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# Potassium channel gain of function in epilepsy: an unresolved paradox

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## Abstract

Exome and targeted sequencing have revolutionized clinical diagnosis. This has been particularly striking in epilepsy and neurodevelopmental disorders, for which new genes or new variants of pre-existing candidate genes are being continuously identified at increasing rates every year. A surprising finding of these efforts is the recognition that gain of function potassium channel variants are actually associated with certain types of epilepsy, such as malignant migrating partial seizures of infancy or early-onset epileptic encephalopathy. This development has been difficult to understand as traditionally potassium channel loss-of-function, not gain-of-function, has been associated with hyperexcitability disorders. Here, we describe the current state of the field regarding the gain-of-function potassium channel variants associated with epilepsy (KCNA2, KCNB1, KCND2, KCNH1, KCNH5, KCNJ10, KCNMA1, KCNQ2, KCNQ3, and KCNT1) and speculate on the possible cellular mechanisms behind the development of seizures and epilepsy in these patients. Understanding how potassium channel gain-of-function leads to epilepsy will provide new insights into the inner working of neural circuits and aid in developing new therapies.

## Introduction

Potassium channels play important roles in a range of cellular physiological processes during normal brain function. Due to their diverse gating properties and extensive temporal and spatial expression profiles, potassium channels can regulate cellular excitability across development in multiple ways. For example, they can control the resting membrane potential, regulate membrane resistance, control the repolarization rate of action potentials, or control the extent of spike frequency adaptation (Jan and Jan, 2012; Kole and Stuart, 2012; Storm, 1990). Potassium channel dysfunction can lead to multiple neurological disorders associated with epilepsy, including benign familial neonatal seizures, Ohthara syndrome, Temple-Baraitser syndrome, and malignant migrating partial seizures of infancy(Brenner and Wilcox, 2012; Kohling and Wolfart, 2016).

The vast majority of pathogenic potassium channel variants exhibit a loss-of-function (LOF) phenotype, characterized by a reduction in potassium channel activity due to decreased open probability, changes in the voltage dependence of activation, or reduced surface expression. However, surprisingly several recent studies that primarily used exome sequencing identified

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gain-of-function (GOF) variants associated with human epilepsy syndromes, thus raising the possibility that enhanced K+ channel activity leads to hyperexcitability. This creates an unexpected paradox: how could both increasing and decreasing potassium channel activity lead to comparable cellular or network hyperexcitability?

To understand how GOF variants lead to seizures and epileptogenesis, we must first establish (1) whether a GOF variant in a potassium channel assessed in a heterologous system is also GOF in neurons and (2) what ramifications an increased potassium conductance has on neuronal firing properties of excitatory and inhibitory neurons and neurons with distinct firing properties (i.e., regular, tonic, and bursting firing neurons). These clarifications are important as network excitability and synchronization leading to seizure generation by potassium channel GOF could be achieved through either disinhibition (i.e., reduction in inhibitory interneuron activity), elevated firing properties of excitatory cells due to the prevention of sodium channel inactivation, or even homeostatic plasticity of excitatory pyramidal neurons manifested as increased synaptic drive, an increase in synapse number, or changes in their intrinsic neuronal properties. Unfortunately, most studies have only defined the biophysical properties of GOF variants in heterologous cells; as such, we have little information on the impact of these variants on neuronal physiology and network excitability.

In this review, we discuss our current understanding of GOF potassium channel variants (Figure 1) in human epilepsy syndromes and speculate on their possible effects on both cell-intrinsic and network excitability.

## Potassium Channels: Basic Structure

As the majority of GOF potassium channel variants are found in voltage-gated potassium channels, we will use them as a model to discuss the potassium channel molecular structure. Voltage-gated potassium channels are tetramers arranged around a central pore permeation pathway (Gonzalez and others, 2012; Yellen, 2002) (Figure 1). Each subunit of the tetramer has a pore module domain and a tightly packed voltage-sensing domain. The voltage sensor domain is made of four transmembrane helices (S1-S4), whereas the pore module has two helices and a re-entrant pore loop (S5-P-S6). The two modules are connected to each other through an S4-S5 linker. Importantly, the pore and voltage sensor module are domain swapped; that is, the voltage-sensor of one subunit interacts with the pore module of the neighboring subunit. Such an arrangement likely contributes to the cooperative gating between the different subunits and pore opening. We note, however, that recent data suggest that domain swapping might not be a property of all voltage-gated potassium channels (James and Zagotta, 2017; Zhou and others 2017).

The S4 helix contains a series of positively charged arginines and lysines that sense the change in the membrane potential(Catterall and others 2017; Vargas and others 2012; Yellen, 2002). Depolarization of the membrane potential leads to a vertical translation of the S4, allowing the positively charged residues to slide past the charge transfer center giving rise to a gating current. This current is followed by the opening of the gate and flux of potassium ions across the membrane. The S5-P-S6 pore-forming region of the channel, which contains

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the TXGYG selectivity motif, forms the central pore. In addition to the pore and voltage-sensor module, potassium channels have intracellular N- and C-termini that substantially differ among potassium channels including those that are voltage gated.

## KCNA2 (Kv1.2)

Kv1.2 channels belong to the largest superfamily of potassium channels: the voltage-gated potassium channel family. Kv1.2 has widespread expression throughout the central and peripheral nervous system(Trimmer, 2015; Vacher and others 2008). Kv1.2 channels compartmentalize in the distal axon initial segment (AIS) and juxtaparanodes neighboring the nodes of Ranvier(Trimmer, 2015). Both Kv1.2 homomers and heteromers formed with Kv1.1 or Kv1.4 partially mediate a voltage-dependent potassium “delay” current known as the D-type current(Brew and others 2003; Grissmer and others 1994; Storm, 1990). The D-type current is a key regulator of neuronal excitability as it activates at subthreshold membrane potentials, quickly delaying action potential onset and preventing repetitive firing(Storm, 1988, 1990). Kv1.2 is also a delayed rectifier, as blocking Kv1.2 and D-type currents causes an increase in action potential duration(Kole and others 2007; Shu and others 2007) (Figure 2). Such broadening of the action potentials leads to greater calcium influx in the presynaptic terminals and, in turn, greater glutamate release. Kv1.2 knockout mice also highlight the channel’s critical role in brain function, as deletion of Kv1.2 leads to increased seizure susceptibility and, ultimately, reduced survivability and premature death beginning at the second week of life (Brew and others 2007).

Pathogenic Kv1.2 variants leading to either LOF or GOF channel activity have been identified in patients with epileptic encephalopathy (Masnada and others 2017; Pena and Coimbra, 2015; Syrbe and others 2015). In general, patients with GOF Kv1.2 have more severe phenotypes than patients with LOF variants. Patients with GOF variants exhibit generalized seizures (and in some instances status epilepticus) beginning at a neonatal age (~9 months), followed by extensive developmental delay and cognitive impairment (see Masnada and others 2017 for details). Studies identified two GOF variants in the voltage-sensing S4 domain (R297Q and L298F) and one in the N-terminus before the first transmembrane domain (E175K). These *de novo* missense variants lead to a large increase in the Kv1.2 current and a left-shifted current-to-voltage relationship. Additional GOF variants have been identified (L290R and L293H); however, these are considered LOF as they shift Kv1.2 inactivation towards negative membrane potentials, thus decreasing the availability of Kv1.2 channels.

One explanation, although not tested, for how both LOF and GOF Kv1.2 variants lead to seizure disorders is that the LOF variants primarily increase pyramidal neuron excitability whereas the GOF variants quiet interneuron activity, thus leading to disinhibition and network excitability(Syrbe and others 2015). A challenge with this theory is understanding how the GOF variants could spare pyramidal neuron activity, considering the well-documented role of D-type currents and expression of Kv1.2 in pyramidal neurons(Storm, 1990; Trimmer, 2015). Could GOF variants functionally act as LOF in pyramidal neurons? D-type currents exhibit fast activation (~20ms) and slow, long-lasting inactivation (~1–5s) at subthreshold membrane potentials(Storm, 1990). Shifting the Kv1.2 current-to-voltage

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relationship to negative membrane potentials may activate Kv1.2 channels at resting membrane potentials likely leading to their inactivation(Debanne and others 2013; Debanne and others 2011). The decrease in Kv1.2 and D-type current availability would allow incoming activity to reach action potential threshold with minimal delay, thus increasing pyramidal neuron excitability(Cudmore and others 2010; Rama and others 2017). In addition, the decreased current density of axonal Kv1.2 channels would increase presynaptic calcium influx, leading to greater glutamate release(Debanne and others 2013). In this way, GOF variants might decrease the activity of interneurons and in parallel increase the activity of pyramidal neurons (Figure 2).

Alternatively, GOF Kv1.2 variants could increase interneuron activity causing hyperexcitable pyramidal neurons to synchronize. In support of this idea, blocking D-type currents and Kv1.2 channels speeds up action potential onset and decreases action potential threshold in fast-spiking interneurons(Campanac and others 2013). This would be akin to the mechanism by which low concentrations of 4-AP, a blocker of the D-type current and Kv1.2 channels, exert pro-convulsive effects *ex vivo*(Avoli and Jefferys, 2015; Jefferys and others 2012).

However, if GOF and LOF variants are both functionally LOF, then why do GOF variants have a more severe phenotype? Although many factors could explain this, we point out that non-inactivated GOF variants would also hyperpolarize or prevent large depolarization of the AIS and axon, as only a subset of the Kv1.2 channels would be inactivated. This in turn might maintain axonal sodium channel availability, allowing neurons to fire at a higher frequency than those expressing LOF variants. Future studies using Kv1.2-variant knock-in mice are needed to determine the mechanism by which Kv1.2 GOF mutations lead to seizures.

## KCNB1 (Kv2.1)

$K_V$2.1 channels contribute a large portion of the delayed-rectifier potassium currents in hippocampal and cortical pyramidal neurons, underlying the afterhyperpolarization (AHP) trough of their action potentials(Guan and others 2013; Liu and Bean, 2014). Consequently, pharmacological block of $K_V$2.1 channels leads to wider somatic action potentials and a higher instantaneous action potential firing frequency. Consistent with this function and the strong somatodendritic distribution of $K_V$2.1(Trimmer, 2015), mice lacking these channels have increased excitatory network activity, are hyperactive, and have lower chemoconvulsant seizure thresholds(Speca and others 2014). On the other hand, suppression of Kv2.1 activity could lead to depolarization block due to sodium channel inactivation following prolong stimuli. As a result, the contribution of Kv2.1 to neuronal activity can be either excitatory or inhibitory depending on the duration of the stimulus (Liu and Bean, 2014).

Two recent studies identified several variants of Kv2.1 in patients with epileptic encephalopathy: S347, T374I, and V378A in the pore domain, and G379R in the selectivity filter(Thiffault and others 2015; Torkamani and others 2014). Each of these variants decreases the maximal potassium current, reduces the potassium selectivity, and concomitantly increases the sodium permeability of the channels. S347, T374I, and G379R

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also have reduced voltage sensitivity(Torkamani and others 2014). The altered ion selectivity (gained sodium flux, reduced potassium flux) would likely lead to increased neuronal excitability as neurons would depolarize more readily. Importantly, the reduced somatodendritic potassium conductance through $K_V2.1$ would also lead to a greater excitation due to spike coupling as incoming excitatory postsynaptic potentials would more easily depolarize dendrites. Additionally, Kv2.1 channels are found in the proximal AIS(Trimmer, 2015), where an increase in sodium flux might decrease the rheobase, allowing smaller stimuli to generate action potentials. Considering the biophysical properties imparted by the pathogenic variants on Kv2.1, it is more accurate to consider them as LOF rather than GOF.

One final consideration for neuronal Kv2.1 channels stems from their complex interactions with other Kv channel family members. In addition to homotetramers, Kv2.1 channels are known to form heterotetramers with silent alpha subunits belonging to the Kv6 (Ottschytsch and others 2002) and Kv8 (Hugnot and others 1996) families or associate with auxiliary subunits such as AMIGO and KCNE1–3(Gordon and others 2006; Peltola and others 2011). These heterotetramers expand the properties of Kv2.1 channels in neurons; however, we do not currently know whether association with the aforementioned subunits would decrease or enhance the aberrant effects of Kv2.1.

## KCND2 (Kv4.2)

One of the earliest identified currents in neurons was the A-type, a voltage-activated potassium current(Storm, 1990). The A-type current is considered transient because it activates, inactivates, and recovers from inactivation rapidly. It is now well accepted that, in pyramidal neurons, Kv4.2 channels contribute to the A-type current, especially in distal dendrites(Kim and others 2005; Norris and Nerbonne, 2010). Kv4.2 channels regulate dendritic excitability by attenuating back-propagating action potentials, thwarting them from invading distal dendrites. This is supported by a series of studies that used dominant-negative subunits and Kv4.2 knockout mice(Andrasfalvy and others 2008; Kim and others 2007). However, to recapitulate the biophysical properties of the native A-type current, Kv4.2 channels need to associate with the auxiliary subunits dipeptidyl-peptidase (DPP) 6 or DPP10, or members of the KChip family(Amarillo and others 2008).

Surprisingly, Lee and colleagues (2014) reported a GOF Kv4.2 variant (V404I) in a patient with autism and intractable seizures(Lee and others 2014). This variant is located in the S6 helix after the proline-X-proline (PVP in Kv4.2) motif. In Kv channels, the conserved PXP site acts as a molecular hinge that bends to allow channel gating(Webster and others 2004). The presence of an isoleucine rather than a valine in the 404 position decreases closed-state inactivation of the Kv4.2 channels(Lee and others 2014). Consequently, the channels stay open for a longer period of time. Such prolongation would likely increase the duration of the somatic action potentials, decrease firing frequency, and possibly introduce additional delays for neurons to reach action potential threshold; this would be more pronounced in dendrites. Additionally, Kv4.2 GOF would further attenuate back-propagating action potentials(Sandler and others 2016), thus limiting dendritic depolarization, calcium influx in

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dendrites, and spike-time-dependent plasticity. Altogether, Kv4.2 GOF would quiet the dendritic activity of pyramidal neurons.

How does Kv4.2 GOF lead to hyperexcitability? We consider two possibilities. First, dampening dendritic excitability might lead to homeostatic plasticity. Multiple studies have demonstrated that silencing neuronal activity leads to the scaling up of synaptic transmission(Turrigiano, 2012; Turrigiano, 2017). Such an increase in excitatory synaptic transmission either through an increase in postsynaptic glutamate receptors or synapse number could lead to seizures. This might be more pronounced for Kv4.2 as it is expressed early in development and has been implicated in synapse development(Kim and Hoffman, 2012). One such example of homeostatic plasticity is neurons lacking the enzyme phosphatase and tensin homolog deleted on chromosome 10 (PTEN). PTEN loss makes neurons hypertrophic, significantly decreasing their intrinsic excitability by shifting the rheobase to higher values(Chen and others 2015; Williams and others 2015). In response to this, PTEN-deficient neurons acquire a higher density of synapses to overcome the hypertophic deficit and, as a result, become hyperactive(Williams and others 2015).

The second possibility that we consider is that Kv4.2 alters interneuron activity. Traditionally, Kv4.2 has been associated with pyramidal neurons; however, a recent transcriptome study reported that Kv4.2 transcripts are highly enriched in chandelier cells, almost twice as much as in other interneuron cell types(Paul and others 2017). Chandelier cells are unique as they make axo-axonic synapses at the distal AIS of pyramidal neurons(Inan and Anderson, 2014), the site of action potential initiation(Kole and Stuart, 2012). Indeed, electrical stimulation of chandelier cells inhibits pyramidal neuron spiking(Woodruff and others 2011). Thus, it is possible that Kv4.2 GOF changes the balance between excitation and inhibition at the AIS of pyramidal neurons.

## KCNH1 (Eag1/Kv10.1) and KCNH5 (Eag2/Kv10.2)

The ether-a-go-go (Eag) potassium channel family consists of two known members in humans, Eag1 and Eag2(Gonzalez and others 2012). Eag1 and Eag2, along with all members of the KCNH gene family, contain a Per-Arnt-Sim (PAS) domain in their N-terminus and a cyclic nucleotide-binding domain (CNBD) in their C-terminus which regulate their gating(James and Zagotta, 2017). Eag channels have some unique functional properties, most notably the dependence of their activation kinetics on extracellular divalent ion concentration (namely $Mg^{++}$) and on the holding membrane potential(James and Zagotta, 2017). Physiological $Mg^{++}$ concentrations slow the channel activation rate and shift the voltage activation to more positive values.

Eag1 dysfunction has been associated with two developmental disorders, Temple-Baraitser syndrome and Zimmermann-Laband syndrome, both of which include epilepsy (Fukai and others 2016; Mastrangelo and others 2016; Simons and others 2015). Four variants in Temple-Baraitser syndrome (K217N, L489F, I494V, and Q503R) have GOF channel properties in that they left shift the voltage activation to more negative membrane potentials. These variants also slow Eag1 deactivation kinetics, delaying channel closure. Similarly, multiple variants in Zimmermann-Laband syndrome (I467V, S325Y/V356L – both variants

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presenting in one patient, G348R, and L352V) lead to increased Eag1 activity as well a left-shifted current-to-voltage activity.

More recently, a variant in the Eag2 voltage-sensing domain S4, R327H, was linked to a patient with epileptic encephalopathy(Veeramah and others 2013). The R327H variant induced two major GOF biophysical changes: (1) an increased activation rate at more hyperpolarized potentials coupled with decreased voltage dependence and (2) a significantly left-shifted (~ −70 mV) conductance-to-voltage relationship(Yang and others 2013). Molecular modeling studies suggest that the loss of positive charge and reduced side-chain size weakened the interactions between a highly conserved voltage-sensing S4 arginine and nearby glutamate and aspartate residues at the S1-S3 transmembrane helixes, resulting in easier transitions to the open state(Yang and others 2013).

Despite studies probing the gating mechanism behind Eag1 and Eag2, little is known about the role of these channels in regulating neuronal excitability. Previous work in cerebellar granule cells showed that Eag1 ablation increased presynaptic activity through increased $Ca^{++}$ influx, suggesting a presynaptic locale as no changes were found in somatic action potentials(Mortensen and others 2015). Importantly, mice lacking Eag1 did not exhibit major phenotypic issues beyond a mild increase in spontaneous locomotor activity. In the neocortex, eag1 and eag2 mRNA is primarily enriched to pyramidal neurons(Saganich and others 2001), although these channels have not been shown to regulate the excitability of these cells. This paucity of data on the role of eag1 and eag2 in pyramidal neurons might be due to the lack of KCNH-specific inhibitors or due to a tonic inhibition of Eag channels by membrane PIP2 levels, masking a possible role in neuronal excitability. PIP2 is typically a positive allosteric regulator of potassium channels(Hansen, 2015), either increasing their probability of opening or shifting their voltage dependence to negative membrane potentials. In contrast, eag1 channels are readily inhibited by PIP2, even by basal levels, shifting the voltage dependence to positive values(Han and others 2016). Due to the lack of functional data on Eag1 and Eag2 in neurons, it is difficult to speculate on how their GOF could lead to epilepsy. However, a recent study has shown increasing activity of Eag channels in drosophila, leads to decrease presynaptic activity and an increase in postsynaptic activity through homeostatic plasticity(Bronk and others 2018). This raise the question on whether the Eag GOF in mammalian neurons leads to hyperexcitability through secondary effects.

## KCNJ10 (Kir4.1)

KCNJ10 encodes the inward-rectifier potassium channel Kir4.1. Inward-rectifier channels contain two putative transmembrane segments (M1 and M2) with one pore-forming reentrant loop (H5)(Gonzalez and others 2012). Inward rectification is a result of intracellular $Mg^{++}$ blocking the pore or the polyamine spermine at membrane potentials positive to potassium equilibrium potential ($E_K$). Kir4.1 channels exist as either homomers or heteromers with Kir5.1. Biophysically, homomers of Kir4.1 exhibit moderate single-channel conductance with intermediate inward rectification when compared to Kir4.1/Kir5.1 heteromers, which have greater conductance and stronger rectification.

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Kir4.1 channels are most notably expressed in astrocytes in the brain and Müller glia in retina(Seifert and others 2018). These channels play a crucial role in clearing and buffering extracellular potassium as well as setting the membrane potential of astrocytes(Kuffler and others 1966; Orkand and others 1966). Kir4.1 knockout mice highlight the significance of these channels, as they exhibit numerous health problems including retinal dysfunction, motor impairment resulting from hypomyelination and aberrant axonal development, deafness due to improper cochlear development, and premature death within the first few weeks of life(Kofuji and others 2000; Neusch and others 2001). Conditional deletion of Kir4.1 from astrocytes causes severe ataxia and seizure susceptibility(Djukic and others 2007).

Researchers only recently identified variants in Kir4.1 in patients with autism and epilepsy, and two variants in particular were found to increase channel function(Sicca and others 2016; Sicca and others 2011). R18H, a recurrent variant, increases cell surface expression and current density. By contrast, the R348H variant increases channel function by decreasing sensitivity to intracellular pH, a known inhibitor of Kir4.1 activity. The GOF phenotype of these variants was present in astrocyte-like cells.

How could a GOF in Kir4.1 activity lead to hyperexcitability? It is difficult to understand how increasing channel activity, which promotes further hyperpolarization of astrocytes, could lead to hyperexcitability. One possibility is that greater astrocyte hyperpolarization or clamping the resting membrane potential at $E_K$ might prevent the release of gliotransmitters, which typically inhibit presynaptic glutamate release. The physiological relevance of gliotransmission, however, is still under debate(Fiacco and McCarthy, 2018; Savtchouk and Volterra, 2018). Alternatively, increasing Kir4.1 activity would further increase the potassium buffering capacity of astrocytes. A recent simulation study nicely showed that Kir4.1 channel's main function is to prevent build-up of extracellular potassium following repetitive neuronal activity. In its absence, potassium elevation depolarizes neurons leading to sodium channel inactivation, which in turn dampens neuronal activity(Sibille and others 2015). This is consistent with earlier experimental findings in the hippocampus and cerebellum(Kocsis and others 1983; Poolos and others 1987). Thus, Kir4.1 GOF might allow neurons to fire for longer periods of times or at a higher frequency by preventing sodium channel inactivation due to an accumulation of extracellular potassium following continuous activity (Figure 3). Lastly, further hyperpolarization of the astrocytes by increased Kir4.1 activity might reduce the activity of electrogenic sodium bicarbonate transporters leading to extracellular alkalosis. Increasing extracellular pH has been associated with epileptic activity(Schuchmann and others 2011; Schuchmann and others 2006). In summary, Kir4.1 GOF might leads to multiple effects and further work using animal modes is needed to decipher the link between Kir4.1 GOF and seizures.

## KCNMA1 (BK)

KCNMA1 encodes a large calcium- and voltage-activated potassium channel known as the Big K (BK), maxi, or slo (slowpoke gene in drosophila) channel(Brenner and Wilcox, 2012; Zhou and others 2017). For the remainder of this section, we will refer to KCNMA1 as BK. BK channels have a large single-channel conductance, a selectivity gate, and a large C-

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terminus that contains two calcium-binding domains, regulator of conductance of potassium (RCK) 1 and 2. Binding of calcium to the RCK domains of BK channels shifts the conductance-to-voltage relationship towards negative membrane potentials(Zhou and others 2017).

In pyramidal neurons, calcium influx during the repolarization phase of the action potential drives activation of BK channels leading to a fast AHP phase that lasts 10–20 milliseconds. This fast AHP shortens the action potential width, resulting in briefer action potentials. This rapid repolarization promotes faster recovery of sodium channels from inactivation and limits activation of delayed rectifiers and calcium-activated channels such as SK channels. Consequently, BK channel activation is typically associated with a higher firing frequency. Indeed, blocking BK channels leads to broader action potentials and a rapid form of spike frequency adaptation(Faber and Sah, 2003; Gu and others 2007; Shao and others 1999). BK channels are also found in dendrites of excitatory cells, of which the main function is to curtail the duration of dendritic calcium spike depolarization and limit subsequent action potential bursts(Bock and Stuart, 2016). In addition, BK channels are localized in presynaptic excitatory cell terminals; however, the role of these channels in neurotransmitter release is not well defined.

In 2005, Du and colleagues reported that a family with coexistent generalized epilepsy and paroxysmal dyskinesia carried a KCNMA1 variant that led to a GOF(Du and others 2005). The D434G variant is located within the RCK1 domain, which couples calcium binding to channel opening. D434G resides at the N-terminal region of the RCK1 in proximity to the calcium-coordinating site. Thus, the D434G variant increases the allosteric coupling between calcium binding and channel opening(Wang and others 2009; Yang and others 2010). This in turn translates to a higher calcium sensitivity of the BK channels and an increase in their probability of opening. These functional changes would lead to a more robust activation of BK channels, quickening the action potential in the soma and possibly the AIS.

Could generation of quicker action potentials be the mechanism by which BK channel GOF leads to epilepsy? Support for this hypothesis stems from *Kcnmb4* knockout mice(Brenner and others 2005). *Kcnmb4* encodes for the β4 auxiliary subunit, a small transmembrane protein found only in the brain. The association of β4 with BK slows channel activation kinetics, thus decreasing BK channel activation during an action potential. Ablation of *Kcnmb4* leads to faster activating BK channels, reduced interspike intervals, and increased neuronal excitability of dentate granule cells, which are highly enriched in β4. The increased neuronal excitability results in temporal seizures(Brenner and others 2005). Further support that GOF variants of BK channels could increase firing comes from work examining the function of BK channels in suprachiasmatic nucleus (SCN) neurons. Montgomery and Meredith developed transgenic mice expressing a GOF variant of BK channels in SCN neurons(Montgomery and Meredith, 2012). They found that expression of this GOF variant led to higher firing frequency; however, this result depended on the underlying conductances resident in neurons expressing BK channels. Therefore, based on the current data, GOF BK channels are likely to lead to a higher firing frequency of excitatory neurons and an increase in network excitability.

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## KCNQ2 (Kv7.2), KCNQ3 (Kv7.3), and KCNQ5 (Kv7.5)

In 1998, two groups independently showed that KCNQ2 and KCNQ3 channel variants lead to benign familial neonatal seizures(Biervert and others 1998; Charlier and others 1998; Singh and others 1998). Soon after these reports, Wang and colleagues (1998) demonstrated that KCNQ2 and KCNQ3 channels form heteromers that mediate a voltage-activated, slow-activating, non-inactivating potassium current known to neurophysiologists as the M-current(Wang and others 1998). In the ensuing years, our understanding of KCNQ2/3 channels has exponentially increased. It is now well accepted that KCNQ2/3 channels are enriched in the AIS and nodes of Ranvier, where they control the firing properties of pyramidal neurons either by setting the AIS membrane potential, limiting the afterdepolarization following an action potential, setting their input resistance both at rest and as neurons approach action potential threshold, or mediating the medium and, in some cell types, the slow AHP following a train of action potentials(Greene and Hoshi, 2017). Furthermore, KCNQ2/3 channel voltage activation and probability of opening depends on PIP2(Kim and others 2016; Li and others 2005), allowing PIP2-depleting neuromodulators to tune neuronal activity by inhibiting KCNQ2/3 channels(Brown and Passmore, 2009).

In addition to benign familial neonatal seizures, KCNQ2, and to a lesser degree KCNQ3, channel dysfunction leads to severe forms of epileptic encephalopathy. Current estimates suggest that as many as 10% of patients with some early-onset epileptic encephalopathies have dysfunctional KCNQ2 channels(Afawi and others 2016; Martin and others 2014; Olson and others 2017). Although the vast majority of KCNQ2 and KCNQ3 variants are LOF some of the identified variants are GOF(Mulkey and others 2017). This includes four variants in the KCNQ2 voltage-sensing module (R144Q, R198Q, R201C, and R201H) and one KCNQ3 variant (R230C – analogous to the KCNQ2 R201C)(Miceli and others 2015; Millichap and others 2017; Mulkey and others 2017). The GOF variants in KCNQ2/3 channels increase channel activity in multiple ways; for example, incorporation of either KCNQ2 R201C or KCNQ3 R230C into the KCNQ2/3 channel complex increases the maximal current density, alters the activation kinetics, and decreases the deactivation kinetics, delaying channel closing. KCNQ2 R201H has similar effects, though to a lesser extent(Miceli and others 2015). We note that although KCNQ2 R201C and KCNQ3 R230C have a similar effect on the KCNQ2/3 channel complex, they do not share the same clinical phenotypes; patients with KCNQ2 GOF have a much more severe clinical presentation.

More recently, four variants in another KCNQ channel member, KCNQ5, have been linked to epileptic encephalopathy, with one variant being GOF (P369R)(Lehman and others 2017). This variant is in the C-terminus and is likely involved in PIP2 binding and KCNQ5 channel regulation. KCNQ5 channels can also control the excitability of both pyramidal neurons and hippocampal interneurons, thus regulating inhibitory inputs in the hippocampal network(Fidzinski and others 2015). Additionally, KCNQ5 channels have been shown to localize at presynaptic terminals rather than the AIS.

The concept that GOF variants of KCNQ2/3 channels lead to epileptic encephalopathy is paradoxical considering that retigabine (ezogabine), a Food and Drug Administration-approved anticonvulsant, is a KCNQ2–5 channel opener(Jensen and others 2005; Tatulian

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and others 2001). In multiple cell types, including pyramidal neurons and interneurons, application of retigabine reduces spiking and dampens network excitability. How then could increasing KCNQ2/3 activity lead to network hyperexcitability and seizure susceptibility? The predominant hypothesis for the surprising GOF phenotype is that these variants preferentially dampen the excitability of interneurons(Miceli and others 2015), thus leading to disinhibition and hyperexcitability of the excitatory network. KCNQ2/3 channels are indeed expressed in cortical interneurons and simulations support this hypothesis(Cooper and others 2001; Miceli and others 2015). An alternative explanation is that the left-shifted KCNQ2/3 channel GOF hyperpolarizes the AIS, decreasing steady-state inactivation of sodium channels. This would increase the rate of action potential activation and action potential conduction. Currently, no GOF *Kcnq2* or *Kcnq3* mice are available to test these ideas.

## KCNT1 (Slack, Slo2.2, KCa4.1)

KCNT1 encodes a ligand-gated potassium channel that is activated by intracellular sodium. KCNT1 channels have an expansive C-terminus, which makes them much larger than most potassium channels. $Na^+$ binding, which is necessary for opening KCNT1 channels following activity, occurs within the C-terminus via two RCK domains(Kim and Kaczmarek, 2014; Villa and Combi, 2016).

Variants in KCNT1 have been implicated in: (1) malignant migrating partial seizures of infancy, (2) autosomal-dominant nocturnal frontal lobe epilepsy, and (3) Ohtahara syndrome, a rare form of epilepsy in neonates(Barcia and others 2012; Heron and others 2012; Villa and Combi, 2016). Pathogenic variants are present in several domains of KCNT1, including the RCK1 domain and the $NAD^+$-binding domain also found in the C-terminus (Figure 4). Binding of $NAD^+$ or NADP increases KCNT1 sodium affinity(Tamsett and others 2009). GOF variants of KCNT1 lead to larger KCNT1 currents, although there is little agreement in the field regarding the precise mechanism underlying the GOF. Kim and colleagues (2014) (Kim and others 2014) suggested that the GOF is a result of cooperativity in KCNT1 channel opening between neighboring channels. By contrast, Tang and colleagues (Tang and others 2016) showed that increased channel activity is a product of (i) increased sodium sensitivity and (ii) increased maximum probability of opening. Additional research is necessary to fully elucidate the mechanism of KCNT1 GOF.

How does KCNT1 GOF lead to hyperexcitability? Some studies suggest that sodium-activated potassium currents could activate during an action potential, thereby shortening its duration(Yang and others 2007). Consequently, a GOF KCNT1 might speed up action potential repolarization and increase the fast AHP, thereby limiting sodium channel inactivation and causing a higher action potential firing frequency. In short, KCNT1 GOF may act similarly to BK channel GOF variants. Furthermore, in cortical neurons, sodium-activated potassium currents mediate a slow AHP following a train of action potentials(Schwindt and others 1989). Although a larger slow AHP would induce a pronounced spike frequency adaptation, studies show that slow AHPs can also synchronize excitatory networks(Fernandez de Sevilla and others 2006).

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In addition to pyramidal neurons, KCNT1 GOF variants possibly induce spike frequency adaptation within fast spiking interneurons, thus dampening their activity and causing disinhibition and network excitability. *Ex vivo* and *in vivo* neurophysiology studies show that fast spiking interneurons slowly adapt their firing frequency after extended stimulation (>20s)(Descalzo and others 2005). This adaptation correlates with the emergence of a slow AHP speculated to result from sodium-activated potassium channel activity(Descalzo and others 2005). As the KCNT1 GOF variants potentially increase sodium affinity, a KCNT1-mediated slow AHP could emerge with weaker, shorter stimuli. As a result, interneuron activity would be depressed, leading to disinhibition and reduced feed-forward inhibition of cortical pyramidal neurons. We can only test these hypotheses directly once animal models become available.

## Conclusions

The identification of GOF variants in patients with epilepsy emphasizes the fact that our understanding of potassium channel function in neuronal circuits and the brain is far from complete. Here, we have reviewed recent work detailing the effects of GOF potassium channel variants on the biophysical properties of different potassium channel families. These studies have revealed that GOF variants manifest in multiple ways, including shifts in current-to-voltage relationships, increases in surface trafficking, and changes in sodium and calcium affinity for ligand-gated potassium channels. However, we still do not know whether the observed GOF seen in heterologous cells are indeed GOF in neurons. Potassium channels in neurons can associate with auxiliary subunits or other members of the same family, which potentially regulate their trafficking to the membrane or targeting to the appropriate neuronal subcompartment. Moreover, it is still unclear how potassium channel GOF leads to hyperexcitability. A common prediction is that potassium channel GOF will decrease interneuron activity and lead to disinhibition. Although this may explain some cases, it is unlikely to be the universal cause given the diversity of potassium channels associated with GOF variants linked to hyperexcitable pathologies.

To fully understand the mechanism by which GOF variants control neuronal activity and circuits, the development of new tools that leverage current DNA editing technologies is essential. Future efforts using constitutive and conditional potassium channel GOF knock-in mice are necessary to determine whether GOF variants lead to seizures, whether GOF variants increase potassium channel activity in neurons, whether specific cell types are more sensitive to the presence of GOF variants, and how these variants impact neuronal circuit development. This knowledge will be paramount for identifying new targets and devising new treatments for epilepsy and neurodevelopmental disorders in patients with GOF potassium channel activity.

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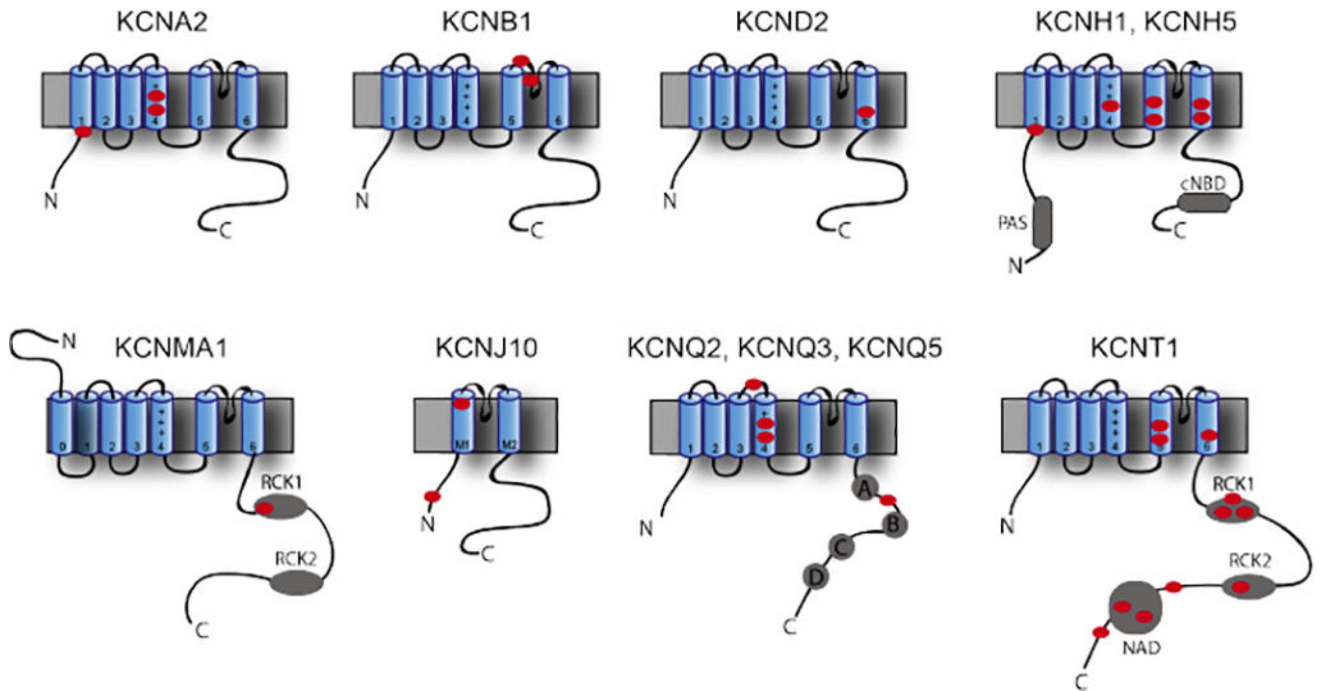


**Figure 1. Gain-of-function variants have been identified in multiple potassium channels**

Illustration showing different potassium channels associated with epilepsy channelopathies. Red marks indicate locations of identified gain-of-function variants.

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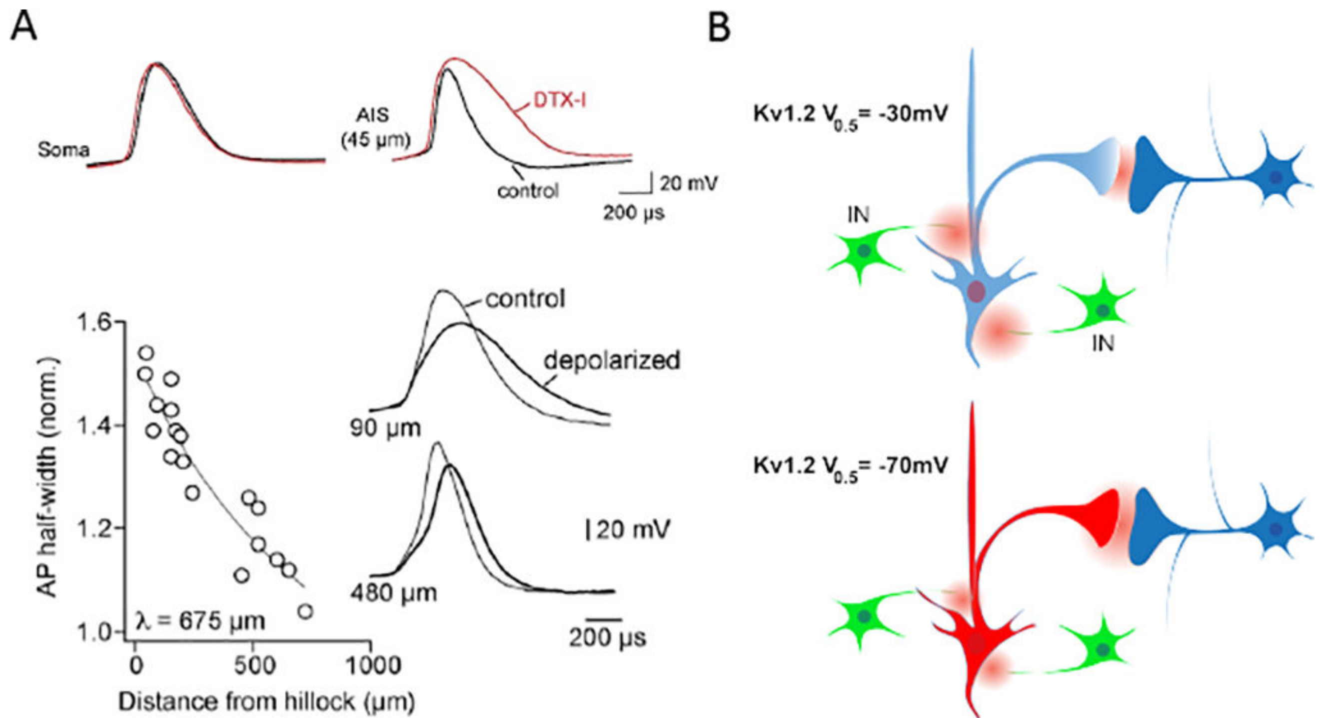


**Figure 2. Kv1.2 channels regulate axonal excitability**

(A) Top, blocking Kv1 channels in Layer 5 pyramidal neurons prolongs the axonal but not somatic action potential. Bottom, subthreshold depolarization inactivates Kv1 channels leading to alter action potential waveform. Reprint with permission from Kole and others (2007), with permission from Elsevier. (B) Illustration showing that Kv1.2 gain-of-funciton variants could shift activation of Kv1.2 channels at resting membrane potential leading to their inactivation and subsequent greater glutamate release.

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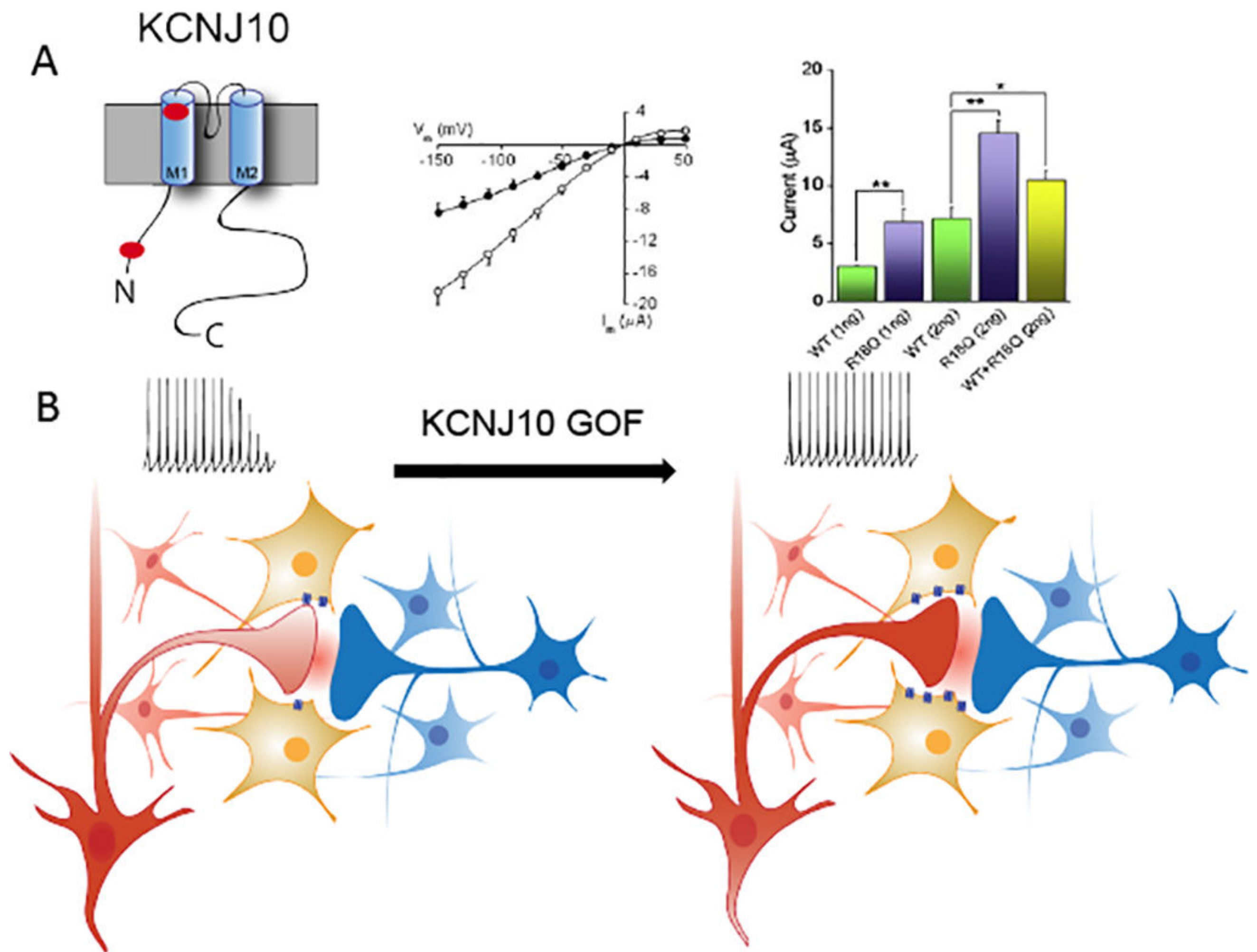


**Figure 3. KCNJ10 channels regulate neuronal excitability**

(A) Left, illustration showing location of identified KCNJ10 variants in patients with epilepsy and autism. Right, examples of a KCNJ10 gain-of-function variant from a patient with epilepsy and autism. Reprint with permission from Sicca and others (2011), with permission from Elsevier. (B) Illustration showing that repetitive firing leads to build of extracellular potassium and axonal sodium channel inactivation. KCNJ10 GOF variants might prevent the potassium ion build up allowing neurons to fire in higher frequency.

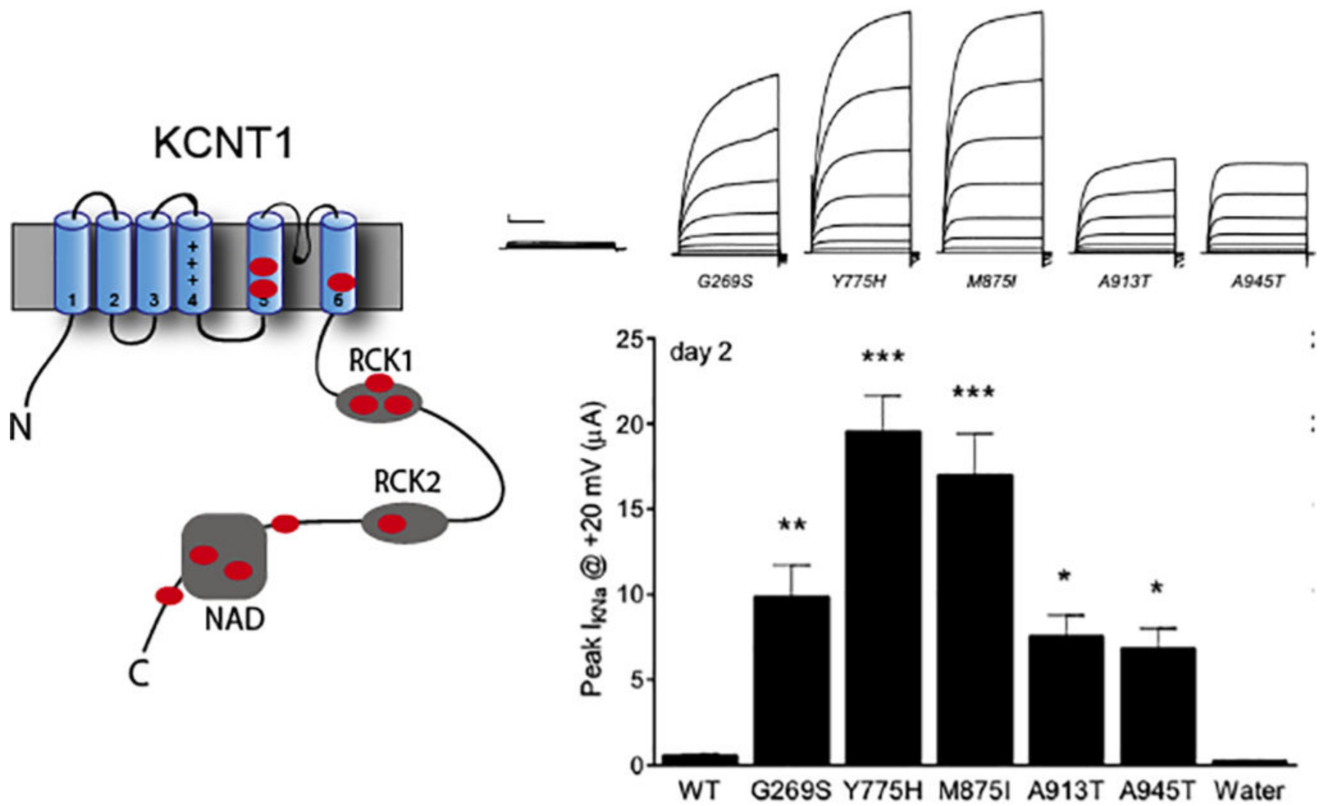


**Figure 4. KCNT1 gain-of-function variants lead to greater KCNT1 currents**

Voltage clamp recordings of of KCNT1 variants identified in patients with epilepsy. Notice that most variants lead to several fold greater KCNT1 currents than wild-type KCNT1 responses. Reprint with permission from Kim and others (2014), with permission from Elsevier.



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