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Brugada Syndrome

Synonym: Sudden Unexpected Nocturnal Death Syndrome

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Summary

Clinical characteristics

Brugada syndrome is characterized by cardiac conduction abnormalities (ST segment abnormalities in leads V_1-V_3 on EKG and a high risk for ventricular arrhythmias) that can result in sudden death. Brugada syndrome presents primarily during adulthood, although age at diagnosis may range from infancy to late adulthood. The mean age of sudden death is approximately 40 years. Clinical presentations may also include sudden infant death syndrome (SIDS; death of a child during the first year of life without an identifiable cause) and sudden unexpected nocturnal death syndrome (SUNDS), a typical presentation in individuals from Southeast Asia. Other conduction defects can include first-degree AV block, intraventricular conduction delay, right bundle branch block, and sick sinus syndrome.

Diagnosis/testing

The diagnosis of Brugada syndrome is established clinically in an individual with characteristic EKG findings and suggestive clinical history and/or family history. A molecular diagnosis can be established in an individual with characteristic features and identification of a heterozygous pathogenic variant in *SCN5A* or one of the additional 42 genes associated with Brugada syndrome.

Management

Treatment of manifestations: Implantable cardioverter defibrillator (ICD) in individuals with a history of syncope or cardiac arrest; isoproterenol for electrical storms. During surgery and in the postsurgical recovery period persons with Brugada syndrome should be monitored by EKG.

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Prevention of primary manifestations: Quinidine (1-2 g daily). Treatment of asymptomatic individuals is controversial.

Surveillance: EKG monitoring every one to two years for at-risk individuals with a family history of Brugada syndrome or who have a known pathogenic variant that can lead to Brugada syndrome.

Agents/circumstances to avoid: High fever, vagotonic agents, alpha-adrenergic agonists, beta-adrenergic antagonists, tricyclic antidepressants; first-generation antihistamines (dimenhydrinate); cocaine; class 1C antiarrhythmic drugs (flecainide, propafenone) and class 1A agents (procainamide, disopyramide).

Evaluation of relatives at risk: Identification of relatives at risk using EKG or (if the pathogenic variant in the family is known) molecular genetic testing enables use of preventive measures and avoidance of medications that can induce ventricular arrhythmias.

Genetic counseling

In most instances Brugada syndrome is inherited in an autosomal dominant manner; the exception is *KCNE5*-related Brugada syndrome, which is inherited in an X-linked manner. Most individuals diagnosed with Brugada syndrome have an affected parent or another affected close relative. The proportion of individuals with Brugada syndrome caused by a *de novo* pathogenic variant is very low (~1%). Each child of an individual with autosomal dominant Brugada syndrome has a 50% chance of inheriting the pathogenic variant. The risk that a child will inherit the familial pathogenic variant and develop Brugada syndrome may be less than 50% because of reduced penetrance and the possibility of other genetic and environmental factors. Reduced penetrance and variable expressivity are hallmarks of Brugada syndrome. Once the Brugada syndrome-related pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for Brugada syndrome are possible.

Diagnosis

Brugada syndrome is a channelopathy, caused by genetic changes in transmembrane ion channels that create action potentials, in this case leading to an increased risk of cardiac arrhythmia [Benito et al 2009].

Suggestive Findings

Brugada syndrome **should be suspected** in individuals with any of the following findings:

- Recurrent syncope
- Ventricular fibrillation
- Self-terminating polymorphic ventricular tachycardia
- Cardiac arrest
- Family history of sudden cardiac death

AND one of the following EKG patterns:

- **Type 1 EKG** (elevation of the J wave ≥2 mm with a negative T wave and ST segment that is coved type and gradually descending) in more than one right precordial lead (V_1-V_3)* (see Figure 1) with or without administration of a sodium channel blocker (e.g., flecainide, pilsicainide, ajmaline, or procainamide)

  * No other factor(s) should account for the EKG abnormality.

- **Type 2 EKG** (elevation of the J wave ≥2 mm with a positive or biphasic T wave; ST segment with saddleback configuration and elevated ≥1 mm) in more than one right precordial lead under baseline conditions with conversion to type 1 EKG following challenge with a sodium channel blocker

- **Type 3 EKG** (elevation of the J wave ≥2 mm with a positive T wave; ST segment with saddleback configuration and elevated <1 mm) in more than one lead under baseline conditions with conversion to type 1 EKG following challenge with a sodium channel blocker

Establishing the Diagnosis

The clinical diagnosis of Brugada syndrome can be **established** in a proband based on clinical diagnostic criteria, or the molecular diagnosis can be established in a proband with suggestive findings and a heterozygous (or hemizygous in the case of *KCNE5* in a male) pathogenic (or likely pathogenic) variant in one of the genes listed in Table 1. (See Figure 2 for a diagnostic algorithm for Brugada syndrome.)

Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Clinical Diagnosis

The clinical diagnosis of Brugada syndrome can be **established** in a proband with **both** of the following findings:

- **Type 1 EKG** (elevation of the J wave ≥2 mm with a negative T wave and ST segment that is coved type and gradually descending) in more than one right precordial lead (V_1-V_3)* (see Figure 1) with or without administration of a sodium channel blocker (i.e., flecainide, pilsicainide, ajmaline, or procainamide)

  * No other factor(s) should account for the EKG abnormality.

- **At least one** of the following:
  - Documented ventricular fibrillation
  - Self-terminating polymorphic ventricular tachycardia
  - A family history of sudden cardiac death
  - Coved-type EKGs in family members
  - Electrophysiologic inducibility
  - Syncope or nocturnal agonal respiration

Note: In approximately 75% of persons affected by Brugada syndrome the diagnosis is established based on clinical history and EKG results. Molecular genetic testing confirms the diagnosis and may complement clinical testing [Benito et al 2009].

Molecular Genetic Testing

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (serial single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see **Option 1**), whereas those with a phenotype indistinguishable from many other inherited disorders with cardiac conduction abnormalities are more likely to be diagnosed using genomic testing (see **Option 2**).

Option 1

Serial single-gene testing can be considered starting with *SCN5A*. Alternatively, serial single-gene testing may be considered if factors including clinical findings, laboratory findings, and ancestry indicate that mutation of a

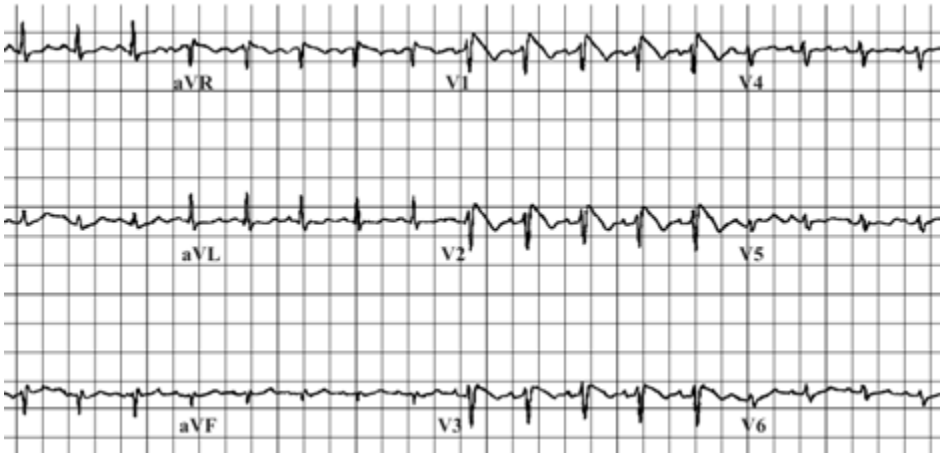


Figure 1. Characteristic EKG in Brugada syndrome. Note presence of ST segment elevation in leads V_1-V_3, coved type.

particular gene is most likely. Sequence analysis of the gene of interest is performed first, followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.

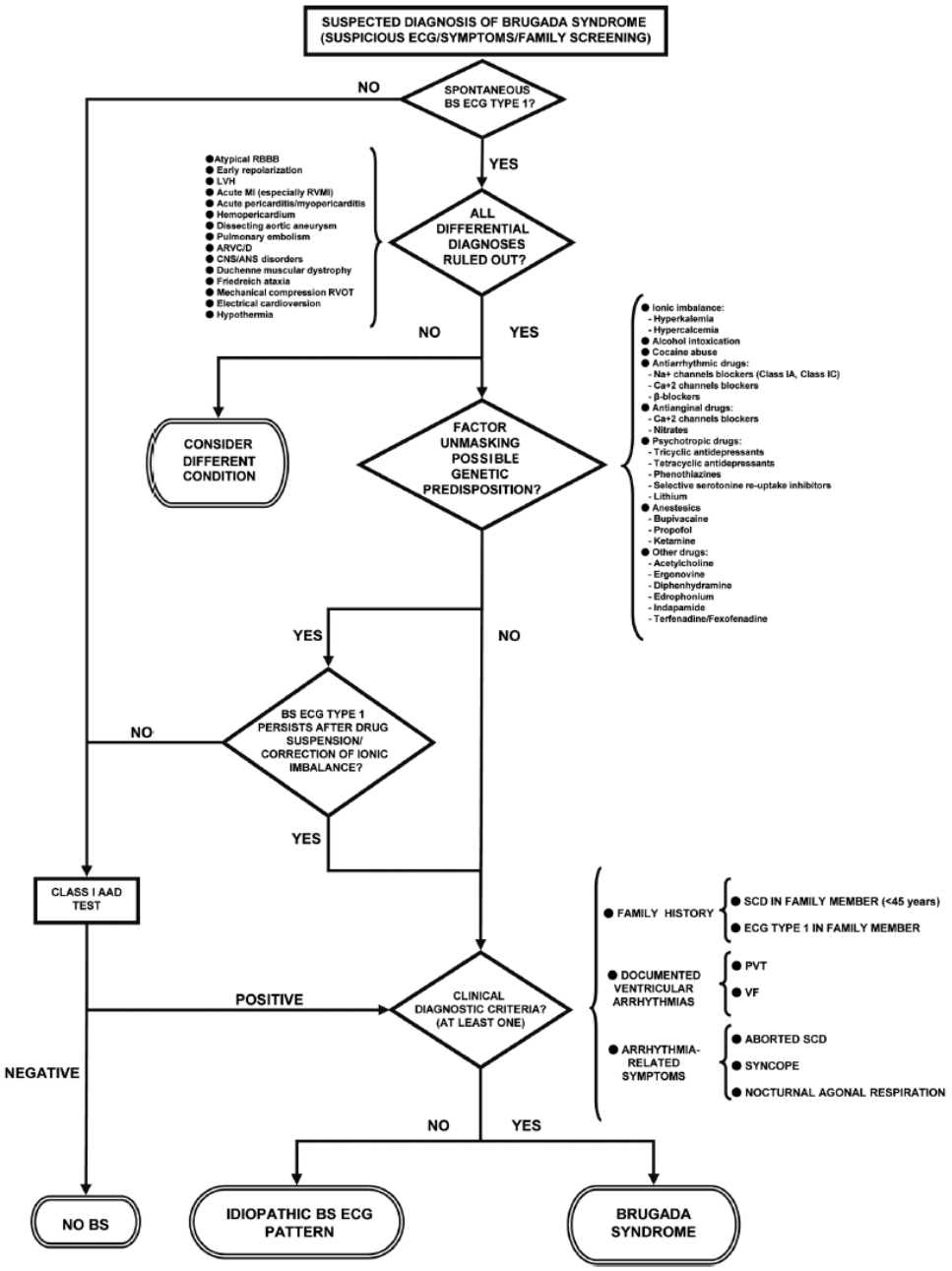
A multigene panel that includes the genes listed in Table 1 and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.



Diagnostic algorithm for Brugada syndrome

Abbreviations

AAD: antiarrhythmic drugs
ANS: autonomic nervous system
ARVC/D: arrhythmogenic right ventricular cardiomyopathy/dysplasia
BS: Brugada syndrome
CNS: central nervous system
ECG: elecrocardiogram
LVH: left ventricular hypertrophy
MI: myocardial infarction
PVT: polymorphic ventricular tachycardia
RBBB: right ventricular bundle branch block
RVMI: right ventricular myocardial infarction
RVOT: right ventricular outflow tract
SCD: sudden cardiac death
VF: ventricular fibrillation

Figure 2. Diagnostic algorithm for Brugada syndrome

Reproduced from Berne & Brugada [2012] with permission

Table 1. Molecular Genetic Testing Used in Brugada Syndrome

Gene [1]	Phenotype Designation	% of Brugada Syndrome Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
			Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
SCN5A	Brugada syndrome 1	30% [5]	99%	~1% [6]
ABCC9		<1%	100%	None reported [7]
AKAP9				
ANK2				
CACNA1C	Brugada syndrome 3			
CACNB2	Brugada syndrome 4			
CACNA2D1				
CASQ2				
DSG				
DSP				
FGF12				
GPD1L	Brugada syndrome 2			
HCN4	Brugada syndrome 8			
HEY2				
KCNAB2				
KCNB2				
KCND2				
KCND3	Brugada syndrome 9			
KCNE2				
KCNE3	Brugada syndrome 6			
KCNE5				
KCNH2				
KCNJ8				
KCNJ16				
LRRC10				
PKP2				
PLN				
RANGRF				
RyR2				
SCN1B	Brugada syndrome 5			
SCN2B				
SCN3B	Brugada syndrome 7			

Table 1. continued from previous page.

Gene [1]	Phenotype Designation	% of Brugada Syndrome Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
			Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
SCN4A				
SCN10A				
SCNN1A				
SEMA3A				
SLMAP				
TBX5				
TKT				
TRPM4				
TTN				
XIRP1				
XIRP2				
Unknown		~65% [8]		

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in these genes.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. Kapplinger et al [2010], Wilde et al [2022], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
7. Mates et al [2020]
8. Wilde et al [2022]

Clinical Characteristics

Clinical Description

Age at diagnosis. Brugada syndrome manifests primarily during adulthood, with a mean age of sudden death of approximately 40 years. The youngest individual was diagnosed at two days of life and the oldest was diagnosed at age 85 years [Huang & Marcus 2004].

Sex differences. Although Brugada syndrome is more prevalent among males, it affects females as well, and both sexes are at a high risk for ventricular arrhythmias and sudden death [Hong et al 2004b].

Presentation. Currently, the most common presentation is that of a person in the fifth decade with malignant arrhythmias and a previous history of syncopal episodes. Syncope is a common presenting symptom [Mills et al 2005, Benito & Brugada 2006, Karaca & Dinckal 2006].

Affected individuals in whom sustained ventricular arrhythmias are easily induced and who have a spontaneously abnormal EKG have a 45% likelihood of having an arrhythmic event at any time during life [Benito et al 2009]. Electrical storms (also known as arrhythmic storms) – multiple episodes of ventricular

arrhythmias that occur over a short period of time – are malignant but rare phenomena in Brugada syndrome. Incessant ventricular tachycardia (VT) is defined as hemodynamically stable VT continuing for hours.

Brugada syndrome can occur in conjunction with conduction disease. The presence of first-degree AV block, intraventricular conduction delay, right bundle branch block, and sick sinus syndrome in Brugada syndrome is not unusual [Smits et al 2005].

Clinical presentations of Brugada syndrome may also include sudden infant death syndrome (SIDS; death of a child during the first year of life without an identifiable cause) [Priori et al 2000, Antzelevitch 2001, Skinner et al 2005, Van Norstrand et al 2007] and sudden unexpected nocturnal death syndrome (SUNDS) [Vatta et al 2002], a syndrome seen in Southeast Asia in which young people die from cardiac arrest with no identifiable cause. The same pathogenic variant in *SCN5A* was identified in individuals with Brugada syndrome and SUNDS, thus supporting the hypothesis that they are the same disease [Hong et al 2004a].

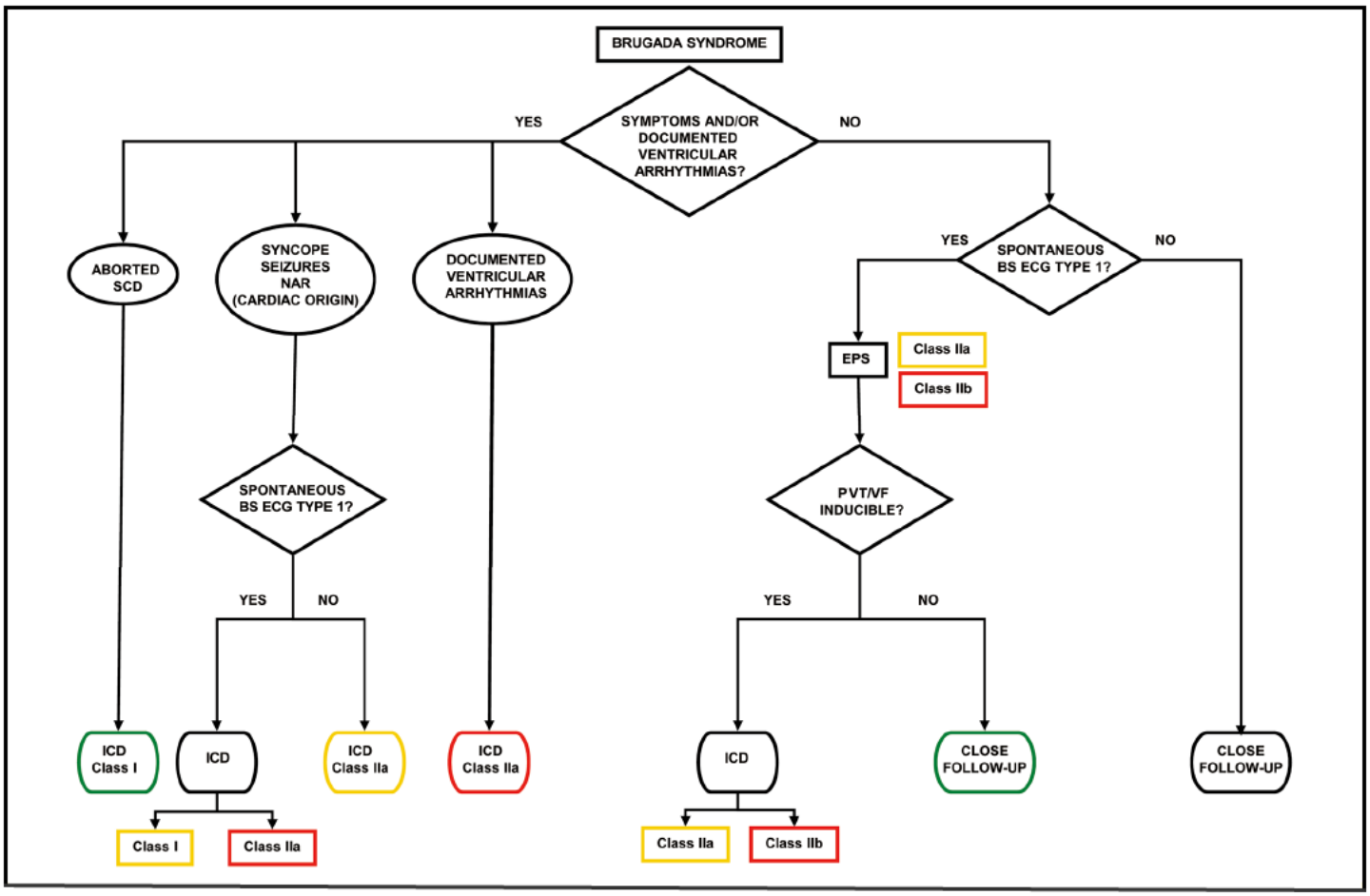
Precipitating factors for the Brugada EKG pattern and the syndrome of sudden cardiac death include fever, cocaine use, electrolyte disturbances, and use of class I antiarrhythmic medications and a number of other noncardiac medications [Francis & Antzelevitch 2005]. Most importantly, in some (usually young) persons, the presence of the induced EKG pattern has been associated with sudden cardiac death. The pathophysiologic mechanisms behind this association remain largely unknown.

Predicting risk of malignant arrhythmias. Several parameters have been investigated to improve stratification of the risk of developing malignant arrhythmias (see Figure 3).

- **Inducibility during electrophysiologic study** (EPS) is the only parameter currently used for clinical decision making. During such a study the heart is electrically stimulated using intracardiac catheters. Although the inducibility of arrhythmias in an asymptomatic individual during the EPS is highly predictive of subsequent malignant events (arrhythmias and sudden cardiac death), the data remain controversial. Several groups do not use EPS for risk stratification in asymptomatic individuals. Several multiparametric approaches to determine risk are available. However, their predictive abilities remain modest in individuals with Brugada syndrome and in asymptomatic individuals [Rodríguez-Mañero et al 2022]. Thus, decisions regarding timing of implantation of a defibrillator vary widely among physicians and investigators [Eckardt et al 2005, Glatter et al 2005, Ikeda et al 2005, Al-Khatib 2006, Delise et al 2006, Gehi et al 2006, Imaki et al 2006, Ito et al 2006, Ott & Marcus 2006, Tatsumi et al 2006, Benito et al 2009].
- **Genotype** has been proposed as an additional parameter for risk stratification. Meregalli et al [2009] found that among individuals with an *SCN5A* pathogenic variant, those who were more symptomatic had more EKG signs of conduction slowing, supporting the notion that conduction slowing, mediated by loss-of-function *SCN5A* pathogenic variants, was a key pathophysiologic mechanism in Brugada syndrome. This limited study indicates that it may be possible in the future to use genotype information in risk stratification; however, at present this remains an area of investigation.

Pathophysiology. Brugada syndrome, caused by a sodium channelopathy, is associated with age-related progressive conduction abnormalities, such as prolongation of the EKG PQ, QRS, and HV intervals [Smits et al 2002, Yokokawa et al 2007]. Sodium current dysfunction contributes to local conduction block in the epicardium, resulting in multiple spikes within the QRS complex and triggering of atrial and ventricular fibrillation [Morita et al 2008].

Sodium channelopathies exhibited typical Brugada-type EKG and frequent arrhythmogenesis during bradycardia [Makiyama et al 2005]; both quinidine and isoproterenol normalized the J-ST elevation and prevented arrhythmias.



Proposed risk stratification scheme and recommendations of ICD in Brugada syndrome patients

Line colors

Yellow — Recommendations from 2nd Consensus on Brugada Syndrome

Red — Recommendations from ACC/AHA/EXC Practice Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (2006)

Green — Recommendations in Agreement with 2nd Consensus on Brugada Syndrome and Practice Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (2006)

Recommendation classes

Class I: clear evidence that the treatment/intervention is useful or effective
Class II: conflicting evidence about usefulness or efficacy
Class IIa: weight of evidence in favor of usefulness or efficacy
Class IIb: usefulness or efficacy less well established

Abbreviations

BS: Brugada syndrome
ECG: elecrocardiogram
EPS: electrophysiological study
ICD: implantable cardioverter-defibrillator
NAR: nocturnal agonal respiration
PVT: polymorphic ventricular tachycardia
SCD: sudden cardiac death
VF: ventricular fibrillation

Figure 3. Proposed risk stratification scheme and recommendations of ICD in individuals with Brugada syndrome
Reproduced from Berne & Brugada [2012] with permission

Phenotype Correlations by Gene

***SCN5A*.** The degree of ST elevation and the occurrence of arrhythmias were similar between persons with Brugada syndrome with and without a heterozygous *SCN5A* pathogenic variant [Morita et al 2009].

Genotype-Phenotype Correlations

Few studies have investigated genotype-phenotype correlations [Ciconte et al 2021].

SCN5A

- In general, the *SCN5A* pathogenic variants which cause LQT3 (see Long QT Syndrome) are associated with a gain of function rather than the loss of function associated with Brugada syndrome and progressive conduction system disease; however, pathogenic variants that are associated with both diseases in the same family have been described.
- By restoring (at least partially) sodium current defects, the common *SCN5A* variant p.His558Arg appears to modulate the phenotypic effects of heterozygous *SCN5A* pathogenic variants [Lizotte et al 2009] such as p.Thr512Ile, which results in clinically significant cardiac conduction disturbances [Viswanathan et al 2003], and p.Arg282His, which results in Brugada syndrome [Poelzing et al 2006].

Penetrance

***SCN5A*.** Among individuals with an *SCN5A* pathogenic variant approximately 20%-30% have an EKG diagnostic of Brugada syndrome; and approximately 80% manifest the characteristic EKG changes when challenged with a sodium channel blocker (e.g., ajmaline) [Hong et al 2004b, Benito et al 2009].

Nomenclature

Vatta et al [2002] and Hong et al [2004a] determined that sudden unexpected nocturnal death syndrome (SUNDS) and Brugada syndrome are phenotypically, genetically, and functionally the same disorder. SUNDS was originally described in individuals from Southeast Asia. Other names for SUNDS include sudden and unexpected death syndrome (SUDS), *bangungut* (Philippines), *non-lai tai* (Laos), *lai-tai* (Thailand), and *pokkuri* (Japan).

Prevalence

Brugada syndrome occurs worldwide. The prevalence of the disease in endemic areas (South Asia) is on the order of 1:2,000 persons. In countries in Southeast Asia in which SUNDS is endemic, it is the second leading cause of death (following accidents) of men under age 40 years.

Data from published studies indicate that Brugada syndrome is responsible for 4%-12% of unexpected sudden deaths and for up to 20% of all sudden death in individuals with an apparently normal heart [Brugada et al 1999a].

A prospective study of an adult Japanese population (22,027 individuals) showed 12 individuals (prevalence of 0.05%) with EKGs compatible with Brugada syndrome [Tohyou et al 1995]. A second study of adults in Awa, Japan, showed a prevalence of 0.6% (66:10,420 individuals) [Namiki et al 1995]. In contrast, a third study in Japanese children showed only a 0.0006% (1:163,110) prevalence of EKGs compatible with Brugada syndrome [Hata et al 1997]. Therefore, in the absence of symptoms and/or molecular genetic testing, these studies provide an estimate of the prevalence of the Brugada syndrome EKG pattern (not of Brugada syndrome) in the population studied. The results suggest that Brugada syndrome manifests primarily during adulthood, a finding in concordance with the mean age of sudden death (age 35-40 years).

Genetically Related (Allelic) Disorders

Disorders known to be caused by germline pathogenic variants in Brugada syndrome-related genes are summarized in Table 2.

Note: Data on genetic modifiers (e.g., susceptibility loci / polymorphisms identified through genome-wide association studies) in Brugada syndrome-related genes that may contribute in small ways to risk of a given phenotype are not included in Table 2.

Table 2. Disorders Caused by Germline Pathogenic Variants in Brugada Syndrome-Related Genes

Gene	Allelic Disorder(s)
ABCC9	Cantú syndrome
	Dilated cardiomyopathy
	Atrial fibrillation (reported in 1 person to date [Olson et al 2007])
	Early repolarization syndrome [Hu et al 2014]
CACNA1C	Long QT syndrome
	Timothy syndrome (See *CACNA1C*-Related Disorders.)
	Short QT syndrome (See *CACNA1C*-Related Disorders.)
CACNA2D1	Short QT syndrome [Templin et al 2011]
	Early repolarization syndrome [Burashnikov et al 2010]
CACNB2	No phenotypes other than Brugada syndrome are known to be caused by germline pathogenic variants in *CACNB2*.
FGF12	Cerebellar atrophy w/epileptic encephalopathy (reported in 1 family to date [Siekierska et al 2016])
GPD1L	No phenotypes other than Brugada syndrome are known to be caused by germline pathogenic variants in *GPD1L*.
HCN4	Epilepsy [Becker et al 2017, Campostrini et al 2018]
KCND2	Epilepsy (reported in 1 person to date [Singh et al 2006])
	J-wave syndromes assoc w/sudden cardiac death (reported in 1 person to date [Perrin et al 2014])
KCND3	Spinocerebellar ataxia
KCNE2	Atrial fibrillation [Yang et al 2004]
	Long QT syndrome
KCNE3	No phenotypes other than Brugada syndrome are known to be caused by germline pathogenic variants in *KCNE3*.
KCNE5	Atrial fibrillation (reported in 1 person to date [Ravn et al 2008])
KCNH2	Long QT syndrome
	Short QT syndrome [Brugada et al 2004, Grunnet et al 2008]
KCNJ8	Cantú syndrome
PKP2	Arrhythmogenic right ventricular cardiomyopathy
RANGRF	No phenotypes other than Brugada syndrome are known to be caused by germline pathogenic variants in *RANGRF*.
SCN1B	Temporal lobe epilepsy [Scheffer et al 2007]
	Generalized epilepsy w/febrile seizures plus type 1 (GEFS+1) [Scheffer et al 2007]
	Atrial fibrillation [Watanabe et al 2009]
	Developmental & epileptic encephalopathy [Ramadan et al 2017]
SCN2B	Atrial fibrillation [Watanabe et al 2009]

Table 2. continued from previous page.

Gene	Allelic Disorder(s)
SCN3B	Atrial fibrillation [Wang et al 2010]
SCN5A	Long QT syndrome
	Progressive conduction system disease (PCCD, Lenegre disease, isolated cardiac conduction disease) [Schott et al 1999, Tan et al 2001, Wang et al 2002]
	Atrial fibrillation [Olson et al 2005]
	Dilated cardiomyopathy
	Sick sinus syndrome [Benson et al 2003]
	Familial paroxysmal ventricular fibrillation [Watanabe et al 2011]
SCN10A	Familial episodic pain syndrome [Faber et al 2012]
SEMA3A	Kallmann syndrome (See Isolated Gonadotropin-Releasing Hormone Deficiency.)
TRPM4	Erythrokeratodermia variabilis et progressiva [Wang et al 2019]
	Progressive familial heart block type 1B [Kruse et al 2009]

Differential Diagnosis

Brugada syndrome should always be considered in the differential diagnosis of the following:

- **Sudden cardiac death and syncope** in persons with a structurally normal heart
- **SIDS.** Brugada syndrome does not usually cause problems at such a young age; however, *SCN5A* pathogenic variants have been described in a few infants with SIDS. SIDS is believed to be etiologically and genetically heterogeneous [Weese-Mayer et al 2007] with an unknown proportion attributed to Brugada syndrome.
- **Sick sinus syndrome.** Brugada syndrome could be observed in persons with sick sinus syndrome given the defects observed in cardiac conduction [Nakazato et al 2004].

Other conditions that can be associated with ST segment elevation in right precordial leads include the following (adapted from de Oliveira Neto et al [2019] and Wilde et al [2002] with permission).

Abnormalities that can lead to ST segment elevation in the right precordial leads

- Right or left bundle branch block, left ventricular hypertrophy
- Acute myocardial ischemia or infarction
- Acute myocarditis
- Hypothermia, causing Osborn wave in EKGs and sometimes resembling Brugada syndrome
- Right ventricular ischemia or infarction
- Dissecting aortic aneurysm
- Acute pulmonary thromboemboli
- Various central and autonomic nervous system abnormalities
- Heterocyclic antidepressant overdose
- Duchenne muscular dystrophy
- Friedreich ataxia
- Thiamine deficiency
- Hypercalcemia
- Hyperkalemia
- Cocaine intoxication

- Mediastinal tumor compressing the right ventricular outflow tract
- Arrhythmogenic right ventricular cardiomyopathy

Other conditions that can lead to ST segment elevation in the right precordial leads

- Early repolarization syndrome
- Other normal variants (particularly in males)

Most of the above conditions can give rise to a type 1 EKG, whereas ARVC and Brugada syndrome can both give rise to type 2 and type 3 EKGs. Therefore, it is important to distinguish between these two disorders.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Brugada syndrome, the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Electrocardiogram (EKG)
- Induction with sodium blockers (ajmaline, procainamide, pilsicainide, flecainide) in persons with a type 2 EKG or type 3 EKG and suspicion of the disease
- Electrophysiologic study to assess risk of sudden cardiac death. Although the data are controversial, no other risk stratification parameter is presently available for asymptomatic individuals [Nunn et al 2010].
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of Brugada syndrome to facilitate medical and personal decision making

Treatment of Manifestations

Brugada syndrome is characterized by the presence of ST segment elevation in leads V_1-V_3. Implantable cardioverter defibrillators (ICDs) are the only therapy currently known to be effective in persons with Brugada syndrome with syncope or cardiac arrest [Brugada et al 1999b, Wilde et al 2002]. See Figure 3 for risk stratification and recommendations of ICD in individuals with Brugada syndrome.

Electrical storms respond well to infusion of isoproterenol (1-3 µg/min), the first line of therapy before other antiarrhythmics [Maury et al 2004].

It is important to:

- Eliminate/treat agents/circumstances such as fever, cocaine use, electrolyte disturbances, and use of class I antiarrhythmic medications and other noncardiac medications that can induce acute arrhythmias;

  AND

- Hospitalize the patient at least until the EKG pattern has normalized.

Controversy exists regarding the treatment of asymptomatic individuals. Recommendations vary [Benito et al 2009, Escárcega et al 2009, Nunn et al 2010, Brugada et al 2018] and include the following:

- Observation until the first symptom develops (Note: The first symptom can also be sudden cardiac death.)
- Placement of an ICD if the family history is positive for sudden cardiac death
- Use of electrophysiologic study (EPS) to identify those most likely to experience arrhythmias and thus benefit the most from placement of an ICD

During surgery and in the postsurgical recovery period persons with Brugada syndrome should be monitored by EKG.

Prevention of Primary Manifestations

Quinidine (1-2 g daily) has been shown to restore ST segment elevation and decrease the incidence of arrhythmias [Belhassen et al 2004, Hermida et al 2004, Probst et al 2006].

Surveillance

At-risk individuals with a family history of Brugada syndrome or a known pathogenic variant should undergo EKG monitoring every one to two years beginning at birth [Oe et al 2005]. The presence of type 1 EKG changes should be further investigated.

Agents/Circumstances to Avoid

The following can unmask the Brugada syndrome EKG [Antzelevitch et al 2002]:

- Febrile state
- Vagotonic agents
- Alpha-adrenergic agonists [Miyazaki et al 1996]
- Beta-adrenergic antagonists
- Tricyclic antidepressants
- First-generation antihistamines (dimenhydrinate)
- Cocaine toxicity

The following should be avoided [Antzelevitch et al 2003]:

- Class 1C antiarrhythmic drugs including flecainide and propafenone
- Class 1A agents including procainamide and disopyramide

Evaluation of Relatives at Risk

If the Brugada syndrome-related pathogenic variant has been identified in an affected family member, molecular genetic testing of at-risk relatives (including children) is appropriate because:

- EKG changes have low sensitivity in establishing the diagnosis [Corcia 2022];
- Identification of individuals at risk allows preventive measures such as fever control and avoidance of medications that can induce ventricular arrhythmias;
- Cardiac surveillance can be limited to family members who have the familial Brugada syndrome-related pathogenic variant [Benito et al 2009, Escárcega et al 2009, Nunn et al 2010].

Individuals with a known pathogenic variant should undergo EKG monitoring every one to two years beginning at birth (see Surveillance).

If the pathogenic variant has not been identified in the family, relatives should undergo EKG monitoring every one to two years beginning at birth (see Surveillance). If a type I EKG is identified, further investigation is warranted.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Hormonal changes during pregnancy can precipitate arrhythmic events in women with Brugada syndrome. Recurrent ventricular tachyarrhythmia can be inhibited, and the electrocardiographic pattern can normalize following IV infusion of low-dose isoproterenol followed by oral quinidine [Sharif-Kazemi et al 2011].

Quinidine is not known to be teratogenic to the developing fetus and is a preferred drug to treat arrhythmia in pregnancy. See MotherToBaby for more information about medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Brugada syndrome is inherited in an autosomal dominant manner with the exception of one family with Brugada syndrome associated with a pathogenic variant in *KCNE5*, an X-linked gene [Ohno et al 2011].

Risk to Family Members (Autosomal Dominant Inheritance)

Parents of a proband

- Most individuals diagnosed with Brugada syndrome have an affected parent or another affected close relative.
- A proband with Brugada syndrome may have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with Brugada syndrome caused by a *de novo* pathogenic variant is very low (~1%).
- If a diagnosis of Brugada syndrome has not already been established in the mother or the father of the proband, recommendations for the evaluation of parents of a proband include electrocardiographic analysis, attention to a family history of sudden death, and (if the pathogenic variant in the proband has been identified) molecular genetic testing.
- If the proband has a known pathogenic variant that is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- Although most individuals diagnosed with Brugada syndrome have inherited the pathogenic variant from a parent, the family history may appear to be negative because of failure to recognize the disorder in family members, incomplete penetrance, early death of the parent before the onset of symptoms, or late onset of the symptoms in the affected parent. Therefore, an apparently negative family history cannot be

confirmed unless the proband has a known Brugada syndrome-related pathogenic variant that is not identified in either parent.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected, or unaffected but known to be heterozygous for the pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.
  - The risk that a sib will inherit the familial pathogenic variant and develop Brugada syndrome may be less than 50% because of reduced penetrance and the possibility of other genetic and environmental factors (see Penetrance). Reduced penetrance and variable expressivity are hallmarks of Brugada syndrome.
  - Sibs who do not inherit the variant identified in the proband are at approximately the same risk for Brugada syndrome as the general population due to the possibility of other genetic variants.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs of inheriting the pathogenic variant is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but their genetic status is unknown (because the parents have not undergone molecular genetic testing and/or a causative pathogenic variant has not been identified in the proband), sibs are still at increased risk for Brugada syndrome because of the possibility of reduced penetrance in a parent (i.e., a clinically unaffected parent may be heterozygous for a pathogenic variant) and the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant Brugada syndrome has a 50% chance of inheriting a Brugada syndrome-related pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has a pathogenic variant, the parent's family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the Brugada syndrome-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for Brugada syndrome are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Fundación Brugada**
  Barcelona
  Spain
  Phone: 34 872 98 70 87 extension 63
  Email: fundacio@brugada.org
  www.brugada.org
- **MedlinePlus**
  Brugada syndrome
- **Canadian SADS Foundation**
  Canada
  Email: info@sads.ca
  www.sads.ca
- **Sudden Arrhythmia Death Syndromes (SADS) Foundation**
  Phone: 801-948-0654
  www.sads.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Brugada Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ABCC9	12p12.1	ATP-binding cassette sub-family C member 9	ABCC9 database	ABCC9	ABCC9
CACNA1C	12p13.33	Voltage-dependent L-type calcium channel subunit alpha-1C	CACNA1C database CACNA1C @ ZAC-GGM	CACNA1C	CACNA1C
CACNA2D1	7q21.11	Voltage-dependent calcium channel subunit alpha-2/delta-1		CACNA2D1	CACNA2D1
CACNB2	10p12.33-p12.31	Voltage-dependent L-type calcium channel subunit beta-2	CACNB2 database	CACNB2	CACNB2
FGF12	3q28-q29	Fibroblast growth factor 12		FGF12	FGF12
GPD1L	3p22.3	Glycerol-3-phosphate dehydrogenase 1-like protein	GPD1L database	GPD1L	GPD1L

Table A. continued from previous page.

HCN4	15q24.1	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4	HCN4 database	HCN4	HCN4
KCND2	7q31.31	Potassium voltage-gated channel subfamily D member 2		KCND2	KCND2
KCND3	1p13.2	Potassium voltage-gated channel subfamily D member 3	KCND3 @ LOVD	KCND3	KCND3
KCNE2	21q22.11	Potassium voltage-gated channel subfamily E member 2	KCNE2 database KCNE2 @ ZAC-GGM	KCNE2	KCNE2
KCNE3	11q13.4	Potassium voltage-gated channel subfamily E member 3	KCNE3 database	KCNE3	KCNE3
KCNE5	Xq23	Potassium voltage-gated channel subfamily E regulatory beta subunit 5	KCNE1L @ LOVD	KCNE5	KCNE5
KCNH2	7q36.1	Potassium voltage-gated channel subfamily H member 2	KCNH2 database KCNH2 @ ZAC-GGM	KCNH2	KCNH2
KCNJ8	12p12.1	ATP-sensitive inward rectifier potassium channel 8		KCNJ8	KCNJ8
PKP2	12p11.21	Plakophilin-2	PKP2 @ LOVD ARVD/C Genetic Variants Database - PKP2	PKP2	PKP2
RANGRF	17p13.1	Ran guanine nucleotide release factor		RANGRF	RANGRF
SCN1B	19q13.11	Sodium channel subunit beta-1	SCN1B database	SCN1B	SCN1B
SCN2B	11q23.3	Sodium channel subunit beta-2		SCN2B	SCN2B
SCN3B	11q24.1	Sodium channel subunit beta-3	SCN3B database	SCN3B	SCN3B
SCN5A	3p22.2	Sodium channel protein type 5 subunit alpha	SCN5A @ LOVD SCN5A @ ZAC-GGM	SCN5A	SCN5A
SCN10A	3p22.2	Sodium channel protein type 10 subunit alpha		SCN10A	SCN10A
SEMA3A	7q21.11	Semaphorin-3A		SEMA3A	SEMA3A
SLMAP	3p14.3	Sarcolemmal membrane-associated protein		SLMAP	SLMAP
TRPM4	19q13.33	Transient receptor potential cation channel subfamily M member 4	TRPM4 database	TRPM4	TRPM4

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Brugada Syndrome (View All in OMIM)

114204	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, ALPHA-2/DELTA SUBUNIT 1; CACNA2D1
114205	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, L TYPE, ALPHA-1C SUBUNIT; CACNA1C

Table B. continued from previous page.

152427	POTASSIUM CHANNEL, VOLTAGE-GATED, SUBFAMILY H, MEMBER 2; KCNH2
300328	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED FAMILY, MEMBER 1-LIKE; KCNE1L
600003	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, BETA-2 SUBUNIT; CACNB2
600163	SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 5; SCN5A
600235	SODIUM VOLTAGE-GATED CHANNEL, BETA SUBUNIT 1; SCN1B
600935	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 8; KCNJ8
601144	BRUGADA SYNDROME 1; BRGDA1
601327	SODIUM VOLTAGE-GATED CHANNEL, BETA SUBUNIT 2; SCN2B
601439	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9; ABCC9
601513	FIBROBLAST GROWTH FACTOR 12; FGF12
602701	SARCOLEMMAL-ASSOCIATED PROTEIN; SLMAP
602861	PLAKOPHILIN 2; PKP2
603796	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED SUBFAMILY, MEMBER 2; KCNE2
603961	SEMAPHORIN 3A; SEMA3A
604427	SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 10; SCN10A
604433	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED SUBFAMILY, MEMBER 3; KCNE3
605206	HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE-GATED POTASSIUM CHANNEL 4; HCN4
605410	POTASSIUM VOLTAGE-GATED CHANNEL, SHAL-RELATED SUBFAMILY, MEMBER 2; KCND2
605411	POTASSIUM VOLTAGE-GATED CHANNEL, SHAL-RELATED SUBFAMILY, MEMBER 3; KCND3
606936	TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL, SUBFAMILY M, MEMBER 4; TRPM4
607954	RAN GUANINE NUCLEOTIDE RELEASE FACTOR; RANGRF
608214	SODIUM VOLTAGE-GATED CHANNEL, BETA SUBUNIT 3; SCN3B
611777	BRUGADA SYNDROME 2; BRGDA2
611778	GLYCEROL-3-PHOSPHATE DEHYDROGENASE 1-LIKE; GPD1L
611875	BRUGADA SYNDROME 3; BRGDA3
611876	BRUGADA SYNDROME 4; BRGDA4
612838	BRUGADA SYNDROME 5; BRGDA5
613119	BRUGADA SYNDROME 6; BRGDA6
613120	BRUGADA SYNDROME 7; BRGDA7
613123	BRUGADA SYNDROME 8; BRGDA8
616399	BRUGADA SYNDROME 9; BRGDA9

Molecular Pathogenesis

Table 3. Ion Channels and Associated Brugada Syndrome Phenotype Designations, Genes, and Proteins

Channel	Phenotype Designation [1]	Gene	Common Protein Names
Sodium	BrS 1	*SCN5A*	Nav1.5
	BrS 2	*GPD1L*	Glycerol-3-P-DH-1
	BrS 5	*SCN1B*	Navb1
	BrS 7	*SCN3B*	Navb3
	BrS 16	*SCN2B*	Navb2
Sodium-related	BrS 10	*RANGRF*	RAN-G-release factor
	BrS 14	*SLMAP*	Sarcolemma-assoc protein
Potassium	BrS 6	*KCNE3*	MiRP2
	BrS 8	*KCNJ8*	Kv6.1
	BrS 9	*HCN4*	Hyperpolarization cyclic nucleotide-gated 4
	BrS 11	*KCNE5*	Potassium voltage-gated channel subfamily E member 1-like
	BrS 12	*KCND3*	Kv4.3 Kir4.3
Calcium	BrS 3 & shorter QT	*CACNA1C*	Cav1.2
	BrS 4 & shorter QT	*CACNB2*	Voltage-dependent b-2
	BrS 13	*CACNA2D1*	Voltage-dependent a2/d1
	BrS 15	*TRPM4*	Transient receptor potential M4

BrS = Brugada syndrome
1. Author, personal communication

SCN5A encodes the alpha subunit of the cardiac sodium channel and is responsible for the initial upstroke of the action potential in the EKG. This integral membrane protein mediates the voltage-dependent sodium ion permeability of excitable membranes. Assuming opened or closed conformations in response to the voltage difference across the membrane, the protein forms a sodium-selective channel through which Na+ ions may pass in accordance with their electrochemical gradient. *SCN5A* is expressed in human atrial and ventricular cardiac muscle.

Mechanism of disease causation. Pathogenic variants in *SCN5A* result in decrease in Na^+ current availability by affecting the structure, function, and trafficking of the sodium channel.

Table 4. Notable *SCN5A* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000335.5 NP_000326.2	c.845G>A	p.Arg282His	See Genotype-Phenotype Correlations.
	c.1535C>T	p.Thr512Ile	
	c.1673A>G	p.His558Arg	
	c.2893C>T	p.Arg965Cys	Founder variant in Thailand [Chimparlee et al 2021]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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- **Clinical interest.** As a clinical and noninvasive cardiologist, Dr Brugada is interested in the management of patients with inherited disorders of the heart.
- **Research interest.** Dr Brugada's research interests are focused on molecular genetics of cardiovascular disease with an emphasis on genetics of cardiac arrhythmias. His research achievements include the identification of the chromosome locus on 10q22 for familial atrial fibrillation, the gene for familial idiopathic ventricular fibrillation (Brugada syndrome), and the gene for short QT syndrome.

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Revision History

- 25 August 2022 (sw) Comprehensive update posted live
- 17 November 2016 (ma) Comprehensive update posted live
- 10 April 2014 (me) Comprehensive update posted live
- 16 August 2012 (cd) Revision: multigene panels for Brugada syndrome and sudden cardiac death available clinically
- 12 January 2012 (cd) Revision: clinical testing for mutations in *CACNB2* and *HCN4* now listed in the GeneTests™ Laboratory Directory; large deletion in *SCN5A* reported [Eastaugh et al 2011]
- 8 September 2011 (me) Comprehensive update posted live
- 11 August 2009 (cd) Revision: prenatal testing for *SCN5A* available clinically
- 7 December 2007 (me) Comprehensive update posted live
- 31 March 2005 (me) Review posted live
- 11 March 2004 (rb) Original submission

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