré et al 2010, Zimoń et al 2010, Echaniz-Laguna et al 2014]. The typical presenting symptoms are difficulty with phonation and breathing (inspiratory stridor and hoarseness) and distal leg weakness and atrophy.

Individuals with severe features may have a decreased life span secondary to respiratory complications [Santoro et al 2002, McEntagart et al 2005].

Skeletal Dysplasias

Familial digital arthropathy-brachydactyly is not evident at birth because the hands and feet and skeletal examination (including radiographs) are normal. In early childhood relative shortening of the middle and distal phalanges and swelling and decreased range of motion of the interphalangeal joints become apparent. Later, in the first decade and beyond, the other joints of the hands and feet become painful and deformed. No overlap is currently recognized with the manifestations of the other autosomal dominant *TRPV4* skeletal dysplasias.

The remaining autosomal dominant *TRPV4* skeletal disorders are characterized by varying degrees of disproportionate short stature and progressive spinal deformity with scoliosis with or without kyphosis.

Autosomal dominant brachyolmia is the mildest of the short stature *TRPV4* skeletal conditions. Its name derives from the Greek roots *brachy-*, meaning "short," and *-olmos*, meaning "trunk" or "shoulder." Affected individuals have only mild short stature and the limbs are typically unaffected; thus, physical function is unaffected.

Spondylometaphyseal dysplasia, Kozlowski type is characterized by short-trunk short stature, although the chest is broader than in some of the more severe autosomal dominant *TRPV4* skeletal dysplasias. Birth length is average. Affected children usually come to medical attention in early childhood when poor growth with disproportionate stature and a waddling gait with genu varum become evident. Premature osteoarthritis of the joints is common.

Spondyloepiphyseal dysplasia, Maroteaux type is characterized by short-trunk dwarfism and brachydactyly. Birth length is usually average. Poor growth with a short trunk and overall short stature become evident in childhood. Over time, genu valgum and kyphoscoliosis develop. Osteoporosis has been described.

Parastremmatic dysplasia, probably the rarest of the autosomal dominant *TRPV4* skeletal dysplasias, is characterized by severe limb deformities and joint malalignment, short stature, and kyphoscoliosis, which are present at birth and progressively worsen throughout life.

Metatropic dysplasia (from the Greek *metatropos,* meaning "with change/changing pattern") was named after the striking reversal of body proportions between birth and childhood. At birth, the limbs are disproportionately

short (due to the long bone metaphyseal abnormalities) compared to the trunk. In childhood, when the platyspondyly and scoliosis and/or kyphosis become more severe, the trunk becomes relatively short compared to the limbs.

Metatropic dysplasia may be lethal in the prenatal or perinatal period, largely due to an extremely narrow chest and hypoplastic lung parenchyma. Infants who survive the perinatal period typically develop severe kyphoscoliosis that eventually compromises pulmonary function. Other skeletal findings in some individuals with severe metatropic dysplasia are poor joint range of motion, joint contractures, and torticollis; these arthrogryposis multiplex congenita-like contractures represent an overlap between the neuromuscular and skeletal phenotypes of autosomal dominant *TRPV4* disorders [Unger et al 2011].

Genotype-Phenotype Correlations

In general, specific sets of *TRPV4* pathogenic variants have been associated with either neuromuscular disorders or skeletal dysplasia; overlap may occur, however, making genotype-phenotype correlations difficult (see Molecular Genetics) [Unger et al 2011, Sullivan & Earley 2013].

Functional studies suggest that *TRPV4* pathogenic variants associated with neuromuscular disorders and skeletal dysplasias may cause a gain-of-channel function [Rock et al 2008, Krakow et al 2009, Nilius & Voets 2013, Sullivan et al 2015], whereas the pathogenic variants associated with familial digital arthropathy-brachydactyly (FDAB) may cause a loss-of-channel function.

***TRPV4* neuromuscular disorders.** Several studies suggest that most *TRPV4* pathogenic variants associated with a neuromuscular phenotype cluster on the highly positively charged convex surface of the ankyrin repeats domain and target arginine residues that are strictly conserved throughout 27 available *TRPV4* orthologs [Auer-Grumbach et al 2010, Deng et al 2010, Landouré et al 2010, Sullivan et al 2015]. These surface pathogenic variants are located in three consecutive finger loops of the protein, a distinct region of the *TRPV4* ankyrin repeats. The most commonly reported and best validated pathogenic *TRPV4* variants are the following: p.Arg186Gln, p.Arg232Cys, p.Arg269Cys, p.Arg269His, p.Arg315Trp, p.Arg316Cys, and p.Arg316His [Auer-Grumbach et al 2010, Deng et al 2010, Landouré et al 2010, Klein et al 2011, Landouré et al 2012]. Variable phenotypes have been reported, even among members of the same family [Landouré et al 2010].

***TRPV4* skeletal dysplasias.** In total, more than 50 pathogenic variants in *TRPV4* have been reported to cause brachyolmias. While the pathogenic variants are spread throughout the gene, two hot spots have been observed at residues Pro799 in exon 15 and Arg594 in exon 11 [Nishimura et al 2012], which localize to the channel pore region.

The familial digital arthropathy-brachydactyly-causing pathogenic variants are restricted to finger 3 of the ankyrin repeats domain (pathogenic variants p.Gly270Val, p.Arg271Pro, p.Phe273Leu) [Nilius & Voets 2013].

Overlap of *TRPV4* neuromuscular disorders and skeletal dysplasias. Of note, the pathogenic variants p.Ala217Ser, p.Glu278Lys, p.Arg269Cys, p.Arg315Trp, p.Tyr591Cys, p.Arg594His, p.Val620Ile, p.Glu797Lys, and p.Pro799Arg have been associated with both neuromuscular disease and skeletal dysplasia [Zimoń et al 2010, Cho et al 2012, Faye et al 2019]. In addition, the pathogenic variant p.Ser542Tyr caused both CMT2C and short stature in one family [Chen et al 2010].

Penetrance

Autosomal dominant *TRPV4* neuromuscular disorders. Penetrance is reduced with the neuromuscular disease-associated pathogenic variants.

Autosomal dominant *TRPV4* skeletal dysplasias. In contrast, penetrance of the skeletal dysplasia phenotype appears to be high; however, intra- and interfamilial variability is significant [Dai et al 2010].

Nomenclature

Charcot-Marie-Tooth neuropathy type 2C is also referred to as hereditary motor and sensory neuropathy type 2C.

Spondyloepiphyseal dysplasia, Maroteaux type is also referred to as pseudo-Morquio syndrome type 2.

Prevalence

The prevalence of the autosomal dominant *TRPV4* neuromuscular and skeletal dysplasias has not been well studied.

Fawcett et al [2012] determined that 13 (<1%) of 422 individuals with a CMT2 (axonal CMT) phenotype were heterozygous for a *TRPV4* pathogenic variant. Of note, the detection of a *TRPV4* pathogenic variant increased to between 9% and 16% in those with a CMT2 phenotype with additional unusual features (e.g., vocal fold weakness, diaphragmatic paresis, skeletal dysplasia) [Fawcett et al 2012, Echaniz-Laguna et al 2014].

Genetically Related (Allelic) Disorders

Biallelic *TRPV4* variants have been reported in the following individuals:

- A single individual with homozygous p.Ser94Leu pathogenic variants and a combined phenotype of axonal neuropathy, vocal cord paresis, and arthrogryposis multiplex congenita (in vitro analysis of the p.Ser94Leu variant demonstrated gain of abnormal function) [Velilla et al 2019];
- Two sibs with compound partial loss-of-function *TRPV4* variants and complex phenotypes consisting of microcephaly, dystonia, sensorineural hearing loss, retinopathy, skeletal abnormalities, and neuropathy [Thibodeau et al 2017]. Further studies would be required to establish pathogenicity of these variants.

No phenotypes other than those discussed in this *GeneReview* are known to be associated with a heterozygous germline pathogenic variant in *TRPV4*.

Differential Diagnosis

Autosomal Dominant *TRPV4* Neuromuscular Disorders

Autosomal dominant *TRPV4* neuromuscular disorders (Charcot-Marie-Tooth disease type 2C, scapuloperoneal spinal muscular atrophy, and congenital distal spinal muscular atrophy) resemble several other disorders (see Table 4).

Note: See Charcot-Marie-Tooth Hereditary Neuropathy Overview for a general overview of CMT2.

Table 4. Genes of Interest in the Differential Diagnosis of Autosomal Dominant *TRPV4* Neuromuscular Disorders

Gene	MOI	Disorder
ATP7A	XL	dSMA (See *ATP7A*-Related Copper Transport Disorders.)
BICD2	AD	Lower extremity-predominant SMA (SMA2A; SMA2B) (OMIM 615290)
BSCL2	AD	dHMN5A (See *BSCL2* Neurologic Disorders/Seipinopathy.)
DCTN1	AD	dHMN7B (OMIM 607641): motor neuropathy w/vocal cord paralysis
DYNC1H1	AD	CMT2O (see CMT Overview); lower extremity-predominant SMA

Table 4. continued from previous page.

Gene	MOI	Disorder
GARS1	AD	*GARS1*-associated axonal neuropathy (CMT2D; dSMA-V)
HSPB1	AD	dHMN2B; CMT2F (See CMT Overview.)
HSPB3	AD	dHMN2C (OMIM 613376)
HSPB8	AD	dHMN2A (OMIM 158590)
IGHMBP2	AR	CMT2S (see CMT Overview); dSMA1
JAG1	AD	CMT2C [1]: mild neuropathy w/severe vocal cord paralysis
MYH14	AD	Peripheral neuropathy, myopathy, hoarseness, and hearing loss (OMIM 614369): hoarseness w/o vocal cord paralysis; reported in 1 family
PLEKHG5	AR	Intermediate CMTC (see CMT Overview); dSMA4: variably assoc w/scapular winging & diaphragmatic weakness
SETX	AD	Juvenile ALS (dHMN)
SLC5A7	AD	dHMN7A (OMIM 158580): motor neuropathy w/vocal cord paralysis

Genes are listed in alphabetic order.
AD = autosomal dominant; ALS = amyotrophic lateral sclerosis; AR = autosomal recessive; CMT = Charcot-Marie-Tooth neuropathy; dHMN = distal hereditary motor neuropathy; dSMA = distal spinal muscular atrophy; MOI = mode of inheritance; SMA = spinal muscular atrophy; XL = X-linked
1. Sullivan et al [2020]

Autosomal Dominant *TRPV4* Skeletal Dysplasias

Autosomal dominant *TRPV4* skeletal dysplasias have a broad phenotypic spectrum and, thus, many skeletal dysplasias to consider in the differential diagnosis.

Mild (familial digital arthropathy-brachydactyly). The differential diagnosis includes reactive arthropathy, diabetic arthropathy, and other forms of brachydactyly [Amor et al 2002].

Intermediate (autosomal dominant brachyolmia; spondylometaphyseal dysplasia, Kozlowski type; and spondyloepiphyseal dysplasia, Maroteaux type) and **severe** (parastremmatic dysplasia and metatropic dysplasia). See Table 5.

Table 5. Genes of Interest in the Differential Diagnosis of Intermediate and Severe Autosomal Dominant *TRPV4* Skeletal Dysplasias

Phenotype	Gene	MOI	Disorder
Intermediate	*COL2A1*	AD (AR)	Spondyloepiphyseal dysplasia congenita (see Type II Collagen Disorders Overview)
	GALNS	AR	Morquio syndrome type A (MPS IVA)
	GLB1	AR	Morquio syndrome type B (MPS IVB)
	TRAPPC2	XL	X-linked spondyloepiphyseal dysplasia tarda

Table 5. continued from previous page.

Phenotype	Gene	MOI	Disorder
Severe	*COL2A1*	AD	Kniest dysplasia (see Type II Collagen Disorders Overview): platyspondyly & coronal cleft, shortened tubular bones & metaphyseal flaring, broad & short thorax
	COL11A1 *COL11A2*	AR AD	Fibrochondrogenesis 1 & 2 (OMIM PS228520): rhizomelic limb shortening, broad dumbbell-shaped metaphyses, pear-shaped vertebral bodies, short & distally cupped ribs
	COL11A2	AR AD	Otospondylomegaepiphyseal dysplasia [1] (OMIM 184840, 215150)
	HSPG2	AR	Dyssegmental dysplasia, Silverman-Handmaker type (OMIM 224410)

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; MPS = mucopolysaccharidosis; XL = X-linked
1. Autosomal recessive otospondylomegaepiphyseal dysplasia may also be referred to as Weissenbacher Zweymuller syndrome.

Brachyolmia types 1 and 2 (OMIM 271530 and 613678) can also be considered in the differential diagnosis of intermediate autosomal dominant *TRPV4* skeletal dysplasias. The molecular basis of these disorders is unknown.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with an **autosomal dominant *TRPV4* neuromuscular disorder**, the evaluations summarized in Table 6a (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6a. Recommended Evaluations Following Initial Diagnosis in Individuals with an Autosomal Dominant *TRPV4* Neuromuscular Disorder

System/Concern	Evaluation	Comment
Neurologic	Physical/neurologic exam	To determine extent of weakness & atrophy, pes cavus, gait stability, & sensory loss
	EMG w/NCV	As needed to document status of neuropathy
	ENT consult w/laryngoscopy	As needed to document status of vocal folds
Respiratory	Pulmonary function testing & dynamic breathing chest x-ray	As needed to assess pulmonary & respiratory function
Audiologic	Hearing assessment	See Hereditary Hearing Loss and Deafness Overview for different types of hearing assessment.
Skeletal	Skeletal x-rays	To identify any assoc skeletal dysplasia
Genetic counseling	By genetics professionals [1]	To inform individuals & families re nature, MOI, & implications of *TRPV4* disorders to facilitate medical & personal decision making
Family support/ resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral; • Referral to physiatry, PT, OT, & speech therapy.	

EMG = electromyography; NCV = nerve conduction velocity; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

To establish the extent of disease and needs in an individual diagnosed with an **autosomal dominant *TRPV4* skeletal dysplasia**, the evaluations summarized in Table 6b (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6b. Recommended Evaluations Following Initial Diagnosis in Individuals with an Autosomal Dominant *TRPV4* Skeletal Dysplasia

System/Concern	Evaluation	Comment
Skeletal	Skeletal x-rays	To document involvement of long bones & spine, which can help determine individual needs & provide baseline for comparison w/future studies
	Flexion/extension cervical spine films	To determine if there is atlanto-axial instability secondary to odontoid hypoplasia
Respiratory	Pulmonary function testing &/or sleep study	If thorax is particularly narrow &/or kyphoscoliosis is progressive
Audiology	Hearing assessment	See Hereditary Hearing Loss and Deafness Overview for different types of hearing assessment.
Genetic counseling	By genetics professionals [1]	To inform individuals & families re nature, MOI, & implications of *TRPV4* disorders to facilitate medical & personal decision making
Family support/ resources	Assess need for: • Community or online resources such as Parent to Parent & Little People of America; • Social work involvement for parental support; • Home nursing referral; • Referral to physiatry, PT, & OT.	

MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Treatment is focused on symptom management. Affected individuals are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, ENT specialists, and physical and occupational therapists.

Table 7a. Treatment of Manifestations in Individuals with an Autosomal Dominant *TRPV4* Neuromuscular Disorder

Manifestation/Concern	Treatment	Considerations/Other
Neuropathy	• Special shoes, incl those w/good ankle support • AFO to correct foot drop & aid walking • Orthopedic surgery to correct severe pes cavus deformity as needed • Forearm crutches, canes/walkers for gait stability, & wheelchairs • Exercise w/in person's capability (Many remain physically active.)	
Pain & depression	Symptomatic treatment	
Vocal cord involvement	• Laryngeal surgery for vocal fold paresis (arytenoidectomy & tracheostomy) • Speech therapy	
Respiratory dysfunction	Respiratory therapy/support (e.g., BiPAP)	

Table 7a. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
SNHL	Treatment per hearing loss specialists to determine best habilitation options	See Hereditary Hearing Loss and Deafness Overview for discussion of mgmt issues.

AFO = ankle-foot orthosis; BiPAP = bilevel positive airway pressure; SNHL = sensorineural hearing loss

Table 7b. Treatment of Manifestations in Individuals with an Autosomal Dominant *TRPV4* Skeletal Dysplasia

Manifestation/Concern	Treatment	Considerations/Other
Contractures	PT/exercise	To maintain as much function as possible
	Daily heel cord-stretching exercises	To prevent Achilles tendon shortening
Kyphoscoliosis	Orthopedic eval w/consideration of surgical intervention (e.g., spinal fusion)	If kyphoscoliosis results in pain &/or compromised pulmonary function
Odontoid hypoplasia / Cervical myelopathy	Occipito-cervical or upper cervical decompression & fusion are required to stabilize upper cervical spine & relieve cervical cord compression when upper cervical spine instability is documented or when clinical findings of cervical myelopathy are present.	It is preferred that intervention in children occur when signs of cervical compression are present by MRI (even in absence of symptoms) to minimize neurologic injury & maximize function. Those undergoing surgical fusion typically do well; minor secondary complications can incl pin site infections, pressure sores, & long-term difficulty w/endotracheal intubation.
	If myelopathy is suspected: • Obtain cervical spine radiographs & MRI; • Refer for eval by pediatric orthopedic surgeon or neurosurgeon at tertiary care facility.	Upper cervical instability may result in deteriorating endurance & worsening gait.
SNHL	Treatment per hearing loss specialists to determine best habilitation options	See Hereditary Hearing Loss and Deafness Overview for discussion of mgmt issues.
Pain & depression	Symptomatic treatment	Chronic pain mgmt preceding or following orthopedic surgery is standard & often required.

PT = physical therapy; SNHL = sensorineural hearing loss

Surveillance

Table 8a. Recommended Surveillance for Individuals with an Autosomal Dominant *TRPV4* Neuromuscular Disorder

System/Concern	Evaluation	Frequency
Neuropathy	Neurologic exam to determine extent of weakness & atrophy, & sensory loss	Annually
	PT exam to monitor feet to determine need for bracing, special shoes, &/or surgery	
Vocal cord involvement	ENT consult w/laryngoscopy	
Respiratory dysfunction	Dynamic breathing chest x-ray	
SNHL	Hearing assessment	

PT = physical therapy; SNHL = sensorineural hearing loss

Table 8b. Recommended Surveillance for Individuals with an Autosomal Dominant *TRPV4* Skeletal Dysplasia

System/Concern	Evaluation	Frequency
Musculoskeletal	Assessment for development of joint pain & scoliosis	Annually
	Cervical spinal films to assess for clinically significant odontoid hypoplasia	Before: • A child reaches school age; • Surgical procedures involving general anesthesia.
SNHL	Hearing assessment	Annually

SNHL = sensorineural hearing loss

Agents/Circumstances to Avoid

In general, obesity is to be avoided because it makes walking more difficult for individuals with neuropathy, skeletal dysplasia, or both

For neuromuscular disorders. Preventive health care to avoid diabetes-related complications is recommended. Neurotoxic medications should be avoided. Medications that are toxic or potentially toxic to persons with CMT comprise a spectrum of risk ranging from definite high risk to negligible risk. See the Charcot-Marie-Tooth Association website (pdf) for an up-to-date list. See also the Inherited Neuropathy Consortium website for additional information.

For skeletal dysplasias

- In individuals with odontoid hypoplasia, avoid extreme neck flexion and extension.
- Avoid activities and occupations that place undue stress on the spine and weight-bearing joints.

Evaluation of Relatives at Risk

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

Pregnancy Management

There is no registry or data regarding the frequency or outcome of pregnancies in women with a *TRPV4*-related disorder; however, the following general information may be reasonable to consider. Ideally a woman with an autosomal dominant *TRPV4* disorder would seek consultation from a high-risk OB-GYN or maternal-fetal medicine specialist to evaluate her risks for pregnancy and delivery. Increased risk of ectopic pregnancy has been reported [Li et al 2019].

Autosomal dominant *TRPV4* neuromuscular disorders. Argov & de Visser [2009] reviewed pregnancy issues in hereditary neuromuscular disorders including CMTs. About 50% of women with CMT described increased weakness during pregnancy that usually resolved post partum [Rudnik-Schöneborn et al 1993]. Operative deliveries were reported more commonly in women with CMT in Norway [Hoff et al 2005]. Greenwood & Scott [2007] described the obstetric approach to women with mild and severe forms of CMT. Brock et al [2009] describe use of anesthesia during delivery in a single case study, indicating that regional management is the preferred and safer method, compared to general anesthesia. A German study reviewed 63 pregnancies in 33 women with CMT [Awater et al 2012] and found no increase in the frequency of cesarean section, forceps delivery, premature birth, or neonatal problems. About one third of mothers felt a worsening of CMT symptoms during pregnancy; in one fifth of mothers the changes were felt to be persistent.

Autosomal dominant *TRPV4* skeletal dysplasias. In autosomal dominant *TRPV4* skeletal dysplasias, the degree of pulmonary compromise (from the short trunk and decreased lung capacity) may affect the ability to carry a

pregnancy to term. Thus, it is unlikely that a woman with metatropic dysplasia could carry a pregnancy. Pregnant women with a *TRPV4* skeletal dysplasia generally undergo cesarean section delivery because of the small size of the pelvis.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Mathis et al [2015] have reviewed the future of therapeutic options in CMT.

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. Note: There may not be clinical trials for this disorder.

Other

Career and employment choices may be influenced by persistent weakness of hands and/or feet and orthopedic involvement.

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

TRPV4 neuromuscular and skeletal disorders caused by a heterozygous *TRPV4* pathogenic variant are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Because the most severe *TRPV4* skeletal phenotypes can be lethal in childhood (or in utero), children with these phenotypes typically have a *de novo* pathogenic variant and unaffected parents.
- Individuals with less severe skeletal phenotypes or neuromuscular phenotypes often have the disorder as the result of a *TRPV4* pathogenic variant inherited from a heterozygous parent. (Note: A heterozygous parent may appear asymptomatic or have more or less severe clinical manifestations than the proband; see Penetrance and Genotype-Phenotype Correlations.) *De novo* variants have also been described in individuals with these phenotypes.
- Molecular genetic testing is recommended for the parents of a proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].

- The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.

- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotype or reduced penetrance in the parent with the pathogenic variant. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing indicates that neither parent has the pathogenic variant identified in 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 is known to have the *TRPV4* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- The specific phenotype, age of onset, and disease severity cannot be predicted accurately in a sib who inherits a familial pathogenic variant because of reduced penetrance and variable expressivity. A heterozygous sib may have the same phenotype as the proband or have less severe or more severe clinical manifestations (see Penetrance and Genotype-Phenotype Correlations).
- If the *TRPV4* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *TRPV4* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for a *TRPV4* disorder because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband

- Each child of an individual with a *TRPV4* disorder has a 50% chance of inheriting the *TRPV4* pathogenic variant. Specific phenotype, age of onset, and disease severity cannot be predicted accurately because of reduced penetrance and variable expressivity.

- Because many individuals with short stature have reproductive partners with short stature, offspring of individuals with a *TRPV4* skeletal disorder may be at risk of having double heterozygosity for two dominantly inherited bone growth disorders. The phenotypes of these individuals may be distinct from those of the parents.

  If the proband and the proband's reproductive partner are affected with different dominantly inherited skeletal dysplasias, each child has a 25% likelihood of having average stature, a 25% likelihood of having the same skeletal dysplasia as the father, a 25% likelihood of having the same skeletal dysplasia as the mother, and a 25% likelihood of inheriting a pathogenic variant from both parents and being at risk for a potentially poor outcome.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *TRPV4* pathogenic variant, 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.
- Genetic counseling is recommended when both parents have a skeletal dysplasia.

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *TRPV4* pathogenic variant has been identified in an affected family member. If identified to have inherited a *TRPV4* pathogenic variant, further clinical evaluation, electromyography/nerve conduction velocity testing, and/or skeletal survey may be appropriate. No treatment is available to individuals early in the course of the disease. Thus, such testing is for personal decision making only.
- Potential consequences of such testing (including, but not limited to, socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of a *TRPV4* disorder, it is appropriate to consider testing of symptomatic individuals regardless of age.

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 [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *TRPV4* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for an autosomal dominant *TRPV4* disorder are possible. However, specific phenotype, age of onset, and/or disease severity cannot be reliably predicted based on the results of prenatal testing.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. 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.

- **Medical Home Portal**
  Charcot-Marie-Tooth Disease (Hereditary Motor Sensory Neuropathy)
- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)

Fax: 202-337-8314
Email: info@agbell.org
Listening and Spoken Language Knowledge Center

- **Charcot-Marie-Tooth Association (CMTA)**
  Phone: 800-606-2682 (toll-free); 610-427-2971
  Email: info@cmtausa.org
  www.cmtausa.org
- **Child Growth Foundation**
  United Kingdom
  Phone: 0208 995 0257
  Email: nfo@childgrowthfoundation.org
  www.childgrowthfoundation.org
- **Hereditary Neuropathy Foundation**
  Phone: 855-435-7268 (toll-free); 212-722-8396
  Fax: 917-591-2758
  Email: info@hnf-cure.org
  www.hnf-cure.org
- **Inherited Neuropathy Consortium (INC)**
  Phone: 319-353-8400
  Fax: 319-384-7199
  Email: Shawna-Feely@uiowa.edu
  www.rarediseasesnetwork.org/cms/inc
- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

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. Autosomal Dominant TRPV4 Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TRPV4	12q24.11	Transient receptor potential cation channel subfamily V member 4	TRPV4 database	TRPV4	TRPV4

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 Autosomal Dominant TRPV4 Disorders (View All in OMIM)

113500	BRACHYOLMIA TYPE 3; BCYM3
156530	METATROPIC DYSPLASIA; MTD
168400	PARASTREMMATIC DWARFISM
181405	SCAPULOPERONEAL SPINAL MUSCULAR ATROPHY; SPSMA

Table B. continued from previous page.

184095	SPONDYLOEPIPHYSEAL DYSPLASIA, MAROTEAUX TYPE
184252	SPONDYLOMETAPHYSEAL DYSPLASIA, KOZLOWSKI TYPE; SMDK
600175	NEURONOPATHY, DISTAL HEREDITARY MOTOR, AUTOSOMAL DOMINANT 8; HMND8
605427	TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL, SUBFAMILY V, MEMBER 4; TRPV4
606071	HEREDITARY MOTOR AND SENSORY NEUROPATHY, TYPE IIC; HMSN2C
606835	DIGITAL ARTHROPATHY-BRACHYDACTYLY, FAMILIAL; FDAB
606845	GOLGI-ASSOCIATED PDZ AND COILED-COIL DOMAINS-CONTAINING PROTEIN; GOPC
617383	AVASCULAR NECROSIS OF FEMORAL HEAD, PRIMARY, 2; ANFH2

Molecular Pathogenesis

TRPV4 encodes a nonselective Ca2+-permeable cation channel that is predominantly expressed at the plasma membrane [Garcia-Elias et al 2014]. TRPV4 can be activated by a wide range of stimuli including hypo-osmolarity, heat, and mechanical stretch, as well as numerous endogenous (e.g., endocannabinoid anandamide, arachidonic acid) and synthetic compounds (4α-phorbol-12,13-didecanoate [4αPDD]) [Garcia-Elias et al 2014]. TRPV4 is broadly expressed and has diverse physiologic roles in different tissues types:

- Osmosensation and flow sensing in the kidney [Pochynyuk et al 2013]
- Endothelial barrier function in the vascular system [Villalta & Townsley 2013]
- Mechanosensation and nociception in the sensory nervous system [Suzuki et al 2003, Alessandri-Haber et al 2009]
- Stretch sensation in the bladder [Gevaert et al 2007]
- Skin barrier function [Kida et al 2012]
- Chondrogenesis [Muramatsu et al 2007]
- Bone homeostasis [Masuyama et al 2012]
- Regulation of adipose oxidative metabolism [Ye et al 2012]

While the precise mechanisms of pathogenesis in *TRPV4* disorders are not completely understood, the preponderance of evidence suggests that pathogenic variants cause toxicity through gain of ion channel function [Nilius & Voets 2013]. Given the incredibly diverse signaling pathways regulated by intracellular calcium influx, many possible downstream pathologic events are conceivable, including activation of calcium-sensitive proteases (such as calpains) or kinases (such as CaMKII), alterations in calcium-sensitive transcriptional programs, disruption of axonal transport, dysregulation of cytoskeletal remodeling, and altered neuronal excitability, among others. In addition, the downstream consequences of TRPV4 gain-of-channel function are likely to be dependent on cell type- and tissue-specific factors.

Mechanism of disease causation. *TRPV4* disorders are diverse, but are likely linked through gain of TRPV4 ion channel function with tissue-specific downstream consequences. Notably, the vast majority of pathogenic variants reported are missense variants.

- **Neuromuscular disorders.** Gain of ion channel function, potentially via altered gating properties or altered responsiveness to activating stimuli has been proposed. The majority of disease variants causing neuromuscular disorders result in increased calcium influx in vitro [Deng et al 2010, Landouré et al 2010, Klein et al 2011, Sullivan et al 2015], and a *Drosophila* model of *TRPV4* neuropathy demonstrated several neurologic phenotypes that could be ameliorated by genetic or pharmacologic inhibition of TRPV4 ion channel activity [Woolums et al 2020].

The p.Arg186Gln, p.Arg237Leu, p.Arg269His, p.Arg269Cys, p.Arg316Cys, p.Arg316His, and p.Arg232Cys pathogenic variants showed increased ion channel activity resulting in intracellular calcium levels in vitro, and p.Arg269Cys led to increased intracellular calcium in vivo [Deng et al 2010, Landouré et al 2010, Klein et al 2011, Sullivan et al 2015, Woolums et al 2020].

- **Skeletal dysplasias.** The vast majority of skeletal dysplasia pathogenic variants are missense variants that are believed to cause gain of function, although frameshift and deletion variants have been reported [Dai et al 2010, Nishimura et al 2010]. Like pathogenic variants associated with neuromuscular disorders, skeletal dysplasia-associated variants also generally cause increased basal calcium influx [Loukin et al 2011]. The precise downstream pathogenic events remain unknown, although excessive inhibition of bone morphogenic protein with resultant impairment in endochondral ossification has been proposed based on in vitro studies and a knock-in mouse model [Leddy et al 2014a, Leddy et al 2014b].

Table 9. Notable *TRPV4* Pathogenic Variants

Reference Sequences	Predominant Phenotype	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_021625.4 NP_067638.3	Neuromuscular	c.557G>A	p.Arg186Gln	See Genotype-Phenotype Correlations [Auer-Grumbach et al 2010, Deng et al 2010, Landouré et al 2010, Klein et al 2011, Landouré et al 2012].
		c.694C>T	p.Arg232Cys [1]	
		c.710G>T	p.Arg237Leu	
		c.805C>T	p.Arg269Cys	
		c.806G>A	p.Arg269His	
		c.943C>T	p.Arg315Trp	
		c.946C>T	p.Arg316Cys	
		c.947G>A	p.Arg316His	
	Skeletal	NA	NA	Two mutation hot spots identified. See Genotype-Phenotype Correlations [Nishimura et al 2012].
	Familial digital arthropathy-brachydactyly	c.809G>T	p.Gly270Val	See Genotype-Phenotype Correlations [Nilius & Voets 2013].
		c.812G>C	p.Arg271Pro	
		c.819C>G	p.Phe273Leu	

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.
1. Denotes a combined neuromuscular and skeletal phenotype

Chapter Notes

Revision History

- 17 September 2020 (sw) Comprehensive update posted live
- 15 May 2014 (me) Review posted live
- 30 July 2013 (as) Original submission

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