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This article was originally published in *Journal of Neuroscience Research* in 2023. [https://doi.org/10.1002/jnr.25233](https://doi.org/10.1002/jnr.25233)

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Funding information
American Heart Association, Grant/Award Number: 23AIREA1039423; National Institutes of Health, Grant/Award Number: 4R33NS101182-03

Abstract
One group of the K+ ion channels, the small-conductance Ca2+-activated potassium channels (KCa2.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 Ca2+-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 Ca2+. According to the phylogenetic research done on the KCa2.x channels family, there are three channels' subtypes: KCa2.1, KCa2.2, and KCa2.3, which are encoded by KCNN1, KCNN2, and KCNN3 genes, respectively. The KCa2.x channels regulate neuronal excitability and responsiveness to synaptic input patterns. KCa2.2 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 KCa2.2 channel encoded by the KCNN2 gene on chromosome 5. Of particular interest, rat cerebellar Purkinje cells express KCa2.2 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 KCa2.2 channel is promising for 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 KCa2.2 modulators are promising potential therapeutics for SCAs.

KEYWORDS
Cerebellar ataxia, KCa2.2 channels, medium afterhyperpolarization, Purkinje cells, spinocerebellar ataxias

Abbreviations: BK, large-conductance Ca2+-activated K+; Ca2+, calcium; CaM, calmodulin; CK2, Casein Kinase 2; EA, episodic ataxia; EDH, endothelium-dependent hyperpolarization; EPSPs, excitatory postsynaptic potentials; K+, potassium; KCa2.x or SK, small-conductance Ca2+-activated K+; Kᵥ, voltage-gated K+; LOF, loss-of-function; mAHP, medium afterhyperpolarization; PIP2, phosphatidylinositol bisphosphate; PP2A, protein phosphatase 2A; SCA, channels spinocerebellar ataxias; TMs, transmembrane helices; WT, wild type.

Edited by Cristina Antonella Ghiani and Joshua L. Plotkin. Reviewed by Sharan Srinivasan.

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1 | K\textsubscript{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\textsuperscript{+}) across the cell membrane is mediated by the K\textsuperscript{+} 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\textsuperscript{+} 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\textsuperscript{2+}-activated potassium channels), and seven transmembrane segments (7TM) (large-conductance Ca\textsuperscript{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\textsuperscript{2+}-activated channels (Figure 1) (González et al., 2012; Weaver et al., 2006). Regardless of the class to which it belongs, a potassium channel can be split into two domains: the pore-forming domain and the regulatory domain. The pore-forming domain, which transports K\textsuperscript{+}, 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\textsuperscript{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).

Small-conductance Ca\textsuperscript{2+}-activated potassium channels (K\textsubscript{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\textsubscript{Ca}2.x channels are voltage-independent but are activated by increases in intracellular Ca\textsuperscript{2+} with a half-maximal activation in the 300–800nM range (Brown et al., 2020). They are named small-conductance Ca\textsuperscript{2+}-activated potassium channels due to their comparatively low single-channel conductance which is about 10 pS compared to the intermediate channels conductance (20–60pS) K\textsuperscript{+} channels (IK or K\textsubscript{Ca}3.1), and the large-conductance (150–300pS) K\textsuperscript{+} channels (K\textsubscript{Ca}1.1 or BK\textsubscript{Ca}) (Orfali & Albanyan, 2023; Skibsbye et al., 2014; Zheng & Trudeau, 2023).

**Significance**

The K\textsubscript{Ca}2.2 channel is part of the small-conductance Ca\textsuperscript{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\textsubscript{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\textsubscript{Ca}2.2 channel is a novel drug target for therapeutics in neurodegenerative diseases, especially that of spinocerebellar ataxia.

![Figure 1](https://example.com/figure1.png)

**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\textsubscript{Ca}2.x, and K\textsubscript{Ca}3.1), and seven TM (BK). K\textsubscript{Ca}2.x family is subdivided into K\textsubscript{Ca}2.1, K\textsubscript{Ca}2.2, and K\textsubscript{Ca}2.3 (González et al., 2012; Nam et al., 2022).
Based on their phylogenic analysis, the KCa2.x channels family (KCa2.1, KCa2.2, and KCa2.3) are encoded by KCNN1, KCNN2, and KCNN3 (Table 1) (Köhler et al., 1996; Sailer et al., 2004).

2 | KCa2.2 CHANNELS

The human KCa2.2 (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: KCa2.2-S (49 kDa) and KCa2.2-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 KCa2.2-L having an extra 207 amino acids at the N terminus (Strassmaier et al., 2005). Cysteine-rich KCa2.2-L N-terminal extension facilitates the formation of disulfide bonds between KCa2.2-L subunits or heterologous proteins. The KCa2.2-S and KCa2.2-L are expressed separately and combined to create functional homomeric KCa2.2 channels with comparable Ca\(^{2+}\) sensitivities, producing a whole-cell current with comparable amplitudes. However, KCa2.2-L excised patches have significantly lower KCa2.2-L currents than KCa2.2-S currents (Allen et al., 2011; Weaver et al., 2006). The longer N terminus of KCa2.2-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. KCa2.2-L controls KCa2.2-containing channels (KCa2.2-L and KCa2.2-S) in the postsynaptic density of dendritic spines on mouse CA1 pyramidal neurons and is required for synaptic function. For example, in mice lacking KCa2.2-L, the KCa2.2-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 KCa2.2 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 KCa2.2 channel (Dwivedi & Bhalla, 2021; Weaver et al., 2006) (Table 2).

The KCa2.2 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 KCa2.2.x subtypes, while voltage-gated K\(^{+}\) channels and KCa2.2 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. KCa2.2 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 KCa2.2 channels. KCa2.2 channels contribute to the medium subsequent to afterhyperpolarization (mAHP) that occurs after action potential bursts (Skibsbye et al., 2014) (Figure 3). In neurons, KCa2.2 channels drive an apamin-sensitive K\(^{+}\) current known as ImAHP, which helps to generate mAHP (Stocker et al., 1999).
TABLE 1 The KCNN gene family.

<table>
<thead>
<tr>
<th>KCx &amp; KCx α subunit</th>
<th>Gene</th>
<th>Other names</th>
<th>Amino acids</th>
<th>Human chromosomal location</th>
<th>Tissue distribution</th>
<th>Physiological roles</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCx2.1</td>
<td>KCNN1</td>
<td>SK1</td>
<td>543 (Girault et al., 2012)</td>
<td>19p13.11 (Aldrich et al., 2021)</td>
<td>Brain (Aldrich et al., 2021) Heart (Rahm et al., 2021) Lungs (Bardou et al., 2009)</td>
<td>The KCx2 channels underlie the medium AHP and regulate neuronal firing frequency (Brown et al., 2020; Orfali &amp; Albanay, 2023)</td>
</tr>
<tr>
<td>KCx2.2</td>
<td>KCNN2</td>
<td>SK2</td>
<td>579 (Aldrich et al., 2021)</td>
<td>5q22.3 (Aldrich et al., 2021)</td>
<td>Brain and heart Adrenal gland, lungs, prostate, bladder, and liver (Aldrich et al., 2021; Chen et al., 2004)</td>
<td></td>
</tr>
<tr>
<td>KCx2.3</td>
<td>KCNN3</td>
<td>SK3</td>
<td>731 (Aldrich et al., 2021)</td>
<td>1q21.3 (Aldrich et al., 2021)</td>
<td>Brain and heart vascular endothelium, lungs, and bladder (Aldrich et al., 2021; Brown et al., 2020; Orfali &amp; Albanay, 2023)</td>
<td>KCx2.3 and KCx3.1 mediate the endothelium-derived hyperpolarization response (Nam, Downey, et al., 2023; Wulff &amp; Köhler, 2013)</td>
</tr>
<tr>
<td>KCx3.1</td>
<td>KCNN4</td>
<td>SK4</td>
<td>427 (Aldrich et al., 2021)</td>
<td>19q13.31 (Aldrich et al., 2021)</td>
<td>Vascular endothelium, T and B lymphocytes, microglia, placentas, colon, red blood cells, lungs, and bladder (Aldrich et al., 2021; Brown et al., 2020)</td>
<td>KCx3.1 channels regulate calcium signaling cellular activation, and cell volume (Brown et al., 2020; Orfali &amp; Albanay, 2023)</td>
</tr>
</tbody>
</table>

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

3.1 IMPORTANT REGULATORS FOR KCx 2 CHANNELS

The regulation of KCx2 channels relies on Ca2+, Calcudol (CaM), Phosphorylisoaminyl bisphosphate (PAP), Casin Kinase 2 (CK2), and Protein Phosphatase 2A (PP2A) (Pap et al., 1988). Phosphorylation of KCx2.2 channels on Ca2+, Calcudol (CaM), and Protein Phosphatase 2A (PP2A) (Figure 2) (Pap et al., 1988; Li et al., 2011; Liu et al., 2011).

The regulation of KCx2 channels includes calcium-dependent phosphatase (CAMP), and protein phosphatase 2A (PP2A) (Pap et al., 1988). Phosphorylation of KCx2 channels on Ca2+, Calcudol (CaM), and Protein Phosphatase 2A (PP2A) (Figure 2) (Pap et al., 1988; Li et al., 2011; Liu et al., 2011).
TABLE 2 Major expression sites and function of KCa2.2 channels.

<table>
<thead>
<tr>
<th>Major expression site of KCa2.2 channels</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>In central neurons (Hosy et al., 2011)</td>
<td>Activation of KCa2.2 channels causes membrane hyperpolarization, which modulates neuronal excitability (Hammond et al., 2006; Lin et al., 2008)</td>
</tr>
<tr>
<td>In hippocampal neurons (Stocker et al., 1999)</td>
<td>KCa2.2 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)</td>
</tr>
<tr>
<td>In cerebellar Purkinje neurons (Womack &amp; Khodakhah, 2003)</td>
<td>KCa2.2 channels are important in controlling regular tonic firing (Hosy et al., 2011)</td>
</tr>
<tr>
<td>In the heart (Humphries &amp; Dart, 2015; Zhang et al., 2021)</td>
<td>KCa2.2 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)</td>
</tr>
<tr>
<td>In cardiac inner mitochondrial membrane (Xu et al., 2003; Zhang et al., 2021)</td>
<td>KCa2.2 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)</td>
</tr>
</tbody>
</table>

3.1 | Ca2+

KCa2.2 channels open in response to elevated intracellular Ca2+ concentration. KCa2.2 channels can be activated by Ca2+ influx through Ca2+-permeable channels and/or Ca2+ release from intracellular storage (Stocker, 2004).

3.2 | CaM

All eukaryotic cells have the Ca2+-binding protein CaM, which is composed of 148 amino acids (~17kDa) in humans. Numerous intracellular activities, including cell motility, growth, proliferation, and death, are regulated by CaM, which plays crucial roles in Ca2+ signaling. A flexible linker connects the protein’s two homologous globular domains. Two Ca2+ ions are cooperatively bound by EF-hands, each domain’s pair of Ca2+-binding motifs. The interhelical angles in the EF-hand motifs shift as Ca2+ 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 | PIP2

The apparent PIP2 affinity for the KCa2.2/CaM complex and the Ca2+-dependent channel activation of KCa2.2 channels are well correlated (Pedrazani & Stocker, 2008; Zhang et al., 2014).

3.4 | CK2

At the molecular level, it has been demonstrated that KCa2.2 channels form a multiprotein complex with CK2 and PP2A. CK2 decreases the sensitivity of KCa2.2 channels to Ca2+ 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 KCa2.2-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 KCa2.2 channel activity and a quicker deactivation of KCa2.2-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 KCa2.2 channels (Pedrazani & Stocker, 2008).

4 | DRUG CANDIDATES TARGETING KCa2.2 CHANNELS

Apamin, a peptide derived from bee venom, is the most studied KCa2.x inhibitor (Brown et al., 2020; Stocker et al., 1999).
Moreover, \( K_{Ca2} \) 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-EBI\( \text{O} \) (Pedarzani et al., 2001), NS309 (Chen et al., 2019), and SKA-31 (John et al., 2020) and they activate all three \( K_{Ca2}.x \) channels equally well. Examples of subtype-specific \( K_{Ca2}.x \) activators are CyPPA (Balint et al., 2020), NS13001, and 2q, a new compound recently reported by our group. GW542573X selectively activates \( K_{Ca2.1} \) 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), \( K_{Ca2}.x \) 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 \( K_{Ca2.2} \) 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 \( K_{Ca2.2} \) channel (Stocker, 2004).

### 5 | LOSS-OF-FUNCTION MUTATIONS IN \( K_{Ca2.2} \) CHANNELS

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

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**Table 3** Summary of different mAHP channels' inhibitors and activators.

<table>
<thead>
<tr>
<th>Activators</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorzoxazone (Cao et al., 2001)</td>
<td>Apamin (Bee venom) (Jäger et al., 2000)</td>
</tr>
<tr>
<td>1-EBIO (Weatherall et al., 2010)</td>
<td>Skvllatoxin (Scorpion venom toxin) (Naseem et al., 2023)</td>
</tr>
<tr>
<td>CyPPA (Hougaard et al., 2009)</td>
<td>( \text{d-tubocurarine} ) (Ishii et al., 1997)</td>
</tr>
<tr>
<td>Riluzole (Dimitriadi et al., 2013)</td>
<td>EGTA, EDTA (Oliván-Vigueria et al., 2015)</td>
</tr>
<tr>
<td>NS 309 (Pedarzani et al., 2005)</td>
<td>NS8593 (Diness et al., 2010; Jenkins et al., 2011)</td>
</tr>
<tr>
<td>SKS-11 &amp; SKS-14 (Nam et al., 2017)</td>
<td>Cadmium (Braga &amp; Rowan, 1994)</td>
</tr>
</tbody>
</table>
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 KCa2.2 channel function (Table 4). All examined variations abolished KCa2.2 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 KCa2.2 mutations. Rat tremors

<table>
<thead>
<tr>
<th>Species</th>
<th>Mutation</th>
<th>KCa2.2 current</th>
<th>Electrophysiological recording</th>
<th>Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Y160*</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Rat</td>
<td>L174P (Nam, Rahman, et al., 2023)</td>
<td>No current</td>
<td>Inside out (Nam, Downey, et al., 2023)</td>
<td>HEK-293</td>
</tr>
<tr>
<td>Human</td>
<td>I288S (Mochel et al., 2020)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Rat</td>
<td>I289N (Kuramoto et al., 2017; Nam, Downey, et al., 2023)</td>
<td>Reduced current</td>
<td>Whole-cell (Kuramoto et al., 2017), Inside out (Nam, Downey, et al., 2023)</td>
<td>HEK-293</td>
</tr>
<tr>
<td>Human</td>
<td>L321del (Mochel et al., 2020)</td>
<td>No current</td>
<td>Whole-cell (Braga &amp; Rowan, 1994)</td>
<td>CHO-K1</td>
</tr>
<tr>
<td>Human, rat</td>
<td>I359M (Mochel et al., 2020), I360M (Nam, Rahman, et al., 2023)</td>
<td>No current</td>
<td>Whole-cell (Mochel et al., 2020), Inside out (Nam, Rahman, et al., 2023)</td>
<td>CHO-K1, HEK-293</td>
</tr>
<tr>
<td>Human, rat</td>
<td>Y361C (Mochel et al., 2020), Y362C (Nam, Rahman, et al., 2023)</td>
<td>No current</td>
<td>Inside out (Nam, Rahman, et al., 2023)</td>
<td>HEK-293</td>
</tr>
<tr>
<td>Human</td>
<td>G362S (Mochel et al., 2020), G363S (Nam, Rahman, et al., 2023)</td>
<td>No current</td>
<td>Whole-cell (Mochel et al., 2020), Inside out (Nam, Rahman, et al., 2023)</td>
<td>CHO-K1, HEK-293</td>
</tr>
<tr>
<td>Human</td>
<td>G371E (Balint et al., 2020)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Human, rat</td>
<td>L388V (Mochel et al., 2020), L389V (Nam, Rahman, et al., 2023)</td>
<td>No current</td>
<td>Whole-cell (Mochel et al., 2020), Inside out (Nam, Rahman, et al., 2023)</td>
<td>CHO-K1, HEK-293</td>
</tr>
<tr>
<td>Human, rat</td>
<td>L432P (Mochel et al., 2020), L438P (Nam, Rahman, et al., 2023)</td>
<td>No current</td>
<td>Whole-cell (Mochel et al., 2020), Inside out (Nam, Rahman, et al., 2023)</td>
<td>CHO-K1, HEK-293</td>
</tr>
</tbody>
</table>

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 KCa2.2 channel subunit. The pathogenic LOF mutations are shown as red circles (Mochel et al., 2020; Nam, Downey, et al., 2023).
have been associated with a mutation called loss-of-function rK\textsubscript{Ca2.2} I289N that reduces K\textsubscript{Ca2.2} channel activity. Human neurodevelopmental problems are caused by the homologous hK\textsubscript{Ca2.2} I288S mutation (Pedarzani et al., 2001). Additionally, the human KCNN2 gene mutations hK\textsubscript{Ca2.2} L321del, hK\textsubscript{Ca2.2} I359M, hK\textsubscript{Ca2.2} Y361C, hK\textsubscript{Ca2.2} G362S, hK\textsubscript{Ca2.2} L388V, and hK\textsubscript{Ca2.2} L432P result in neurodevelopmental conditions including cerebellar ataxia, delayed motor and language development, and intellectual disability. Table 3 summarizes the effects of pathogenic K\textsubscript{Ca2.2} mutations on channel activity species (Chen et al., 2019), and Figure 5 depicts the sites of mutations in the K\textsubscript{Ca2.2} channel subunit. Given the substantial link between clinically significant ventricular tachyarrhythmias and KCNN2 (encoding K\textsubscript{Ca2.2} 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\textsubscript{Ca2.2} 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).

7 | DRPLA: DENTATORUBRAL-PALLIDOLUYSIAN ATROPHY

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.

ACKNOWLEDGMENTS

We thank the Chapman University Writing Center for revising the manuscript. Figures are created with BioRender and published with permission.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/jnr.25233.

DATA AVAILABILITY STATEMENT

Data sharing not applicable.

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REFERENCES


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How to cite this article: Rahaman, M. A., Orfali, R., Dave, N., Lam, E., Naguib, N., Nam, Y.-W., & Zhang, M. (2023). K_Ca2.2 (KCNN2): A physiologically and therapeutically important potassium channel. *Journal of Neuroscience Research*, 00, 1–12. https://doi.org/10.1002/jnr.25233