HHS Public Access

Author manuscript

J Neurosci Res. Author manuscript; available in PMC 2024 May 01.

Published in final edited form as:

J Neurosci Res. 2023 November ; 101(11): 1699–1710. doi:10.1002/jnr.25233.

$K_{CA}2.2$ (*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 regulates 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 *KCNN*2 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 and is one of the first signs of pathology. Thus, selective $K_{Ca}2.2$ modulators are promising potential therapeutics for SCAs.

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M.A.R. drafted manuscript; R.O., N.D., E.L., and N.N. edited and revised manuscript; Y-W.N. and M.Z. approved final version of manuscript. All authors contributed to the manuscript and the figures.

Conflict of interest: The authors declare no conflict of interest.

Keywords

K_{Ca}2.2 channels; Purkinje cells; cerebellar ataxia; spinocerebellar ataxias; medium afterhyperpolarization

1.1 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 non-excitable cells rely on them significantly[1–3]. They are tetrameric integral membrane proteins that create trans-membrane aqueous pores where K^+ passes through. Transmembrane helices (TMs) traversing the lipid bilayer are present in potassium channels [4]. 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 1.1) [5,6]. Regardless of the class to which it belongs to, a potassium channel can be split into two domains: the pore-forming domain and regulatory domain. The pore-forming domain, which transports K^+, has a consistent structure across the potassium channels. The regulatory domain detects a variety of stimuli that is varied amongst the potassium channels (Figure 1.2) [7,8]. 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 [5]. Mutations of potassium channel genes results in several human genetic illnesses, including pathologies involving cardiac arrhythmias, deafness, epilepsy, diabetes, and improper blood pressure regulation [3,5,9].

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 [10–13]. 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 [14]. They are named small-conductance Ca^{2+}-activated potassium channels due to their comparatively low single-channel conductance that 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})[12,13,15].

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 1.1) [11,16].

1.2 K_{Ca}2.2 Channels

The human K_{Ca}2.2 (SK2) channel is encoded by the *KCNN2* gene on chromosome 5 [18,24], 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[17,25]. 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 [26]. Cysteine-rich K_{Ca}2.2-L N-terminal extension facilitates the formation of disulfide bonds between K_{Ca}2.2-L subunits or the heterologous proteins. The K_{Ca}2.2-S and K_{Ca}2.2-L are expressed separately and combine 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 [6,27]. 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 extra synaptic membrane rather than the postsynaptic density, resulting in abnormal synaptic signaling [15,17]. 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 [6,28](Table 1.2).

The K_{Ca}2.2 pore-forming subunits form complexes with calmodulin, protein kinase CK2, and protein phosphatase 2A. About sixty percent 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 1.2)[10,37]. 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 [9,38,39](Figure 1.2).

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 toafterhyperpolarization (mAHP) that occurs after action potential bursts [12](Figure 1.3). In neurons, K_{Ca}2.2 channels drive an apamin-sensitive K^+ current known as I_{mAHP}, which helps to generate mAHP [31].

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 [40]. 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 [41]. K_{Ca}2.2 channels mediate I_{mAHP} [42]. 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 [29,43]. 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 [28]. 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 [44]. 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 [45].

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 1.4) [38]. Ca^{2+} influx that is triggered by synapses causes the spine's $K_{Ca}2.x$ channels to open, which causes hyperpolarization [47].

In the human heart, atria express $K_{Ca}2.x$ channels, and these channels take part in repolarization [35]. 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 [48,49].

1.4 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 1.2)[27,50].

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 [38].

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 [51–53].

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 [54,55].

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 [31,40,50]. 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 [56]. 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 [55].

1.5 Drug Candidates Targeting $K_{Ca}2.2$ Channels.

Apamin, a peptide derived from bee venom, is the most studied $K_{Ca}2.x$ inhibitor [14,31]. 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 [57]. The three activators that are most frequently used are known as 1-EBIO [58], NS309 [57], and SKA-31[59] and they activate all three $K_{Ca}2.x$ channels equally well. Examples of subtype specific $K_{Ca}2$ activators are CyPPA [60], 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+} [1,61]. 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 [9,57]. Table 1.3 shows the potential drug candidates targeting different types of the $K_{Ca}2.2$ channel [38].

1.6 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 all (2020) used exome sequencing to identify the variants responsible for learning disabilities, cerebellar ataxia, and white matter abnormalities [75], and performed the patch-clamp studies to examine the effects of six chosen variations on the $K_{Ca}2.2$ channel function (Table 1.4). All examined variations abolished KCa2.2 channel activity except one, which was downgraded to unclear relevance[1,61]. 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 [75]. Another study showed that the mutations in the *KCNN2* gene likely cause myoclonus-dystonia [76]. Neurodevelopmental problems result from loss-of-function $K_{Ca}2.2$ mutations. Rat tremors 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 [58]. 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 1.3) summarizes the effects of pathogenic $K_{Ca}2.2$ mutations on channel activity species [57], and (Figure 1.5) 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 [22]. 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) [34].

1.7 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 [78,79]. 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 [80]. Many genes have been linked to the disease, and there are now over 50 genetically unique SCAs that have been documented [81]. SCA type 3, or Machado-Joseph illness, SCA type 10, SCA types 7, 2, 1, and 6 are the most prevalent varieties [75]. Depending on the nature of SCA, patients can develop SCAs from an age range of 25–80 years old [60,80]. (Figure 1.6) 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 [78]. 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 [75]. In addition to DNA damage, altered chromatin acetylation, and alterations in transcription, other nuclear processes that may contribute to the pathophysiology of SCAs include non-protein-coding repeat expansions that sequester RNA-binding proteins and induce some SCAs. Repeated cytoplasmic expansions of SCA disease proteins can also result in non-canonical translation, producing polypeptides that are prone to aggregation [75,82].

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-SCAs drugs [88].

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 [89]. 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.

Acknowledgments:

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

Data availability:

Data sharing not applicable

Abbreviations:

Ca^{2+}	Calcium
CaM	Calmodulin
CK2	Casein Kinase 2
EDH	Endothelium-dependent hyperpolarization
EA	Episodic ataxia
EPSPs	Excitatory postsynaptic potentials
LOF	Loss-of-function
BK	Large-conductance Ca+2-activated K+
mAHP	Medium afterhyperpolarization
PIP2	Phosphatidylinositol bisphosphate
K^+	Potassium
PP2A	Protein phosphatase 2A
KCa2.x or SK	Small-conductance Ca2+-activated K+
TMs	Transmembrane helices
SCA	Channels spinocerebellar ataxias

K_V	Voltage-gated K+
WT	Wild type

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A Significance Statement

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.

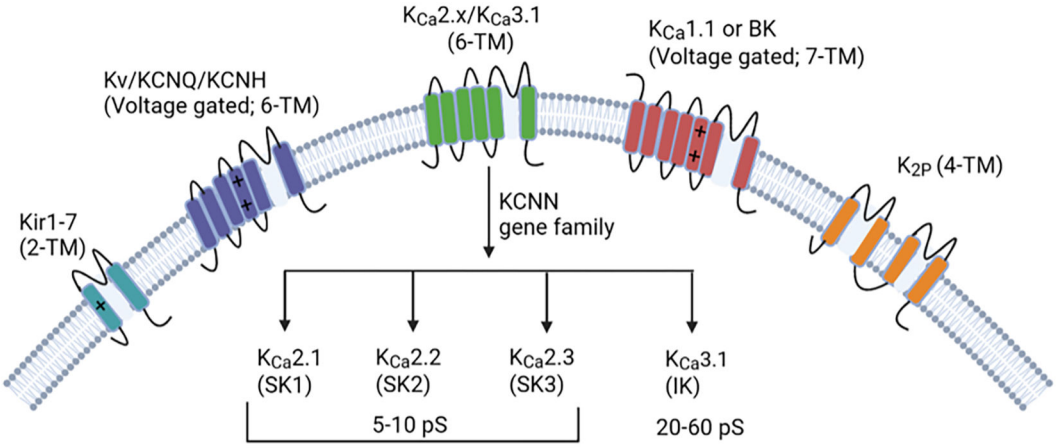

Figure 1.1. Subfamilies of potassium channels.

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 $K_{Ca}2.3$ [5], [9].

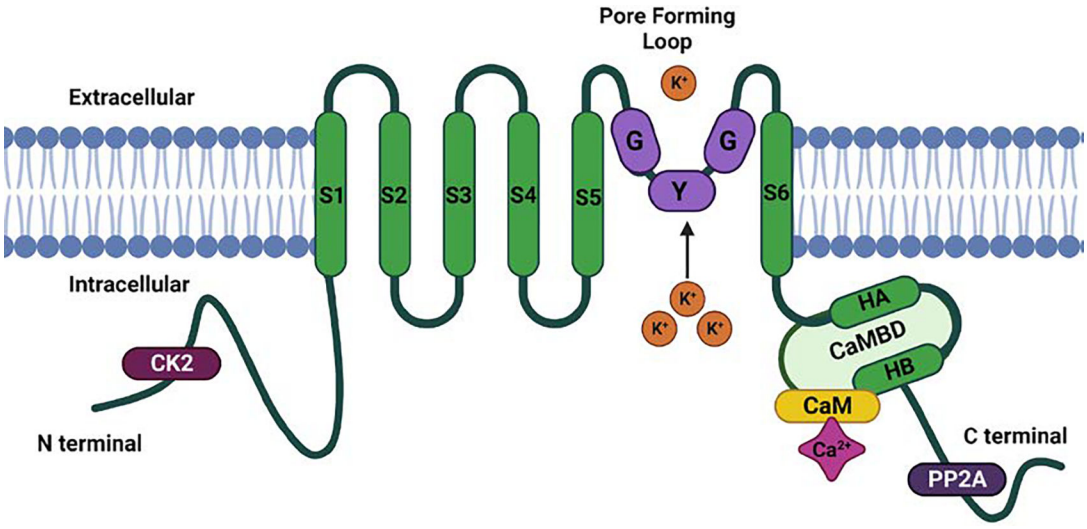

Figure 1.2. Pore-forming unit and regulatory unit of $K_{Ca}2.2$ channels.
Channels are regulated at their N and C termini by binding protein phosphatases and kinases[38].

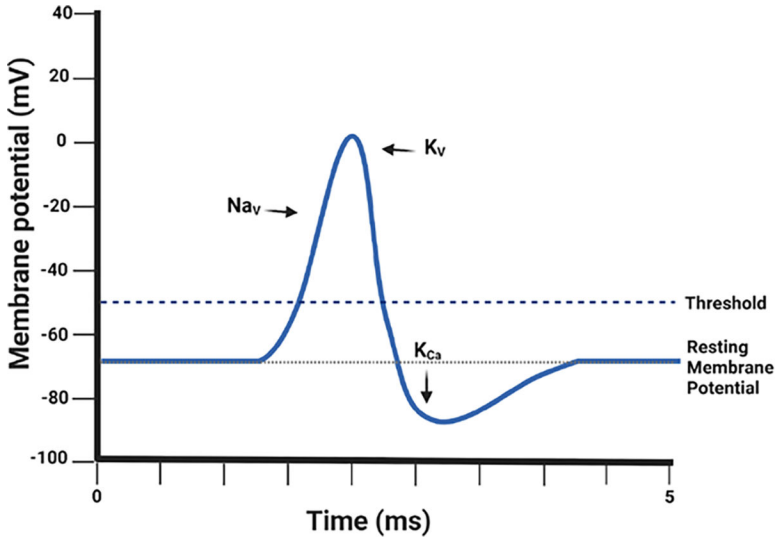

Figure 1.3. $K_{Ca}2.2$ channels roles in medium after-hyperpolarization.

Upon neuronal activity, voltage-gated & Ca^{2+}-activated K^+ channels are engaged during repolarization (K_V) and during after-hyperpolarization to provide feedback inhibition at nerve terminals. They do so by restricting action potential duration and thus neurotransmitter release[46].

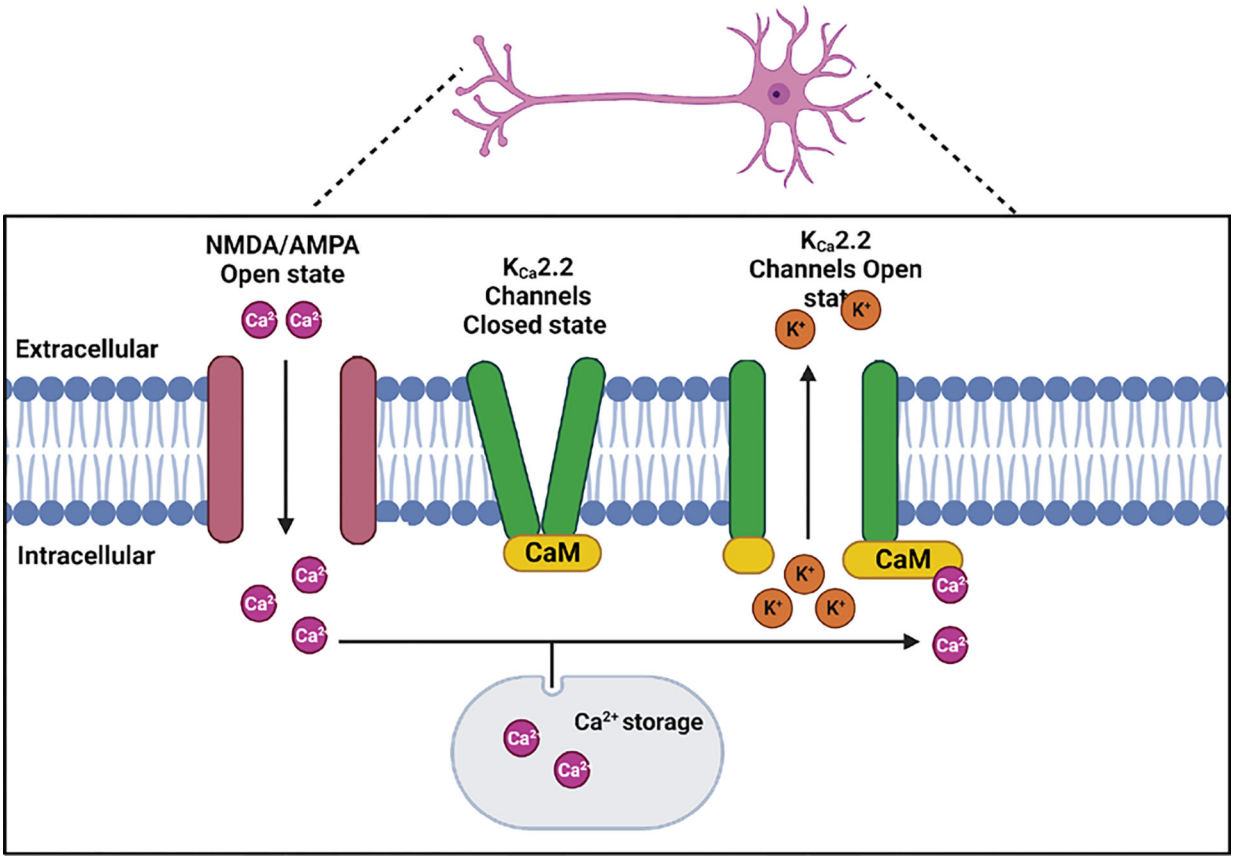

Figure 1.4. A schematic illustrating the localization and regulatory pathways involving the K_{Ca}2.2 channel in neurons [30].

The K_{Ca}2.2 channel couplesg 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+} [27].

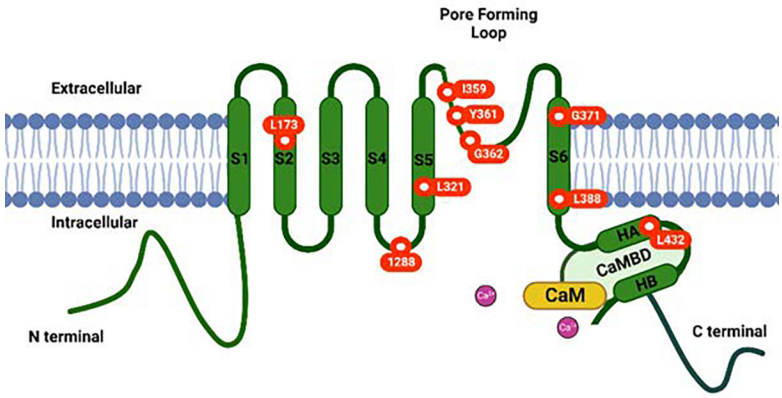

Figure 1.5. A schematic representation of one $K_{Ca}2.2$ channel subunit.
The pathogenic LOF mutations are shown as red circles [22,75].

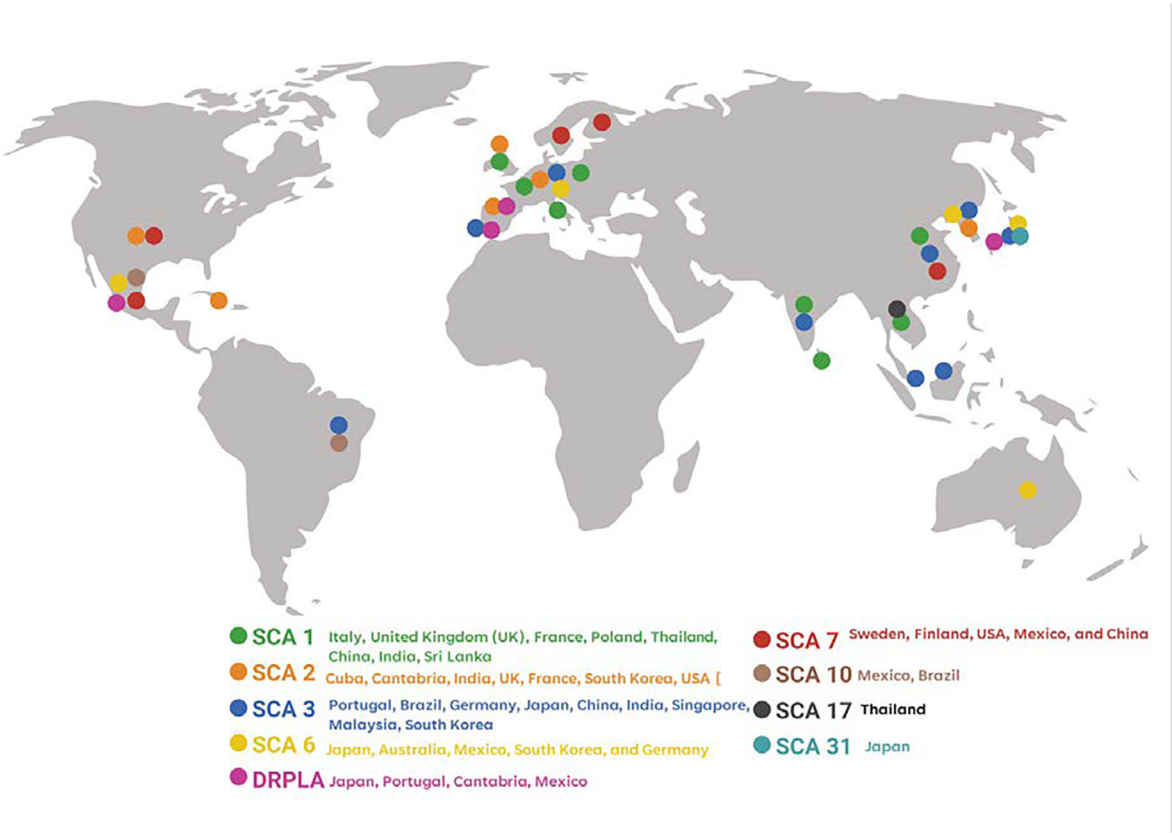

Figure 1.6. Prevalence of SCAs based on geographical location [83–87].

Table 1.1

The *KCNN* gene family. Human chromosomal location, tissue distribution, functional effects.

$K_{Ca}2$ & $K_{Ca}3$ α subunit	Gene	Other names	Amino acids	Human chromosomal location	Tissue distribution	Physiological roles
$K_{Ca}2.1$	*KCNN1*	SK1	543[17]	19p13.11[18]	Brain[18] Heart[19] Lungs[20]	The $K_{Ca}2$ channels underlie the medium AHP and regulate neuronal firing frequency[13,14].
$K_{Ca}2.2$	*KCNN2*	SK2	579[18]	5q22.3[18]	Brain and heart Adrenal gland, lungs, prostate, bladder, and liver [18,21].	
$K_{Ca}2.3$	*KCNN3*	SK3	731[18]	1q21.3 [18]	Brain and heart v ascular endothelium, l ungs, and bladder [13,14,18]	$K_{Ca}2.3$ and $K_{Ca}3.1$ mediate the endothelium-derived hyperpolarization response [22,23]
$K_{Ca}3.1$	*KCNN4*	SK4 IK	427[18]	19q13.31 [18]	Vascular endothelium, T and B lymphocytes, m icroglia, placenta, colon, red blood cells, l ungs and bladder [14,18]	$K_{Ca}3.1$ channels regulate calcium signaling, cellular activation, and cell volume[13,14]

Table 1.2

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

Major expression site of $K_{Ca}2.2$ channels	Function
- In central neurons [29]	Activation of $K_{Ca}2.2$ channels causes membrane hyperpolarization, which modulates neuronal excitability [25,30]
- In hippocampal neurons [31]	$K_{Ca}2.2$ channels underlie the mAHP current in CA1 hippocampal neurons, regulate the hippocampal synaptic plasticity, play a critical role in modulating learning and memory [25], regulate the formation of contextual fear memory [32], play a role in drug-induced plasticity [24], and are neuroprotective against ischemia-induced cell death [31].
- In cerebellar Purkinje neurons [33]	$K_{Ca}2.2$ channels are important in controlling the regular tonic firing [29].
- In the heart [34,35]	$K_{Ca}2.2$ channels play a critical role in cardiac repolarization [34] by underlying the mAHP current in cardiac myocytes and regulating action potential duration [36].
- In cardiac inner mitochondrial membrane [34,36]	$K_{Ca}2.2$ channels have an important role in intracellular signaling and mitochondrial function as the activation of the mitochondrial K^+ channels results in cardio protective effects against ischemia-reperfusion injury [34].

Table 1.3

Summary of different mAHP channels' inhibitors and activators

Activators	**Inhibitors**
Chlorzoxazone [62]	Apamin (Bee venom) [63]
1-EBIO [64]	Skyllatoxin (Scorpion venom toxin)[65]
CyPPA [66]	d-tubocurarine [67]
Riluzole [68]	EGTA, EDTA [69]
NS 309 [70]	NS8593 [71,72]
SKS-11 & SKS-14 [73]	Cadmium [74]

Table 1.4

Changes in channel activity caused by pathogenic $K_{Ca}2.2$ mutations. Asterix (*) sign represents early stop codons in human Y160 and Y267 mutations [22].

Species	Mutation	$K_{Ca}2.2$ current	Electrophysiological Recording	Cells
human	Y160*	N/A	N/A	N/A
rat	L174P [61]	No current	Inside out [22]	HEK-293
human	I288S [75]	N/A	N/A	N/A
rat	I289N [22,77]	Reduced current	Whole-cell [77] Inside out [22]	HEK-293
human	L321del [75]	No current	Whole-cell [74]	CHO-K1
human, rat	I359M [75], I360M [61]	No current	Whole-cell [75], Inside out [61]	CHO-K1 HEK-293
human, rat	Y361C [75], Y362C [61]	No current	Inside out [61]	HEK-293
human, rat	G362S [75], G363S [61]	No current	Whole-cell [75], Inside out [61]	CHO-K1 HEK-293
human	G371E [60]	N/A	N/A	N/A
human, rat	L388V[75], L389V [61]	No current	Whole-cell [75], Inside out [61]	CHO-K1 HEK-293
human, rat	L432P [75], L438P [61]	No current	Whole-cell [75], Inside out [61]	CHO-K1 HEK-293