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# Potassium channels in behavioral brain disorders. Molecular mechanisms and therapeutic potential: A narrative review

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ABSTRACT

Potassium channels ($K^+$-channels) selectively control the passive flow of potassium ions across biological membranes and thereby also regulate membrane excitability. Genetic variants affecting many of the human $K^+$-channels are well known causes of Mendelian disorders within cardiology, neurology, and endocrinology. $K^+$-channels are also primary targets of many natural toxins from poisonous organisms and drugs used within cardiology and metabolism. As genetic tools are improving and larger clinical samples are being investigated, the spectrum of clinical phenotypes implicated in $K^+$-channels dysfunction is rapidly expanding, notably within immunology, neurosciences, and metabolism. $K^+$-channels that previously were considered to be expressed in only a few organs and to have discrete physiological functions, have recently been found in multiple tissues and with new, unexpected functions. The pleiotropic functions and patterns of expression of $K^+$-channels may provide additional therapeutic opportunities, along with new emerging challenges from off-target effects. Here we review the functions and therapeutic potential of $K^+$-channels, with an emphasis on the nervous system, roles in neuropsychiatric disorders and their involvement in other organ systems and diseases.

## 1. Introduction

Ion channels are found in all living organisms, from bacteria to advanced multicellular organisms, including humans. Such channels serve a remarkable diversity of physiological functions, yet their fundamental structure and functional properties are conserved across phyla and millions of years of evolution. Potassium channels ($K^+$-channels) are involved in various physiological processes by controlling selectively the flow of potassium ions across the membrane and controlling cellular membrane excitability (Choe, 2002; Miller, 2000). It is well established that $K^+$-channels regulate the contractility of the cardiac muscle cells, and thereby heart function, by modulating the coordinated cardiac repolarization (Snyders, 1999; Coetzee et al., 1999; Nerbonne, 2000; Grandi et al., 2017). Similarly, in neuronal cells, $K^+$-channels maintain homeostasis and regulate neuronal firing properties and membrane potential (Bean, 2007; Jan and Jan, 2012; Trimmer, 2015). Moreover, it has been shown that these channels have roles in other cellular processes such as glucose homeostasis through insulin secretion, regulation of neurotransmitter release in muscle and brain cells, regulation of heart contractility, and immune functions (Abbott and Goldstein, 2001; Chen et al., 2023; Choi and Kim, 2022). Since the discovery of the electrochemical nature of nerve signal conduction in the early 1900s, introduction of patch-clamp recordings in late 1970s (Neher, Sakmann, and Steinbach, 1978), and determination of the first molecular structures of $K^+$-channels 30 years later (MacKinnon et al., 1998), the function of $K^+$-channels has been intensively investigated and subject to many reviews, also focusing on their roles in health and disease.

A literature search using the PubMed database revealed > 77,000 articles mentioning $K^+$-channels, with > 20,000 articles being published

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between 2013 and 2023. As it obviously is an impossible task to satisfactorily cover all relevant aspects of the > 100 reported human $K^+$-channel genes and proteins in a single review article, we have limited our scope to $K^+$-channels that we consider most relevant for understanding and treating neuropsychiatric disorders and recently emerging functions of $K^+$-channels in the interplay between the endocrine and nervous system. For the purpose of this review, we have mainly focused on the following $K^+$-channels: KCNQ1–5, KCNT1, KCNA2, KCNB1, KCNC1, KCND3, KCNA1, $K_{ATP}$, and KCNH2. Furthermore, considering the diversity of results, methods and study designs cited, this is presented as a narrative review and not a systematic one. Firstly, we briefly introduce some fundamental structural properties of the major classes of $K^+$-channels. Next, we present an overview of their tissue distribution and biological functions, with an emphasis on the central nervous system (CNS). Finally, we discuss recent emerging associations of $K^+$-channels, endocrine and neuropsychiatric disorders and future prospects of pharmacological modification of $K^+$-channel functions. The literature covering these subjects comes from many disciplines, including physiology, genetics, structural biology, clinical medicine and pharmacology. In this narrative review we aim to integrate and discuss these findings, with an emphasis on discoveries reported during the past decade, until March 2023. We conclude that $K^+$-channels are important drug targets in several therapeutic areas, but that many obstacles remain in terms of achieving the necessary selectivity and potency in clinical context.

## 2. Organization and structural properties

Traditionally, $K^+$-channels have been subcategorized into three to five major classes based on their structural and functional properties (Fig. 1). This nomenclature is based on gene families and whether the channels have 2, 4 or 6/7 transmembrane domains. Fig. 1 lists members of the four major groups of K-channels. Alternative classifications have also been suggested, such as a separate family of sodium-activated channels ($K_{Na}$ channels), see section 4.22. For historical reasons, the corresponding genes have a different nomenclature. Here we mainly use protein-based terminology but also refer to the $K^+$-channel encoding genes when appropriate. The largest family is the voltage gated ($K_V$) $K^+$-channels, with over 40 distinct members identified in the human genome and usually grouped into 12 subfamilies (Wulff, Castle, and Pardo, 2009; Tian et al., 2014). These channels are highly conserved, all having four identical α-subunits, each formed by six transmembrane (TM) segments (S1-S6) (Fig. 2), allowing $K^+$ to pass through the channels (Long, Campbell, and Mackinnon, 2005). The ion permeability of the voltage-gated channels depends on their ability to detect changes of the voltage with respect to the membrane potential in the cell (Swartz, 2004; del Camino, Kanevsky, and Yellen, 2005; del Camino and Yellen, 2001), making these channels well suited for maintaining physiological processes in the nervous system, heart, pancreas and other tissues (Wulff, Castle, and Pardo, 2009). Additionally, the function of $K_V$ channels is also regulated by a smaller beta subunit (see Section 4.1.3)

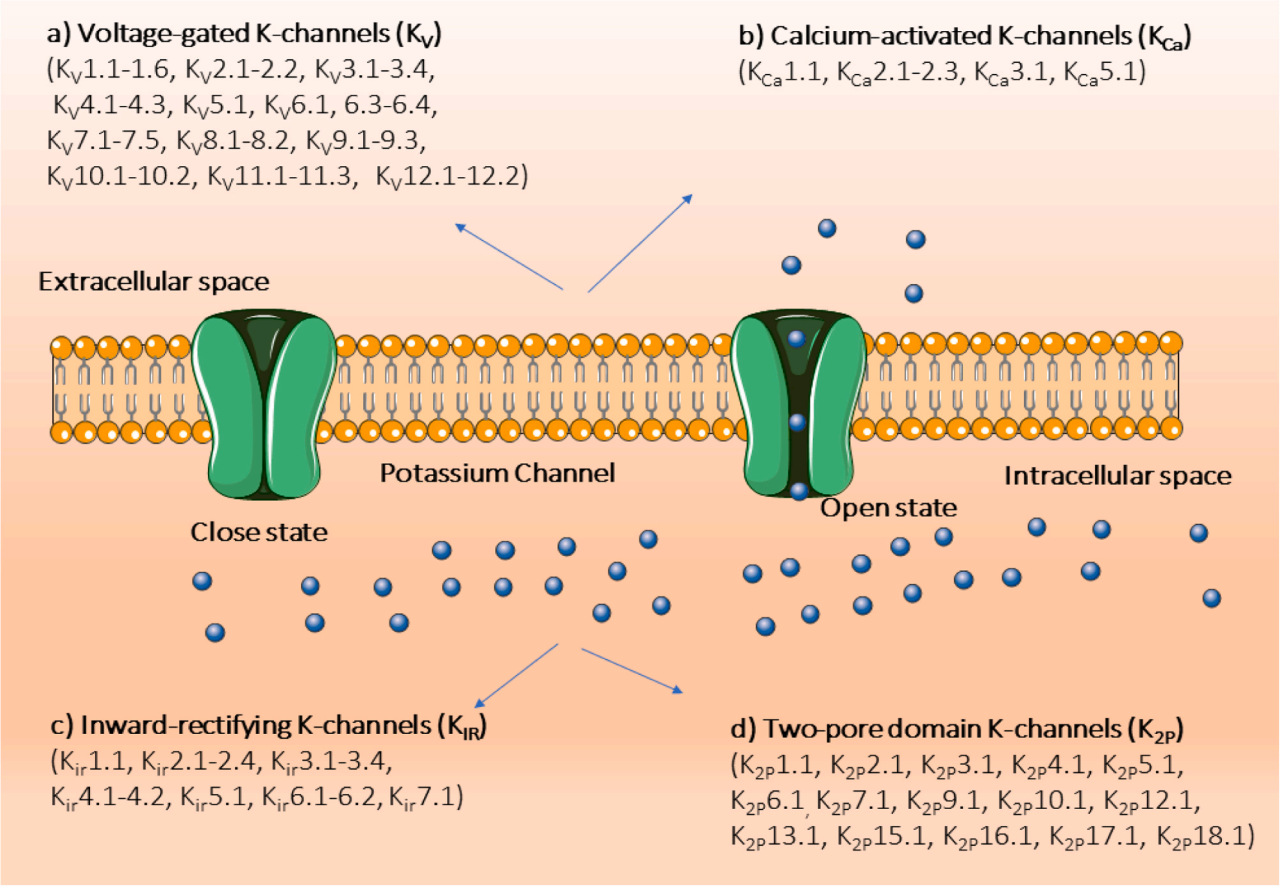


**Fig. 1.** Potassium channels are grouped into four major types according to their structural and functional properties. The channels are named according to their protein sequence nomenclature and potassium ions are marked as blue spheres. a) Voltage-gated $K^+$-channels ($K_V$) are regulated by membrane potential and sub-grouped into 12 classes which include $K_V$1–12 (Gutman et al., 2005). b) Calcium-activated $K^+$-channels ($K_{Ca}$) are regulated by calcium gating. The $K_{Ca}$ are further classified as large conductance (BK), intermediate conductance (IK), and small conductance (SK) calcium-activated $K^+$-channel. c) Inward rectifying $K^+$-channels allow $K^+$ to inward direction into the cell and are sub-divided into 7 classes, $K_{ir}$1–7 (Kubo et al., 2005). d) Two-pore domain or tandem pore domain ($K_{2P}$) K- channels consist of 15 members (Goldstein et al., 2005). $K_{2P}$ $K^+$-channels have two pores and exist both in excitable and non-excitable cells (Lesage and Lazdunski, 2000). The figure was created using the Servier Medical Art Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

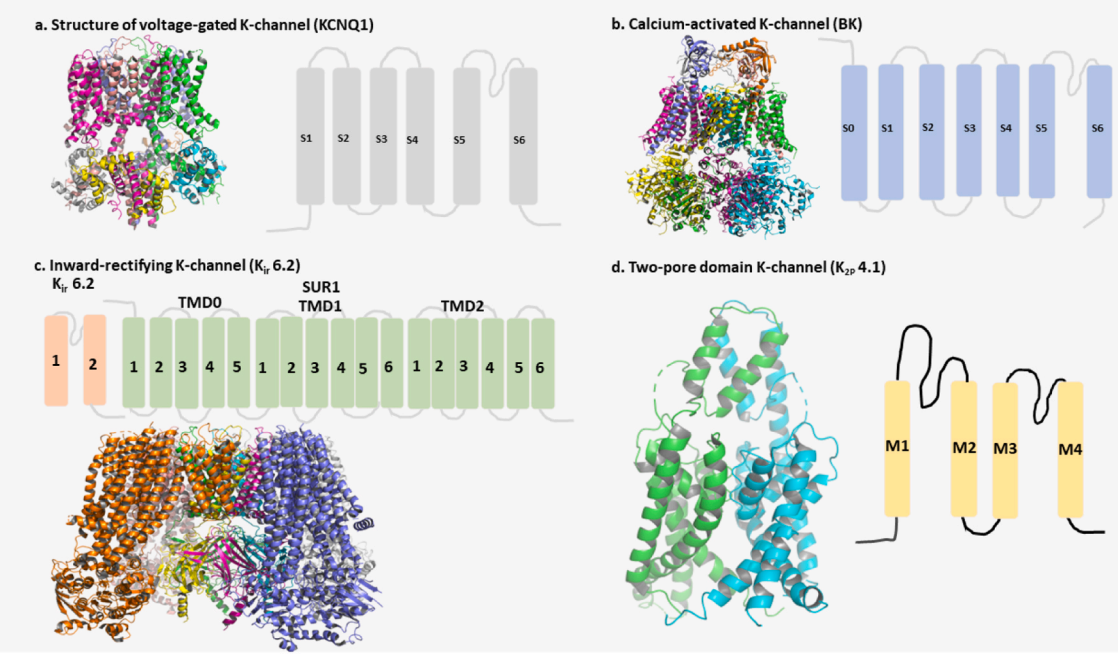


**Fig. 2.** Representative structures of four major types of potassium channels families based on 3D-structures (cartoon representations) and sequence (schematic representation of TM helices). a) KCNQ1 (PDB ID: 7XNK) is a member of voltage-gated $K^+$-channel and consists of four identical subunits, each containing six TM segments (S1-S6). b) Calcium-activated $K^+$-channel, $K_{Ca}1.1$ (PDB ID: 6V22), is a tetramer complex with seven TM segments (S0-S7). c) Inward-rectifying $K^+$-channel, $K_{ir}6.2$ consists of two transmembrane domains (PDB ID: 6C3O) (Lee et al., 2017). $K_{ir}6.2$ forms the channel with SUR (Sulfonylurea receptor) in the pancreatic β-cells and regulate insulin secretion (Martin et al., 2017). SUR is composed of three TM domains (TMD0-TMD2) where each domain has six segments except TMDO. d) $K_{2\,P}4.1$ is a member of two-pore domain $K^+$-channel (PDB ID: 3UM7), which has two pore forming domains (P-loop domains) and four TM segments (M1-M4) (Brohawn, del Marmol, and MacKinnon, 2012). The figures were made using PyMOL (Schrodinger).

(Abbott and Goldstein, 2001; McCrossan and Abbott, 2004).

The calcium-activated $K^+$-channels ($K_{Ca}$) include the six/seven TM family of $K^+$-channels which are activated by the intracellular $Ca^{2+}$ concentration and regulate the resting membrane potential and $K^+$ conductance (Vergara et al., 1998; Stocker, 2004; Swarthout and Walling, 2000). $K_{Ca}$ channels are sub-grouped into three types; large conductance (big potassium; BK), small conductance ($SK_{Ca}$), and intermediate conductance ($IK_{Ca}$) calcium-activated $K^+$-channels (Weaver, Bomben, and Sontheimer, 2006). Like $K_V$ channels, $K_{Ca}$ channels have six TM segments, with the exception of seven TM elements (Fig. 2) found in $K_{Ca}1$ (Tian et al., 2014). $K_{Ca}$ channels are expressed throughout the CNS and regulate neuronal firing, the vascular tone of blood vessels, and neurotransmitter release (Sah and Davies, 2000; Sah and Faber, 2002; Bahia et al., 2005; Berkefeld, Fakler, and Schulte, 2010).

The inward-rectifying $K^+$-channels ($K_{ir}$) have seven different subtypes, that allow $K^+$ to move inside the cell through a homo- or hetero tetramer pore structure (Hibino et al., 2010). The channel consists of two transmembrane domains (Fig. 2) and the extracellular loop making up the channel (Hibino et al., 2010; Heginbotham et al., 1994). The $K_{ir}$ channels are widely expressed in the cells and the channels are regulated by cellular metabolism, G protein-coupled receptors, and $K^+$ transport channels (Hibino et al., 2010).

The two-pore domain $K^+$-channel family ($K_{2\,P}$) includes 15 different members, each consisting of four TM segments (Fig. 2) forming two pore domains (Alexander et al., 2021). The expression of these channel is widespread in the CNS and peripheral tissues (Medhurst et al., 2001). They have distinct structural properties and can be constitutively open or show inward (TASK-1) or outward (TREK1) rectification, presenting leaky channel properties (Innamaa et al., 2013; Niemeyer et al., 2010; Lesage and Lazdunski, 2000).

## 3. Potassium channel expression

Some members of the $K^+$-channels family appear to be expressed in nearly every cell type in all organisms that have been studied (Littleton and Ganetzky, 2000). It is therefore not surprising to find that $K^+$-channels in general are also widely expressed in various human tissues. Among 97 different $K^+$-channel genes listed in the human protein atlas (Accessed February 2023), at least some tissue expression information is available for all members (www.proteinatlas.org). In particular, the voltage-gated, and inward rectifying $K^+$-channels are highly expressed in brain, endocrine, kidney, skeletal muscle, and heart tissues (https://gtexportal.org/home/)(Tian et al., 2014). Calcium-activated, and two-pore domain $K^+$-channels are also expressed in the heart, lung, intestine, reproductive system, and other organs. Possibly reflecting their diverse physiological roles, *KCNJ1* ($K_{ir}1.1$) is highly expressed in kidney, while the structurally related channels *KCNJ6* is mainly expressed in brain, *KCNJ10* in brain and digestive tract, *KCNJ11* in heart and skeletal muscle and *KCNJ15* is expressed in kidney and multiple endocrine tissues. *KCNMA1* ($K_{Ca}1.1$) and *KCNMB1* appear to be highly expressed in arteries, colon, uterus, fallopian tube, and bladder, and higher expression of *KCNK3* is observed in lungs and heart (www.proteinatlas.org). This highly distributed pattern of expression is consistent with diverse functions of $K^+$-channels in many different organs. As this review is particularly focused on the role of $K^+$-channels in behavioral and endocrine disorders, their pattern of expression in brain and pancreatic tissue is briefly reviewed below.

### 3.1. $K^+$-channels in the central nervous system (CNS)

Inward-rectifying, and voltage-gated K-channels are expressed in multiple regions of the CNS, including the cerebellar hemispheres, frontal cortex, and basal ganglia (https://gtexportal.org/home/multiGeneQueryPage/KCNJ11). Disease related variants within several classes of K-channels have been described, including variants of *KCNJ16* ($_{Kir}5.1$), *KCNJ11* ($K_{ir}6.2$), *KCNJ8* ($K_{ir}6.1$), *KCND3* ($K_V4.3$), *KCNJ5* ($K_{ir}3.4$) and *KCNQ1* ($K_V7.1$) (Goldman et al., 2009; Karschin et al., 1997; Noh et al., 2019). Among the voltage gated $K^+$-channels; *KCNQ2–5* are

highly expressed in the CNS. In comparison, only a moderate expression of *KCNQ1* has been reported in brain tissues. Still, variants in all of these $K^+$-channels have been linked to behavioral phenotypes (see 4.2.1) (https://gtexportal.org/home/multiGeneQueryPage/KCNQ1).

### 3.2. Pancreas

Many of the inward-rectifying channels, *KCNJ5* ($K_{ir}3.4$), *KCNJ8* ($K_{ir}6.1$), *KCNJ11* ($K_{ir}6.2$), *KCNJ15* ($K_{ir}4.2$), and *KCNJ16* ($K_{ir}5.1$), are highly expressed in the pancreas (see 4.1.1) (Ferrer et al., 1995). Among the voltage-gated $K^+$-channels; *KCNQ1* is highly expressed in pancreas, apparently different from the other members of the $K_V7$ family. *KCNQ4* has moderate expression and *KCNQ2*, *KCNQ3*, and *KCNQ5* have low expression levels in the pancreas (https://gtexportal.org).

## 4. $K^+$-channels in human disease

Because of their wide range of functions and patterns of expression, altered functions of $K^+$-channels have been implicated in a range of human conditions, including common cardiovascular, brain, and metabolic diseases (Tian et al., 2014). Rare Mendelian inherited channel defects can also cause syndromic disease with various symptoms from different organs in the same patients, as illustrated in the DEND syndrome (development delay with epilepsy in addition to neonatal diabetes) in patients with *KCNJ11/ABCC8* ($K_{ir}6.2$/SUR1) mutations and neonatal diabetes (Hattersley and Ashcroft, 2005). It is highly likely that other constellations of symptoms might not yet have been recognized as having common pathophysiologic pathways related to $K^+$-channel dysfunction.

### 4.1. Diabetes

#### 4.1.1. Type 2 diabetes mellitus (T2DM)

Several studies have established that *KCNQ1* plays a role in insulin secretion in pancreatic β-cells and that channel dysregulation is associated with T2DM (Asahara et al., 2015). A similar voltage-gated channel, *KCNE2* has also been implicated in diabetes, with knockout mice (*Kcne2*$^{-/-}$) developing diabetes mellitus at five weeks of age (Hu et al., 2014; Lee et al., 2017). Acute application of insulin suppressed the KCNQ1/KCNE1 currents, but the use of insulin for more than 6 h had opposite effects in *Xenopus oocyte* studies (Wu et al., 2017). Combined, these results point to both *KCNQ1* and *KCNE1* as important interaction partners in insulin secretion and T2DM pathophysiology (Wu et al., 2017). Genome-wide association studies (GWAS) have also implicated common *KCNQ1* gene variants in T2DM in several populations (Unoki et al., 2008; Yasuda et al., 2008; Voight et al., 2010; Li, Wang, and Lu, 2014; Qian et al., 2015). Yasuda and co-workers showed that the polymorphism rs223782 had the strongest link with the T2DM (Yasuda et al., 2008). However, the molecular mechanisms of *KCNQ1* involvement in diabetes are not fully understood. It has been suggested that impaired KCNQ1 ($K_V7.1$) activity could delay repolarization of β-cells, and by this mechanism increase insulin secretion. Correspondingly, knockdown of *KCNQ1* with siRNA enhances insulin secretion (Rosengren et al., 2012), while overexpression of *KCNQ1* in MIN6 cells decreases insulin secretion (Yamagata et al., 2011). Mutations leading to a loss-of-function (LOF) of the *KCNQ1* increase insulin secretion (Fig. 3). Patients may present with hyperinsulinemia and symptomatic hypoglycemia, but later in life, insulin secretion may shift to hyposecretion, and these patients therefore have an elevated risk of developing T2DM (Torekov et al., 2014). Additionally, studies in mice carrying a *KCNQ1* mutation (KCNQ1-A340V) demonstrated that insulin production can shift from hypo- to hyper secretion as the mice get older (Lubberding et al., 2021). The observation that patients with long QT syndrome (LQTS) have an increased risk of diabetes and that inhibition of *KCNQ1* increases insulin secretion in β-cells diabetes strengthen the association of variants in voltage-gated $K^+$-channels with diabetes (Torekov et al., 2014; Yasuda et al., 2008). Thus, LOF mutations in *KCNQ1* or *KCNH2* (hERG or $K_V11.1$) in LQTS patients are accompanied by increased insulin secretion (Torekov et al., 2014; Engelbrechtsen et al., 2018; Hyltén-Cavallius et al., 2017).

In contrast, gain-of-function (GOF) variants in *KCNQ1* reduce glucose stimulated insulin secretion (Zhang et al., 2020). In studies using GWAS and single-cell epigenomics, Chiou and co-workers showed that the *KCNQ1* locus is linked to the T2DM variant and co-accessibility of the insulin (INS) promoter in β-cells. This may explain why the variant rs231361 at the *KCNQ1* locus was found to regulate insulin synthesis (Chiou et al., 2021). In addition, the C-allele of *KCNQ1* rs2237895, which is associated with an increased risk of T2DM, was found to result

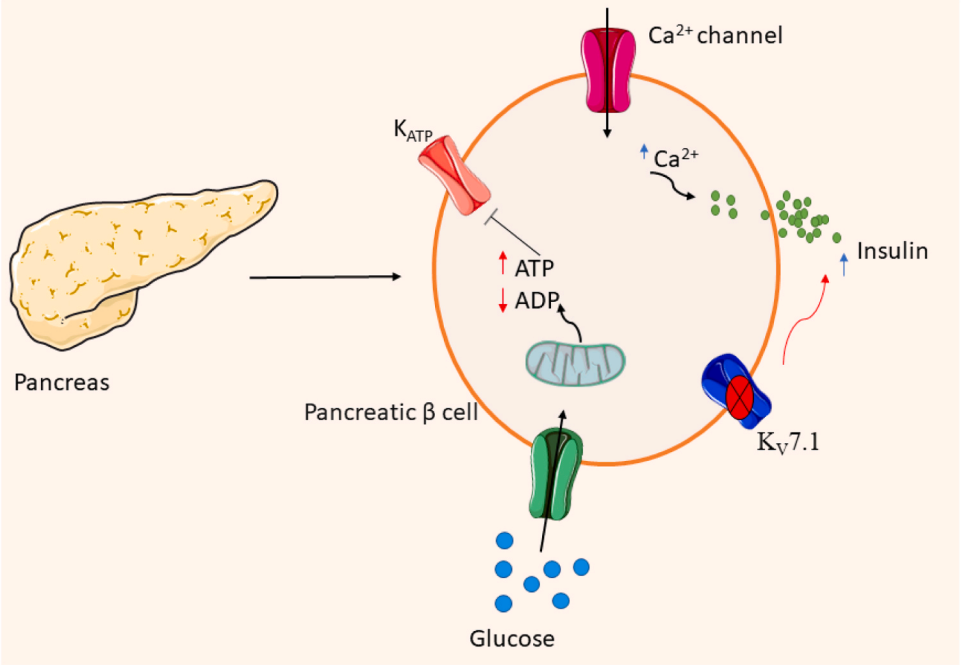


**Fig. 3.** Insulin secretion in pancreatic β-cell. High glucose level induces uptake of glucose in β-cell which is mediated through GLUT2 transporters and lead to increased ATP/ADP ratio in the cell. Increased ATP initiated a cascade mechanism by closing the ATP sensitive ion channel, $K_{ATP}$ and causes depolarization and subsequently opening of the $Ca^{2+}$ channel and releasing of insulin (Ashcroft, 2005). Opening of KCNQ1 ($K_V7.1$) inhibits insulin secretion by an unknown mechanism, possibly by hyperpolarization. However, inhibition or LOF of KCNQ1 increases insulin secretion in pancreatic β-cell (Torekov et al., 2014). The mechanism by which of $K_V7.1$ causes higher insulin secretion is not understood yet.

in reduced glucose-stimulated insulin secretion in human islets (Jonsson et al., 2009).

#### 4.1.2. Gestational diabetes mellitus (GDM)

*KCNQ1* is a candidate gene for gestational diabetes mellitus (GDM) which is characterized by maternal glucose intolerance during pregnancy. GDM affects both mother and offspring as the neonate may be born large for gestational age and furthermore suffer from hypoglycemia after delivery due to a glucose-induced hypersecretion of insulin in the fetus (Ortega-Contreras et al., 2022). Genetic studies have shown an association between the variant rs2237892 in *KCNQ1,* increased glucose levels, reduced β-cell function, and decreased insulin secretion in the cells which pose a higher risk for GDM (Jonsson et al., 2009; Wang et al., 2013; Yasuda et al., 2008; Shin et al., 2010; Ao et al., 2015; Fatima et al., 2016).

#### 4.1.3. Neonatal diabetes mellitus (NDM)

Neonatal diabetes mellitus (NDM) is a rare disorder affecting 1 in 160 000–520 000 live births, with around half of patients presenting with a permanent type (PNDM) and the remainder having transient symptoms (TNDM) (Shield et al., 1997; Slingerland et al., 2009; Stanik et al., 2007; Vonmuhlendahl and Herkenhoff, 1995; Wiedemann et al., 2010). The majority of cases are caused by a dysfunctional pancreatic ATP-sensitive potassium channel ($K_{ATP}$ channel) (Vaxillaire et al., 2004) due to mutations in one of the two genes coding for the heterodimeric subunits, *KCNJ11* encoding the $K_{ir}6.2$-channel pore, and the ATP-binding cassette transporter sub-family (*ABCC8)* gene, encoding the regulatory subunit sulfonylurea receptor (SUR1). The $K_{ATP}$ channel translates the signal of energy excess from glucose metabolism to membrane activity and ultimately insulin release by controlling $K^+$ influx through the $K_{ir}6.2$ pore (Ashcroft, Harrison, and Ashcroft, 1984), (Fig. 3). Activating mutations compromising channel closure halt insulin secretion and neonatal diabetes is usually diagnosed before the age of six months (Ashcroft, 2005; Hattersley and Ashcroft, 2005; Rubio-Cabezas et al., 2012; Proks et al., 2006). The neonate is often born small for gestational age (birth weight <10 percentile) since fetal insulin is important for normal growth *in utero* (Gloyn et al., 2004; Slingerland and Hattersley, 2006; Vaxillaire et al., 2004). The SUR1 protein regulates channel activity and contains the binding site for the sulfonylureas (Ashcroft and Gribble, 2000; Gribble and Reimann, 2003). A genotype-phenotype correlation to the severity of mutations has been observed, both within the phenotype of neonatal diabetes, but also reaching across the spectrum of monogenic diabetes. Certain genetic variants are causing later debut of diabetes with maturity onset diabetes of the young (MODY) or give increased risk of T2DM (Hattersley, Greeley, Polak, Rubio-Cabezas, Njolstad et al., 2018; Martagón et al., 2018; Najmi et al., 2017).

##### 4.1.3.1. Neurological defects associated with neonatal diabetes mellitus (NDM).

$K_{ATP}$ channels are expressed in pancreas but also in other tissues, including many brain areas, such as the hippocampus, neocortex, midbrain, brainstem nuclei and cerebellum (see Section 3). Thus, it is not unexpected that patients with $K_{ATP}$ channelopathies also may suffer from neurological symptoms (Clark et al., 2010; Karschin et al., 1997). Hattersley and Ashcroft defined two syndromes in *KCNJ11*-carriers with the acronyms DEND (Developmental delay, Epilepsy, Neonatal Diabetes) or intermediate DEND (iDEND) for patients without epilepsy (Hattersley and Ashcroft, 2005). A genotype-phenotype correlation to this neurological phenotype has been reported in several studies (Gloyn et al., 2004; Hattersley and Ashcroft, 2005; Sagen et al., 2004) where *ABCC8* mutation carrier status also is associated with DEND (Proks et al., 2006). Since these early observations, multiple studies have revealed a high prevalence of learning disabilities, visuospatial disability, ADHD, anxiety, autism spectrum disorders or developmental coordination disorder including dyspraxia and hypotonia in $K_{ATP}$ -associated neonatal diabetes (Beltrand et al., 2015; Bowman et al., 2019; Bowman et al., 2017; Bowman et al., 2021; Bowman et al., 2020; Busiah, Drunat, and Vaivre-Douret, 2013; Carmody et al., 2016; Landmeier et al., 2017; Svalastoga et al., 2020). These clinical features are not found in other types of monogenic diabetes e.g., due to mutations in the insulin gene (*INS)* (Bowman et al., 2019). Formal cognitive testing of carriers of variants affecting the gating properties in *KCNJ11* (e.g., V59M) demonstrate moderate intellectual disability and high prevalence of psychiatric comorbidity (Svalastoga et al., 2020). This pathogenic effect is likely to be neuronal in origin as recombinant mice with altered nerve-*KCNJ11* isoforms displayed a similar phenotype (Clark et al., 2010). In summary, there are reports in the literature that the $K_{ATP}$ channel in NDM is linked with developmental delay within DEND. Now, with the latest reports providing additional data from larger cohorts over ten years and also cohorts containing deeper phenotyping for carriers of specific gene variants, a clear genotype-phenotype correlation of severity has been established. We believe there is a scientific basis for this relationship, as those carrying genotypes highly affecting the open-close probability of the channel (e.g. KCNJ11, p.V59M) show a higher burden of psychiatric morbidity and intellectual disability. Moreover, studies in rodents also find the same genotype when the mutation occurs in neuronal $K_{ATP}$ channels. Reports on other types of neonatal diabetes (e.g. *INS* mutations) are not associated with developmental delay. What remains to be settled is the role of sulfonylurea to prevent brain injury, and whether there is a time sensitive period of this effect. Itś a question of much debate. The field currently lacks studies on children switched to sulfonylurea early in life. The characterization of the phenotypic changes following treatment change have not yet been fully assessed across sites. While some clinical centers recommend high-dose sulfonylurea, its impact in moderating effects induced by $K_{ATP}$ channel mutations require investigation.

#### 4.1.4. Congenital hyperinsulinism (CHI)

Congenital hyperinsulinism (CHI) is a rare condition affecting between 1:25.000–1:70.000 of live births (Sandal et al., 2009; Glaser et al., 2000; Otonkoski et al., 1999), with higher prevalence (up to 1:2700) in isolated and or highly consanguineous populations (Otonkoski et al., 1999; Mathew et al., 1988; Levy-Shraga et al., 2013). In CHI, recessive inactivating mutations in *ABCC8* or more rarely *KCNJ11* cause $K_{ATP}$ channel closure leading to membrane depolarization in the β-cells, and ultimately inappropriate insulin secretion with a risk of hypoglycemia (Thomas et al., 1995; De Franco et al., 2020). CHI is categorized into a transient type, spontaneously reaching remission during infancy, and a persistent type, where patients typically will require medical and surgical interventions before remitting during childhood. Based on histological examination of pancreas tissue, it is possible to distinguish between focal and diffuse subtypes that may be used to guide treatment options (Sempoux et al., 2004).

Usually, CHI present as isolated hypoketotic hypoglycemia, but facial dysmorphic features (high forehead, bulbous nose, smooth philtrum) have also been described (de Lonlay et al., 2002). In severe cases, the neonate can present within the first few days with poor feeding, floppiness, jitteriness, lethargy, cyanosis and hypothermia, seizures or coma (Cosgrove et al., 2004), but CHI can also be discovered by routine testing of blood glucose. Macrosomia is a common feature due to intrauterine hyperinsulinemia, but birth weight can also be low or normal, and some are born prematurely (Cosgrove et al., 2004). In rare cases hypertrophic cardiomyopathy and hepatomegaly are seen, also caused by the elevated insulin (Demirbilek and Hussain, 2017). CHI can also present in infancy, and more rarely in childhood or adulthood, usually with a milder phenotype. Some patients are only diagnosed when they regress into the opposite phenotype, diabetes, and a history of unexplained hypoglycemia is revealed (Descamps et al., 2021; Vieira et al., 2010). Although rare syndromic cases exist (e.g. Beckwith-Wiedemann, Sotos, Perlman, Kabuki, congenital disorders of glycosylation) CHI is, for the most part, isolated and caused by $K_{ATP}$ channel deficiency (Arnoux

et al., 2010) in 40–70% (Thomas et al., 1995; Thomas, Ye, and Lightner, 1996; Sandal et al., 2009; Gloyn, Siddiqui, and Ellard, 2006; Fernández-Marmiesse et al., 2006; Tanizawa et al., 2000; Raicevic et al., 2021; Park et al., 2011). $K_{ATP}$ channel CHI is more common in treatment-resistant cases (82%) (Bellanné-Chantelot et al., 2010) than in diazoxide-responsive patients (approx. 15%) (Flanagan et al., 2010). Mutations affecting the *ABCC8* gene are implicated up to tenfold more often than *KCNJ11* (Sandal et al., 2009; Bellanné-Chantelot et al., 2010). As expected, homozygosity in carriers tend to be more prevalent in consanguineous populations (Razzaghy-Azar et al., 2022; Amaratunga et al., 2022).

As the neonate brain has a high energy need, it is particularly susceptible to hypoglycemic injury (Rodrigues Vilela et al., 2014). As the elevated insulin levels in CHI suppress utilization of alternative energy sources such as ketone bodies it increases the risk of neonatal brain injury. No exact definition or critical value of hypoglycemia in neonates exists, but both the severity and the duration of hypoglycemia may have long-term neurological and developmental consequences (Stomnaroska-Damcevski et al., 2015). Hypoglycemic injury can cause intellectual disability, cerebral palsy, seizure disorder, microencephaly, spasticity, and ataxia (Steinkrauss et al., 2005). Therefore, early diagnosis and prompt management of hypoglycemia is essential to avoid long-term neurological complications (Demirbilek and Hussain, 2017; Gataullina et al., 2013; Steinkrauss et al., 2005; Helleskov et al., 2017).

*4.1.4.1. Neurological defects associated with CHI.* Similar to what is seen in neonatal diabetes, early reports indicated that up to half of children with CHI suffered from developmental delay and psychomotor disturbances, and a third was diagnosed with epilepsy (Meissner et al., 2003; Menni et al., 2001; Cresto et al., 1998; Jack et al., 2003; Rother et al., 2001; Steinkrauss et al., 2005). It has been debated whether surgical or medical interventions would improve the long-term outcome in CHI (Jack et al., 2003). There are also disagreements as to whether an early diagnosis is associated with an increased risk (Menni et al., 2001), or whether early treatment can improve the long-term prognosis, since later debut age and milder symptoms have been correlated with poor neurodevelopmental outcomes (Jack et al., 2003; Meissner et al., 2003). As these historic records lack detailed genetic data, it is unclear to what extent the intellectual disability is linked to a primary channelopathy or to hypoglycemic sequela. In more recent studies, high rates of neurological comorbidity have also been confirmed, with up to a third of patients showing neurocognitive problems and epilepsy. However, as some of these cases are found in highly consanguineous populations, careful interpretation will be needed to establish the causal effect in a genotype, as multiple genetic traits might be shared in these carriers (Laimon, Aboelenin, and El Tantawi, 2021; Razzaghy-Azar et al., 2022; Levy-Shraga et al., 2013). In non-consanguineous populations, abnormal behaviors were observed in a third of British CHI cases, showing that a late diagnosis was associated with higher rates of comorbidity (Salomon-Estebanez et al., 2017). Furthermore, 28 out of 60 German CHI patients (38% with $K_{ATP}$ channel CHI) revealed delay in at least one developmental area. A third of these had motor problems, but only four patients were diagnosed with mild to moderate intellectual disability (Ludwig et al., 2018). Similar findings were published by a Finnish group, reporting that CHI patients did not differ in intellectual functioning compared to the general population. Even so, retrospective analyses revealed intellectual disability in up to 7% (Muukkonen et al., 2019). Since only a subset of patients was systematically assessed, 11 of which were $K_{ATP}$ channel CHI, no conclusions as to the association between genotype and phenotype could be reached either in the German or Finnish studies. In a smaller Serbian study, where five *ABCC8* carriers were identified, two heterozygotic carriers suffered from neurodevelopmental delay and seizures (Raicevic et al., 2021), and both were reported diazoxide responsive. We appreciate that the evidence to date within the CHI field is equivocal in some respects and strong in others and have sought to clarify within this section where the knowledge gaps are within the $K_{ATP}$ field.

### 4.2. $K^+$-channels implicated in epilepsy

#### 4.2.1. KCNQ channels

Mutations in $K^+$-channels are found in many diseases affecting the brain and peripheral tissues (see Supplementary Table S1 and Supplementary figs. S1-S8 for a list of mutations and diseases). Mutations in *KCNQ1* are strongly associated with LQTS, an autosomal dominantly inherited heart condition where an unusually long repolarization causes life-threatening arrythmias and even sudden cardiac death (Algra et al., 1993; Lamberts et al., 2015; Surges et al., 2010; Seyal et al., 2011). In addition to the well-established role of KCNQ1 in cardiac arrythmias, this ion channel has also been implicated in epilepsy, including sudden unexpected death in epilepsy (SUDEP), which is responsible for 20% of epilepsy-related mortality (Tiron et al., 2015; Nashef, Hindocha, and Makoff, 2007; Tomson, Nashef, and Ryvlin, 2008). The molecular mechanism for the involvement of *KCNQ1* in epilepsy is still not resolved; Tiron et. al, and González et al., have presented family cases of patients linking *KCNQ1* variants (L273F, Q530X) to LQTS epilepsy (Tiron et al., 2015; González et al., 2018). The pathogenic variant L273F is conserved among $K_V7$ mutation family members (Fig. 4).

The *KCNQ2* gene encodes KCNQ2 ($K_V7.2$), which is a voltage-gated slowly activating and deactivating $K^+$-channel (M-channel) that regulates neuronal excitability. Mutations in *KCNQ2* result in many pathogenic protein variants that cause various neurological diseases. Examination of *KCNQ2* pathogenic and likely pathogenic variants as assembled in the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/) shows that KCNQ2 variants are implicated in early infantile epileptic encephalopathy with suppression bursts, benign familial neonatal seizures, developmental and epileptic encephalopathy, childhood epilepsy with centrotemporal spikes, and intellectual disability (Supplementary Table S1). More than 100 different pathogenic or likely pathogenic *KCNQ2* mutations have been reported. Nonsense mutations of *KCNQ2* are found in patients with the autosomal dominant epilepsy form termed Benign familial neonatal convulsions (BFNC) (Biervert et al., 1998). As KCNQ2 and KCNQ3 form the heteromeric M-channel, mutations in KCNQ*3* are also associated with BFNC (Hirose, 2000; Charlier et al., 1998; Allen et al., 2014). Missense variants in KCNQ2 have also been associated with abnormalities in cortical development (Legros et al., 2022) and early onset epilepsy and encephalopathy (EOEE) (Devaux et al., 2016).

Likewise, coding variants in *KCNQ3* ($K_V7.3$) have been associated with epilepsy (Supplementary Table S1, Fig. S1), including Juvenile myoclonic epilepsy (a monogenic form of human epilepsy) (Vijai et al., 2003). The variant (W309R in KCNQ3) which changes the function of the channel has been identified in human epilepsy, explaining the CNS hyper-excitability in patients with BFNC.

In the brain, *KCNQ5* ($K_V7.5$) shows high expression in the neocortex and hippocampus where it is important in regulating neuronal excitability (Tasic et al., 2018; Tzingounis et al., 2010). Several *de novo* *KCNQ5* variants have been found in children with epilepsy, intellectual disability (ID) or language delay (Supplementary Table S1, Fig. S3). Functional characterization of these variants showed both GOF and LOF (nonsense) mutations, both of which are associated with neurological impairment (Wei et al., 2022).

#### 4.2.2. KCNT1 ($K_{Na}1.1$)

$K_{Na}1.1$ is a sodium-activated potassium channel encoded by the human gene *KCNT1*. This channel, also known as SLACK, SLO2.2, or $K_{Ca}4.1$ (Borlot et al., 2020), is opened by increased cytoplasmic sodium concentrations. The resulting potassium outflux counteracts the membrane potential change caused by sodium influx and regulates neuronal firing patterns, e.g. in response to hypoxia (Ruffin et al., 2008; Bhattacharjee and Kaczmarek, 2005). Mutations of $K_{Na}1.1$are associated with

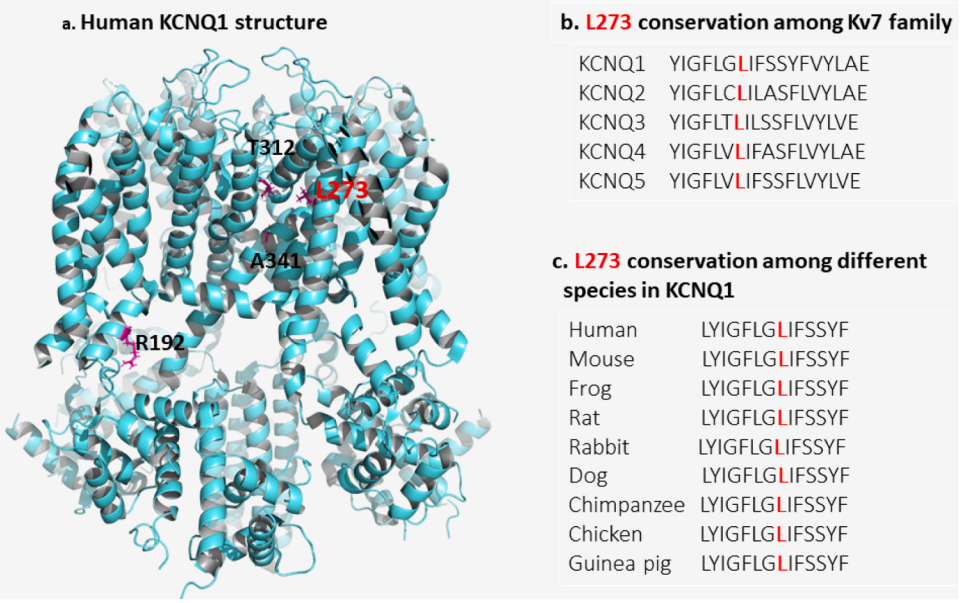


**Fig. 4.** The structure of KCNQ1 and the conservation of L73. a) Human KCNQ1 structure (PDB ID: 7XNK). Residues associated with LQTS and epileptic phenotype, as is the case for pathogenic variants L273F and R192C, are marked as stick in magenta. The variants T312I and A341F are, both found to be pathogenic and associated with LQTS in human. Mice with the corresponding mutations (T311I and A341E) developed epilepsy (Goldman et al., 2009). b) The residue L273 located in the S5 TM segment (see Fig. 2) is quite conserved among $K_V7$ family members. c). Sequence alignment of KCNQ1 across different species shows the conservation of L273.

epilepsy (Supplementary Table S1) such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and epilepsy of infancy with migrating focal seizures (EIMFS) (Lim et al., 2016). *De novo* mutations have been observed in patients with epilepsy, with the most frequent variants being A394T, and G288S (Borlot et al., 2020; Khamdiyeva et al., 2021). Functional assays revealed that a GOF mutation in *KCNT1* affects the gating properties and activates the channel, an effect that can be reversed by quinidine, a classic antiarrhythmic pharmacological agent (Milligan et al., 2014).

#### 4.2.3. *KCNA2($K_V$1.2)*

The gene *KCNA2* encodes the $K_V$1.2 voltage-gated potassium channel which is expressed in the CNS and acts on regulating neurotransmitter release and neuronal excitability (Sheng et al., 1993; Lai and Jan, 2006). Variants of *KCNA2* (Supplementary Table S1, Fig. S7) are found in patients with epileptic encephalopathy, and both LOF and GOF are implicated with disease (Syrbe et al., 2015).

#### 4.2.4. *KCNB1($K_V$2.1)*

The $K_V$2.1 is a voltage-gated delayed rectifier potassium channel encoded by the *KCNB1* gene. Expression of *KCNB1* is prominent in various parts of the brain and regulates neuronal excitability (Bishop et al., 2015). A *KCNB1* variant was found to cause developmental and epileptic encephalopathy with intellectual disability (Torkamani et al., 2014; Saitsu et al., 2015; Bar et al., 2020,2020; Bar et al., 2020,2020; Kang et al., 2019) (Supplementary Table S1, Fig. S8). A *de novo* mutation in the *KCNB1* (V378A), located in the pore-helix domain of the channel, was discovered in a family with idiopathic epileptic encephalopathy. This mutation affected the normal function of the channel, including expression levels, subcellular localization, and ion selectivity (Thiffault et al., 2015). Similar results were also observed for a mutation in the equivalent position in the *Drosophila melanogaster* Shaker $K_V$ channel (Heginbotham et al., 1994).

#### 4.2.5. *KCNC1($K_V$3.1)*

$K_V$3.1 and $K_V$3.3 channels are expressed at high levels in parvalbumin positive GABAergic, inhibitory interneurons where they are involved in action potential propagation and synaptic transmission (Goldberg et al., 2005). $K_V$3.1 undergoes alternative splicing to generate two channel isoforms, AUT00206, a $K^+$-channel modulator, was recently found to modulate resting state electroencephalogram (EEG) recordings and psychiatric symptoms in patients with schizophrenia (Kaar et al., 2023). Loss-of-function variants in *KCNC1* ($K_V$3.1) have been associated with neurological disorders, including developmental delay, intellectual disability, and epilepsy (Supplementary Table S1, Fig. S5) (Cameron et al., 2019). A coding variant (R320H) in the voltage-sensing domain of $K_V$3.1 causes the progressive myoclonus epilepsy and ataxia (Carpenter et al., 2021). The diverse clinical features for *KCNC1* variants might indicate that they have multiple disease mechanisms (Oliver et al., 2017).

#### 4.2.6. *KCND3 ($K_V$4.3)*

Kv4.3 is encoded by the *KCND3* gene and expressed in the brain, smooth muscle, and the heart (Postma et al., 2000; Gutman et al., 2005). *KCND3* ($K_V$4.3) plays a role in action potential firing and neuronal excitability by mediating subthreshold-operating transient (A-type) $K^+$ currents (Nadal et al., 2001). $K_V$4.3 mutants are linked to spinocerebellar ataxia type 19 and 22 (SCA19/22) (Lee et al., 2012). Whole exome sequencing identified the heterozygous variant R419H that displayed a dominant increase in potassium current amplitudes and changes in voltage-dependent gating properties (Hsiao et al., 2021).

#### 4.2.7. *KCNA1($K_V$1.1)*

Coding variants in *KCNA1* ($K_V$1.1) are found in several human neurological diseases, including episodic ataxia type 1, episodic epilepsy, severe developmental and epileptic encephalopathy (Browne et al., 1994). Related to their role in renal magnesium reabsorption, mutations in the *KCNA1* are also associated with hypomagnesemia with myokymia and tetanic crises (Bianchi et al., 2020). For some of the mutations in *KCNA1* (Fig. 5), functional assays in human embryonic kidney cells have demonstrated loss of function (Tomlinson et al., 2013).

#### 4.2.8. *KCNH2($K_V$11.1)*

The human gene KCNH2 (Ether-à-go-go-Related Gene, hERG) encodes the pore-forming subunit protein called Kv11.1 which is essential for cardiac repolarization (Sanguinetti and Tristani-Firouzi, 2006). Kv11.1 also controls the electrical activity of neurons by delaying the repolarization phase. Dysregulation of the Kv11.1 channel have been associated with various neurological and cardiovascular disorders such as epilepsy, schizophrenia, and arrhythmias (Huffaker et al., 2009; Lubberding et al., 2022; Sanchez-Conde et al., 2022; Partemi et al., 2013; Zamorano-León et al., 2012, Sanguinetti and Tristani-Firouzi,

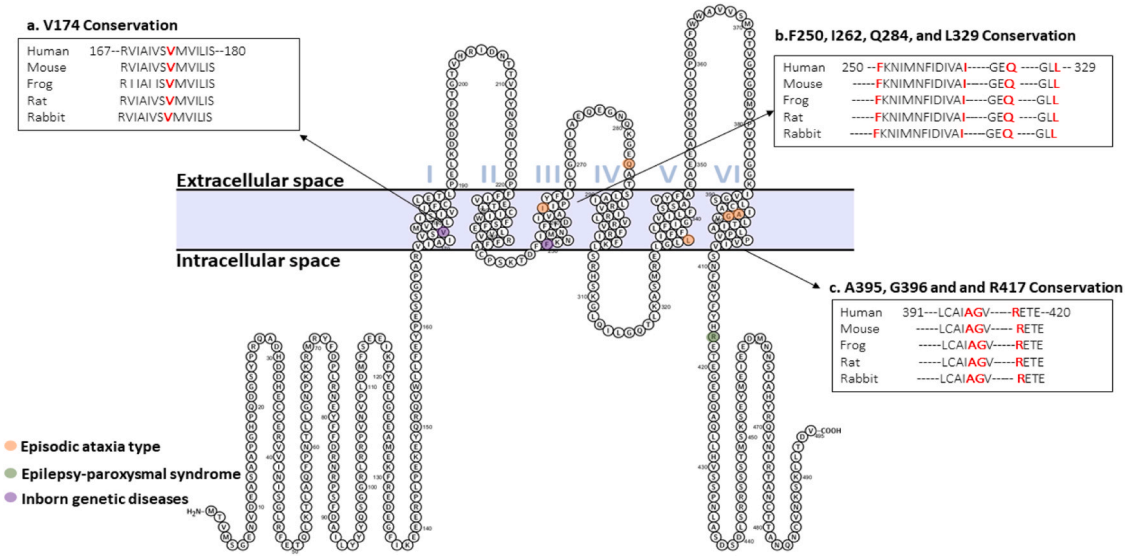


**Fig. 5.** The schematic diagram of KCNA1($K_V$1.1) shows pathogenic variant and their location in the protein. Amino acid residues are numbered according to human Kv1.1. a) The variant V174F is situated at the S1 TM, and all the pathogenic mutations are conserved among human, mouse, frog, rat, and rabbit species. b) and c) Residue conservation at the position of the indicated variants in different species and their location in the channel. The 2D diagram was generated by Protter (Omasits et al., 2014).

2006). Mutations in Kv11.1 are linked to long QT syndrome (LQTS) which is characterized by a prolongation of the repolarization phase of the cardiac action potential with increased risk of cardiac arrhythmias and sudden death (Dekker et al., 1994; Splawski et al., 2000). LQTS patients carrying Kv11.1 mutations may also have increased insulin secretion in pancreatic islets and decreased glucagon release (Engelbrechtsen et al., 2018). In addition, it appears that disease associated mutations in Kv11.1 also can impact on the trafficking of the protein to the plasma membrane (Anderson et al., 2014).

### *4.3. Obsessive-compulsive disorder (OCD) and other neuropsychiatric dysfunctions*

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by uncontrollable obsessive thoughts or an insurmountable urge to perform repetitive actions (American Psychiatric Association, 2013), with a lifetime prevalence of 2.5% (Weissman et al., 1994; Ruscio et al., 2010). Although OCD is highly polygenic and published GWAS studies have not identified genome wide significantly associated genetic markers, a link between OCD and insulin signaling has been suggested based on human GWAS studies, murine models, and epidemiological data. Analysis of GWAS studies in OCD, led van de Vondervoort and colleagues to identify a genetic signature that is enriched in genes of insulin and insulin-related signaling cascades (van de Vondervoort et al., 2016), which was also confirmed in murine models (van de Vondervoort et al., 2019). At the genetic level, it was reported that the genes *INS* (encoding insulin) and *IGF2*, are located on a region on chromosome 11p15, in a region previously identified by linkage analysis in families with OCD (Wang et al., 2009). Bralten et al., noted genetic correlations between OCD and obsessive-compulsive symptoms in the general population with the gene-set for insulin signaling in the central and peripheral nervous systems (Bralten et al., 2020) which confirmed a role for insulin signaling in cognitive flexibility established in preclinical models (van de Vondervoort et al., 2019). Together with analyses of GWAS data sets, *KCNQ1* was identified as a possible treatment target in OCD (van de Vondervoort et al., 2016). Possibly, the association between *KCNQ1* and OCD traits may occur via its regulation of pancreatic insulin release which reaches the brain, or via another CNS mechanism under the control of *KCNQ1*. In this regard, *KCNQ1* imprinting may be important as Beckwidth-Wiedemann syndrome, a disorder of *KCNQ1* imprinting, is associated with an increased incidence of diabetes and autistic-like traits (including increased compulsivity, a feature common to both autism and OCD) (Valente et al., 2019).

## 5. Pharmacology of $K^+$-channel directed drugs and their therapeutic targets

Due to their role in the regulation of neuronal excitability and cardiac rhythm, $K^+$-channels have long been considered promising drug targets on one side, but also risky in terms of potential side-effect profiles. For ligands targeting $K^+$-channels, it has generally been difficult to achieve satisfactory target selectivity and specificity. Off-target effects at other channels or receptors are frequent and dose dependent. Furthermore, different $K^+$-channels often have complex structures with multiple subunits, and lack of high-resolution channel structural data has made structure-based drug discovery difficult. Moreover, the expression of different $K^+$-channels within the same cell, coupled to frequent expression of multiple $K^+$-channel subtypes in the same tissue, makes drug development often challenging, but theoretically amenable to drug delivery approaches such as those offered through nanotechnology (Wulff, Castle, and Pardo, 2009). Modulation of potassium channels by activators or inhibitors could potentially influence a range of clinical conditions, including epilepsy, diabetes, atrial fibrillation, multiple sclerosis, Parkinson's disease, schizophrenia, and musculoskeletal disorders (Li, Zhang et al., 2021; Bajaj, Ong, and Chandy, 2020; Wulff, Castle, and Pardo, 2009; Grandi et al., 2017; Sturgess et al., 1988), but has so far been limited by their potential side effect profiles. As an example, activation of $K^+$-channels relaxes smooth muscles and reduces neuropathic pain (Weston and Edwards, 1992; Tian et al., 2014). In contrast, inhibition of the $K^+$-channel increases cell excitability and prolongs repolarization (Lenz and Hilleman, 2000) while also stimulating insulin secretion from pancreatic β-cells. The pharmacological potential of these compounds (Tables 1 and 2, Figs. 6–8) targeting voltage-gated potassium channel KCNQs and $K_{ir}$, an inward-rectifying potassium channel are described below.

### *5.1. KCNQ Activators*

The Kv7 activators, which are in different stages of development, are summarized in Fig. 6a. ML277 is a KCNQ1 specific activator which has

**Table 1**
Voltage-gated $K^+$-channel ($K_V7$ and $K_{ir}$) activators, development status, disease, human studies, and targets.

| Drug | Target channel | Disease (indication) | Human Studies (n) | Status | Reference |
|---|---|---|---|---|---|
| ML277 | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Mattmann et al., 2012) |
| L364373(R-L3) | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Salata et al., 1998) |
| Zinc pyrithione (ZnPy) | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Eid and Gurney, 2018) |
| Phenyl boronic acid | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Mruk and Kobertz, 2009) |
| Compound 41 | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Amato et al., 2011) |
| Retigabine | *KCNQ2*(KV7.2) | Epilepsy | 376 (NCT00310388) | FDA approved, 2011 (Discontinue, 2017) | (Epilepsy, 2016; Stafstrom, Grippon, and Kirkpatrick, 2011) |
| ML213 | *KCNQ2–5*(Kv7.2–7.5) | Epilepsy | Not tested | Investigative | (Seefeld et al., 2018) |
| ZTZ-240 | *KCNQ1–3*(Kv7.1–7.3) | Epilepsy | Not tested | Investigative | (Gao et al., 2010) |
| Compound 51 | *KCNQ2*($K_V7.2$)/ *KCNQ3*($K_V7.3$) | Epilepsy | Not tested | Preclinical | |
| ICA-27243 | *KCNQ2–5*(Kv7.2-Kv7.5) | Epilepsy | Not tested | Investigative | (Padilla et al., 2009) |
| Flupirtine | *KCNQ2–5*(Kv7.2-Kv7.5) | Epilepsy | 20 (NCT01450865) | Clinical Trial | (Szelenyi, 2013; Fleckenstein et al., 2013) |
| XEN1101 | *KCNQ* (Kv 7) | Epilepsy | 360 (NCT05614063) | Clinical Trial | (Bajaj, Ong, and Chandy, 2020) |
| Diazoxide | *KCNJ11*($K_{ir}6.2$) | Hypoglycemia, Type 1 diabetes | 12 (NCT01488136) | FDA approved, 1973 | (Edwards and Weston, 1993; Alexander et al., 2021; George et al., 2015) |
| Minoxidil | *KCNJ11*($K_{ir}6.2$) | Blood pressure | 558 (NCT00283686) | FDA approved, 1979 | (Edwards and Weston, 1993; Alexander et al., 2021; Schrier et al., 2014) |
| Bimakalim | *KCNJ11*($K_{ir}6.2$) | Arrhythmia, Hypertension | Not tested | Investigative | (Edwards and Weston, 1993) |
| Cromakalim | *KCNJ11*($K_{ir}6.2$) | Arrhythmia, Hypertension | Not tested | Investigative | (Edwards and Weston, 1993) |
| Aprikalim | *KCNJ11*($K_{ir}6.2$) | Arrhythmia, Hypertension | Not tested | Investigative | (Edwards and Weston, 1993) |
| BMS-180448 | *KCNJ11*($K_{ir}6.2$) | Ischaemic heart disorder | Not tested | Investigative | (Lawson, 2000; Lee et al., 2007) |
| BMS-182264 | *KCNJ11*($K_{ir}6.2$) | Ischaemic heart disorder | Not tested | Investigative | (Lawson, 2000) |
| Pinacidil | *KCNJ11*($K_{ir}6.2$) | Blood pressure | NA | FDA approved, 1989 (markering: discontinued) | (Lawson, 2000; Alexander et al., 2021) |
| Nicorandil | *KCNJ11*($K_{ir}6.2$) | Angina | 402 (NCT01396395) | Approved 2009 in UK | (Lawson, 2000; Alexander et al., 2021; Jiang et al., 2016) |

been identified by high-throughput screening (Mattmann et al., 2012). The binding affinity of ML277 (Fig. 7a) is 260 nM for KCNQ1, for which it has > 100-fold selectivity over KCNQ2 and KCNQ4 (Mattmann et al., 2012). ML277 enhances $I_{KS}$ (slow delayed rectifier potassium current), reduces the action potential (Hou et al., 2019; Xu et al., 2015; Willegems et al., 2022), and temporarily suppressed QT interval prolongation (van Bavel et al., 2023).

However, the properties and pharmacological sensitivity of KCNQ1 are affected by its binding to the auxiliary subunit KCNE1 (Yu et al., 2013). Another ligand R-L3 (L364373), is also reported to enhance channel activity, which is modified by KCNE1 subunit (Salata et al., 1998). Zinc pyrithione is another activator of the KCNQ channels identified by high-throughput screening and this compound can restore channel function (Xiong, Sun, and Li, 2007). Zinc pyrithione, however, is not selective across pharmacophores and also activates KCNQ4, and KCNQ5, besides KCNQ1 (Gao et al., 2008).

The KCNQ channel activator retigabine was originally developed by GlaxoSmithKline and Valent Pharmaceuticals and approved by FDA in 2011 as an antiepileptic agent (Stafstrom, Grippon, and Kirkpatrick, 2011). Retigabine activates KCNQ2-KCNQ5, augments the current, limits the neuronal excitability, and has anticonvulsant activity in seizure models (Blackburn-Munro et al., 2005; Humphries and Dart, 2015; Tatulian et al., 2001). Retigabine binds at the pore-helix of KCNQ2 (Fig. 7b) and activates the channel by allosteric modulation (Li, Zhang et al., 2021). XEN1101 is an analogue of retigabine, selective for KCNQ2/KCNQ3 potassium channel opener in the development stage for the treatment of epilepsy and major depressive disorder (MDD). XEN1101, developed by Xenon pharmaceuticals and is now in Phase 3 clinical trials (Bialer, M., Johannessen, S. I., Koepp, M. J., Levy, R. H., Perucca, E., Perucca, P., Tomson, T., & White, H. S., 2020; Premoli et al., 2019).

Flupirtine is a structural analogue of retigabine that works as a KCNQ channel opener with nonopioid features and is in use for chronic pain (Szelenyi, 2013). The compound activates KCNQ2–5, reduces excitatory postsynaptic firing frequency in neurons and exhibits analgesic activity in rat models (Sun and Kapur, 2012; Blackburn-Munro and Jensen, 2003).

ICA-27243, a benzanilide compound, also activates the KCNQ2–5 channels. The activity of this compound is pronounced in the hetero-multimeric channels KCNQ2/KCNQ3 compared to KCNQ3/KCNQ5. Anticonvulsant activity of ICA-27243 has been observed in a rodent seizure model (Wickenden et al., 2008; Padilla et al., 2009; Roeloffs et al., 2008). Another activator of KCNQ channels, Ztz-240, was identified by screening 20,000 compounds in a cell-based rubidium flux assay. Ztz-240 activates all KCNQ channels except KCNQ1 in a concentration dependent manner, increases the KCNQ2 outward current amplitude and delays its deactivation (Gao et al., 2010; Li et al., 2013). A recent comparison of cryo-electron microscopy (cryo-EM) structures of KCNQ2 with retigabine and with ztz-240 revealed different patterns of binding. Ztz-240 binds at the voltage sensing domain and coordinates stabilization of the channel while retigabine binds at the pore domain (Li, Zhang et al., 2021). These two ligands have slightly different ways of modulating channel functions, which may be relevant at different membrane potentials.

### 5.2. $K_{ir}$ Activators

A number of activators (Table 1) of $K_{ir}$ channels are in different

**Table 2**
Voltage-gated $K^+$-channel ($K_V7$ and Kir) Inhibitors, development status, disease, human studies, and targets.

| Drug | Target channel | Disease (indication) | Human studies (n) | Status | Reference |
|---|---|---|---|---|---|
| Chromanol 293B | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Gerlach et al., 2001) |
| Azimilide | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | NA | Clinical Trial (Dogs) | (Wulff, Castle, and Pardo, 2009; Nattel, Liu, and St-Georges, 1998) |
| Compound 19 S | *KCNQ1*($K_V7.1$)-*KCNE1* | LQTS, Arrhythmia | Not tested | Investigative | (Lloyd et al., 2001) |
| Compound 24 A | *KCNQ1*($K_V7.1$)-*KCNE1* | LQTS, Arrhythmia | Not tested | Investigative | (Lloyd et al., 2001) |
| Bepridil | *KCNQ1*, *KCNQ4*(Kv7.1, Kv7.4) | LQTS, Arrhythmia | NA | FDA approved 1990 as a calcium blocker | (Chouabe et al., 2000; Alexander et al., 2021) |
| MK-0448 | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Wolkenberg et al., 2017) |
| S-5557 | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Butcher et al., 2003) |
| L-365260 | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Towart et al., 2009) |
| JNJ-303 | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Towart et al., 2009) |
| BDBM50106236 | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Gerlach et al., 2001) |
| L-735821 | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Lynch et al., 1999) |
| ICA-15451 | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Coghlan, Carroll, and Gopalakrishnan, 2001) |
| DMP-543 | *KCNQ2–5*(Kv7.2-Kv7.5) | LQTS, Arrhythmia | Not tested | Investigative | (Zaczek et al., 1998) |
| XE-991 | *KCNQ1–2,4–5*(Kv7.1-Kv7.2, Kv7.4-Kv7.5) | LQTS, Arrhythmia | Not tested | Investigative | (Porter et al., 2019) |
| L-768673 | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Stump et al., 2003) |
| L-761710 | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Stump et al., 2003) |
| L-763540 | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Stump et al., 2003) |
| L-761334 | *KCNQ1*($K_V7.1$) | LQTS, Arrhythmia | Not tested | Investigative | (Stump et al., 2003) |
| Linopirdine | *KCNQ2–5*(Kv7.2-Kv7.5) | LQTS, Arrhythmia | Not tested | Investigative | |
| Chlorpropamide | *KCNJ11/ABCC8*($K_{ir}6.2$/SUR) | Type II diabetes | NA, NCT00004363 | FDA approved, 1958 | (Alexander et al., 2021) |
| Acetohexamide | *KCNJ11/ABCC8*($K_{ir}6.2$/SUR) | Type II diabetes | NA | FDA approved, 1964 | (Alexander et al., 2021) |
| Mitiglinide | *KCNJ11/ABCC8*($K_{ir}6.2$/SUR) | Type II diabetes | 367 (NCT00519142) | not yet Approved FDA, but in Japan | (Alexander et al., 2021) |
| Gliclazide (Diamicron) | *KCNJ11/ABCC8*($K_{ir}6.2$/SUR) | Type II diabetes | 357 (NCT01798706) | FDA approved, 1972 | (Bajaj, Ong, and Chandy, 2020) |
| Tolbutamide | *KCNJ11/ABCC8*($K_{ir}6.2$/SUR) | Type II diabetes | 12 (NCT05097716) | FDA approved, 1979 | (Isomoto et al., 1996; Alexander et al., 2021) |
| Glipizide | *KCNJ11/ABCC8*($K_{ir}6.2$/SUR) | Type II diabetes | 1000 (NCT01762046) | FDA approved, 1984 | (Alexander et al., 2021) |
| Glibenclamide | *KCNJ11/ABCC8*($K_{ir}6.2$/SUR) | Type II diabetes | 58 (NCT00232583) | FDA approved, 1984 | (Alexander et al., 2021) |
| Glisoxepide | *KCNJ11/ABCC8*($K_{ir}6.2$/SUR) | Type II diabetes | 1499650 (NCT02456428) | Clinical Trial | (Alexander et al., 2021) |
| Tolazamide | *KCNJ11/ABCC8*($K_{ir}6.2$/SUR) | Type II diabetes | 246 (NCT01068860) | FDA approved 1986 (marketing-Discontinued) | (Alexander et al., 2021) |
| Glimepiride | *KCNJ11/ABCC8*($K_{ir}6.2$/SUR) | Type II diabetes | 100 (NCT00353691) | FDA approved, 1995 | (Alexander et al., 2021) |
| Repaglinide | *KCNJ11/ABCC8*($K_{ir}6.2$/SUR) | Type II diabetes | 560 (NCT00399711) | FDA approved, 1997 | (Alexander et al., 2021) |
| Nateglinide | *KCNJ11/ABCC8*($K_{ir}6.2$/SUR) | Type II diabetes | 28 (NCT00402909) | FDA approved, 2001 | (Alexander et al., 2021) |
| Amifampridine | *KCNJ11/ABCC8*($K_{ir}6.2$/SUR) | Lambert-Eaton-myasthenic syndrome | 26 (NCT02970162) | FDA approved, 2019 | (Alexander et al., 2021) |

phases of clinical development and some of them are already FDA approved (Fig. 6b). Diazoxide, a $K_{ir}$ channel drug (FDA approved in 1973), stimulates the opening of $K_{ATP}$ channels, hyperpolarizes the membrane of pancreatic β-cells and inhibits insulin secretion (Dunne, Illot, and Peterson, 1987; Sturgess et al., 1988). It is used to reduce blood glucose concentrations and to treat hypertension and congenital hyperinsulinism (Hibino et al., 2010; van Hamersvelt et al., 1996). The first line of treatment for CHI is to avoid hypoglycemia with continuous enteral feeding with carbohydrate-enriched diet and glucose infusions in addition to precision medicine with the oral $K_{ATP}$ channel opener diazoxide (Arnoux et al., 2010). However, as diazoxide is not always effective, especially when the $K_{ATP}$ harbors pathogenic mutations (Bellanné-Chantelot et al., 2010), the somatostatin analog octreotide is the second option. In rare cases, the calcium-channel blocker nifedipine (Baş et al., 1999) or sirolimus (Maria et al., 2019) have been successfully tried. Like diazoxide, other $K_{ir}$ activators are potent, but their mechanism of action is restricted in a cell specific manner (Lawson, 2000).

### 5.3. KCNQ inhibitors

Theoretically, KCNQ inhibitors can be used to modify cardiac and neuronal action potentials and as such adjust heart rate and neuronal activity. However, there are still no KCNQ blockers on the market—some are in clinical development and others have failed due to serious side effects (Towart et al., 2009). Although the development of potent inhibitors targeting KCNQ is of great interest for the treatment of arrhythmia, their therapeutic utility in the nervous system remains unclear (Wulff, Castle, and Pardo, 2009). The compound XE991 and its structural analogue linopirdine both block KCNQ2 and KCNQ3 channels (Wang, H. S., Pan, Z., Shi, W., Brown, B. S., Wymore, R. S., Cohen, I. S., Dixon, J. E., & McKinnon, D., 1998). Chromaol-293B and HMR-1556 are $I_{KS}$ inhibitors, with different stereochemistry developed from the sulfonamide scaffold of the $K_{ATP}$ channel activator cromakalim (Gerlach et al., 2001; Hamilton, Weir, and Weston, 1986). Chromanol-293B exhibits higher potency against KCNQ1 ($IC_{50}$ = 120 nM) compared to other KCNQ 2–5 members and hERG channels in *Xenopus* oocytes (Lerche et al., 2007; Gerlach et al., 2001). Chromanol-293B prolongs cardiac action potentials in anaesthetized guinea pigs (Yang et al., 2004)

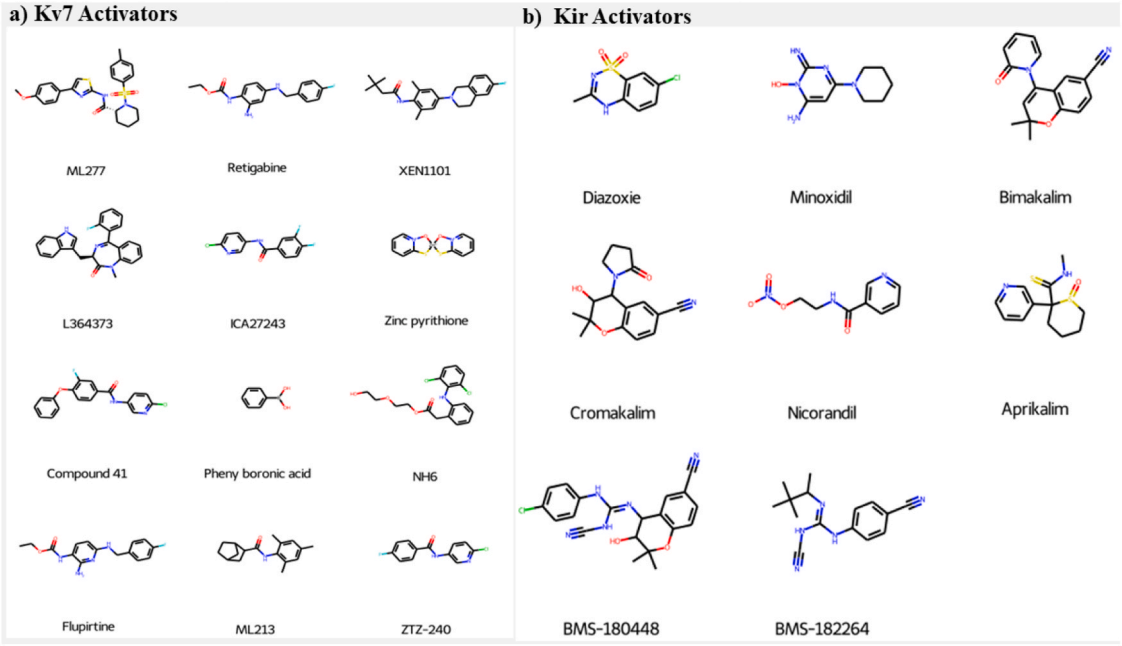


**Fig. 6.** The chemical structure of $K_V7$ and $K_{ir}$ activators. a) Activators of $K_V7$ that have been used in investigative and clinical studies in various stages. b) Structure of $K_{ir}$ activators that are FDA approved and in the clinical phase. The figures were generated using "RDKit: Open source chemoinformatics. https://www.rdkit.org".

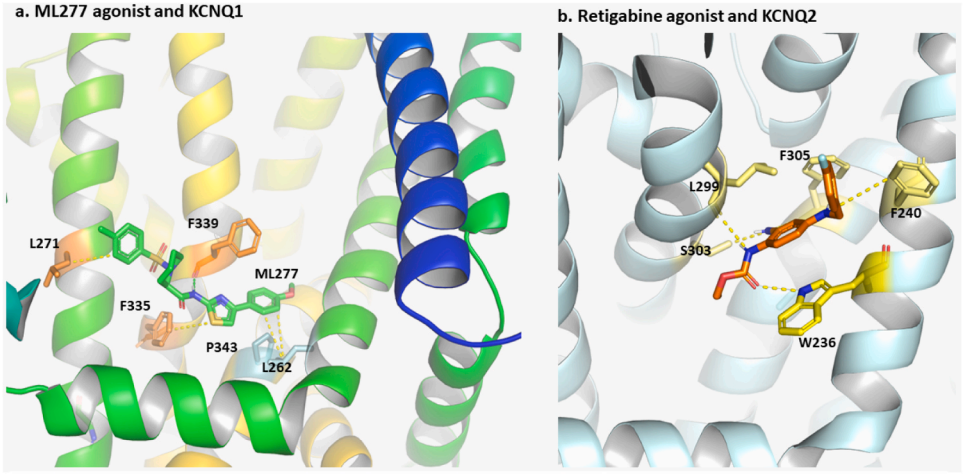


**Fig. 7.** The structure of complexes of ML277 (KCNQ1) and retigabine (KCNQ2) a.) ML277 is a potent agonist for KCNQ1. ML277 binds to KCNQ1 in an elbow manner (PDB ID: 7XNK) and interacts in a hydrophobic pocket, including the residues F335, F339, and L271 (orange). L262 and P343 also interact with the ligand. The residues L271, F335 and F339 are critical for ML277 binding as their mutation reduces the agonist effect (Ma et al., 2022). b.) Retigabine, binds to KCNQ2–5, but with weaker affinity than for KCNQ1. The structure of KCNQ2 with the agonist retigabine bound (PDB ID: 7CR2) reveals the pore binding mechanism. Retigabine aslo interacts with a hydrophobic environment including the residues W236, F240, F305, L299, and S303 (Li, Zhang et al., 2021).

and as such should be considered carefully regarding any potential side effects before investigating other medical uses.

A series of compounds with a benzodiazepine scaffold (L-735821, L-768673, L-365260, L-761334, L-763540, L-761710), developed by Eli Lilly, induced an increase in the ventricular refractory period and a decrease in the sinus heart rate in a canine model (Stump et al., 2003; Lynch et al., 1999). ICA-15451 is a 2-Fluorophenyl-4-fluorophenyl-phenylacetamide $I_{KS}$ blocker that inhibits the KCNQ1 current and has a binding affinity $IC_{50}$ of 2 μM for this $K^+$-channel (Coghlan, Carroll, and Gopalakrishnan, 2001). However, the compound showed ~ 200-fold selectivity for KCNN4 ($K_{Ca}3.1$) over KCNQ1 (Coghlan, Carroll, and Gopalakrishnan, 2001). Several other $I_{KS}$ inhibitors (listed in Table 2) are promising in the preclinical phase, but none have yet completed clinical trials.

### 5.4. $K_{ir}$ inhibitors

$K_{ir}6.2$ is an ATP-sensitive potassium channel consisting of a pore-forming subunit with a regulatory subunit, SUR. Blocking of the Kir channel activity leads to membrane depolarization and stimulates insulin secretion in pancreatic β-cells (Trapp, Tucker, and Ashcroft, 1997). Diabetes treatment has changed greatly over the last two decades as it was discovered that oral sulfonylurea, which acts specifically on the $K_{ATP}$ channel, could achieve better metabolic control than insulin injections (Sagen et al., 2004). Currently, high-dose glibenclamide (Fig. 8b), a second-generation sulfonylurea, is the first-choice treatment, being an effective and well-tolerated treatment in larger cohort studies (Pearson et al., 2006; Bowman et al., 2018) but to what extent this can treat DEND is still unclear. A concern is whether sulfonylurea can reach the brain in therapeutic doses since the drug is restricted by the blood-brain barrier and is also normally actively transported out of the brain (Lahmann, Kramer, and Ashcroft, 2015). Due to this uncertainty, early, high-dose sulfonylurea is still the recommended treatment as a neuroprotective measure (Hattersley, Greeley, Polak, Rubio-Cabezas, Njolstad et al., 2018). Early intervention may be more effective in targeting the brain as the blood-brain-barrier might be more permeable in the post-natal period, but the effect on early intervention is still not established. In a recent publication, sulfonylurea therapy was effective

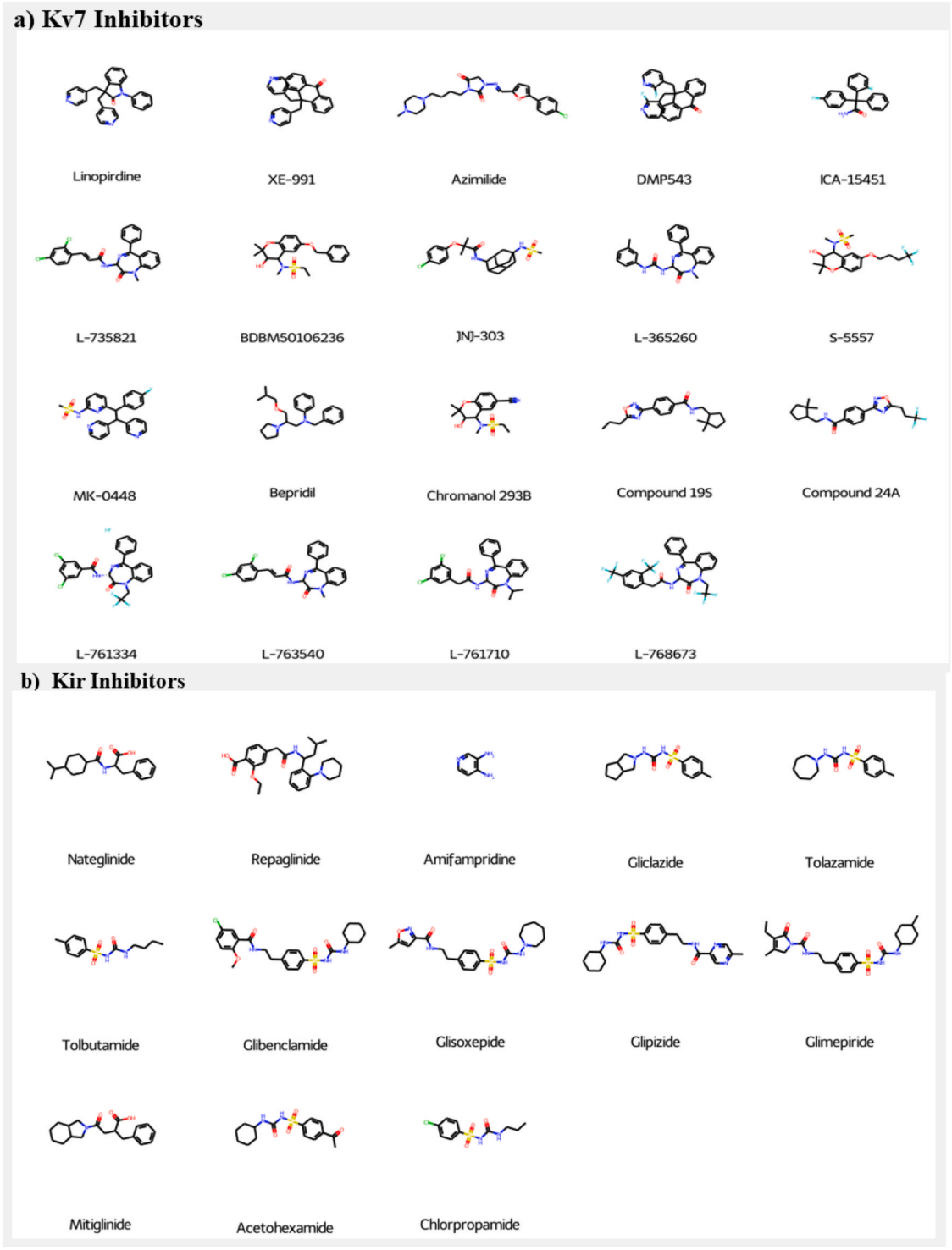


**Fig. 8.** Inhibitors of $K_V7$ and $K_{ir}$ with chemical structure. a) Kv7 inhibitors developed by industry and academia. L-768673 which showed promising results against Kv7.1 but it has off-target activity against $K_V11.1$(hERG). b) $K_{ir}$ inhibitors with chemical structure that are FDA approved except Mitiglinide which is approved in Japan. i The figures were generated using "RDKit: Open source chemoinformatics. https://www.rdkit.org".

and tolerated even before term in a premature *KCNJ11* carrier (Walton-Betancourth et al., 2022). It has been proposed that inhibition of overactive neuronal $K_{ATP}$ channels could mediate the therapeutic effect, as these ion channels are composed mainly of $K_{ir}6.2$/SUR1 isoforms, and are sensitive to sulfonylurea (Koster et al., 2008). Several case reports have claimed that sulfonylurea treatment improves motor functions (Oka et al., 2014; Mlynarski et al., 2007; Mohamadi et al., 2010; Slingerland et al., 2006), supported by the observation of increased cerebellar perfusion in one study (Mlynarski et al., 2007). However, two other larger multi-center studies following 115 *KCNJ11/ABCC8* carriers for more than ten years, revealed persistent CNS pathology and neuropsychiatric comorbidity in most of the patients (Bowman et al., 2018; Bowman et al., 2021). Interestingly, glibenclamide has also been shown to ameliorate Alzheimer's pathology indirectly through the neurovascular $K_{ATP}$ channels (Macauley et al., 2021).

## 6. Challenges and future outlook

$K^+$-channels are important for regulating neuronal excitability, hormone secretion, and neurotransmitter release (Abbott and Goldstein, 2001; Miller, 2000). $K^+$-channels can be homomeric or heteromeric, with functions modulated through interaction with different partner proteins and small molecules; for example, KCNQ channel functions are regulated by KCNE, phosphatidylinositol 4, 5-bisphosphate (PIP2) and calmodulin. Understanding their biological function and the effect of mutations is still challenging as the channel function is also dependent on the location and coupling to partner proteins. As detailed above, mutations in these channels have been linked to dysregulation and various diseases. With the application of next-generation sequencing, there has been a dramatic increase in information regarding the functional consequences of potassium channel mutations. Mutations in $K^+$-channels have been observed in different locations from transmembrane to extracellular and cytoplasmic domains (S1-S6). Many $K^+$-channel structures are available, but most are still at low resolution and detailed X-ray crystallography, or high-resolution cryo-EM studies are still missing for most channels and their ligand complexes.

Pharmacological targeting of $K^+$-channels remains challenging, partially due to their critical physiological functions and risk of serious side effects. Ligand-based drug discovery and virtual screening programs are gradually emerging, but progress has been hampered by the shortage of high-resolution ligand-bound channel structures. However, recently published cryo-EM structures of channel complexes with ML277 and Retigabine, two agonists for modulating KCNQ function, may pave the way for future structure and ligand-based drug discovery targeting these proteins (Li, Zhang et al., 2021; Willegems et al., 2022). There is no antagonist-bound KCNQ structure available except linopirdine with KCNQ4 (Li, Wu et al., 2021).

## 7. Conclusion

Here, we have reviewed the function and regulation of the human $K^+$-channel families. Establishing causality in relation to $K^+$-channel functions in somatic and behavioural brain disorders is difficult especially given that many conditions are polygenic in nature and the $K^+$ related changes may be only one factor contributing to the phenotypes. Moreover, many expression profiling studies either on the transcriptome or proteome level in these behavioural brain disorders do not establish causal relationships but simply report patterns of up-/down-regulated expression. With the exception of certain (rare) monogenetic diseases and where loss/gain of function studies of a particular $K^+$ channel have been performed in animal models, it is difficult to establish the direction of causality. Where known, we have reported this, but we anticipate that it will be a focus on the next wave of research to examine these causal relationships more thoroughly, something which may be easier to establish in model systems.

We have summarized the involvement of these channels in diseases such as cardiac arrhythmias, diabetes, CHI, ataxia, epilepsy, and various neuropsychiatric conditions which may involve some common pathophysiological mechanisms. Recent progress in molecular genetics and pharmacology has improved our understanding of $K^+$-channel functions and channelopathies. So far, development of new drugs targeting $K^+$-channels has been challenging due to lack of specificity and off-target effects. With the introduction of new computational and experimental techniques in pharmacology and structural biology (e.g. genetic cell and animal models, machine learning protein folding algorithms and cryo-EM), we expect that structural and functional insights into these important drug targets will rapidly increase in the coming years, also paving the way for fundamentally new drugs targeting these channels.

## Conflicts of interest

The authors have no conflict of interest to disclose.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105301.

## References

Abbott, G.W., Goldstein, S.A., 2001. Potassium channel subunits encoded by the KCNE gene family: physiology and pathophysiology of the MinK-related peptides (MiRPs). Mol. Inter. 1, 95–107.

Alexander, S.P., Mathie, A., Peters, J.A., Veale, E.L., Striessnig, J., Kelly, E., Armstrong, J. F., Faccenda, E., Harding, S.D., Pawson, A.J., Southan, C., Davies, J.A., Aldrich, R. W., Attali, B., Baggetta, A.M., Becirovic, E., Biel, M., Bill, R.M., Catterall, W.A., Conner, A.C., Davies, P., Pawson, M., Virgilio, F.D., Falzoni, S., Fenske, S., George, C., Goldstein, S.A.N., Grissmer, S., Ha, K., Hammelmann, V., Hanukoglu, I., Jarvis, M., Jensen, A.A., Kaczmarek, L.K., Kellenberger, S., Kennedy, C., King, B., Kitchen, P., Lynch, J.W., Perez-Reyes, E., Plant, L.D., Rash, L., Ren, D., Salman, M. M., Sivilotti, L.G., Smart, T.G., Snutch, T.P., Tian, J., Trimmer, J.S., Van den Eynde, C., Vriens, J., Wei, A.D., Winn, B.T., Wulff, H., Xu, H., Yue, L., Zhang, X., Zhu, M., 2021. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: ion channels. Br. J. Pharm. 178 (Suppl 1), S157–S245.

Algra, A., Tijssen, J.G., Roelandt, J.R., Pool, J., Lubsen, J., 1993. QT interval variables from 24 h electrocardiography and the two year risk of sudden death. Br. Heart J. 70, 43.

Allen, N.M., Mannion, M., Conroy, J., Lynch, S.A., Shahwan, A., Lynch, B., King, M.D., 2014. The variable phenotypes of KCNQ-related epilepsy. Epilepsia 55, e99–e105.

Amaratunga, S.A., Tayeb, T.H., Dusatkova, P., Pruhova, S., Lebl, J., 2022. Invaluable role of consanguinity in providing insight into paediatric endocrine conditions: lessons learnt from congenital hyperinsulinism, monogenic diabetes, and short stature. Horm. Res Paediatr. 95, 1–11.

Amato, G., Roeloffs, R., Rigdon, G.C., Antonio, B., Mersch, T., McNaughton-Smith, G., Wickenden, A.D., Fritch, P., Suto, M.J., 2011. N-pyridyl and pyrimidine benzamides as KCNQ2/Q3 potassium channel openers for the treatment of epilepsy. Acs Med. Chem. Lett. 2, 481–484.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013American Psychiatric Association, D, and American Psychiatric Association. 2013. Diagnostic and statistical manual of mental disorders: DSM-5 (American psychiatric association Washington, DC).

Anderson, C.L., Kuzmicki, C.E., Childs, R.R., Hintz, C.J., Delisle, B.P., C. T, 2014. Large-scale mutational analysis of Kv11.1 reveals molecular insights into type 2 long QT syndrome. Nat. Commun. 5.

Ao, D., Wang, H.J., Wang, L.F., Song, J.Y., Yang, H.X., Wang, Y., 2015. The rs2237892 polymorphism in KCNQ1 influences gestational diabetes mellitus and glucose levels: a case-control study and meta-analysis. PLoS One 10, e0128901.

Arnoux, J.B., de Lonlay, P., Ribeiro, M.J., Hussain, K., Blankenstein, O., Mohnike, K., Valayannopoulos, V., Robert, J.J., Rahier, J., Sempoux, C., Bellanne, C., Verkarre, V., Aigrain, Y., Jaubert, F., Brunelle, F., Nihoul-Fekete, C., 2010. Congenital hyperinsulinism. Early Hum. Dev. 86, 287–294.

Asahara, S., Etoh, H., Inoue, H., Teruyama, K., Shibutani, Y., Ihara, Y., Kawada, Y., Bartolome, A., Hashimoto, N., Matsuda, T., Koyanagi-Kimura, M., Kanno, A., Hirota, Y., Hosooka, T., Nagashima, K., Nishimura, W., Inoue, H., Matsumoto, M., Higgins, M.J., Yasuda, K., Inagaki, N., Seino, S., Kasuga, M., Kido, Y., 2015. Paternal allelic mutation at the Kcnq1 locus reduces pancreatic β-cell mass by epigenetic modification of Cdkn1c. Proc. Natl. Acad. Sci. USA 112, 8332–8337.

Ashcroft, F.M., 2005. ATP-sensitive potassium channelopathies: focus on insulin secretion. J. Clin. Invest 115, 2047–2058.

Ashcroft, F.M., Gribble, F.M., 2000. Tissue-specific effects of sulfonylureas lessons from studies of cloned K-ATP channels'. J. Diabetes Its Complicat. 14, 192–196.

Ashcroft, F.M., Harrison, D.E., Ashcroft, S.J.H., 1984. Glucose induces closure of single potassium channels in isolated rat pancreatic beta-cells. Nature 312, 446–448.

Bahia, P.K., Suzuki, R., Benton, D.C., Jowett, A.J., Chen, M.X., Trezise, D.J., Dickenson, A.H., Moss, G.W., 2005. A functional role for small-conductance calcium-

activated potassium channels in sensory pathways including nociceptive processes. J. Neurosci.: Off. J. Soc. Neurosci. 25, 3489–3498.
Bajaj, S., Ong, S.T., Chandy, K.G., 2020. Contributions of natural products to ion channel pharmacology. Nat. Prod. Rep. 37, 703–716.
Bar, C., Barcia, G., Jennesson, M., Le Guyader, G., Schneider, A., Mignot, C., Lesca, G., Breuillard, D., Montomoli, M., Keren, B., Doummar, D., Billette de Villemeur, T., Afenjar, A., Marey, I., Gerard, M., Isnard, H., Poisson, A., Dupont, S., Berquin, P., Meyer, P., Genevieve, D., De Saint Martin, A., Poisson, S., Chelly, J., Guët, A., Scalais, E., Dorison, N., Myers, C.T., Mefford, H.C., Howell, K.B., Marini, C., Freeman, J.L., Nica, A., Terrone, G., Sekhara, T., Lebre, A.S., Odent, S., Sadleir, L.G., Munnich, A., Guerrini, R., Scheffer, I.E., Kabashi, E., Nabbout, R., 2020. Expanding the genetic and phenotypic relevance of KCNB1 variants in developmental and epileptic encephalopathies: 27 new patients and overview of the literature. Hum. Mutat. 41, 69–80.
Bar, C., Kuchenbuch, M., Barcia, G., Schneider, A., Jennesson, M., Le Guyader, G., Lesca, G., Mignot, C., Montomoli, M., Parrini, E., Isnard, H., Rolland, A., Keren, B., Afenjar, A., Dorison, N., Sadleir, L.G., Breuillard, D., Levy, R., Rio, M., Dupont, S., Negrin, S., Danieli, A., Scalais, E., De Saint Martin, A., El Chehadeh, S., Chelly, J., Poisson, A., Lebre, A.S., Nica, A., Odent, S., Sekhara, T., Brankovic, V., Goldenberg, A., Vrielynck, P., Lederer, D., Maurey, H., Terrone, G., Besmond, C., Hubert, L., Berquin, P., Billette de Villemeur, T., Isidor, B., Freeman, J.L., Mefford, H. C., Myers, C.T., Howell, K.B., Rodríguez-Sacristán Cascajo, A., Meyer, P., Genevieve, D., Guët, A., Doummar, D., Durigneux, J., van Dooren, M.F., de Wit, M.C. Y., Gerard, M., Marey, I., Munnich, A., Guerrini, R., Scheffer, I.E., Kabashi, E., Nabbout, R., 2020b. Developmental and epilepsy spectrum of KCNB1 encephalopathy with long-term outcome. Epilepsia 61, 2461–2473.
Baş, F., Darendeliler, F., Demirkol, D., Bundak, R., Saka, N., Günöz, H., 1999. Successful therapy with calcium channel blocker (nifedipine) in persistent neonatal hyperinsulinemic hypoglycemia of infancy. J. Pedia Endocrinol. Metab. 12, 873–878.
Bean, B.P., 2007. The action potential in mammalian central neurons. Nat. Rev. Neurosci. 8, 451–465.
Bellanné-Chantelot, C., Saint-Martin, C., Ribeiro, M.J., Vaury, C., Verkarre, V., Arnoux, J. B., Valayannopoulos, V., Gobrecht, S., Sempoux, C., Rahier, J., Fournet, J.C., Jaubert, F., Aigrain, Y., Nihoul-Fékété, C., de Lonlay, P., 2010. 'ABCC8 and KCNJ11 molecular spectrum of 109 patients with diazoxide-unresponsive congenital hyperinsulinism. J. Med Genet 47, 752–759.
Beltrand, J., Elie, C., Busiah, K., Fournier, E., Boddaert, N., Bahi-Buisson, N., Vera, M., Bui-Quoc, E., Ingster-Moati, I., Berdugo, M., Simon, A., Gozalo, C., Djerada, Z., Flechtner, I., Treluyer, J.M., Scharfmann, R., Cave, H., Vaivre-Douret, L., Polak, M., GlidKir Study Grp, 2015. Sulfonylurea therapy benefits neurological and psychomotor functions in patients with neonatal diabetes owing to potassium channel mutations. Diabetes Care 38, 2033–2041.
Berkefeld, H., Fakler, B., Schulte, U., 2010. Ca2+-activated K+ channels: from protein complexes to function. Physiol. Rev. 90, 1437–1459.
Bhattacharjee, A., Kaczmarek, L.K., 2005. For K+ channels, Na+ is the new Ca2+. Trends Neurosci. 28, 422–428.
Bialer, M., Johannessen, S. I., Koepp, M. J., Levy, R. H., Perucca, E., Perucca, P., Tomson, T., & White, H. S., 2020. Progress report on new antiepileptic drugs: a summary of the Fifteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XV). I. Drugs in preclinical and early clinical development. Epilepsia 61, 2340–2364.
Bianchi, F., Simoncini, C., Brugnoni, R., Ricci, G., Siciliano, G., 2020. Neuromuscular tetanic hyperexcitability syndrome associated to a heterozygous Kv1.1 N255D mutation with normal serum magnesium levels. Acta Myol. 39, 36–39.
Biervert, C., Schroeder, B.C., Kubisch, C., Berkovic, S.F., Propping, P., Jentsch, T.J., Steinlein, O.K., 1998. A potassium channel mutation in neonatal human epilepsy. Science 279, 403–406.
Bishop, H.I., Guan, D., Bocksteins, E., Parajuli, L.K., Murray, K.D., Cobb, M.M., Misonou, H., Zito, K., Foehring, R.C., Trimmer, J.S., 2015. Istinct cell- and layer-specific expression patterns and independent regulation of Kv2 channel subtypes in cortical pyramidal neurons. J. Neurosci.: Off. J. Soc. Neurosci. 35, 14922–14942.
Blackburn-Munro, G., Jensen, B.S., 2003. The anticonvulsant retigabine attenuates nociceptive behaviours in rat models of persistent and neuropathic pain. Eur. J. Pharmacol. 460, 109–116.
Blackburn-Munro, G., Dalby-Brown, W., Mirza, N.R., Mikkelsen, J.D., Blackburn-Munro, R.E., 2005. Retigabine: chemical synthesis to clinical application. CNS Drug Rev. 11, 1–20.
Borlot, F., Abushama, A., Morrison-Levy, N., Jain, P., Puthenveettil Vinayan, K., Abukhalid, M., Aldhalaan, H.M., Almuzaini, H.S., Gulati, S., Hershkovitz, T., Konanki, R., Lingappa, L., Luat, A.F., Shafi, S., Tabarki, B., Thomas, M., Yoganathan, S., Alfadhel, M., Arya, R., Donner, E.J., Ehaideb, S.N., Gowda, V.K., Jain, V., Madaan, P., Myers, K.A., Otsubo, H., Panda, P., Sahu, J.K., Sampaio, L.P.B., Sharma, S., Simard-Tremblay, E., Zak, M., Robyn, W., 2020. KCNT1-related epilepsy: an international multicenter cohort of 27 pediatric cases. Epilepsia 61, 679–692.
Bowman, P., Hattersley, A.T., Knight, B.A., Broadbridge, E., Pettit, L., Reville, M., Flanagan, S.E., Shepherd, M.H., Ford, T.J., Tonks, J., 2017. Neuropsychological impairments in children with KCNJ11 neonatal diabetes. Diabet. Med. 34, 1171–1173.
Bowman, P., Sulen, A., Barbetti, F., Beltrand, J., Svalastoga, P., Codner, E., Tessmann, E. H., Juliusson, P.B., Skrivarhaug, T., Pearson, E.R., Flanagan, S.E., Babiker, T., Thomas, N.J., Shepherd, M.H., Ellard, S., Klimes, I., Szopa, M., Polak, M., Iafusco, D., Hattersley, A.T., Njolstad, P.R., Group Neonatal Diabetes International Collaborative, 2018. Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. Lancet Diabetes Endocrinol. 6, 637–646.
Bowman, P., Day, J., Torrens, L., Shepherd, M.H., Knight, B.A., Ford, T.J., Flanagan, S.E., Chakera, A., Hattersley, A.T., Zeman, A., 2019. Cognitive, Neurological, and behavioral features in adults With KCNJ11 neonatal diabetes. Diabetes Care 42, 215–224.
Bowman, P., Shepherd, M.H., Barbetti, F., Mathews, F., Rawlins, E., Sanchez, J., Ellard, S., Flanagan, S.E., Hattersley, A.T., Neonatal Diabet Int Collaboration, 2020. 'Ten-year follow-up of an international series of patients with permanent neonatal diabetes due to ABCC8 mutations shows excellent long-term glycaemic response to sulphonylureas and high frequency of neurological features. Diabet. Med. 37.
Bowman, P., Mathews, F., Barbetti, F., Shepherd, M.H., Sanchez, J., Piccini, B., Beltrand, J., Letourneau-Freiberg, L.R., Polak, M., Greeley, S.A.W., Rawlins, E., Babiker, T., Thomas, N.J., De Franco, E., Ellard, S., Flanagan, S.E., Hattersley, A.T., 2021. Long-term follow-up of glycemic and neurological outcomes in an international series of patients with sulfonylurea-treated abcc8 permanent neonatal diabetes. Diabetes Care 44 (1), 35–42.
Bralten, J., Widomska, J., Witte, W., Yu, D., Mathews, C.A., Scharf, J.M., Buitelaar, J., Crosbie, J., Schachar, R., Arnold, P., Lemire, M., Burton, C.L., Franke, B., Poelmans, G., 2020. Shared genetic etiology between obsessive-compulsive disorder, obsessive-compulsive symptoms in the population, and insulin signaling. Transl. Psychiatry 10, 121.
Brohawn, S.G., del Marmol, J., MacKinnon, R., 2012. Crystal structure of the human K2P TRAAK, a lipid- and mechano-sensitive K+ ion channel. Science 335, 436–441.
Browne, D.L., Gancher, S.T., Nutt, J.G., Brunt, E.R., Smith, E.A., Kramer, P., Litt, M., 1994. Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA1. Nat. Genet. 8, 136–140.
Busiah, K., Drunat, S., Vaivre-Douret, L., 2013. Neuropsychological dysfunction and developmental defects associated with genetic changes in infants with neonatal diabetes mellitus: a prospective cohort study. Lancet Diabetes Endocrinol. vol 1, 199.
Butcher, J.W., Liverton, N.J., Claremon, D.A., Freidinger, R.M., Jurkiewicz, N.K., Lynch, J.J., Salata, J.J., Wang, J., Dieckhaus, C.M., Slaughter, D.E., Vyas, K., 2003. Novel 5-cyclopropyl-1,4-benzodiazepin-2-ones as potent and selective I(Ks)-blocking class III antiarrhythmic agents. Bioorg. Med. Chem. Lett. 13, 1165–1168.
Cameron, J.M., Maljevic, S., Nair, U., Aung, Y.H., Cogné, B., Bézieau, S., Blair, E., Isidor, B., Zweier, C., Reis, A., Koenig, M.K., Maarup, T., Sarco, D., Afenjar, A., Huq, Ahmm, Kukolich, M., Billette de Villemeur, T., Nava, C., Héron, B., Petrou, S., Berkovic, S.F., 2019. Encephalopathies with KCNC1 variants: genotype-phenotype-functional correlations. Ann. Clin. Transl. Neurol. 6, 1263–1272.
Carmody, D., Pastore, A.N., Landmeier, K.A., Letourneau, L.R., Martin, R., Hwang, J.L., Naylor, R.N., Hunter, S.J., Msall, M.E., Philipson, L.H., Scott, M.N., Greeley, S.A.W., 2016. Patients with KCNJ11-related diabetes frequently have neuropsychological impairments compared with sibling controls. Diabet. Med. 33, 1380–1386.
Carpenter, J.C., Mannikko, R., Heffner, C., Heneine, J., Sampedro-Castaneda, M., Lignani, G., Schorge, S., 2021. 'Progressive myoclonus epilepsy KCNC1 variant causes a developmental dendritopathy. Epilepsia 62, 1256–1267.
Charlier, C., Singh, N.A., Ryan, S.G., Lewis, T.B., Reus, B.E., Leach, R.J., Leppert, M, 1998. A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. Nat. Genet. 18, 53–55.
Chen, X., Feng, Y., Quinn, R.J., Pountney, D.L., Richardson, D.R., Mellick, G.D., Ma, L., 2023. Potassium channels in Parkinson's disease: potential roles in its pathogenesis and innovative molecular targets for treatment. Pharm. Rev. 75, 758–788.
Chiou, J., Zeng, C., Cheng, Z., Han, J.Y., Schlichting, M., Miller, M., Mendez, R., Huang, S., Wang, J., Sui, Y., Deogaygay, A., Okino, M.L., Qiu, Y., Sun, Y., Kudtarkar, P., Fang, R., Preissl, S., Sander, M., Gorkin, D.U., Gaulton, K.J., 2021. Single-cell chromatin accessibility identifies pancreatic islet cell type– and state-specific regulatory programs of diabetes risk. Nat. Genet. 53, 455–466.
Choe, S., 2002. Potassium channel structures. Nat. Rev. Neurosci. 3, 115–121.
Choi, J.H., Kim, M.S., 2022. Homeostatic regulation of glucose metabolism by the central nervous system. Endocrinol. Metab. 37, 9–25.
Chouabe, C., Drici, M.D., Romey, G., Barhanin, J., 2000. Effects of calcium channel blockers on cloned cardiac K+ channels IKr and IKs. Therapie 55, 195–202.
Clark, R.H., McTaggart, J.S., Webster, R., Mannikko, R., Iberl, M., Sim, X.L., Rorsman, P., Glitsch, M., Beeson, D., Ashcroft, F.M., 2010. 'Muscle dysfunction caused by a KATP channel mutation in neonatal diabetes is neuronal in origin'. Science 329, 458–461.
Coetzee, W.A., Amarillo, Y., Chiu, J., Chow, A., Lau, D., McCormack, T., Moreno, H., Nadal, M.S., Ozaita, A., Pountney, D., Saganich, M., Vega-Saenz de Miera, E., Rudy, B., 1999. Molecular diversity of K+ channels. Ann. N. Y Acad. Sci. 868, 233–285.
Coghlan, M.J., Carroll, W.A., Gopalakrishnan, M., 2001. Recent developments in the biology and medicinal chemistry of potassium channel modulators: Update from a decade of progress. J. Med. Chem. 44, 1627–1653.
Cosgrove, K.E., Shepherd, R.M., Fernandez, E.M., Natarajan, A., Lindley, K.J., Aynsley-Green, A., Dunne, M.J., 2004. Genetics and pathophysiology of hyperinsulinism in infancy. Horm. Res. 61 (6), 270–288.
Cresto, J.C., Abdenur, J.P., Bergada, I., Martino, R., 1998. Long-term follow up of persistent hyperinsulinaemic hypoglycaemia of infancy. Arch. Dis. Child 79, 440–444.
De Franco, E., Saint-Martin, C., Brusgaard, K., Knight Johnson, A.E., Aguilar-Bryan, L., Bowman, P., Arnoux, J.B., Larsen, A.R., Sanyoura, M., Greeley, S.A.W., Calzada-Leon, R., Harman, B., Houghton, J.A.L., Nishimura-Meguro, E., Laver, T.W., Ellard, S., Del Gaudio, D., Christesen, H.T., Bellanne-Chantelot, C., Flanagan, S.E., 2020. Update of variants identified in the pancreatic beta-cell KATP channel genes KCNJ11 and ABCC8 in individuals with congenital hyperinsulinism and diabetes. Hum. Mutat. 41, 884–905.
del Camino, D., Yellen, G., 2001. Tight steric closure at the intracellular activation gate of a voltage-gated K(+) channel. Neuron 32, 649–656.

del Camino, D., Kanevsky, M., Yellen, G., 2005. Status of the intracellular gate in the activated-not-open state of shaker K+ channels. J. Gen. Physiol. 126, 419–428.
Demirbilek, H., Hussain, K., 2017. Congenital hyperinsulinism: diagnosis and treatment update. J. Clin. Res Pedia Endocrinol. 9, 69–87.
Descamps, J., Ruello, C., Perge, K., de Bellescize, J., Saint-Martin, C., Nicolino, M., 2021. Epileptic phenotype in late-onset hyperinsulinemic hypoglycemia successfully treated by diazoxide. J. Pedia Endocrinol. Metab. 34, 667–673.
Devaux, J.é., Abidi, A., Roubertie, A., Molinari, F., Becq, H.é., Lacoste, C., Villard, L., Milh, M., Anikstejn, L., 2016. A Kv7.2 mutation associated with early onset epileptic encephalopathy with suppression-burst enhances Kv7/M channel activity. Epilepsia 57, e87–e93.
Dunne, M.J., Illot, M.C., Peterson, O.H., 1987. Interaction of diazoxide, tolbutamide and ATP4- on nucleotide-dependent K+ channels in an insulin-secreting cell line. J. Membr. Biol. 99, 215–224.
Edwards, G., Weston, A.H., 1993. The pharmacology of ATP-sensitive potassium channels. Annu Rev. Pharm. Toxicol. 33, 597–637.
Eid, B.G., Gurney, A.M., 2018. Zinc pyrithione activates K+ channels and hyperpolarizes the membrane of rat pulmonary artery smooth muscle cells. PLoS One 13, e0192699.
Engelbrechtsen, L., Mahendran, Y., Jonsson, A., Gjesing, A.P., Weeke, P.E., Jørgensen, M. E., Færch, K., Witte, D.R., Holst, J.J., Jørgensen, T., Grarup, N., Pedersen, O., Vestergaard, H., Torekov, S., Kanters, J.K., Hansen, T., 2018. Common variants in the hERG (KCNH2) voltage-gated potassium channel are associated with altered fasting and glucose-stimulated plasma incretin and glucagon responses. BMC Genet 19, 15.
Epilepsy, 2016. Epilepsy drug Trobalt (retigabine) to be discontinued. Epilepsy Soc.
Fatima, S.S., Chaudhry, B., Khan, T.A., Farooq, S., 2016. KCNQ1 rs2237895 polymorphism is associated with Gestational Diabetes in Pakistani Women. Pak. J. Med Sci. 32, 1380–1385.
Fernández-Marmiesse, A., Salas, A., Vega, A., Fernández-Lorenzo, J.R., Barreiro, J., Carracedo, A., 2006. Mutation spectra of ABCC8 gene in Spanish patients with Hyperinsulinism of Infancy (HI). Hum. Mutat. 27, 214.
Ferrer, J., Nichols, C.G., Makhina, E.N., Salkoff, L., Bernstein, J., Gerhard, D., Wasson, J., Ramanadham, S., Permutt, A., 1995. Pancreatic islet cells express a family of inwardly rectifying K+ channel subunits which interact to form G-protein-activated channels. J. Biol. Chem. 270, 26086–26091.
Flanagan, S.E., Kapoor, R.R., Mali, G., Cody, D., Murphy, N., Schwahn, B., Siahanidou, T., Banerjee, I., Akcay, T., Rubio-Cabezas, O., Shield, J.P., Hussain, K., Ellard, S., 2010. Diazoxide-responsive hyperinsulinemic hypoglycemia caused by HNF4A gene mutations. Eur. J. Endocrinol. 162, 987–992.
Fleckenstein, J., Sittl, R., Averbeck, B., Lang, P.M., Irnich, D., Carr, R.W., 2013. Activation of axonal Kv7 channels in human peripheral nerve by flupirtine but not placebo - therapeutic potential for peripheral neuropathies: results of a randomised controlled trial. J. Transl. Med 11, 34.
Gao, Z.B., Xiong, Q.J., Sun, H.Y., Li, M., 2008. Desensitization of chemical activation by auxiliary subunits - convergence of molecular determinants critical for augmenting KCNQ1 potassium channels. J. Biol. Chem. 283, 22649–22658.
Gao, Z.B., Zhang, T.Z., Wu, M., Xiong, Q.J., Sun, H.Y., Zhang, Y.A., Zu, L.S., Wang, W., Li, M., 2010. Isoform-specific prolongation of Kv7 (KCNQ) potassium channel opening mediated by new molecular determinants for drug-channel interactions. J. Biol. Chem. 285, 28322–28332.
Gataullina, S., Lonlay, P., Dellatolas, G., Valayannapoulos, V., Napuri, S., Damaj, L., Touati, G., Altuzarra, C., Dulac, O., Boddaert, N., 2013. Topography of brain damage in metabolic hypoglycaemia is determined by age at which hypoglycaemia occurred. Dev. Med Child Neurol. 55, 162–166.
George, P.S., Tavendale, R., Palmer, C.N., McCrimmon, R.J., 2015. Diazoxide improves hormonal counterregulatory responses to acute hypoglycemia in long-standing type 1 diabetes. Diabetes 64, 2234–2241.
Gerlach, U., Brendel, J., Lang, H.J., Paulus, E.F., Weidmann, K., Brüggemann, A., Busch, A.E., Suessbrich, H., Bleich, M., Greger, R., 2001. Synthesis and activity of novel and selective IKs-channel blockers. J. Med. Chem. 44, 3831–3837.
Glaser, B., Thornton, P., Otonkoski, T., Junien, C., 2000. Genetics of neonatal hyperinsulinism. Arch. Dis. Child. Fetal Neonatal Ed. 82, F79–F86.
Gloyn, A.L., Pearson, E.R., Antcliff, J.F., Proks, P., Bruining, G.J., Slingerland, A.S., Howard, N., Srinivasan, S., Silva, J.M.C.L., Molnes, J., Edghill, E.L., Frayling, T.M., Temple, I.K., Mackay, D., Shield, J.P.H., Sumnik, Z., van Rhijn, A., Wales, J.K.H., Clark, P., Gorman, S., Aisenberg, J., Ellard, S., Njolstad, P.R., Ashcroft, F.M., Hattersley, A.T., 2004. 'Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. New Engl. J. Med. 350, 1838–1849.
Gloyn, A.L., Siddiqui, J., Ellard, S., 2006. Mutations in the genes encoding the pancreatic beta-cell KATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) in diabetes mellitus and hyperinsulinism. Hum. Mutat. 27, 220–231.
Goldberg, E.M., Watanabe, S., Chang, S.Y., Joho, R.H., Huang, Z.J., Leonard, C.S., Rudy, B., 2005. Specific functions of synaptically localized potassium channels in synaptic transmission at the neocortical GABAergic fast-spiking cell synapse. J. Neurosci.: Off. J. Soc. Neurosci. 25, 5230–5235.
Goldman, A.M., Glasscock, E., Yoo, J., Chen, T.T., Klassen, T.L., Noebels, J.L., 2009. Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. Sci. Transl. Med 1, 2ra6.
Goldstein, S.A., Bayliss, D.A., Kim, D., Lesage, F., Plant, L.D., Rajan, S., 2005. International Union of Pharmacology. LV. Nomenclature and molecular relationships of two-P potassium channels. Pharm. Rev. 57, 527–540.
González, A., Aurlien, D., Haugaa, K.H., Taubøll, E., 2018. Epilepsy in patients with long QT syndrome type 1: A Norwegian family. Epilepsy Behav. Case Rep. 10, 118–121.
Grandi, E., Sanguinetti, M.C., Bartos, D.C., Bers, D.M., Chen-Izu, Y., Chiamvimonvat, N., Colecraft, H.M., Delisle, B.P., Heijman, J., Navedo, M.F., Noskov, S., Proenza, C., Vandenberg, J.I., Yarov-Yarovoy, V., 2017. 'Potassium channels in the heart: structure, function and regulation'. J. Physiol. 595, 2209–2228.
Gribble, F.M., Reimann, F., 2003. Sulphonylurea action revisited - the post-cloning era. Diabetologia 46, 875–891.
Gutman, G.A., Chandy, K.G., Grissmer, S., Lazdunski, M., McKinnon, D., Pardo, L.A., Robertson, G.A., Rudy, B., Sanguinetti, M.C., Stühmer, W., Wang, X., 2005. International Union of Pharmacology. LIII. Nomenclature and molecular relationships of voltage-gated potassium channels. Pharm. Rev. 57, 473–508.
Hamilton, T.C., Weir, S.W., Weston, A.H., 1986. Comparison of the effects of BRL 34915 and verapamil on electrical and mechanical activity in rat portal vein. Br. J. Pharm. 88, 103–111.
Hattersley, A.T., Ashcroft, F.M., 2005. 'Activating mutations in Kir6.2 and neonatal diabetes - new clinical syndromes, new scientific insights, and new therapy'. Diabetes 54, 2503–2513.
Hattersley, A.T., Greeley, S.A.W., Polak, M., Rubio-Cabezas, O., Njolstad, P.R., Mlynarski, W., Castano, L., Carlsson, A., Raile, K., Chi, D.V., Ellard, S., Craig, M.E., 2018. ISPAD Clinical Practice Consensus Guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. Pedia Diabetes 19 (Supplement 27), 47–63.
Heginbotham, L., Lu, Z., Abramson, T., MacKinnon, R., 1994. Mutations in the K+ channel signature sequence. Biophys. J. 66, 1061–1067.
Helleskov, A., Melikyan, M., Globa, E., Shcherderkina, I., Poertner, F., Larsen, A.M., Filipsen, K., Brusgaard, K., Christiansen, C.D., Hansen, L.K., Christesen, H.T., 2017. Both low blood glucose and insufficient treatment confer risk of neurodevelopmental impairment in congenital hyperinsulinism: a multinational cohort study. Front Endocrinol. (Lausanne) 8, 156.
Hibino, H., Inanobe, A., Furutani, K., Murakami, S., Findlay, I., Kurachi, Y., 2010. Inwardly rectifying potassium channels: their structure, function, and physiological roles. Physiol. Rev. 90, 291–366.
Hirose, S., 2000. A novel mutation of KCNQ3 in a Japanese family with benign neonatal familiar convulsion (BFNC2). Ann. Neurol. 47, 822–826.
Hou, P.P., Shi, J.Y., White, K.M., Gao, Y., Cui, J.M., 2019. ML277 specifically enhances the fully activated open state of KCNQ1 by modulating VSD-pore coupling. Elife 8.
Hsiao, C.T., Tropea, T.F., Fu, S.J., Bardakjian, T.M., Gonzalez-Alegre, P., Soong, B.W., Tang, C.Y., Jeng, C.J., 2021. Rare gain-of-function KCND3 variant associated with cerebellar ataxia, parkinsonism, cognitive dysfunction, and brain iron accumulation. Int J. Mol. Sci. 22. ⟨https://gtexportal.org/home/multiGeneQueryPage/KCNJ11⟩.
Hu, Z., Kant, R., Anand, M., King, E.C., Krogh-Madsen, T., Christini, D.J., Abbott, G.W., 2014. Kcne2 deletion creates a multisystem syndrome predisposing to sudden cardiac death. Circ. Cardiovasc Genet 7, 33–42.
Humphries, E.S.A., Dart, C., 2015. Neuronal and cardiovascular potassium channels as therapeutic drug targets: promise and pitfalls. J. Biomol. Screen. 20, 1055–1073.
Hyltén-Cavallius, L., Iepsen, E.W., Wewer Albrechtsen, N.J., Svendstrup, M., Lubberding, A.F., Hartmann, B., Jespersen, T., Linneberg, A., Christiansen, M., Vestergaard, H., Pedersen, O., Holst, J.J., Kanters, J.K., Hansen, T., Torekov, S.S., 2017. Patients with Long-QT syndrome caused by Impaired hERG-encoded K(v)11.1 Potassium channel have exaggerated endocrine pancreatic and incretin function associated with reactive hypoglycemia. Circulation 135, 1705–1719.
Innamaa, A., Jackson, L., Asher, V., Van Shalkwyk, G., Warren, A., Hay, D., Bali, A., Sowter, H., Khan, R., 2013. Expression and prognostic significance of the oncogenic K2P potassium channel KCNK9 (TASK-3) in ovarian carcinoma. Anticancer Res 33, 1401–1408.
Isomoto, S., Kondo, C., Yamada, M., Matsumoto, S., Higashiguchi, O., Horio, Y., Matsuzawa, Y., Kurachi, Y., 1996. A novel sulfonylurea receptor forms with BIR (Kir6.2) a smooth muscle type ATP-sensitive K+ channel. J. Biol. Chem. 271, 24321–24324.
Jack, M.M., Greer, R.M., Thomsett, M.J., Walker, R.M., Bell, J.R., Choong, C., Cowley, D. M., Herington, A.C., Cotterill, A.M., 2003. The outcome in Australian children with hyperinsulinism of infancy: early extensive surgery in severe cases lowers risk of diabetes. Clin. Endocrinol. 58, 355–364.
Jan, L., Y., Jan, Y.N., 2012. Voltage-gated potassium channels and the diversity of electrical signalling. J. Physiol. 590, 2591–2599.
Jiang, J., Li, Y., Zhou, Y., Li, X., Li, H., Tang, B., Dai, X., Ma, T., Li, L., Huo, Y., 2016. Oral nicorandil reduces ischemic attacks in patients with stable angina: a prospective, multicenter, open-label, randomized, controlled study. Int J. Cardiol. 224, 183–187.
Jonsson, A., Isomaa, B., Tuomi, T., Taneera, J., Salehi, A., Nilsson, P., Groop, L., Lyssenko, V., 2009. A variant in the KCNQ1 gene predicts future type 2 diabetes and mediates impaired insulin secretion. Diabetes 58, 2409–2413.
Kaar, S.J., Nottage, J.F., Angelescu, I., Marques, T.R., Howes, O.D., 2023. Gamma oscillations and potassium channel modulation in schizophrenia: targeting GABAergic dysfunction. Clin. EEG Neurosci.
Kang, S.K., Vanoye, C.G., Misra, S.N., Echevarria, D.M., Calhoun, J.D., O'Connor, J.B., Fabre, K.L., McKnight, D., Demmer, L., Goldenberg, P., Grote, L.E., Thiffault, I., Saunders, C., Strauss, K.A., Torkamani, A., van der Smagt, J., van Gassen, K., Carson, R.P., Diaz, J., Leon, E., Jacher, J.E., Hannibal, M.C., Litwin, J., Friedman, N. R., Schreiber, A., Lynch, B., Poduri, A., Marsh, E.D., Goldberg, E.M., Millichap, J.J., George Jr., A.L., Kearney, J.A., 2019. Spectrum of K(V) 2.1 dysfunction in KCNB1-associated neurodevelopmental disorders. Ann. Neurol. 86, 899–912.
Karschin, C., Ecke, C., Ashcroft, F.M., Karschin, A., 1997. Overlapping distribution of K-ATP channel-forming Kir6.2 subunit and the sulfonylurea receptor SUR1 in rodent brain. FEBS Lett. 401, 59–64.
Khamdiyeva, O., Tileules, Z., Baratzhanova, G., Perfilyeva, A., Djansugurova, L., 2021. The study of sodium and potassium channel gene single-nucleotide variation significance in non-mechanical forms of epilepsy. Egypt. J. Med. Hum. Genet. 22.
Koster, J.C., Cadario, F., Peruzzi, C., Colombo, C., Nichols, C.G., Barbetti, F., 2008. The G53D mutation in Kir6.2 (KCNJ11) is associated with neonatal diabetes and motor

dysfunction in adulthood that is improved with sulfonylurea therapy. J. Clin. Endocrinol. Metab. 93, 1054–1061.
Kubo, Y., Adelman, J.P., Clapham, D.E., Jan, L.Y., Karschin, A., Kurachi, Y., Lazdunski, M., Nichols, C.G., Seino, S., Vandenberg, C.A., 2005. International Union of Pharmacology. LIV. Nomenclature and molecular relationships of inwardly rectifying potassium channels. Pharm. Rev. 57, 509–526.
Lahmann, C., Kramer, H.B., Ashcroft, F.M., 2015. Systemic administration of glibenclamide fails to achieve therapeutic levels in the brain and cerebrospinal fluid of rodents. PLoS One 10, e0134476.
Lai, H.C., Jan, L.Y., 2006. The distribution and targeting of neuronal voltage-gated ion channels. Nat. Rev. Neurosci. 7, 548–562.
Laimon, W., Aboelenin, H.M., El Tantawi, N.T., 2021. Clinical characteristics, outcome, and predictors of neurological sequelae of persistent congenital hyperinsulinism: a single tertiary center experience. Pedia Diabetes 22, 388–399.
Lamberts, R.J., Blom, M.T., Novy, J., Belluzzo, M., Seldenrijk, A., Penninx, B.W., Sander, J.W., Tan, H.L., Thijs, R.D., 2015. Increased prevalence of ECG markers for sudden cardiac arrest in refractory epilepsy. J. Neurol., Neurosurg. Psychiatry 86, 309.
Landmeier, K.A., Lanning, M., Carmody, D., Greeley, S.A.W., Msall, M.E., 2017. ADHD, learning difficulties and sleep disturbances associated with KCNJ11-related neonatal diabetes. Pediatr. Diabetes 18, 518–523.
Lawson, K., 2000. Potassium channel openers as potential therapeutic weapons in ion channel disease. Kidney Int. 57, 838–845.
Lee, J.H., Jung, I.S., Lee, S.H., Yang, M.K., Hwang, J.H., Lee, H.D., Cho, Y.S., Song, M.J., Yi, K.Y., Yoo, S.E., Kwon, S.H., Kim, B., Lee, C.S., Shin, H.S., 2007. Cardioprotective effects of BMS-180448, a prototype mitoK(ATP) channel opener, and the role of salvage kinases, in the rat model of global ischemia and reperfusion heart injury. Arch. Pharm. Res 30, 634–640.
Lee, K.P.K., Chen, J., MacKinnon, R., 2017. Molecular structure of human KATP in complex with ATP and ADP. Elife 6.
Lee, S.M., Baik, J., Nguyen, D., Nguyen, V., Liu, S., Hu, Z., Abbott, G.W., 2017. Kcne2 deletion impairs insulin secretion and causes type 2 diabetes mellitus. FASEB J. 31, 2674–2685.
Lee, Y.C., Durr, A., Majczenko, K., Huang, Y.H., Liu, Y.C., Lien, C.C., Tsai, P.C., Ichikawa, Y., Goto, J., Monin, M.L., Li, J.Z., Chung, M.Y., Mundwiller, E., Shakkottai, V., Liu, T.T., Tesson, C., Lu, Y.C., Brice, A., Tsuji, S., Burmeister, M., Stevanin, G., Soong, B.W., 2012. Mutations in KCND3 cause spinocerebellar ataxia type 22. Ann. Neurol. 72, 859–869.
Legros, L., Adle-Biassette, H., Dozieres-Puyravel, B., Khung, S., Elmaleh-Berges, M., Lesca, G., Delanoe, C., Biran, V., Auvin, S., 2022. Neuropathology findings in KCNQ2 neonatal epileptic encephalopathy. Seizure 99, 36–39.
Lenz, T.L., Hilleman, D.E., 2000. Dofetilide, a new class III antiarrhythmic agent. Pharmacotherapy 20, 776–786.
Lerche, C., Bruhova, I., Lerche, H., Steinmeyer, K., Ad, W., Strutz-Seebohm, N., Lang, F., Ae, B., Bs, Z., Seebohm, G., 2007. Chromanol 293B binding in KCNQ1 (Kv7.1) channels involves electrostatic interactions with a potassium ion in the selectivity filter. Mol. Pharmacol. vol 71, 1503.
Lesage, F., Lazdunski, M., 2000. Molecular and functional properties of two-pore-domain potassium channels. Am. J. Physiol. Ren. Physiol. 279, F793–F801.
Levy-Shraga, Y., Pinhas-Hamiel, O., Kraus-Houminer, E., Landau, H., Mazor-Aronovitch, K., Modan-Moses, D., Gillis, D., Koren, I., Dollberg, D., Gabis, L.V., 2013. Cognitive and developmental outcome of conservatively treated children with congenital hyperinsulinism. J. Pedia Endocrinol. Metab. 26, 301–308.
Li, P., Chen, Z.X., Xu, H.Y., Sun, H.F., Li, H., Liu, H., Yang, H.Y., Gao, Z.B., Jiang, H.L., Li, M., 2013. The gating charge pathway of an epilepsy-associated potassium channel accommodates chemical ligands. Cell Res. 23, 1106–1118.
Li, T., Wu, K., Yue, Z.L., Wang, Y.F., Zhang, F., Shen, H.Z., 2021. Structural basis for the modulation of human KCNQ4 by small-molecule drugs. Mol. Cell 81, 25–37.
Li, X.X., Zhang, Q.S., Guo, P.P., Fu, J., Mei, L.H., Lv, D.S., Wang, J.Q., Lai, D.W., Ye, S., Yang, H.Y., Guo, J.T., 2021. Molecular basis for ligand activation of the human KCNQ2 channel. Cell Res. 31, 52–61.
Li, Y.Y., Wang, X.M., Lu, X.Z., 2014. KCNQ1 rs2237892 C–>T gene polymorphism and type 2 diabetes mellitus in the Asian population: a meta-analysis of 15,736 patients. J. Cell Mol. Med 18, 274–282.
Lim, C.X., Michael, G.R., Leanne, M., Dibbens, Sarah, E.H., 2016. KCNT1 mutations in seizure disorders: the phenotypic spectrum and functional effects. J. Med. Genet. 53, 217–225.
Littleton, J.T., Ganetzky, B., 2000. Ion channels and synaptic organization: analysis of the Drosophila genome. Neuron 26, 35–43.
Lloyd, J., Schmidt, J.B., Rovnyak, G., Ahmad, S., Atwal, K.S., Bisaha, S.N., Doweyko, L. M., Stein, P.D., Traeger, S.C., Mathur, A., Conder, M.L., DiMarco, J., Harper, T.W., Jenkins-West, T., Levesque, P.C., Normandin, D.E., Russell, A.D., Serafino, R.P., Smith, M.A., Lodge, N.J., 2001. Design and synthesis of 4-substituted benzamides as potent, selective, and orally bioavailable I-Ks blockers. J. Med. Chem. 44, 3764–3767.
Long, S.B., Campbell, E.B., Mackinnon, R., 2005. Crystal structure of a mammalian voltage-dependent Shaker family K+ channel. Science 309, 897–903.
de Lonlay, P., Cormier-Daire, V., Amiel, J., Touati, G., Goldenberg, A., Fournet, J.C., Brunelle, F., Nihoul-Fékété, C., Rahier, J., Junien, C., Robert, J.J., Saudubray, J.M., 2002. Facial appearance in persistent hyperinsulinemic hypoglycemia. Am. J. Med. Genet. 111, 130–133.
Lubberding, A.F., Zhang, J., Lundh, M., Nielsen, T.S., Sondergaard, M.S., Villadsen, M., Skovhoj, E.Z., Boer, G.A., Hansen, J.B., Thomsen, M.B., Treebak, J.T., Holst, J.J., Kanters, J.K., Mandrup-Poulsen, T., Jespersen, T., Emanuelli, B., Torekov, S.S., 2021. Age-dependent transition from islet insulin hypersecretion to hyposecretion in mice with the long QT-syndrome loss-of-function mutation Kcnq1-A340V. Sci. Rep. 11, 12253.
Ludwig, A., Enke, S., Heindorf, J., Empting, S., Meissner, T., Mohnike, K., 2018. Formal neurocognitive testing in 60 patients with congenital hyperinsulinism. Horm. Res. Paediatr. 89 (1), 1–6.
Lynch Jr., J.J., Houle, M.S., Stump, G.L., Wallace, A.A., Gilberto, D.B., Jahansouz, H., Smith, G.R., Tebben, A.J., Liverton, N.J., Selnick, H.G., Claremon, D.A., Billman, G. E., 1999. Antiarrhythmic efficacy of selective blockade of the cardiac slowly activating delayed rectifier current, I(Ks), in canine models of malignant ischemic ventricular arrhythmia. Circulation 100, 1917–1922.
Ma, D., Zhong, L., Yan, Z., Yao, J., Zhang, Y., Ye, F., Huang, Y., Lai, D., Yang, W., Hou, P., Guo, J., 2022. Structural mechanisms for the activation of human cardiac KCNQ1 channel by electro-mechanical coupling enhancers. Proc. Natl. Acad. Sci. USA 119, e2207067119.
Macauley, S. L., Molly, S. S., Emily, E. C., William, R. M., Annie, R. B., Nildris, C.D., C.M., Carroll, S. M., Day, J. G., Thomas, E. M., James, A. S., T, E. Orr., Joseph, P. C., Maria, S. R., Colin, G. N., Celeste, M. K., Laura, A. Cox., Debra, I. D., Adam, Q. B., and David, M. H., 2021. 'Sulfonylureas target the neurovascular response to decrease Alzheimer's pathology', bioRxiv: 2021.08.11.455969.
MacKinnon, R., Cohen, S.L., Kuo, A., Lee, A., Chait, B.T., 1998. Structural conservation in prokaryotic and eukaryotic potassium channels. Science 280, 106–109.
Maria, G., Antonia, D., Michael, A., Kate, M., Sian, E., Sarah, F.E., Mehul, D., Pratik, S., 2019. Sirolimus: efficacy and complications in children with hyperinsulinemic hypoglycemia: a 5-year follow-up study. J. Endocr. Soc. 3, 699–713.
Martagón, A.J., Bello-Chavolla, O.Y., Arellano-Campos, O., Almeda-Valdés, P., Walford, G.A., Cruz-Bautista, I., Gómez-Velasco, D.V., Mehta, R., Muñoz-Hernández, L., Sevilla-González, M., Viveros-Ruiz, T.L., Ordoñez-Sánchez, M.L., Rodríguez-Guillen, R., Florez, J.C., Tusié-Luna, M.T., Aguilar-Salinas, C.A., 2018. Mexican carriers of the HNF1A p.E508K variant do not experience an enhanced response to sulfonylureas. Diabetes Care 41, 1726–1731.
Martin, G.M., Yoshioka, C., Rex, E.A., Fay, J.F., Xie, Q., Whorton, M.R., Chen, J.Z., Shyng, S.L., 2017. Cryo-EM structure of the ATP-sensitive potassium channel illuminates mechanisms of assembly and gating. Elife 6.
Mathew, P.M., Young, J.M., Abu-Osba, Y.K., Mulhern, B.D., Hammoudi, S., Hamdan, J. A., Sa'di, A.R., 1988. Persistent neonatal hyperinsulinism. Clin. Pedia 27, 148–151.
Mattmann, M.E., Yu, H.B., Lin, Z.H., Xu, K.P., Huang, X.F., Long, S.Y., Wu, M., McManus, O.B., Engers, D.W., Le, U.M., Li, M., Lindsley, C.W., Hopkins, C.R., 2012. Identification of (R)-N-(4-(4-methoxyphenyl)thiazol-2-yl)-1-tosylpiperidine-2-carboxamide, ML277, as a novel, potent and selective K(v)7.1 (KCNQ1) potassium channel activator. Bioorg. Med. Chem. Lett. 22, 5936–5941.
McCrossan, Z.A., Abbott, G.W., 2004. The MinK-related peptides. Neuropharmacology 47, 787–821.
Medhurst, A.D., Rennie, G., Chapman, C.G., Meadows, H., Duckworth, M.D., Kelsell, R. E., Gloger II, Pangalos, M.N., 2001. Distribution analysis of human two pore domain potassium channels in tissues of the central nervous system and periphery. Brain Res Mol. Brain Res 86, 101–114.
Meissner, T., Wendel, U., Burgard, P., Schaetzle, S., Mayatepek, E., 2003. Long-term follow-up of 114 patients with congenital hyperinsulinism. Eur. J. Endocrinol. 149, 43–51.
Menni, F., de Lonlay, P., Sevin, C., Touati, G., Peigné, C., Barbier, V., Nihoul-Fékété, C., Saudubray, J.M., Robert, J.J., 2001. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. Pediatrics 107, 476–479.
Miller, Christopher, 2000. An overview of the potassium channel family. *Genome Biol.* 004, 1.
Milligan, C.J., Li, M., Gazina, E.V., Heron, S.E., Nair, U., Trager, C., Reid, C.A., Venkat, A., Younkin, D.P., Dlugos, D.J., Petrovski, S., Goldstein, D.B., Dibbens, L.M., Scheffer, I.E., Berkovic, S.F., Petrou, S., 2014. KCNT1 gain of function in 2 epilepsy phenotypes is reversed by quinidine. Ann. Neurol. 75, 581–590.
Mlynarski, W., Tarasov, A.I., Gach, A., Girard, C.A., Pietrzak, I., Zubcevic, L., Kusmierek, J., Klupa, T., Malecki, M.T., Ashcroft, F.M., 2007. Sulfonylurea improves CNS function in a case of intermediate DEND syndrome caused by a mutation in KCNJ11. Nat. Clin. Pract. Neurol. 3, 640–645.
Mohamadi, A., Clark, L.M., Lipkin, P.H., Mahone, E.M., Wodka, E.L., Plotnick, L.P., 2010. Medical and developmental impact of transition from subcutaneous insulin to oral glyburide in a 15-yr-old boy with neonatal diabetes mellitus and intermediate DEND syndrome: extending the age of KCNJ11 mutation testing in neonatal DM. Pedia Diabetes 11, 203–207.
Mruk, K., Kobertz, W.R., 2009. Discovery of a novel activator of KCNQ1-KCNE1 K channel complexes. PLoS One 4, e4236.
Muukkonen, L., Männistö, J., Jääskeläinen, J., Hannonen, R., Huopio, H., 2019. The effect of hypoglycaemia on neurocognitive outcome in children and adolescents with transient or persistent congenital hyperinsulinism. Dev. Med. Child Neurol. 61, 451–457.
Nadal, M.S., Amarillo, Y., Vega-Saenz de Miera, E., Rudy, B., 2001. Evidence for the presence of a novel Kv4-mediated A-type K(+) channel-modifying factor. J. Physiol. 537, 801–809.
Najmi, L.A., Aukrust, I., Flannick, J., Molnes, J., Burtt, N., Molven, A., Groop, L., Altshuler, D., Johansson, S., Bjorkhaug, L., Njolstad, P.R., 2017. Functional investigations of HNF1A identify rare variants as risk factors for type 2. Diabetes Gen. Popul. *Diabetes* 66, 335–346.
Nashef, L., Hindocha, N., Makoff, A., 2007. Risk factors in sudden death in epilepsy (SUDEP): the quest for mechanisms. Epilepsia 48, 859–871.
Nattel, S., Liu, L., St-Georges, D., 1998. Effects of the novel antiarrhythmic agent azimilide on experimental atrial fibrillation and atrial electrophysiologic properties. Cardiovasc Res 37, 627–635.

Neher, E., Sakmann, B., Steinbach, J.H., 1978. 'The extracellular patch clamp: a method for resolving currents through individual open channels in biological membranes'. Pflug. Arch. 375, 219–228.
Nerbonne, J.M., 2000. Molecular basis of functional voltage-gated K+ channel diversity in the mammalian myocardium. J. Physiol. 525 (Pt 2), 285–298.
Niemeyer, M.I., Cid, L.P., Peña-Münzenmayer, G., Sepúlveda, F.V., 2010. Separate gating mechanisms mediate the regulation of K2P potassium channel TASK-2 by intra- and extracellular pH. J. Biol. Chem. 285, 16467–16475.
Noh, W., Pak, S., Choi, G., Yang, S., Yang, S., 2019. Transient potassium channels: therapeutic targets for brain disorders. Front. Cell. Neurosci. 13.
Oka, H., Suzuki, S., Furuya, A., Matsuo, K., Amamiya, S., Oshima, M., Oka, T., Mukai, T., Okayama, A., Araki, A., Azuma, H., Tanahashi, Y., 2014. Glycemic control and motor development in a patient with intermediate DEND. Pedia Int 56, 432–435.
Oliver, K.L., Franceschetti, S., Milligan, C.J., Muona, M., Mandelstam, S.A., Canafoglia, L., Boguszewska-Chachulska, A.M., Korczyn, A.D., Bisulli, F., Di Bonaventura, C., Ragona, F., Michelucci, R., Ben-Zeev, B., Straussberg, R., Panzica, F., Massano, J., Friedman, D., Crespel, A., Engelsen, B.A., Andermann, F., Andermann, E., Spodar, K., Lasek-Bal, A., Riguzzi, P., Pasini, E., Tinuper, P., Licchetta, L., Gardella, E., Lindenau, M., Wulf, A., Møller, R.S., Benninger, F., Afawi, Z., Rubboli, G., Reid, C.A., Maljevic, S., Lerche, H., Lehesjoki, A.E., Petrou, S., Berkovic, S.F., 2017. Myoclonus epilepsy and ataxia due to KCNC1 mutation: analysis of 20 cases and K(+) channel properties. Ann. Neurol. 81, 677–689.
Omasits, U., Ahrens, C.H., Müller, S., Wollscheid, B., 2014. Protter: interactive protein feature visualization and integration with experimental proteomic data. Bioinformatics 30, 884–886.
Ortega-Contreras, B., Armella, A., Appel, J., Mennickent, D., Araya, J., González, M., Castro, E., Obregón, A.M., Lamperti, L., Gutiérrez, J., Guzmán-Gutiérrez, E., 2022. Pathophysiological role of genetic factors associated with gestational diabetes mellitus. Front Physiol. 13, 769924.
Otonkoski, T., Ammala, C., Huopio, H., Cote, G.J., Chapman, J., Cosgrove, K., Ashfield, R., Huang, E., Komulainen, J., Ashcroft, F.M., Dunne, M.J., Kere, J., Thomas, P.M., 1999. A point mutation inactivating the sulfonylurea receptor causes the severe form of persistent hyperinsulinemic hypoglycemia of infancy in Finland. Diabetes 48 (2), 408–415.
Padilla, K., Wickenden, A.D., Gerlach, A.C., McCormack, K., 2009. The KCNQ2/3 selective channel opener ICA-27243 binds to a novel voltage-sensor domain site. Neurosci. Lett. 465, 138–142.
Park, S.E., Flanagan, S.E., Hussain, K., Ellard, S., Shin, C.H., Yang, S.W., 2011. Characterization of ABCC8 and KCNJ11 gene mutations and phenotypes in Korean patients with congenital hyperinsulinism. Eur. J. Endocrinol. 164, 919–926.
Pearson, E.R., Flechtner, I., Njolstad, P.R., Malecki, M.T., Flanagan, S.E., Larkin, B., Ashcroft, F.M., Klimes, I., Codner, E., Iotova, V., Slingerland, A.S., Shield, J., Robert, J.J., Holst, J.J., Clark, P.M., Ellard, S., Sovik, O., Polak, M., Hattersley, A.T., 2006. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. New Engl. J. Med. 355 (5), 467–477.
Porter, J.D., Vivas, O., Weaver, C.D., Alsafran, A., DiMilo, E., Arnold, L.A., Dickson, E.J., Dockendorff, C., 2019. An anthrone-based Kv7.2/7.3 channel blocker with improved properties for the investigation of psychiatric and neurodegenerative disorders. Bioorg. Med. Chem. Lett. 29 (126681).
Postma, A.V., Bezzina, C.R., de Vries, J.F., Wilde, A.A., Moorman, A.F., Mannens, M.M., 2000. Genomic organisation and chromosomal localisation of two members of the KCND ion channel family, KCND2 and KCND3. Hum. Genet. 106, 614–619.
Premoli, I., Rossini, P.G., Goldberg, P.Y., Posadas, K., Green, L., Yogo, N., Pimstone, S., Abela, E., Beatch, G.N., Richardson, M.P., 2019. TMS as a pharmacodynamic indicator of cortical activity of a novel anti-epileptic drug, XEN1101. Ann. Clin. Transl. Neurol. 6, 2164–2174.
Proks, P., Arnold, A.L., Bruining, J., Girard, C., Flanagan, S.E., Larkin, B., Colclough, K., Hattersley, A.T., Ashcroft, F.M., Ellard, S., 2006. A heterozygous activating mutation in the sulphonylurea receptor SUR1 (ABCC8) causes neonatal diabetes. Hum. Mol. Genet. 15, 1793–1800.
Qian, Y., Dong, M., Lu, F., Li, H., Jin, G., Hu, Z., Shen, C., Shen, H., 2015. Joint effect of CENTD2 and KCNQ1 polymorphisms on the risk of type 2 diabetes mellitus among Chinese Han population. Mol. Cell. Endocrinol. 407, 46–51.
Raicevic, M., Milenkovic, T., Hussain, K., Djordjevic, M., Martic, J., Todorovic, S., Mitrovic, K., Sarajlija, A., Vukovic, R., 2021. Clinical and genetic characteristics of patients with congenital hyperinsulinism in 21 non-consanguineous families from Serbia. Eur. J. Pedia 180, 2815–2821.
Razzaghy-Azar, M., Saeedi, S., Dayani, S.B., Enayati, S., Abbasi, F., Hashemian, S., Eshraghi, P., Karimdadi, S., Tajdini, P., Vakili, R., Amoli, M.M., Yaghootkar, H., 2022. Investigating genetic mutations in a large cohort of iranian patients with congenital hyperinsulinism. J. Clin. Res Pedia Endocrinol. 14, 87–95.
Rodrigues, Vilela V., de Castro Ruiz Marques A., Schamber, C.R., Bazotte, R.B., 2014. Hypoglycemia induced by insulin as a triggering factor of cognitive deficit in diabetic children. ScientificWorldJournal 2014, 616534.
Roeloffs, R., Wickenden, A.D., Crean, C., Werness, S., McNaughton-Smith, G., Stables, J., McNamara, J.O., Ghodadra, N., Rigdon, G.C., 2008. In vivo profile of ICA-27243 [N-(6-Chloro-pyridin-3-yl)-3,4-difluoro-benzamide], a potent and selective KCNQ2/Q3 (Kv7.2/Kv7.3) activator in rodent anticonvulsant models. J. Pharmacol. Exp. Ther. 326, 818–828.
Rosengren, A.H., Braun, M., Mahdi, T., Andersson, S.A., Travers, M.E., Shigeto, M., Zhang, E., Almgren, P., Ladenvall, C., Axelsson, A.S., Edlund, A., Pedersen, M.G., Jonsson, A., Ramracheya, R., Tang, Y., Walker, J.N., Barrett, A., Johnson, P.R., Lyssenko, V., McCarthy, M.I., Groop, L., Salehi, A., Gloyn, A.L., Renstrom, E., Rorsman, P., Eliasson, L., 2012. Reduced insulin exocytosis in human pancreatic beta-cells with gene variants linked to type 2 diabetes. Diabetes 61, 1726–1733.
Rother, K.I., Matsumoto, J.M., Rasmussen, N.H., Schwenk, W.F., 2001. Subtotal pancreatectomy for hypoglycemia due to congenital hyperinsulinism: long-term follow-up of neurodevelopmental and pancreatic function. Pedia Diabetes 2, 115–122.
Rubio-Cabezas, O., Flanagan, S.E., Damhuis, A., Hattersley, A.T., Ellard, S., 2012. KATP channel mutations in infants with permanent diabetes diagnosed after 6 months of life. Pediatr. Diabetes 13, 315–318.
Ruffin, V.A., Gu, X.Q., Zhou, D., Douglas, R.M., Sun, X., Trouth, C.O., Haddad, G.G., 2008. The sodium-activated potassium channel Slack is modulated by hypercapnia and acidosis. Neuroscience 151, 410–418.
Ruscio, A.M., Stein, D.J., Chiu, W.T., Kessler, R.C., 2010. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol. Psychiatry 15, 53–63.
Sagen, J.V., Raeder, H., Hathout, E., Shehadeh, N., Gudmundsson, K., Baevre, H., Abuelo, D., Phornphutkul, C., Molnes, J., Bell, G.I., Gloyn, A.L., Hattersley, A.T., Molven, A., Sovik, O., Njolstad, P.R., 2004. Permanent neonatal diabetes due to mutations in KCNJ11 encoding Kir6.2 - Patient characteristics and initial response to sulfonylurea therapy. Diabetes 53, 2713–2718.
Sah, P., Davies, P., 2000. Calcium-activated potassium currents in mammalian neurons. Clin. Exp. Pharm. Physiol. 27, 657–663.
Sah, P., Faber, E.S., 2002. Channels underlying neuronal calcium-activated potassium currents. Prog. Neurobiol. 66, 345–353.
Saitsu, H., Akita, T., Tohyama, J., Goldberg-Stern, H., Kobayashi, Y., Cohen, R., Kato, M., Ohba, C., Miyatake, S., Tsurusaki, Y., Nakashima, M., Miyake, N., Fukuda, A., Matsumoto, N., 2015. De novo KCNB1 mutations in infantile epilepsy inhibit repetitive neuronal firing. Sci. Rep. 5, 15199.
Salata, J.J., Jurkiewicz, N.K., Wang, J., Evans, B.E., Orme, H.T., Sanguinetti, M.C., 1998. A novel benzodiazepine that activates cardiac slow delayed rectifier K+ currents. Mol. Pharm. 54, 220–230.
Salomon-Estebanez, M., Mohamed, Z., Michaelidou, M., Collins, H., Rigby, L., Skae, M., Padidela, R., Rust, S., Dunne, M., Cosgrove, K., Banerjee, I., Nicholson, J., 2017. Vineland adaptive behavior scales to identify neurodevelopmental problems in children with Congenital Hyperinsulinism (CHI). Orphanet J. Rare Dis. 12, 96.
Sandal, T., Laborie, L.B., Brusgaard, K., Eide, S.A., Christesen, H.B., Sovik, O., Njolstad, P. R., Molven, A., 2009. The spectrum of ABCC8 mutations in Norwegian patients with congenital hyperinsulinism of infancy. Clin. Genet. 75, 440–448.
Sanguinetti, M.C., Tristani-Firouzi, M., 2006. hERG potassium channels and cardiac arrhythmia. Nature 440, 463–469.
Schrier, R.W., Abebe, K.Z., Perrone, R.D., Torres, V.E., Braun, W.E., Steinman, T.I., Winklhofer, F.T., Brosnahan, G., Czarnecki, P.G., Hogan, M.C., Miskulin, D.C., Rahbari-Oskoui, F.F., Grantham, J.J., Harris, P.C., Flessner, M.F., Bae, K.T., Moore, C.G., Chapman, A.B., 2014. Blood pressure in early autosomal dominant polycystic kidney disease. New Engl. J. Med. 371, 2255–2266.
Seefeld, M.A., Lin, H., Holenz, J., Downie, D., Donovan, B., Fu, T., Pasikanti, K., Zhen, W., Cato, M., Chaudhary, K.W., Brady, P., Bakshi, T., Morrow, D., Rajagopal, S., Samanta, S.K., Madhyastha, N., Kuppusamy, B.M., Dougherty, R.W., Bhamidipati, R., Mohd, Z., Higgins, G.A., Chapman, M., Rouget, C., Lluel, P., Matsuoka, Y., 2018. Novel K(V)7 ion channel openers for the treatment of epilepsy and implications for detrusor tissue contraction. Bioorg. Med. Chem. Lett. 28, 3793–3797.
Sempoux, C., Guiot, Y., Jaubert, F., Rahier, J., 2004. Focal and diffuse forms of congenital hyperinsulinism: the keys for differential diagnosis. Endocr. Pathol. 15, 241–246.
Seyal, M., Pascual, F., Lee, C.Y, Li, C.S, Bateman, L.M., 2011. Seizure-related cardiac repolarization abnormalities are associated with ictal hypoxemia. Epilepsia 52, 2105–2111.
Sheng, M., Liao, Y.J., Jan, Y.N., Jan, L.Y., 1993. Presynaptic A-current based on heteromultimeric K+ channels detected in vivo. Nature 365, 72–75.
Shield, J.P.H., Gardner, R.J., Wadsworth, E.J.K., Whiteford, M.L., James, R.S., Robinson, D.O., Baum, J.D., Temple, I.K., 1997. Aetiopathology and genetic basis of neonatal diabetes. Arch. Dis. Child. -Fetal Neonatal Ed. 76, F39–F42.
Shin, H.D., Park, B.L., Shin, H.J., Kim, J.Y., Park, S., Kim, B., Kim, S.H., 2010. Association of KCNQ1 polymorphisms with the gestational diabetes mellitus in Korean women. J. Clin. Endocrinol. Metab. 95, 445–449.
Slingerland, A.S., Hattersley, A.T., 2006. Activating mutations in the gene encoding Kir6.2 alter fetal and postnatal growth and also cause neonatal diabetes. J. Clin. Endocrinol. Metab. 91, 2782–2788.
Slingerland, A.S., Nuboer, R., Hadders-Algra, M., Hattersley, A.T., Bruining, G.J., 2006. Improved motor development and good long-term glycaemic control with sulfonylurea treatment in a patient with the syndrome of intermediate developmental delay, early-onset generalised epilepsy and neonatal diabetes associated with the V59M mutation in the KCNJ11 gene. Diabetologia 49, 2559–2563.
Slingerland, A.S., Shields, B.M., Flanagan, S.E., Bruining, G.J., Noordam, K., Gach, A., Mlynarski, W., Malecki, M.T., Hattersley, A.T., Ellard, S., 2009. Referral rates for diagnostic testing support an incidence of permanent neonatal diabetes in three European countries of at least 1 in 260,000 live births. Diabetologia 52, 1683–1685.
Snyders, D.J., 1999. Structure and function of cardiac potassium channels. Cardiovasc Res. 42, 377–390.
Stafstrom, C.E., Grippon, S., Kirkpatrick, P., 2011. Ezogabine (retigabine). Nat. Rev. Drug Discov. 10, 729–730.
Stanik, J., Gasperikova, D., Paskova, M., Barak, L., Javorkova, J., Jancova, E., Ciljakova, M., Hlava, P., Michalek, J., Flanagan, S.E., Pearson, E., Hattersley, A.T., Ellard, S., Klimes, I., 2007. Prevalence of permanent neonatal diabetes in Slovakia and successful replacement of insulin with sulfonylurea therapy in KCNJ11 and ABCC8 mutation carriers. J. Clin. Endocrinol. Metab. 92, 1276–1282.

Steinkrauss, L., Lipman, T.H., Hendell, C.D., Gerdes, M., Thornton, P.S., Stanley, C.A., 2005. Effects of hypoglycemia on developmental outcome in children with congenital hyperinsulinism. J. Pedia Nurs. 20, 109–118.
Stocker, M., 2004. Ca(2+)-activated K+ channels: molecular determinants and function of the SK family. Nat. Rev. Neurosci. 5, 758–770.
Stomnaroska-Damcevski, O., Petkovska, E., Jancevska, S., Danilovski, D., 2015. Neonatal Hypoglycemia: A Continuing Debate in Definition and Management. Pril. (Make Akad. Nauk. Umet. Odd. Med Nauk. ) 36, 91–97.
Stump, G.L., Smith, G.R., Tebben, A.J., Jahansouz, H., Salata, J.J., Selnick, H.G., Claremon, D.A., Lynch Jr., J.J., 2003. 'In vivo canine cardiac electrophysiologic profile of 1,4-benzodiazepine IKs blockers. J. Cardiovasc Pharm. 42, 105–112.
Sturgess, N.C., Kozlowski, R.Z., Carrington, C.A., Hales, C.N., Ashford, M.L., 1988. Effects of sulphonylureas and diazoxide on insulin secretion and nucleotide-sensitive channels in an insulin-secreting cell line. Br. J. Pharm. 95, 83–94.
Sun, J., Kapur, J., 2012. M-type potassium channels modulate Schaffer collateral-CA1 glutamatergic synaptic transmission. J. Physiol. 590, 3953–3964.
Surges, R., Catherine, A.S., Matthew, C.W., 2010. Enhanced QT shortening and persistent tachycardia after generalized seizures. Neurology 74, 421.
Svalastoga, P., Sulen, A., Fehn, J.R., Aukland, S.M., Irgens, H., Sirnes, E., Fevang, S.K.E., Valen, E., Elgen, I.B., Njolstad, P.R., 2020. Intellectual disability in K(ATP) channel neonatal diabetes. Diabetes Care 43, 526–533.
Swarthout, J.T., Walling, H.W., 2000. Lysophosphatidic acid: receptors, signaling and survival. Cell Mol. Life Sci. 57, 1978–1985.
Swartz, K.J., 2004. Opening the gate in potassium channels. Nat. Struct. Mol. Biol. 11, 499–501.
Syrbe, S., Hedrich, U.B.S., Riesch, E., Djemie, T., Muller, S., Moller, R.S., Maher, B., Hernandez-Hernandez, L., Synofzik, M., Caglayan, H.S., Arslan, M., Serratosa, J.M., Nothnagel, M., May, P., Krause, R., Loffler, H., Detert, K., Dorn, T., Vogt, H., Kramer, G., Schols, L., Mullis, P.E., Linnankivi, T., Lehesjoki, A.E., Sterbova, K., Craiu, D.C., Hoffman-Zacharska, D., Korff, C.M., Weber, Y.G., Steinlin, M., Gallati, S., Bertsche, A., Bernhard, M.K., Merkenschlager, A., Kiess, W., Euro, Epinomics R.E.S. consortium, Gonzalez, M., Zuchner, S., Palotie, A., Suls, A., De Jonghe, P., Helbig, I., Biskup, S., Wolff, M., Maljevic, S., Schule, R., Sisodiya, S.M., Weckhuysen, S., Lerche, H., Lemke, J.R., 2015. De novo loss- or gain-of-function mutations in KCNA2cause epileptic encephalopathy. Nat. Genet 47, 393–399.
Szelenyi, I., 2013. Flupirtine, a re-discovered drug, revisited. Inflamm. Res 62, 251–258.
Tanizawa, Y., Matsuda, K., Matsuo, M., Ohta, Y., Ochi, N., Adachi, M., Koga, M., Mizuno, S., Kajita, M., Tanaka, Y., Tachibana, K., Inoue, H., Furukawa, S., Amachi, T., Ueda, K., Oka, Y., 2000. Genetic analysis of Japanese patients with persistent hyperinsulinemic hypoglycemia of infancy: nucleotide-binding fold-2 mutation impairs cooperative binding of adenine nucleotides to sulfonylurea receptor 1. Diabetes 49, 114–120.
Tasic, B., Yao, Z., Graybuck, L.T., Smith, K.A., Nguyen, T.N., Bertagnolli, D., Goldy, J., Garren, E., Economo, M.N., Viswanathan, S., Penn, O., Bakken, T., Menon, V., Miller, J., Fong, O., Hirokawa, K.E., Lathia, K., Rimorin, C., Tieu, M., Larsen, R., Casper, T., Barkan, E., Kroll, M., Parry, S., Shapovalova, N.V., Hirschstein, D., Pendergraft, J., Sullivan, H.A., Kim, T.K., Szafer, A., Dee, N., Groblewski, P., Wickersham, I., Cetin, A., Harris, J.A., Levi, B.P., Sunkin, S.M., Madisen, L., Daigle, T.L., Looger, L., Bernard, A., Phillips, J., Lein, E., Hawrylycz, M., Svoboda, K., Jones, A.R., Koch, C., Zeng, H., 2018. Shared and distinct transcriptomic cell types across neocortical areas. Nature 563, 72–78.
Tatulian, L., Delmas, P., Abogadie, F.C., Brown, D.A., 2001. Activation of expressed KCNQ potassium currents and native neuronal M-type potassium currents by the anti-convulsant drug retigabine. J. Neurosci.: Off. J. Soc. Neurosci. 21, 5535–5545.
Thiffault, I., Speca, D.J., Austin, D.C., Cobb, M.M., Eum, K.S., Safina, N.P., Grote, L., Farrow, E.G., Miller, N., Soden, S., Kingsmore, S.F., Trimmer, J.S., Saunders, C.J., Sack, J.T., 2015. A novel epileptic encephalopathy mutation in KCNB1 disrupts Kv2.1 ion selectivity, expression, and localization. J. Gen. Physiol. 146, 399–410.
Thomas, P., Ye, Y., Lightner, E., 1996. Mutation of the pancreatic islet inward rectifier Kir6.2 also leads to familial persistent hyperinsulinemic hypoglycemia of infancy. Hum. Mol. Genet 5, 1809–1812.
Thomas, P.M., Cote, G.J., Wohllk, N., Haddad, B., Mathew, P.M., Rabl, W., Aguilar-Bryan, L., Gagel, R.F., Bryan, J., 1995. Mutations in the sulfonylurea receptor gene in familial persistent hyperinsulinemic hypoglycemia of infancy. Science 268, 426–429.
Tian, C.A., Zhu, R.X., Zhu, L.X., Qiu, T.Y., Cao, Z.W., Kang, T.G., 2014. Potassium channels: structures, diseases, and modulators. Chem. Biol. Drug Des. 83, 1–26.
Tiron, C., Campuzano, O., Pérez-Serra, A., Mademont, I., Coll, M., Allegue, C., Iglesias, A., Partemi, S., Striano, P., Oliva, A., Brugada, R., 2015. Further evidence of the association between LQT syndrome and epilepsy in a family with KCNQ1 pathogenic variant. Seizure 25, 65–67.
Tomlinson, S.E., Rajakulendran, S., Tan, S.V., Graves, T.D., Bamiou, D.E., Labrum, R.W., Burke, D., Sue, C.M., Giunti, P., Schorge, S., Kullmann, D.M., Hanna, M.G., 2013. Clinical, genetic, neurophysiological and functional study of new mutations in episodic ataxia type 1. J. Neurol. Neurosurg. Psychiatry 84, 1107–1112.
Tomson, T., Nashef, L., Ryvlin, P., 2008. Sudden unexpected death in epilepsy: current knowledge and future directions. Lancet Neurol. 7, 1021–1031.
Torekov, S.S., Iepsen, E., Christiansen, M., Linneberg, A., Pedersen, O., Holst, J.J., Kanters, J.K., Hansen, T., 2014. KCNQ1 long QT syndrome patients have hyperinsulinemia and symptomatic hypoglycemia. Diabetes 63, 1315–1325.
Torkamani, A., Bersell, K., Jorge, B.S., Bjork Jr., R.L., Friedman, J.R., Bloss, C.S., Cohen, J., Gupta, S., Naidu, S., Vanoye, C.G., George Jr., A.L., Kearney, J.A., 2014. De novo KCNB1 mutations in epileptic encephalopathy. Ann. Neurol. 76, 529–540.
Towart, Rob, Linders, Joannes T.M., Hermans, An.N., Rohrbacher, Jutta, van der Linde, Henk J., Ercken, Martine, Cik, Miroslav, Roevens, Peter, Teisman, Ard, Gallacher, David J., 2009. Blockade of the IKs potassium channel: an overlooked cardiovascular liability in drug safety screening? J. Pharmacol. Toxicol. Methods 60, 1–10.
Trapp, S., Tucker, S.J., Ashcroft, F.M., 1997. Activation and inhibition of K-ATP currents by guanine nucleotides is mediated by different channel subunits. Proc. Natl. Acad. Sci. USA 94, 8872–8877.
Trimmer, J.S., 2015. Subcellular localization of K+ channels in mammalian brain neurons: remarkable precision in the midst of extraordinary complexity. Neuron 85, 238–256.
Tzingounis, A.V., Heidenreich, M., Kharkovets, T., Spitzmaul, G., Jensen, H.S., Nicoll, R. A., Jentsch, T.J., 2010. The KCNQ5 potassium channel mediates a component of the afterhyperpolarization current in mouse hippocampus. Proc. Natl. Acad. Sci. USA 107, 10232–10237.
Unoki, H., Takahashi, A., Kawaguchi, T., Hara, K., Horikoshi, M., Andersen, G., Ng, D.P., Holmkvist, J., Borch-Johnsen, K., Jørgensen, T., Sandbaek, A., Lauritzen, T., Hansen, T., Nurbaya, S., Tsunoda, T., Kubo, M., Babazono, T., Hirose, H., Hayashi, M., Iwamoto, Y., Maeda, S., 2008. SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. Nat. Genet. 40, 1098–1102.
Valente, F.M., Sparago, A., Freschi, A., Hill-Harfe, K., Maas, S.M., Frints, S.G.M., Alders, M., Pignata, L., Franzese, M., Angelini, C., Carli, D., Mussa, A., Gazzin, A., Gabbarini, F., Acurzio, B., Ferrero, G.B., Bliek, J., Williams, C.A., Riccio, A., Cerrato, F., 2019. Transcription alterations of KCNQ1 associated with imprinted methylation defects in the Beckwith-Wiedemann locus. Genet Med 21, 1808–1820.
van Bavel, J.J.A., Beekman, H.D.M., Smoczynska, A., van der Heyden, M.A.G., Vos, M.A., 2023. I(Ks) activator ML277 mildly affects repolarization and arrhythmic outcome in the CAVB dog model. Biomedicines 11.
van de Vondervoort, I., Poelmans, G., Aschrafi, A., Pauls, D.L., Buitelaar, J.K., Glennon, J.C., Franke, B., 2016. An integrated molecular landscape implicates the regulation of dendritic spine formation through insulin-related signalling in obsessive-compulsive disorder. J. Psychiatry Neurosci. 41, 280–285.
van de Vondervoort, I.I.G.M., Amiri, H., Bruchhage, M.M.K., Oomen, C.A., Rustogi, N., Cooper, J.D., van Asten, J.J.A., Heerschap, A., Bahn, S., Williams, S.C.R., Buitelaar, J.K., Poelmans, G., Glennon, J.C., 2019. Converging evidence points towards a role of insulin signaling in regulating compulsive behavior. Transl. Psychiatry 9.
van Hamersvelt, H.W., Kloke, H.J., de Jong, D.J., Koene, R.A., Huysmans, F.T., 1996. Oedema formation with the vasodilators nifedipine and diazoxide: direct local effect or sodium retention? J. Hypertens. 14, 1041–1045.
Vaxillaire, M., Populaire, C., Busiah, K., Cave, H., Gloyn, A.L., Hattersley, A.T., Czernichow, P., Froguel, P., Polak, M., 2004. Kir6.2 mutations are a common cause of permanent neonatal diabetes in a large cohort of French patients'. Diabetes 53, 2719–2722.
Vergara, C., Latorre, R., Marrion, N.V., Adelman, J.P., 1998. Calcium-activated potassium channels. Curr. Opin. Neurobiol. 8, 321–329.
Vieira, T.C., Bergamin, C.S., Gurgel, L.C., Moises, R.S., 2010. 'Hyperinsulinemic hypoglycemia evolving to gestational diabetes and diabetes mellitus in a family carrying the inactivating ABCC8 E1506K mutation. Pedia Diabetes 11, 505–508.
Vijai, J., Kapoor, A., Ravishankar, H.M., Cherian, P.J., Girija, A.S., Rajendran, B., Rangan, G., Jayalakshmi, S., Mohandas, S., Radhakrishnan, K., Anand, A., 2003. Genetic association analysis of KCNQ3 and juvenile myoclonic epilepsy in a South Indian population. Hum. Genet 113, 461–463.
Voight, B.F., Scott, L.J., Steinthorsdottir, V., Morris, A.P., Dina, C., Welch, R.P., Zeggini, E., Huth, C., Aulchenko, Y.S., Thorleifsson, G., McCulloch, L.J., Ferreira, T., Grallert, H., Amin, N., Wu, G., Willer, C.J., Raychaudhuri, S., McCarroll, S.A., Langenberg, C., Hofmann, O.M., Dupuis, J., Qi, L., Segrè, A.V., van Hoek, M., Navarro, P., Ardlie, K., Balkau, B., Benediktsson, R., Bennett, A.J., Blagieva, R., Boerwinkle, E., Bonnycastle, L.L., Bengtsson Boström, K., Bravenboer, B., Bumpstead, S., Burtt, N.P., Charpentier, G., Chines, P.S., Cornelis, M., Couper, D.J., Crawford, G., Doney, A.S., Elliott, K.S., Elliott, A.L., Erdos, M.R., Fox, C.S., Franklin, C.S., Ganser, M., Gieger, C., Grarup, N., Green, T., Griffin, S., Groves, C.J., Guiducci, C., Hadjadj, S., Hassanali, N., Herder, C., Isomaa, B., Jackson, A.U., Johnson, P.R., Jørgensen, T., Kao, W.H., Klopp, N., Kong, A., Kraft, P., Kuusisto, J., Lauritzen, T., Li, M., Lieverse, A., Lindgren, C.M., Lyssenko, V., Marre, M., Meitinger, T., Midthjell, K., Morken, M.A., Narisu, N., Nilsson, P., Owen, K.R., Payne, F., Perry, J.R., Petersen, A.K., Platou, C., Proença, C., Prokopenko, I., Rathmann, W., Rayner, N.W., Robertson, N.R., Rocheleau, G., Roden, M., Sampson, M.J., Saxena, R., Shields, B.M., Shrader, P., Sigurdsson, G., Sparsø, T., Strassburger, K., Stringham, H.M., Sun, Q., Swift, A.J., Thorand, B., Tichet, J., Tuomi, T., van Dam, R.M., van Haeften, T.W., van Herpt, T., van Vliet-Ostaptchouk, J.V., Walters, G.B., Weedon, M.N., Wijmenga, C., Witteman, J., Bergman, R.N., Cauchi, S., Collins, F.S., Gloyn, A.L., Gyllensten, U., Hansen, T., Hide, W.A., Hitman, G.A., Hofman, A., Hunter, D.J., Hveem, K., Laakso, M., Mohlke, K.L., Morris, A.D., Palmer, C.N., Pramstaller, P.P., Rudan, I., Sijbrands, E., Stein, L.D., Tuomilehto, J., Uitterlinden, A., Walker, M., Wareham, N.J., Watanabe, R.M., Abecasis, G.R., Boehm, B.O., Campbell, H., Daly, M.J., Hattersley, A.T., Hu, F.B., Meigs, J.B., Pankow, J.S., Pedersen, O., Wichmann, H.E., Barroso, I., Florez, J.C., Frayling, T.M., Groop, L., Sladek, R., Thorsteinsdottir, U., Wilson, J.F., Illig, T., Froguel, P., van Duijn, C.M., Stefansson, K., Altshuler, D., Boehnke, M., McCarthy, M.I., 2010. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat. Genet 42, 579–589.
Vonmuhlendahl, E., Herkenhoff, H., 1995. Long-term course of neonatal diabetes. New Engl. J. Med. 333, 704–708.
Walton-Betancourth, S., Ashford, J., Beardsall, K., Gooding, N., Gurnell, E.M., Hendriks, E., Hysted, H., Lee, J., Thankamony, A., Tseretopoulou, X., Win, M., Williams, R.M., 2022. Early postnatal use of glibenclamide in permanent neonatal

diabetes secondary to antenatally diagnosed KJCN11 mutation. Horm. Res. Paediatr. 95, 476–483.
Wang, H. S., Pan, Z., Shi, W., Brown, B. S., Wymore, R. S., Cohen, I. S., Dixon, J. E., & McKinnon, D., 1998. KCNQ2 and KCNQ3 potassium channel subunits: molecular correlates of the M-channel. Science 282, 1890–1893.
Wang, H., Miao, K., Zhao, J., Liu, L., Cui, G., Chen, C., Wang, D.W., Ding, H., 2013. Common variants in KCNQ1 confer increased risk of type 2 diabetes and contribute to the diabetic epidemic in East Asians: a replication and meta-analysis. Ann. Hum. Genet 77, 380–391.
Wang, Y., Samuels, J.F., Chang, Y.C., Grados, M.A., Greenberg, B.D., Knowles, J.A., McCracken, J.T., Rauch, S.L., Murphy, D.L., Rasmussen, S.A., Cullen, B., Hoehn-Saric, R., Pinto, A., Fyer, A.J., Piacentini, J., Pauls, D.L., Bienvenu, O.J., Riddle, M., Shugart, Y.Y., Liang, K.Y., Nestadt, G., 2009. Gender differences in genetic linkage and association on 11p15 in obsessive-compulsive disorder families. Am. J. Med. Genet. Part B-Neuropsychiatr. Genet. 150b, 33–40.
Weaver, A.K., Bomben, V.C., Sontheimer, H., 2006. Expression and function of calcium-activated potassium channels in human glioma cells. Glia 54, 223–233.
Wei, Aguan, D., Wakenight, Paul, Theresa, A.Zwingman, Bard, Angela M., Sahai, Nikhil, Willemsen, Marjolein H., Schelhaas, Helenius J., Stegmann, Alexander P.A., Verhoeven, Judith S., de Man, Stella A., Wessels, Marja W., Kleefstra, Tjitske, Shinde, Deepali N., Helbig, Katherine L., Basinger, Alice, Wagner, Victoria F., Rodriguez-Buritica, David, Bryant, Emily, Millichap, John J., Millen, Kathleen J., Dobyns, William B., Ramirez, Jan-Marino, Kalume, Franck K., 2022. Human KCNQ5 de novo mutations underlie epilepsy and intellectual disability. J. Neurophysiol. 128, 40–61.
Weissman, M.M., Bland, R.C., Canino, G.J., Greenwald, S., Hwu, H.G., Lee, C.K., Newman, S.C., Oakley-Browne, M.A., Rubio-Stipec, M., Wickramaratne, P.J., et al., 1994. The cross national epidemiology of obsessive compulsive disorder. The Cross National Collaborative Group. J. Clin. Psychiatry 55 (Suppl: 5–10).
Weston, A.H., Edwards, G., 1992. Recent progress in potassium channel opener pharmacology. Biochem. Pharmacol. 43, 47–54.
Wickenden, A.D., Krajewski, J.L., London, B., Wagoner, P.K., Wilson, W.A., Clark, S., Roeloffs, R., McNaughton-Smith, G., Rigdon, G.C., 2008. N-(6-chloro-pyridin-3-yl)-3,4-difluoro-benzamide (ICA-27243): a novel, selective KCNQ2/Q3 potassium channel activator. Mol. Pharmacol. 73, 977–986.
Wiedemann, B., Schober, E., Waldhoer, T., Koehle, J., Flanagan, S.E., Mackay, D.J., Steichen, E., Meraner, D., Zimmerhackl, L.B., Hattersley, A.T., Ellard, S., Hofer, S., 2010. 'Incidence of neonatal diabetes in Austria-calculation based on the Austrian Diabetes Register. Pedia Diabetes 11, 18–23.
Willegems, K., Eldstrom, J., Kyriakis, E., Ataei, F., Sahakyan, H., Dou, Y., Russo, S., Van, F., Petegem, Fedida, D., 2022. 'Structural and electrophysiological basis for the modulation of KCNQ1 channel currents by ML277. Nat. Commun. 13, 3760.
Wolkenberg, S.E., Nolt, M.B., Bilodeau, M.T., Trotter, B.W., Manley, P.J., Kett, N.R., Nanda, K.K., Wu, Z.C., Cato, M.J., Kane, S.A., Kiss, L., Spencer, R.H., Wang, J.X., Lynch, J.J., Regan, C.P., Stump, G.L., Li, B., White, R., Yeh, S.Z., Dinsmore, C.J., Lindsley, C.W., Hartman, G.D., 2017. Discovery of MK-1832, a Kv1.5 inhibitor with improved selectivity and pharmacokinetics. Bioorg. Med. Chem. Lett. 27, 1062–1069.
Wu, M., Obara, Y., Ohshima, S., Nagasawa, Y., Ishii, K., 2017. Insulin treatment augments KCNQ1/KCNE1 currents but not KCNQ1 currents, which is associated with an increase in KCNE1 expression. Biochem Biophys. Res Commun. 493, 409–415.
Wulff, H., Castle, N.A., Pardo, L.A., 2009. Voltage-gated potassium channels as therapeutic targets. Nat. Rev. Drug Discov. 8, 982–1001.
Xiong, Q.J., Sun, H.Y., Li, M., 2007. Zinc pyrithione-mediated activation of voltage-gated KCNQ potassium channels rescues epileptogenic mutants. Nat. Chem. Biol. 3, 287–296.
Xu, Y., Wang, Y.H., Zhang, M., Jiang, M., Rosenhouse-Dantsker, A., Wassenaar, T., Tseng, G.N., 2015. Probing binding sites and mechanisms of action of an I-Ks activator by computations and experiments. Biophys. J. 108, 62–75.
Yamagata, K., Senokuchi, T., Lu, M., Takemoto, M., Fazlul Karim, M., Go, C., Sato, Y., Hatta, M., Yoshizawa, T., Araki, E., Miyazaki, J., Song, W.J., 2011. Voltage-gated K+ channel KCNQ1 regulates insulin secretion in MIN6 β-cell line. Biochem Biophys. Res Commun. 407, 620–625.
Yang, Z., Shi, G., Li, C., Wang, H., Liu, K., Liu, Y., 2004. Electrophysiologic effects of nicorandil on the guinea pig long QT1 syndrome model. J. Cardiovasc Electro 15, 815–820.
Yasuda, K., Miyake, K., Horikawa, Y., Hara, K., Osawa, H., Furuta, H., Hirota, Y., Mori, H., Jonsson, A., Sato, Y., Yamagata, K., Hinokio, Y., Wang, H.Y., Tanahashi, T., Nakamura, N., Oka, Y., Iwasaki, N., Iwamoto, Y., Yamada, Y., Seino, Y., Maegawa, H., Kashiwagi, A., Takeda, J., Maeda, E., Shin, H.D., Cho, Y.M., Park, K.S., Lee, H.K., Ng, M.C., Ma, R.C., So, W.Y., Chan, J.C., Lyssenko, V., Tuomi, T., Nilsson, P., Groop, L., Kamatani, N., Sekine, A., Nakamura, Y., Yamamoto, K., Yoshida, T., Tokunaga, K., Itakura, M., Makino, H., Nanjo, K., Kadowaki, T., Kasuga, M., 2008. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. Nat. Genet 40, 1092–1097.
Yu, H., Lin, Z., Mattmann, M.E., Zou, B., Terrenoire, C., Zhang, H., Wu, M., McManus, O. B., Kass, R.S., Lindsley, C.W., Hopkins, C.R., Li, M., 2013. Dynamic subunit stoichiometry confers a progressive continuum of pharmacological sensitivity by KCNQ potassium channels. Proc. Natl. Acad. Sci. USA 110, 8732–8737.
Zaczek, R., Chorvat, R.J., Saye, J.A., Pierdomenico, M.E., Maciag, C.M., Logue, A.R., Fisher, B.N., Rominger, D.H., Earl, R.A., 1998. Two new potent neurotransmitter release enhancers, 10,10-bis(4-pyridinylmethyl)-9(10H)-anthracenone and 10,10-bis (2-fluoro-4-pyridinylmethyl)-9(10H)-anthracenone: comparison to linopirdine. J. Pharm. Exp. Ther. 285, 724–730.
Zhang, J., Juhl, C.R., Hylten-Cavallius, L., Salling-Olsen, M., Linneberg, A., Holst, J.J., Hansen, T., Kanters, J.K., Torekov, S.S., 2020. Gain-of-function mutation in the voltage-gated potassium channel gene KCNQ1 and glucose-stimulated hypoinsulinemia - case report. BMC Endocr. Disord. 20, 38.