Brugada Syndrome Unmasked by Fever and Associated with Early Repolarization

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Case report

A 52 year-old man underwent a prostate biopsy for suspected prostate cancer. Seventy two hours later he presented with fever and chills followed by a syncope episode. He had a history of two previous syncope episodes. The physical examination was within normal limits.

Two initial electrocardiograms performed during his febrile state (Figures 1 and 2) are diagnostic of Brugada syndrome (BrS), since they display the typical type 1 pattern. The ECG illustrated in Figure 3, when he became afebrile, shows only the non-diagnostic type 2 Brugada pattern.
**Electrocardiographic diagnosis:** Sinus tachycardia; J point and ST segment elevation with upward convexity ≥2 mm (coved type) followed by negative T waves in the right precordial leads (V1-V2) illustrative of the type I Brugada pattern. Also, J waves with ST segment elevation are present in the high lateral leads I and aVL, and J waves without ST elevation are noted in lead II (red arrow) indicative of the early repolarization pattern. Both Brugada syndrome (BrS) and idiopathic ventricular fibrillation (IVF) when associated with early repolarization pattern in the **infero-lateral leads** have been grouped within the so-called “J wave syndromes” *Shinohara 2014* (1).
Electrocardiographic diagnosis: Similar findings as seen in Figure 1: sinus tachycardia, type 1 Brugada pattern and early repolarization pattern with ST segment elevation in the high lateral leads (I and aVL) and J wave without ST segment elevation in lead II.

The patient was treated initially with antipyretics. After collecting serial blood cultures, antibiotic therapy was initiated with ECG and temperature monitoring. When the patient became afebrile a third ECG was obtained (Figure 3).
Electrocardiographic diagnosis: Sinus tachycardia with the typical saddleback pattern of ventricular repolarization in V2 characteristic of the type 2 Brugada ECG pattern. Figure 4 further illustrates the characteristics of the saddleback pattern in the present case.
In both tracings the triphasic QRS pattern stands out imitating right bundle branch block (rSr’ and qRSr’) followed by J point and ST segment elevation that resembles a saddleback. The most important ECG findings that differentiate type 2 Brugada pattern from “innocent” incomplete right bundle branch block (IRBBB) are the rounded aspect of the r’ wave and the angle between the ascending limb of S and the descending limb of r’, always greater than 50°, i.e. a greater angle than in the cases of “innocent” IRBBB.

The following discussion will review the relevant aspects of the present case:

I) Early repolarization patterns and clinical significance;
II) Brugada syndrome;
III) The significance of fever as trigger of events in Brugada syndrome.

Early Repolarization and Clinical Significance

Until recently the concept of the early repolarization pattern (ERP) or variant (ERV), required the presence of both J point and ST segment elevation ≥1 mm in at least two contiguous precordial leads. ERP, considered a benign idiopathic electrocardiographic pattern, is further characterized by diffuse, upwardly concave ST segment elevation with wide, upright symmetrical T waves matching the polarity of the preceding QRS from V2 through V4, V5 or V6. Frequently the J point and ST segment elevation is associated with notching or slurring on the descending limb of R wave (J wave).

The concept of ERP is now being reconsidered. It is acknowledged that in ERP elevation of the ST segment is not a mandatory electrocardiographic element. ERP can be characterized only by the notch or slur at the end of the QRS (J wave) that is observed in at least two contiguous lateral (I, aVL, V5-V6) and/or inferior (II, III and aVF), and/or
anterior leads (V3-V4) but not in the septal precordial leads (V1-V2) Sinner 2010 (2). Any two precordial leads beyond V2 that are next to each other are contiguous even if representing different regions of the left ventricle. For example, leads V4 and V5 are considered contiguous, although V4 is a lead that belongs to the anterior wall and V5 to the lateral wall, since both are close to each other in the chest of the patient (Figure 5).

**Figure 5 – Correlation in the walls of the heart with precordial leads.**

S – Interventricular septum, V1-V2  
A – Anterior wall, V3-V4  
L – Lateral wall, V5-V6  
P – Posterior wall, accessory leads V7-V8-V9  
Right ventricle (RV) – V4R

Two contiguous leads are required for diagnosis because more than 90% of healthy men have ≥1 mm (0.1 mV) of ST segment elevation in at least one precordial lead Wang 2003 (3). There are conflicting data in the literature with regards to the prognosis of ERP. Much of the confusion is due to the different definitions used by various authors to define ERP, suggesting the urgent need for standardizing the defining criteria. Pérez, Friday and Froelicher Pérez 2012 (4) have recently clarified concepts of ERP (Figure 6) to include notched or slurred aspects of the descending R waves but without ST segment elevation in the ECG criteria of ERP (Figure 6 C and 6D).
In spite this clarification malignant variants of early repolarization syndrome have been reported. One variant, called the Lambda variant resembling the Greek letter Lambda, is very similar to type C of the new classification seen in Figure 6 but with negative T waves Gussak 2004 (5) (Figure 7). The tangent line method is used to locate the J point to be where the descending slope of the R wave moves away from the tangent line.

This variant has been found to be highly malignant and it has been observed in atypical forms of BrS Riera 2004 (6). In the setting of acute myocardial infarction it is considered a high risk marker for the development of ventricular fibrillation Kukla 2008 (7).
This malignant variant of early repolarization is characterized by marked transient ST segment elevation immediately before episodes of VT/VF as reported by Haissaguerre et al Haïssaguerre 2009 (8), and illustrated in Figure 8.

**Figure 8**

In these cases there is a transient increase in J wave amplitude that precedes the onset of the ventricular arrhythmia.

Antzelevitch and Yan Antzelevitch 2010 (9), proposed the existence of three categories ERP:

**Type 1:** ERP is observed only in the lateral precordial leads. This type is benign and highly prevalent in young male athletes Tikkanen 2009 (10).

**Type 2:** ERP is observed in the inferior or infero-lateral leads. This type is associated with increased risk of sudden cardiac death in middle-aged people Tikkanen 2009 (10).

**Type 3:** ERP is observed concomitantly in the inferior (II, III and aVF), lateral (I, aVL, V5-V6) and anterior walls (V3-V4). Type 3 is also associated with increased risk of malignant arrhythmias.

These authors proposed that Brugada syndrome and malignant variants of ERP differ only in relation to the magnitude and the location of the affected leads. In Brugada syndrome the leads corresponding to the septum (V1-V2) are only affected. Both entities represent a continuum with different phenotypic expressions. Our group reported a case where sequential ECGs clearly showed the coexistence of Brugada syndrome and ERP suggesting an overlap between the two entities McIntyre 2012 (11).
A *type 4 ERP* is the same as the type 1 Brugada pattern with J point and upwardly convex ST segment elevation followed by negative T waves in the right precordial leads. The prevalence of ERP ranges from 1% to 5% in the general population. ERP has been characterized by different authors in the following ways:

- As a normal variant with electrocardiographic features of its own Wasserburger 1961 (12).
- As pathological J waves:
  1. *In idiopathic ventricular fibrillation associated with ERP: known by the eponym Haïssaguerre pattern.*
  2. *Patients with Brugada syndrome with documented VF* Kawata 2013 (13).
  3. *In congenital short QT syndrome* Pérez-Riera 2012 (14).
  4. *In Torsade des pointes with normal QT intervals and initial extrasystole with short coupling preceding the VT* Durand-Dubief 2003 (15).

**Criteria for the benign or normal pattern of early repolarization.**

The normal benign ERP is mainly observed in young healthy individuals, more frequently in those with sinus bradycardia, predominantly males (≈70% of cases), blacks, and athletes with a low body mass index (close to 18.5 (kg/m²) and low triglyceride levels Walsh 2013 (16). This pattern frequently disappears as age advances although a greater QRS duration (QRSd) is associated with maintenance of the pattern over time. There is a negative family history of sudden cardiac death in young relatives Tikkanen 2009 (10).

**A) Electrocardiographic characterization of benign ERP:**

- Sinus bradycardia;
- QRS, ST segment and T wave axes in the frontal plane are in the same direction;
- Deep, narrow Q waves followed by large voltage R waves in the left precordial leads;
- Terminal notching or slurring in the descending limb of R wave as it transitions into the onset of ST segment Rautaharju 2009 (17);
- Presence of J waves defined as upward deflections or a delay in conduction in the final part of R wave downslope (slur);
- Clockwise rotation of QRS in the precordial leads where the transition area (defined as the time when the QRS complex with predominantly negative polarity becomes predominantly positive) is shifted to the left (also known as poor R progression);
- ≥0.1 mV J point and upwardly concave ST segment elevation (usually <0.2 mV, rarely >0.5 mV) in 2 or more adjacent middle and/or left precordial leads, occasionally in the inferior leads, with or without J waves or slurs;
- Reduction in J point and ST segment elevation during exercise, increased sympathetic activity, or sympathomimetic drugs;
- Absence of reciprocal ST segment depression except in lead aVR Pérez-Riera 2008;
- Wide, symmetrical T waves matching the polarity of preceding QRS in at least two contiguous leads. Large T wave in V6 ≥0.3 mV differentiates ERP from pericarditis; the $\frac{ST}{T}$ ratio in V6 differentiates the ECG of acute pericarditis from ERP. $\frac{ST}{T}$ ratio ≥0.25 indicates acute pericarditis and not ERP. If V6 is not available, $\frac{ST}{T}$ ratio ≥0.24 in V4-V5 or in lead I is also suggestive of acute pericarditis Ginzton 1982 (19).
In a large epidemiological study from a health care system in Palo Alto, California 29,281 ambulatory ECGs were evaluated using the PR segment as the isoelectric line. In subjects with ERP, defined as ≥0.1 mV ST segment elevation with J waves and/or slurs at the QRS end, there was no association between ERP and mortality Uberoi 2011 (20).

In benign ERP a voltage gradient without increased transmural dispersion of repolarization of monophasic action potentials has been observed in ventricular wall thickness (Figure 9). This parameter, known as Transmural Dispersion of Repolarization (TDP), is expressed on the surface ECG by the interval from T wave peak to T wave end (Tp-Te). For this reason a normal Tp-Te in individuals with benign ERP is not associated with an increased likelihood of malignant arrhythmias. Figure 10 shows a typical example of benign ERP.

**Figure 9**

![Figure 9](image)

**An elevated takeoff of the ST segment at the J point of the QRS complex, varying from 1 to 4 mm relative to the isoelectric line**

**Figure 10**

![Figure 10](image)

**Electrocardiographic diagnosis:** typical early repolarization pattern: sinus bradycardia, upwardly concave ST segment elevation from V3 to V6 followed by wide and positive T
waves, matching the polarity of QRS, and J waves in the descending R wave downslope; reciprocal ST depression only in lead aVR.

Figure 11 shows characteristics of benign ERP in lead V4 with a J wave followed by concave upwards ST segment elevation resembling a “smiley face”.

Figure 11

B) Electrocardiographic characteristics of pathological or malignant J waves.

*Idiopathic ventricular fibrillation associated with early repolarization pattern, known as the Haïssaguerre pattern.*

Patients in this category are predominantly young men who rarely have a positive family history of sudden cardiac death in first-degree relatives (<40 years old). They are without structural heart abnormalities (i.e., essentially an electrical heart disease) as documented by normal transthoracic echo, coronary angiography, and biventricular ventriculography. This pattern is also unrelated to the effects of drugs or hypothermia.

The ECG shows an ERP with ST segment elevation in the lateral, inferior or infero-lateral leads but with horizontal or descending ST segments of upward convexity. This pattern indicates a worse prognosis for malignant arrhythmias *Viskin 2009* (21). A transient, marked increase in J wave width characteristically precedes the onset of the ventricular tachyarrhythmia which predominately occur at night and are which may occasionally be triggered by fever in a similar fashion to BrS. The presence of wide J waves recorded in multiple leads has been shown to be more prevalent in IVF and, in the presence of ERP with >2 mm ST elevation in the inferior leads, there is significantly increased the risk of cardiac death *Kambara 1976* (22). In asymptomatic adults with this pattern the risk of arrhythmic death is three times greater during long-term follow-up *Rosso 2011* (23).

In a large prospective, population-based, case-cohort study of individuals of central-European ancestry, Sinner et al *Sinner 2010* (2) observed a high prevalence of ERP in middle-age individuals between 35 and 54 years of age. The presence of ERP in the inferior leads was associated with a significantly increased risk of cardiac death.

Cappato et al *Cappato 2010* (24) reported that ERP characterized by marked J waves and/or QRS slurring was four times more prevalent among athletes with a history of cardiac arrest or sudden cardiac death than among healthy individuals in a control group.

As with BrS, patients with IVF have a positive therapeutic response to arrhythmic storm when treated with isoproterenol and quinidine. In both entities arrhythmic storms are refractory to treatments with beta blockers and amiodarone.
**Similarities between idiopathic ventricular fibrillation and Brugada syndrome.**
1) Both are more frequent in men;
2) Both occur preferentially in the productive ages of life;
3) Both have more frequent arrhythmic events at night as a result of nocturnal vagotonia;
4) Both have apparently structurally normal hearts;
5) Both may be the result of mutations in the SCN5A gene;
6) Both may be related to mutations in the CACNA1C gene. Thus, type 3 Brugada syndrome and IVF are related to mutations in this gene *Tallila 2014* (25). This variant of Brugada syndrome affects the alpha-1C subunit of the slow L-type voltage-gated calcium channel *Antzelevitch 2007* (26);
7) Both may be due to mutations in the KCNE1L (KCNE5) gene which modulates the initial transient outward Ito current causing a gain of function in this channel *Ohno 2011* (27);
8) Both affect the same locus (3p24-p21) (they are allelic);
9) Both share the same OMIM number (OMIM NO 600163);
10) Both are associated to early repolarization pattern (ERP);
11) Both are part of the so-called J wave syndromes, type 1 Brugada syndrome (T1-AER) and non-type 1 anterior early repolarization (NT1-AER);
12) Both entities show a dramatic increase in J wave amplitude preceding arrhythmic events;
13) In both entities the first extrasystole of arrhythmic events have extremely short coupling intervals;
14) In both, the ventricular tachycardia events may originate in the RVOT *Noda 2005* (28);
15) Both respond well to isoproterenol and quinidine as well as the combination of bepridil and cilostazol *Shinohara 2014* (1);
16) Both benefit from the ablation of Purkinje potentials *Samo 2013* (29) Shah(30);
17) In both the electrical storms are refractory to beta blockers and amiodarone.

**Electrocardiographic Characteristics in Brugada syndrome**
In the first consensus report regarding the Brugada syndrome made in 2002 *Wilde 2002* (31), three ECG repolarization patterns in the right precordial leads were described: type 1, type 2 and type 3, with only type 1 being diagnostic of the syndrome. Table 1 shows the characteristics of the three ventricular repolarization patterns.

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td><strong>J point, ST segment and T wave alterations in the 3 types of Brugada syndrome</strong></td>
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<tr>
<td><strong>Type 1</strong></td>
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<tr>
<td>J point and ST segment elevation (J wave amplitude)</td>
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<tr>
<td>ST segment and T wave aspect</td>
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followed by negative T waves: coved type.

<table>
<thead>
<tr>
<th>Terminal portion of ST segment</th>
<th>Gradually descending</th>
<th>Elevated ≥1 mm</th>
<th>Elevated &lt;1 mm</th>
</tr>
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</table>

The diagnosis of Brugada Syndrome requires the Type 1 ECG pattern with or without provocation using a sodium channel blocker such as flecainide and without evidence of structural heart disease, CAD, electrolyte abnormalities, drug effects, or compression of the RVOT Asterious 2002 (32), and at least one of the following Antzelevitch 2005 (33):

1) Documented history of ventricular fibrillation (VF);
2) Very fast polymorphic ventricular tachycardia (PVT); when observed, with very short initial coupling of the first extrasystole;
3) Family history of sudden cardiac death in young (less than age 45) first-degree relatives;
4) Types 1 or 2 ECG patterns in a first-degree relative;
5) Inducibility of VT/VF with programmed electrical pacing;
6) Syncope;
7) Episodes of nocturnal agonal breathing.

A new consensus report in 2012 defined only two ECG types: type 1 and a new type 2 that combined the previous types 2 and 3. The criteria proposed for type 2 include the typical saddleback pattern observed in V1 and V2 along with the following: Bayés de Luna 2012 (34):

1. The highest point of r’ (high take-off) ≥2 mm.
2. The r’ is rounded rather than pointed in contrast to incomplete right bundle branch block (IRBBB), the triphasic rSr’ pattern of athletes, and pectus excavatum where the final r’ wave is more pointed.
3. The descending limb of r’ coincides with the onset of ST segment
4. Discrete ST segment elevation ≥0.5 mm above baseline.
5. ST segments are followed by positive T waves in V2 but with variable morphology in V1.
6. The β angle averages 62° (±20°). This angle is formed by the ascending slope of the S wave in V2 and the descending slope of r’ as illustrated in Figure 12. In contrast the β angle in IRBBB, triphasic rSr’ pattern of athletes, and pectus excavatum is considerably smaller, averaging 35°.
7. Duration of the base of the β angle triangle at 5 mm from the apex is >3.5 mm. Figure 12.

8. **Figure 12**
The QRS duration (QRSd) in V2 is greater in type 2 Brugada pattern than in innocent IRBBB, and the QRSd in V2 is greater than the QRSd in V6.

To differentiate the type 2 BrS pattern from the ECG of athletes, analyzing only the characteristics of the triangle made up by the β angle and its base in V1-V2, the ECGs from 50 patients with Brugada syndrome were compared with ECGs of 58 normal athletes Serra 2014 (35). The authors concluded that:

- The duration of the base of the triangle at 0.5 mV (5 mm) from the apex (high take-off) ≥160 ms (4 mm) has a specificity (Sp) of 95.6%, sensitivity (Se) of 85%, positive predictive value (PPV) of 94.4% and negative predictive value (NPV) of 87.9%.
- Duration of the base of triangle in the isoelectric line ≥60 ms (1.5 mm) in V1-V2 has Sp of 78%; Se of 94.8%, PPV of 79.3% and NPV of 93.5%.
- Isoelectric line base ratio/height from the baseline until the peak of r’ wave in V1-V2 have a Sp of 92.1%, Se of 82%, PPV of 90.1% and NPV of 83.3%.

The differential diagnosis of a triphasic QRS pattern in the right precordial leads in incomplete right bundle branch block (IRBBB) or triphasic type 2 Brugada pattern can be made by measuring the degrees of the angle made up by the ascending slope of S wave in V1 or V2, with the descending line of the final r’ (β angle) Chevalier 2014 (36). In type 2 Brugada pattern the beta angle (β) is significantly greater (in average 60°) than the β angle of innocent IRBBB (in average 38°). On the other hand, the r’ wave is rounded in aspect, unlike in innocent IRBBB in which it is pointed. Figure 13.

**Figure 13**

Typical wide β angle of type 2 Brugada electrocardiographic pattern.

The β angle exceeds 60° because the descending limb of r’ moves more slowly than in innocent IRBBB.
In the cases of innocent IRBBB, this angle is more acute, averaging 36°.
In the paper by Chevalier et al, (36) a cutoff value of 58° had a positive predictive value of 73% and a negative predictive value of 87%. These authors also proposed measuring the so-called alpha angle (α) defined as the angle made up by the vertical line that goes through the apex of r’ and the descending slope of r’ in V1 or V2 (Figure 14). In a similar fashion to the β angle, the α angle will always be greater in the type 2 triphasic Brugada pattern than in innocent IRBBB. The value of the α angle proved to be slightly less sensitive and less specific in comparison to the β angle to differentiate type 2 Brugada pattern of innocent IRBBB.

Figure 14

Concept of α angle

The alpha (α) angle is defined as the angle formed by the vertical line that goes through the apex of r’ and the descending slope of r’ of V1 or V2.
The sensitivity of the ECG to identify Brugada syndrome is improved with the addition of high accessory precordial leads one or two intercostal spaces above leads V1 and V2 (V1H-V2H-V3H), as reported in numerous papers Farre 2000 (37); Sangwananaroj 2001-2001 (38;39); Nagatomo 2002 (40); Nagase 2002 (41); Takagi 2002 (42); Cabezon Ruiz 2003 (43); Butz 2010 (44). Figure 15.
$V_1$ – in the 4$^{th}$ intercostal space, in the right border of the sternum;
$V_2$ – in the 4$^{th}$ intercostal space, in the left border of the sternum;
$V_3$ – halfway between $V_2$ and $V_4$;
$V_{1H}$ – in the 3$^{rd}$ or 2$^{nd}$ intercostal space, in the right border of the sternum;
$V_{2H}$ – in the 3$^{rd}$ or 2$^{nd}$ intercostal space, in the left border of the sternum.

The ECGs of Brugada patients may change over time going from type 1 into a type 2 or 3. A type 3 ECG pattern is very common and considered a normal variant, but the type 2 pattern is also a normal variant, although there are characteristics that allow differentiating it from benign incomplete right bundle branch block.

Fever unmasks the type 1 electrocardiographic pattern and triggers events in patients with Brugada syndrome.

Figure 16 illustrates the ECG changes that occurred in this patient as the fever resolved.
Figure 16 shows ventricular repolarization morphologies in the right precordial leads during fever (two columns at the right) and when afebrile (column at the left). Only in the febrile state is there a Type 1 ECG pattern diagnostic of Brugada syndrome. When afebrile (36.7°C), the ECG diagnosis is not possible because the observed type 2 Brugada ECG pattern is not diagnostic.

Since temperature affects the permeability of sodium and other membrane channel ions, it is reasonable to infer it may influence the functional state of these channels Antzelevitch 2002 (45). Experimental studies show that the transmembrane kinetics of the sodium cation is strongly influenced by temperature Nagatomo 1998 (46). Thus, an increase of 10°C augments the opening time and the number of times the channel opens by threefold. In addition, activation and inactivation of early sodium channel kinetics is processed twice faster with temperature increase, and this modifies the activation and inactivation from a
stationary state Gonzalez-Rebollo 2000 (47). For this reason, the febrile state is considered an important trigger of arrhythmic events in BrS by modifying the conductance of sodium ions resulting in ST segment elevation and phase 2 functional reentry, considered the pathophysiological basis of the arrhythmias in this entity.

In addition to fever other factors may trigger events in BrS including antimalarial agents, tricyclic antidepressants, some class IA (ajmaline and procainamide) and class IC antiarrhythmics (flecainide and pilsicainide), hyperglycemia, nocturnal bradycardia (by vagal predominance), alcohol consumption, mental stress, cocaine, etc.

Experimental studies by Dumaine et al Dumaine 1999 (48), showed that certain mutations in the SCN5A gene encoding the sodium channel increase the sensitivity to fever (temperature-dependent) triggering the type 1 ECG phenotype. These authors found that at more physiological temperatures, a missense mutation in the SCN5A gene may alter the propagation of the sodium cation in such a way that its inflow is drastically increased during the initial phase of the action potential in the right ventricular outflow tract. The authors tested this hypothesis using mammalian cells with the Thr1620Met mutation by means of the patch-clamp technique to study the inward Na+ currents at 32°C. They concluded that the kinetics of the Thr1620Met cells in the right ventricular epicardium leads to faster decay and slower reactivation of the sodium channel compared to the wild type at 32°C. These results explain the characteristics of ECG of patients with the Brugada syndrome and illustrated for the first time, that an I_{Na+} channel mutation may modify the electrophysiological behavior and foster a greater arrhythmogenicity during febrile states. In fact, the study by Nagatomo et al Nagatomo 1998 (46) showed experimentally that the sodium channel is temperature-dependent in the conditioning mutation of the variant 3 of LQT3, considered the mirror image of Brugada syndrome.

There are numerous reports of the action of fever on patients with Brugada syndrome as evidenced by:

1) ST segment elevation with worsening of the coved type 1 pattern or causing it to appear when not initially present:
2) Presence of type 1 pattern only during fever and disappearance when the patient becomes afebrile as in the present case Patruno 2003 (49); Wakita 2004 (50);
3) Spontaneous T wave alternans;
4) Appearance of premature ventricular contractions;
5) Appearance of events of polymorphic VT with syncope;
6) Incessant monomorphic ventricular tachycardia;
7) Fatal electrical storms Morita 2002(51); Porres 2002(52); Dinckal 2003(53); Amin 2010(54); Wakita (50); Matsubara 2004(55); Keller 2005(56).

BrS is a primary electrical disorder of the heart that is frequently associated with syncope and sudden cardiac death. The prevalence around the world has been estimated to average 5:10,000 for any ethnicity Hedley 2009 (57). It is an inherited disease having variable penetrance of dominant autosomal transmission Brugada P 1992 (58); Probst(59). Syncope or sudden cardiac death due to polymorphic ventricular tachycardia and ventricular fibrillation generally occur at rest or during sleep.

Currently, more than 100 mutations affecting 15 different genes are known. Sixty five percent of cases are sporadic without mutation. The mutations in the SCN5A gene are by far the most frequent; the 14 remaining genes make up less than 1% of all cases. The following are the affected genes:
1) **SCN5A**: type 1 Brugada syndrome occurs in 15%-30% of the cases. The main mutation in the SCN5A gene, encoding the alpha subunit of the sodium channel (I\(Na^+\)) Na(v)1.5, leads to reduction in the channel function during phase 0, most often in people with a positive family history. It was identified by Chen et al, in 1998 Chen 1998(60); Morita 2009(61).

2) **GPDIL**: NAD-dependent glyceraldehyde-3-phosphate dehydrogenase. **Type 2 Brugada syndrome Weiss 2002(62).**

3) **CACNA1C**: type 3 Brugada syndrome. Alpha-1C subunit of the slow L-type voltage-dependent calcium channel Antzelevitch 2007 (26).

4) **CACNB2**: type 4 Brugada syndrome Antzelevitch 2007 (26).

5) **SCN1B**: beta 1 subunit of the voltage-gated sodium channel. **Type 5 Brugada syndrome Watanabe 2008 (63).**

6) **KCNE3**: it encodes the ancillary \(\beta\) subunit of several potassium channels, including kv4.3, which regulates the Ito channel: **type 6 Brugada syndrome Delpón 2008(64).**

7) **SCN3B**: it encodes the beta subunit of the Na(v)1.5 channel. **Type 7 Brugada syndrome Hu 2009(65).**

8) **HCN4**: type 8 Brugada syndrome Ueda 2004(66).

9) **SCN2B**: type 9 Brugada syndrome Burashnikov 2010(67).

10) **KCND3**: type 10 Brugada syndrome Giudicessi 2011(68).

11) **KCNE1L** (**KCNE5**): it modulates the initial outward K+ I(to) channel, causing a gain in function in this channel, and the BrS and IVF phenotypes Ohno 2011 (27).

12) **KCNJ8**: Medeiros-Domingo 2010(69).

13) **RANGRF**: Campuzano 2014(70).

14) **SLMAP**: this mutation may cause Brugada syndrome via modulation of the intracellular traffic in the hNav1.5 channel Ishikawa 2012(71).

15) **TRPM4**: Liu2013(72).

Table 2 shows a summary in the 10 main genetic types of BrS.

<table>
<thead>
<tr>
<th>BrS</th>
<th>Gene</th>
<th>Locus</th>
<th>Protein</th>
<th>Affected channel</th>
<th>Effect on the channel</th>
</tr>
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<tr>
<td>BrS1</td>
<td>SCN5A</td>
<td>3p21-p23</td>
<td>Nav1.5</td>
<td>Subunit-(\alpha) I(Na)</td>
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<td>BrS2</td>
<td>GPD-1L</td>
<td>3p24</td>
<td>G3PD1L</td>
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<td>BrS3</td>
<td>CACNA1C</td>
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<td>Cav1.2</td>
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<td>Loss</td>
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<td>Nav(\beta)1/(\beta)1b</td>
<td>Subunit-(\beta) I(Na)</td>
<td>Loss</td>
</tr>
</tbody>
</table>

Table 2
<table>
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<tr>
<th>OMIM</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Subunit</th>
<th>Function</th>
<th>Type</th>
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</thead>
<tbody>
<tr>
<td>604433</td>
<td>KCNE3</td>
<td>11q13-q14</td>
<td>MiRP2</td>
<td>Subunit-β Iₖs/Iₖo</td>
<td>Gain-of-Function</td>
</tr>
<tr>
<td>600235</td>
<td>SCN3B</td>
<td>11q24.1</td>
<td>Navβ3</td>
<td>Subunit-β Iₙa</td>
<td>Loss</td>
</tr>
<tr>
<td>BrS6</td>
<td>KCNJ8</td>
<td>12p11.23</td>
<td>Kir6.1</td>
<td>IₔATP</td>
<td>Gain-of-Function</td>
</tr>
<tr>
<td>BrS7</td>
<td>CACNA2D1,</td>
<td>7q21.11</td>
<td>Ca₉.217</td>
<td>I₉Ca</td>
<td>Loss</td>
</tr>
<tr>
<td>BrS8</td>
<td>KCND3</td>
<td>1p 13.2</td>
<td>K₄.3</td>
<td>Iₙo</td>
<td>Gain-of-Function</td>
</tr>
</tbody>
</table>

All the genetic mutations are related to functional alterations of the inward Na⁺ current or outward Ca²⁺ or K⁺ currents. The very low frequency of genetic mutations associated with calcium or potassium currents made the genotype-phenotype correlations for these genes not studied to the extent as those related to the SCN5A gene. The SCN5A-related Brugada syndrome phenotypes can overlap with other phenotypes including long QT syndrome, sick sinus disease, and Lenegre’s disease. Figures 17 illustrate examples from Holter tracings of the dynamic electrocardiographic features of ventricular repolarization in BrS.

**Figure 17**

![Type 2 pattern](image1)

![Type 1 pattern](image2)

![Type 2 pattern](image3)

Figure 17. 24-hour Holter tracing of the right precordial leads, displaying the intermittent aspect of BrS. The alternation between types 1 and 2 patterns is clearly seen. Figure 18 illustrates the confusion that may occur in differentiating incomplete RBBB from the Type 2 Brugada ECG phenotype.
Electrocardiographic diagnosis: Type 2 Brugada pattern that may be confused with an innocent IRBBB.

Electrocardiographic markers of increased risk in Brugada syndrome

1) Fragmented QRS (fQRS) on the 12-lead ECG is a marker of depolarization abnormality. fQRS refers to the presence of various QRS morphologies with or without Q waves including the presence of an additional R wave (R’) or notching around the nadir of the R’ (fragmentation) in two contiguous leads corresponding to the territory of a major coronary artery. fQRS represents conduction delays from inhomogeneous activation of the ventricles due to myocardial scar. It is highly predictive of myocardial scar and is associated with increased mortality in patients with CAD. In addition fQRS predicts arrhythmic events and mortality in patients with implantable defibrillators. It also signifies poor prognosis in patients with nonischemic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and Brugada syndrome. However, fQRS is a nonspecific finding and its prognostic value should only be interpreted in the presence of pertinent clinical evidence and type of myocardial involvement (structurally abnormal vs. structurally normal heart) Jain 2014(73). Using ECG with computerized multipolar precordial leads may identify fragmented QRS not visible in the conventional 12-lead ECG Batchvorov 2014(74). Figure 19.
Presence of a notch within a non-wide QRS complex in two adjacent leads (V₁-V₂): fQRS.

2) A form of early repolarization syndrome Robers 2013(75) secondary to a transmural gradient during early cellular repolarization results in ST segment and J wave elevation during the final part of the descending R wave slope. The presence of this pattern creates an electric substrate for increased risk of malignant arrhythmias in different clinical situations such as acute myocardial ischemia, BrS and IVF. The challenge is in differentiating this early repolarization malignant ECG marker from the more common benign ERP.

3) A terminal R wave in lead aVR characterized by R wave voltage ≥0.3 mV or R/q ratio ≥0.75 is called the aVR sign. This is a risk marker for fatal events in patients with BrS Babai Bigi 2007(76). Figure 20.

The figure shows the presence of prominent final R wave in the unipolar aVR lead called “aVR sign” (R≥0.3 mV or 3 mm or R/q ratio≥0.75. This sign constitutes a risk factor for the appearance of arrhythmic events in patients with BrS.

4) Increase in QRS duration in the right precordial leads with QRSd in V₂ > QRSd in V₆;

5) Prolonged T peak -to- T end (Tpe) interval as a consequence of increased transmural heterogeneity in the thickness of the ventricular wall Letsas 2010(77);

6) Intraatrial conduction disorders consisting of discrete prolongation of P wave duration in patients with this syndrome related to SCN5A gene mutations or an increase in P duration after IV ajmaline. This disorder of atrial conduction may contribute to arrhythmias in BrS Kofune 2010(78). Figure 21.
Figure 21

The tracing shows the P wave in a patient with BrS and positive SNC5A mutation performed before and immediately after ajmaline test (1 mg/kg). P wave duration (Pd) before the injection is prolonged (Pd=135 ms). After drug administration Pd further increased (Pd=162 ms).

7) First-degree AV block, observed in 50% of the cases, is due to HV interval prolongation or split His mainly when associated with SCN5A mutation. In asymptomatic individuals prolonged HV interval during sinus rhythm is associated with a greater risk of arrhythmic events during follow-up Brugada P 2001(79). First-degree AV block is considered an independent risk marker in BrS.

8) A greater frequency of supraventricular arrhythmias especially paroxysmal atrial fibrillation is a risk marker. The prevalence of AF or atrial flutter in patients with BrS is greater than in the general population in this age group. When these arrhythmias are identified before the appearance of the BrS phenotype the prognosis is worse. The response to quinidine, however, is good Giustetto2014(80).

9) Extreme QRS axis shift to the left is observed in approximately 10% of the cases indicative of LAFB or right superior fascicular block in the right ventricular outflow tract. Fascicular blocks were found in 16% of the cases of a large series of 365 patients Maury 2013(81).

10) A combination of depolarization and repolarization abnormalities in the same patient is a strong marker of fatal events. Depolarization alterations such as QRS duration ≥120 ms, fragmented QRS (fQRS), infero-lateral early repolarization, and QT interval prolongation are highly sensitive and specific for fatal events in BrS Tokioka 2014(82).

11) The presence of late potentials in high resolution ECG is a highly sensitive noninvasive marker for adverse events Alvarez-Gómez 2006(83).

12) The presence of T wave alternans (TWA) is a marker for events leading to sudden cardiac death. Time domain TWA on Holter recordings in patients with Brugada syndrome predicted malignant arrhythmias Uchimura-Makita(84).
References


