



Your Guide to Understanding
Genetic Conditions

KCNB1

potassium voltage-gated channel subfamily B member 1

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Normal Function

From NCBI Gene:

Voltage-gated potassium (Kv) channels represent the most complex class of voltage-gated ion channels from both functional and structural standpoints. Their diverse functions include regulating neurotransmitter release, heart rate, insulin secretion, neuronal excitability, epithelial electrolyte transport, smooth muscle contraction, and cell volume. Four sequence-related potassium channel genes - shaker, shaw, shab, and shal - have been identified in *Drosophila*, and each has been shown to have human homolog(s). This gene encodes a member of the potassium channel, voltage-gated, shab-related subfamily. This member is a delayed rectifier potassium channel and its activity is modulated by some other family members. [provided by RefSeq, Jul 2008]

From UniProt:

Voltage-gated potassium channel that mediates transmembrane potassium transport in excitable membranes, primarily in the brain, but also in the pancreas and cardiovascular system. Contributes to the regulation of the action potential (AP) repolarization, duration and frequency of repetitive AP firing in neurons, muscle cells and endocrine cells and plays a role in homeostatic attenuation of electrical excitability throughout the brain (PubMed:23161216). Plays also a role in the regulation of exocytosis independently of its electrical function (By similarity). Forms tetrameric potassium-selective channels through which potassium ions pass in accordance with their electrochemical gradient. The channel alternates between opened and closed conformations in response to the voltage difference across the membrane. Homotetrameric channels mediate a delayed-rectifier voltage-dependent outward potassium current that display rapid activation and slow inactivation in response to membrane depolarization (PubMed:8081723, PubMed:1283219, PubMed:10484328, PubMed:12560340, PubMed:19074135, PubMed:19717558, PubMed:24901643). Can form functional homotetrameric and heterotetrameric channels that contain variable proportions of KCNB2; channel properties depend on the type of alpha subunits that are part of the channel (By similarity). Can also form functional heterotetrameric channels with other alpha subunits that are non-conducting when expressed alone, such as KCNF1, KCNG1, KCNG3, KCNG4, KCNH1, KCNH2, KCNS1, KCNS2, KCNS3 and KCNV1, creating a functionally diverse range of channel complexes (PubMed:10484328, PubMed:11852086, PubMed:12060745, PubMed:19074135, PubMed:19717558, PubMed:24901643). Heterotetrameric channel activity formed with KCNS3 show increased current amplitude with the threshold for action potential activation shifted towards more negative values in hypoxic-treated pulmonary artery smooth muscle cells (By similarity). Channel properties are also modulated by cytoplasmic ancillary beta subunits such as AMIGO1, KCNE1, KCNE2 and KCNE3, slowing activation and inactivation rate of the delayed rectifier potassium channels (By similarity). In vivo, membranes probably contain a mixture of heteromeric potassium channel complexes, making it difficult to assign currents observed in intact tissues to any particular potassium channel family member. Major contributor to the slowly inactivating delayed-rectifier voltage-gated potassium current in neurons of the central nervous system, sympathetic ganglion neurons, neuroendocrine cells, pancreatic beta cells, cardiomyocytes and smooth muscle cells. Mediates the major part of the somatodendritic delayed-rectifier potassium current in hippocampal and cortical pyramidal neurons and sympathetic superior cervical ganglion (CGC) neurons that acts to slow down periods of firing, especially during high frequency stimulation. Plays a role in the induction of long-term potentiation (LTP) of neuron excitability in the CA3 layer of the hippocampus (By similarity). Contributes to the regulation of glucose-induced action potential amplitude and duration in pancreatic beta cells, hence limiting calcium influx and insulin secretion (PubMed:23161216). Plays a role in the regulation of resting membrane potential and contraction in hypoxia-treated pulmonary artery smooth muscle cells. May contribute to the regulation of the duration of both the action potential of cardiomyocytes and the heart ventricular repolarization QT interval. Contributes to the pronounced pro-apoptotic potassium current surge during neuronal apoptotic cell death in response to oxidative injury. May confer neuroprotection in response to hypoxia/ischemic insults by suppressing pyramidal neurons hyperexcitability in hippocampal and cortical regions (By similarity). Promotes trafficking of KCNG3, KCNH1 and KCNH2 to the cell surface membrane, presumably by forming heterotetrameric channels with these subunits (PubMed:12060745). Plays a role in the calcium-dependent recruitment and release of fusion-competent vesicles from the soma of neurons, neuroendocrine and glucose-induced pancreatic beta cells by binding key components

of the fusion machinery in a pore-independent manner.

Health Conditions Related to Genetic Changes

From NCBI Gene:

- Epileptic encephalopathy, early infantile, 26

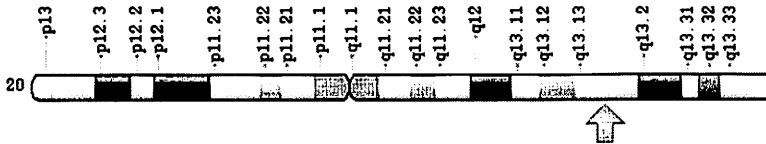
From UniProt:

Epileptic encephalopathy, early infantile, 26 (EIEE26): A form of epileptic encephalopathy, a heterogeneous group of severe childhood onset epilepsies characterized by refractory seizures, neurodevelopmental impairment, and poor prognosis. Development is normal prior to seizure onset, after which cognitive and motor delays become apparent. EIEE26 patients manifest multiple types of seizures, delayed psychomotor development, poor or absent speech, hypotonia, hypsarrhythmia. [MIM:616056]

Chromosomal Location

Cytogenetic Location: 20q13.2, which is the long (q) arm of chromosome 20 at position 13.2

Molecular Location: base pairs 49,363,877 to 49,484,042 on chromosome 20 (Homo sapiens Annotation Release 107, GRCh38.p2) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- DRK1
- Kv2.1

Additional Information & Resources

Genetic Testing Registry (1 link)

- GTR: Genetic tests for KCNB1 (<http://www.ncbi.nlm.nih.gov/gtr/tests/?term=3745%5Bgeneid%5D>)

OMIM (2 links)

- OMIM: EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 26 (<http://omim.org/entry/616056>)
- OMIM: POTASSIUM CHANNEL, VOLTAGE-GATED, SHAB-RELATED SUBFAMILY, MEMBER 1 (<http://omim.org/entry/600397>)

Research Resources (4 links)

- HGNC Gene Family: Potassium voltage-gated channels (<http://www.genenames.org/cgi-bin/genefamilies/set/274>)

- HGNC Gene Symbol Report (http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=6231)
- NCBI Gene (<http://www.ncbi.nlm.nih.gov/gene/3745>)
- UniProt (<http://www.uniprot.org/uniprot/Q14721>)

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#616056

ORPHA: 442835

EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 26; EIEE26**Phenotype-Gene Relationships**

Location	Phenotype	Phenotype MIM number	Inheritance (in progress)	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
20q13.13	Epileptic encephalopathy, early infantile, 26	616056	AD	3	KCNB1	600397

[Clinical Synopsis](#)
[Phenotypic Series](#)
TEXT

A number sign (#) is used with this entry because epileptic encephalopathy-26 (EIEE26) is caused by heterozygous mutation in the KCNB1 gene (600397) on chromosome 20q13.

For a general phenotypic description and a discussion of genetic heterogeneity of EIEE, see EIEE1 (308350).

Clinical Features

Torkamani et al. (2014) reported 3 unrelated children with early-onset epileptic encephalopathy. A 9-year-old girl had delayed psychomotor development, cognitive impairment, and intermittent agitation. In infancy, she showed hypotonia and excessive somnolence. Although onset of generalized tonic-clonic seizures occurred at age 4.75 years, she had previously manifested behavior likely representing other seizure types. The seizures were poorly controlled. EEG showed multifocal epileptiform discharges, even during sleep. Brain MRI showed subtle asymmetric volume loss in the left hippocampus. The second child was a 7-year-old boy with poor seizure control, cognitive and motor developmental delay, absent speech, and stereotyped hand-wringing movements. He had onset of intractable seizures at age 8 months following early developmental delay. EEG showed hypsarrhythmia and multifocal epileptiform discharges with polyspike waves. Brain MRI was normal. The third child was a 5-year-old girl with developmental delay who had onset of multiple seizure types in the first year of life. ⁽³⁾

Molecular Genetics

In 3 unrelated patients with early-onset epileptic encephalopathy, Torkamani et al. (2014) identified 3 different de novo heterozygous missense mutations in the KCNB1 gene (600397.0001-600397.0003). The mutations were found by whole-exome sequencing and confirmed by Sanger sequencing. All mutations affected the pore domain of the channel, and in vitro expression studies in CHO-K1 cells showed that the mutations led to a loss of potassium ion selectivity with gain of a depolarizing inward cation conductance. Coexpression of the mutations with wildtype KCNB1 resulted in a dominant-negative effect, causing depolarizing shifts in the resting potential and the voltage dependence of activation as well as impaired membrane repolarization, resulting in increased cellular excitability. ⁽⁴⁾

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*600397

POTASSIUM CHANNEL, VOLTAGE-GATED, SHAB-RELATED SUBFAMILY, MEMBER 1; KCNB1*Alternative titles; symbols*

KV2.1

HGNC Approved Gene Symbol: KCNB1**Cytogenetic location:** 20q13.13 **Genomic coordinates (GRCh38):** 20:49,363,876-49,484,041 (from NCBI)**Gene-Phenotype Relationships**

Location	Phenotype	Phenotype MIM number	Inheritance (in progress)	Phenotype mapping key
20q13.13	Epileptic encephalopathy, early infantile, 26	616056	AD	3

TEXT**Description**

The KCNB1 gene encodes Kv2.1, the main contributor to delayed rectifier potassium currents in pyramidal neurons of the hippocampus and cortex (summary by Torkamani et al., 2014). [\[↗\]](#)

Cloning and Expression

Ottshytsch et al. (2002) cloned KCNB1, which they called Kv2.1, from a brain cDNA library. Sequence analysis revealed the typical topology of Kv subunits, including 6 transmembrane segments (S1 to S6) and a potassium-selective motif, GYG, in the P loop between S5 and S6. PCR detected robust, ubiquitous expression of KCNB1, with highest levels in brain, skeletal muscle, pancreas, and small intestine. [\[↗\]](#)

Gene Function

Ottshytsch et al. (2002) found that, when transfected alone into murine fibroblasts, Kv2.1 formed homotetramers to produce a typical rapidly activating delayed outward rectifier K(+) current. Coexpression with KCNG4 (607603), KCNV2 (607604), or KCNG3 (606767) resulted in altered channel properties. By confocal microscopy, they found that Kv2.1 expression was required for the trafficking of KCNG4, KCNV2, and KCNG3 to the plasma membrane. [\[↗\]](#)

Sano et al. (2002) found that KCNG3 decreased the rate of deactivation of channels formed by Kv2.1 when coexpressed in COS-7 cells. [\[↗\]](#)

Park et al. (2006) used mass spectrometry-SILAC (stable isotope labeling with amino acids in cell culture) to identify 16 Kv2.1 phosphorylation sites, of which 7 were dephosphorylated by calcineurin (see 114105). Mutation of individual calcineurin-regulated sites to alanine produced incremental shifts mimicking dephosphorylation, whereas mutation to aspartate yielded equivalent resistance to calcineurin. Mutations at multiple sites were additive, showing that variable phosphorylation of Kv2.1 at a large number of sites allows graded activity-dependent regulation of channel gating and neuronal firing properties. [\[↗\]](#)

Xu et al. (2008) showed that the Kv2.1 channel may interact with several species of phospholipid and that enzymatic removal of their phospho-heads creates an insuperable energy barrier for the positively charged voltage sensor to move through the initial gating step(s), thus immobilizing it, and also raises the energy barrier for the downstream step(s). [\[↗\]](#)

Biochemical Features**Crystal Structure**

Long et al. (2007) described the structure of a chimeric voltage-dependent potassium-ion channel, which they called the 'paddle-chimera channel,' in which the voltage sensor paddle has been transferred from K(v)2.1 to K(v)1.2 (176262). When crystallized in complex with lipids, the complete structure at 2.4-angstrom resolution revealed the pore and voltage sensors embedded in a membrane-like arrangement of lipid molecules. The detailed structure, which

can be compared directly to a large body of functional data, explains charge stabilization within the membrane and suggested a mechanism for voltage-sensor movements and pore gating. [↗](#)

Mapping

Using genomic P1 clones for fluorescence in situ hybridization, Melis et al. (1995) mapped a human delayed rectifier potassium channel gene to 20q13.2. A polymorphic (GA) microsatellite repeat was identified in 1 of the P1 clones. This SSR marker was genotyped in 4 CEPH pedigrees with demonstration of linkage to D20S109. The assignment to 20q13.2 eliminated it as a candidate for benign familial neonatal convulsions (BFNC; 121200), which maps to 20q13.3. By linkage analysis, the KCNB1 gene mapped more than 30 cM proximal to the BFNC locus. Lock et al. (1994) showed that the mouse gene, *Kcnb1*, maps to the distal region of mouse chromosome 2. [↗](#)

Molecular Genetics

In 3 unrelated patients with early infantile epileptic encephalopathy-26 (EIEE26; 616056), Torkamani et al. (2014) identified 3 different de novo heterozygous missense mutations in the KCNB1 gene (600397.0001-600397.0003). The mutations were found by whole-exome sequencing. All mutations affected the pore domain of the channel, and in vitro expression studies in CHO-K1 cells showed that the mutations led to a loss of potassium ion selectivity with gain of a depolarizing inward cation conductance. Coexpression of the mutations with wildtype KCNB1 resulted in a dominant-negative effect, causing depolarizing shifts in the resting potential and the voltage dependence of activation as well as impaired membrane repolarization, resulting in increased cellular excitability. [↗](#)

ALLELIC VARIANTS (3 Selected Examples):

[Table View](#)
[ClinVar](#)

.0001 EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 26

KCNB1, SER347ARG [dbSNP:rs587777848] [ClinVar]

In a child with early-infantile epileptic encephalopathy-26 (EIEE26; 616056) Torkamani et al. (2014) identified a de novo heterozygous mutation in the KCNB1 gene, resulting in a ser347-to-arg (S347R) substitution at a highly conserved residue in the pre-pore transmembrane domain. The mutation, which was found by whole-exome sequencing and confirmed by Sanger sequencing, was not present in the unaffected parents or an unaffected sib. The variant was filtered against the 1000 Genomes Project and Exome Sequencing Project databases. [↗](#)

.0002 EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 26

KCNB1, GLY379ARG [dbSNP:rs587777850] [ClinVar]

In a child with EIEE26 (616056), Torkamani et al. (2014) identified a de novo heterozygous mutation in the KCNB1 gene, resulting in a gly379-to-arg (G379R) substitution at a highly conserved residue in the GYG motif that defines the potassium selectivity filter. The mutation, which was found by whole-exome sequencing and confirmed by Sanger sequencing, was filtered against the 1000 Genomes Project and Exome Sequencing Project databases. Two additional heterozygous mutations in other genes (NPC2, 601015 and GRIN2A, 138253) that were inherited from an unaffected parent were also found but were thought not to contribute to the phenotype in the proband. [↗](#)

Srivastava et al. (2014) identified a de novo heterozygous c.1135G-A transition in the KCNB1 gene, resulting in a gly379-to-arg (G379R) substitution in a patient with epileptic encephalopathy. This patient was ascertained from a large cohort of 78 individuals with neurologic disabilities who underwent whole-exome sequencing. [↗](#)

.0003 EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 26

KCNB1, THR374ILE [dbSNP:rs587777849] [ClinVar]

In a child with EIEE26 (616056), Torkamani et al. (2014) identified a de novo heterozygous mutation in the KCNB1 gene, resulting in a thr374-to-ile (T374I) substitution at a highly conserved residue in the pore helix domain. The mutation, which was found by whole-exome sequencing and confirmed by Sanger sequencing, was filtered against the 1000 Genomes Project and Exome Sequencing Project databases. [↗](#)

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