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Gene Section

Review

TRPV2 (transient receptor potential cation channel, subfamily V, member 2)

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Identity

Other names: VRL, VRL-1, VRL1

HGNC (Hugo): TRPV2

Location: 17p11.2

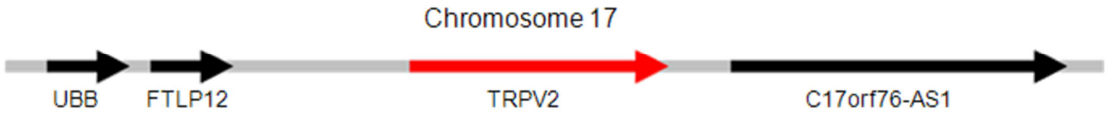
Local order:

Colocolizes upstream with UBB (ubiquitin B) and FTLP12 (ferritin, light polypeptide pseudogene 12), and downstream with C17orf76-AS1 (C17orf76 antisense RNA 1) (non-protein coding).

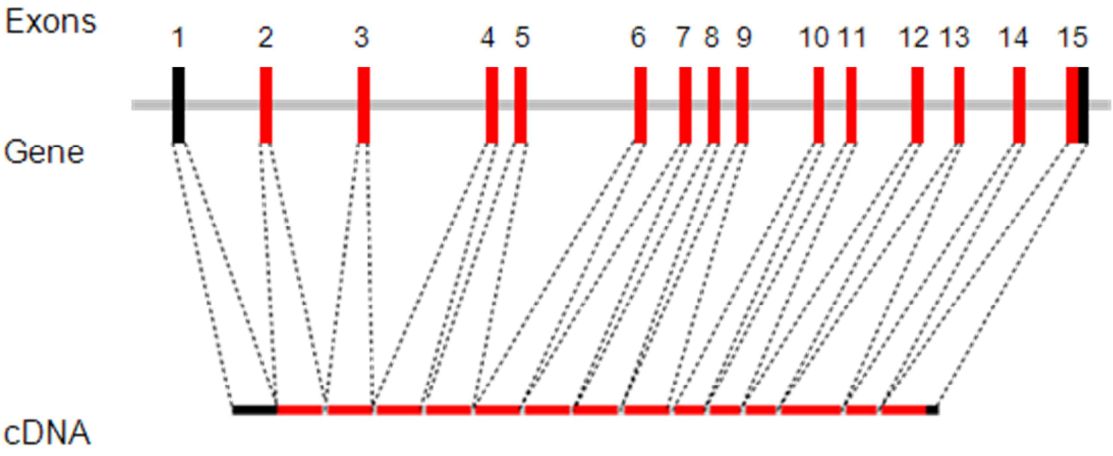
DNA/RNA

Description

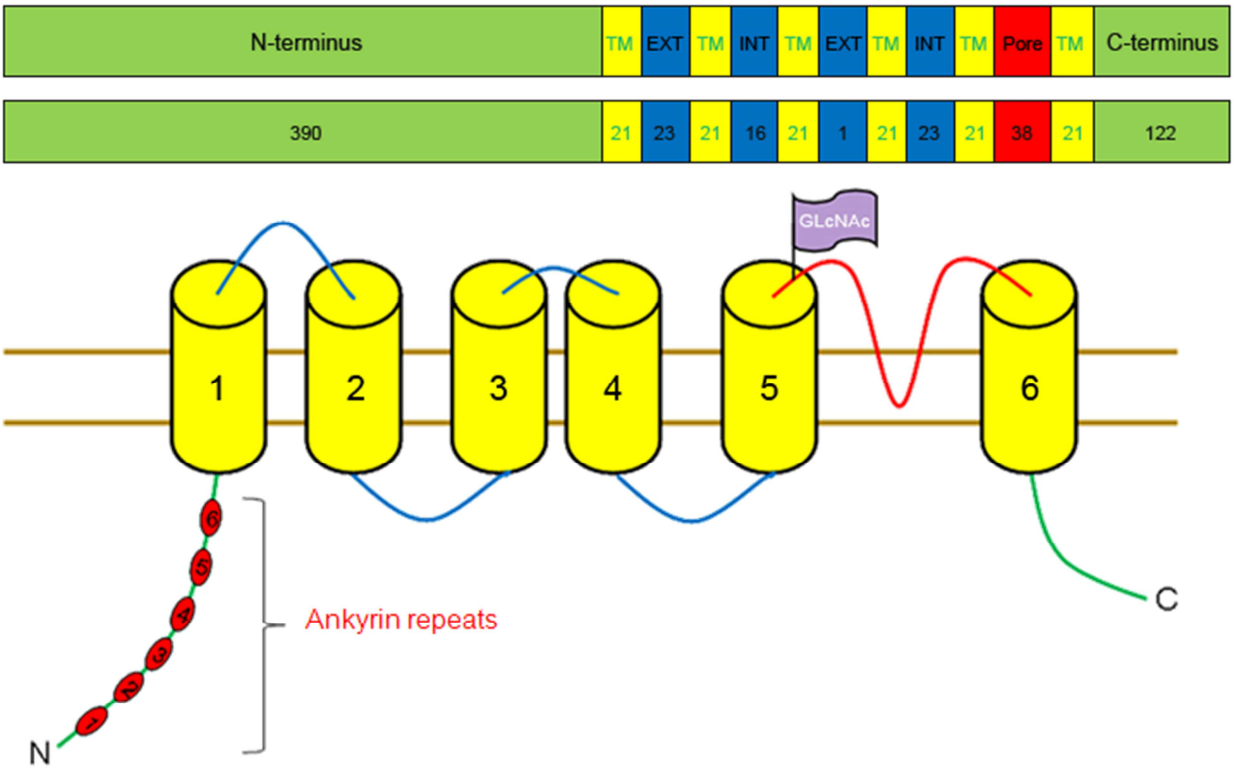
TRPV2 gene consists of 15 exons and 14 introns spanning 1 to 21462 bp of DNA from 17p11.2 and includes a 5'-/3'- non-coding regions. The position of exons is: 1-292, 2021-2327, 4574-4707, 7058-7348, 7928-8226, 10558-10728, 11181-11336, 11908-12006, 12776-12846, 13276-13441, 16243-16309, 16425-16759, 18033-18157, 19349-19428, 21248-21462.



Schematic representation of human TRPV2 gene and neighbouring genes. UBB: ubiquitin B; FTLP12: ferritin, light polypeptide pseudogene 12; C17orf76-AS1: C17orf76 antisense RNA 1 non-protein coding.



Genomic structure of human TRPV2 gene. The coding region is shown with red colour. The non-translated regions are shown with black colour.



The canonical form comprises 764 aa (MW ~86 kDa) and is composed of six transmembrane spanning domains and a pore forming region between transmembrane domains 5 and 6. The N-terminal and C-terminal tails are in cytoplasmatic side. Six N-terminal ankyrin (ANK) repeats are present in N-terminal tail.

Transcription

mRNA product length 2829 bp. No alternative splice variants have been found so far.

Protein

Note

A transmembrane protein of vanilloid family, member 2, TRPV2 channel.

Description

It is a glycosylated membrane protein (764 aa, MW ~86 kDa) with 6 transmembrane regions and a pore-forming loop. N- and C-terminal tails are in cytoplasmic side. TRPV2 contains 6 ankyrin repeats may play a role in the interaction between subunits and is probably homotetramer. Interacts with a cAMP-dependent protein kinase type II regulatory subunit (PRKAR2A or PRKAR2B) and ACBD3. Interacts with SLC50A1; the interaction probably occurs intracellularly and depends on TRPV2 N-glycosylation. This protein forms a non-selective cationic channel in the plasma membrane and is activated by temperatures higher than 52 degrees Celsius; and is not activated by vanilloids and acidic pH.

Expression

TRPV2 channel is expressed in the advanced stages of prostate cancer. TRPV2 transcript levels are higher in patients with metastatic cancer (stage M1) compared with primary solid tumors (stages T2a and T2b). TRPV2 channel is expressed in PC3 and DU-145 cell lines derived from bone and brain metastasis, respectively (Monet et al., 2009; Monet et al., 2010). TRPV2 protein is expressed in human hepatoblastoma (HepG2) cells (Vriens et al., 2004). TRPV2 was found to be more expressed at both the mRNA and protein levels in cirrhotic livers compared with chronic hepatitis, whereas it also occurred in moderately and well-differentiated tumors compared with that of poorly differentiated tumors (Liu et al., 2010). In hepatocellular carcinoma the increased expression of TRPV2 was identified in 16/55 (29%) cases. The enhanced TRPV2 mRNA and protein expression was also found in high-grade and -stage urothelial carcinoma specimens and urothelial carcinoma cell lines. Both the full-length TRPV2 (hTRPV2) and a short splice-variant (s-TRPV2) were detected in normal human urothelial cells and normal bladder specimens, whereas a progressive decline of s-TRPV2 in pTa, pT1, and pT2 stages was observed, up to a complete loss in pT3 and pT4 urothelial carcinoma specimens (Caprodossi et al., 2008). TRPV2 mRNA was abundantly expressed in T24 cells as well (a poorly differentiated urothelial carcinoma cell line). TRPV2 is also expressed in the rat dorsal root ganglia and in F-11 cells, a hybridoma derived from rat dorsal root ganglia and mouse neuroblastoma (Yamada et al., 2010).

TRPV2 is expressed in the human larynx, which may act as laryngeal nociceptors perceiving luminal noxious stimuli. TRPV2 mRNA and protein are expressed in benign astrocyte tissues, and its expression progressively declined in high-grade glioma tissues as histological grade increased (n = 49 cases), and in U87MG cells and in MZC, FCL and FSL primary glioma cells (Nabissi et al., 2010).

Localisation

The biotinylation studies as well as calcium imaging experiments in some works suggest its expression on the plasma membrane (Monet et al., 2009; Monet et al., 2010). It translocates from the cytoplasm to the plasma membrane upon ligand stimulation.

Function

TRPV2 is a calcium-permeable, non-selective cation channel with an outward rectification. Seems to be regulated, at least in part, by IGF-I, PDGF and neuropeptide head activator. May transduce physical stimuli in mast cells. Activated by temperatures higher than 52 degrees Celsius; is not activated by vanilloids and acidic pH.

Homology

TRPV2 channel shares around 50% homology with TRPV1.

Mutations

Note

An experimental mutation published in the C-Terminus. In this study the authors identified a calmodulin binding site on the C-termini of TRPV2 (654-683). The R679 and K681 single mutants of TRPV2 caused a 50% decrease in binding affinity and a double mutation of K661/K664 of the same peptide lowered the binding affinity by up to 75% (Holakovska et al., 2011).

Implicated in

Liver cancer

Disease

TRPV2 protein is expressed in human hepatoblastoma (HepG2) cells and human hepatocellular carcinoma (Vriens et al., 2004).

Prognosis

Quantitative RT-PCR and Western blotting analysis revealed that expression of TRPV2 at both the mRNA and protein levels were increased in cirrhotic livers compared with chronic hepatitis, whereas that also occurred in moderately and well-differentiated tumors compared with that of poorly differentiated tumors (Liu et al., 2010). Immunohistochemistry of the 55 human hepatocellular carcinoma samples showed that the expression of TRPV2 increased when going from normal liver or chronic hepatitis to cirrhosis. Increased TRPV2 expression was observed in tissues of liver cirrhosis (31/37, 83,8%). In HCC, increased expression of TRPV2 was identified in 16/55 (29%) cases. Clinicopathologic assessment suggested a significant association between TRPV2 expression and portal vein invasion and histopathologic differentiation (P = 0,036 and 0,001, respectively). The data suggest that TRPV2 plays a role in human hepatocarcinogenesis and might be a prognostic marker of patients with human hepatocellular carcinoma.

Oncogenesis

Heat induces calcium entry into HepG2 cells.

Bladder cancer

Disease

TRPV2 channel is expressed in urothelial carcinoma and TRPV2 mRNA is abundantly expressed in T24 cells (a poorly differentiated urothelial carcinoma cell line) (Yamada et al., 2010).

Prognosis

Enhanced TRPV2 mRNA and protein expression was found in high-grade and -stage UC specimens and UC cell lines. Both the full-length TRPV2 (hTRPV2) and a short splice-variant (s-TRPV2) were detected in NHUC and normal bladder specimens, whereas a progressive decline of s-TRPV2 in pTa, pT1, and pT2 stages was observed, up to a complete loss in pT3 and pT4 UC specimens (Caprodossi et al., 2008).

Oncogenesis

The expression level in UC cells is correlated with high-grade disease. The administration of CBD increased intracellular calcium concentrations in T24 cells. In addition, the viability of T24 cells progressively decreases with increasing concentrations of CBD, whereas RT4 cells are mostly unaffected. Cell death occurs via apoptosis caused by continuous influx of calcium through TRPV2.

Glia cancer

Disease

TRPV2 channel is expressed in glioma cells: U87MG, MZC, FCL and FSL primary human glioma cells (Nabissi et al., 2010).

Prognosis

The findings indicate that TRPV2 negatively controls glioma cell survival and proliferation.

Oncogenesis

TRPV2 silencing increases U87MG cell proliferation as shown by the increased percentage of cells incorporating 5-bromo-2-deoxyuridine expressing beta(III)-tubulin and rescued glioma cells to Fas-induced apoptosis. In addition, transfection of TRPV2 in MZC glioma cells, by inducing Fas overexpression, resulted in a reduced viability and an increased spontaneous and Fas-induced apoptosis. These findings indicate that TRPV2 negatively controls glioma cell survival and proliferation, as well as resistance to Fas-

induced apoptotic cell death in an ERK-dependent manner (Nabissi et al., 2010).

Prostate cancer

Disease

TRPV2 channel is expressed in the advanced stages of prostate cancer. TRPV2 transcript levels are higher in patients with metastatic cancer (stage M1) compared with primary solid tumors (stages T2a and T2b). TRPV2 channel is expressed in PC3 and DU-145 cell lines derived from bone and brain metastasis, respectively (Monet et al., 2009; Monet et al., 2010).

Prognosis

TRPV2 channel indicated that it is primarily involved in cancer cell migration and not in cell growth. A role for TRPV2 in prostate cancer progression to the aggressive castration-resistant stage has been suggested, prompting evaluation of TRPV2 as a potential prognostic marker and therapeutic target in the setting of advanced prostate cancer.

Oncogenesis

TRPV2 silencing decreases prostate cancer cell migration not affecting cell proliferation (Monet et al., 2009). Introducing TRPV2 into androgen-dependent LNCaP cells enhanced cell migration along with expression of invasion markers matrix metalloproteinase (MMP) 9 and cathepsin B. Small interfering RNA-mediated silencing of TRPV2 reduced the growth and invasive properties of PC3 prostate tumors established in nude mice xenografts, and diminished expression of invasive enzymes MMP2, MMP9, and cathepsin B (Monet et al., 2010).

Muscular dystrophy

Note

Mechanisms: TRPV2 is a principal Ca(2+)-entry route leading to a sustained [Ca(2+)](i) increase and muscle degeneration (Zanou et al., 2009).

Disease

When transgenic mice expressing a TRPV2 mutant in muscle are crossed with mdx mice, the [Ca(2+)](i) increase in muscle fibers is reduced by dominant-negative inhibition of endogenous TRPV2 (Iwata et al., 2009).

Prognosis

It was suggested a promising therapeutic target for the treatment of muscular dystrophy.

Duchenne myopathy

Note

Mechanisms: a role of TRPV2 channel in the physiopathology of Duchenne muscular dystrophy has been suggested cause muscles from dystrophin-deficient mice typically present an exaggerated susceptibility to eccentric work characterized by an important force drop and an increased membrane permeability consecutive to repeated lengthening contractions (Zanou et al., 2009).

Disease

Duchenne myopathy is a lethal disease due to the absence of dystrophin, a cytoskeletal protein (Zanou et al., 2009).

Prognosis

Muscles from dystrophin-deficient mice are largely protected from eccentric work-induced damage by overexpressing a dominant negative mutant of TRPV2 ion channel.

Norrbottnian congenital insensitivity to pain

Note

Mechanisms: a dramatic loss of such nerve fibers was seen in skin from individuals with Norrbottnian congenital insensitivity to pain, further suggesting that these ion channels are expressed primarily on nociceptive primary sensory neurons in human skin (Axelsson et al., 2009).

Disease

Nerve fibers immunoreactive for TRPV2 are absent or substantially reduced in number in individuals with Norrbottnian congenital insensitivity to pain, an autosomal disease selectively affecting the development of C-fiber and Adelta-fiber primary afferents (Axelsson et al., 2009).

Prognosis

Nerve fibers in human skin express TRPV2 that co-localizes with the sensory neuropeptides CGRP and SP, but not with NF200, VIP or TH.

Hyperalgesia

Note

Mechanisms: upregulation of TRPV2 may play important roles in the mechanical hyperalgesia induced by cisplatin (Hori et al., 2010).

Disease

TRPV2 is expressed in sensory neurons and affects mechanical and thermal hyperalgesia examined in a rat model of cisplatin-induced peripheral neuropathy (Kasama et al., 2007).

To be noted

Note

TRPV2 knockout mice have been generated. Behavioral and electrophysiological responses to heat and mechanical stimuli were examined TRPV2 knock-out mice (Park et al., 2011). TRPV2 knock-out mice showed reduced embryonic weight and perinatal viability. TRPV2 knock-out mice showed normal behavioral responses to noxious heat over a broad range of temperatures and normal responses to punctate mechanical stimuli, both in the basal state and under hyperalgesic conditions such as peripheral inflammation and L5 spinal nerve ligation. Electrophysiological recordings from skin afferents showed that C-fiber responses to heat and C- and Aδ-

fiber responses to noxious mechanical stimuli were unimpaired in the absence of TRPV2. The prevalence of thermosensitive Aδ-fibers was too low to permit comparison between genotypes. Thus, TRPV2 is important for perinatal viability but is not essential for heat or mechanical nociception or hypersensitivity in the adult mouse (Park et al., 2011).

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