Title: Brugada Syndrome *GeneReview* – Less Common Genetic Causes
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Note: The following information is provided by the authors and has not been reviewed by *GeneReviews* staff.

CACNA1C
CACNA2D1
CACNB2
GPD1L
HCN4
KCND3
KCNE3
KCNE5 (KCNE1L)
KCNJ8
RANGRF
SCN1B
SCN2B
SCN3B
SLMAP
TRPM4

CACNA1C

Two other genes associated with the Brugada syndrome encode the α1 (*CACNA1C*) and β (*CACNB2*) subunits of the L-type cardiac calcium channel. The pathogenic variants in the α1 and β2b subunits of the cardiac calcium channel were often found to be associated with a familial sudden cardiac death (SCD) syndrome in which a Brugada syndrome phenotype is combined with shorter than normal QT secondary to a loss of function of the calcium channel current (I_{Ca}).

Gene structure. The transcript variant NM_000719.6 comprises 47 exons. Multiple alternative transcripts have been described.

Pathogenic variants

Table 5. *CACNA1C* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.116C>T	p.Ala39Val [1]	NM_000719.6 NP_000710.5
c.1468G>A	p.Gly490Arg [1]	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Antzelevitch et al [2007]

Normal gene product. The genomic sequence encodes a protein of 2221 amino acids. *CACNA1C* encodes a number of isoforms of the pore-forming α1 subunit of the long-lasting (L-type) voltage-gated calcium channel ($Ca_v1.2$). The $Ca_v1.2$ channel is activated upon depolarization of the cardiomyocyte, and is responsible for the depolarizing influx of calcium, the L-type calcium current (I_{CaL}). I_{CaL} inactivates very slowly; thus, it is of major significance for maintaining the plateau phase of the AP. Furthermore, it is the most important source of intracellular calcium and it represents the coupling between excitation and contraction by inducing release of calcium from the sarcoplasmic reticulum through calcium activation of the ryanodine receptors.

Abnormal gene product. When expressed with other $Ca_v1.2$ subunits in CHO cells, a clearly reduced I_{CaL} was found in both cases. Thus, the mechanism of Brugada syndrome with these pathogenic variants (i.e., decreased depolarizing current during AP) was independent of *SCN5A* [Antzelevitch et al 2007].

CACNA2D1

Gene structure. The longest transcript NM_001110843.1 comprises 39 exons and encodes the longest isoform NP_001104313.1 which has 1103 amino acids. Alternatively spliced transcript variants have been described.

Pathogenic variants and **normal and abnormal gene products.** For descriptions see locus-specific and HGMD databases in Table A, Antzelevitch et al [2007], Burashnikov et al [2010], Pérez-Riera et al [2012], and Risgaard et al [2013].

CACNB2

Gene structure. The transcript NM_201590.2 comprises 13 exons. Alternatively spliced variants encoding different isoforms have been described.

Pathogenic variants. The missense variant c.1442C>T is located in the region of the gene that encodes the C-terminal part of $Ca_{v\beta2}$ close to the $Ca_v1.2$ binding domain.

Table 6. *CACNB2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1442C>T	p.Ser481Leu	NM_201590.2 NP_963884.2

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Normal gene product. The genomic sequence encodes a protein of 660 amino acids. *CACNB2* encodes the β2 subunit ($Ca_{v\beta2}$) of $Ca_v1.2$, which modifies gating (increasing the I_{CaL}) and has been associated with Brugada syndrome 4. $Ca_{v\beta2}$ functions as a

chaperone for the α subunit of $Ca_v1.2$, ensuring its transport to the plasma membrane. It is the dominantly expressed $Ca_v1.2$ β subunit in the heart.

Abnormal gene product. Because the pathogenic variant is located in close proximity to the DI–DII linker of $Ca_v1.2$, interference with the stimulatory role of $Ca_{v\beta2}$ on I_{Ca} is a likely pathogenic mechanism for this pathogenic variant. The mechanism of Brugada syndrome 4 involves a reduction of the depolarizing I_{Ca} [Cordeiro et al 2009].

GPD1L

Gene structure. The *GPD1L* transcript NM_015141.3 has 4068 nucleotides and comprises eight exons.

Pathogenic variants. In 2007, the pathogenic variant c.839C>T and the novel SIDS-associated pathogenic variant c.247G>A were both shown to decrease cardiac I_{Na} amplitude. The pathogenic variant c.839C>T (p.Ala280Val) reduces inward sodium currents by approximately 50% and *SCN5A* cell surface by approximately 31% [London et al 2007, Van Norstrand et al 2007]. *GPDIL* pathogenic variant c.839C>T is linked to Brugada syndrome in a large pedigree in which Brugada syndrome is associated with progressive conduction disease, a low sensitivity to procainamide, and a relatively good prognosis [London et al 2007, Van Norstrand et al 2007].

Table 7. *GPDIL* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.247G>A	p.Glu83Lys	NM_015141.3 NP_055956.1
c.839C>T [1]	p.Ala280Val	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

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1. SIDS-associated pathogenic variant

Normal gene product. The gene encodes a protein of 351 amino acids (NP_055956.1). The protein glycerol 3-phosphate dehydrogenase 1-like (G3PD1L) affects the trafficking of the cardiac Na^+ channel to the cell surface.

Abnormal gene product. The G3PD1L protein containing the p.Ala280Val substitution results in a partial reduction of I_{Na} caused, at least in part, by a trafficking defect.

HCN4

Computer simulation showed that the I_f channel produced a background current contributing to the action potential repolarization of ventricular cardiomyocytes. The background current was generated by a mixed ion-selectivity for Na^+ and K^+, and incomplete closure for the deactivation gate of I_f channels.

Gene structure. The transcript NM_005477.2 comprises eight exons and encodes a protein of 1203 amino acids. Two pseudogenes have been identified on chromosome 15.

Pathogenic variants. An *HCN4* pathogenic variant that caused abnormal splicing was identified in a symptomatic individual with Brugada syndrome. *HCN4* pathogenic variants affect channel properties even in the absence of overt clinical findings [Ueda et al 2009].

Abnormal gene product. Computer simulation showed that the I_f channel produced a background current contributing to the action potential repolarization of ventricular cardiomyocytes. The background current was generated by a mixed ion-selectivity for Na^+ and K^+, and incomplete closure for the deactivation gate of I_f channels.

KCND3

Giudicessi et al [2011] provided the first molecular and functional evidence implicating novel gain-of-function *KCND3* pathogenic variants (Kir4.3 protein) in the pathogenesis and phenotypic expression of Brugada syndrome, with the potential for a lethal arrhythmia being precipitated by a genetically enhanced I_{to} current gradient within the right ventricle where *kcnd3* expression is the highest.

Gene structure. The longest transcript NM_004980.4 comprises eight exons and encodes a 655-amino acid protein NP_004971.2.

KCNE3

The Brugada syndrome-related gene *KCNE3* encodes MiRP2, a regulatory β subunit of the transient outward potassium channel I_{to}, which is one of five homologous auxiliary β subunits (KCNE peptides) of voltage-gated potassium ion channels.

Gene structure. The transcript NM_005472.4 comprises three exons.

Pathogenic variants. The relation between pathogenic variants in *KCNE3* and Brugada syndrome 6 was established in a Danish family with four individuals who had a type 1 Brugada syndrome ECG pattern and normal QT interval and the heterozygous *KCNE3* missense pathogenic variant p.Arg99His. When the mutated *KCNE3* was coexpressed in CHO cells with $K_V4.3$ (the α subunit of the I_{to} channel), an increase in the I_{to} as well as an accelerated inactivation of the current were observed [Delpón et al 2008].

Normal gene product. The genomic sequence encodes a protein of 103 amino acids. *KCNE3* encodes MiRP2, one of five homologous auxiliary β subunits (KCNE peptides) of voltage-gated potassium ion channels. The KCNE peptides modulate several potassium currents in the heart, including I_{Ks}, I_{Kr}, and I_{to}.

Abnormal gene product. See ***KCNE3,* Pathogenic variants**.

KCNE5 (*KCNE1L*)

Although it is well established that Brugada syndrome has mainly an autosomal pattern of inheritance, a pathogenic variant in this X-linked gene has been described in one family with Brugada syndrome [Ohno et al 2011].

Gene structure. The transcript NM_012282.2 comprises one exon and encodes a protein of 142 amino acids.

KCNJ8

Previously related to early repolarization syndrome [Haïssaguerre et al 2009], *KCNJ8* was implicated as a novel J-wave syndrome susceptibility gene, pathogenic variants in which results in a marked gain of function in the cardiac $K_{(ATP)}$ Kir6.1 channel [Medeiros-Domingo et al 2010].

Gene structure. The transcript XM_005253358.2 encodes a protein of 424 amino acids.

RANGRF

Gene structure. The transcript variant NM_016492.4 represents the shortest transcript and encodes the longest isoform of 186 amino acids. Alternative splicing results in multiple transcripts.

Pathogenic variants and **normal and abnormal gene products.** See descriptions in Olesen et al [2011] and Campuzano et al [2014].

SCN1B

Gene structure. The gene comprises three coding exons. *SCN1B* transcripts were expressed in the human heart and were abundant in Purkinje fibers that play a critical role in electric pulse conduction in heart. The longer transcript NM_001037.4 encodes the shorter isoform (a) NP_001028.1.

Pathogenic variants. Three pathogenic variants that segregated with arrhythmia in families have been identified.

Normal gene product. The genomic sequence encodes a protein of 218 amino acids (isoform a). *SCN1B* encodes the β1 subunit of the cardiac sodium channel conducting the I_{Na} current. In the heart the biophysical function of the β1 subunits and β1b splicing variant is to modify the function of $Na_v1.5$, by increasing the I_{Na} (+69% and +76%, respectively).

Abnormal gene product. Electrophysiologic study of heterologously expressed sodium channels revealed loss of sodium current with mutated subunits [Watanabe et al 2008].

SCN2B

Gene structure. The transcript NM_004588.4 has four exons.

Pathogenic variants. See locus specific and HGMD databases in Table A, Haug et al [2000], Watanabe et al [2009], and Riuró et al [2013].

Normal gene product. The transcript NM_004588.4 encodes the sodium channel subunit beta-2 with 215 amino acids (NP_004579.1).

Abnormal gene product. See Riuró et al [2013].

SCN3B

Gene structure. The gene comprises five coding exons (NM_018400.3).

Pathogenic variants. A pathogenic variant in *SCN3B* was found associated with Brugada syndrome [Hu et al 2009].

Table 8. *SCN3B* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.29T>C	p.Leu10Pro	NM_018400.3 NP_060870.1

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Normal gene product. The genomic sequence encodes a protein of 215 amino acids (NP_060870.1). *SCN3B* encodes the β3 subunit of the cardiac sodium channel conducting the I_{Na} current. In the heart the function of the β3 subunit is to modify the function of $Na_v1.5$ by increasing the I_{Na} as for the β1 subunit, albeit with another kinetics.

Abnormal gene product. When the mutated protein with p.Leu10Pro was expressed in TSA201 cells together with *SCN5A* and *SCN1B*, the mutated protein was found to result in defective trafficking of $Na_v1.5$ and reduced I_{Na} [Hu et al 2009].

SLMAP

Gene structure. The transcript NM_007159.2 comprises 21 exons and encodes a protein of 811 amino acids.

Pathogenic variants and **normal and abnormal gene products.** See descriptions in Ishikawa et al [2012].

TRPM4

Gene structure. The longest transcript variant NM_017636.3 comprises 25 exons and encodes a protein of 1214 amino acids.

Pathogenic variants. See locus specific and HGMD databases in Table A.

Normal gene product. Ion channel that mediates transport of monovalent cations across membranes resulting in depolarization

Abnormal gene product. See Duthoit et al [2012], Stallmeyer et al [2012], Liu et al [2013], and Mathar et al [2014].

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