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REVIEW

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$K_{Ca}2.2$ (*KCNN2*): A physiologically and therapeutically important potassium channel

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Abstract

One group of the K^+ ion channels, the small-conductance Ca^{2+}-activated potassium channels ($K_{Ca}2.x$, also known as SK channels family), is widely expressed in neurons as well as the heart, endothelial cells, etc. They are named small-conductance Ca^{2+}-activated potassium channels (SK channels) due to their comparatively low single-channel conductance of about ~10 pS. These channels are insensitive to changes in membrane potential and are activated solely by rises in the intracellular Ca^{2+}. According to the phylogenic research done on the $K_{Ca}2.x$ channels family, there are three channels' subtypes: $K_{Ca}2.1$, $K_{Ca}2.2$, and $K_{Ca}2.3$, which are encoded by *KCNN1*, *KCNN2*, and *KCNN3* genes, respectively. The $K_{Ca}2.x$ channels regulate neuronal excitability and responsiveness to synaptic input patterns. $K_{Ca}2.x$ channels inhibit excitatory postsynaptic potentials (EPSPs) in neuronal dendrites and contribute to the medium afterhyperpolarization (mAHP) that follows the action potential bursts. Multiple brain regions, including the hippocampus, express the $K_{Ca}2.2$ channel encoded by the *KCNN2* gene on chromosome 5. Of particular interest, rat cerebellar Purkinje cells express $K_{Ca}2.2$ channels, which are crucial for various cellular processes during development and maturation. Patients with a loss-of-function of *KCNN2* mutations typically exhibit extrapyramidal symptoms, cerebellar ataxia, motor and language developmental delays, and intellectual disabilities. Studies have revealed that autosomal dominant neurodevelopmental movement disorders resembling rodent symptoms are caused by heterozygous loss-of-function mutations, which are most likely to induce *KCNN2* haploinsufficiency. The $K_{Ca}2.2$ channel is a promising drug target for spinocerebellar ataxias (SCAs). SCAs exhibit the dysregulation of firing in cerebellar Purkinje cells which is one of the first signs of pathology. Thus, selective $K_{Ca}2.2$ modulators are promising potential therapeutics for SCAs.

KEYWORDS
cerebellar ataxia, $K_{Ca}2.2$ channels, medium afterhyperpolarization, Purkinje cells, spinocerebellar ataxias

Abbreviations: BK, large-conductance Ca^{+2}-activated K^+; Ca^{2+}, calcium; CaM, calmodulin; CK2, Casein Kinase 2; EA, episodic ataxia; EDH, endothelium-dependent hyperpolarization; EPSPs, excitatory postsynaptic potentials; K^+, potassium; $K_{Ca}2.x$ or SK, small-conductance Ca^{2+}-activated K^+; K_V, voltage-gated K^+; LOF, loss-of-function; mAHP, medium afterhyperpolarization; PIP_2, phosphatidylinositol bisphosphate; PP2A, protein phosphatase 2A; SCA, channels spinocerebellar ataxias; TMs, transmembrane helices; WT, wild type.

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1 | K_{Ca}2.x CHANNELS (SK CHANNELS)

Potassium channels exist in nearly all kingdoms of life and perform diverse but essential functions. The movement of potassium ions (K^+) across the cell membrane is mediated by the K^+ channels. Both excitable and nonexcitable cells rely on them significantly (Kuang et al., 2015; Littleton & Ganetzky, 2000; Shieh et al., 2000). They are tetrameric integral membrane proteins that create transmembrane aqueous pores where K^+ passes through. Transmembrane helices (TMs) traversing the lipid bilayer are present in potassium channels (Kuang et al., 2015). Potassium channel families can be divided into those with two transmembrane segments: (2TM; inwardly rectifying potassium channels), four transmembrane segments (4TM; two-pore domain), six transmembrane segments (6TM; voltage-gated, small-and intermediate-conductance Ca^+-activated potassium channels), and seven transmembrane segments (7TM) (large-conductance Ca^{+2}-activated potassium (BK) channels). Four families make up the 6TM domain class: voltage-gated (Kv), voltage-gated KCNQ-type (KCNQ), ether-a-go-go (Eag), and small- and intermediate-conductance Ca^{2+}-activated channels (Figure 1) (González et al., 2012; Weaver et al., 2006). Regardless of the class to which it belongs to, a potassium channel can be split into two domains: the pore-forming domain and the regulatory domain. The pore-forming domain, which transports K^+, has a consistent structure across the potassium channels. The regulatory domain detects various stimuli that vary among the potassium channels (Figure 2) (Jiang et al., 2002; Miller, 2000). Numerous potassium channel subfamilies have been identified. Their nomenclatures roughly correspond to the physiological signals that regulate pore opening, such as voltage, Ca^{2+}, G proteins, and polyamines (González et al., 2012). Mutations of potassium channel genes result in several human genetic illnesses, including pathologies involving cardiac arrhythmias, deafness, epilepsy, diabetes, and improper blood pressure regulation (González et al., 2012; Nam et al., 2022; Shieh et al., 2000).

Significance

The K_{Ca}2.2 channel is part of the small-conductance Ca^{2+}activated potassium channel family and is commonly found in neurons, making it an apt target for spinocerebellar ataxia. This channel inhibits excitatory postsynaptic potentials, leading to a medium hyperpolarization following action potential bursts. Mutations in K_{Ca}2.2 channels may cause delays in speech, loss of muscle coordination, and other intellectual disabilities, such as those commonly seen in spinocerebellar ataxias. Thus, this research focuses on how the K_{Ca}2.2 channel is a novel drug target for therapeutics in neurodegenerative diseases, especially that of spinocerebellar ataxia.

Small-conductance Ca^{2+}-activated potassium channels (K_{Ca}2.x or SK channels) are widely expressed in neurons as well as the heart, endothelial cells, and other cell types (Köhler et al., 1996; Orfali & Albanyan, 2023; Skibsbye et al., 2014; Weisbrod et al., 2016). K_{Ca}2.x channels are voltage-independent but are activated by increases in intracellular Ca^{2+} with a half-maximal activation in the 300–800 nM range (Brown et al., 2020). They are named small-conductance Ca^{2+}-activated potassium channels due to their comparatively low single-channel conductance which is about 10 pS compared to the intermediate channels conductance (20–60 pS) K^+ channels (IK or K_{Ca}3.1), and the large-conductance (150–300 pS) K^+ channels (K_{Ca}1.1 or BK_{Ca}) (Orfali & Albanyan, 2023; Skibsbye et al., 2014; Zheng & Trudeau, 2023).

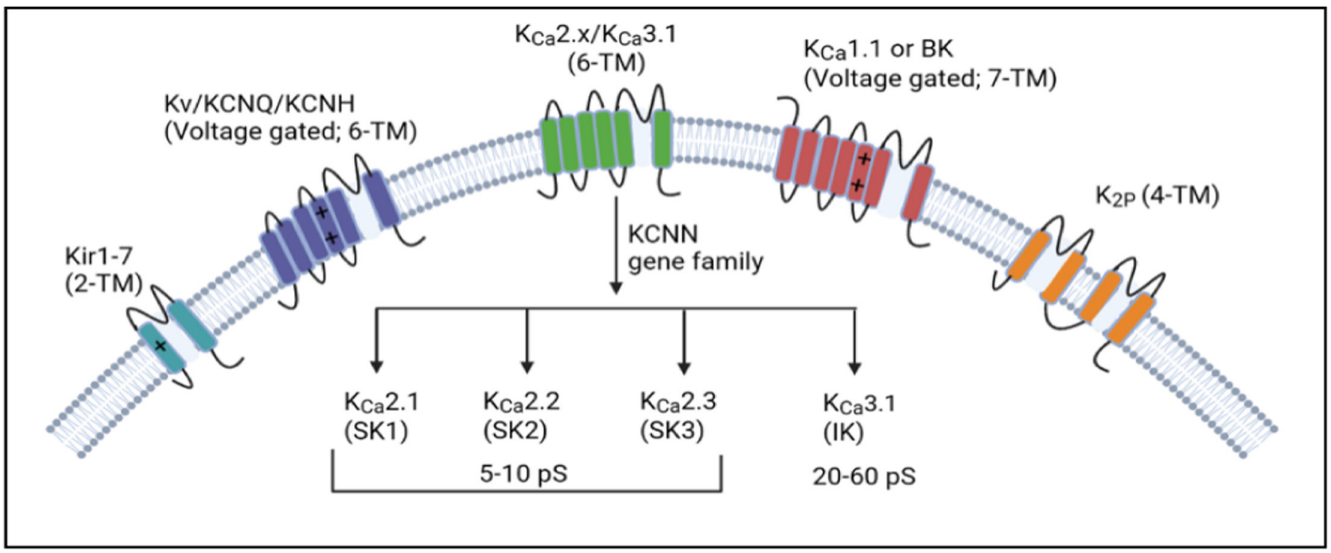

FIGURE 1 Subfamilies of potassium channels. Subfamilies of potassium channels include two transmembrane segments (two TM; Kir), four TM (two-pore domain), six TM (voltage-gated, K_{Ca}2.x, and K_{Ca}3.1), and seven TM (BK). K_{Ca}2.x family is subdivided into K_{Ca}2.1, K_{Ca}2.2, and K_{Ca}2.3 (González et al., 2012; Nam et al., 2022).

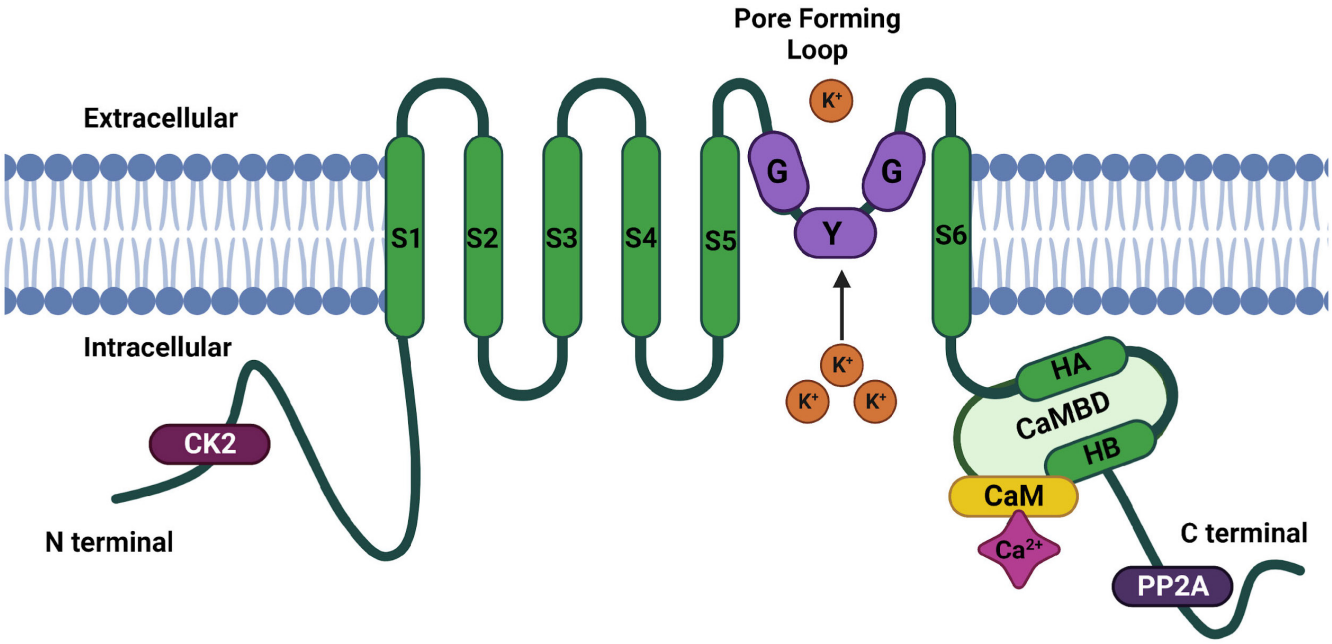

FIGURE 2 Pore-forming unit and regulatory unit of $K_{Ca}2.2$ channels. Channels are regulated at their N and C termini by binding protein phosphatases and kinases (Stocker, 2004).

Based on their phylogenic analysis, the $K_{Ca}2.x$ channels family ($K_{Ca}2.1$, $K_{Ca}2.2$, and $K_{Ca}2.3$) are encoded by *KCNN1*, *KCNN2*, and *KCNN3* (Table 1) (Köhler et al., 1996; Sailer et al., 2004).

2 | $K_{Ca}2.2$ CHANNELS

The human $K_{Ca}2.2$ (SK2) channel is encoded by the *KCNN2* gene on chromosome 5 (Aldrich et al., 2021; Willis et al., 2017), with two different-sized human isoforms: $K_{Ca}2.2$-S (49 kDa) and $K_{Ca}2.2$-L (78 kDa). Their mRNAs are transcribed from independent promoters (Girault et al., 2012; Hammond et al., 2006). Numerous areas of the brain, including the hippocampus, express the two isoforms in tandem. The two isoforms co-assemble into heteromeric channels but differ only in the length of the intracellular N-terminal domain, with $K_{Ca}2.2$-L having an extra 207 amino acids at the N terminus (Strassmaier et al., 2005). Cysteine-rich $K_{Ca}2.2$-L N-terminal extension facilitates the formation of disulfide bonds between $K_{Ca}2.2$-L subunits or heterologous proteins. The $K_{Ca}2.2$-S and $K_{Ca}2.2$-L are expressed separately and combined to create functional homomeric $K_{Ca}2.2$ channels with comparable Ca^{2+} sensitivities, producing a whole-cell current with comparable amplitudes. However, $K_{Ca}2.2$-L excised patches have significantly lower $K_{Ca}2.2$-L currents than $K_{Ca}2.2$-S currents (Allen et al., 2011; Weaver et al., 2006). The longer N terminus of $K_{Ca}2.2$-L contains potential regulatory sites, such as phosphorylation sites, that may be involved in the localization of the channel at the plasma membrane and, therefore, its function. $K_{Ca}2.2$-L controls $K_{Ca}2.2$-containing channels ($K_{Ca}2.2$-L and $K_{Ca}2.2$-S) in the postsynaptic density of dendritic spines on mouse CA1 pyramidal neurons and is required for synaptic function. For example, in mice lacking $K_{Ca}2.2$-L, the $K_{Ca}2.2$-containing channels were expressed in the extrasynaptic membrane rather than the postsynaptic density, resulting in abnormal synaptic signaling (Girault et al., 2012; Zheng & Trudeau, 2023). Rat cerebellar Purkinje cells express $K_{Ca}2.2$ channels during development and throughout maturity. These channels are essential for a variety of cellular functions, including controlling the frequency of spike firing and modifying Ca^{2+} transients in dendritic spines. The ability of these Purkinje cells and other types of neurons to modulate their intrinsic excitability and change the likelihood of inducing synaptic learning appears to be facilitated by the $K_{Ca}2.2$ channel (Dwivedi & Bhalla, 2021; Weaver et al., 2006) (Table 2).

The $K_{Ca}2.2$ pore-forming subunits form complexes with calmodulin, protein kinase CK2, and protein phosphatase 2A. About 60% of the primary structure's sequences are identical among $K_{Ca}2.x$ subtypes, while voltage-gated K^+ channels and $K_{Ca}2.2$ channels only have a significant sequence identity in the pore region (Figure 2) (Sansom et al., 2002; Weisbrod et al., 2016). These tetrameric channels, like voltage-dependent K^+ channels, have six putative transmembrane spanning sections and cytoplasmic carboxy and amino terminals. $K_{Ca}2.2$ channels specifically have a calmodulin-binding domain. Calmodulin is inherently attached to the channel's C terminus and opens the channel when Ca^{2+} binds to it, which confers the channels' Ca^{2+} sensitivity (Nam et al., 2022; Orfali et al., 2022; Stocker, 2004) (Figure 2).

Neuronal excitability and response to synaptic input patterns are regulated by $K_{Ca}2.2$ channels. $K_{Ca}2.2$ channels contribute to the medium subsequent to afterhyperpolarization (mAHP) that occurs after action potential bursts (Skibsbye et al., 2014) (Figure 3). In neurons, $K_{Ca}2.2$ channels drive an apamin-sensitive K^+ current known as I_{mAHP}, which helps to generate mAHP (Stocker et al., 1999).

TABLE 1 The *KCNN* gene family.

$K_{Ca}2$ & $K_{Ca}3$ α subunit	Gene	Other names	Amino acids	Human chromosomal location	Tissue distribution	Physiological roles
$K_{Ca}2.1$	*KCNN1*	SK1	543 (Girault et al., 2012)	19p13.11 (Aldrich et al., 2021)	Brain (Aldrich et al., 2021) Heart (Rahm et al., 2021) Lungs (Bardou et al., 2009)	The $K_{Ca}2$ channels underlie the medium AHP and regulate neuronal firing frequency (Brown et al., 2020; Orfali & Albanyan, 2023)
$K_{Ca}2.2$	*KCNN2*	SK2	579 (Aldrich et al., 2021)	5q22.3 (Aldrich et al., 2021)	Brain and heart Adrenal gland, lungs, prostate, bladder, and liver (Aldrich et al., 2021; Chen et al., 2004)	
$K_{Ca}2.3$	*KCNN3*	SK3	731 (Aldrich et al., 2021)	1q21.3 (Aldrich et al., 2021)	Brain and heart vascular endothelium, lungs, and bladder (Aldrich et al., 2021; Brown et al., 2020; Orfali & Albanyan, 2023)	$K_{Ca}2.3$ and $K_{Ca}3.1$ mediate the endothelium-derived hyperpolarization response (Nam, Downey, et al., 2023; Wulff & Köhler, 2013)
$K_{Ca}3.1$	*KCNN4*	SK4 IK	427 (Aldrich et al., 2021)	19q13.31 (Aldrich et al., 2021)	Vascular endothelium, T and B lymphocytes, microglia placenta, colon, red blood cells, lungs, and bladder (Aldrich et al., 2021; Brown et al., 2020)	$K_{Ca}3.1$ channels regulate calcium signaling cellular activation, and cell volume (Brown et al., 2020; Orfali & Albanyan, 2023)

Note: Human chromosomal location, tissue distribution, functional effects.

Blocking of the $K_{Ca}2.2$ channel by apamin increases the number of action potentials induced by current injection and the spike frequency of neurons within bursts of action potentials. This is consistent with the observation that $K_{Ca}2.2$ channels contribute to mAHP (Lam et al., 2013). Voltage-clamp recordings show three separate kinetic phases of the AHP current: a fast component (I_{fAHP}) with time constants of around 50 ms, a medium component (I_{mAHP}) with a time constant of about 200 ms, and a slow component (I_{sAHP}) with a decay time of about seconds (Bond et al., 2004). $K_{Ca}2.2$ channels mediate I_{mAHP} (Tsantoulas & McMahon, 2014). The $K_{Ca}2$ channels have been shown to underlie the mAHP in a wide variety of neurons such as spinal motor neurons, pyramidal neurons in the sensory cortex, cerebellar Purkinje neurons, and the lateral and basolateral amygdala (Hosy et al., 2011; Xia et al., 1998). Additionally, $K_{Ca}2.2$ channels regulate Ca^{2+} transients in dendritic spines and drive the repolarization of dendritic plateau potentials, suggesting that $K_{Ca}2.2$ channels influence dendritic integration characteristics. These findings collectively imply that the primary role of $K_{Ca}2.2$ channels is to dampen neuronal firing frequency and dendritic excitability in response to even mild increases in the cytosolic Ca^{2+} concentration (Dwivedi & Bhalla, 2021). Ca^{2+} signals are precisely localized in time and space in order to regulate the Ca^{2+}-dependent reactions selectively; the intracellular Ca^{2+} concentration is increased only for short periods of time and within spatially restricted regions (Fakler & Adelman, 2008). Therefore, once Ca^{2+} enters the cells through Ca^{2+} voltage-gated channels in the neurons, Ca^{2+} buffer systems limit Ca^{2+} diffusion to the "local Ca^{2+}" signaling domains. $K_{Ca}2.2$ channels most likely exist within a microdomain of a Ca^{2+} source that provides Ca^{2+} for its activation (Augustine et al., 2003).

Specialized compartments called dendritic spines serve as the postsynaptic locations for excitatory neurotransmission. On the spines, $K_{Ca}2.x$ channels are localized and control synaptic response. Ca^{2+} influx from several sources, primarily voltage-dependent Ca^{2+} channels, ionotropic glutamate receptors, and Ca^{2+} release from the endoplasmic reticulum, regulate the $K_{Ca}2.2$ channels located on the spines (Figure 4) (Stocker, 2004). Ca^{2+} influx that is triggered by synapses causes the spine's $K_{Ca}2.x$ channels to open, which causes hyperpolarization (Ngo-Anh et al., 2005).

In the human heart, atria express $K_{Ca}2.x$ channels, and these channels take part in repolarization (Humphries & Dart, 2015). In chronic atrial fibrillation, $K_{Ca}2.2$ and $K_{Ca}2.3$ display functional significance. Pharmacological blockage of $K_{Ca}2.x$ channels may be a prospective atrial-selective target for future antiarrhythmic medication therapy (Park et al., 2008; Qi et al., 2021).

3 | IMPORTANT REGULATORS FOR $K_{Ca}2.2$ CHANNELS

The regulation of $K_{Ca}2.2$ channels relies on Ca^{2+}, Calmodulin (CaM), Phosphatidylinositol bisphosphate (PIP_2), Casein Kinase 2 (CK2), and Protein Phosphatase 2A (PP2A) (Figure 2) (Allen et al., 2011; Liu et al., 1998).

TABLE 2 Major expression sites and function of $K_{Ca}2.2$ channels.

Major expression site of $K_{Ca}2.2$ channels	Function
In central neurons (Hosy et al., 2011)	Activation of $K_{Ca}2.2$ channels causes membrane hyperpolarization, which modulates neuronal excitability (Hammond et al., 2006; Lin et al., 2008)
In hippocampal neurons (Stocker et al., 1999)	$K_{Ca}2.2$ channels underlie the mAHP current in CA1 hippocampal neurons, regulate the hippocampal synaptic plasticity, play a critical role in modulating learning and memory (Hammond et al., 2006), regulate the formation of contextual fear memory (Murthy et al., 2015), play a role in drug-induced plasticity (Willis et al., 2017), and are neuroprotective against ischemia-induced cell death (Stocker et al., 1999)
In cerebellar Purkinje neurons (Womack & Khodakhah, 2003)	$K_{Ca}2.2$ channels are important in controlling regular tonic firing (Hosy et al., 2011)
In the heart (Humphries & Dart, 2015; Zhang et al., 2021)	$K_{Ca}2.2$ channels play a critical role in cardiac repolarization (Zhang et al., 2021) by underlying the mAHP current in cardiac myocytes and regulating action potential duration (Xu et al., 2003)
In cardiac inner mitochondrial membrane (Xu et al., 2003; Zhang et al., 2021)	$K_{Ca}2.2$ channels have an important role in intracellular signaling and mitochondrial function, as the activation of the mitochondrial K^+ channels results in cardioprotective effects against ischemia–reperfusion injury (Zhang et al., 2021)

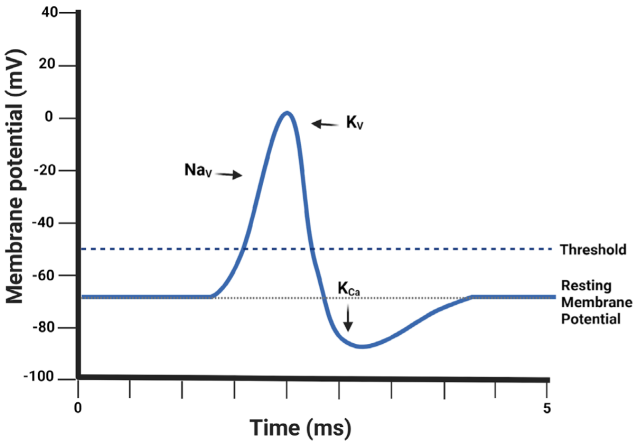

FIGURE 3 $K_{Ca}2.2$ channels roles in medium afterhyperpolarization. Upon neuronal activity, voltage-gated & Ca^{2+}-activated K^+ channels are engaged during repolarization (K_V) and during afterhyperpolarization to provide feedback inhibition at nerve terminals. They do so by restricting action potential duration and, thus, neurotransmitter release (Skibsbye et al., 2014).

3.1 | Ca^{2+}

$K_{Ca}2.2$ channels open in response to elevated intracellular Ca^{2+} concentration. $K_{Ca}2.2$ channels can be activated by Ca^{2+} influx through Ca^{2+}-permeable channels and/or Ca^{2+} release from intracellular storage (Stocker, 2004).

3.2 | CaM

All eukaryotic cells have the Ca^{2+}-binding protein CaM, which is composed of 148 amino acids (~17 kDa) in humans. Numerous intracellular activities, including cell motility, growth, proliferation, and death, are regulated by CaM, which plays crucial roles in Ca^{2+} signaling. A flexible linker connects the protein's two homologous globular domains. Two Ca^{2+} ions are cooperatively bound by EF-hands, each domain's pair of Ca^{2+}-binding motifs. The interhelical angles in the EF-hand motifs shift as Ca^{2+} binds to each globular domain, switching the conformation from "closed" to "open." Hydrophobic sites are exposed as a result, and many target proteins can then bind and be activated (Adelman, 2015; Mourre et al., 2017; Zhang et al., 2014).

3.3 | PIP_2

The apparent PIP_2 affinity for the $K_{Ca}2.2$/CaM complex and the Ca^{2+}-dependent channel activation of $K_{Ca}2.2$ channels are well correlated (Pedarzani & Stocker, 2008; Zhang et al., 2014).

3.4 | CK2

At the molecular level, it has been demonstrated that $K_{Ca}2.2$ channels form a multiprotein complex with CK2 and PP2A. CK2 decreases the sensitivity of $K_{Ca}2.2$ channels to Ca^{2+} by phosphorylating CaM at T79 when complexed with the channel (Lam et al., 2013; Liu et al., 1998; Stocker et al., 1999). The phosphorylation status of the $K_{Ca}2.2$-CaM-CK2-PP2A complex may control the amplitude and duration of the after-hyperpolarizing potentials, influencing the firing patterns of neurons, as evidenced by the decreased $K_{Ca}2.2$ channel activity and a quicker deactivation of $K_{Ca}2.2$-mediated currents (Nam et al., 2021). PP2A counteracts the impact of CK2 in this situation. The phosphorylation status at T79 is controlled by the joint actions of CK2 and PP2A, which both directly interact with $K_{Ca}2.2$ channels (Pedarzani & Stocker, 2008).

4 | DRUG CANDIDATES TARGETING $K_{Ca}2.2$ CHANNELS

Apamin, a peptide derived from bee venom, is the most studied $K_{Ca}2.x$ inhibitor (Brown et al., 2020; Stocker et al., 1999).

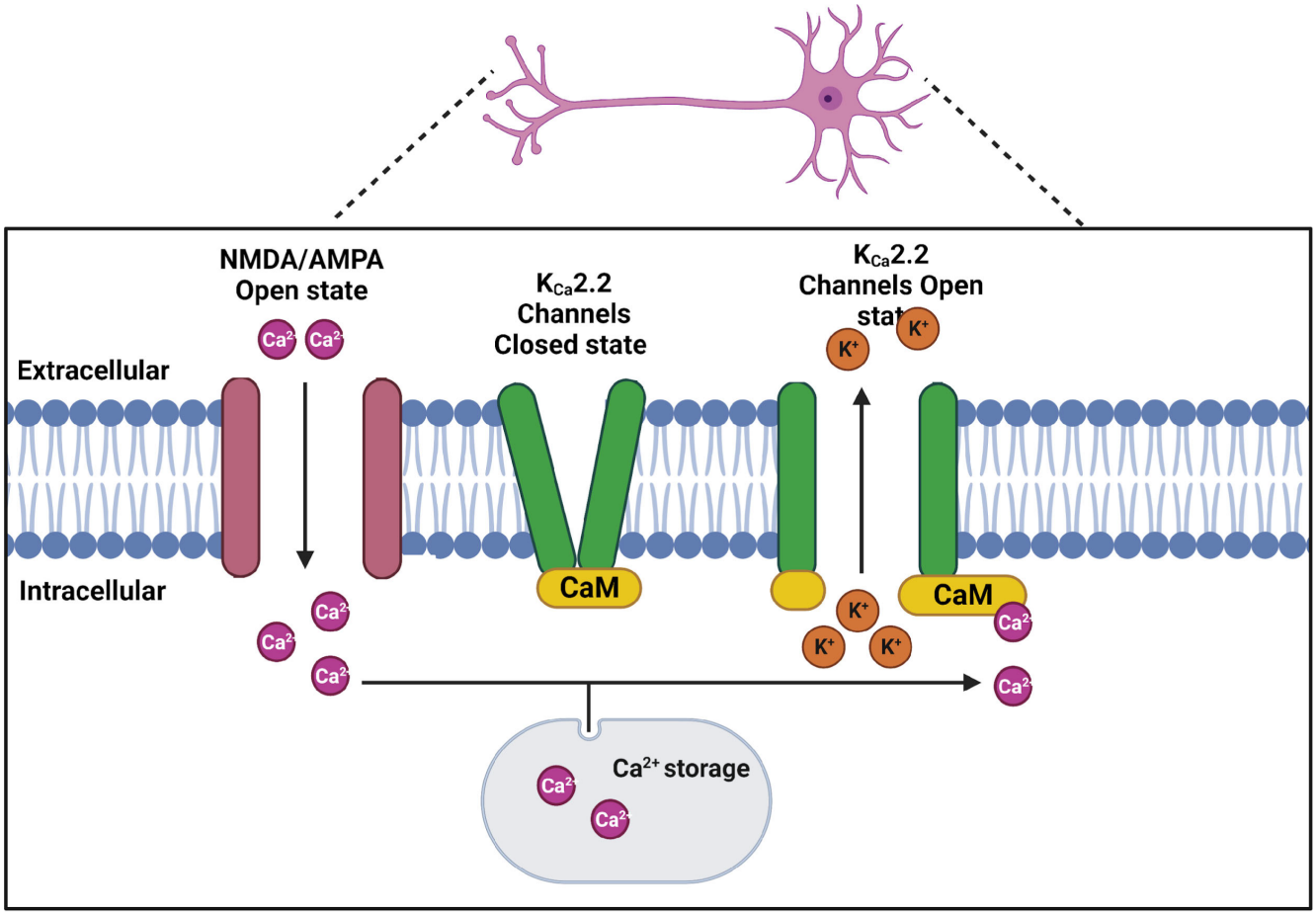

FIGURE 4 A schematic illustrating the localization and regulatory pathways involving the $K_{Ca}2.2$ channel in neurons (Lin et al., 2008). The $K_{Ca}2.2$ channel couples to Ca^{2+} sources on a physical and functional level. This figure illustrates the simplified graphical view of Ca^{2+} sources and $K_{Ca}2.2$ channels gating upon binding with Ca^{2+} (Allen et al., 2011).

Moreover, $K_{Ca}2$ channels feature activators and inhibitors that cause the Ca^{2+} concentration-response curves of these channels to shift to the left or right by increasing or decreasing the channels' apparent Ca^{2+} sensitivity (Chen et al., 2019). The three activators that are most frequently used are known as 1-EBIO (Pedarzani et al., 2001), NS309 (Chen et al., 2019), and SKA-31 (John et al., 2020) and they activate all three $K_{Ca}2.x$ channels equally well. Examples of subtype-specific $K_{Ca}2$ activators are CyPPA (Balint et al., 2020), NS13001, and 2q, a new compound recently reported by our group. GW542573X selectively activates $K_{Ca}2.1$ channels and has been dubbed "a real activator" because it can do so even in the absence of Ca^{2+} (Littleton & Ganetzky, 2000; Nam, Rahman, et al., 2023). In mouse models of episodic ataxia (EA) and spinocerebellar ataxias (SCAs), $K_{Ca}2.x$ activators, including 1-EBIO, SKA-31, and NS13001, alleviate motor impairments. Riluzole is said to improve ataxia in a modest clinical trial, though riluzole itself is poorly selective to $K_{Ca}2.2$ and has effects on multiple neural receptors (Chen et al., 2019; Nam et al., 2022). Table 3 shows the potential drug candidates targeting different types of the $K_{Ca}2.2$ channel (Stocker, 2004).

TABLE 3 Summary of different mAHP channels' inhibitors and activators.

Activators	Inhibitors
Chlorzoxazone (Cao et al., 2001)	Apamin (Bee venom) (Jäger et al., 2000)
1-EBIO (Weatherall et al., 2010)	Skyllatoxin (Scorpion venom toxin) (Naseem et al., 2023)
CyPPA (Hougaard et al., 2009)	d-tubocurarine (Ishii et al., 1997)
Riluzole (Dimitriadi et al., 2013)	EGTA, EDTA (Oliván-Viguera et al., 2015)
NS 309 (Pedarzani et al., 2005)	NS8593 (Diness et al., 2010; Jenkins et al., 2011)
SKS-11 & SKS-14 (Nam et al., 2017)	Cadmium (Braga & Rowan, 1994)

5 | LOSS-OF-FUNCTION MUTATIONS IN $K_{Ca}2.2$ CHANNELS

Patients with loss-of-function *KCNN2* mutations have intellectual disabilities, motor and linguistic development delays, and

early-onset movement abnormalities with cerebellar ataxia and/or extrapyramidal symptoms. Mochel et al. (2020) used exome sequencing to identify the variants responsible for learning disabilities, cerebellar ataxia, and white matter abnormalities (Mochel et al., 2020) and performed the patch-clamp studies to examine the effects of six chosen variations on the $K_{Ca}2.2$ channel function (Table 4). All examined variations abolished $K_{Ca}2.2$ channel activity except one, which was downgraded to unclear relevance (Littleton & Ganetzky, 2000; Nam, Rahman, et al., 2023). Studies have shown that heterozygous mutations, which are most likely responsible for *KCNN2* haploinsufficiency, cause unique autosomal dominant neurodevelopmental movement abnormalities that mimic rodent symptoms (Mochel et al., 2020). Another study showed that the mutations in the *KCNN2* gene likely cause myoclonus dystonia (Lamy et al., 2010). Neurodevelopmental problems result from loss-of-function $K_{Ca}2.2$ mutations. Rat tremors

TABLE 4 Changes in channel activity caused by pathogenic $K_{Ca}2.2$ mutations.

Species	Mutation	$K_{Ca}2.2$ current	Electrophysiological recording	Cells
Human	Y160*	N/A	N/A	N/A
Rat	L174P (Nam, Rahman, et al., 2023)	No current	Inside out (Nam, Downey, et al., 2023)	HEK-293
Human	I288S (Mochel et al., 2020)	N/A	N/A	N/A
Rat	I289N (Kuramoto et al., 2017; Nam, Downey, et al., 2023)	Reduced current	Whole-cell (Kuramoto et al., 2017), Inside out (Nam, Downey, et al., 2023)	HEK-293
Human	L321del (Mochel et al., 2020)	No current	Whole-cell (Braga & Rowan, 1994)	CHO-K1
Human, rat	I359M (Mochel et al., 2020), I360M (Nam, Rahman, et al., 2023)	No current	Whole-cell (Mochel et al., 2020), Inside out (Nam, Rahman, et al., 2023)	CHO-K1 HEK-293
Human, rat	Y361C (Mochel et al., 2020), Y362C (Nam, Rahman, et al., 2023)	No current	Inside out (Nam, Rahman, et al., 2023)	HEK-293
Human, rat	G362S (Mochel et al., 2020), G363S (Nam, Rahman, et al., 2023)	No current	Whole-cell (Mochel et al., 2020), Inside out (Nam, Rahman, et al., 2023)	CHO-K1 HEK-293
Human	G371E (Balint et al., 2020)	N/A	N/A	N/A
Human, rat	L388V (Mochel et al., 2020), L389V (Nam, Rahman, et al., 2023)	No current	Whole-cell (Mochel et al., 2020), Inside out (Nam, Rahman, et al., 2023)	CHO-K1 HEK-293
Human, rat	L432P (Mochel et al., 2020), L438P (Nam, Rahman, et al., 2023)	No current	Whole-cell (Mochel et al., 2020), Inside out (Nam, Rahman, et al., 2023)	CHO-K1 HEK-293

Note: Asterix (*) sign represents early stop codons in human Y160 and Y267 mutations (Nam, Downey, et al., 2023).

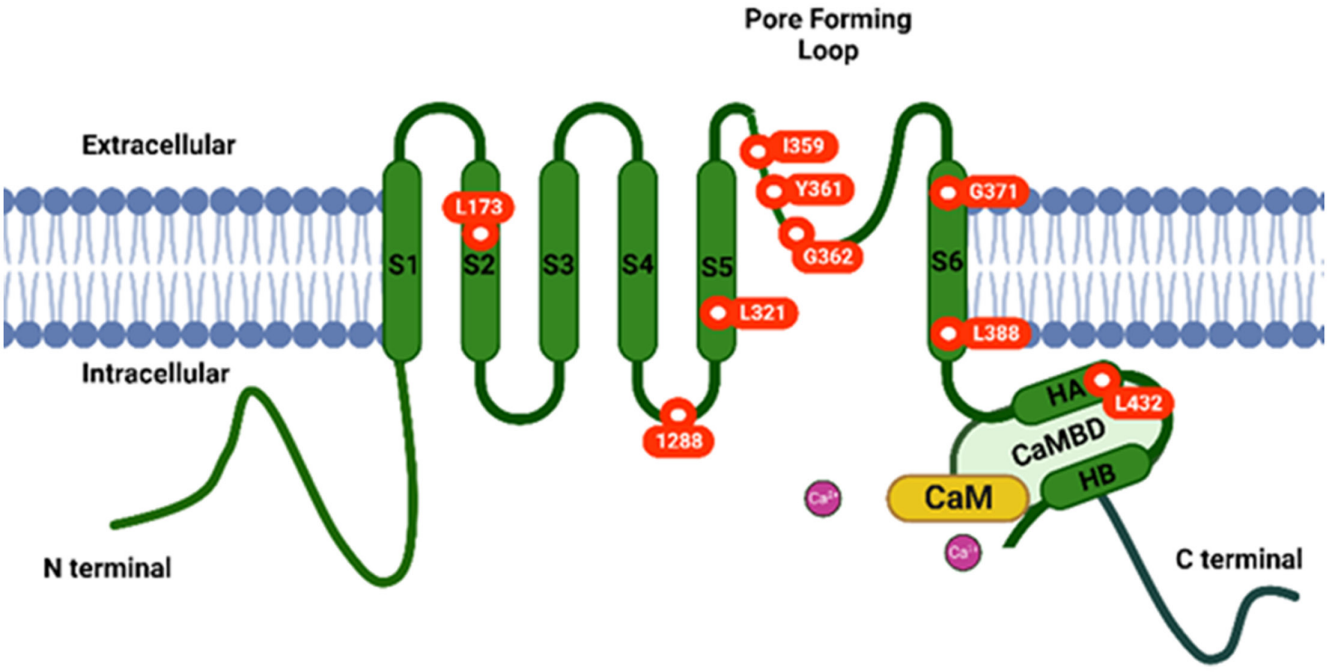

FIGURE 5 A schematic representation of one $K_{Ca}2.2$ channel subunit. The pathogenic LOF mutations are shown as red circles (Mochel et al., 2020; Nam, Downey, et al., 2023).

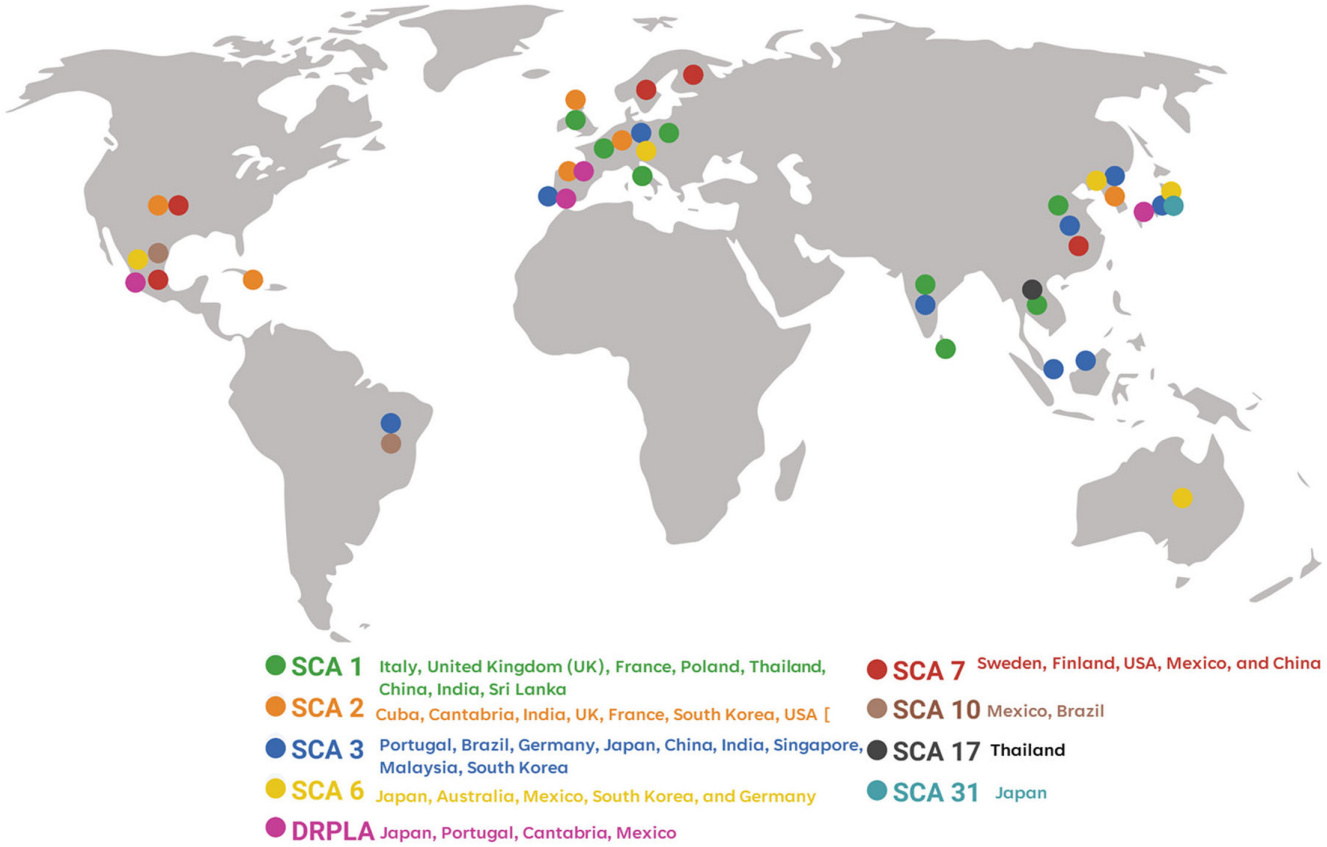

FIGURE 6 Prevalence of SCAs based on geographical location (Krysa et al., 2016; Ruano et al., 2014; Soong & Morrison, 2018; Teive, 2009; Teive et al., 2019).

have been associated with a mutation called loss-of-function rK_{Ca}2.2 I289N that reduces K_{Ca}2.2 channel activity. Human neurodevelopmental problems are caused by the homologous hK_{Ca}2.2 I288S mutation (Pedarzani et al., 2001). Additionally, the human *KCNN2* gene mutations hK_{Ca}2.2 L321del, hK_{Ca}2.2 I359M, hK_{Ca}2.2 Y361C, hK_{Ca}2.2 G362S, hK_{Ca}2.2 L388V, and hK_{Ca}2.2 L432P result in neurodevelopmental conditions including cerebellar ataxia, delayed motor and language development, and intellectual disability. Table 3 summarizes the effects of pathogenic K_{Ca}2.2 mutations on channel activity species (Chen et al., 2019), and Figure 5 depicts the sites of mutations in the K_{Ca}2.2 channel subunit. Given the substantial link between clinically significant ventricular tachyarrhythmias and *KCNN2* (encoding K_{Ca}2.2 channels) mutations, *KCNN2* could be employed as additional risk markers in sudden cardiac death (SCD)-vulnerable patients (Nam, Downey, et al., 2023). Following partial dopamine denervation, the physiological adaptation to enhanced subthalamic excitability may be mediated by the activation of K_{Ca}2.2 channels in the subthalamic nucleus (STN) (Zhang et al., 2021).

6 | SPINOCEREBELLAR ATAXIAS (SCAs)

The term "ataxia" describes a particular class of neurodegenerative disorders that cause coordination issues. The spinocerebellar ataxias (SCAs) are autosomal dominantly inherited disorders that fall within the category of ataxia (Angstadt et al., 2021; Bushart et al., 2018). SCAs are a diverse collection of neurodegenerative disorders characterized by progressive cerebellar ataxia and one, some, or all of the following conditions: movement disorders, dementia, pigmentary retinopathy, ophthalmoplegia, pyramidal symptoms, peripheral neuropathy, and cognitive impairment (Shakkottai et al., 2011). Many genes have been linked to the disease, and there are now over 50 genetically unique SCAs that have been documented (Müller, 2021). SCA type 3, or Machado-Joseph illness, SCA type 10, SCA types 7, 2, 1, and 6 are the most prevalent varieties (Mochel et al., 2020). Depending on the nature of SCA, patients can develop SCAs from an age range of 25–80 years old (Balint et al., 2020; Shakkottai et al., 2011). Figure 6 depicts the prevalence of SCAs by region.

SCAs are classified genetically into two categories: (1) polyglutamine (PolyQ) repeat expansion in a variety of cytosolic proteins called ataxins and (2) point mutations in a variety of ion channels, transporters, or other signaling proteins. These mutations severely harm cerebellar Purkinje neurons, followed by cerebellar atrophy. Additionally, other components of the neurological system, including the brainstem's pontine nuclei, basal ganglia, and spinal cord, may also be implicated (Angstadt et al., 2021). The increase of polyQ repeats is one important mechanism highlighting SCAs. The proteins' changed conformations from PolyQ

repeat expansions alter their functionality, change how they interact with other proteins, cause them to oligomerize, and create intranuclear inclusions, all of which result in proteotoxicity (Mochel et al., 2020). In addition to DNA damage, altered chromatin acetylation, and alterations in transcription, other nuclear processes that may contribute to the pathophysiology of SCAs include nonprotein-coding repeat expansions that sequester RNA-binding proteins and induce some SCAs. Repeated cytoplasmic expansions of SCA disease proteins can also result in noncanonical translation, producing polypeptides that are prone to aggregation (Mochel et al., 2020; Vishwakarma et al., 2018).

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Currently, only symptomatic treatment and palliative care methods are prescribed to the patients. No drug that slows or halts SCAs is available. A proper understanding of the pathophysiology of SCAs can facilitate anti-SCA drugs (Brooker et al., 2021).

Age-related behavioral and neuropathological abnormalities in SCA2 transgenic mice are reduced by oral administration of a selective activator of $K_{Ca}2.2/K_{Ca}2.3$ channels (NS130001), suggesting that $K_{Ca}2.2$ channels are a promising therapeutic target for treating SCA2 and probably other cerebellar ataxias (Klockgether et al., 2019). Numerous causes of SCA may involve modifications in the excitability of the Purkinje neuron membrane. Activators of $K_{Ca}2.2$ channels may represent potential pan-ataxia therapeutics.

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

AUTHOR CONTRIBUTIONS

Mohammad Asikur Rahman: Writing – original draft. **Razan Orfali:** Writing – review & editing. **Nikita Dave:** Writing – review & editing. **Elyn Lam:** Writing – review & editing. **Nadeen Naguib:** Writing – review & editing. **Young-Woo Nam:** Conceptualization. **Miao Zhang:** Conceptualization; Funding acquisition.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable.

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