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REVIEWS

Roles of *KCNA2* in Neurological Diseases: from Physiology to Pathology

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Abstract
Potassium voltage-gated channel subfamily a member 2 (Kv1.2, encoded by *KCNA2*) is highly expressed in the central and peripheral nervous systems. Based on the patch clamp studies, gain-of function (GOF), loss-of-function (LOF), and a mixed type (GOF/LOF) variants can cause different conditions/disorders. *KCNA2*-related neurological diseases include epilepsy, intellectual disability (ID), attention deficit/hyperactive disorder (ADHD), autism spectrum disorder (ASD), pain as well as autoimmune and movement disorders. Currently, the molecular mechanisms for the reported variants in causing diverse disorders are unknown. Consequently, this review brings up to date the related information regarding the structure and function of Kv1.2 channel, expression patterns, neuronal localizations, and tetramerization as well as important cell and animal models. In addition, it provides updates on human genetic variants, genotype–phenotype correlations especially highlighting the deep insight into clinical prognosis of *KCNA2*-related developmental and epileptic encephalopathy, mechanisms, and the potential treatment targets for all *KCNA2*-related neurological disorders.

Keywords KCNA2 · Kv1.2 · Genotype–phenotype correlations · Mechanisms · Epilepsy · Intellectual disability

Introduction

Potassium voltage-gated channel subfamily a member 2 (Kv1.2, encoded by *KCNA2*) belongs to the Kv1 family, which has eight members (Kv1.1–8). Kv1.2 channel is composed of four alpha-subunits with six transmembrane domains (S1-S6), in which S4 is the voltage sensor, and S5 and S6 constitute the pore region [1]. The opening and closing of the Kv1.2 channel depend on the voltage-dependent gating and de-wetting of the water cavity [2, 3]. More information about the structure and regulation of the Kv1.2 channel can be found in a recent review [2]. The C- and N-terminal cytosolic domains of the Kv1.2 channel are less conserved, and they can bind to other modifying subunits to modulate tetramerization [4]. The Kv1.2 belongs to the delayed rectifying potassium channel family, and is expressed in the central nervous system (CNS), myocardium, skeletal muscle, and retina. *KCNA2*-related neurological diseases include epilepsy, intellectual disability (ID)/global developmental delay (GDD), attention deficit/hyperactive disorder (ADHD), autism spectrum disorder (ASD), pain, autoimmune diseases, and movement disorders. *KCNA2* variants were recognized to cause developmental epileptic encephalopathy since 2015 [1], and are characterized by drug-resistant epilepsy with psychomotor and developmental delay. Based on the electrophysiological studies, gain-of function (GOF), loss-of-function (LOF), and a mixed type (GOF/LOF) variants can lead to the diverse phenotypes [1]. Putting aside the electrophysiological studies that have been carried out in cell models, the molecular mechanisms for the reported variants in causing heterogeneous phenotypes are unknown. It is evident that the electrophysiological studies are insufficient to explain the multiple roles of Kv1.2 channels in causing different phenotypes. The functional Kv1.2 channel characteristics depend on homo- or heterotetramers made by the α-subunits comprising variable proportions of Kv-subfamily members [5], thus complicating the possible underlying mechanisms for the variants. The different neuronal localization of the Kv1.2 channels and its heteromization capacity can probably explain the diverse phenotypes

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of epilepsy, ID, ADHD, ASD, pain, autoimmune diseases, and movement disorders.

Masnada S et al. classified *KCNA2*-related encephalopathies into three different functional groups: GOF, LOF, and a mixed type [6]. Döring JH et al. summarized *KCNA2* phenotypes and genotypes from all published cases with epilepsy [7]. Pinatel D et al. reviewed and discussed the assembly and function of the juxtaparanodal (JXP) Kv1 complex in health, de-myelinating neuropathy, and autoimmune diseases [8]. Catacuzzeno L et al. reviewed the structure of the Kv channel emphasizing the role of Kv1.2/2.1 chimera channel [2]. Nevertheless, these previous reviews did not discuss in detail the possible underlying mechanisms for all *KCNA2*-related neurological disorders, and did not provide deep insight about the possible clinical prognostic factors. We hypothesized that different neuronal localization of the Kv1.2 channels and its heteromization capacity can probably explain the diverse conditions of epilepsy, ID, ADHD, ASD, pain, autoimmune diseases, and movement disorders. This review brings up to date the related information regarding the recent structure and function of Kv1.2 channel, reported human genetic changes, genotype–phenotype correlations, mechanisms, cell models, animal models, and the potential treatment targets for all *KCNA2*-related neurological disorders.

Kv 1.2 Channel Expression and Functions in the Central Nervous System

The JXP are membrane bound axonal domains that contain Kv1.1/Kv1.2 channels situated under the myelin at the paranodes borders [8]. In the CNS, Kv1.2 channels are mainly expressed in the pons, medulla, cerebellum, hippocampus [9], thalamus, cerebral cortex, and spinal cord [10, 11]. The expression and distribution of the Kv1.2 channels can differ according to the animal models. The Kv1.2 channels can be found at the axon initial segment (AIS) of human cortical pyramidal neurons [8]. In the mouse brain, Kv1.2 protein exists in several subcellular locations including the synaptic terminals, cell somata, JXP regions of myelinated axons, unmyelinated axons, proximal dendrites, and specialized junctions among axons [12]. Besides, Kv1.2 channels are found in axons close to synaptic terminals in the middle molecular layer of the dentate gyrus in the mouse hippocampus whereas, in cerebellum they are localized in the axon terminals, and in the plexus region of basket cells [12]. While in rat brain neurons, Kv1.2 protein has a complex subcellular distribution as it is more concentrated in the dendrites for the hippocampal, cortical pyramidal cells, and Purkinje cells whereas, for the cerebellar basket cells, it is predominantly localized in the nerve terminals [13].

The expression and distribution of the Kv1.2 channels can also differ according to the parts of the brain. The medial layer II neurons of the entorhinal cortex express high levels of Kv1.2 mRNA [13]. This cortex regulates fear memory formation and neuroplasticity in the mouse lateral amygdala via cholecystokinin (CCK) [14]. The Kv1.2 protein is located in all layers of the cerebral cortex, but mostly in layer V. It is found along the whole length of the apical dendrite and in its terminal branches in cerebral cortical layer I [13]. For the cerebellum, Kv 1.2 channel is localized in the nerve terminals (at the base and AIS of purkinje cells). Kv1.2 mRNA is highly expressed in several cell bodies in the deep half of the molecular layer of the cerebellar cortex as well as in purkinje cells (soma, cell bodies and dendritic branches) [13]. For the white matter, Kv 1.2 protein is more expressed in the corpus callosum (more on ventral part) and in axons of projection neurons [13].

The expression and distribution of the Kv1.2 channels might also differ according to the types of neurons. In myelinated axons, Kv channels are buried under the myelin sheath in the JXP regions, whereby they are linked with contactin-associated protein (Caspr2). The Kv1.1 and Kv1.2 channels cluster at JXP regions where they regulate neuronal excitability and play a major role in axonal conduction [15]. When there is a demyelination, Kv1.1/Kv1.2 channels function increases, resulting to the suppression of the membrane potential nearly to the resting potential of potassium ions, thus axonal conduction blockade [15]. Kv1.2 can also be found in striatal medium spiny neurons, somato-dendritic region where they modulate transitions and repetitive discharge [16]. In a nutshell, Kv1.2 channel is mostly expressed in axons and presynaptic terminals of the CNS [17] where they play important roles in maintaining cell membrane potential and regulating neuronal excitability [9, 16, 18–23]. Importantly, Kv1.2 channels distribution and expression can differ according to the types of animal models, parts of the brain, and types of neurons.

Kv1.2 Channel and Heteromerization

The functional Kv1.2 channel characteristics depend on homo- or heterotetramers made by α-subunits comprising variable proportions of Kv-subfamily members [5]. Heteromerization of Kv1 channels can involve assembly either with other Kv1 subfamilies or with auxiliary proteins like the Kvβ subunits [24, 25]. The Kv1.2 channel makes heteromers with diverse Kv subunits based on the neuronal cell type implying its different function in different neuronal compartments [13]. Since Kv1.2 protein has a complex subcellular distribution in different neurons, it has been shown that Kv1.2 can participate in different heteromultimeric potassium channels in different

subcellular domains. The Kv1.2-containing potassium channels might have diverse functional roles in several neuronal compartments where they modulate presynaptic or postsynaptic membrane excitability, according to the neuronal cell type [13]. The Kv channel members of a subfamily can assemble to produce channels with different properties [1]. Specifically, axonal Kv1 channels in the mammalian CNS are heteromeric, and it has been shown that Kv1.1 is more likely to associate with Kv1.4 in striatal efferents in globus pallidus and pars reticulata of substantia nigra. Whereas, Kv1.1 is more likely to form heterotetramers with Kv1.2 in cerebellar basket cell terminals and the JXP membrane adjacent to nodes of Ranvier in which they regulate neuronal excitability and neurotransmitter release [26, 27]. The targeting of the Kv1 channels at the AIS and JXP is very complicated owing to the heteromeric assembly of Kv1.1, Kv1.2, or Kv1.4 –subunits in tetramers, which forms the pore of the channels [8]. The surface expression and axonal transport of the Kv1.1/Kv1.2 tetramers depend on their association with the Kvβ subunits. The Kv1.1/1.2 channels are linked with their β2 auxiliary subunits early via secretory pathway and are organized in axonal transport vesicles via Kif3/kinesin-2 and EB1 [8]. The Kv1.1-subunit is retained in the endoplasmic reticulum and its link with the Kv1.2 -subunit supports its exit from the endoplasmic reticulum, cell surface expression, and axonal targeting specificity [8]. The Kv1.1/Kv1.2 subunits connect to each other early in the endoplasmic reticulum via their T1 tetramerization domain with four Kvβ subunits (Kvβ2 isoform in the brain) [8].

The JXP of myelinated axons comprise mostly heteromeric Kv1.1 and Kv1.2 channels connected with Kvβ2 auxiliary subunits [8]. The Kvβ is distributed widely with Kv1.2 in mammalian brain in the JXP region of nodes of Ranvier as well as in the axons and terminals of cerebellar basket cells signifying that a portion of the total pool of some of the Kv1 α-subunit in the brain is present in complexes that contain Kvβ1 [28]. Kv1.2 is codistributed with Kvβ in the hippocampus, cerebellum (axon terminal plexuses of cerebellar granule cells and basket cell terminals or at nodes of Ranvier in the cerebellar white matter) as well as in dentate gyrus [28]. It has been shown that a chimeric Kv1.2 channel has a voltage sensor from Kv2.1 (Kv1.2/2.1 (paddle) chimera [2, 29]. Interestingly, both Kv1.1 and Kv1.2 subunits can colocalize with the Nav1.6 subunit in AIS of the rat cortical interneurons [30]. Therefore, in addition to the fact that Kv1.2 channels can form heteromers with other Kv channels, they can also co-distribute with other Kvβ subunits and other channels in different parts of the brain making the pathogenesis even more complex.

Kv1.2 Channel Interactions with Other Molecules in Normal Physiology

Kv1.2 channels are linked with other molecules that help them to function properly. The interactions between cell adhesion molecules and cytoskeletal linkers coordinate the assembling of Kv1.1/Kv1.2 channels at the AIS and JXP [8]. Postsynaptic scaffolding protein DLG2 (PSD93) and postsynaptic density protein-95 (PSD95) are responsible for the Kv1.2 recruitment at the AIS [8]. The cytoplasmic tail of Caspr prompts the recruitment of MAGUK P55 Scaffold Protein 2 (MPP2) and Calcium/Calmodulin Dependent Serine Protein Kinase (CASK) at the AIS of hippocampal neurons that correlates with the level of Kv1.2 enrichment [8]. The myelinated axons both in the CNS and in peripheral nervous system (PNS) have Kv1.1/Kv1.2 channels localized at the JXP under the myelin sheath [8]. The Kv1.2 channels co-localizes with Caspr2 in human cortical pyramidal neurons, and in rat retinal ganglion cells where they are constrained at the distal region of the AIS [8]. The Kv1.2 channels, Caspr2, and Contactin2 are concentrated at the JXP and neighboring areas in 4.1G KO mice peripheral nerves [8]. The Contactin2 is involved in the internodal gathering of the Kvl channels by facilitating the phosphorylation of Kv1.2 [8]. The Peroxisomal Biogenesis Factor 5 (PEX5) mutant displays abnormal internodal clusters of Kv1.1/Kv1.2 channels linked with Caspr2 and Contactin2 [8]. The conditional deletion of ADAM Metallopeptidase Domain 23 (ADAM23) in parvalbumin-positive neurons can alter the Kv1.2 JXP recruitment in the CNS (hippocampal inhibitory neurons) as well as in the PNS [8]. Caspr2 and TAG-1 form a scaffold that is crucial for the maintenance of the Kv channels at the JXP region [31]. Altogether, these studies suggest that there are several molecules involved in the regulation of the Kv1.2 functions.

Kv1.2 Channel and Synaptic Complex

The synaptic complex contains three components: the presynaptic membrane (an axon terminal), a synaptic cleft, and a postsynaptic membrane (dendritic spine). Kv1.2 channel contributes to the formation of the synaptic complex and its dysfunction can result to neurological diseases. For example, for the Kv1.2 somatodendritic expression, Kv1.2 is more localized to distal apical dendrites whereby perforant pathway synaptic inputs for learning arrive [32]. The distal dendritic Kv1.2 subunits modulates the threshold for dendritic sodium channel-dependent amplification of perforant pathway-evoked excitatory

postsynaptic potential [19, 32] which is consistent with the theory that D-type potassium current produced by Kv1.2 is activated by low voltage depolarization near the action potential threshold [33]. The downregulation of Kv1.2 in CA3-pyramidal cells facilitates mossy fibers-induced heterosynaptic long-term potentiation of pyramidal cells-excitatory postsynaptic potentials by enhancing the activation of sodium channels at distal apical dendrites [19]. Kv1 channels regulates spike threshold dynamics and spike timing in cortical pyramidal neurons [20]. Kv1 channels are also strategically positioned at AIS to regulate slow subthreshold signals, presynaptic action potential, and synaptic coupling in local cortical circuits (layer 5 pyramidal neurons) [22]. In presynaptic region, Kv1.2 channels suppress terminal hyperexcitability during the depolarizing after-potential as shown in rats [23]. It has been suggested that Kv1.2-containing potassium channels might have diverse functional roles in several neuronal compartments where they modulate synaptic transmission, and the blockage of Kv1.2 in cortical synaptosomes is an underlying mechanism for the 5-HT-induced glutamate release from thalamocortical terminals [34].

KCNA2 and Calcium Hemostasis

The activation of potassium channels also has a role to play in maintaining the elevated levels of the cytoplasmic calcium ions because potassium channels sustain the hyperpolarization at the plasma membrane that is necessary for the calcium ions influx [35–37]. Calcium ions have several crucial functions inside the cells. Calcium ions act as a second messenger that activates numerous physiological processes including oocytes fertilization, embryonic formation, cell growth, differentiation, proliferation, contraction, secretion, metabolism, gene expression, cell survival, and cell death [38, 39]. Calcium-calmodulin (CaM)-dependent protein kinase II (CaMKII) is expressed in excitatory synapses where it is crucial for the regulation of the synaptic plasticity, learning, and memory [40]. The CaMKII can work with other potassium channels like the large-conductance calcium-activated potassium channel (BK, KCNMA1) channels [41], potassium voltage-gated channel subfamily H member (KNCH, Kv 11) channels [42], and potassium voltage-gated channel, shal-related subfamily, member 3 (KCND3, Kv4.3) channels [43] to regulate synaptic plasticity. The intracerebroventricular injection of GSK1016790A (a CaMKII antagonist) for 3 days in pilocarpine-induced status epilepticus model demonstrated lowered hippocampal protein levels of Kv1.2 and Kv2.1 channels suggesting that there could some connections between CaMKII and Kv1.2 [44]. Rats exposed to subacute hypoxia exhibit reduced expression of mRNA for Kv1.2, Kv1.5, and Kv2.1 resulting to depolarized resting membrane potential, and elevation of the cytosolic calcium levels in the cell [45].

BK channels are distributed in the plasma membrane of neurons where they modulate action potentials, as well as the release of neurotransmitter from presynaptic terminals [46]. The BK channels have been identified in the lysosomes whereby they maintain lysosome functions, including the calcium signaling, membrane potential, pH stability, membrane trafficking as well as degradation [47]. They can sense concurrently augmented intracellular calcium levels and membrane depolarization, which is suitable in excitable cells, as they regulate cellular activity through negative feedback modulation of calcium influx via voltage-activated calcium channels [46]. Faults of the BK channels have been associated with neurodegenerative and lysosomal storage diseases [47]. Several potassium channels including calcium-activated potassium channels, ATP-sensitive potassium channels, potassium permeable trimeric intracellular cation channels, and the potassium-hydrogen exchange are expressed in the endoplasmic reticulum where they regulate endoplasmic reticulum calcium homeostasis [48]. It has also been shown that the potassium channel opener (NS1619) modulates calcium homeostasis in muscle cells by inhibiting SERCA [49]. The malfunction of the mitochondrial calcium-activated potassium channels can decrease mitochondrial calcium ions overload and reactive oxygen species generation [50]. Thus, *KCNA2* variants might affect calcium signaling indirectly similar to other potassium channelopathies resulting to the pathological conditions; however, more studies are needed to explore this theory. Future studies can explore the relationship between the Kv1.2 channel and calcium signaling in the lysosomes, mitochondria, and endoplasmic reticulum.

KCNA2-Related Neurological Disorders

The Kv1.2 channels maintain cell membrane potential and regulate neuronal excitability. Their distribution and expression can differ according to the parts of the brain and types of neurons. Neurological disorders including epilepsy, ID/GDD, ASD, ADHD, and movement disorders can caused by the *KCNA2* variants according to our systematic literature review. In addition to the *KCNA2* pathogenic/likely pathogenic variants, the dysfunctions of the Kv1.2 channels have been implicated directly or indirectly to other neurological disorders such as pain, amyotrophic lateral sclerosis (ALS), depressive like phenotypes, and autoimmune encephalitis according to our review.

KCNA2-Related Neurological Disorders Caused by Pathogenic/Likely Pathogenic Variants

We found 84 patients with neurological disorders (epilepsy, ID/GDD, ASD, ADHD, and movement disorders) caused by the *KCNA2* variants according to our systematic literature review (Table 1). Thirty pathogenic/likely pathogenic variants including six recurrent ones were identified in those 84 patients. Out of those 30 variants, eight were LOF, three were GOF, five were mixed LOF/GOF, and the rest had unknown functional changes (Fig. 1A). Types of the variants included missense, deletions, and complex mosaicism. The six recurrent variants included Met255-Ile257del, Arg294His, Pro405Leu, Arg297Gln, and Thr374Ala, Arg65* (Fig. 1B). Table 2 summarizes the overall genotype–phenotype correlations for the 84 cases.

KCNA2-Related Epilepsy

Clinical Features of *KCNA2*-Related Epilepsy Overall, about 84.52% (71/84) of the reported patients presented with *KCNA2*-related epilepsy. The phenotypic spectrum was wide, ranging from mild febrile seizures to severe epileptic encephalopathy. The mean onset age of seizures was 13.44 (0–156) months. Approximately 72.72% (48/66) of patients had seizures in the first year of life. The seizure types were variable among patients, including generalized tonic–clonic seizures (44/62), and focal seizures (22/62). Noteworthy, 42.11% (24/57) of patients were sensitive to fever. Sixty out of seventy-four patients had ID/GDD, of which 25 had mild to moderate ID/GDD, and 35 had moderate to severe ID/GDD. Some epileptic patients presented with behavioral disturbances such as ASD, ADHD, irritability, hyperactivity, stereotypic movements, aggressiveness, and stubbornness. The proportions of patients with ataxia, tremor, and spasticity among epileptic patients were 74 0.13% (43/58), 28.85% (15/52), and 17.86% (10/46), respectively. Thirteen variants (13/34) led to ataxia, seven variants (7/32) could cause tremor, and two variants (2/34) were related to spasticity. About 46/54 (85.19%) of the patients showed abnormal electroencephalography (EEG) at seizure onset, characterized by the slow background activity, focal and multifocal spikes. In addition, 40.32% (25/62) of the patients had abnormal brain magnetic resonance imaging (MRI, Table 2); cerebellar atrophy (17/25) was the most common.

Table 1 Summary of clinical features of *KCNA2*-related neurological disorders according to the available information

Clinical features	Numbers of patients (N)	Numbers of patients (N)
Sex	Males (45)	Females (36)
Onset age	< 1y (18)	> 1y (48)
Seizures	Yes (71)	No (12)
Seizure types	Generalized seizures (44/62)	Focal seizures (22/62)
Febrile sensitivity	Yes (24)	No (33)
ID/GDD	Mild to moderate (25)	Moderate to severe (35)
ASD	Yes (5)	No (30)
ADHD	Yes (5)	No (30)
Ataxia	Yes (43)	No (15)
Tremor	Yes (15)	No (37)
Spasticity	Yes (10)	No (36)
Brain MRI	Abnormal (25)	Normal (37)
EEG	Abnormal (46)	Normal (8)

ASD, autism spectrum disorder; *ADHD,* attention deficit/ hyperactive disorder; *EEG,* electroencephalography; *GDD,* global developmental delay; *ID,* intellectual disability; *MRI*, magnetic resonance imaging

Prognostic Factors of the *KCNA2*-Related Epilepsy Clinical phenotypes may correlate to genotypes based on biophysical properties. For instance, on one side, LOF variants correlated with milder phenotypes of epilepsy and ID/GDD; milder clinical phenotypes, including focal convulsions, focal seizure-like discharges, and a better prognosis [7]. On the other side, patients with GOF variants presented with generalized epileptic seizures and epileptic discharges, severe cognitive ID/GDD, cerebellar ataxia, and cerebellar atrophy. Interestingly, patients with mixed GOF/LOF variants had similar phenotypes to those with GOF variants; however, seizures occurred earlier, and were rarely triggered by a fever [6]. It is still difficult for clinicians to evaluate prognosis and select suitable treatments. In this review, we focused on the associations between the clinical features and the seizure outcome by comparing seizure-controlled cases and seizure-uncontrolled groups according to the information of all patients reported in the previous studies (Table 3, Figs. 2–5, and Supplementary Table 1). Although some patients responded well to anti-seizure medications, we did not observe any significant difference in the types of anti-seizure medications used among the two groups (Figs. 2 and 3). In addition, lacosamide (LCM), ketogenic diet (KD), and zonisamide (ZNS) had little benefit to the patients (Fig. 3). Noteworthy, patients who carried p.Pro405Leu or p.Arg297Gln or p.Thr374Ala variants appeared in both seizure-controlled and seizure-uncontrolled groups but it is difficult to tell if patients in both groups received the same therapies. Interestingly, we found one patient in the seizure-controlled group who harbored p.Arg297Gln and had normal brain MRI, in contrast, there were six patients in the seizure-uncontrolled group who harbored the same variant (p.Arg297Gln) and yet had abnormal brain MRIs, including cerebellar atrophy (4), small hippocampus (1), hyperintense subcortical white matter lesions (1), and cerebellar hypoplasia (1). LOF variants were more observed in seizure-controlled group than seizure-uncontrolled group

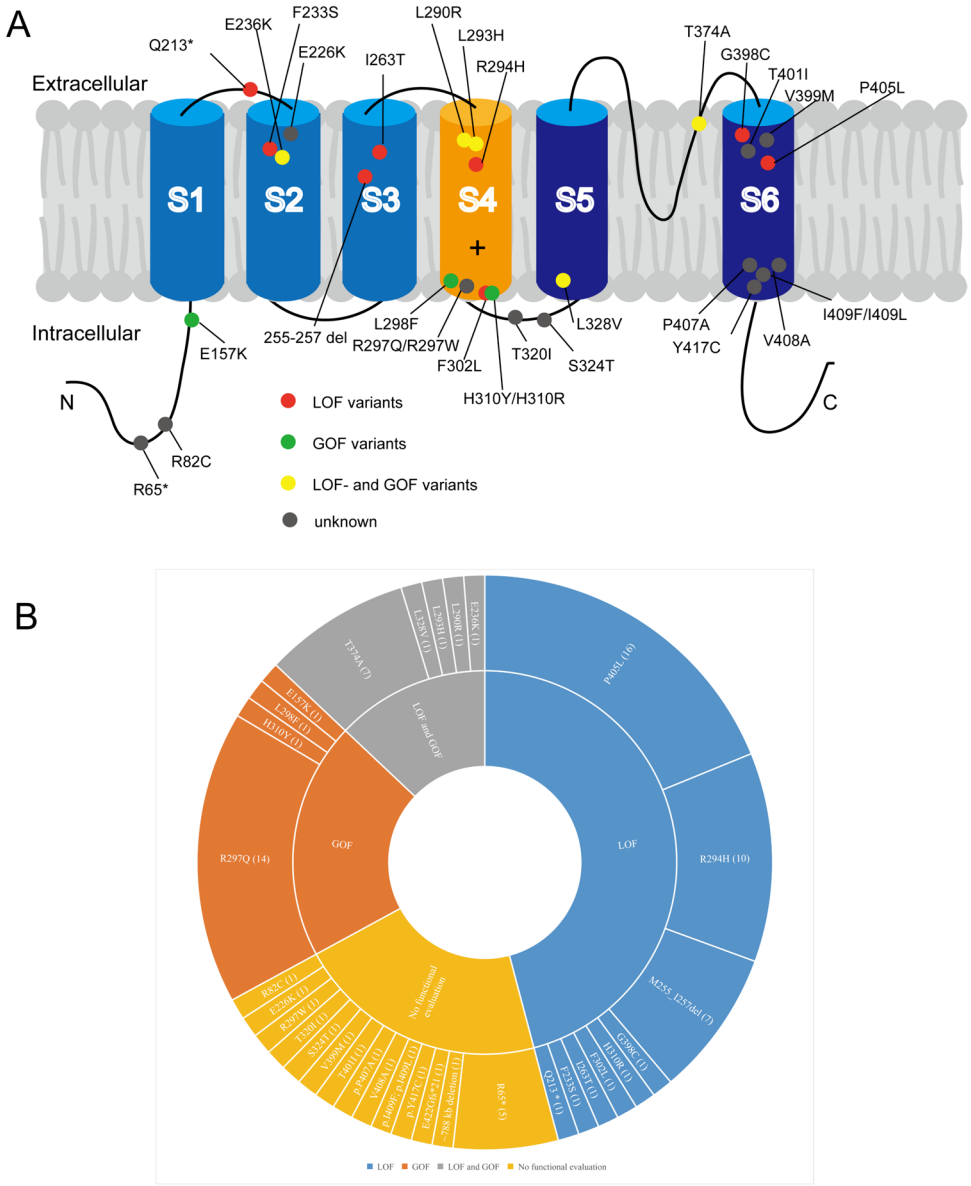

Fig. 1 **A** Schematic presentation of the Kv1.2 channel with six transmembrane domains (S1-S6). This figure depicts the locations and functions of all *KCNA2* reported pathogenic/likely pathogenic variants. Most of the variants are located in S4 and S6. Variants in red correspond to loss-of- function (LOF) effects, variants in green correspond to gain-of- function (GOF) effects, variants in yellow correspond to mixed type (GOF/LOF) variants, and variants in black stand for the variants with unknown or unclear effect. **B** The distribution of variants based on functional changes. There are several variants without functional evaluation. There are several recurrent variants in all three groups; LOF, GOF, and mixed type variants

($P = 0.02$, Pearson λ^2 test). There was no difference when proportions of patients with GOF variants were compared to those with mixed LOF/GOF variants between the two groups (Fig. 4). The proportions of patients with ataxia or ID/GDD in seizure-controlled group were lower than in seizure-uncontrolled group ($P = 0.04$, $P < 0.0001$, Pearson λ^2 test, respectively). Other clinical manifestations such as febrile seizures, speech delay, continuous spikes and waves during sleep, and brain MRI showed no significant difference between the two groups (Fig. 5). Therefore, we speculate that LOF variants might stand as a good prognostic factor, while the presence of the ataxia or ID/GDD can indicate a bad outcome.

KCNA2-Related Intellectual Disability/Global Developmental Delay

Potassium channelopathies have been associated with ID/GDD [51] and *KCNA2* is among the causative genes. GOF, LOF, and mixed type variants were related to different severity of ID/GDD ranging from mild to severe, but mostly severe form. The mixed type variants were the commonest cause of the severe ID/GDD; p.Leu293His ($n = 1$), p.Leu328Val ($n = 1$) [6], and p.Thr374Ala ($n = 6$) [6, 52, 53], followed by the GOF variant; p.Leu298Phe ($n = 2$) [6, 54], and LOF variant; p.Pro405Leu ($n = 2$) [6]. For the mild-moderate ID/GDD, most of the cases

Table 2 Summary of the genotype–phenotype correlations for the 84 cases

Variants	Altered protein function	Stereotypies/ movement disorders	ASD	ADHD	Aggressiveness	Hyperactivity	Irritability	Aggressiveness	Cerebellar atrophy	ID/GDD	Epilepsy	Stubbornness
p.Gln213*	LOF	Y									Y	
p.Gly398Cys	LOF		Y								Y	
p.Pro405Leu	LOF		Y	Y	YYY	Y	Y	YY		YYY	YYYY	
p.Glu157Lys	GOF									Y	Y	
p.Arg297Gln	GOF		YY		Y	Y		Y	YYYYY	YYYYY	YYYYYY	YYYY
p.Leu290Arg	Mixed GOF/LOF			Y		Y				Y	Y	
p.Leu293His	Mixed GOF/LOF			Y		Y				Y	Y	
p.Leu328Val	Mixed GOF/LOF			Y		Y			Y	Y	Y	
p.Arg294His	LOF	Y	Y							Y	Y	
p.Ile263Thr	LOF									Y		
p.Leu298Phe	GOF								Y	Y	Y	
p.Glu422Glyfs*21	LOF			Y	Y	Y			Y		Y	
p.Thr374Ala	Mixed GOF/LOF	Y							YY	Y	YY	
p.Ile263Thr	LOF								Y		Y	
p.Ile409Leu	??LOF					Y			Y		Y	
p.Val408Ala	Unknown								Y			
p.255_257del	LOF								Y	Y	YY	
p.Glu226Lys	Unknown										Y	
p.Arg297Trp	GOF										Y	
p.Ile409Phe	Unknown					Y					Y	
p.Tyr417Cys	Unknown										Y	
p.Arg65*	Unknown										Y	
p.Pro407Ala	Unknown										Y	
p.Arg82Cys	Unknown										Y	
p.Val399Met	Unknown										Y	
p.Phe302Leu	LOF										Y	
p.Glu236Lys	Mixed GOF/LOF										Y	
p.Phe233Ser	LOF										Y	
p.Thr401Ile	Unknown									Y	Y	
p.Ser324Thr	Unknown										Y	

ASD, autism spectrum disorder; *ADHD*, attention deficit/ hyperactive disorder; *GDD*, global developmental delay; *GOF*, gain-of-function; *ID*, intellectual disability; *LOF*, loss-of-function; *Y*, yes

Table 3 The genetic and phenotypic features grouped according to seizure outcome

Clinical characteristic	Seizure controlled group (n = 26)	Seizure uncontrolled group (n = 40)
Mean age at seizure onset	18.0 months	10.6 months
Pathogenic/likely pathogenic variants	p.Ile263Thr; p.Pro405Leu; p.Glu157Lys; p.Arg297Gln; p.255_257del; p.Thr374Ala; p.Glu226Lys; p.Arg65*; p.Glu422Glyfs*21; p.Arg297Trp; p.Tyr417Cys; p.Pro407Ala; p.Ile409Phe; p.Ile409Leu; p.Arg297Trp; p.Arg82Cys; p.Phe302Leu	p.Gln213*; p.Gly398Cys; p.Pro405Leu; p.Arg297Gln; p.Leu298Phe; p.Leu290Arg; p.Leu293His; p.Leu328Val; p.Thr374Ala; p.255_257del; p.Val399Met; p.Val408Ala; Thr401Ile;Thr320Ile; p.Val399Met; Arg294His; p.Glu236Lys; p.Phe233Ser
Locations of the variants	N-terminal (3); S2 (1); S3 (2); S4 (4); S6 (5); pore loop (1)	S1-S2 (1); S2(2); S3 (1); S4 (5); S4-S5 (1); S5 (1); S6 (5); pore loop (2)
Functional changes	LOF (14/18); GOF (2/18); mixed LOF and GOF (2/18)	LOF (16/36); GOF (10/36); mixed LOF and GOF (10/36)
Seizure type	Tonic–clonic seizures (15/24); focal seizures (4/24); absence seizures (3/24); status epilepticus (3/24)	Tonic–clonic seizures (17/33); tonic seizures (4/33); focal seizures (7/33); absence seizures (5/33); infantile spasms (2/33)
Severity of the ID/GDD	Normal (13/25); mild-moderate (9/25); moderate—severe (3/25)	Normal (1/34); mild-moderate (16/34); moderate—severe (17/34)
Presence of the febrile seizure	Yes (11/24)	Yes (13/33)
Speech development	Normal (3/19); delayed (16/19)	Normal (1/30); delayed (29/30)
Ataxia	Normal (9/22); Yes (13/22)	Normal (4/27); Yes (23/27)
Presence of the continuous Spikes and waves during sleep	Yes (6/15)	Yes (4/23)
Brain MRI	Normal (16/22); abnormal (6/22)	Normal (19/35); abnormal (16/35)

GDD, global development delay; *GOF*, gain-of-function; *ID*, intellectual disability; *LOF*, loss-of-function; *MRI*, magnetic resonance imaging

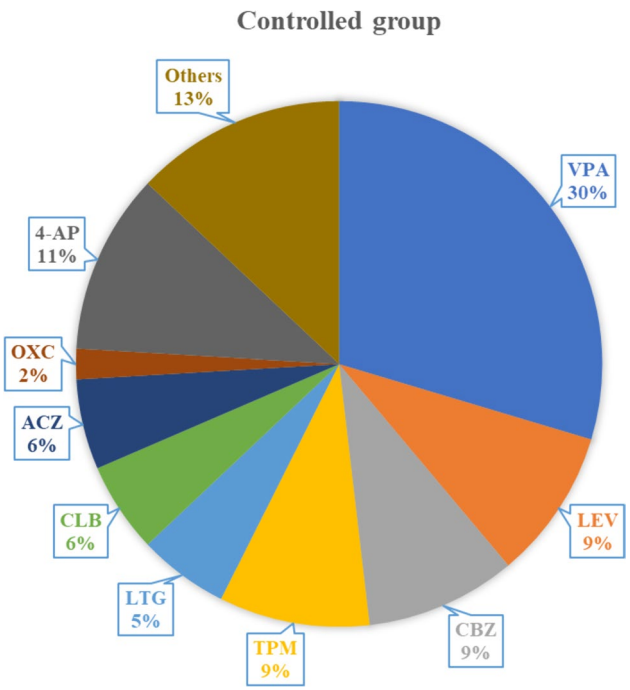

Fig. 2 Anti-seizure medications used in the seizure-controlled group. ACZ, acetazolamide; CBZ, carbamazepine; CLB, clobazam; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine, TPM, topiramate; VPA, sodium valproate

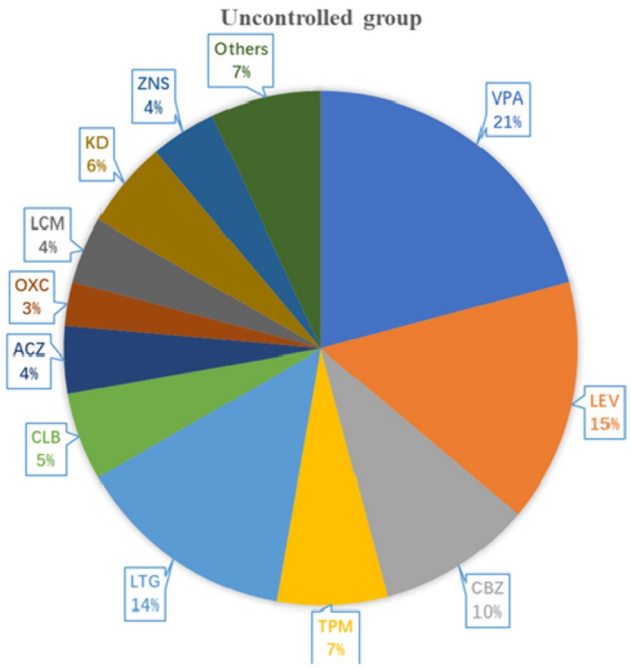

Fig. 3 Therapies used in the seizure-uncontrolled group. ACZ, acetazolamide; CLB, clobazam; CBZ, carbamazepine; KD, ketogenic diet; LEV, levetiracetam; LTG, lamotrigine; LCM, lacosamide; OXC, oxcarbazepine; TPM, topiramate; VPA, sodium valproate; ZNS: Zonisamide

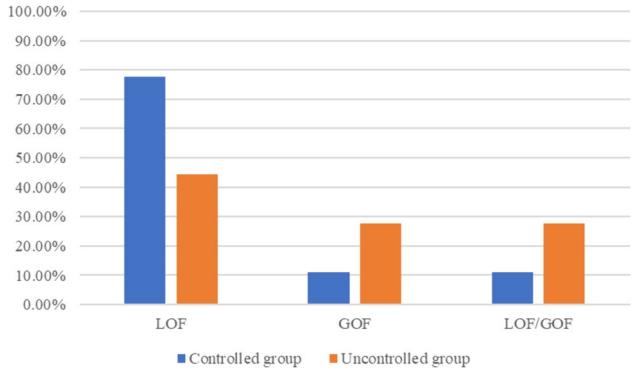

Fig. 4 Functional characteristics of variants among the seizure-controlled and seizure-uncontrolled groups. GOF, gain-of-function; LOF, loss-of-function

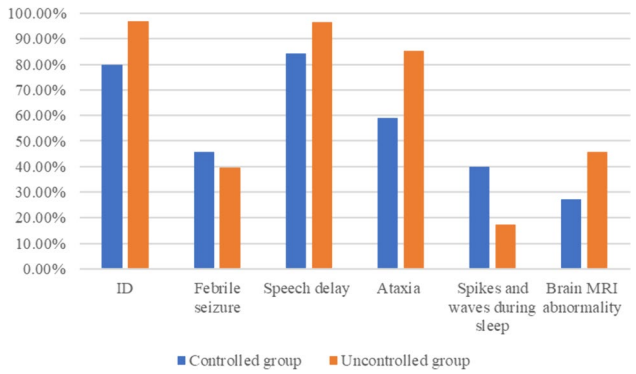

Fig. 5 The distribution of the clinical characteristics among the seizure-controlled and seizure-uncontrolled groups. ID, intellectual disability; MRI, magnetic resonance imaging

harbored variants with the LOF effects: p.Ile263Thr for two cases [6, 54], p.Pro405Leu for 14 cases [6, 52, 54–56], p.Arg294His for four cases [6, 57], and p.255_257del for one case [58]. In addition, some few cases with mild-moderate ID/GDD had variants with either mixed or GOF effects; p.Leu290Arg in two cases due to mixed type functional effect [6, 59], and GOF activity alone: p.Glu157Lys in one case [6], and p.Arg297Gln in five cases [6, 54, 58, 60]. Table 2 summarizes this information. Therefore, it seems that cases carrying variants with mixed GOF/LOF properties are more likely to have severe ID/GDD in contrast to those having variants with either LOF or GOF effect alone. The reason as why variants with mixed GOF/LOF properties are more likely to relate with severe ID/GDD is not clear now. Nevertheless, we hypothesize that these variants could have affected calcium signaling, then interfered with neurotransmitter release, synaptic plasticity, and long-term potentiation. Future animal model studies are invited to explore this theory.

KCNA2-Related Autism Spectrum Disorder

ASD is a neurodevelopmental disorder that affect social interaction, communication, learning, and behavior. It affects 1 in 36 children [61]. Based on available evidences, ASD occurs due to the dysregulation of the molecular signaling cascades that can involve dendritic spines, receptors, synaptic function, and synaptic plasticity [62, 63]. Since Kv1.2 channel participates in the formation of the synaptic complex, it is obvious that it can also cause ASD. To date, some reported *KCNA2* variants have been linked to ASD including the p.Gly398Cys and p.Pro405Leu with LOF effects and p.Arg297Gln with GOF property [6]. Notably, the carriers of these variants (p.Gly398Cys and p.Pro405Leu) suffered severe ID on top of ASD emphasizing the theory that ID and ASD might be sharing the same pathophysiology. Moreover, p.Arg297Gln with GOF effect has been reported in two cases with ASD [64]. Table 2 summarizes this information. Future animal model studies are needed to explain the relationship between *KCNA2* and ASD, especially by exploring the specific neuronal subcellular localization of the variants.

KCNA2-Related Attention Deficit/ Hyperactive Disorder

ADHD is the commonest neurodevelopmental disorder in childhood. The impairment of the neurotransmission in the dopaminergic pathway has been proposed to play a crucial role in the pathogenesis of ADHD [65]. The Kvβ2 can regulates Kv1 channels and dopamine neurotransmission in the adult mouse brain [66]. The p.Leu290Arg variant with a mixed GOF/LOF property has been reported to associate with ADHD and mild ID [6]. Besides, hyperactivity along with different degrees of ID/GDD have been observed in carriers of several *KCNA2* pathogenic variants including p.Leu293His, and p.Leu328Val, both with mixed GOF/LOF properties [6] as well as p.Pro405Leu with LOF effect [6]. Moreover, the p.Glu422Glyfs*21 has been linked with ADHD and ID in one case [67]. Table 2 summarizes this information. There is a theory that prefrontal cortex plays a major role in occurrence of ADHD [65]. Therefore, we think some of these variants might be localized in synapses in frontal cortex; however, more studies are needed to prove it.

KCNA2-Related Movement Disorders

It has been shown that the slow inactivation of Kv1.2 channel at the AIS of spinal motoneurons stimulates the nonlinear spiking accompanied with the rhythmic locomotor activity [8]. The reported *KCNA2* variants were related to the wide range of movement disorders including hereditary spastic paraplegia (HSP), ataxia, and tremors and so on. HSP belong to the heterogeneous category of neurodegenerative disorders whose clinical features include spasticity and weakness in the lower

extremities. It can concur with other neurodegenerative disorders such as ID, epilepsy, ataxia, and polyneuropathy [68]. The p.Arg294His located in the voltage sensor-forming S4 transmembrane segment of Kv1.2 channel was recently found in five cases originated from two unrelated families who presented with HSP accompanied by ID, ataxia, and tremor [57]. Electrophysiological study on Xenopus laevis oocytes revealed dominant negative loss of Kv1.2 channel function [57] resulting to proton conduction at hyperpolarized potentials [69]. Likewise, p.T374A variant with mixed GOF/LOF effects has been reported in three cases who manifested clinically with spastic tetraplegia, choreoathetosis, hypotonia, intractable epilepsy, ID, hypotonia, and optic atrophy [6]. Table 2 summarizes this information. Since Kv1.2 is expressed in striatal medium spiny neurons somato-dendritic region where they modulate transitions and repetitive discharge [16], we think this can explain the presence of the spasticity. Currently, there is no animal study that explored the subcellular neuronal localization of this variant.

KCNA2-Related Cerebellar Atrophy

There is a growing body of evidence that suggests the role of cerebellum in cognition. Abnormal functioning of the cerebellum can result to several neurodevelopmental disorders such as ID [70, 71], ASD [71–73], ADHD [74], and movement disorders [75, 76]. Several pathogenic *KCNA2* variants have been found in cases with cerebellar atrophy: p.Arg297Gln with GOF effect in 4 cases [6, 60, 64, 67, 77], and p. Leu298Phe with GOF effect in 1 case [54]. Additional variants include p.Leu328Val with mixed GOF/LOF effect in one case [6], p.Thr374Ala with mixed GOF/LOF effects in three cases [6, 53], p.Ile263Thr with LOF effect in two cases [6, 54], p.255_257del with LOF effect in 1 case [58], p.Val408Ala with unknown function in one case [78], and p.Glu422Glyfs*21 with unknown function in one case [67]. Table 2 summarizes this information. Similar to severe ID, most of the variants with mixed GOF/ LOF properties seem to relate with cerebellar atrophy, and the reason is not clear now. We speculate that these variants might be located in the cerebro-cerebellar networks that are involved in learning and memory. Interestingly, cerebellar atrophy is also common in ID related calcium channelopathies [79]. Therefore, similar to calcium channelopathies it seems *KCNA2* can cause cerebellar morphological changes leading to ID, epilepsy, ASD, and ADHD [80, 81].

The Underlying Mechanisms of Neurological Diseases Caused by *KCNA2* Pathogenic/Likely Pathogenic Variants

The neuronal excitability in the embryo is necessary for the nervous system development; therefore, the suppression of excitability may contribute to the developmental delay and seizure generation [82]. Besides, attenuated action may fail to propagate thus, disturbing communications between excitatory and inhibitory neurons resulting in excitatory/inhibitory imbalance of the developed brain [82]. It has been shown that LOF, GOF, and mixed LOF/GOF variants have different effects on the excitability of neurons by affecting the resting membrane potential and action potential release [83]. On the one hand, LOF variants can reduce the post-hyperpolarization amplitude as well as current threshold of action potential, broaden the action potentials in the axons and increase the peak amplitude and the number of action potentials of either excitatory or inhibitory neurons leading to the hyperexcitabilty of neurons. For example, the variant of *KCNA2*-Phe302Leu (LOF) located in the voltage-sensor region showed enhanced inactivation, prompting excitatory neurons to release more neurotransmitters [84]. Reduced Kv1.2 expression increased excitability of basket cells, and enhanced inhibitory neurotransmission of Purkinje cells [85]. On the other hand, GOF and mixed LOF/GOF may increase the rheobase of action potential, reduce the number of action potential spikes, and thus inhibit neuronal excitability, which has been confirmed by the action of Arg297Gln (GOF) variant in the hippocampal neurons [85]. Since neuronal excitability in the embryo is necessary for nervous system development, suppression of excitability may contribute to ID/GDD, ASD, ADHD, and seizure generation (Fig. 6).

From the perspective of cellular molecular mechanism, the process of transcription, translation and post-translational modification may be affected by *KCNA2* variants, which can form unstable tetramers, resulting in reduced expression in the whole cell or cell membrane. A recent study revealed that Kv1.2 (Phe233Ser) variant impaired both Kv1.2 and Kv1.4 trafficking and reduced the surface expression of the Kv1.2 and Kv1.4 wild type (a dominant-negative phenotype) [86]. In addition, the loss of Kvβ1-dependent inactivation enhanced the GOF effect [82]. Two variants (p.His310Tyr and p.His310Arg) have been reported in pediatric patients with epilepsy and GDD, and it was revealed that the p.His310Tyr variant produced a GOF effect: increased both cell-surface trafficking and activity, delayed channel closure and eradicated 'ball and chain' inactivation of the Kv1.2 by Kvβ1 subunits [82]. Whereas, the p.His310Arg led to LOF effect by reducing the expression of the subunits on the cell surface, by distracting both early (folding, translocation) and late (endoplasmic reticulum trafficking) events in biosynthesis and secretion, as well as inhibition of the voltage-dependent opening [82].

In transgenic animal models, *Kcna2* knockout mice showed spontaneous seizures and reduced life span [85, 87]. Besides, in *Pingu* mutant mice which harbor *KCNA2* variant (Ile402Thr) demonstrated epilepsy and ataxia. In the *FMR1* knockout mice, reduced Kv1.2 expression

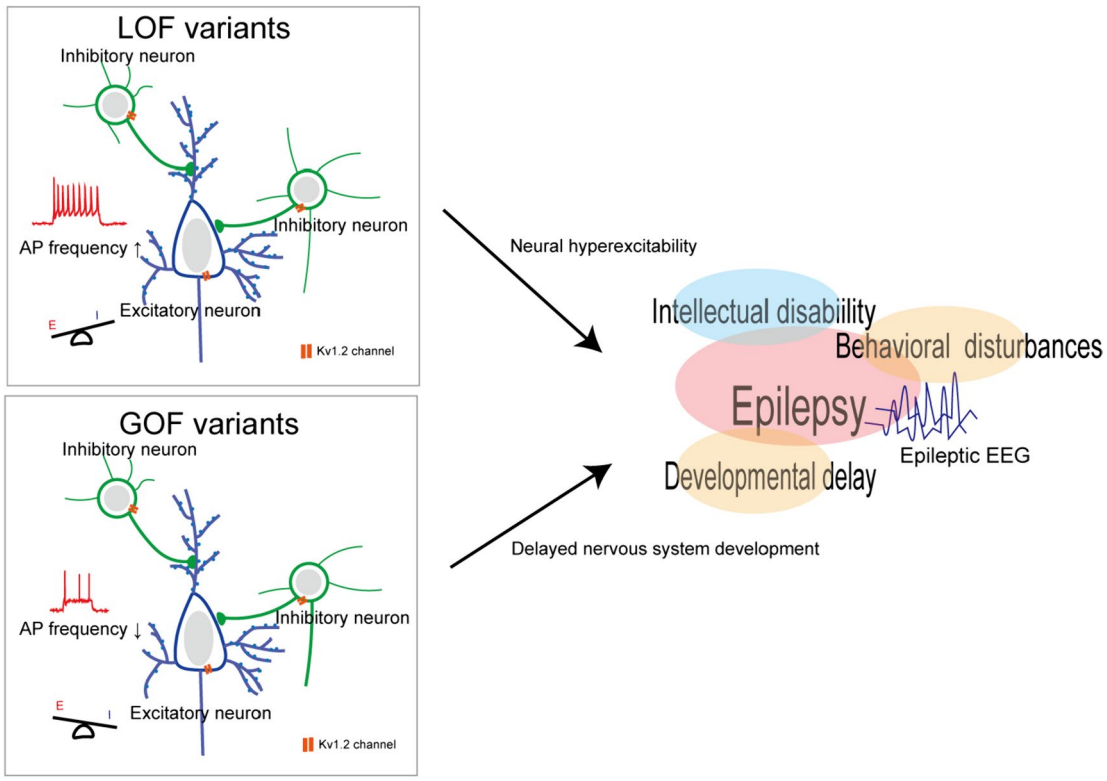

Fig. 6 Schematic representation of neuronal mechanisms involved in neurological disease caused by *KCNA2* variants. *KCNA2* LOF variants cause neuronal hyperexcitability, thus producing neurological disease. *KCNA2* GOF variants inhibit neuronal excitability, impair nervous system development perhaps leading to developmental encephalopathy and behavioral disturbances

enhanced excitability of basket cells as well as inhibitory neurotransmission of Purkinje cells [88]. The Arg-297Gln (GOF) variant reduced action potential firing in hippocampal neurons [83]; however, the deficiency of Kv1.2 in auditory neurons led to hypoexcitability [85]. It has been shown in the mice that the interaction between sigma-1 receptor and Kv1.2 shapes neuronal and behavioral responses to cocaine suggesting that the consequences of sigma-1 receptor binding to Kv1.2 channels can play a role in other chronic diseases in which maladaptive intrinsic plasticity and sigma-1 receptors are engaged [89]. The heterosynaptic potentiation of perforant path-excitatory / inhibitory postsynaptic potential is facilitated by downregulation of Kv1.2 at distal apical dendrites of CA3 pyramidal cells, which is referred to as the long-term potential of intrinsic excitability [90]. The lack of tyrosine phosphatases-facilitated dephosphorylation of Kv1.1, Kv1.2, and Kv7.3 in cultured neurons of the non-receptor tyrosine phosphatases knockout mice reduces potassium current density and heightened the after-depolarization [91]. One study compared the distribution of the Kv1.1, Kv1.2, and Kv4.2 mRNAs in rat brain, and studied the activity-dependent changes following treatment with the pentylenetetrazole. Their study revealed regional and cell type-specific differences in gene expression, and seizure activity reduced Kv1.2 and Kv4.2 mRNAs in the dentate granule cells of the hippocampus suggesting that Kv1 gene regulation can play a role in long-term neuronal plasticity [92]. Kv1.2 channels play a major role in the flexibility of the intracortical axons and may participate considerably in the intracortical processing of rats [93].

In summary, variants in the human *KCNA2* gene can cause epilepsy directly, which stands as a very clear etiology as discussed in the previous sections. However, the expression of *KCNA2* gene and Kv1.2 channel can be altered in other types of epilepsy, suggesting that *KCNA2* is involved in the occurrence and development of epilepsy. Consequently, two mechanisms can play a role in the occurrence of epilepsy. On the one hand, *KCNA2* encodes Kv1.2 channels that regulate neuronal excitability directly thus, its impairment can cause seizures. On the other hand, Kv1.2 can form tetramers with Kv1.1 and Kv1.4; can interact with proteins such as Lgi1 and Adam22 and their dysregulations can cause epilepsy (Table 4). Therefore, the underlying mechanisms of Kv1.2-related epilepsy are complicated depending on types of variants, neuronal types and tetramization with other molecules.

Table 4 Kv1.2 channel interactions with other molecules in the pathological conditions

Neurological disease	Molecules	Mechanisms	Effects	References
Epilepsy and/or ataxia	Kv1.1	Forms heterotetramers with Kv1.2	Immunochemical experiments showed reduced expression of Kv1 channels in the basket cell terminals of Pingu (*Kcna2* mice carrying Ile402Thr) mice. The homomeric and heteromeric channels expression containing the Kv1.2 cultured in CHO cells unveiled minimal changes in the biophysical properties but significant reduction of the amount of useful Kv1 channels	[143]
	Secretin	Regulates Kv1.2 trafficking in the cerebellum	Protein kinase A modulates secretin, which in turn regulates Kv1.2 endocytosis	[144]
	Kv1.4	Forms heterotetramers with Kv1.2	Kv1.2 (Phe233Ser) variant impaired both Kv1.2 and Kv1.4 trafficking and reduced the surface expression of the Kv1.2 and KV1.4 wild type (a dominant-negative phenotype)	[82, 86]
	Lgi1	Regulates Kv1.2 expression	Reduced expression of LGI1 lowers expression of Kv1.1 and Kv1.2 through the post-transcriptional mechanism, which makes neurons overexcited and induces the release of excitatory neurotransmitter glutamate, leading to epilepsy	[138]
	SLC7a5	Regulates Kv1.2 expression and current	Co-expression of the Kv1.2 with Slc7a5 channels decreases total Kv1.2 protein and current. Besides, epilepsy-linked GOF Kv1.2 variants display heightened sensitivity to Slc7a5	[145]
Fragile X Syndrome	Fmr1	The N-terminus of FMRP directly binds to a phosphorylated serine motif on the C-terminus of Kv1.2	Loss of Kv1.2 and FMRP interaction in basket cells amplifies GABA release in basket cells, affecting the firing activity of Purkinje neurons and thus, the output from the cerebellar circuitry leading to Fragile X Syndrome and autism	[88]
Neurological disease	**Molecules**	**Mechanisms**	**Effects**	**References**
Attention deficit/ hyperactive disorder	Kvβ2	Forms heterotetramers with Kv1.2	The Kvβ2 can regulates Kv1 channels and dopamine neurotransmission in the adult mouse brain	[66]
Autoimmune encephalitis	CASPR2	Forms molecular complex with transient axonal glycoprotein-1 and Kv1.1 and Kv1.2	Regulates neuronal activity and is required for Kv1 proper positioning. CASPR2 autoimmune antibodies reduced Kv1.2 membrane surface expression in the HEK293 and cultured hippocampal neurons	[142]

Table 4 (continued)

Neurological disease	Molecules	Mechanisms	Effects	References
Pain	DNA methyltransferase	Regulates Kv1.2 expression	The blockage of the DNMT upregulation stops nerve injury-induced DNA methylation within the promoter and 5'-untranslated region of *Kcna2* gene, salvages Kv1.2 expression and total Kv current, mitigates hyperexcitability in the traumatized DRG neurons, and relieves nerve injury-induced pain hypersensitivities	[100]
	lncRNA	Regulates Kv1.2 expression	lncRNA (DS-lncRNA) downregulation escalated RALY-triggered Ehmt2/G9a expression which was accompanied with the reduction of opioid receptor and Kv1.2 expression in DRG, resulting to neuropathic pain symptoms in male mice, and DS-lncRNA rescue could attenuate nerve injury-induced pain hypersensitivities	[101]
	DNMT3a	Regulates Kv1.2 expression	Upregulation of the dorsal horn DNMT3a expression leads to bone cancer pain by silencing dorsal horn Kv1.2 expression, and DNA methyltransferase DNMT3a shRNA can rescue the decreased mRNA and protein levels of DRG neurons Kv1.2, thereby alleviating neuropathic pain	[105]
	Ube2b	Regulates Kv1.2 expression	Ubiquitin conjugating enzyme E2B (Ube2b) upregulation in rats ameliorates neuropathic pain by modulating Kcna2 in primary afferent neurons	[107]

Nonvariants Kv1.2 Channels-Related Neurological Disorders and Possible Mechanisms

Dysfunctions of the Kv1.2 channels have been implicated directly or indirectly to other neurological disorders such as pain, amyotrophic lateral sclerosis (ALS), depressive like phenotypes, and autoimmune encephalitis according to our review. Nonvariants Kv1.2 -related neurological disorders and possible underlying mechanisms have been summarized below based on the current knowledge and understanding.

KCNA2-Related Pain

The distribution and composition of Kv1 channels change after sciatic nerve axotomy in the rat; there is a decrease of the Kv1.2, Kv1.4 and Kv1.6 expression at the JXP [8]. A strong decrease of JXP Kv1.2 channels is detected, whereas Kv1.1 and Kvβ2 subunits are not affected [8]. The dorsal root ganglia (DRG) is a primary sensory neuron and is closely associated with pathological pain caused by nerve damage. Notably, Kv1.2 is highly expressed in DRG [94] along with *Oprm1* (encodes for the μ-opioid receptor (MOR)), lncRNAs Gm21781 and 4732491K20Rik [95]. In the animal models of inflammatory pain and neuropathic pain, decreased expression of DRG Kv1.2 promotes the development of neuropathic pain [94, 96, 97]. The reduced expression of the Kv1.2 in DRG depolarizes the neuronal resting membrane potential, and increases the number of action potential, thus leading to neuronal hyperexcitabilty [98], which may be the main cause of pathological pain. Methyl-CpG-binding domain protein 1 (MBD1), is an epigenetic repressor gene that regulates gene transcription. It has be shown that MBD1 which is found in the primary sensory neurons of DRG is important for the occurrence of the acute pain and neuropathic pain because DRG *MBD1*-deficient mice have diminished responses to stimuli (acute mechanical, cold, heat, and cold), and the dull nerve injury-induced pain hypersensitivities [99]. Furthermore, it was unveiled that MBD1 leads to acute and neuropathic pain by silencing *Oprm1* and *Kcna2* genes in primary sensory neurons [99].

Likewise, DNA methyltransferase (DNMT)-triggered DNA methylation contributes to the genesis of the neuropathic pain partially by suppressing *Kcna2* gene expression in primary afferent neurons of male mice [100]. Besides, the blockage of the DNMT upregulation stops nerve injury-induced DNA methylation within the promoter and 5'-untranslated region of *Kcna2* gene, salvages *Kcna2* expression and total Kv current, mitigates hyperexcitability in the traumatized DRG neurons, and relieves nerve injury-induced pain hypersensitivities [100]. DRG-specifically enriched lncRNA (DS-lncRNA) downregulation escalated RALY-triggered Ehmt2/G9a expression which was accompanied with the reduction of opioid receptor and Kv1.2 expression in DRG, resulting to neuropathic pain symptoms in male mice, and DS-lncRNA rescue could attenuate nerve injury-induced pain hypersensitivities [101]. Consequently, G9a acts as a promising target for the neuropathic pain management [102, 103]. Upregulation of the dorsal horn DNMT3a expression leads to bone cancer pain by silencing dorsal horn Kv1.2 expression [104], and DNA methyltransferase DNMT3a shRNA can rescue the decreased mRNA and protein levels of DRG neurons Kv1.2, thereby alleviating neuropathic pain [105]. Octamer transcription factor 1 (OCT1) can activate Dnmt3a via transcription in rats, and then silence Oprm1 and Kcan2 in the DRG leading to neuropathic pain. Therefore, OCT1 can serve as a potential therapy target of the neuropathic pain [106].

Ubiquitin conjugating enzyme E2B (Ube2b) upregulation in rats ameliorates neuropathic pain by modulating *Kcna2* in primary afferent neurons [107]. *KCNA2* antisense RNA (*KCNA2*-AS) is highly expressed in the spinal cord tissue of postherpetic neuralgia model rat and the down-regulation of *KCNA2*-AS relieves postherpetic neuralgia partly by decreasing the translocation of pSTAT3 cytoplasm to the nucleus, and thereafter inhibiting the activation of spinal astrocytes [108]. It has been shown that peripheral nerve injury increases *KCNA2*-AS expression in traumatized DRG via the activation of myeloid zinc finger protein 1 which downregulates *Kcna2* expression resulting to the reduction of the total voltage-gated potassium current, increase of the excitability in DRG neurons, and thus neuropathic pain [98]. The blockage of the increase of the *KCNA2*-AS expression could reverse nerve injury implying that endogenous *KCNA2*-AS can stand as a therapeutic target for the treatment of neuropathic pain [98]. The overexpression of the DRG translocation methylcytosine dioxygenase 1 (TET1) could alleviate neuropathic pain by rescuing MOR and Kv1.2 expression in the ipsilateral DRG implying that TET1 can be a good target for the neuropathic pain management [109]. The miR-137-mediated Kv1.2 impairment plays a role in the pathogenesis of the nerve injury-induced neuropathic pain too as inhibition of the miR-137 in chronic constriction injury rats rescues the Kv1.2 expression resulting to the restoration of the abnormal Kv currents, prevents hyperexcitability in DRG neurons, and alleviates mechanical allodynia as well as thermal hyperalgesia [110]. The Contactin 2 knockout mice demonstrated that the Kv1.2 was missed in 70% of the JXP of the sciatic nerves and the Kv1.2 immunoreactivity occupied much reduced areas bordering the paranodes in the optic nerves [8]. As pain is a complex physiological and psychological activity, the above research is limited to the pathophysiological study of sensory neurons in spinal cord, and the response of related brain areas to pain needs further studies.

KCNA2-Related Amyotrophic Lateral Sclerosis

Potassium channels modulate microglial functions in both physiological and pathological conditions such as ALS, Alzheimer's disease, and Parkinson's disease [111]. Abnormalities in potassium and sodium conductance are important for the development of membrane hyperexcitability in ALS. Potassium and sodium currents dysfunctions can result to muscle cramps, fasciculations and neurodegeneration via calcium signaling [112]. Several potassium channelopathies including Kv1.2 have been associated with ALS. A decrease of the JXP Kv1.2 has been observed in ventral roots of the autopsy cases of ALS [8]. Axonal excitability has been linked with augmented persistent currents and reduced fast currents in ALS patients that may be interrelated with reduced Kv1.1, Kv1.2 and Kv7.2 mRNA expression as well as altered axonal transport [8]. Human ALS patients' post-mortem tissue samples of motor cortex and cervical and thoracic spinal cord revealed that potassium ATP-sensitive potassium (KATP) channels play a role in the pathomechanisms of the ALS. There is an impairment of the Kir4.1 expression and function in oligodendrocytes of the rat model of ALS implying that oligodendrocyte Kir4.1 channel also play a role in the ALS pathophysiology [113]. Notably, potassium channel defects were related with early axon degeneration of motor axons in the G127X SOD1 mouse model of ALS [114]. The KCa 3.1 channels modulate feeding behavior of ALS mouse models and its inhibition with TRAM-34 can counteract weight loss [115].

Besides, ALS associates with a reduced HCN and KCNQ channels expression [116]. The KCNQ channel activator (ezogabine) reduced cortical and spinal motor neuron excitability in ALS patients according to the clinical trial [117]. Reduced potassium currents were observed in in 53 ALS patients in comparison to 50 healthy subjects via threshold tracking transcranial magnetic stimulation (TMS) and motor nerve excitability testing [118]. Astrocytes can be targeted for the treatment of ALS via potassium inward rectifier channels and IP3 receptor signaling pathway as well as by using stem cell therapy [119]. High levels of the neuropeptide Y correlates with progression of the ALS both in mice and in human beings [120]. It has a wide range of neuroprotective roles in neurodegenerative diseases by regulating potassium channel activity, increasing the production of neurotrophins, inhibiting endoplasmic reticulum stress and autophagy, reducing excitotoxicity, oxidative stress, neuroinflammation, and hyperexcitability [120]. The 4-Aminopyridine has been reported to be effective in two ALS patients; it improved quality of life and decreased disease progression rate [121]. Consequently, Kv1.2 might play a major role in the pathogenesis of ALS similar to other potassium channelopathies, more studies are warranted.

KCNA2-Related Depressive-Like Phenotypes

The amygdala regulates stress and related disorders including anxiety and depression [122]. The entorhinal cortex expresses high levels of Kv1.2 mRNA [13] and it regulates fear memory formation and neuroplasticity in the mouse lateral amygdala via CCK [14]. The CCK is greatly expressed in the amygdala where it regulates depressive-like behavior [123], and in the entorhinal cortex where it modulates neural plasticity in the auditory cortex [124].The basolateral amygdala-entorhinal cortex pathways can also modulate the extra-amygdala area [122], consequently, they also modulate aversive memories and anxiety [122]. Abnormal CCK mRNA levels have been detected in entorhinal cortex of the patients with schizophrenia [125]. It has been shown that the CCK co-localized with GABA and glutamate cortical neurons where they regulate neuronal transmission and synaptic plasticity [125]. The enhanced GABAergic neuronal activities in the basolateral amygdala lessen stress-induced depressive behaviors in mice [126]. The N -methyl-D-aspartate receptors (NMDARs) regulates the release of CCK, which facilitates neocortical long-term potentiation, and the formation of the associative memory [127]. CCK facilitates neuronal excitability in the entorhinal cortex via activation of TRPC-like channels [128]. The CCK released from the entorhino-neocortical pathway induced by high-frequency electrical stimulation regulates the neuroplasticity of the interhemispheric auditory cortical afferents [129].

A recent study that aimed to explore how the CCK and CCK-B receptor in the basolateral amygdala are implicated in depressive-like behavior unveiled that CCK-B receptor knockout mice showed impaired long-term potentiation in the basolateral amygdala and the CCK-B receptor antagonists blocked high-frequency stimulation induced long-term potentiation in the basolateral amygdala[130]. Besides, CCK- knockout mice and CCK-B receptor knockout mice displayed considerably lower levels of depression and anxiety than the wildtype control mice implying that CCKBR might be a potential target for the treatment of depression [123, 130]. The CCK-4 infusion can lead to acute panic attacks in patients with panic disorders and in the healthy human subjects [123]. It has been shown that ketamine employs its continuous antidepressant effects via cell-type-specific modulation of Kcnq2 channel in mice glutamatergic neurons of the ventral hippocampus [131]. In addition, this study revealed that the retigabine (a KCNQ activator) could augment ketamine's antidepressant-like effects in mice [131], highlighting the importance of hippocampal KCNQ2 channel in regulating antidepressant actions of ketamine [132]. The fact that ketamine can exert its antidepressant effects via both KCNA2 and KCNQ2 channels suggest that they might have some connections. Future studies can explore this phenomenon. Besides, ketamine works by

blocking the release of CCK, which in turn clock the long-term potentiation [123]. Likewise, acute stress prompted a substantial reduction in BK channel expression in the amygdala of mice, which was associated with anxiety-like behaviors [133]. The coming studies can explore if ketamine can work via the BK channel too. In summary, there is a potential interplay between Kv1.2 channel and CCK signaling in the entorhinal cortex, which can contribute to depressive-like phenotypes.

KCNA2-Related Autoimmune Encephalitis

Autoimmune encephalitis is an autoimmune disease in which the proteins of the CNS are recognized by the autoimmune system, and produce an immune response, resulting to the specific anti-inflammatory antibody response against normal tissues. The main clinical manifestations of autoimmune encephalitis are cognitive dysfunction, mental abnormalities, seizures, and consciousness disorders. In recent years, it has been found that self-produced Kv1.2 antibodies are associated with autoimmune encephalitis [134, 135]. Kv1.2 antibody-associated borderline encephalitis presents with epileptic seizures, progressive cognitive impairment, and sensory abnormalities. Injection of Kv1.2 antibody from patients' cerebrospinal fluid into rats can increase the excitability of neurons in hippocampal CA1 region of rats and promote the occurrence of epilepsy [136]. Moreover, Kv1.2 may be involved in the pathophysiological process of anti-leucine-rich glioma inactivation 1 protein (LGI1) and anti-contactin CASPR2 antibody associated encephalitis because they interact with each other in neural tissues [137].

LGI1 is very important and plays a crucial role in regulating the function of potassium ion channels. LGI1 and Kv1.2 are co-expressed at the beginning of the axons, and the expression of Kv1.1 and Kv1.2 is regulated to achieve the regulation of neuronal discharge [138]. Decreased expression of LGI1 leads to decreased expression of Kv1.1 and Kv1.2 through the post-transcriptional mechanism, which makes neurons overexcited and induces the release of excitatory neurotransmitter glutamate, leading to epilepsy [138]. LGI1 is expressed in the synaptic cleft and binds with adam-22, an important component of Kv1 channel complex, to form a protein complex on the cell [139, 140]. LGI1 antibody inhibits the function of LGI1 protein, hinders its ability to regulate potassium ion channel (activates and closes potassium ion channel), thus depolarizes membrane potential leading to neuronal hyperexcitabilty and hence seizures. The LGI3 LOF variants cause a potentially clinically recognizable peripheral nerve hyperexcitability syndromes trait characterized by GDD, ID, deformities, diminished reflexes, facial myokymia, and electromyographic features suggestive of motor nerve instability[141]. Lgi3-null mice exhibited diminished and mislocalized Kv1 channel complexes in myelinated peripheral axons [141].

CASPR2 antibody-associated encephalitis may involve the brain, cerebellum, neuromuscular junction, peripheral nerves, etc. Clinical manifestations may include cognitive decline, epilepsy, cerebellar symptoms, increased peripheral nerve excitability, accompanied by autonomic nerve symptoms, insomnia, neuropathic pain, and some patients may lose body weight. In addition, the hyperexcitability of peripheral nerves in CASPR2 antibody-associated encephalitis constitutes part of Morvan syndrome and neuromyotonia. CASPR2 antibody inhibits the formation of the transmembrane axon complex by contactin protein 2, thus impinges on the regulation of potassium channels by PSD-95 and affects the maintenance of cell membrane potential, leading to epilepsy. CASPR2 autoimmune antibodies reduce Kv1.2 on the membrane surface of HEK293 and cultured hippocampal neurons [142].Consequently, there is a potential interplay between LGI1, anti-contactin CASPR2, and Kv1.2 signaling in causing *KCNA2*-related autoimmune encephalitis.

Available *KCNA2* Cell and Animal Models

Table 5 summarizes the available animal models, key findings along with the available modulators as discussed in different sections. The available animal models explored the role of the Kv1.2 in physiological conditions such as sleep, behavior, learning and memory, movement, hearing as well as nerves and pain development. In addition, some animal model studies explored the role of the Kv1.2 in the pathological conditions such as *KCNA2*-related epilepsy, autosomal dominant lateral temporal epilepsy, Fragile X Mental Retardation 1, ataxia, and neuropathic pain. There are some Kv1.2 modulators including 4-aminopyridine, cyclooxygenase 2, docosahexaenoic acid, tityustoxin-Kα, secretin, acetazolamide, and so on. Table 6 summarizes the available important human induced pluripotent stem cell (iPSC) lines for the developmental and epileptic encephalopathies and electrical status epilepticus during sleep.

Progress in the Treatment of *KCNA2*-Related Neurological Disease

Recently, with the development of precise therapy, advances in treating *KCNA2*-related neurological disease, including potassium ion channels targets, sodium ion channels targets, gene therapy and other drugs that have shown great promise in preclinical or clinical studies. Epilepsy is the most common *KCNA2*-related neurological disease, and *KCNA2* variants are the direct cause of epilepsy, which has a significant

Table 5 Available *KCNA2* animal models

Condition	Animal model	Key findings including modulators	References
Epilepsy	*Kcna2* knockout mice	Mice lacking the Kv1.2 subunit demonstrated seizures, reduced life span, hypoexcitability, and enlarged Kv1 currents in auditory neurons	[85]
Epilepsy	Xenopus laevis oocytes, mammalian CHO cells, and murine hippocampal neurons	The 4-aminopyridine could antagonize GOF defects caused by *KCNA2* variants in vitro, by decreasing current amplitudes and negative shifts of steady-state activation and increasing the firing rate of transfected neurons	
Autosomal dominant lateral temporal epilepsy	$LGI1^{-/-}$ mice	The Kv1.2 was considerably downregulated while the cytosolic phospholipase A2 (cPLA2)-cyclooxygenase 2 (Cox2) signaling was heightened in LGI1-/- mice. The Cox2 inhibition successfully restored the Kv1.2 expression and decreased the intrinsic excitability of pyramidal neurons	[146]
Fragile X Mental Retardation 1	*Fmr1* knockout mice	The N-terminus of FMRP binds to the C-terminus of Kv1.2, and the loss of this interaction in basket cells amplifies GABA release, compromising the firing activity in the cerebellar circuitry. The Kv1.2 agonist (docosahexaenoic acid) corrects the dysregulated inhibition in vitro and in vivo	[88]
Learning and memory	*Kcna2* ± mice	Haploinsufficiency of Kv1.2 (*Kcna2* ±) in CA3 pyramidal cells lowered the threshold for long-term potentiation at the synapses and exhibited impaired discrimination	[147]
Behavior	Rat cerebellar slices	Secretin reduced Kv1.2 cell surface expression by regulating Kv1.2 endocytic trafficking. The Kv1.2 inhibitor (tityustoxin-Kα), or the Kv1.2 regulator (secretin) can rescue the abnormality and enhance the attainment of eyeblink conditioning in rats	
Ataxia	Pingu (carries a missense mutation, an Ile402Thr in *Kcna2*)	Acetazolamide as well as transgenic complementation of the variant with wild-type *Kcna2* cDNA partially rescued ataxia in Pingu mice	[143]
Dopamine neuron firing	*Kcnab2*	*Kcnab2* reduces surface expression of Kv1.2, the primary Kv1 pore-forming subunit expressed in dopamine neurons, and shifts the voltage dependence of inactivation of potassium channel currents toward more hyperpolarized potential	[66]
Condition	**Animal model**	**Key findings including modulators**	**References**
Megencephaly	Mceph/mceph mice	*Kcna2* and *Kcna3* mRNA expression in Mceph/mceph mice is normal but the hippocampus displays decreased amounts of Kv1.2 and Kv1.3 proteins	[148]

Table 5 (continued)

Condition	Animal model	Key findings including modulators	References
Sleep	*Kcna2* knockout mice	*Kcna2* knockout mice pups have considerably less non-rapid eye movement sleep (-23%) duration and considerably more waking (+ 21%) than wild type siblings with no change in rapid eye movement sleep time	[87]
Sleep	*Kcna2* morpholino oligonucleotide knock-down in larval zebrafish	Transient knock-down of *kcna2* reduces sleep in larval zebrafish	[149]
Acoustic stimuli	Preweanling mice	Sound localization was more affected by deleting the *Kcna1* gene than deleting *Kcna2* gene	[150]
Developmental plasticity in spiral ganglion neurons	*Kcna2* null mutant mice	Heteromultimerization of Kv1.2 and Kv1.4 α-subunits causes unexpected alterations in the properties of spiral ganglion neurons	[151]
Development of peripheral nerves	Normal and galactolipids-deficient [ceramide galactosyl transferase (CGT) − / −] mice	Caspr2 and Kv1.2 were firstly detected at the paranodes before repositioning to the adjacent juxtaparanodal region during development of wild-type peripheral nerves. However, the Caspr2 and Kv1.2 remained in the paranodal for the CGT mice	[152]
Development of the myelinating schwann cells	Mice	Caspr is localized to the paranode; Kv1. 1, Kv1.2 and their beta2 subunit are localized to the juxtaparanode	[153]
Myelin and lymphocyte protein (MAL) maintenance	Mal-deficient mice	Mal-deficient mice was observed to have cytoplasmic inclusions in myelin away from the axon as well as disorganized transverse bands at the paranode–axon interface in the central nervous system. These changes were went together with significant reduction of contactin-associated protein/paranodin, neurofascin 155, and the potassium channel Kv1.2	[154]
Condition	**Animal model**	**Key findings including modulators**	**References**
Neuropathic pain caused by chronic constriction injury	Mice	Dorsal root ganglion (DRG) EBF1 downregulation causes neuropathic pain by losing its connection to *Kcna2* promoter and then silencing Kv1.2 expression in primary sensory neurons. The administration of the EBF1 may alleviate neuropathic pain by rescuing DRG Kv1.2 expression	[155]
Acute pain and neuropathic pain	Dorsal root ganglia (DRG) Methyl-CpG-binding domain protein 1 (MBD1)-deficient mice	DRG MBD1 participates in the genesis of acute pain and neuropathic pain by modulating DNMT3a-controlled *Oprm1* and *Kcna2* gene expression in the DRG neurons	[99]
Neuropathic pain	Injured rat DRG	TET1 overexpression alleviates neuropathic pain by rescuing the expression of μ-Opioid receptor and Kv1.2 in the primary sensory neurons	[109]

Table 5 (continued)

Condition	Animal model	Key findings including modulators	References
Neuropathic pain	Nerve injury-induced pain hypersensitivities in male mice	Downregulation of DRG-specifically enriched lncRNA leads to neuropathic pain via negative modulation of RALY-triggered Ehmt2/G9a	[101]
Neuropathic pain	Male Sprague–Dawley rats and Mouse hippocampal neuronal cell line (HT22)	Upregulation of ubiquitin conjugating enzyme E2B improves neuropathic pain by regulating Kcna2 in primary afferent neurons	[107]
Nerve injury	G9afl/fl mice	The G9a leads to neuropathic pain via epigenetic silencing of *Kcna2* in the axotomized DRG	[103]
Postherpetic neuralgia	Postherpetic neuralgia rat model	The down-regulation of IncRNA *KCNA2* antisense RNA relieves postherpetic neuralgia by decreasing the translocation of pSTAT3 cytoplasm to the nucleus and thereafter, hindering the activation of the astrocytes	[108]
Peripheral nerve injury	Nerve injury-induced neuropathic pain rat model	DNMT3a causes neuropathic pain by inhibiting *Kcna2* expression in the dorsal root ganglion	[156]
Neuropathic Pain	Spinal nerve ligation model	DRG DNMT1 causes neuropathic pain partially by suppressing DRG *Kcna2* gene expression	[100]
Condition	**Animal model**	**Key findings including modulators**	**References**
Neuropathic pain	Rat models of neuropathic pain	Long noncoding RNA causes neuropathic pain by silencing *Kcna2* in primary afferent neurons	[98]
Neuropathic pain	Spinal nerve ligation -induced neuropathic pain model	There is a preservation of the acute pain in rats overexpressing Kv1.2 in primary afferent neurons	[94]
Bone cancer pain	Rat model	Increased DNMT3a causes bone cancer pain by silencing Kv1.2 expression	[104]

Table 6 Available *KCNA2* cell models

Condition	Cell model	Key findings	References
Developmental and epileptic encephalopathies (c.890G > A, p.Arg297Gln)	Human induced pluripotent stem cell (iPSC) line (HIHDNEi002-A)	Cells exhibited stable amplification and several pluripotency markers on RNA and protein levels were verified	[157]
Developmental and epileptic encephalopathies (c.1120A > G, p.Thr374Ala)	Human induced pluripotent stem cell (iPSC) line (HIHDNEi003-A)	Cells exhibited stable amplification and several pluripotency markers on RNA and protein levels were verified	[158]
Developmental and epileptic encephalopathies (c.982 T > G, p.Leu328Val)	Human induced pluripotent stem cells (iPSCs) (HIHDNEi001-A)	Cells exhibited stable amplification and several pluripotency markers on RNA and protein levels were verified	[159]
Electrical status epilepticus during sleep carrying a mutation (c.1214C > T, p.Pro405Leu)	Human induced pluripotent stem cell (iPSC)	Cells exhibited stable amplification and several pluripotency markers on RNA and protein levels were verified	[160]
Developmental epileptic encephalopathy (c.869 T > G; p.Leu290Arg)	Human induced pluripotent stem cell (iPSC) (NUIGi052-A, NUIGi052-B, NUIGi052-C)	Cells exhibited stable amplification and several pluripotency markers on RNA and protein levels were verified	[161]

impact on human health. Therefore, treatment methods for epilepsy are of great concern to clinicians; however, there is a limited research on it. Herein, we collect and summarize the most recent studies about the progress in therapeutic strategies of *KCNA2*-related neurological disease.

Potassium Ion Channels Therapeutic Targets

Potassium channel blockers may be potential therapeutic targets for *KCNA2* GOF or mixed LOF/GOF variants. The 4-aminopyridine is a Food and Drug Administration (FDA) approved oral potassium channel blocker for multiple sclerosis and demyelinating disease [162]. The 4-aminopyridine enhances axon conduction and neuromuscular transmission by blocking Kv1 channel, thus improving patients' walking ability [163]. The 4-aminopyridine could block the GOF current of the Arg297Gln and Glu236Lys variants [83]. In a multi-center clinical study [83], 11 patients carrying both GOF, and mixed GOF and LOF variants were treated with 4-aminopyridine, and nine of them had improvement in terms of seizures, gait, ataxia, attention, cognition, and language. However, a small number of patients did not respond to 4-aminopyridine treatment and some even worsen. Likewise, the Glu236Lys variant which was found in one case, with mixed GOF/LOF biophysical phenotype exhibited sensitivity to the 4-aminopyridine whereby it inhibited both Kv1.2WT and Kv1.2-Glu236Lys channels in HEK293 with similar potency [164]. Thus, 4-aminopyridine remains a potentially effective treatment for *KCNA2* -associated encephalopathy. In addition, *Slc7a5* may be a potential therapeutic approach via its ability to decrease Kv1.2 expression and inhibiting Kv1.2 channel function by hyperpolarizing the activation curve [145]. Potassium channel enhancers may be effective in treating LOF mutations. Docosahexaenoic acid (DHA), a major component of omega-3 fatty acids and a Kv1.2 conformation agonist, promotes the firing frequency of action potentials in Purkinsoni cells, increases the release of inhibitory neurotransmitters, and inhibits neuronal excitation. Besides, DHA improved the social behavior of autistic mice [88, 142].

Sodium Ion Channels Therapeutic Targets

As mentioned above, Kv1.2 channel mediated D-type current regulates the width and threshold of action potential [20, 32, 144, 165, 166]. The translocation of Kv1.2 mutant into neurons and conditional deletion of *Kcna2* in mice resulted in increased action potential half-width and decreased action potential threshold, resulting to neuronal hyperexcitabilty. As some sodium channels and Kv1.2 are co-expressed in the AIS and jointly regulate action potential release, sodium channel blockers have attracted more and more attention. More importantly, some commonly used antiseizure medications have blocking effects on sodium ion channels. A study done by using computer simulations found that a 25% reduction in the current could repair the reduced threshold for convulsions caused by a reduction in D-type current. Common sodium channel blockers (SCBs) include phenytoin, carbamazepine, oxcarbazepine, LCM, lamotrigine and ZNS. Riluzole can not only block the sodium channel, but also increase the potassium current mediated by Kv1 channel [167–170].

Gene Therapy

Overexpression of Kv1.2 channel in excitatory neurons by constructing viral expression vectors can improve the seizure frequency and duration of focal epilepsy and temporal lobe epilepsy induced by red alginic acid in rats [171]. However, it is difficult to predict the expression of transgenic virus

vectors, so gene therapy is still facing problems of safety and stability. Long non-coding RNAs are emerging as critical players in the gene regulation. A conserved lncRNA, named *KCNA2* antisense RNA, was found in rat DRG primary sensory neurons. Antisense RNA of *KCNA2* down regulated the expression of *KCNA2*, reduced the gated potassium current, increased the excitability of DRG neurons, and produced pain symptoms. However, blocking the expression of *KCNA2* antisense RNA could reverse this process and relieved neuropathic pain. Therefore, endogenous *KCNA2* antisense RNA may be a target for pain treatment [98].

Other Treatment Strategies

Acetazolamide is a carbonic anhydrase inhibitor that can be used for periodic paralysis and ataxia type 1 caused by potassium channel variants [172]. Acetazolamide was approved in 1953 for the treatment of focal attacks, myoclonus, absence, and generalized attacks [173]. Intraperitoneal injection of acetazolamide 30 mg/ml improved cerebellar ataxia in *Kcna2* Ile402Thr mutant mice [143]. Patients with epileptic encephalopathy carrying *KCNA2* Arg297Gln received acetazolamide 375 mg/ day, and their ataxia and seizure frequency were lowered [174]. For the treatment of patients with Leu290Arg, acetazolamide and zonisamide could improve paroxysmal ataxia [59]. However, more studies that are clinical are needed to confirm the effectiveness of these drugs. Cyclooxygenase-2 (COX-2) is highly expressed in the brain tissues of epileptic patients and experimental animals, so it may be involved in the development of epilepsy. COX-2 specific inhibitors, such as rofecoxib, nimesulib and celeoxib, can increase the threshold of epilepsy occurrence in animals and slow down the development of epilepsy, which has a protective effect on the brain [175–177]. However, some studies suggest that COX-2 inhibitors have no significant effect on epileptic seizures [178] and cannot aggravate them, which may be due to differences in animal models of epilepsy, drug dosage and mode of action. In *Lgi1 knockout* mice, crecoxib inhibited the COX-2 signaling pathway, enhanced the function of Kv1.2, reduced the excitability of pyramidal neurons, and slowed down seizures [146]. Therefore, COX-2 inhibitors may shed light on the treatment of *KCNA2*-related epileptic encephalopathy.

Conclusions and Future Directions

KCNA2 variants are related to a wide range of phenotypes including epilepsy, ID, ADHD, ASD, pain, autoimmune diseases, and movement disorders. Interestingly, GOF, LOF, and mixed type (GOF/LOF) variants can contribute to the occurrence of those diverse phenotypes. However, whether *KCNA2* variants are related to pain, autoimmune encephalitis, depression and anxiety remains unknown. The Kv1.2 channel can make homo- or heterotetramers with diverse Kv subunits according to the neuronal cell type, and subcellular distribution, which can result to different function in different neuronal compartments. However, most of the reported variants in the literature were studied in heterologous cells, not to mention that the experiments were limited to the electrophysiological studies alone rather than molecular experiments. Future studies should be based on animal models with the aim of exploring the expression patterns, neuronal localizations, and tetramerization. In addition, the coming studies can explore how can *KCNA2* variants can affect the calcium signaling. Future research can utilize the whole-exome sequencing technology to further identify novel *KCNA2* mutation sites in patients with neurological disorders. Transgenic techniques can be employed to establish point mutation models. Furthermore, the combination of chemogenetics and optogenetics can be used to elucidate the mechanisms underlying Kv1.2 dysfunction in different brain regions and neural circuits, aiming to identify the precise therapeutic targets.

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Data Availability The datasets generated and/or analyzed during the current study are available in the article.

Declarations

Ethics Approval and Consent to Participate Not applicable.

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