TRPV4 gene
transient receptor potential cation channel subfamily V member 4

Normal Function

The TRPV4 gene provides instructions for making a protein that acts as a calcium channel. This channel, which transports positively charged atoms of calcium (calcium ions) across cell membranes, is found in many types of cells and tissues. Studies suggest that the TRPV4 channel plays a role in a number of different functions in the body. These include the development of bones and cartilage, the tough but flexible tissue that makes up much of the skeleton during early development. It is also be involved in maintaining the body's water balance (osmoregulation) and in certain types of sensation, particularly the sensation of pain. The TRPV4 channel may also play a role in the self-destruction of cells (apoptosis). It likely has additional functions that have not been identified.

Health Conditions Related to Genetic Changes

Charcot-Marie-Tooth disease

Metatropic dysplasia

At least 30 mutations in the TRPV4 gene have been identified in people with metatropic dysplasia, a skeletal disorder characterized by short stature (dwarfism) with other skeletal abnormalities. Most of these mutations change single protein building blocks (amino acids) in the TRPV4 calcium channel. However, a few mutations insert or delete pieces of DNA in the TRPV4 gene.

Studies suggest that the TRPV4 gene mutations that cause metatropic dysplasia overactivate the TRPV4 calcium channel. The resulting increase in calcium in cartilage-forming cells (chondrocytes) may disrupt the early development of cartilage and bone. However, it remains unclear why these mutations affect chondrocytes specifically and how changes in TRPV4 channel activity result in the particular skeletal abnormalities associated with metatropic dysplasia.

Other disorders

Mutations in the TRPV4 gene cause a variety of other conditions, most of which affect the developing skeleton or the nervous system.

In addition to metatropic dysplasia, skeletal disorders associated with TRPV4 gene mutations include autosomal dominant brachyolmia; spondylometaphyseal dysplasia, Kozlowski type; spondyloepiphyseal dysplasia, Maroteaux type; and parastremmatic dysplasia. These related conditions involve combinations of short stature, abnormal
side-to-side and back-to-front curvature of the spine (kyphoscoliosis), and other problems with developing bones.

Mutations in the TRPV4 gene also cause neurological disorders. This spectrum of related conditions includes Charcot-Marie-Tooth disease type 2C, congenital distal spinal muscular atrophy, which is characterized by weakness of muscles in the legs and hips, and scapuloperoneal spinal muscular atrophy, which involves weakness and wasting (atrophy) of muscles in the shoulders and lower legs.

Most of the TRPV4 gene mutations that cause these skeletal and neurological disorders change single amino acids in the TRPV4 calcium channel. These mutations likely result in an overactive channel, although some research suggests that the mutations may have different effects on channel function in different tissues. Certain TRPV4 gene mutations have been found to cause skeletal disorders in some people and neurological disorders in others. Additionally, some TRPV4 gene mutations can cause both skeletal and neurological features in the same individual. Researchers are working to determine how TRPV4 gene mutations can cause this wide variety of signs and symptoms.

Another bone disorder, known as familial digital arthropathy-brachydactyly, has also been associated with mutations in the TRPV4 gene. This condition is characterized by arthritis in the joints of the fingers and toes (arthropathy) and shortened fingers and toes (brachydactyly). The mutations that cause this condition appear to impair the function of the TRPV4 calcium channel, preventing it from transporting calcium ions effectively. It is unclear how a loss of channel function leads to the specific features of this condition.

Common variations (polymorphisms) in the TRPV4 gene have been associated with two additional disorders: hyponatremia, which is a condition of water imbalance that can cause dangerous brain swelling, and chronic obstructive pulmonary disease (COPD), a common lung disease that causes difficulty breathing. It has not been determined how differences in the function of the TRPV4 calcium channel are related to these two conditions.

Because mutations in the TRPV4 gene are associated with such a wide array of conditions, some researchers have proposed referring to all TRPV4-related disorders as TRPV4-associated peripheral neuropathy and bony dysplasias (TRPV4-PNAB) or TRPV4-opathies.
Chromosomal Location

Cytogenetic Location: 12q24.11, which is the long (q) arm of chromosome 12 at position 24.11

Molecular Location: base pairs 109,783,087 to 109,833,407 on chromosome 12 (Homo sapiens Annotation Release 109, GRCh38.p12) (NCBI)

[Diagram showing chromosome 12 with markers]

Credit: Genome Decoration Page/NCBI

Other Names for This Gene

• osm-9-like TRP channel 4
• OSM9-like transient receptor potential channel 4
• osmosensitive transient receptor potential channel 4
• OTRPC4
• SPSMA
• SSQTL1
• transient receptor potential cation channel, subfamily V, member 4
• transient receptor potential protein 12
• TRP12
• TRPV4_HUMAN
• vanilloid receptor-like channel 2
• vanilloid receptor-related osmotically activated channel
• VR-OAC
• VRL-2
• VRL2
• VROAC
**Educational Resources**

**TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades (2007):** TRPV4: A Multifunctional Nonselective Cation Channel with Complex Regulation
https://www.ncbi.nlm.nih.gov/books/NBK5242/#ch9

**Clinical Information from GeneReviews**

- TRPV4-Associated Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK201366

**Scientific Articles on PubMed**

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28TRPV4%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

**Catalog of Genes and Diseases from OMIM**

- BRACHYOLMIA TYPE 2
  http://omim.org/entry/613678

- BRACHYOLMIA TYPE 3
  http://omim.org/entry/113500

- DIGITAL ARTHROPATHY-BRACHYDACTYLY, FAMILIAL
  http://omim.org/entry/606835

- NEURONOPATHY, DISTAL HEREDITARY MOTOR, TYPE VIII
  http://omim.org/entry/600175

- PARASTREMMATIC DWARFISM
  http://omim.org/entry/168400

- PULMONARY DISEASE, CHRONIC OBSTRUCTIVE
  http://omim.org/entry/606963

- SCAPULOPERONEAL SPINAL MUSCULAR ATROPHY
  http://omim.org/entry/181405

- SPONDYLOEPIPHYSEAL DYSPLASIA, MAROTEAUX TYPE
  http://omim.org/entry/184095
• SPONDYLOMETAPHYSEAL DYSPLASIA, KOZLOWSKI TYPE  
  http://omim.org/entry/184252
• TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL, SUBFAMILY V, MEMBER 4  
  http://omim.org/entry/605427

Research Resources
• Atlas of Genetics and Cytogenetics in Oncology and Haematology  
  http://atlasgeneticsoncology.org/Genes/GC_TRPV4.html
• ClinVar  
  https://www.ncbi.nlm.nih.gov/clinvar?term=TRPV4%5Bgene%5D
• HGNC Gene Family: Ankyrin repeat domain containing  
  https://www.genenames.org/cgi-bin/genefamilies/set/403
• HGNC Gene Family: Transient receptor potential cation channels  
  https://www.genenames.org/cgi-bin/genefamilies/set/249
• HGNC Gene Symbol Report  
• Monarch Initiative  
  https://monarchinitiative.org/gene/NCBIGene:59341
• NCBI Gene  
• UniProt  
  https://www.uniprot.org/uniprot/Q9HBA0

Sources for This Summary
• Andreucci E, Aftimos S, Alcausin M, Haan E, Hunter W, Kannu P, Kerr B, McGillivray G,  
  McKinlay Gardner RJ, Patricelli MG, Sillence D, Thompson E, Zacharin M, Zankl A, Lamandé SR,  
  Savarirayan R. TRPV4 related skeletal dysplasias: a phenotypic spectrum highlighted by clinical,  
  radiographic, and molecular studies in 21 new families. Orphanet J Rare Dis. 2011 Jun 9;6:37. doi:  
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21658220  
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3135501/
  Petty R, Longman C, Anderson NE, Padberg GW, Schelhaas HJ, van Ravenswaaij-Arts CM, Pieber TR,  
  Crosby AH, Guelly C. Alterations in the ankyrin domain of TRPV4 cause congenital distal SMA,  
  2009 Dec 27.  
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20037588  
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3272392/


Reprinted from Genetics Home Reference:

Reviewed: March 2013
Published: October 23, 2018

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services