

# TRPV3: Time to Decipher a Poorly Understood Family Member!

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## Abstract

The vanilloid transient receptor potential channel TRPV3 differs in several aspects from other members of the TRPV subfamily. This  $\text{Ca}^{2+}$ , ATP and calmodulin regulated channel constitutes a target for many natural compounds and has a unique expression pattern as the most prominent and important TRP channel in keratinocytes of the skin. Although TRPV3 is considered as a thermosensitive channel, its function as a thermosensor in the skin is challenged. Nevertheless, it plays important roles in other skin functions such as cutaneous sensations, hair development and barrier function. More recently, mutations in TRPV3 were link with a rare genodermatotic disorder known as the Olmsted syndrome. This review gives an overview on properties of TRPV3 and its functions in the skin and skin diseases.

## TRPV3 identity

The vanilloid transient receptor potential (TRPV) subfamily comprise 6 homologous cation channels (Nilius & Owsianik, 2011) (Figure 1A). The founding member of this subfamily, TRPV1, was identified as vanilloid receptor (VR1) constituting a target for capsaicin, a vanilloid found in chilli pepers. The *TRPV3* gene ([ENSG00000167723](#)) spans 18 exons that might be differentially

spliced, yielding 790, 791 and 765 amino acid (aa) variants in humans. The most prevalent form of TRPV3 (790 aa) shares 43% sequence homology with TRPV1 and has been originally described as a thermosensitive channel (Peier *et al.*, 2002; Smith *et al.*, 2002; Xu *et al.*, 2002). Similar to other TRP channels, TRPV3 seems to form tetrameric complex in which each subunit contains 6 transmembrane spanning segments (S1-6) and cytoplasm facing amino- (N-) and carboxy- (C-) termini. The putative cation permeable pore is believed to be located between S5 and S6 segments. The N terminal part of the channel (from aa 167-363) comprises 6 ankyrin repeats (AR) that form an ankyrin repeat domain (ARD) involved in protein-protein interactions (more detailed information see (Clapham *et al.*, 2009) and [TRP channel data base Clapham/Owsianik/Nilius](#)). Very likely, all TRPVs seem to share structural similarity with recently obtain cryo-electronmicroscopic structure of TRPV1 that shows fourfold symmetry and has two distinct regions: a large open basket-like domain, likely corresponding to the cytoplasmic N- and C-terminal portions, and a more compact transmembrane domain (Figure 1B) (Moiseenkova-Bell *et al.*, 2008). A region between AR2 and AR3 of TRPV3 as well as TRPV1 comprises a conserved site that is involved in binding of ATP and calmodulin (CaM) (Figure 2A, B) (Phelps *et al.*, 2010).

So far, TRPV3 has been identified as an interacting partner of A-kinase anchor protein 5 (AKAP-5) (Zhang *et al.*, 2008), CaM (Phelps *et al.*, 2010), epithelial growth factor receptor (EGFR) (Cheng *et al.*, 2010), and TRPV1 (Smith *et al.*, 2002). However, like other TRPV members it can form heteromeric complexes with other TRP channels such as TRPC1 and TRPP2 (Gaudet, 2008; Köttgen *et al.*, 2008; Ma *et al.*, 2011).

TRPV3 is highly expressed in the skin, mainly in keratinocytes and in cells surrounding the hair follicles (Valdes-Rodriguez *et al.*, 2013). Its expression has been also detected in other organs such as the tongue, testis, the cornea, the distal colon, the larynx, and the inner ear (Peier *et al.*, 2002; Xu *et al.*, 2002; Moqrich *et al.*, 2005; Hamamoto *et al.*, 2008; Ishibashi *et al.*, 2008; Ueda *et al.*, 2009; Borbiero *et al.*, 2011; Mergler *et al.*, 2011). In sensory neurons of dorsal root (DRG) and trigeminal ganglia (TG) TRPV3 expression is rather low comparing to other TRP channels and results in formation of heteromeric channels with TRPV1. Heteromeric TRPV1/TRPV3 channels display distinct single-channel conductance and voltage-dependence from homomeric channels and are activated by heat and capsaicin (Cheng *et al.*, 2012).

In contrast to TRPV5 and TRPV6, the only highly  $\text{Ca}^{2+}$  selective channels in the entire TRP family, TRPV3, like other TRPVs, is modestly permeable to  $\text{Ca}^{2+}$  (the  $P_{\text{Ca}}/P_{\text{Na}}$  permeability ratio  $\sim 10$ ) (Gees *et al.*, 2010). Similar to TRPV1, the pore of TRPV3 seems to be prone for a pore dilation during stimulation, rendering permeability for large cations (Chung *et al.*, 2008). As for all TRPVs, negatively charged amino acids in the pore play a central role for cation permeation and, furthermore, the opened pore is blocked by both extra- and intracellular  $\text{Mg}^{2+}$ . This effect is

attenuated by neutralization of the aspartic acid residue in the extracellular pore loop or two glutamic acid in the inner pore region (Cao *et al.*, 2012).

Single channel properties of TRPV3 are strongly temperature dependent. At room temperature TRPV3 has an inward and outward slope conductance of 201 and 147 pS, respectively, whereas at 39°C, both conductances are respectively increased to 337 and 256 pS (Chung *et al.*, 2004). TRPV3 is unique in its activation properties. In contrast to other TRPV channels that desensitize during repetitive activation, TRPV3 channel activity successively increases upon repeated stimulation (Peier *et al.*, 2002; Xu *et al.*, 2002; Chung *et al.*, 2004) (Xiao *et al.*, 2008a) (see Figure 2A for action sites of different TRPV3 modulators). This TRPV3 sensitivity and potentiation by repeated agonist stimulations is reduced by ATP. In contrast, TRPV1 is sensitized by ATP. Although ATP and CaM competitively bind to a very conserved binding site within the ARD they both generate different sensitivity and adaptation profiles of TRPV1 and TRPV3 (Phelps *et al.*, 2010). The opposite effect of ATP on both channels might be due to changes in Ca<sup>2+</sup> dependent inactivation. TRPV3 sensitization during repetitive activation is due to a decrease in Ca<sup>2+</sup>-dependent channel inhibition resulting from TRPV3-dependent increases of intracellular Ca<sup>2+</sup> concentration ([Ca<sup>2+</sup>]<sub>i</sub>) (Xiao *et al.*, 2008a). At low [Ca<sup>2+</sup>]<sub>i</sub>, CaM binds at the ARD domain of TRPV3 and inhibits the channel. An increase in [Ca<sup>2+</sup>]<sub>i</sub> supports Ca<sup>2+</sup> binding to CaM, which is then released from the channel and mediates sensitization (Xiao *et al.*, 2008a; Phelps *et al.*, 2010). Besides this Ca<sup>2+</sup> dependent mechanism, TRPV3 sensitization is also an intrinsic property of the channel. In cell-free patches (i.e. in a membrane delimited manner), 1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA), a fast calcium chelator, accelerates the sensitization by a direct potentiation effect on channel activation (Liu *et al.*, 2011).

TRPV3, similarly to TRPV1 and TRPV2 (and, albeit not yet shown, for TRPV4) has an intrinsic voltage dependence. Depolarization activates the channel at very positive potentials with a half maximal activation of ~+50mV. TRPV3 currents evoked by channel agonists such as 2-aminoethoxydiphenyl borate (2-APB) are potentiated by Gq/11-coupled receptor stimulation in HEK-293 cells and human keratinocytes (Xu *et al.*, 2006). Exposure of human keratinocytes to the purinergic P2Y receptor agonist ATP also induced a dramatic increase of currents through TRPV3 (Doerner *et al.*, 2011). This increase is due to a more than 60 mV shift of the midpoint of the potentials at steady state activation toward more negative potentials, e.g. shifting TRPV3 activation into a more physiological voltage range. In addition, the fraction of constitutive open channels is also increased. Similarly, activation of muscarinic M1-receptors with carbamylcholin (CCh) caused a more than 100 mV shift of TRPV3 activation towards negative potentials. This shift is decreased in the absence of intracellular Ca<sup>2+</sup>. This dramatic modulation of the voltage dependence is explained by a depletion of phosphatidyl inositol (4,5) bisphosphate (PI(4,5)P2). Contrary to the most of TRP channels, PI(4,5)P2 hydrolysis or pharmacological inhibition of PI 4 kinase, which blocks PI(4,5)P2 synthesis, potentiates TRPV3. PI(4,5)P2 directly binds to a

specific residues in the TRP box of TRPV3 (R696 and K705), resulting in reduced open channel probability. Mutations of both residues to alanines (R696A and K705A) diminish the PI(4,5)P<sub>2</sub> depletion-induced channel activation while 2-APB-activated and voltage-dependent whole cell currents are unchanged (Doerner *et al.*, 2011). On the other hand, 17(R)-resolvin D1 (17R-RvD1), a naturally occurring pro-resolving lipid, specifically inhibits the TRPV3 activity at nanomolar and micromolar ranges due to a shift of the voltage dependence of TRPV3 to more positive potentials (Bang *et al.*, 2012).

### **Does TRPV3 really play a role in thermosensation?**

TRPV3 is activated by innocuous warm temperatures above 30-33 °C and, therefore, it was proposed as a putative thermo-sensor in the skin. Unlike TRPV1, TRPV3 is sensitized by repeated stimulations with temperature (Xu *et al.*, 2002). Furthermore, *Trpv3* knockout mice show strong deficits in responses to innocuous and noxious heat whereas other sensory modalities are not affected (Moqrich *et al.*, 2005). Sensitization of TRPV3 to warm temperatures is also influenced by different endogenous pro-inflammatory agents as bradykinin, histamine, ATP (binding to ARD), the protein kinase C isoenzyme PKC $\epsilon$  and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) (Mandadi *et al.*, 2006; Huang *et al.*, 2008; Phelps *et al.*, 2010). Thus, an obvious puzzle emerged, how activation of a channel expressed in keratinocytes can signal to thermo-sensing C-type nerve fibers. First, heating of keratinocytes causes ATP release that activates purinergic receptors in these nerves fibers. In *Trpv3* knockout mice, this signaling pathway is defective (Mandadi *et al.*, 2009). Second, activation of TRPV3 also results in the release of an intercellular messenger, PGE<sub>2</sub> (Huang *et al.*, 2008), which in addition to ATP release, might function as a missing intercellular signaling molecule. This suggests that TRPV3 might also play a role in thermal hyperalgesia during inflammation. However, it has been recently shown that accumulation of interstitial ATP does not occur during local heating of the skin (Gifford *et al.*, 2012). Therefore, TRPV3 might not have a role in temperature sensation or the related vasodilator responses in the skin.

Another open question, evident for the so-called “thermoTRPs”, concerns a mechanism of temperature sensation. From a total of more than 14.000 random mutant clones of mouse TRPV3, only five single point mutations abolish activation of TRPV3 by heat whereas all other activation mechanisms, such as chemical activation of the voltage dependence, remain intact. These mutations are located in a putative S6 and an extracellular part of the pore region, suggesting that a specific TRPV3 region accounts for temperature sensing (Grandl *et al.*, 2008). However, the molecular requirement for such a “thermosensing module” is highly speculative and so far does not reveal any mechanistic inside insight to temperature sensing (Voets, 2012).

Therefore, it is speculated whether the activation of skin TRPV3 has any physiological effects in thermo-regulation. Intra-gastric application of natural TRPV3 stimulators, thymol and ethyl vanillin, does not exert changes in thermogenesis or heat dissipation, indicating a restricted effects of TRPV3 on autonomic thermoregulation (Masamoto *et al.*, 2009). In addition, investigations on another strain of TRPV3 knockout mice with defined backgrounds revealed that these animals exhibit minor (if any) alterations in thermal preference behavior, again strongly indicating that TRPV3 and TRPV4, also found in keratinocytes, are not involved in thermoregulation (Huang *et al.*, 2011). Nevertheless, TRPV3 seems to play a role in the evolution of thermoregulation. In lower vertebrates such as a frog *Xenopus tropicalis*, TRPV3 is not activated by heat but detects noxious cold temperatures of these cold blooded animals (Saito *et al.*, 2011). In contrast, TRPV3 of mammals and other warm blooded animals senses innocuous warm that is close to an optimal environmental temperature, indicating flexibility of the TRPV3 channel function during evolution.

### TRPV3 modulation

TRPV channels show a complex pharmacology including compounds that range from very selective agonists such as capsaicin for TRPV1 to less selective ones that activate or inhibit more than one TRPV channel. Ruthenium red blocks voltage-dependently (i.e. at negative potentials) all TRPV channels, albeit with variable potency (for a review see Vennekens *et al.*, 2008). 2-APB activates TRPV3 but also, to a lesser extent, TRPV2 and TRPV1 (see for a comprehensive review Vriens *et al.*, 2009). It likely binds to two TRPV3 cytoplasmic sites, H426 in the N terminus and R696 in the TRP box (Chung *et al.*, 2004; Hu *et al.*, 2004; Hu *et al.*, 2009). Mutations of corresponding residues in TRPV4 to TRPV3 analogues, N426H and W737R, renders 2-APB-insensitivity of TRPV4 into TRPV3-like 2-APB activation pattern. The structurally related compounds such as diphenylboronic anhydride (DPBA) and diphenyltetrahydrofuran (DPTHF) can also modulate TRPV3. DPBA acts as a TRPV3 agonist whereas DPTHF is a potent antagonist. All activators show a biphasic time course, i.e. a sensitizing phase is followed by an abrupt transition to a secondary phase with different biophysical properties of the channels. The second phase is probably due to alteration on the pore during activation (Chung *et al.*, 2005).

TRPV3 is activated by protons. The N-terminal histidine residue, H426, which also participate to the TRPV3 channel activation by 2-APB, is critical for sensing intracellular proton levels.  $\alpha$ -hydroxyl acids (AHAs, e.g. glycolic acid) from natural sources that are used as in the cosmetic industry penetrate the skin and act as proton donors (Cao *et al.*, 2012). AHAs cause exfoliation that has been used for many years to help skin maintenance. In this process, the oldest dead skin cells on the skin's outermost surface are removed and fresh skin cells are exposed.

Intracellular acidification causes activation of TRPV3 that leads to keratinocyte cell death and hence promotes exfoliation.

Monoterpenes are a class of terpenes which comprise natural compounds like camphor, borneol or menthol derived from two isoprene units. TRPV3 is activated by aromatic monoterpenes such as camphor laurel (from *Cinnamomum camphora*), carvacrol (from *Origanum vulgare* and *Satureja*), thymol and its derivatives (from thyme, *Thymus vulgaris*), eugenol (from the evergreen tree *Syzygium aromaticum*), cresol (a phenol from coal or wood tar), cinnamon (from the bark of *Cinnamomum verum*), menthol (from mint *Mentha piperita*), borneol (from the genus *Artemisia*), and thujone (from the genus *Thuja*) (Moqrich *et al.*, 2005); (Macpherson *et al.*, 2006; Xu *et al.*, 2006; for a review see Vriens *et al.*, 2009). In many cases these compounds also potentiate temperature response of TRPV3 (Macpherson *et al.*, 2006; Xu *et al.*, 2006). Non-aromatic monocyclic monoterpenes, e.g. dihydrocarveol, carveol, and acyclic monoterpenes, e.g. linalool, geraniol, and also propofol are also potent TRPV3 activators (Vogt-Eisele *et al.*, 2007). On the other hand, prolonged exposure of TRPV3 with monoterpenoids results in agonist-specific desensitization of the channel, whereas the non-terpenoid agonist such 2-APB induces sensitization, demonstrating an agonist-dependent modulation of TRPV3 (Sherkheli *et al.*, 2009).

Incensole and incensole acetate are found in incense, crude extracts from incense species like *Boswellia papyrifera*. Burning of *Boswellia* resin as incense has been part of religious and cultural ceremonies for millennia and is believed to contribute to the spiritual exaltation associated with such events. Both compounds are potent bioactive diterpenic cembrenoids that activate TRPV3. Incensole acetate causes anxiolytic-like and antidepressive-like behavioral effects in mice that are absent in *Trpv3* knockout animals (Moussaieff *et al.*, 2008; Paul & Jauch, 2012).

Plant cannabinoids, like  $\Delta(9)$ -tetrahydrocannabinol (THC) and cannabidiol (CBD), modulate most, if not all TRPV channels. CBD and tetrahydrocannabivarin (THCV) stimulate TRPV3 with high efficacy and potency whereas the derivatives cannabigerovarin (CBGV) and cannabigerolic acid (CBGA) desensitize the channel (De Petrocellis *et al.*, 2012).

Farnesyl pyrophosphate (FPP) is an endogenous substance produced in the mevalonate pathway that plays an important role in the maintenance of cell membranes. It has been shown that FPP is a specific activator of TRPV3. Interestingly, isopentenyl pyrophosphate (IPP), an upstream metabolite in the same pathway, is an inhibitor of TRPV3, suggesting possible requirement of highly controlled TRPV3 function in this process (Bang *et al.*, 2010, 2011). Since the super-cooling agent icilin, a potent activator of TRPM8, was shown to inhibit TRPV3 at low concentrations (Sherkheli *et al.*, 2012), it was also postulated that application of such agents to the skin might be beneficial in diseases with an increased TRPV3 activity. Novel inhibitors of TRPV3 have promising analgesic effects which (as also shown below) implicates that TRPV3 is involved in the nociceptive signaling as well (Reilly & Kym, 2011).

## TRPV3: role in skin physiology and pathology

A growing body of evidence implicates the role of TRPV3, which is most abundantly expressed by skin cells, in multiple cutaneous mechanisms. In addition, TRPV3 was also associated with certain skin diseases and symptoms. Since we have recently detailed these TRPV3-coupled (patho)physiological regulatory mechanisms in a quite comprehensive review (Nilius & Biro, 2013), here we only highlight some of these processes.

TRPV3 is a central player in regulating the physiological skin homeostasis.

- It regulates proliferation, differentiation, and apoptosis of human (as well as mouse) epidermal keratinocytes (Cals-Grierson & Ormerod, 2004; Radtke *et al.*, 2011); (Miyamoto *et al.*, 2011) (Cao *et al.*, 2012). Specifically, its activation results in the inhibition of keratinocyte proliferation and the induction of apoptosis.
- Its activation was shown to control keratinocyte migration and wound healing, most probably via the release of nitric oxide (Miyamoto *et al.*, 2011).
- It is involved in both hair morphogenesis (mouse) and hair follicle cycling (human and mouse) (Borbiro *et al.*, 2011) (Cheng *et al.*, 2010) (Asakawa *et al.*, 2006) (Xiao *et al.*, 2008b). Indeed, activation of TRPV3 in human hair follicle organ culture leads to premature, apoptosis-driven organ-involution (catagen). Likewise, “gain-of-function” (Gly573Ser) mutation of the channel results in a hairless phenotype in rodents.
- In mice, as part of the epidermal growth factor (EGFR) and transforming growth factor- $\alpha$  (TGF- $\alpha$ ) signalplex, TRPV3 was found to play a role in the formation of the epidermal barrier (Cheng *et al.*, 2010) (Denda *et al.*, 2007).

Besides its physiological regulatory roles, altered TRPV3 channel activities were also associated to certain pathological cutaneous conditions. These diseases and symptoms further strengthen the concept on the central role of TRPV3-coupled signaling in numerous skin functions.

- Multiple “gain-of-function” mutations (the above G573S as well as G573C and W692G) of TRPV3 were identified in Olmsted syndrome, the first cutaneous TRPopathy (Lin *et al.*, 2012) (Lai-Cheong *et al.*, 2012). This rare genodermatosis is characterized by the development of hyper-orthokeratosis and (mostly periorificial) keratomas, diffuse alopecia, and extreme pruritus (which symptoms perfectly mirror those found in mice bearing similar “gain-of-function” mutations of the *Trpv3* gene, see above) (Figure 3).
- Besides the hereditary Olmsted syndrome, TRPV3 is also involved in the development of several acquired skin diseases and symptoms. Indeed, activation of TRPV3 on

keratinocytes lead to the release of a plethora of algogenic and pruritogenic substances (e.g. certain interleukins, ATP, PGE<sub>2</sub>) which, by acting as intercellular messengers, stimulate the adjacent sensory afferents of the skin and hence induce cutaneous pain and itch (Mandadi *et al.*, 2009) (Xu *et al.*, 2006) (Huang *et al.*, 2008) (Mandadi *et al.*, 2006) (Phelps *et al.*, 2010). In good agreement with these findings, the above “gain-of-function” TRPV3 mutations in mice also leads to severe itching (Asakawa *et al.*, 2006) (Xiao *et al.*, 2008b) (Yoshioka *et al.*, 2008) and TRPV3-KO animals exhibited a markedly suppressed itch-associated behavior (Yamamoto-Kasai *et al.*). Furthermore, it is noteworthy that the aforementioned endogenous activator of the keratinocyte TRPV3 (FPP) – similar to the irritative effects of topically applied natural plant-derived TRPV3 activators – induced pain and irritation whereas the TRPV3 antagonists (IPP, 17R-RvD1) inhibited nociceptive behavior in experimental models (Bang *et al.*, 2010, 2011). Accordingly, small molecule novel inhibitors of TRPV3 are now in clinical trials as potent analgesic agents (Moran *et al.*, 2011) (Ferrer-Montiel *et al.*, 2012).

- The above intercellular messengers, released from keratinocytes upon TRPV3 stimulation, exert not only algogenic and pruritogenic effects but also profound pro-inflammatory actions (Xu *et al.*, 2006) (Huang *et al.*, 2008). Moreover, as detailed above, multiple pro-inflammatory agents (e.g. ATP, bradykinin) were shown to sensitize TRPV3 expressed by keratinocytes. Of further importance, mice with the above “gain-of-function” TRPV3 mutations develop various degrees of cutaneous inflammation which resembles to the characteristic symptoms of human atopic dermatitis (Asakawa *et al.*, 2006) (Xiao *et al.*, 2008b) (Yoshioka *et al.*, 2008). These data collectively argue for that TRPV3 is also involved in the pathogenesis of cutaneous inflammation.
- Finally, it should be mentioned that TRPV3 expression is markedly upregulated in rosacea, a chronic inflammatory skin condition (Sulk *et al.*, 2012).

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## Legends

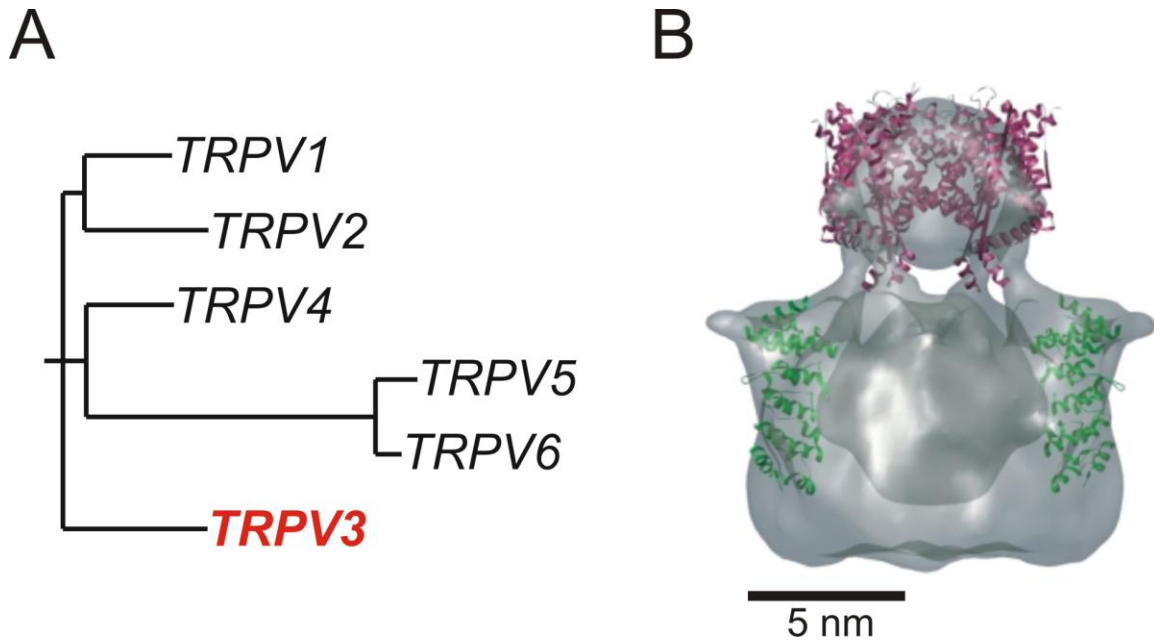


Figure 1.

TRPV3 is a member of vanilloid subfamily of TRP channels. A) Phylogenetic relationship between TRPV channels. B) Electron cryomicroscopy structure of TRPV1 channel (Moiseenkova-Bell et al., 2008). Docking of the high-resolution structure of Kv1.2 transmembrane domains (maroon; PDB entry 2A79) and TRPV1 ankyrin domains (green; PDB entry 2PNN; two of four such domains are shown) into TRPV1 3D reconstruction (adopted with permissions from (Moiseenkova-Bell et al., 2008)).

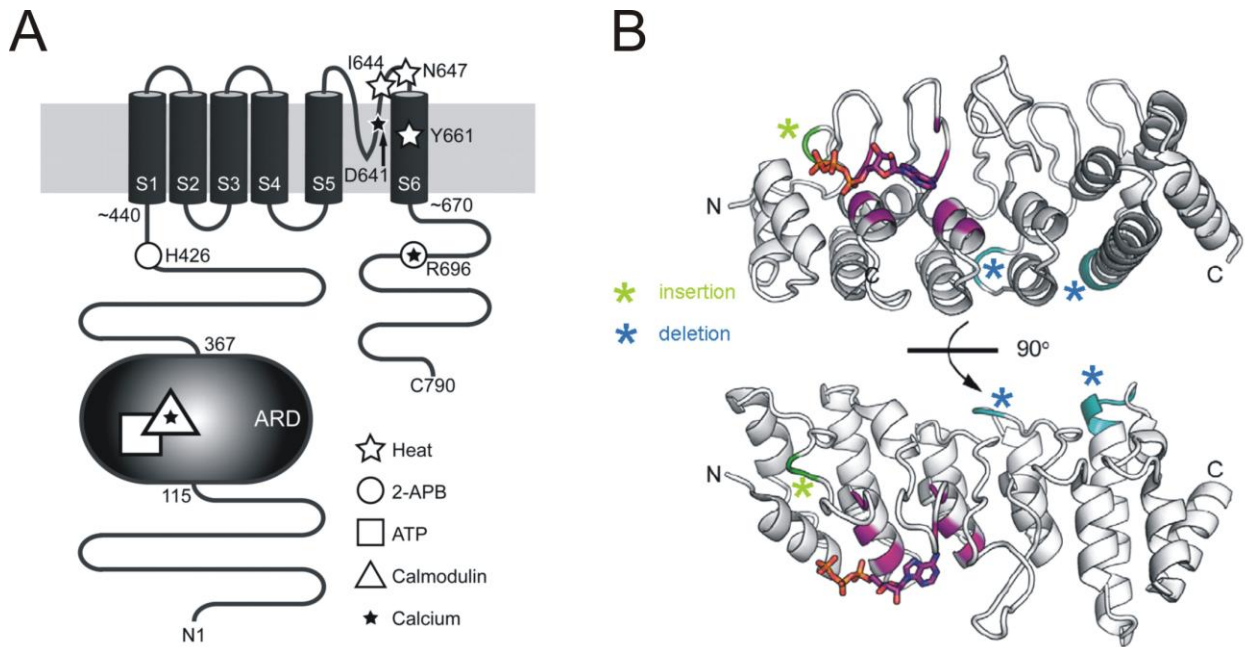


Figure 2.

Predicted structural topology of TRPV3. A) Localization of major functional domains and residues in TRPV3. Residues involved in heat activation (Ile644, Asn647, and Tyr661), activation by 2-APB (His426 and Arg696), and calcium sensitivity (Arg696) as well as the extracellular site Asp641 are indicated. B) ARD of TRPV3 shows an insertion and 2 deletions (indicated by green and blue, respectively) when compared to TRPV1 ARD structure. ATP binding site with docked ATP are colored in purple, between AR2 and AR3, established by K169, K174, L177, Y213, Q216, I221, E224 (adopted with permission from (Phelps et al., 2010)).

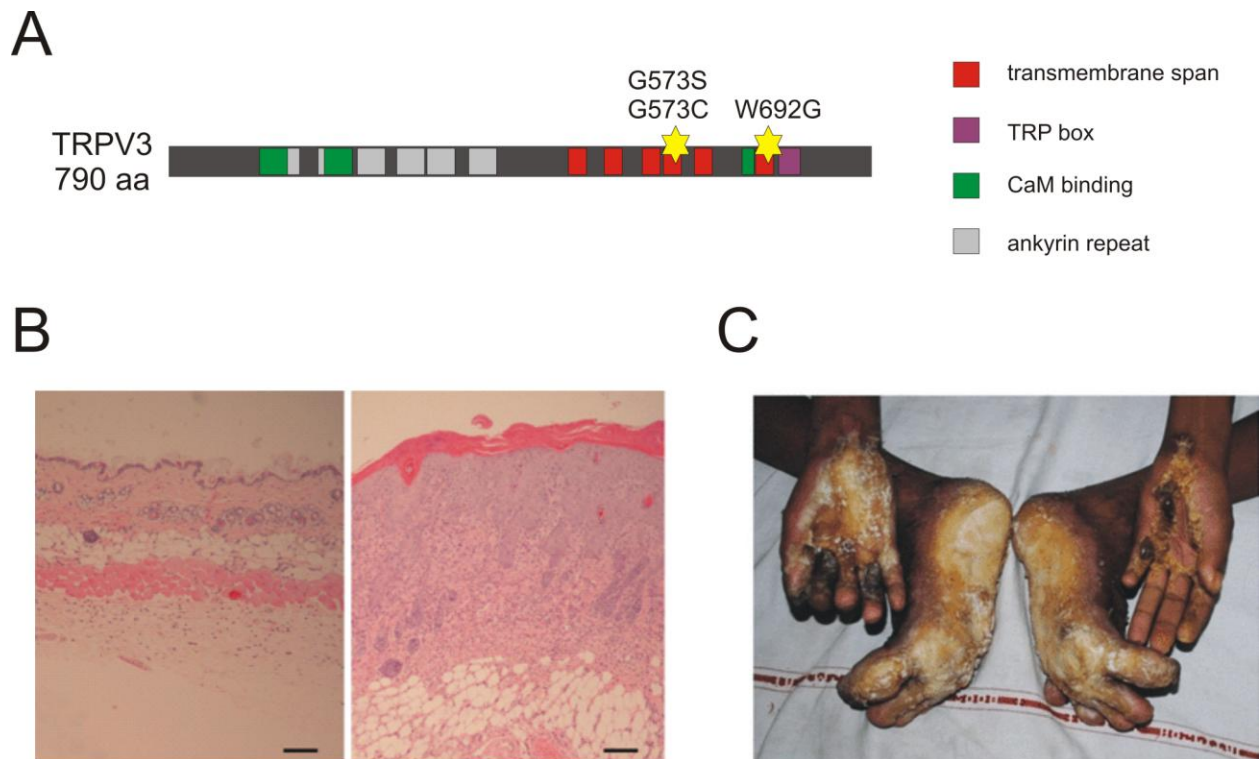


Figure 3.

Missense mutations in TRPV3 are involved in the Olmsted syndrome. A) Linear representation of TRPV3 with annotations of OLM mutations. B) Transgenic mouse with the G573S mutation (right picture) shows hyperkeratosis and thickening of the back skin when compared to the control DS animals (left picture; adopted with permissions from (Yoshioka et al., 2008)). C) Keratoderma involving most of the palmar and plantar aspects in 12 year-old boy with the Olmsted syndrome (adopted with permissions from (Lai-Cheong et al., 2012)).

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Figure 1

A

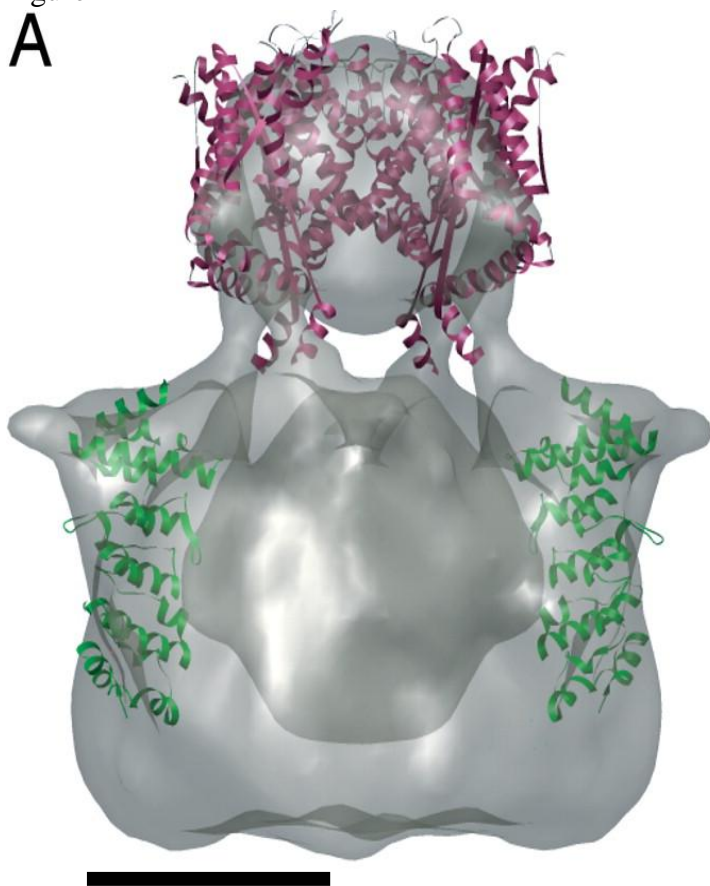


Figure 2

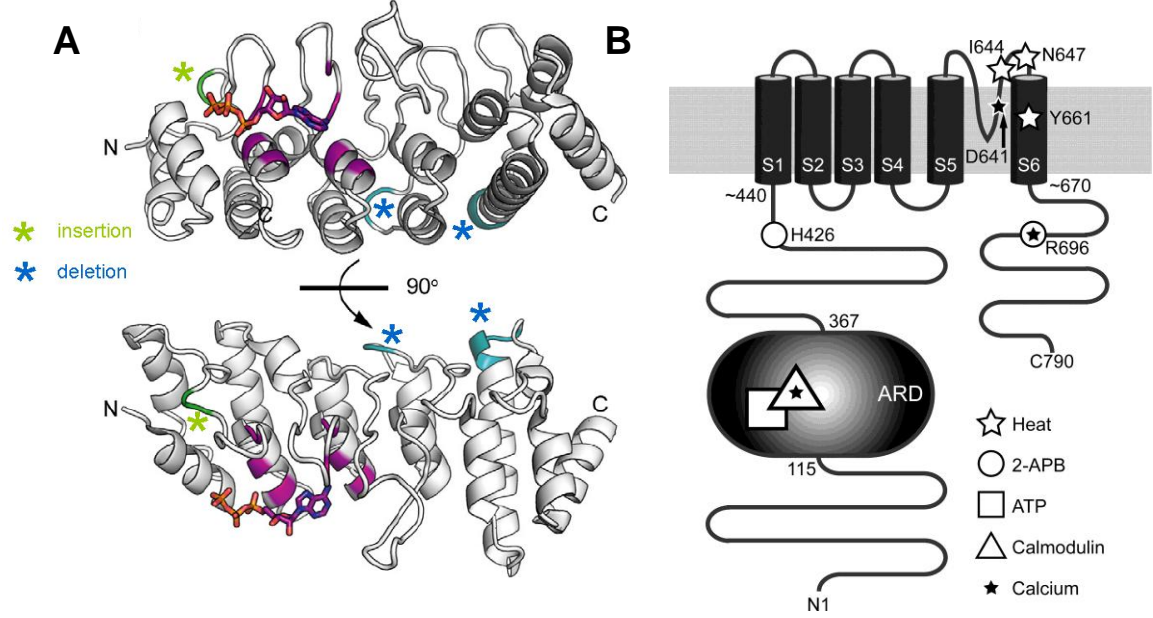


Figure 3

