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REVIEW

Voltage-gated calcium channels in genetic epilepsies

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Abstract

Voltage-gated calcium channels (VGCC) are abundant in the central nervous system and serve a broad spectrum of functions, either directly in cellular excitability or indirectly to regulate Ca^{2+} homeostasis. Ca^{2+} ions act as one of the main connections in excitation–transcription coupling, muscle contraction and excitation–exocytosis coupling, including synaptic transmission. In recent years, many genes encoding VGCCs main α or additional auxiliary subunits have been associated with epilepsy. This review sums up the current state of knowledge on disease mechanisms and provides guidance on disease-specific therapies where applicable.

KEYWORDS
genetic epilepsy, ion channel, precision therapy, voltage gated calcium channel

1 | INTRODUCTION

Voltage-gated calcium channels (VGCC) form a class of transmembrane proteins with a main pore forming α-subunit which is comprised of 4 domains, each containing 6 transmembrane segments. Historically, different channels have been named according to their electrophysiological properties and sensitivity to blockers. A total of 10 α-subunits of VGCCs can be found in the human genome, forming subfamilies of the high voltage-activated long-lasting, L-type $Ca_V1.X$ VGCCs, the high and intermediate voltage-activated $Ca_V2.x$ VGCC with P/Q-, N-, R-type current conducting channels, or the low-voltage-activated, transient-current (T-type) $Ca_V3.x$ channels. $Ca_V1.x$ and $Ca_V2.x$ channels assemble into multi-subunit complexes comprising also β-, $\alpha_2\delta$ - and γ-subunits beside the channel's main α -subunit in a 1:1:1:1 ratio (Figure 1) (Takahashi et al., 1987; Müller et al., 2010). T-type VGCCs do not depend on additional subunits to produce current, but their gating characteristics may be influenced by these auxiliary subunits (Dolphin et al., 1999; Gao et al., 2000; Lacinová & Klugbauer, 2004; Lambert et al., 1997; Leuranguer et al., 1998; see also review by Zamponi et al., 2015). β-Subunits are intracellular proteins that enhance calcium currents by increasing the membrane expression and facilitating the open state of the channel (Bichet et al., 2000; Williams et al., 1994; Yasuda et al., 2004). $\alpha_2\delta$-Subunits are post-translationally cleaved and rejoined by a disulphide bond and further promote currents through calcium channels (Hobom et al., 2000; Yasuda et al., 2004). Both β- and $\alpha_2\delta$-subunits show distinct expression patterns and do not assemble with specific α-subunits (Hobom et al., 2000; Ludwig et al., 1997; Yasuda et al., 2004). The association of γ-subunits with the channel complex is uncertain, with differences between the individual subtypes, whereas their function in the trafficking of AMPA receptors is more clear (see review Chen et al., 2007). The channel complex is embedded in a rich nano-environment of mostly calcium-binding proteins serving to directly translate an elevation in intracellular calcium to downstream pathways (Müller et al., 2010). In comparison to other voltage-gated ion channels, VGCCs take a

Abbreviations: ASM, anti-seizure medication; CNS, central nervous system; DEE, developmental and epileptic encephalopathy; EA2, episodic ataxia type 2; FHM1, familial hemiplegic migraine type 1; GOF, gain of function; KO, knockout; LOF, loss of function; o/e, observed/expected; OMIM, online Mendelian inheritance in man; pLI, probability of being loss-of-function intolerant; SUDEP, sudden unexpected death in epilepsy patients; VGCC, voltage-gated calcium channel.

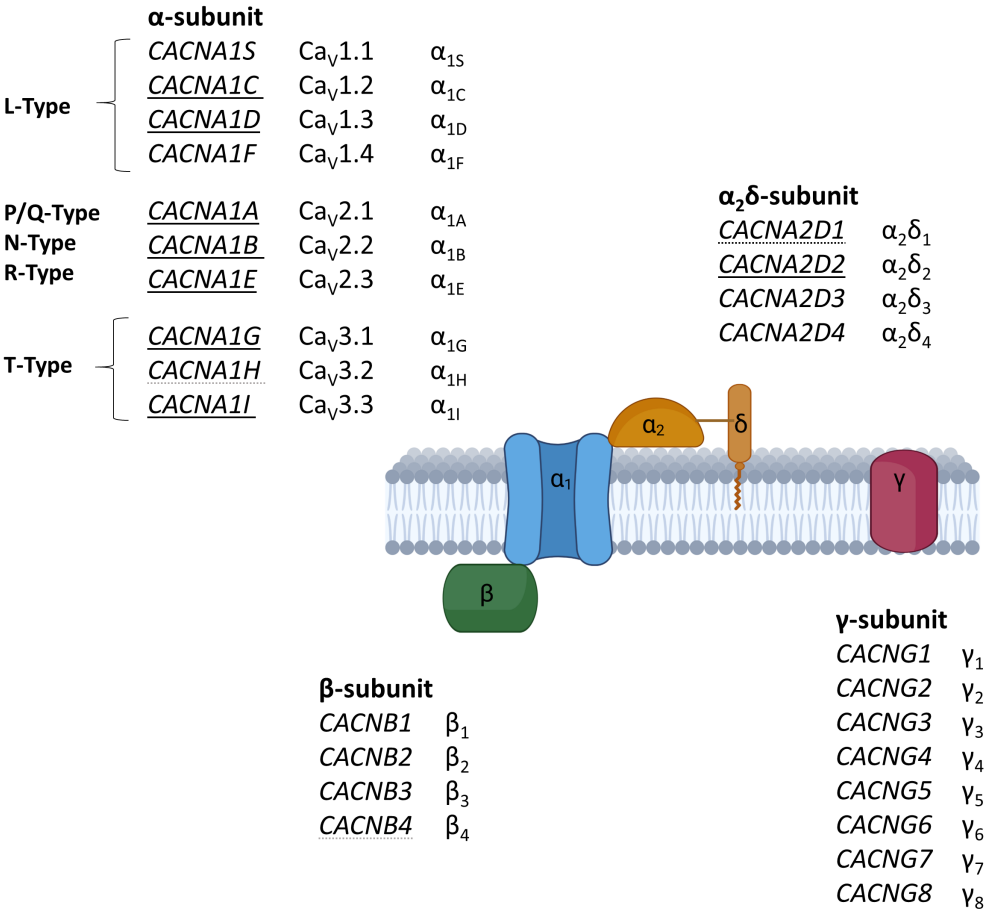

FIGURE 1 The calcium channel complex. Genes with a clear association with epilepsy are underlined. Genes with disputed disease association are underlined with dotted lines. Created with BioRender.com.

special role, as the conducted ions render them directly linked to downstream effects beyond their contribution to electrophysiological processes such as exocytosis of neurotransmitters, altered transcription, excitotoxicity and apoptosis (Bucurenciu et al., 2010; Cano-Abad et al., 2001; Hardingham et al., 1997; Li et al., 2016; Stanika et al., 2012; Stanley, 1993). Furthermore, the expression of VGCCs is not limited to neurons and they can also be found in glia cells (D'Ascenzo et al., 2004).

In recent years, all VGCC α-subunits and a progressing number of auxiliary subunits expressed in the brain have been associated with epilepsy (Table 1). This review will give an overview of the channel family and the associated epileptic and some other phenotypes.

2 | L-TYPE CALCIUM CHANNELS ($Ca_V1.x$)

L-type calcium channels are long-lasting, high-voltage activated VGCCs. They are widely expressed in the body with subunit-specific distinct expression patterns. *CACNA1S*, encoding $Ca_V1.1$, is mainly expressed in skeletal muscle and is not expressed in the central nervous system (CNS) to a significant amount (Sinnegger-Brauns et al., 2009; https://www.proteinatlas.org/ENSG00000081248-CACNA1S;Uhlén et al., 2015). *CACNA1F*/$Ca_V1.4$ expression is most distinct but not limited to the retina (Doering et al., 2014; Strom et al., 1998). Apart from other tissues, there is some expression in the spinal cord and in the pineal gland (Doering et al., 2014; Hemara-Wahanui et al., 2005; McRory et al., 2004; Sinnegger-Brauns et al., 2009). Only *CACNA1C*/$Ca_V1.2$ and *CACNA1D*/$Ca_V1.3$ are significantly expressed in the brain with a variable predominance in different species between the two subunits (Hell et al., 1993; Sinnegger-Brauns et al., 2009; Splawski et al., 2004). Both $Ca_V1.2$ and $Ca_V1.3$ are expressed postsynaptically in clusters in dendritic spines and the soma of glutamatergic and GABAergic cells (Di Biase et al., 2008; Hell et al., 1993; Jenkins et al., 2010; Obermair et al., 2004). Although only detected sparsely, there is also evidence of expression in the axon for both subunits (Obermair et al., 2004; Tippens et al., 2008). Both are also expressed in astrocytes, where $Ca_V1.2$ channels serve an important role in astrocytic activation and astrogliosis (Cheli et al., 2016; Tippens et al., 2008).

Missense variants in *CACNA1C*, encoding $Ca_V1.2$, had been first established in cardiac arrhythmias, such as Long-QT syndrome (Boczek et al., 2013; Fukuyama et al., 2014) and Timothy syndrome, a severe multisystem disorder that among other symptoms includes cardiac arrhythmia, syndactyly, developmental delay and occasionally seizures (Boczek et al., 2015; Splawski et al., 2004, 2005). More recently, variants in this gene have been described in patients with

TABLE 1 Overview of genes, phenotypes and specific therapeutic options for calcium channelopathies.

Gene	Protein	Phenotype	Specific treatment
CACNA1C	$Ca_V1.2$	**GOF**: Timothy syndrome (OMIM #601005) **GOF & LOF**: Neurodevelopmental disorder with hypotonia, language delay and skeletal defects with or without seizures (OMIM #620029)	**GOF**: Verapamil$^+$ (Gershon et al., 2014) Dyhydropyridines?
CACNA1D	$Ca_V1.3$	**GOF**: Primary aldosteronism, seizures and neurologic abnormalities (OMIM #615474) **LOF**: Sinoatrial node dysfunction and deafness (OMIM #614896)	**GOF**: Verapamil? Dyhydropyridines?
CACNA1A	$Ca_V2.1$	**GOF**: Migraine, familial hemiplegic, 1 (OMIM #141500), alternating hemiplegia of childhood, DEE42 (OMIM #617106) **LOF**: Episodic ataxia Type 2 (OMIM #108500), DEE42 with absence seizures (OMIM #617106) **CAG-Expansion**: Spinocerebellar ataxia type 6 (OMIM #183086)	**Mixed cohort**: TPM$^+$ (Le Roux et al., 2021), LEV$^+$ (Le Roux et al., 2021), LTG$^+$ (Byers et al., 2016; Le Roux et al., 2021), VPA$^+$ (Le Roux et al., 2021) **LOF (Episodic ataxia)**: 4-AP^{++} (Muth et al., 2021; Strupp, Kalla, et al., 2011), acetazolamide^{++} (Muth et al., 2021)
CACNA1B	$Ca_V2.2$	**Bi-allelic LOF**: Neurodevelopmental disorder with seizures and nonepileptic hyperkinetic movements (OMIM #618497)	
CACNA1E	$Ca_V2.3$	**GOF**: DEE 69 (OMIM #618285), Developmental delay and regression without epilepsy (Royer-Bertrand et al., 2021) **LOF**: DEE 69 (OMIM #618285)	**GOF**: TPM$^+$ (Helbig, Lauerer, et al., 2018)
CACNA1G	$Ca_V3.1$	**GOF & mixed**: Epilepsy, developmental delay, cerebellar atrophy **LOF & Mixed**: SCA42 (OMIM #616795/#618087)	**GOF**: ESL?, ESX?, ZNS?
CACNA1I	$Ca_V3.3$	**GOF**: Neurodevelopmental disorder with speech impairment and with or without seizures (OMIM #620114) **Mixed effects**: Familial hemiplegic migraine **LOF**: Schizophrenia	**GOF**: ESX$^+$ (El Ghaleb et al., 2021), ESL?, ZNS?
CACNA2D1	$\alpha_2\delta_1$	**Bi-allelic LOF/Monoallelic LOF (debated)**: Developmental and epileptic encephalopathy 110 (OMIM #620149)	Avoid GPB & PGB?
CACNA2D2	$\alpha_2\delta_2$	**Bi-allelic LOF**: Cerebellar atrophy with seizures and variable developmental delay (OMIM #618501)	Avoid GPB & PGB?

Abbreviations: 4-AP, 4-aminopyridine; ESL, eslicarbazepine acetate; ESX, ethosuximide; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; PGB, pregabalin; TPM, topiramate; ZNS, Zonisamide; ?, theoretical consideration, based on in vitro data; +, evidence from single case reports or case series; ++, evidence from randomized clinical trials.

a leading neurodevelopmental syndrome consisting of neonatal onset epilepsy, developmental delay, autistic features, hypotonia, orthopaedic abnormalities and ataxia (Bozarth et al., 2018; Rodan et al., 2021). Strikingly, electrophysiological gain- (GOF) and loss-of-function (LOF) variants as well as variants in which no effect on channel function were described. Truncating variants were only sparsely associated with seizures (Rodan et al., 2021).

Variants in *CACNA1D*, encoding $Ca_V1.3$, have been associated with combined cardiac and inner ear phenotypes. Biallelic LOF variants in this gene have been found in a family with sinuatrial node dysfunction and deafness (Baig et al., 2011). In line with this, KO mice for *CACNA1D* exhibit hearing loss and bradycardia (Platzer et al., 2000). The evidence for seizure disorders in patients carrying missense variants in *CACNA1D* is based on a few case reports: Scholl et al. identified two individuals who suffered from aldosterone-producing adenomas and primary aldosteronism that were associated with somatic and germline *CACNA1D* missense variants with congenital hyperaldosteronism, arterial hypertonia, intellectual disability and focal to bilateral tonic–clonic seizures. One patient showed a movement disorder with spastic quadriplegia and athetosis. Both patients carried *de novo* variants showing a GOF in electrophysiological recordings (Scholl et al., 2013). A report in Russia claims to have found a third similar case carrying a missense variant (Semenova et al., 2018). Pingerra et al. describe a patient with developmental delay, autism spectrum disorder and focal epilepsy carrying a missense variant in the S6 segment of domain I in $Ca_V1.3$ that results in an electrophysiological mixed effect with a tendency to a GOF of the channel (Pinggera et al., 2017). Another study by Rinné et al. describes a family in which the p.Arg930His variant in *CACNA1D* cosegregated with a phenotypic variable syndrome of sinus node dysfunction, focal epilepsy and attention deficit hyperactivity disorder (Rinné et al., 2022). However, the interpretation of this variant is intensely debated in genetic databases such as ClinVar, as its frequency is 1:4000 in gnomAD and the functional electrophysiological characterisation produced a heterogenic isoform-specific GOF or LOF effect. The very same variant was also reported in a patient with primary aldosteronism, seizures and neurological abnormalities in a study on monogenic hypertension in China (Bao

et al., 2020). Taken together, there is limited evidence for an epilepsy phenotype in patients carrying missense GOF variants in *CACNA1D*. Based on the few cases reported in the literature, *CACNA1D* should be treated as a candidate gene for epilepsy, especially in the context of additional developmental delay.

Even though both genes are expressed in the brain and heart and are associated with cardiac arrhythmia, we could not find evidence in the literature for an involvement of *CACNA1C* or *CACNA1D* in sudden unexpected death in epilepsy patients (SUDEP), although *CACNA1C* variants had been described in cases of sudden unexpected death in youth (Narula et al., 2015). This is not surprising as the currently preferred pathophysiological explanation of SUDEP is a central dysregulation leading to secondary cardiac arrhythmia based on the results of the MORTEMUS study (Ryvlin et al., 2013).

$Ca_V1.2$ and $Ca_V1.3$ channels differ in their electrophysiological properties (Helton et al., 2005; Koschak et al., 2001; Xu & Lipscombe, 2001). The dissection of the individual function of channels in the brain is difficult and given the overlapping expression patterns and the lack of specific blockers for the subunits can only be obtained by KO models, which on the other hand can imply compensatory mechanisms (Jurkovičová-Tarabová et al., 2012). $Ca_V1.2$ is involved in long-term potentiation and spatial memory formation in the hippocampus and modulates the spiking behaviour of neurons (Lacinova et al., 2008; Moosmang et al., 2005). Knockout of $Ca_V1.3$ enhances excitability in principal neurons but reduces long-term potentiation in the basal complex of the amygdala (McKinney et al., 2009). Several studies focused on the function of L-type channels in the nigrostriatal network. Here, both channels can modulate the spiking and pacemaking behaviour of neurons (Guzman et al., 2009; Olson et al., 2005).

Pharmacologically, L-type calcium channels are targeted by phenylalkylamines, such as verapamil, benzothiazepines, such as diltiazem, dihydropyridines, such as nimodipine and to some extent by flunarizine (Hockerman et al., 2000; Tytgat et al., 1988; Xu & Lipscombe, 2001). In a patient carrying the p.Gly402Ser GOF variant in *CACNA1C* in a mosaic pattern, suffering from Timothy syndrome with prominent psychiatric disease and without a history of seizures, verapamil has been used as a treatment with some effect on the cardiac but not on the neuropsychiatric phenotype of the patient (Gershon et al., 2014). Diyhydropyridines, which are commonly used drugs to treat high blood pressure, have been proposed as a possible treatment option for GOF variants in *CACNA1C* (Marcantoni et al., 2020). However, at the time of submitting this article, we could not find any case description in which dihydropyridines were used to treat patients suffering from GOF variants in *CACNA1C* or *CACNA1D*. It is noteworthy, that the dihydropyridine nimodipine reduces hippocampal firing in an *in vitro* model of febrile seizures in *wild type* and $Ca_V1.3$ KO mice and reduces epileptic activity in induced febrile seizures *in vivo* indicating an important role of $Ca_V1.2$ in the generation of febrile seizures (Radzicki et al., 2013). In neurons that were differentiated from induced pluripotent stem cells of patients with Timothy syndrome due to the p.G406R variant in *CACNA1C*, treatment with nimodipine could rescue the elevated calcium in neurons but not the upregulation of tyrosine hydroxylase, resulting in increased catecholamine production in the patient cell line (Paşca et al., 2011). On the other hand, it is noteworthy that dihydropyridines do not cause CNS side effects in patients treated for arterial hypertonia. Furthermore, vascularly expressed alternatively spliced isoforms are more sensitive to dihydropyridines and their use-dependent manner of action makes the blockage of L-type channels by dihydropyridines in the brain less effective (Helton et al., 2005; Welling et al., 1997). Thus, arterial hypotension with an increased risk of syncope would be expected to be a limiting factor in treating patients before a neurological treatment effect is expected. On the contrary, the sensitivity for mutated channels to blocking agents can change in the mutated channel, as can be seen in the p.Val401Leu variant in *CACNA1D* leading to autism spectrum disorder and epilepsy, in which the channel's affinity for isradipine, another dihydropyridine with an extensively higher affinity to $Ca_V1.3$ than $Ca_V1.2$, is increased *in vitro* in comparison to the *wild type* channel (Koschak et al., 2001; Pinggera et al., 2017). Thus, a drug that would not have an extensive effect in healthy individuals might have an effect in patients carrying GOF variants.

To our knowledge, activators of the channel are not available for clinical use. The applicability of commonly used activators *in vitro*, such as BayK8644, is limited due to a dystonic CNS-mediated effect (Bourson et al., 1989). A targeted therapy for patients carrying LOF variants is thus currently not available (see also review in Zamponi et al., 2015).

3 | P/Q-TYPE CALCIUM CHANNELS ($Ca_V2.1$)

CACNA1A encodes for the P/Q-type channel $Ca_V2.1$, which is ubiquitously distributed in the brain with high expression in cerebellar and hippocampal neurons (Ludwig et al., 1997; Schlick et al., 2010; Westenbroek et al., 1995). $Ca_V2.1$ channels are expressed in both inhibitory (Althof et al., 2015; Zaitsev et al., 2007) and excitatory cells (Althof et al., 2015).

CAG expansions in this gene lead to spinocerebellar ataxia type 6 (Zhuchenko et al., 1997). Missense and nonsense variants in *CACNA1A* have been identified as disease-causing in a spectrum of disorders that are often distinct between GOF and LOF variants and can in both cases imply an epileptic phenotype and in most cases, a cerebellar phenotype: GOF variants have been identified in non-epileptic and epileptic paroxysmal disorders such as familial hemiplegic migraine type 1 (FHM1) and alternating hemiplegia of childhood as well as in patients suffering from an epileptic encephalopathy with convulsive seizures often with overlapping phenotypes of the three entities (Chan et al., 2008; Ducros et al., 2001; Le Roux et al., 2021; Stam et al., 2009; Zangaladze et al., 2010). Patients with a leading *CACNA1A* GOF epileptic encephalopathy show often intractable seizures with frequent status epilepticus, developmental delay with autistic features, ataxia and hemiplegic attacks (Le Roux et al., 2021).

The electrophysiological consequences of GOF variants in *CACNA1A* have mostly been studied in the context of FHM1, in

which hemiplegic attacks occur due to a cortical spreading depolarisation, that causes transient neuronal dysfunction (for review see Pietrobon & Moskowitz, 2014). As an extraordinary example, the recurrent p.Ser218Leu missense variant in *CACNA1A* leads to a characteristic phenotype of FHM1 with unprovoked seizures and brain oedema after minor head trauma with subsequent seizures (Chan et al., 2008; Stam et al., 2009; Zangaladze et al., 2010). Homozygous p.Ser218Leu knock-in mice carrying this variant show a similar phenotype to humans with recurrent spontaneous epileptic seizures and often die after epileptic seizures, possibly caused by spreading depolarisations to the brainstem (Loonen et al., 2019; van den Maagdenberg et al., 2010). As expected for familial hemiplegic migraine, the threshold for eliciting cortical spreading depression is lower in these mice (van den Maagdenberg et al., 2010). Due to the shift of the activation and inactivation curves to more hyperpolarised potentials, the basal concentration of calcium in neurons is elevated and leads to stronger and more active excitatory synapses and increased short-term depression (Di Guilmi et al., 2014).

Monoallelic LOF variants in *CACNA1A* have been associated with an often overlapping disease spectrum of episodic ataxia type 2 (EA2), non-episodic, chronic ataxia and cerebellar dysfunction, cognitive impairment and ADHD. Whereas the associated epileptic phenotype with predominant absence seizures is often milder compared to the GOF phenotype, cases of severe DEE have been described (Damaj et al., 2015; Imbrici et al., 2004; Jiang et al., 2019; Jouvenceau et al., 2001; Le Roux et al., 2021; Rajakulendran et al., 2010; Stendel et al., 2020). Furthermore, several missense variants that have not been electrophysiologically characterised have been found in patients with congenital ataxia or EA2 who often also exhibit a seizure phenotype (Byers et al., 2016; Gur-Hartman et al., 2021; Travaglini et al., 2017). The phenotype in patients carrying LOF variants is in many cases strikingly consistent with that of *CACNA1A* knockout (KO) mice which exhibit a prominent ataxia and dystonia and absence seizures with behavioural arrest and spike–wave discharges in EEG (Jun et al., 1999; Llinas et al., 2007; Song et al., 2004). Other mouse models for EA2, such as *tottering* and *leaner*, which carry missense or splice variants resulting in a LOF of $Ca_V2.1$, show a comparable phenotype with ataxia, absence and convulsive seizures (Fletcher et al., 1996; Jun et al., 1999; Noebels & Sidman, 1979; Wakamori et al., 1998).

Absence seizures go along with oscillations in the thalamocortical network between cortex, inhibitory neurons in the reticular thalamic nucleus and thalamo-cortical projection neurons. These oscillations can be triggered both in cortex and in thalamus. They rely on the rebound burst firing mediated by T-type channels in the thalamus and cortex, although these mechanistic details have been critically discussed recently (McCafferty et al., 2018; for review and discussion see Huguenard, 2019 and Crunelli et al., 2020). The global dysfunction of $Ca_V2.1$ function in *tottering* mice triggers a compensatory upregulation of T-type currents, but not the mRNA in thalamo-cortical projection neurons, potentially tipping the balance in the thalamo-cortical loop towards the generation of absence seizures (Zhang et al., 2002). Interestingly, the selective knockout of $Ca_V2.1$ in cortical interneurons is sufficient to generate absence and convulsive seizures without eliciting an ataxic or dystonic phenotype by disrupting the GABA release from parvalbumin positive fast-spiking interneurons. This is consistent with the impaired feedforward inhibition of thalamic projections to layer IV of the cortex in *tottering* mice mediated by these interneurons (Rossignol et al., 2013; Sasaki et al., 2006). Likewise, the isolated disruption of $Ca_V2.1$ in murine layer VI pyramidal neurons is also sufficient to elicit an absence seizure phenotype with compensatory presynaptically driven upregulation of T-type currents in thalamic relay and reticular neurons (Bomben et al., 2016). In other cell types, the loss of $Ca_V2.1$ is compensated by other calcium channels, especially $Ca_V2.2$ channels, partially preserving their function in the release of neurotransmitters (Cao & Tsien, 2005; Jun et al., 1999; Qian & Noebels, 2000; Rossignol et al., 2013). Knockout of $Ca_V2.1$ channels in adult mice still elicits an absence seizure phenotype indicating that the underlying pathophysiology stems from these direct electrophysiological changes and is not due to secondary structural defects in network architecture (Miao et al., 2020). Crossbreeding *tottering* mice with *KCNA1 KO* mice, which as well show a seizure phenotype, masks the absence seizures in these mice. The same effect could be observed when blocking $K_V1.1$ channels with 4-aminopyridine (Glasscock et al., 2007).

There are two established treatments in patients with EA2 carrying LOF variants, the carboanhydrase inhibitor acetazolamide and the potassium channel blocker 4-aminopyridine, with evidence from randomised clinical trials (Muth et al., 2021; Strupp, Kalla, et al., 2011; Strupp, Thurtell, et al., 2011). Topiramate, which is also a partial carboanhydrase inhibitor, showed the best efficacy for treating seizures in a mixed cohort of GOF and LOF patients with *CACNA1A*-associated epilepsy, whereas Levetiracetam, Lamotrigine and Valproate have also been reported as effective (Byers et al., 2016; Le Roux et al., 2021). Single cases have been rendered seizure-free by ACTH or pyridoxine (Du et al., 2017; Le Roux et al., 2021).

4 | N-TYPE CALCIUM CHANNELS ($Ca_V2.2$)

N-type or $Ca_V2.2$ channels, encoded by *CACNA1B*, have been proposed to be potentially involved in genetic generalised epilepsy by the Epi25 Collaborative and the Epi4K Consortium (Epi25 Collaborative, 2021; Epi4K Consortium & Epilepsy Phenome/Genome Project, 2017). In addition, Gorman et al. described three families in which bi-allelic predicted LOF variants due to protein truncation or nonsense-mediated decay of *CACNA1B* led to a developmental and epileptic encephalopathy with a hyperkinetic movement disorder. Epilepsy often began with epileptic spasms and was regularly accompanied by a developmental regression. A majority of the patients died at a young age (Gorman et al., 2019). Contrary to human cases, $Ca_V2.2$ knockout mice display neither seizures nor hyperkinetic movement disorder, but the reduced response to

sensory stimuli and pain, hyperaggressive behaviour, altered sleep architecture and hyperactive behaviour (Beuckmann et al., 2003; Kim et al., 2009; Kim, Jun, et al., 2001). $Ca_V2.2$ is widely expressed in the nervous system including the cortex, hippocampus and cerebellum (Fujita et al., 1993; Jones et al., 1997; Ludwig et al., 1997; Westenbroek et al., 1992). On a subcellular level, $Ca_V2.2$ channels are expressed in dendrites, as well as presynaptic nerve terminals where they mediate neurotransmitter release together with $Ca_V2.1$ (Hirning et al., 1988; Westenbroek et al., 1992). During development, the role of $Ca_V2.2$ in neurotransmitter release is predominantly taken over by $Ca_V2.1$ channels, which are located more closely to the synaptic release machinery (Iwasaki et al., 2000; Wu et al., 1999).

Due to the nature of a homozygous loss of *CACNA1B* as a cause of disease, it is hard to derive a specific therapy for the disease as no functional $Ca_V2.2$ channels will be expressed in these patients. In the small cohort of Gorman et al., no anti-seizure medication did stand out in providing seizure control in the 6 patients described (Gorman et al., 2019). Further research needs to be conducted to get more insights into the clinical course of disease in these patients and successful treatment options.

5 | R-TYPE CALCIUM CHANNELS ($Ca_V2.3$)

CACNA1E encodes the R-type calcium channel $Ca_V2.3$, the third presynaptic calcium channel in this subgroup. Missense variants in this gene have been associated with a complex phenotype including largely pharmacoresistant early onset infantile epileptic encephalopathy with severe developmental delay. Helbig et al. reported 30 patients with *de novo* missense variants. Additional symptoms were congenital contractures with arthrogryposis, perinatal hypotonia and extrapyramidal movement disorders. Three patients with variants predicted to be LOF by nonsense-mediated decay had a milder phenotype (Helbig, Lauerer, et al., 2018). A second cohort of patients with developmental delay and no epileptic phenotype was described later (Royer-Bertrand et al., 2021). A wide phenotypic spectrum can be observed in patients with the same variant, implicating other confounding factors, as has been argued before for monogenic epilepsies in general (Campbell et al., 2022). Seizures in *CACNA1E* encephalopathy are often pharmacoresistant, however, Topiramate, an antiseizure drug (ASM) acting on $Ca_V2.3$ channels, has been identified as an effective treatment option in some patients (Helbig, Lauerer, et al., 2018).

Interestingly, most disease-causing missense variants in *CACNA1E* cluster are in the distal S6 segment of the channel. This mutational hotspot is common in VGCCs, as can be also observed in Timothy syndrome with the common variants p.Gly402Ser and p.Gly406Arg in *CACNA1C*, as well as disease-causing variants in the T-type channel genes *CACNA1G* and *CACNA1I*. These variants in the activation gate of the channels usually result in a GOF effect by facilitating channel activation and prolonging the time course of inactivation (Chemin et al., 2018; El Ghaleb et al., 2021; Helbig, Lauerer, et al., 2018; Splawski et al., 2004, 2005).

$Ca_V2.3$ is expressed ubiquitously in the brain in both excitatory and inhibitory cells as well as astrocytes (D'Ascenzo et al., 2004; Ludwig et al., 1997; Parajuli et al., 2012; Soong et al., 1993; Weiergräber et al., 2006, 2008; Williams et al., 1994). On a subcellular level, the channel has been detected pre- and postsynaptically (Breustedt et al., 2003; Dietrich et al., 2003; Parajuli et al., 2012). However, caution should be exercised when interpreting studies on the localisation of $Ca_V2.3$ as the R-type current does not fully correspond to $Ca_V2.3$ channels and the commonly used regimes of blocking this current with SNX-482 or a low concentration of Ni^+ ions are not fully specific for $Ca_V2.3$ channels (Bourinet et al., 2001; Kimm & Bean, 2014; Lee et al., 1999; Tottene et al., 2000). Before the description of *CACNA1E* as an epilepsy gene in humans, a possible involvement of $Ca_V2.3$ in the pathophysiology of absence seizures had been discussed based on experiments in KO mice (Weiergräber et al., 2008; Zaman et al., 2011). KO mice show reduced susceptibility to seizure induction with pentylenetetrazol and kainate, but not with 4-aminopyridine (Weiergräber et al., 2006, 2007). Furthermore, KO animals showed reduced excitotoxicity in the hippocampus after seizure induction with kainate (Weiergräber et al., 2007). R-type calcium channels are involved in long-term potentiation and rhythmic firing of neurons (Breustedt et al., 2003; Dietrich et al., 2003; Zaman et al., 2011). $Ca_V2.3$ is also a target of CDKL5, a kinase in which variants lead to a similar although not completely identical phenotype as in *CACNA1E*-GOF-DEE patients. Interestingly, the lack of phosphorylation due to a defect in CDKL5 leads to a GOF in $Ca_V2.3$ (Sampedro-Castañeda et al., 2023).

6 | T-TYPE CALCIUM CHANNELS ($Ca_V3.x$)

T-type VGCCs form low-voltage activated channels that conduct transient calcium currents which are essential for rebound burst firing in a subunit-specific manner (Huguenard & Prince, 1992; Klöckner et al., 1999; McRory et al., 2001). T-type channels have been accounted to be crucial for the generation of absence seizures in the network of GABAergic neurons in the reticular thalamic nucleus, excitatory thalamo-cortical neurons of the thalamic relay nucleus and the cortex (for review see Crunelli et al., 2020). They are essential in the neuronal switch from tonic to burst firing, which is elicited by Ca^{2+}-mediated low threshold spikes, an important prerequisite for oscillations in the thalamo-cortical circuitry between somatosensory cortex and the thalamus (Huguenard & Prince, 1992; Kim, Song, et al., 2001). It was recently proposed by experiments in freely moving animals, that T-type channels are involved in the absence seizure generation in the cortex and reticular thalamic nucleus, but not in thalamo-cortical relay neurons (McCafferty et al., 2018). Thus, the distinct expression patterns of the three T-type channel subunits determine their importance in the generation of absence seizures in this network as is outlined below. Although many studies do not distinguish between the three different T-type channels, the expression pattern is distinct. In rats, $Ca_V3.1$ channels are strongly expressed in the lateral

geniculate nucleus, especially in thalamo-cortical projection neurons, but only weakly in the reticular thalamic nucleus, whereas $Ca_V3.2$ is strongly expressed in the reticular thalamic nucleus and not in the corpus geniculatum laterale and intralaminar nuclei of the thalamus. $Ca_V3.3$ is expressed throughout the whole thalamus (Broicher et al., 2007, 2008). Whereas $Ca_V3.1$ is the predominant T-type calcium channel in the cortex, hippocampal pyramidal neurons express all three channels (Talley et al., 1999; Zhang et al., 2002).

All three T-type VGCCs have been associated with epilepsy with a different extent of evidence with either GOF or LOF mechanisms, as outlined in detail below. Besides the well-described pathophysiological role of T-type channels in absence seizures, they are targets of licenced anti-seizure medications, which can help as guidance to preferentially use these drugs in patients carrying GOF variants and avoid them in patients carrying LOF variants. Ethosuximide, a pan-T-type channel blocker, is a first-line treatment for absence seizures (Gomora et al., 2001) and zonisamide, which is used in Japan to treat genetic generalised epilepsies, also blocks all three T-type channels with a preference for $Ca_V3.2$ beside voltage-gated Na^+ channels (Matar et al., 2009; Suzuki et al., 1992). Another combined blocker of Na^+ and T-type Ca^{2+} channels is eslicarbazepine acetate, which has been shown to prevent epileptogenesis in a mouse model of temporal lobe epilepsy (Doeser et al., 2014). Valproic acid, the first line treatment in generalised genetic epilepsy, shows a minor block of T-type channels (Kelly et al., 1990; Todorovic & Lingle, 1998). Recently, it was also shown that stiripentol, another drug, mainly used in Dravet syndrome, also acts on T-type calcium channels beside its GABAergic mechanism of action (Riban et al., 2022). Other drugs blocking T-type channels include pimozide, flunarizine, phytocannabinoids and amiloride (Santi et al., 2002; Tang et al., 1988; for review see also Mirlohi et al., 2022; Zamponi et al., 2015). Another substance, not approved for the use in humans, is Z944, a specifically designed T-type channel blocker that also modifies T-type channel expression and shows promising results in mouse models of temporal lobe epilepsy (Casillas-Espinosa et al., 2015, 2019; Tringham et al., 2012).

6.1 | *CACNA1G* ($Ca_V3.1$)

Missense variants in *CACNA1G* have been identified in patients with DEE with varying severe electroclinical phenotypes with a wide variety of seizure types. Epilepsy and developmental delay are often accompanied by cerebral and/or cerebellar atrophy and digital and facial dysmorphisms (Berecki et al., 2020; Chemin et al., 2018; Kunii et al., 2020). Functional testing of these missense variants in heterologous expression systems frequently revealed mixed GOF and LOF effects, for example, shifting the voltage dependence of both activation and inactivation to more hyperpolarised potentials (Berecki et al., 2020; Chemin et al., 2018; Kunii et al., 2020). *In silico* modelling pointed to a resulting GOF in neurons for some of these variants (Chemin et al., 2018). Another study detected missense variants in families with juvenile myoclonic epilepsy that did not change the gating parameters of the channel significantly, and have not been entered as pathogenic into ClinVar by other submitters since then, rendering this association rather questionable (Singh et al., 2007).

On the broader spectrum, missense variants in *CACNA1G* have also been described in cerebellar phenotypes: LOF variants cause autosomal dominant cerebellar ataxia without seizures (Coutelier et al., 2015), and mixed GOF and LOF variants have been described in spinocerebellar ataxia type 42 without seizures (Morino et al., 2015). Furthermore, patients with microdeletions of the 17q21.33 locus, that involve *CACNA1G* among other genes, show developmental delay and in some cases cerebral atrophy, whereas an epileptic phenotype has not been reported (Bardai et al., 2016; Harbuz et al., 2013; Jewell et al., 2017; Preiksaitiene et al., 2012). This may suggest that a mono-allelic LOF in *CACNA1G* is not sufficient to elicit an epileptic phenotype. However, dominant-negative effects of missense variants leading to the complete disruption of functional $Ca_V3.1$ channels cannot be excluded.

Cacna1g KO mice are less prone to the induction of spike-wave discharges by the application of γ-butyrolactone and baclofen but not to the induction of cortically induced absence seizures with bicuculine or convulsive seizures with 4-aminopyridine (Kim, Song, et al., 2001). The knockout of *Cana1g* in mice abolishes rebound bursts in thalamo-cortical projection neurons within the ventrobasal complex which were deemed to be essential in generating spike–wave discharges in absence seizures (Kim, Song, et al., 2001). More recent studies could show that selective blockage of T-type currents in this region of the thalamus, in which $Ca_V3.1$ is primarily expressed, does not abolish absence seizures (Crunelli et al., 2020; McCafferty et al., 2018). On the contrary, crossbreeding *Cacna1g* KO mice with *Cacna1a* KO mice abolishes the absence seizures that are usually observed upon *Cacna1a* KO, indicating the importance of $Ca_V3.1$ T-type currents in the generation of absence seizures (Jun et al., 1999; Llinas et al., 2007; Song et al., 2004). Similarly, KO of *Cacna1g* reduces the phenotypic severity in mouse models of *Scn1a* and *Scn2a* encephalopathies and kainate-induced hippocampal seizures (Calhoun et al., 2016, 2017; Kim, 2015).

Taken together, there are hints for a GOF mechanism of $Ca_V3.1$ in *CACNA1G* variant carriers with reported epilepsy, and that a LOF is protective against absence seizures, although the mechanistic details remain uncertain. However, the heterogenicity of data may complicate the interpretation of functional effects derived from heterologous expression systems for the clinical geneticist and should be followed by *in vivo* or *in silico* verification.

6.2 | *CACNA1H* ($Ca_V3.2$)

CACNA1H has been proposed as an epilepsy gene first in 2003 when a study in the Chinese Han population found inherited but not co-segregating missense variants in the gene in patients with

childhood absence epilepsy (Chen et al., 2003). Various other reports have observed inherited heterozygous or compound heterozygous missense variants in *CACNA1H* in patients with an extensive variability of phenotypes including the whole phenotypic spectrum of genetic generalised epilepsy as well as febrile seizures, epilepsy with myoclonic–atonic seizures and temporal lobe epilepsy, which co-segregated with an epilepsy phenotype only in few families (Becker et al., 2017; Chourasia et al., 2019; Heron et al., 2007; Liang et al., 2006; Vitko, 2005). Many of the detected missense variants alter the gating mechanisms of $Ca_V3.2$ channels and lead to either GOF or LOF in the channel *in vitro* with a tendency of more GOF variants with mostly small effect sizes, but also functional effects on neuronal firing (Becker et al., 2017; Eckle et al., 2014; Heron et al., 2007; Khosravani et al., 2005; Peloquin et al., 2006; Vitko, 2005). In contrast, missense variants in *CACNA1H* have repeatedly not been identified as enriched in other large cohorts of patients with epilepsy (Chioza et al., 2006; Epi4K Consortium et al., 2013; Epi4K Consortium & Epilepsy Phenome/Genome Project, 2017; Heyne et al., 2019) and the existence of a monogenetic syndrome caused by missense variants in this gene is now strongly debated, leading to the suggestion to exclude the gene from gene panels in clinical testing (Calhoun et al., 2020; Helbig, Riggs, et al., 2018).

Interestingly, a homozygous missense variant leading to an amino acid substitution in the linker between domains III and IV of $Ca_V3.2$ has been described to co-segregate with seizure count and seizure activity in the Genetic Absence Epilepsy in Rats from Strasbourg (*GAERS*) model (Powell et al., 2009). However, even though the variant showed a splice-variant specific GOF with accelerated recovery from inactivation when heterologously expressed, animals not carrying this variant still showed seizures, indicating a polygenic basis of disease in this model (Powell et al., 2009). This is underlined by follow-up experiments of the same group showing that the introduction of this variant into congenic animals derived from a non-epileptic control strain by crossbreeding could not elicit a seizure phenotype but modified the seizure phenotype in *GAERS* animals facilitating absence seizures (Casillas-Espinosa et al., 2023). Epileptogenesis in the hippocampus is largely prevented in *Cacna1h* KO mice, which do not show neuronal cell loss after the induction of status epilepticus with pilocarpine and are less likely to develop chronic epilepsy (Becker et al., 2008). This fits the population statistics in humans that indicate that *CACNA1H* is opposing to other voltage-gated ion channels tolerant to LOF (Calhoun et al., 2020). Also, an additional KO of *Cacna1h* did not alter the seizure susceptibility and survival in a crossbred *Scn1a* KO mouse line to a clinically significant amount (Calhoun et al., 2020).

Taken together, there is currently no clear evidence that missense variants in *CACNA1H* contribute to epilepsy in affected individuals, but experiments in *GAERS* suggest that a homozygous GOF variant facilitates absence seizures in this model. Therefore, the current state of research cannot fully exclude *CACNA1H* to be a candidate gene to contribute to the polygenic burden in generalised genetic epilepsies, especially with missense variants that lead to an electrophysiological GOF in the channel. However, a monogenetic cause of disease should not be proclaimed (Becker et al., 2017; Calhoun et al., 2020; Powell et al., 2009). In addition, the KO of *CACNA1H* and inhibitors of this channel can prevent epileptogenesis in the hippocampus so that blockers of $Ca_V3.2$ channels may be a promising anti-epileptogenic future therapeutic option (Becker et al., 2008; Doeser et al., 2014).

6.3 | *CACNA1I* ($Ca_V3.3$)

Recently, four different *de novo* missense variants in *CACNA1I*, which encodes the $Ca_V3.3$ channel have been described in patients with a neurodevelopmental syndrome of varying severity and epilepsy. In three patients, *de novo* variants led to a severe phenotype with global developmental delay, hypotonia, cortical blindness and epilepsy during the first 2 years of life. Another variant co-segregated in a family with cognitive impairment of affected individuals, and one individual of which developed seizures with 58 years of age. However, in this patient, no MRI but only a CT scan was obtained to rule out other causes of structural epilepsy, which renders an association to the genetic findings questionable. This p.I860M variant showed the weakest electrophysiological alterations of all variants tested, but was affecting the same amino acid as the p.I860N variant identified in more severe cases. All variants induced a GOF by shifting the activation curve and the window current to more hyperpolarised potentials, prolonging inactivation, and in some variants also deactivation. The shift in window current leads to an increase in firing and to a slow oscillation mode when expressed in chromaffin cells. Consistent with a GOF effect, in one severely affected individual, ethosuximide improved seizure control (El Ghaleb et al., 2021). Beyond epilepsy, variants in *CACNA1I* with a mixed effect in heterologous expression systems have been identified in familial hemiplegic migraine, whereas LOF variants were detected in schizophrenia (Andrade et al., 2016; Maksemous et al., 2022).

CACNA1I thus appears to be a promising epilepsy gene in individuals carrying *de novo* GOF variants given the remarkable work by El Ghaleb et al. (2021). Further case descriptions are necessary to establish reproducibility for this gene in epilepsy.

7 | AUXILIARY SUBUNITS

7.1 | *CACNB4*

CACNB4 encodes the β_4 subunit of the calcium channel complex. The first description of *CACNB4* variants in epilepsy in humans was in 1999, when a group of researchers screened patients with familial epilepsy and ataxia for variants in this gene. This was influenced by the mouse model *lethargic*, which carries a bi-allelic LOF *Cacnb4* variant and exhibits an absence seizure phenotype and ataxia (Burgess et al., 1997). The authors identified a missense and a nonsense variant, leading to an early stop codon that co-segregated in the three affected families with disease (Escayg

et al., 2000). However, the identified p.Cys104Phe missense variant did not lead to changes in electrophysiological recordings and has meanwhile been found in gnomAD in 117 cases, whereas the p.Arg482* variant leading to a distal stop codon has not been annotated in ClinVar for a second time but in gnomAD in one healthy individual. Another study identified a heterozygous frameshift variant in *CACNB4* in 3 individuals with epilepsy, predicted to lead to nonsense-mediated decay. However, this study lacks further clinical data and information on segregation for the participants, indicating questionable results (Naseer et al., 2022). Protein-truncating variants in *CACNB4* are not enriched in epilepsy cases in the Epi25 cohort and the gnomAD constraint metrics indicate that the gene is not intolerant to loss of function with a probability of being loss-of-function intolerant (pLI) score of 0.03, and the observed/expected (oe/e) constraint score of 0.28 (confidence interval 0.17–0.49) (Chen et al., 2022; Epi25 Collaborative et al., 2023; Lek et al., 2016). This renders disease association unlikely for all variants described.

De Bagneaux et al. suggested the homozygous p.Leu125Pro missense variant in *CACNB4* to be disease-causing in two siblings born of consanguineous parents with severe developmental delay, hypotonia, athetoid–dystonic movements, cerebellar atrophy and focal tonic seizures. The mutated protein failed to be trafficked in presynaptic terminals and axon hillocks of transfected hippocampal neurons and activity-dependent nuclear targeting was inhibited and led to a LOF with decreased current density and altered inactivation kinetics when co-expressed with $Ca_V2.1$ in a heterologous expression system. Furthermore, the mutant proteins did not bind to other protein interaction partners, such as the serin-threoine kinase TNIK in contrast to the *wild-type* protein (Coste de Bagneaux et al., 2020).

Before the description of biallelic variants, *CACNB4* had been flagged by the ClinGen consortium to be a disputed epilepsy gene as there was a lack of replication after the initial report by Helbig, Riggs, et al. (2018). Furthermore, ultrarare variants in this gene were not enriched in a cohort of patients with neurodevelopmental disorders with epilepsy (Heyne et al., 2019).

Taken together, there is very limited evidence for a monogenetic epilepsy syndrome involving *CACNB4* given the lack of reproducibility and the few cases reported, especially with mono-allelic variants. The overlap of severe phenotypes in the bi-allelic LOF of *CACNB4* in mouse and humans points towards a possible recessively inherited disease but should be backed up by additional case descriptions.

7.2 | *CACNA2D1*

CACNA2D1 encodes the $\alpha_2\delta_1$ subunit of VGCCs. Recently, Dahimene et al. reported two patients with biallelic *CACNA2D1* variants resulting in biallelic LOF of the $\alpha_2\delta_1$ subunit that led to a DEE phenotype with cortical visual impairment, severe developmental delay, hypotonia, a movement disorder with spasticity, choreiform movements and orofacial dyskinesia, facial dysmorphism, cerebral atrophy with an emphasis on corpus callosum and an epilepsy syndrome with generalised absence or hemiclonic seizures. *CACNA2D1* variants in these patients were either predicted to be LOF by nonsense-mediated decay due to an early frameshift variant or failed to fulfil their physiological function of enhancing calcium currents and channel expression when co-expressed with $Ca_V2.2$ (Dahimene et al., 2022).

A mono-allelic predicted LOF variant has been reported in a patient with infantile epileptic spasms (formerly known as West syndrome) without developmental delay (Hino-Fukuyo et al., 2015). Patients with a microdeletion of the 7q21.11 locus involving the *CACNA2D1* gene exhibit developmental delay or reduced cognitive functions and in many but not all cases epilepsy. However, this recurrently deleted sequence contains several candidate genes expressed in CNS, so a clear association with *CACNA2D1* remains unclear (Mazzaschi et al., 2013; Mefford et al., 2011; Siddique et al., 2017; Vergult et al., 2015). Another patient with treatment-resistant epilepsy, intellectual disability and polymicrogyria carried a balanced reciprocal translocation 46,X,t(X;7)(p10;q21.2) potentially disrupting the *CACNA2D1* gene (Vergult et al., 2015). Furthermore, a monoallelic intronic variant predicted to result in a splicing defect was reported in a patient with craniofacial dysmorphism, language delay and epilepsy (Valentino et al., 2021). However, Dahimene et al. raise a serious doubt regarding the pathogenicity of monoallelic LOF variants with regard to epilepsy as the previously reported patients show phenotypic heterogenicity. They furthermore argue that gnomAD and LOVD list various likely LOF variants. Contradicting the authors' theory is that the expected frequency of LOF variants in *CACNA2D1* in gnomAD is lower than expected, resulting in a probability of being loss-of-function intolerant (pLI) score of 1 and the observed/expected (oe/e) constraint score of 0.15 (confidence interval 0.09–0.24) (Chen et al., 2022; Lek et al., 2016). Also, phenotypic heterogeneity is not uncommon in channelopathies even within patients carrying the same variants (Martins Custodio et al., 2023; Royer-Bertrand et al., 2021). On the other hand, *Cacna2d1* KO mice exhibit a mild cardiac phenotype and sensory deficits whereas a seizure phenotype has not been reported (Fuller-Bicer et al., 2009; Patel et al., 2013).

Further supporting the pathogenicity of an LOF of *CACNA2D1*, two patients, seropositive for antibodies in serum and CSF directed against the $\alpha_2\delta_1$ subunit exhibited autoimmune encephalitis with psychiatric alteration and seizures. Interestingly, *in vitro* electrophysiological recordings led to the conclusion that these antibodies result in a loss of protein function downstream of enhancing calcium currents, reducing the frequency of miniature excitatory and inhibitory post-synaptic currents in an autaptic hippocampal neuronal culture model, but not reducing calcium currents at the soma (Lee et al., 2021).

The $\alpha_2\delta_1$ subunit has a primary expression pattern in cortex and hippocampus (Hobom et al., 2000). A LOF in this protein is thus expected to result in a functional loss in calcium currents in these cells, potentially mimicking the pathomechanisms of epileptic encephalopathy with a LOF in co-expressed VGCC α-subunits, most likely $Ca_V2.1$ and $Ca_V2.3$ (Hobom et al., 2000). A compensatory upregulation of

other $\alpha_2\delta$-subunits could not be observed in *Cacna2d1* KO mice (Fuller-Bicer et al., 2009; Patel et al., 2013). Beyond their function as calcium channel subunits, $\alpha_2\delta$-subunits are essential for establishing the physiological architecture of glutamatergic synapses via their function as thrombospondin receptors and interact with NMDA receptors (Chen et al., 2018; Eroglu et al., 2009; Schöpf et al., 2021).

Taken together, a LOF in *CACNA2D1* might lead to an epileptic phenotype although the evidence that a monogenetic LOF is sufficient to lead to a clinical phenotype remains open. Interestingly, a mouse model overexpressing *Cacna2d1* also shows a seizure phenotype with the behavioural arrest that responds to the T-type calcium channel blocker ethosuximide, making GOF missense variants interesting candidates for causing epilepsy (Faria et al., 2017).

$\alpha_2\delta$-subunits are targeted by gabapentin and pregabalin, antiseizure medications that nowadays are more often used to treat neuropathic pain (Bian et al., 2006; Gee et al., 1996). Even though no clinical evidence is present, we suggest therefore to avoid these drugs in patients carrying LOF variants in genes encoding $\alpha_2\delta$-subunits as the additional blockage of these proteins may result in clinical worsening as can be seen in other channelopathies resulting from an LOF such as *SCN1A*-associated Dravet syndrome and *SCN2A* LOF-DEE (Brunklaus et al., 2012; Wolff et al., 2017).

7.3 | *CACNA2D2*

CACNA2D2 encodes for the auxiliary subunit $\alpha_2\delta_2$, which enhances divalent cation currents through VGCCs (Brodbeck et al., 2002; Hobom et al., 2000). Long before the discovery of disease association in man, spontaneous variants in *Cacna2d2* had been associated with epilepsy and ataxia in mutated mouse lines: Truncating variants in *Cacna2d2* have been found in the absence seizure mouse models *ducky* and *ducky2j* (Barclay et al., 2001; Brodbeck et al., 2002). In the *entla* mouse line, a 38 kb duplication in *Cacna2d2* results in an electrophysiological loss of function of the protein (Brill et al., 2004). In all three mouse lines, homozygous animals exhibit ataxia, paroxysmal dyskinesia and seizures with spike–wave activity in EEG recordings, which is consistent with the phenotype in homozygous knockout animals (Barclay et al., 2001; Brill et al., 2004; Ivanov et al., 2004). Homozygous loss of *Cacna2d2* results in a reduced current of $Ca_V2.1$ and other VGCCs, which explains the similar phenotype to *CACNA1A* LOF models such as *tottering* (Brodbeck et al., 2002; Fletcher et al., 1996; Jun et al., 1999; Noebels & Sidman, 1979; Wakamori et al., 1998). In addition, *Cacna2d2* dysfunction can alter neuronal morphology, as mice homozygous for the truncating *ducky* allele show reduced dendritic arbours of Purkinje cells (Brodbeck et al., 2002).

Consistent with the phenotypic similarities in the mouse models, the expression of $\alpha_2\delta_2$ is widely overlapping with the expression of $Ca_V2.1$ and $Ca_V2.3$ with a hotspot in the Purkinje cell layer of the cerebellum, which corresponds with the cerebellar phenotype in mice and humans (Barclay et al., 2001; Brodbeck et al., 2002; Butler et al., 2018; Edvardson et al., 2013; Hobom et al., 2000; Pippucci et al., 2013; Punetha et al., 2019; Valence et al., 2019). $\alpha_2\delta_2$ is furthermore expressed in the thalamus, hypothalamus, the olfactory bulb, the habenulae, the superior and inferior colliculus, the striatum and the septal nuclei with a minor expression in the cortex. There is opposing data on the expression in the hippocampus (Barclay et al., 2001; Hobom et al., 2000).

Years after the first description of these mouse phenotypes, homozygous and compound-heterozygous predicted LOF or missense variants have been described in patients with a DEE phenotype with multifocal tonic, atonic, tonic–clonic and absence seizures refractory to anti-seizure medications. Patients regularly showed dyskinesia, cerebellar atrophy, ataxia and atypical eye movements consistent with the murine phenotype (Butler et al., 2018; Edvardson et al., 2013; Pippucci et al., 2013; Punetha et al., 2019). The monogenetic origin of the disease was debated in the first place, as the first two reported families additionally carried rare homozygous variants in the *CELSR3* gene (Edvardson et al., 2013; Pippucci et al., 2013) and in the third family a common heterozygous variant in *CELSR3* was present (Butler et al., 2018). Later on, additional patients with homozygous variants in *CACNA2D1*, but not *CELSR3*, with similar (Punetha et al., 2019) and milder phenotypes, namely congenital ataxia with one febrile seizure, have been described (Valence et al., 2019). It is noteworthy that missense variants in *CELSR3*, which encodes the cadherin egf lag seven-pass g-type receptor 3, a protein involved in axonal guidance, have also been associated with febrile seizures in a Chinese cohort (Li et al., 2022).

Taken together, bi-allelic LOF variants in *CACNA2D2* seem to be sufficient to explain the phenotype of the reported patients given the concordance with the murine phenotypes in terms of ataxia and absence seizures. The experimental *in vitro* evidence of a reduction of calcium channel currents by the co-expression of the pathological p.L1040P *CACNA2D2* allele found in patients with $Ca_V1.2$ and $Ca_V2.2$ *in Xenopus laevis* oocytes and the reduction of calcium currents in Purkinje cells in the *ducky* and *ducky2j* mouse models supports this conclusion, with the constraint that not all missense variants found in humans have been functionally characterised (Brodbeck et al., 2002; Donato et al., 2006; Edvardson et al., 2013). Nevertheless, it cannot be fully excluded that variants in *CELSR3* serve as modifying factors of disease, given its role in axonal guidance and neuronal development. Regarding a targeted therapy, we propose to avoid drugs that act on $\alpha_2\delta$-subunits in these patients, as with LOF variants in *CACNA2D1*, although to our knowledge no clinical evidence is present for this suggestion.

8 | SUMMARY

All voltage-gated calcium channel α-subunits and some of their auxiliary subunits have been associated with epilepsy in the past with often strikingly overlapping phenotypes in murine models. While the disease association has been reproduced in some of the genes, over time some of these associations have been loosened, such as for *CACNA1H* and *CACNB4*. Further research is needed to extend

our knowledge on pathophysiology in all VGCC-associated syndromes to derive specific therapies for the often severely disabled patients.

AUTHOR CONTRIBUTIONS

Robert Johannes Lauerer-Braun: Conceptualization; data curation; writing – original draft. **Holger Lerche:** Conceptualization; supervision; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

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DATA AVAILABILITY STATEMENT

Data sharing does not apply to this article as no datasets were generated or analysed during the current study.

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