



Brugada

Brugada Syndrome

A Guide for Clinicians

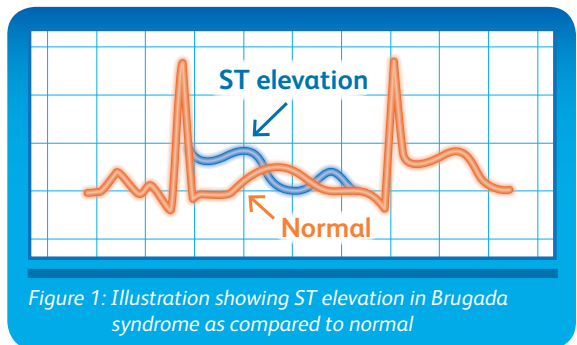


Brugada Syndrome

Introduction

Brugada syndrome (BrS) is a potentially life-threatening cardiac disorder characterized by ST segment elevation in right precordial leads (V1 to V3) on an ECG, incomplete or complete right bundle branch block, and susceptibility to syncope, ventricular tachyarrhythmia and sudden cardiac death.¹ Consensus conferences in 2002 and 2005 refined the diagnostic criteria for Brugada syndrome as detailed in Figure 2 and Side Box 2.²

Brugada syndrome occurs worldwide and is estimated to affect 5 per 10,000 individuals of all ethnicities, with some regional differences.³ BrS is a genetic cardiac channelopathy resulting from loss-of-function mutations causing changes in sodium and calcium ion flux. It is inherited as an autosomal dominant trait, occurring in males and females equally, although males are more likely to be symptomatic.⁴ Family history suggestive of BrS is an important diagnostic factor, as spontaneous mutation occurs rarely and most affected individuals are expected to have an affected parent.¹⁴



SIDE BOX 1: Factors associated with BrS⁵

- Family history of sudden cardiac death
- Personal history of cardiac arrhythmia with sleep, rest, and/or fever
- Personal history of syncope

Clinical diagnosis

SIDE BOX 2: Diagnostic criteria of BrS²

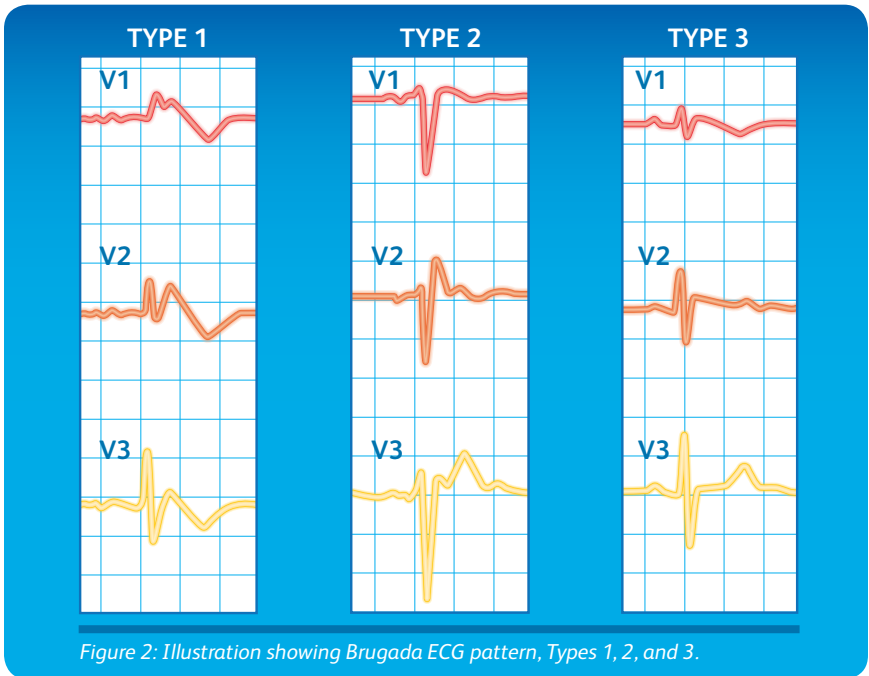
Diagnosis of BrS can be made based upon the characteristic ECG pattern in conjunction with other elements of the history.

- A) ECG repolarization pattern in the right precordial leads characterized by an ST-segment elevation of at least 2 mm with a "coved morphology" (Type 1 ECG). A coved-shaped ECG pattern is associated with right bundle branch block followed by a negative T wave. Related ECG patterns (Types 2 and 3) may also be observed and can be indicative of BrS, but cannot be used for a definitive diagnosis. Some patients exhibiting Type 2 or 3 ECGs are given a drug challenge with a sodium channel blocking agent such as flecainide or procainamide. If the ECG pattern converts from Type 2 or 3 to Type 1 upon drug challenge, the patient can be said to have BrS.
- B) Diagnosis of BrS must include a Type 1 ECG pattern in at least one right precordial lead in conjunction with one or more of the following:
- Documented ventricular fibrillation
 - Polymorphic ventricular tachycardia
 - Family history of sudden cardiac death at age 45 or younger
 - Type 1 ECGs in family members
 - Inducibility of VT with programmed electric stimulation
 - Syncope
 - Nocturnal agonal respiration

Sensitivity of these criteria is not definitively known, but for those symptomatic patients carrying a mutation in the SCN5 gene, the sensitivity is 77%.⁶

Clinical presentation and differential diagnosis

BrS has variable and diverse clinical manifestations. The most common clinical symptoms are syncope and cardiac arrest that occur at rest or during sleep. Some patients with BrS have supraventricular arrhythmias. Most individuals with BrS are asymptomatic. The diagnostic significance of a Brugada-type ECG pattern in asymptomatic individuals is uncertain and is an area of ongoing study. Most symptomatic individuals present between ages 20 and 40, but symptoms have been reported from infancy through late life. Males are 8 to 10 times more likely than females to develop symptoms of Brugada syndrome, for unclear reasons.⁴



It is strongly recommended that structural abnormalities of the heart be excluded before a conclusive diagnosis of BrS is made. The Brugada ECG pattern can be an early subclinical manifestation of arrhythmogenic right ventricular cardiomyopathy (ARVC). Other factors that could account for either the ECG findings or syncope should also be excluded. These include atypical right bundle branch block, left ventricular hypertrophy, early repolarization, acute myocardial infarction, acute pericarditis, and the ECG changes sometimes seen in the right precordial leads in well-trained athletes.

Management

The only proven effective treatment for BrS is an implantable cardioverter defibrillator (ICD). An algorithm has been developed by the Heart Rhythm Association for the use of ICDs in symptomatic patients with BrS.⁹ Management of asymptomatic patients is less clear. Proposed approaches include close observation until symptoms develop and implantation of ICDs in patients with a family history of sudden cardiac death. The clinical manifestations can be triggered by high fever, large meals, cocaine, excessive alcohol consumption, and overdose of tricyclic antidepressants.¹⁰⁻¹³ Research is ongoing for pharmacologic and other management strategies.

Genetics of Brugada syndrome

BrS is a genetic disorder with autosomal dominant transmission. Mutations in at least five genes (see Table 1) influencing sodium and calcium currents in the heart are associated with BrS and account for at least 26 % -41 % of cases with Brugada syndrome.^{8,14} Genetic testing to predict the syndrome in asymptomatic at-risk family members of a patient with Brugada syndrome first requires identification of the disease-causing mutation in the family. If a disease-causing mutation is found in an affected individual, genetic testing of relatives may be appropriate, allowing for evaluation and treatment of only the family members at risk of arrhythmias. Most patients with Brugada syndrome have inherited a disease-causing mutation from a parent, as de novo mutation in BrS is rare. Children of a patient diagnosed with BrS have a 50 % chance of inheriting the mutation associated with the syndrome. As individuals with BrS may be asymptomatic, the lack of a family history does not rule out a heritable disease.

TABLE 1

GENE	GENE NAME
SCN5A	Sodium channel, voltage gated, type V beta subunit
GPD1L	NAD-dependent glycerol-3-phosphate dehydrogenase
CACNA1C	Alpha-1C subunit of the L-type voltage-dependent calcium channel
SCN1B	Voltage-gated sodium channel type 1 beta subunit
CACNB2	Beta-2 subunit of the voltage-dependent L-type calcium channel

Indications and utility of genetic testing

Genetic testing in a patient clinically affected with BrS can be used to confirm the diagnosis. Genetic testing of at-risk family members can then be used to identify those who will benefit from cardiac evaluation and intervention. Conversely, family members who test negative for a specific familial mutation do not need serial cardiac evaluations or intervention.

Genetic test results and what they mean

Diagnostic genetic testing can be considered for patients who have symptoms and ECG findings characteristic of BrS, as well as for asymptomatic patients with a known familial mutation or positive family history of BrS. Testing should initially be performed on a symptomatic family member with BrS. Preferably, the most severely affected family member should be

tested first. In some cases, genetic testing can be performed on a deceased individual if the medical examiner has stored blood or tissue that can be used for genetic testing. Testing a symptomatic family member is done to identify the familial mutation, if one can be identified. The three possible outcomes of genetic testing are positive, negative, and variant of unknown clinical significance (VOUS). All patients who undergo genetic testing should receive pre-test and post-test genetic counseling to understand the implications of testing. Genetic counseling services across the country can be found at www.nsgc.org.

- **A positive result** indicates that a disease-causing mutation was identified in that individual. This finding confirms the diagnosis of BrS and provides valuable information to the physician and family members. All first-degree relatives (children, siblings, parents) of a patient with a positive genetic test result can then be offered predictive genetic testing to clarify the risk for BrS. If a family member is found to be positive for the familial mutation, this individual is considered to be at risk for BrS and should be referred for cardiac evaluation including an ECG. Mutation-positive family members should have a baseline electrocardiogram and annual ECG screening exams. Certain medications should be avoided in patients with BrS (www.brugadadrugs.org), and antipyretics should be used at the first sign of fever. It is important to note that there is variability in symptoms, even within families.
- **A negative result** in an affected individual does not necessarily rule out BrS, and the patient should be managed according to his/her clinical symptoms and ECG findings. Possible reasons for a negative result could be (1) the patient may have a mutation in a gene not covered in the testing panel, (2) the patient may have a mutation in a BrS-associated gene that was not covered in the test, or (3) the patient does not have a heritable form of BrS. **Predictive genetic testing of family members when the affected family member testing is negative will not be informative and is not warranted.** Family members of a clinically affected individual with negative test results may still be at risk for BrS and thus should be evaluated by a cardiologist.

If an asymptomatic individual is negative for a mutation identified in an affected family member, this person is considered a true negative and is not at increased genetic risk for Brugada syndrome. BrS clinical monitoring for this individual is not necessary, but this patient could develop other types of cardiac disease in the future. If there are no symptomatic members of a BrS family available for testing, an asymptomatic individual may pursue predictive genetic testing prior to identification of the familial mutation. However, if the asymptomatic family member is found to have a negative test result, this result is considered an uninformative negative result, and this asymptomatic family member should still be evaluated regularly by a cardiologist.

- **A variant of unknown clinical significance (VOUS)** indicates that the pathogenic role of the variant cannot be clearly established. The VOUS has been tested in a large panel of normal individuals and was not identified in any of the normal individuals. To further clarify the clinical significance of this variant, testing of family members is helpful. If an affected relative is found to have the same variant, it is more likely that it is a disease-causing variant. The greater the number of affected family members who carry the VOUS, the greater the likelihood that the VOUS is pathogenic. With consistent linkage of the VOUS with symptomatic family members, the variant found would be reclassified as a family-specific mutation and extended family members could be offered predictive genetic testing.

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About GeneDx

GeneDx is a highly respected company that specializes in genetic testing for rare inherited disorders. Two scientists from the National Institutes of Health (NIH) founded the company in the year 2000 to address the needs of patients and clinicians concerned with rare inherited disorders. Currently, GeneDx offers testing for more than 200 rare Mendelian disorders, using DNA sequencing and deletion/duplication analysis of the associated gene(s). GeneDx also offers oligonucleotide microarray-based testing for detecting chromosomal abnormalities, testing for autism spectrum disorders, and testing for various inherited cardiac disorders. At GeneDx, our technical services are matched by our scientific expertise and customer support. Our growing staff includes more than 12 experts in molecular and clinical genetics and seven genetic counselors who are just a phone call or email away. We invite you to visit our website, www.genedx.com, to learn more about us and the services we offer.

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