**Brugada Syndrome and Reduced Right Ventricular Outflow Tract Conduction Reserve: a Final Common Pathway?**

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**Abstract**

Brugada syndrome (BrS) was first described as a primary electrical disorder predisposing to the risk of sudden cardiac death (SCD) and characterised by right precordial lead ST elevation. Early description of right ventricular structural abnormalities and of right ventricular outflow tract (RVOT) conduction delay in BrS patients set the stage for the current controversy over the pathophysiology underlying the syndrome: channelopathy or cardiomyopathy; repolarisation or depolarisation. This review examines the current understanding of the BrS substrate, its genetic and non-genetic basis, theories of pathophysiology and the clinical implications thereof. We propose that the final common pathway for BrS could be viewed as a disease of ‘reduced RVOT conduction reserve’.

**Key words:** Brugada syndrome, genetics, depolarisation, right ventricular outflow tract

1. Introduction

Brugada syndrome (BrS) was first described as a primary electrical disorder predisposing to sudden cardiac death (SCD) by the Brugada brothers, although its eponymous title was only bestowed four years later.1 Eight patients had demonstrated an ECG pattern of ‘right bundle branch block, normal QT interval and persistent ST segment elevation in precordial leads V1 to V2-V3 not explainable by electrolyte disturbances, ischemia or structural heart disease’.2 This has now been defined as the type 1 Brugada ECG pattern.3 Three years earlier, a similar ECG pattern had been described in one patient who presented with ventricular fibrillation (VF) and right ventricular structural abnormalities.4 The same group had previously published a case with this same ECG pattern and vector-cardiographic evidence of conduction delay in the right ventricular outflow tract (RVOT).5 These early descriptions set the stage for the current tension over the pathophysiology underlying the syndrome: channelopathy or cardiomyopathy; repolarisation or depolarisation. This review examines the current understanding of the BrS substrate, its genetic basis, theories of pathophysiology and the clinical implications thereof.

1. Genetic basis

The early description of BrS (1992) revealed a significant family history for SCD. Indeed, in two families, other relatives had died suddenly at a young age, and two of the cases were young siblings who both had a cardiac arrest as toddlers.2 Hence, it was speculated that genetics contributed to the pathophysiology of BrS. Segregation studies were consistent with autosomal dominant inheritance with reduced penetrance, although there was a marked male predominance.

***SCN5A* and rare genetic variation**

The first putative BrS-susceptibility gene discovered was the *SCN5A-*encoded α-subunit of the Nav1.5 current.6, 7 Functional studies indicated a loss of sodium current that was exacerbated by higher temperatures, consistent with fever precipitating the type 1 pattern and increased risk.8-10 Thereafter several hundred potentially pathogenic *SCN5A* variants were identified in BrS patients with an average yield of about 20%.11 These included missense, nonsense, frameshift and splice site variants, with a common loss-of-function effect in heterologous expression systems and inducible pluripotent stem cells (iPSC) due to either decreased expression of Nav1.5 proteins in the sarcolemma,12 expression of non-functional channels,13 or altered gating properties (delayed activation, earlier inactivation, faster inactivation, enhanced slow inactivation, and delayed recovery from inactivation).8, 14-17 This impairs the fast upstroke in phase 0 of the action potential (AP) leading to conduction slowing. This correlated well with clinical data; as the degree of Nav1.5 loss-of-function increased, patients had more prolonged conduction intervals and worse outcomes.18, 19 BrS patients with a prolonged PR interval >200ms had a 40% likelihood of being *SCN5A-*positive whereas those with a normal PR interval had <10% chance of being *SCN5A*-positive.20 Furthermore, the severity of the functional impact of *SCN5A* variants in *SCN5A* families has been associated with a greater likelihood of BrS phenotype.21

More than 20 other genes have been implicated in BrS. Some encode calcium channel proteins (*CACNA1C, CACNB2b, CACNA2D1*), sodium channel β-subunits (*SCN1B, SCN3B*), the neuronal sodium channel α-subunit Nav1.8 (*SCN10A*), the transient outward current (Kv4.3 or Ito) (*KCNE3, KCND3, KCNE5*) and the ATP-sensitive potassium channel (*KCNJ8, ABCC9*). Non-ion channel genes have also been implicated and affect the trafficking, scaffolding and/or expression of sodium channels: *PKP2*, *GPD1L*, *MOG1*, *SLMAP,* *RRAD* and *DLG1* (Table 1).22-26 27 28. The common pathophysiology stemming from variants in these BrS-susceptibility genes is either a reduction in the inward sodium or calcium current or an increase in one of the early potassium currents. Importantly, most were identified in single individuals or small families and sound segregation data were not available with the exception of *GPD1L*,although the applied screening method may not have excluded sufficiently a haplotype with a *SCN5A*-associated rare variant.29, 30

Since 2004, it became evident that 2% of Caucasian and 5% of non-Caucasian healthy subjects had rare variants in *SCN5A*.11, 31 Furthermore, putative pathogenic variants in other genes previously associated with BrS were more prevalent in the general population than could be feasible if they conformed to the Mendelian disease model.32 Studies have been unable to provide compelling and reproducible results, for example the case of *SCN10A*.24, 33 It therefore followed that robust comparison was necessary of the prevalence of rare variants in all genes implicated in BrS cases and controls. Next generation sequencing revealed that only rare variants in *SCN5A* are more prevalent in BrS cohorts than controls.32, 34 In addition, comparing genetic findings in BrS with published data in the ExAC exome database revealed a similar frequency of rare variants in all genes except *SCN5A*.35 Finally, a recent reappraisal of genes implicated in BrS, using the stringent ClinGen methodology36 revealed that only *SCN5A* remains undisputed as causal; all other genes were downgraded to ‘disputed evidence’.37

Whilst the role of now disputed genes remains to be explained, variants in some of these may play a role as low frequency susceptibility variants or modifiers.38, 39 This extended to *SCN5A* with Makarawate et al detecting enrichment of low frequency *SCN5A* variants in Thai BrS patients.40

Despite the wealth of data pointing to an important role for *SCN5A* variants in the pathogenesis of BrS, its causal role was questioned for the first time in a study involving several large BrS families hosting pathogenic *SCN5A* variants that failed to co-segregate as predicted.41 In 5 out of 13 families with at least five *SCN5A-*positive individuals, eight genotype negative but phenotype positive individuals were identified.41 This genotype-phenotype mismatch pointed to more genetic causes for BrS.

**Common genetic variation and polygenic risk scores**

Genetic studies therefore addressed the impact of common variants or single nucleotide polymorphisms (SNPs) on the phenotype in BrS. First evidence came from a study of a haplotype of 6 SNPs in the promotor region of *SCN5A*.42 The presence of this haplotype, exclusively in Asians, was associated with reduced expression of Nav1.5 and more significant conduction delay.42 Another SNP, H558R, also impacted significantly on protein expression by rescuing expression of a trafficking defect.43

Concurrently, Bezzina et al performed a genome wide association study (GWAS) of common genetic variation in Caucasian BrS cases compared to healthy controls and identified three genome-wide significant loci, two on chromosome 3 encompassing *SCN5A* and *SCN10A* and one on chromosome 6 near the *HEY2* gene.44 Furthermore, the more ‘risk alleles’ from these three loci that a patient harboured, the more likely it was that an individual manifested BrS.44 This gave rise to the concept of a BrS genetic or polygenic risk score (BrS-PRS) with 5-6 risk alleles being associated with a roughly 20-fold higher risk for the type 1 ECG pattern. This was validated in Japanese probands44, in patients undergoing ajmaline provocation testing for BrS45 and most recently in the Taiwanese and Thai populations.40, 46 The BrS-PRS has also been associated with BrS phenotype in families with pathogenic *SCN5A* variants causing haploinsufficiency, or hosting the commonest *SCN5A* rare variant, *SCN5A*-E1784K. In fact the BrS-PRS’s strongest association with BrS phenotype was in relatives in *SCN5A* families without the pathogenic variant21, explaining in part the aforementioned genotype-phenotype mismatch41. The most recent GWAS in BrS is poised to report many more loci underlying heritability of BrS e, promising a more powerful future BrS-PRS.47

**Implications for heritability and genetic testing**

Based on these data, the current conclusion is that in some families, BrS may behave as a near-monogenic, or quasi-autosomal dominant, disorder stemming from penetrant loss-of-function pathogenic variants in *SCN5A* or a combination of an incompletely penetrant BrS-susceptibility *SCN5A* variants (e.g. *SCN5A*-E1784K) with common genetic variation resulting in an increased PRS (Figure 1). The genetic basis of the remaining BrS probands and families may be explained by an oligogenic/polygenic model encompassing common genetic variation and low frequency susceptibility variants most of which have yet to be described.

Therefore, commercial and clinical genetic testing could be streamlined to a genetic test panel that comprises only *SCN5A* and an emerging optimised BrS-PRS. All the other previously published BrS-susceptibility genes should be removed from clinical testing as the clinical implication for patients and family members are not well defined. These genes should be assessed as part of research until enough additional evidence is generated to promote any of the alleged minor disease genes out of ‘genetic purgatory’ where they currently reside as genes of uncertain significance (GUS).

1. Pathophysiology

Several theories for the primary cellular electrophysiological mechanism(s) underlying BrS have been proposed, each with basic and clinical observations that support their validity. The primary debate surrounds the contribution of abnormalities in cardiomyocyte depolarisation versus repolarisation (Figure 2).

**Repolarisation:** Antzelevitch et al developed a canine right ventricular wedge preparation model that examined AP characteristics across myocardial layers, seeking to explain the anterior ST elevation seen in the type 1 and type 2 Brugada ECG patterns.48 An epicardial-endocardial transmural voltage gradient is created in the context of reduced INa current that leads to more unopposed Ito, and thus the normal spike and dome morphology in phase 1 of the AP is disrupted. Due to differences in distribution of Ito and differences in thickness of the endocardial and epicardial layers, these changes are more exaggerated in the RVOT epicardium than its endocardium and cause accentuation of the AP and therefore the J-point and right precordial ST elevation associated with the Brugada ECG pattern. Variable local repolarisation and refractoriness of the RVOT epicardial cells leads to risk of inducing phase 2 re-entry circuits and subsequently polymorphic ventricular tachycardia (VT) or VF. Supportive observations include that Ito is enhanced in the RV epicardium of males compared to females and may partly explain the male predominance in BrS.49 Furthermore, another canine model that recapitulated the human phenotype was published in 2009 by Morita et al, which proposed that epicardial AP heterogeneity was responsible for the ECG changes, temperature sensitivity and arrhythmias in BrS.50 More recently, Veerman et al demonstrated that *Hey2*, the transcription factor associated with BrS by GWAS, has as role in transmural ion channel gene regulation. In a heterozygous knock-out mouse model, transmural differences in Ito and INa were diminished resulting in changes in J wave morphology.51

**Depolarisation:** An alternative theory is that of genetic and developmental abnormalities in RVOT depolarisation resulting in conduction delay. In conventional isochronal mapping in BrS, the basal portion of the right ventricle (RV) including the RVOT is activated later than normal.52, 53 When there is altered depolarisation, the AP of the RVOT is later than that of the body of the RV. Consequently, there is a more positive myocyte membrane potential in the RV compared with the RVOT, creating a gradient driving current into the RVOT before returning to the RV via the extracellular space.54 Thus, the initial phase is characterised by current flowing toward the right precordial leads, followed by a second phase where the membrane potentials are more positive in the RVOT than the RV, reversing the vector of the current away from the right precordial leads. This leads to the characteristic inverted T wave in those leads that reflect the anatomical location of the RVOT (V1-V3). In this context, arrhythmias are believed to originate in the border zone between early and delayed depolarisation where there are mismatched membrane potentials, similar to that seen in the border zones of ischemic myocardium. In fact, when exposed to a warm water distillate at 40 degrees centigrade, the epicardium of BrS patients shows exaggeration of slow conduction in the anterior RVOT with increased conduction velocity in the surrounding normal epicardium and enhancement of the type 1 pattern.55

Thus, investigation of a structural element within the Brugada phenotype has proceeded, with findings supportive of the depolarisation theory. Transthoracic echocardiography is typically normal, but lacks the ability to image this region of the heart with meaningful resolution. However, Doppler echocardiography shows a linear relationship between delay in RV contraction onset and the degree of ST segment elevation during administration of intravenous flecainide.56 Higher resolution CT and MRI have identified anatomical abnormalities of the RV and RVOT and even late gadolinium enhancement in the left ventricle (LV) that are compelling, but not ubiquitous.57, 58 Furthermore, BrS patients with *SCN5A* pathogenic variants tend to show greater structural abnormalities than similar genotype negative patients.59 The potential contribution of structural abnormalities has taken on renewed interest with the advent of epicardial mapping and ablation, and recent histopathological data from sudden death victims with familial BrS.60-62

Several groups have performed endomyocardial biopsies in patients diagnosed with BrS. These have yielded mixed results, from lymphocytic infiltrates to fibrofatty infiltration suggestive of ARVC.63-65 Frustaci et al also examined 18 consecutive symptomatic BrS patients with endomyocardial biopsy of both ventricles, finding evidence of abnormalities in all patients.63 Histopathology was subsequently shown to be heterogeneous in a subsequent report in 2008; whereby non-specific lymphocytic changes on biopsy in 21 BrS patients could not be classified into any pathognomonic pattern.64 In an evaluation of 6 post-mortem hearts from presumed BrS-related sudden death, epicardial surface and interstitial fibrosis and reduced gap junction expression was seen in the RVOT.62 These findings were similar in biopsies from *in vivo* cases of BrS undergoing open-heart surgical ablation. Fibrosis co-localised with abnormal potentials from epicardial mapping, correlating with the previous observation that epicardial ablation of scar potential attenuates and may even abolish the Brugada phenotype and life-threatening arrhythmias.60 Furthermore, inflammatory infiltrates and fibrosis may be present in RVOT biopsies from BrS patients;61 whether this is due to viral infection is uncertain. The possibility of an inflammatory and pro-fibrotic process has received further support from serological studies in BrS patients indicating that autoantibodies to α-cardiac actin, α-skeletal actin, keratin, and connexin-43 can be found in BrS patients but not controls.66 Inflammation and fibrosis are recognised features of ARVC,67 such that these findings in the RVOT of BrS patients suggest a possible overlap.68, 69

Interestingly, modelling with patient specific cardiomyocytes derived from iPSC has identified a cellular phenotype consistent with slow cardiac conduction in cardiomyocytes derived from *SCN5A* patients with BrS.70, 71 This was absent, however, in non-*SCN5A* patients whose cellular phenotype failed to show any differences from controls, suggesting that extracellular or organ level abnormalities may be necessary to generate the phenotype.72

**Apparent inconsistencies:** Some clinical observations appear to support the repolarisation theory, including electrocardiographic patterns perfectly mimicking acute ischemia, and absence of filtered QRS prolongation on signal averaged ECG in 50% of cases.73 There is also reduced severity of phenotype with adrenergic stimulation in many cases, which augments the L-type Ca-current and elevates the plateau phase of the AP, and in the wedge preparation model would reduce transmural heterogeneity.74 Conversely, by increasing the voltage level and duration of the AP plateau the driving force for propagation of the cardiac impulse is improved.75 Hence, the safety of conduction may subsequently improve in areas with high resistance connections such as Purkinje fibre to ventricular muscle connections or in areas with significant fibrosis,76 and according to the depolarisation theory, would ameliorate the ECG pattern. Another apparent inconsistency is the beneficial effect, in terms of prevention of recurrent arrhythmias, of the sodium channel blocker quinidine.77-79 Sodium channel blockade is expected to worsen conduction (and thus worsen the phenotype) but quinidine is also an Ito blocker. Ito block would prolong AP duration and ameliorate the phenotype in the RVOT following the same mechanism as described for adrenergic stimulation.73 Thus both theories could explain dynamic ECG changes often seen in BrS patients.

The repolarisation theory falls short of explaining fully the fragmented electrograms recorded during epicardial mapping, and that ablation of collocated epicardial tissue, characterised by fibrosis, leads to a dramatic decrease in arrhythmia burden and phenotypic severity.60-62, 80 Szel et al. proposed that phase 2 re-entry is responsible for complex fractionated epicardial signals in the canine wedge model, and is ameliorated by quinidine.81 A similar response to ablation of delayed signals was then demonstrated at the epicardial surface of two different canine wedge preparations with pharmacologically induced Brugada phenotype.82 However, the fractionated epicardial signals found in humans are present continuously and consistently. This would appear unlikely if an unstable electrical phenomenon such as phase 2 re-entry accounted for them. And whilst these data were elegantly presented, they do not explain the consistent findings of structural myocardial abnormalities in humans.

We therefore propose that an impairment of the normal physiological capacity for cardiac conduction in the RVOT at a cellular and organ level is the main pathophysiological mechanism responsible for BrS. This diminished ‘cardiac conduction reserve’ is at least in part genetically mediated and ablation of myocardial tissue exhibiting impaired conduction reserve i.e. the RVOT epicardium, leads to the therapeutic responses already described. An additional role for perturbation of transmural repolarisation cannot, however, be excluded.

1. The role of sodium channel blocker challenge and fever

The original BrS consensus conferences in 2002 and 2005 established the diagnostic importance of the type 1 Brugada ECG pattern (Figure 3): ‘coved type ST-segment elevation in more than one right precordial lead (V1 to V3), in the presence or absence of a sodium channel blocker’. One of the following additional clinical features were required: documented VF; self-terminating polymorphic VT; a family history of SCD (<45 years); coved type ECGs in family members; inducibility of VT; syncope; or nocturnal agonal respiration’. Exclusion of structural and other phenocopies was necessary, emphasising a primary electrical etiology.3, 83

Guidelines in 2013 liberalised the diagnosis of BrS. If the type 1 Brugada ECG pattern was detected in just a single right precordial lead in standard ECG electrode placement or with the so-called high precordial lead Brugada ECG (V1 and V2 leads are placed in the 3rd and 2nd intercostal spaces (ICSs), Figure 3) either spontaneously or during a sodium channel blocker challenge with either ajmaline, procainamide, flecainide, or pilsicainide.84 This was justified by the colocation of the diagnostic pattern with the site of the RVOT on imaging studies85, 86 and the lack of any clinical differences between patients with single or multiple lead involvement.87, 88 Furthermore, there was no need for any additional clinical or family features.

Unfortunately, it became apparent that there may be a significant “background noise rate” with respect to a drug-induced Brugada ECG pattern, particularly with ajmaline challenge. Approximately 4% of ostensibly healthy Turkish individuals undergoing ajmaline provocation demonstrated a type 1 pattern, as did almost 30% of patients with atrioventricular nodal reentrant tachycardia,89 and almost 20% of patients with an accessory pathway.90 Furthermore, 2% of Israeli patients attending their local emergency department with pyrexia showed a type 1 pattern whilst only 0.1% of apyrexial patients were similarly affected.91 This may indicate that these subjects have an increased BrS-PRS rather than true BrS, as suggested by Tadros et al45. Whether their risk of SCD remains elevated or necessitates more than simple lifestyle modification is unknown.

These observations have prompted the most recent consensus conference in 2016 to reinstate the requirement of at least one additional clinical factor in the setting of a drug-induced type 1 ECG pattern (Table 2).92 This was not the case, however, for the pyrexia induced type 1 pattern which received greater weighting in the associated Shanghai scoring system, although insufficient for a definite diagnosis by itself. Interestingly, patients with a drug-induced phenotype required a resting type 2 pattern to receive a score, its absence precluding a diagnosis. A spontaneous type 1 Brugada ECG pattern remained the only finding diagnostic of BrS in an otherwise normal and asymptomatic person without any family history.

The score also gave a weighting, albeit a weak one, to relatives of family members who had died suddenly with a negative autopsy: Sudden Arrhythmic Death Syndrome - SADS. Recent systematic investigation of SADS families in whom all other aetiologies have been excluded has indicated a 28% yield of BrS based on positive ajmaline testing.93 The majority of these families would not have received a definite diagnosis of BrS using the Shanghai score yet appeared indistinguishable from the minority with a definite diagnosis.

Thus, whilst the Shanghai criteria appear to be the most reasonable approach for managing an asymptomatic drug induced type 1 pattern, the scoring system remains to be improved and further validated and will always be limited by the lack of a gold standard for diagnosis. The role of weaker sodium channel blocker challenge such as procainamide94 as a potentially more specific test also remains to be determined, with a need for head to head comparison in at risk patients and healthy controls.

**Conclusions**

The diversity of presentation, electrical signals and related pathology and imaging support a complex confluence of factors in patients with BrS. The majority appear to have focal fibrous tissue and conduction delay in the epicardial RVOT, with a contributory monogenic and oligogenic predisposition. This is in contrast to the prevailing understanding of many clinicians that focuses on both repolarisation and genetic factors as dominant features.

This substrate is mediated at least in part by common genetic variation and therefore it is not surprising that healthy people with a higher burden of the BrS-associated risk alleles (i.e. a high BrS-PRS) may show a positive response to ajmaline provocation.45 Further genetic susceptibility is likely to be mediated by more than rare genetic variation i.e. *SCN5A* variants. The role of ultra-rare genetic variants in non-*SCN5A* genes requires further proof and currently, evidence for a monogenic model of clinical diagnostic testing beyond *SCN5A* is absent. ‘Less rare’ rare variants may play an important role in susceptibility in a gene dosage model, but this remains to be elucidated as does the impact on the human substrate of genetic variation affecting repolarisation.

Much like the concept of reduced repolarisation reserve underlying long QT syndrome,95 we propose that whether mediated by a penetrant *SCN5A* pathogenic variant, an increased PRS and/or additional genetic insults, the final common pathway96 for BrS could be viewed as a disease of ‘reduced RVOT conduction reserve’ (Graphical abstract). Most patients will have a primarily depolarisation-mediated process although perturbations in repolarisation cannot be excluded. In this framework, the patient’s intrinsic RVOT conduction reserve may be age and sex dependent and marginal reserves can be exposed by the use of potent conduction slowing drugs or other acute modulators of cardiac conduction and repolarisation, such as pyrexia and altered vagal tone. Fibrosis on histopathological studies also suggest that there may be a role for superimposed inflammation on the substrate, with a potential overlap with the spectrum of arrhythmogenic cardiomyopathy that requires further evaluation. Indeed, we hypothesise that the majority of patients historically labelled with BrS may be more accurately described as focal epicardial arrhythmogenic cardiomyopathy.

**Funding**

MJA was supported by the Mayo Clinic Windland Smith Rice Comprehensive Sudden Cardiac Death Program.

ADK receives support from the Sauder Family and Heart and Stroke Foundation Chair in Cardiology (Vancouver, BC), the Paul Brunes Chair in Heart Rhythm Disorders (Vancouver, BC) and the Paul Albrechtsen Foundation (Winnipeg, MB).

**Acknowledgements**

We acknowledge the support from the Robert Lancaster Memorial Fund, “the Netherlands CardioVascular Research Initiative": the Dutch Heart Foundation, Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development and the Royal Netherlands Academy of Sciences (PREDICT2).

**Conflict of interest**

MJA is a consultant with Abbott, ARMGO, Audentes Therapeutics, Boston Scientific, Daiichi Sankyo, Invitae, LQT Therapeutics, Medtronic, MyoKardia, and UpToDate. MJA and Mayo Clinic have a potential equity/royalty relationship with AliveCor. However, none of these entities had any involvement in this project.

The rest of the authors report no conflict of interest.

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**Figure legends**

**Figure 1. Monogenic, oligogenic and polygenic models of genetic aetiology.** Rare pathogenic variants in *SCN5A* have the highest associated risk for BrS. Patients with a single highly penetrant pathogenic variant (A1, B1) with or without common susceptibility SNPs (A3, B1) will have sufficient genetic risk for development of the BrS phenotype, supporting a ‘near-monogenic’ model. On the other hand, in the oligogenic/polygenic models, multiple low frequency variants (A2, B2) that have a much lower associated risk for BrS and/or common susceptibility SNPs causing a high PRS (A3, B2), may be needed for disease expression. SNPs, single nucleotide polymorphisms.

**Figure 2.** **Repolarisation versus depolarisation theories for the electrophysiological mechanism underlying Brugada syndrome.** The repolarisation theory suggests that reduced INa current causes unopposed Kv4.3-mediated Ito. This creates an epicardial-endocardial transmural voltage gradient which disrupts the normal spike and dome morphology of the AP. Due to presumed differences in distribution of Ito and in thickness of epicardial and endocardial layers, these changes are more exaggerated in the RVOT epicardium than its endocardium and cause accentuation of the AP and therefore the J-point and right precordial ST elevation characteristic of the Brugada ECG pattern. Heterogeneity in repolarisation and refractoriness in the RVOT epicardium lead to increased risk for phase 2 re-entry and VT or VF. The depolarisation theory suggests that delayed conduction in the RVOT relative to the body of the RV causes the characteristic ECG pattern and arrhythmias. Delayed conduction in the RVOT creates an initial gradient driving current towards the RVOT and right precordial leads. The second phase of current returning to the RV and away from the right precordial leads, leads to the characteristic inverted T wave. Arrhythmias are thought to originate in the border zone between early and delayed depolarisation where there are mismatched potentials. RV, right ventricle; RVOT, right ventricular outflow tract; VF, ventricular fibrillation; VT, ventricular tachycardia.

**Figure 3. High lead placement and type 1 Brugada ECG pattern**. In the high lead placement, leads V1 and V2 are placed in the 3rd and 2nd ICSs, this correlates with RVOT location and increases ECG sensitivity in BrS. The ECG tracings shown were recorded from high and nominal leads V1 and V2. Type 1 Brugada ECG pattern, characterised by a coved ST segment elevation ≥2mm followed by a negative T wave, is evident in the high but not the nominal leads. V1ICS2, lead V1 in the 2nd ICS; V2ICS2, lead V2 in the 2nd ICS; V1ICS3, lead V1 in the 3rd ICS; V2ICS3, lead V2 in the 3rd ICS

**Graphical abstract.** **Brugada syndrome as a disease of impaired RVOT conduction reserve**. Normally, intrinsic RVOT conduction reserve may be affected by a patient’s age and gender. In BrS, cellular and tissue abnormalities cause a reduction of RVOT conduction reserve: Genetic abnormalities, whether mediated by a pathogenic *SCN5A* variant, an increased BrS-PRS, and/or additional genetic insults, may have direct effects on Nav1.5, as well as tissue effects causing RVOT inflammation, fibrosis, and gap junction abnormalities. Decreased Nav1.5 current together with electrical discontinuity caused by RVOT structural changes converge to disrupt normal depolarisation, with or without secondary repolarisation effects, leading to impairment of the conduction reserve of the RVOT. In this framework, the marginal conduction reserve can be exposed by acute modulators such as fever, drugs, and altered vagal tone which further impair conduction and expose the Brugada phenotype. BrS, Brugada syndrome; RVOT, right ventricular outflow tract.

**Table 1**

Brugada associated genes

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Gene | Protein | Effect of mutation | Segregation data37 | Experimental evidence37 | Estimated mutation frequency | ClinGen curation37 |
| Sodium channel alpha-subunits | | | | | | |
| *SCN5A* | Sodium voltage-gated channel alpha-subunit 5 | Loss-of-function | + | + | 20%22 | Definitive |
| *SCN10A* | Sodium voltage-gated channel alpha-subunit 10 | Loss-of-function | - | + | 5-6%33, 34 | Disputed |
| Calcium channel subunits | | | | | | |
| *CACNA1C* | Calcium voltage-gated channel auxiliary subunit alpha-1C | Loss-of-function | - | + | 2-6%20, 34, 97 | Disputed |
| *CACNB2* | Calcium voltage-gated channel auxiliary subunit beta-2 | Loss-of-function | - | + | 1-5%20, 34, 97 | Disputed |
| *CACNA2D1* | Calcium voltage-gated channel auxiliary subunit alpha-2 delta-2 | Loss-of-function | - | + | 0.6-2%20, 34, 97 | Disputed |
| Sodium channel beta-subunit | | | | | | |
| *SCN1B* | Sodium voltage-gated channel beta-subunit 1 | Loss-of-function | - | + | <1%22 | Disputed |
| *SCN3B* | Sodium voltage-gated channel beta-subunit 3 | Loss-of-function | - | + | <1%22 | Disputed |
| Sodium channel trafficking and expression | | | | | | |
| *GPD1L* | Glycerol-3-phosphate dehydrogenase 1-like | Loss-of-function | + | + | <1%22 | Disputed |
| *RANGRF (MOG1)* | Ran guanine nucleotide release factor | Loss-of-function | - | + | <1%22 | Disputed |
| *SLMAP* | Sarcolemma-associated protein | Loss-of-function | - | + | NA22 | Disputed |
| *RRAD* | Ras-associated with diabetes GTPase | Gain-of-function | - | +23 | NA23 | Not curated yet |
| Transient outward current | | | | | | |
| *KCNE3* | Potassium voltage-gated channel subfamily E regulatory subunit 3 | Gain-of-function | + | + | <1%22 | Disputed |
| *KCND3* | Potassium voltage-gated channel subfamily D member 3 | Gain-of-function | - | + | <1%22 | Disputed |
| *KCNE5* | Potassium voltage-gated channel subfamily E regulatory subunit 5 | Gain-of-function | - | + | NA22 | Disputed |
| ATP-sensitive potassium channel | | | | | | |
| *KCNJ8* | Potassium voltage-gated channel subfamily J member 8 | Gain-of-function | - | + | <1%22 | Disputed |
| *ABCC9* | ATP-binding cassette subfamily C member 9 | Gain-of-function | - | + | 0-1%25, 34 | Disputed |

Segregation data and experimental evidence based on Hosseini et al37, unless otherwise specified; + present, - absent

**Table 2**

Shanghai score system for diagnosis of Brugada syndrome

|  |  |
| --- | --- |
|  | Points |
| I. ECG (12-lead/ambulatory)\* |  |
| 1. Spontaneous type 1 Brugada ECG pattern at nominal/high leads | 3.5 |
| 1. Fever-induced type 1 Brugada ECG pattern at nominal/high leads | 3 |
| 1. Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge | 2 |
| II. Clinical history\* |  |
| 1. Unexplained cardiac arrest or documented VF/polymorphic VT | 3 |
| 1. Nocturnal agonal respirations | 2 |
| 1. Suspected arrhythmic syncope | 2 |
| 1. Syncope of unclear mechanism/aetiology | 1 |
| 1. Atrial flutter/fibrillation in patients <30 years without alternative aetiology | 0.5 |
| III. Family history\* |  |
| 1. First- or second-degree relative with definite BrS | 2 |
| 1. Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative | 1 |
| 1. Unexplained SCD <45 years in first- or second-degree relative with negative autopsy | 0.5 |
| IV. Genetic test result |  |
| 1. Probable pathogenic variant in BrS susceptibility gene | 0.5 |
| **Score** (**requires at least one ECG finding**) |  |
| ≥3.5: Probable/definite BrS |  |
| 2-3: Possible BrS |  |
| <2: Non-diagnostic |  |

BrS, Brugada syndrome; SCD, sudden cardiac death; VF, ventricular fibrillation; VT ventricular tachycardia. \*Only award points once for highest score within this category. Adapted from Antzelevitch et al.92