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Review

# Voltage-gated calcium channels in genetic diseases

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**Abstract**

Voltage-gated calcium channels (VGCCs) mediate calcium entry into excitable cells in response to membrane depolarization. During the past decade, our understanding of the gating and functions of VGCCs has been illuminated by the analysis of mutations linked to a heterogeneous group of genetic diseases called "calcium channelopathies". Calcium channelopathies include muscular, neurological, cardiac and vision syndromes. Recent data suggest that calcium channelopathies result not only from electrophysiological defects but also from altered $\alpha_1$/$Ca_V$ subunit protein processing, including folding, posttranslational modifications, quality control and trafficking abnormalities. Overall, functional analyses of VGCC mutations provide a more comprehensive view of the corresponding human disorders and offer important new insights into VGCC function. Ultimately, the understanding of these pathogenic channel mutations should lead to improved treatments of such hereditary diseases in humans.


*Keywords:* Calcium channelopathies; Hypokalemic periodic paralysis; Long QT syndrome; Ataxia; Migraine; Epilepsy; Autism

## 1. From voltage-gated calcium channels to calcium channelopathies

In excitable cells, the membrane potential serves as the primary integrator of numerous ionic channel inputs. In that context, voltage-gated calcium channels (VGCCs) provide a unique route for calcium entry, thereby controlling a wide variety of physiological processes, such as excitation–contraction coupling, neurotransmitter release, hormone secretion and gene expression. Fig. 1 illustrates the overall functional and molecular properties of VGCCs (for review [1]). According to their threshold of activation, VGCCs are categorized as low voltage-activated (LVA) and high voltage-activated (HVA). Based on biophysical and pharmacological features, VGCCs are designated as T-, L-, N-, P/Q- and R-types. VGCCs are composed of a pore forming $\alpha_1$/$Ca_V$ subunit, which is associated – in the case of L-, N-, P/Q- and R-types channels – with regulatory $\alpha_2\delta$, $\beta$ and $\gamma$ subunits (Fig. 1). Ten genes (named CACNA1A-I and CACNA1S, see Fig. 2) are coding for the $\alpha_1$/$Ca_V$ subunits [2]. Alternative splicing largely enhances the number of active forms of the $\alpha_1$/$Ca_V$ proteins (reviewed in [3]). Overall, the bulk of studies performed in the 1990s has greatly contributed to the identification of the key mechanisms that generate multiple forms of VGCC activity (reviewed in [1,4]).

Over the past decade, several inherited disorders in humans have been linked to mutations in the genes encoding VGCCs. These genetic diseases are designated "calcium channelopathies". There are various kinds of disorders, essentially muscular and neurological that involve many of the VGCC genes. Always when considering a channelopathy, an electrophysiological alteration is suspected as a primary cause of the disease. However, emerging evidence indicates that several different aspects of VGCC processing and function can be affected. Here we present the various calcium channelopathies identified to date and discuss the current knowledge regarding the pathogenicity of the corresponding mutations.

## 2. Calcium channelopathies associated with L-type VGCCs

Four genes encode L-type VGCCs (Fig. 2) and their expression is either restricted in specialized tissues, as for $Ca_V$1.1 (CACNA1S) and $Ca_V$1.4 (CACNA1F) in skeletal

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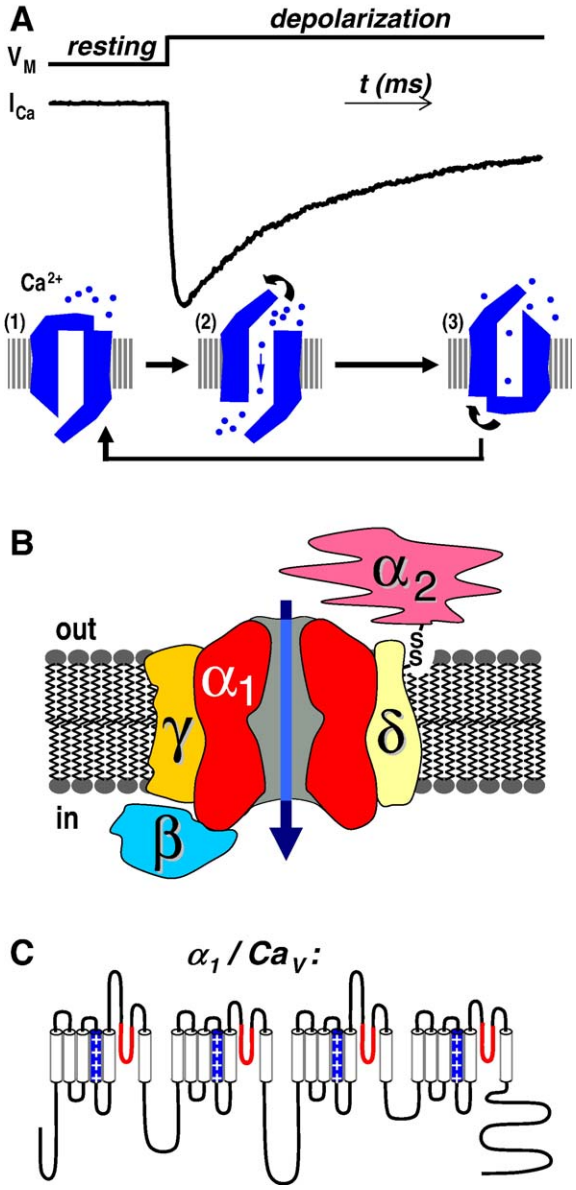


Fig. 1. (A) Macroscopic calcium current ($I_{Ca}$) is activated by membrane depolarization from a negative resting/holding membrane potential. At rest, voltage-gated calcium channels (VGCCs) are in the close state (1). Upon depolarization, these channels move to open state (2), which corresponds to $I_{Ca}$ activation. When depolarization is maintained, the $I_{Ca}$ amplitude decreases as VGCCs switch to the inactivated state (3). (B) A cartoon representing the oligomeric structure of VGCCs. High voltage-activated (HVA) VGCCs comprise both the pore forming subunit, $\alpha_1$, and the auxiliary/regulatory subunits, $\alpha_2/\delta$, $\beta$ and $\gamma$. The oligomeric structure of low voltage-activated (LVA/T-type) VGCCs is yet unknown. (C) The pore-forming subunit, $\alpha_1$, now named $Ca_V$ subunit, comprises both the voltage-sensor (positively charged S4 segments, in blue) and the pore region (in red).

muscle and retina, respectively, or ubiquitously expressed, as for $Ca_V1.2$ (CACNA1C). The first calcium channelopathy described in humans was the hypokalemic periodic paralysis type 1, linked to mutations in the CACNA1S gene (HypoPP1 or HOKPP1, OMIM #170400) that is specifically expressed in skeletal muscle. Missense mutations of arginine residues within the S4 voltage sensor segment (see Fig. 1) of domains II and IV were identified [5,6]. In heterologous expression systems, these mutations result in a reduced calcium current density [7] and only mild changes in the gating properties [8]. At the present time, the precise functional consequences of the HypoPP1 mutations of the $Ca_V1.1$ subunit remain unknown. It is proposed that a reduced calcium channel activity might impair ATP-sensitive potassium channels, since these channels are affected in muscle of HypoPP1 patients [9]. Interestingly, another mutation within CACNA1S was linked to malignant hyperthermia susceptibility type 5 (MHS5, OMIM #601887). This mutation results in an amino-acid substitution (R1086H) within the intracellular III–IV linker [10], suggesting that this region of the $Ca_V1.1$ subunit interacts with the ryanodine receptor (RyR1). Indeed, heterologous expression experiments have revealed that this MHS5 mutation of $Ca_V1.1$ enhances calcium release in skeletal muscle cells [11].

Genetic linkage analysis of incomplete X-linked congenital stationary night blindness type 2 (CSNB2, OMIM #300071), a recessive non-progressive retinal disorder, identified many mutations within a novel calcium channel gene: CACNA1F. This gene encodes a pore-channel protein, $Ca_V1.4/\alpha_{1F}$, that shares strong homology with other dihydropyridine-sensitive (L-type) calcium channel $Ca_V1$ proteins. Over sixty CSNB2 mutations have been identified to date in CACNA1F, including ten in splice acceptor and donor sites. Half of the CACNA1F mutations in the coding region are nonsense and frameshift mutations that are predicted to cause protein truncation and loss of channel function ([12], reviewed in [13]). The other CACNA1F mutations are missense mutations, theoretically leading to functional channels [14]. However, various alterations have been reported in $Ca_V1.4$ channels expressing these missense mutations. Some cause an apparent reduction in current density [15], while some others result in no significant reduced expression at the protein level but display altered channel activity [14,16]. Yet others express as well as the wild type channel and display unchanged macroscopic current properties, suggesting that this later set of $Ca_V1.4$ mutants may be pathogenic via a different mechanism. Of interest, Hoda

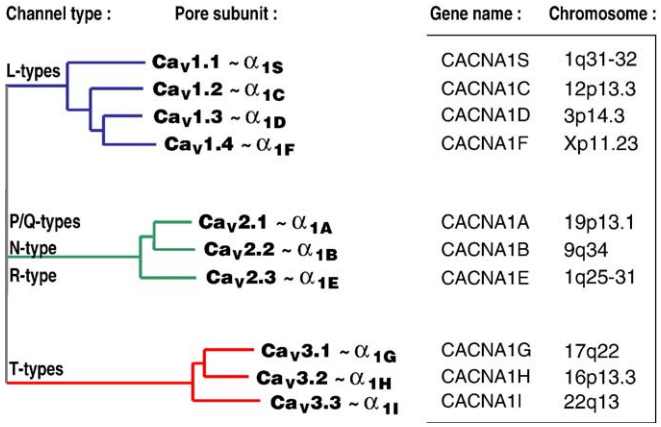


Fig. 2. A schematic phylogenetic tree illustrating the various VGCCs subfamilies. Four genes encode the L-type VGCCs. Three genes encode the neuronal P/Q- N- and R-types. Three genes also code for the T-type VGCCs. Note that all these genes have been localized on human chromosome (see right column) and that detailed information can be found on the OMIM and HUGO/GDB web sites.