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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 α_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 α_1/Ca_V subunit, which is associated – in the case of L-, N-, P/Q- and R-types channels – with regulatory $\alpha_2\delta$, β and γ subunits (Fig. 1). Ten genes (named CACNA1A-I and CACNA1S, see Fig. 2) are coding for the α_1/Ca_V subunits [2]. Alternative splicing largely enhances the number of active forms of the α_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_V1.1 (CACNA1S) and Ca_V1.4 (CACNA1F) in skeletal

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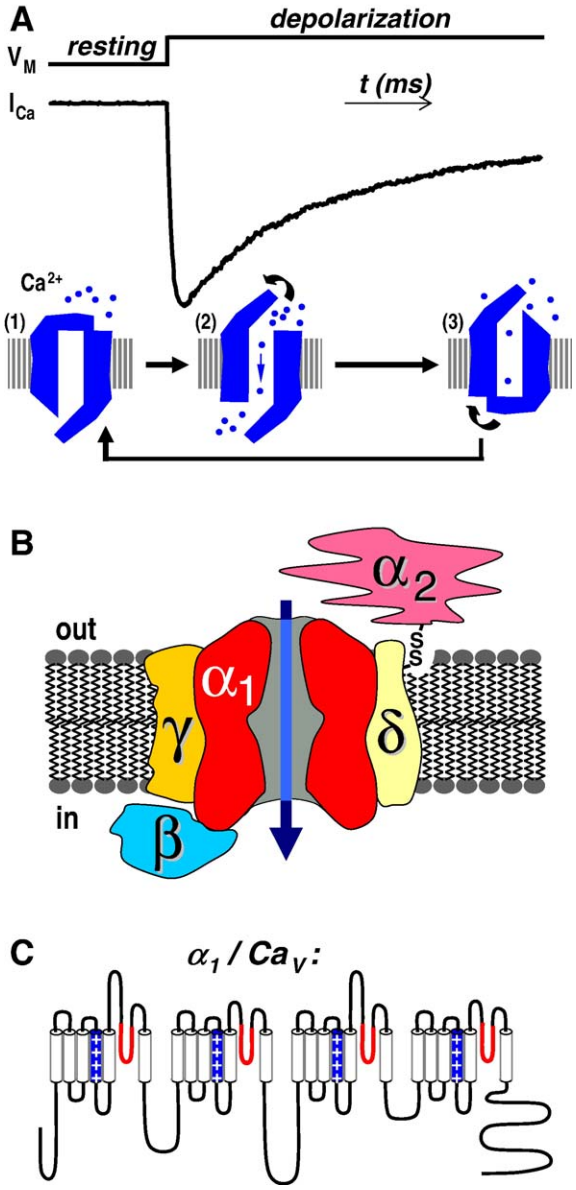

Fig. 1. (A) Macroscopic calcium current (I_{Ca}) is activated by membrane depolarization from a negative resting/holding membrane potential. At rest, voltage-gated calcium channels (VGCCs) are in the close state (1). Upon depolarization, these channels move to open state (2), which corresponds to I_{Ca} 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, α_1, and the auxiliary/regulatory subunits, α_2/δ, β and γ. The oligomeric structure of low voltage-activated (LVA/T-type) VGCCs is yet unknown. (C) The pore-forming subunit, α_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

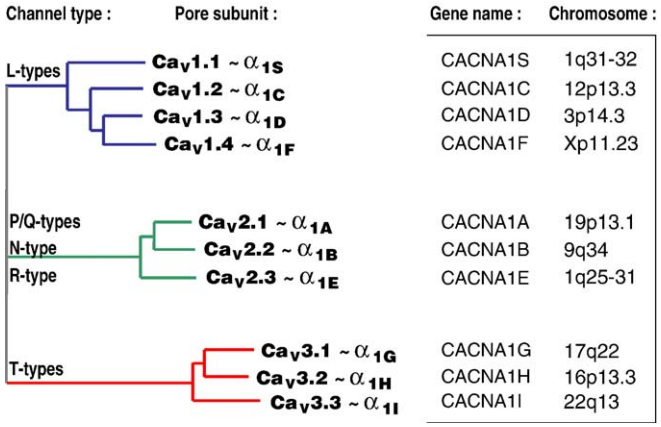

Fig. 2. A schematic phylogenetic tree illustrating the various VGCCs subfamilies. Four genes encode the L-type VGCCs. Three genes encode the neuronal P/Q- N- and R-types. Three genes also code for the T-type VGCCs. Note that all these genes have been localized on human chromosome (see right column) and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

et al. [14] demonstrated that the current amplitude and expression level of the L1364H mutant channels was reduced when functional expression is achieved at physiological temperature, while no such difference is observed when mammalian cells were cultivated at 30 °C, or in *Xenopus* oocytes. These observations indicate that CSNB2 symptoms might not exclusively result from loss of $Ca_V1.4$ channel activity or gating changes (reviewed in [13]) but in some cases could result from a decrease in $Ca_V1.4$ expression at physiological temperature. In light of these data, it is worth considering that some missense mutations affecting $Ca_V1.4$ channels could result in altered protein folding and trafficking.

Interestingly, another recessive retinal disease, the X-linked cone-rod dystrophy type 3 (CORDX3, OMIM #300476) that share some clinical features with CSNB2, was recently linked to a mutation in CACNA1F leading to altered splicing [17]. It is predicted that this mutation results in non-functional $Ca_V1.4$ channels.

Mutations in CACNA1C gene, which codes for the $Ca_V1.2$ subunit – the so-called cardiac calcium channel – have been recently linked to a complex disease named Timothy syndrome (TS, OMIM #601005). TS is a rare childhood multiorgan disorder characterized especially by severe electrophysiological cardiac defects and sudden death. Other prominent features include syndactyly, immune deficiency, intermittent hypoglycemia, cognitive abnormalities and autism. TS appears as a sporadic trait in all but one family [18,19] and, therefore, is linked to *de novo* missense mutation in exon 8A of the $Ca_V1.2$ subunit of L-type channels. The first *de novo* missense mutation identified was a G406R substitution occurring in exon 8A of CACNA1C [18]. Two additional mutations arising in exon 8: G402S and G406R, which lead to slightly different clinical features, were subsequently described [19]. The alternatively spliced exon 8 and 8A code for the S6 segment of domain I, exon 8 being the dominant splice variant in the heart and brain. Both TS mutations cause nearly complete failure of L-type calcium channel inactivation in heterologous expression systems, resulting in maintained inward calcium currents during depolarization. Therefore, TS $Ca_V1.2$ mutations can be depicted as gain of function mutations. Many of the phenotypic abnormalities in TS are likely to be related to an enhanced calcium entry due to the lack of channel inactivation. For instance, absence of L-type channel inactivation is predicted to delay action potential repolarization and consequently to favour long QT syndrome (LQT8), which is observed in TS [18]. In contrast, very little is known regarding the molecular mechanisms of autism spectrum disorders (ASD). These data, as well as the recent identification of T-type channel ($Ca_V3.2$) mutations linked to ASD (see below), suggest that aberrant calcium signalling linked to mutations in VGCCs may contribute to ASD.

3. Calcium channelopathies associated with neuronal P/Q-type VGCCs

While the most common migraine, seizure and ataxia syndromes correspond to complex multigenic syndromes, several monogenic forms of these diseases involving the gene CACNA1A have been characterized (Fig. 2). CACNA1A encodes alternate splice isoforms of the $Ca_V2.1$ subunit that generate the P- and Q-type channels, respectively [20]. P/Q type channels are almost exclusively expressed in neuronal and neuroendocrine cells. They are preferentially located at presynaptic terminals where they play a central role in neurotransmitter release, especially excitatory neurotransmitters, as well as at somatodendritic membranes, where they contribute to neuronal excitability (reviewed in [21]). Among the three genes that code for the so-called "neuronal" VGCCs (or Ca_V2): N-, P/Q- and R-types (Fig. 2), only mutations in CACNA1A have been identified to date. Mutations linked to familial hemiplegic migraine type 1 (FHM1) and episodic ataxia type 2 (EA2) were described originally by Ophoff et al. [22]. This was further documented and expanded by many groups (for a recent review, see [23]). In the meantime, a polymorphic CAG repeat was described in the human CACNA1A gene [24] providing a molecular basis for spinocerebellar ataxia type 6 (SCA6). These allelic $Ca_V2.1$ disorders (Figs. 2 and 3) have been extensively studied in recent years (for review, see [23]).

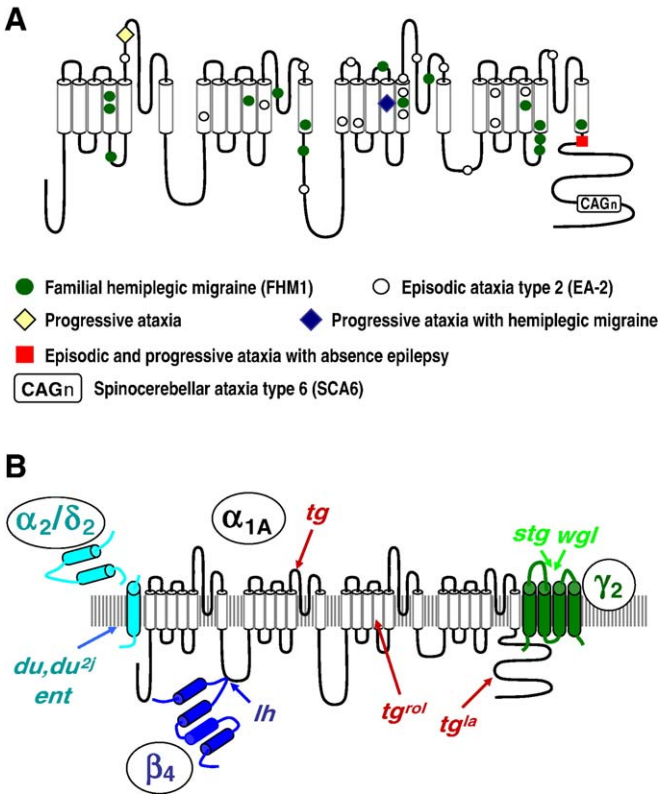

Fig. 3. Human (A) and mouse spontaneous mutations (B) in the $Ca_V2.1/\alpha_1$ subunit of the P/Q-type calcium channel. (A) This schematic secondary structure diagram indicates the location of many (but not all) mutations FHM1 (●), EA2 (○) and SCA6 [CAG] mutations. Mutations that lead to intermediate phenotypes, as progressive ataxia (◇), progressive ataxia with hemiplegic migraine (◆) and episodic and progressive ataxia with absence epilepsy (■) are mentioned. (B) Schematic representation of the putative P/Q-type calcium channel structure in mouse, based on the identified mutations in the $\alpha_{1A}/Ca_V2.1$, $\alpha_2/\delta2$, $\beta4$ and $\gamma2$ subunits (see Table 1 for the mutations symbols).

Familial hemiplegic migraine type 1 (FHM1, OMIM #141500) is a rare autosomal dominant form of migraine with aura, characterized by recurrent attacks of disabling headache and in some cases, progressive cerebellar atrophy. Following the study by Ophoff et al. [22], describing the first missense mutations linked to FHM1, several others have since been reported (up to 10). Although altogether suggestive of a gain of channel activity, electrophysiological characterizations of FHM1 mutant $Ca_V2.1$ channels in heterologous expression systems reveal complex biophysical characteristics both in terms of recovery from inactivation [25] and single channel gating [26]. More compelling evidence for an increase in channel activity of FHM1 mutant was presented by Van den Maagdenberg et al. [27] who generated a knock-in mouse mutant bearing the human R192Q CACNA1A mutation. Recordings from R192Q mice cerebellar granule cells show an increase in $Ca_V2.1$ current density and a hyperpolarizing shift in the voltage-dependence of the current activation. Importantly, the R192Q mice show enhanced neurotransmitter release and increased susceptibility to cortical spreading depression.

Episodic ataxia type 2 (EA2, OMIM #108500) is an autosomal dominant paroxysmal cerebellar disorder, characterized by ataxia, migraine-like symptoms, interictal nystagmus and cerebellar atrophy. In some patients, symptoms can be fully controlled with acetazolamide, a carbonic anhydrase inhibitor. There are now more than 20 known CACNA1A mutations linked to EA2. Most of them are nonsense mutations [28] and a few others are missense mutations [29,30]. Most nonsense mutations are predicted to lead to truncated $Ca_V2.1$ proteins, which would be incorrectly folded. An expected consequence is that these EA2 mutant $Ca_V2.1$ proteins are unable to function as calcium channels. Heterologous expression of truncated EA2 mutant $Ca_V2.1$ protein, together with wild type $Ca_V2.1$ protein significantly decreases P/Q type current, which indicates that truncated EA2 mutant $Ca_V2.1$ proteins can produce a dominant negative effect [31]. In the latter study, a similar result is also obtained with missense EA2 mutations. Originally the mechanism of EA2-mediated reduction of the P/Q-type current density was thought to be due to either defective biosynthetic processing or sequestering of the regulatory β subunits. An alternative hypothesis, which now needs further evaluation, is that misfolded EA2 mutants accumulate in the endoplasmic reticulum (ER, see Fig. 4) and trigger an ER-mediated translation inhibition mechanism known as the unfolded protein response [32,33]. Such "suicide subunits" may be a hallmark of the various P/Q-type channel defects in EA2. Jouvenceau et al. [34] reported that generalized epilepsy can also be found associated with EA2 and described that the primary effect of the R1820x nonsense mutation in heterologous expression systems is a loss of channel activity. Interestingly this mutant protein also displays a dominant-negative effect when co-expressed with wild-type $Ca_V2.1$.

Spinocerebellar ataxia type 6 (SCA6, OMIM #183086) is an autosomal dominant paroxysmal cerebellar disorder characterized by late-onset, slow-progressive ataxia and Purkinje neuron degeneration. SCA6 is associated with an expansion of a CAG repeat (over 19 repeats) at the distal carboxy terminus of $Ca_V2.1$

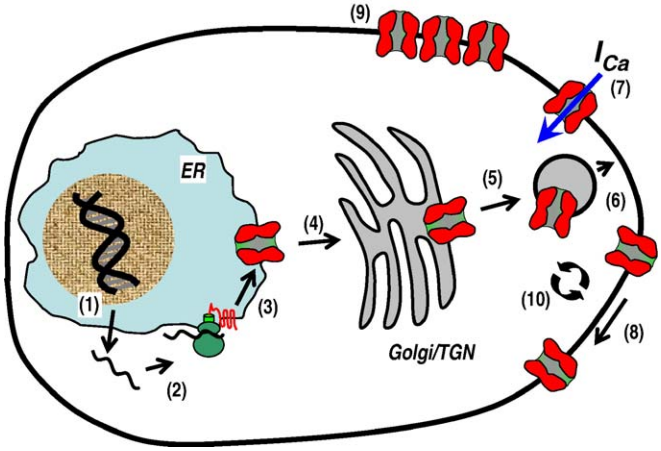

Fig. 4. Mutations in calcium channelopathies possibly affect any of the cellular pathways involved in the VGCC biogenesis and trafficking to the plasma membrane: a working hypothesis. Altered VGCC function may arise from altered protein biogenesis at the level of gene transcription, such as aberrant splicing (1), ribosomal translation (2), folding and assembly (3) that occurs in the endoplasmic reticulum (ER), export from the ER to the Golgi apparatus for maturation (4) and budding from the trans-Golgi network (TGN) and sorting (5). Once at the plasma membrane, besides intrinsic electrophysiological defects (7), ion channels may suffer from improper compartmentalization (8), incorrect clustering (9) or abnormalities in their recycling/degradation (10).

[24,35]. Electrophysiological analysis of SCA6 mutants in heterologous expression systems provided heterogeneous results: either a shift of the voltage-dependent inactivation to more negative potentials, which would reduce the available channel population at resting membrane potential [36]; or increased current density attributable to elevated protein expression at the cell surface [37]. In addition, Kordasiewicz et al. [38] recently reported that a portion of the $Ca_V2.1$ carboxy-terminus is cleaved and directed to the nucleus. While the wild-type carboxy terminal fragment is weakly toxic, a fragment containing an expanded polyglutamine tract corresponding to the SCA6 mutation is highly toxic to Purkinje neurons. This study not only suggests a possible pathogenic mechanism for SCA6 but also reveals a novel form of P/Q-type channel processing that may play a role in nuclear signalling.

The neuronal channelopathies linked to CACNA1A mutations, migraine, ataxia and seizures present significant comorbidity suggesting shared pathophysiological mechanisms [21]. Indeed, many spontaneous mutations in the mouse gene *cacna1a* are also linked to cerebellar ataxia and seizures. The systematic analysis of these mouse models has been instrumental in clarifying how different mutations affect channel function and how altered channel function can produce disease (reviewed in [23,39,]). Several spontaneous mutations in the mouse strains *tottering* (*tg*), *leaner* (tg^{la}), *rolling Nagoya* (tg^{rol}), *rocker* (*rkr*), *lethargic* (*lh*), *ducky* (*du* and du^{2j}), *entla* (*ent*) and *stargazer* (*stg*) are associated with cerebellar ataxia and seizures that resemble generalized absence epilepsy (Table 1). The phenotypes *lethargic*, *ducky* and *stargazer* are linked to mutations in the regulatory subunits, β4, $\alpha_2\delta 2$ and γ2, respectively. The overlapping phenotypes caused by mutations in the four

Table 1
A list of the human inherited calcium channelopathies identified to date (left column) as well as the corresponding mouse mutations/phenotypes (right column)

Human diseases/Calcium channelopathies	Calcium channel gene involved:	Corresponding mouse phenotypes
Spinocerebellar ataxia type 6 (SCA6)	CACNA1A	*tottering (tg)*
Episodic ataxia type 2 (EA-2)		*leaner (tg^{la})*
Familial hemiplegic migraine type 1 (FHM1)		*rolling nagoya (tg^{rol})*
		rocker (rkr)
Timothy syndrome (TS)	CACNA1C	
Congenital stationary night blindness 2 (CSNB2)	CACNA1F	
X-linked cone-rod dystrophy type 3 (CORDX3)		
Childhood absence epilepsy (CAE)	CACNA1H	
Autism spectrum disorder (ASD)		
Hypokalemic periodic paralysis type 1 (HypoPP1)	CACNA1S	*muscular dysgenesis (mdg)*
Malignant Hyperthermia type 5 (MHS5)		
Epilepsy, Episodic ataxia	CACNB4	*lethargic (lh)*
	CACNA2D2	*ducky (du; du^{2J})*
		entla (ent)
	CACNG2	stargazer (stg)
		waggler (wgl)

different genes encoding distinct subunits underline the molecular nature of functional P/Q-type calcium channels in the cerebellum (Fig. 3B). Reminiscent of the *lethargic* phenotype in mouse, which is associated with a mutation in the β_4 subunit, a seizure phenotype has been reported in a patient harbouring a mutation in the CACNB4 gene [40].

4. Calcium channelopathies associated with T-type VGCCs

To date, of the three T-type calcium channel genes (Fig. 2), only mutations in CACNA1H, which codes for the $Ca_V3.2$ subunit, have been identified. Chen et al. [41] found twelve missense mutations in CACNA1H associated with childhood absence epilepsy (CAE) and Heron et al. [42] reported three other missense mutations linked to idiopathic generalized epilepsy (IGE). Although an increase in T-type channel activity has been implicated in absence epilepsy in many instances, electrophysiological characterization of $Ca_V3.2$ CAE mutations has failed to consistently identify a significant gain of channel activity [43,44]. Interestingly, many of the CAE mutations are present in the linker between domain I and II of the $Ca_V3.2$, suggesting a functional role of this intracellular linker that has yet to be identified.

Recently, six missense mutations linked to autism spectrum disorder (ASD) were found within CACNA1H [45]. All these mutations significantly reduced $Ca_V3.2$ channel activity. Mutations in $Ca_V3.2$ channels may not be the major impairment causing the ASD phenotype – autism being a complex, behaviourally defined, static disorder of the immature brain – but rather act as modifiers of the phenotypic expression. Interestingly, it should be noted that one third of the ASD patients suffer from epilepsy [45]. Based on the critical role of T-type calcium channels in neuronal development and excitability [46], it is reasonable to consider that mutations in T-type channels affect proper neuronal function.

5. Calcium channelopathies… what's next?

Studies of calcium channelopathies, as for other ionic channels (reviewed in [47]), have provided important paradigms of (1) how calcium channel subunit interactions take place, (2) how loss – or gain – of channel activity may occur and (3) how dominance can arise through haploinsufficiency, gain of function or through a dominant negative mechanism. It now becomes clear that the large phenotypic variability linked to mutations in calcium channel genes does not simply reflect electrophysiology-related gain or loss of channel activities, or more subtle variations in the biophysical parameters. Indeed, there is growing evidence for alterations in VGCC activity that can be attributed to defects in channel protein biosynthesis and trafficking, as illustrated in Fig. 4. The existence of truncated channel subunits (as in EA2 and CSNB2) has revealed that many mutations may disrupt folding and trafficking of the pore subunit to the cell surface [33,48]. The studies of spontaneous mouse mutants have provided important clues to the pathogenesis of the corresponding human diseases. Importantly, a new generation of mouse models matching human mutations has been successfully developed using knock-in strategies [27], which will undoubtedly help to elucidate in greater details the pathogenicity of the targeted mutations and foster identification of novel therapeutic strategies.

Phenotypes of the monogenic calcium channelopathies can be predicted on the basis of the tissue patterns of gene expression in many cases, especially when the phenotype is restricted to one tissue, as for HypoPP1 and CSNB2, which are limited to skeletal muscle and retina dysfunctions, respectively. In contrast, mutations in $Ca_V1.2$ L-type channel that is ubiquitously expressed, produce complex phenotypic traits, exemplified by Timothy syndrome that includes cardiac (LQT8), secretory (hypoglycaemia) and neuronal (autism) disorders. As several mutations have been described only recently, it is obvious that the list of VGCC mutations identified in the human population will continue to expand, especially for neurological disorders. Epilepsy is one of the most prominent neurological disorders and there is growing evidence establishing P/Q-type and T-type channels as important contributors to seizure genesis [49], although the precise mechanistic details remain unclear. The VGCC mutations provide exciting molecular tools to elucidate the contribution of the various VGCCs to normal and disease states. The ability of mutant VGCCs to cause a wide range of monogenic diseases suggests they are likely to be important contributors to polygenic diseases, especially those of neurological nature. Indeed VGCC mutations are now implicated in some complex multigenic neuropsychiatric disorders, such as ASD [45]. Although calcium channel genes probably reflect only a minority of the relevant etiological candidates in polygenic disorders, they warrant special interest as they represent convenient drug targets for novel therapeutics.

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