ABSTRACT. Brugada syndrome (BrS) is a rare inherited arrhythmia disorder associated with sudden cardiac death secondary to malignant ventricular arrhythmias. Since its first mention approximately 25 years ago, major strides have been made towards unraveling the condition’s genetic and mechanistic underpinnings. Despite considerable progress, however, gaps in the understanding of BrS continue to persist, and clinical management of affected individuals remains challenging. Identification of an underlying genetic culprit continues to be elusive in the majority of patients, while discord regarding the condition’s underlying pathophysiology also persists, with strong lines of evidence present for both the “depolarization” and “repolarization” hypotheses. Exciting new therapeutic options hold significant promise, including substrate-based catheter ablation and the subcutaneous implantable cardioverter-defibrillator, although the decision of when to intervene in the cases of asymptomatic patients remains unclear. Provided that the risk of events in BrS is not truly stochastic, distinct sub-phenotypes of the condition, possessing variable levels of arrhythmic risk, may exist, and their identification may lead to the improved care of BrS patients and their families.

KEYWORDS. Brugada syndrome, catheter ablation, genetics, sudden cardiac death.
and safer, more effective treatment options. Our evolving insights into the genetics and pathophysiology underlying BrS may facilitate identification of at-risk “sub-phenotypes,” while subcutaneous ICDs (S-ICDs) and catheter ablation are promising new forms of therapy that may lead to improved patient outcomes.9,10

Genetic contributions

The recognition of familial clustering in BrS highlighted its being a heritable condition, and ultimately led to the identification of SCN5A as the first genetic culprit, via a candidate gene approach.11 SCN5A encodes the α-subunit of the cardiac voltage-gated sodium channel (Nav1.5), which is responsible for the inward sodium current (INa).12 This seminal finding provided critical mechanistic insight into BrS and highlighted reduced INa as being a cornerstone of the condition’s underlying pathophysiology. Since this initial report, over 300 distinct pathogenic loss-of-function SCN5A mutations have been implicated in the development of BrS and, collectively, are detected in approximately 20% to 25% of all clinical cases.13

Beyond SCN5A, an additional 22 genetic culprits have been identified as predisposing a patient to developing BrS (Table 1).5 Consistent with BrS being reflective of a channelopathy, the majority of the culprits encode ion channels that mediate currents involved in the cardiac action potential. SCN10A encodes a neuronal sodium channel, while SCN1B, SCN2B, and SCN3B encode β-subunits that modulate Nav1.5.14–17 Consistent with SCN5A, identified mutations have been predicted to result in a loss-of-function and in reduced INa. Gain-of-function mutations within KCNE3, KCNE5, KCND2, and KCND3 have been shown to increase Ito (Phase 1; transient outward current), while loss-of-function mutations within CACNA1c, CACNB2b, and CACNA2D1 reduce ICa (Phase 2; inward calcium current) resulting in an abbreviated plateau of Phase 2 of the action potential have also been identified in BrS patients.18–21 KCNJ8 and ABCC9 are constituents of the ATP-sensitive potassium current (IK-ATP), while KCNH2 is the α-subunit of IKr, and increased current secondary to gain-of-function mutations has been suggested to predispose to BrS.22,23 The remaining genetic culprits (i.e. GPD1L, RANGRF, SLMAP, PKP2, FGFI2, HEY2, HCN4, TRPM4, and SEMA3A), although not constituents of the ion channels directly implicated in the cardiac action potential, have all been suggested as being involved in predisposing individuals to BrS, secondary to the modulation of one of the ionic currents described above.5

Although BrS is traditionally viewed as a monogenic autosomal dominant condition, recent studies have increasingly challenged this notion, and current evidence suggests that the BrS phenotype more often develops secondary to oligo- or polygenic influences. Notably, the only BrS gene identified through linkage analysis has been GPD1L, which encodes the glycerol-3-phosphohydrogenase 1-like gene that is hypothesized to predispose to BrS through a reduction in INa.24 Loss-of-function SCN5A mutations are likely sufficient in isolation to give rise to the phenotype, though penetrance is highly variable. Even in the context of SCN5A, however, additional genetic influences are likely operative, a concept that has been highlighted by a study involving 13 families who possess a presumed pathogenic SCN5A mutation.25 Notably, the BrS phenotype was observed

| Table 1: Genetic Culprits Implicated in Brugada Syndrome |
|----------------------------------|---------------------|---------------------|
| Gene                          | Protein                              | Impact on Ionic Current |
| SCN5A                         | z-subunit of Nav1.5            | ↓ INa               |
| GPD1L                         | Glycerol-3-phosphate dehydrogenase 1-Like | ↓ INa               |
| CACNA1c                        | z-subunit of Cav1.2             | ↓ ICa               |
| CACNB2b                        | β-subunit; Cavβ2               | ↓ ICa               |
| SCN1B                         | β-subunit; Navβ1               | ↓ INa               |
| KCNE3                         | β-subunit of potassium channel (MiRP2) | ↑ Ito               |
| SCN3B                         | β-subunit; Navβ3               | ↓ INa               |
| HCN4                          | Hyperpolarization-activated cyclic nucleotide-gated channel 4 | *                  |
| KCND3                         | z-subunit of Kv4.3              | ↑ Ito               |
| KCNH2                         | z-subunit of Kir6.1             | ↑ IK-ATP            |
| CACNA2D1                      | δ-subunit of Cav2δ1             | ↓ ICa-L             |
| KCNE5                         | β-subunit of potassium channel  | ↑ Ito               |
| RANGRF                        | RAN guanine nucleotide release factor | ↓ INa               |
| KCND2                         | z-subunit of Kv4.2              | ↑ Ito               |
| TRPM4                         | Transient receptor potential cation channel subfamily M member 4 | *                  |
| SCN2B                         | β-subunit; Navβ2               | ↓ INa               |
| PKP2                          | Plakophilin-2                   | ↓ INa               |
| ABCC9                         | Sulfonylurea receptor-2         | ↑ IK-ATP            |
| SLMAP                         | Sarcolemmal membrane-associated protein | ↓ INa               |
| KCNH2                         | z-subunit of HERG               | ↑ IKr               |
| SCN10A                        | z-subunit of Nav1.8             | ↓ INa               |
| FGFI2                         | Fibroblast growth factor-12     | ↓ INa               |
| SE MA3A                       | Semaphorin-3A                   | ↑ Ito               |

*The impact on ionic current is not well-established for HCN4 and TRPM4 mutations.
among individuals from five of these families in the absence of the SCN5A mutation.

Beyond SCN5A and GPD1L, the remaining genetic culprits may be better characterized as disease susceptibility variants, rather than BrS-causing mutations. Each of these additional genes was identified through the candidate gene approach following identification of mutations in a limited number of individuals. Although supportive in vitro functional work was often provided, in most instances, the evidence for genotype-phenotype segregation remained lacking. Following the advent of next-generation sequencing and the subsequent establishment of large population-based exome and genome cohorts, it has become evident that the collective prevalence of BrS-linked mutations in these additional genes is much higher than expected for highly penetrant monogenic variants. Notably, within the United States National Heart, Lung, and Blood Institute’s Grand Opportunity Exome Sequencing Project, one in 23 individuals was found to possess a genetic variant classified as pathogenic for BrS.26 These findings serve to emphasize that these genetic variants may predispose certain individuals to BrS; however, additional genetic or environmental influences are likely required for the development of the phenotype.

As further support for a polygenic disease process, a genome-wide association study identified three single-nucleotide polymorphisms in the vicinity of the SCN5A, SCN10A, and HEY2 genes that are associated with an increased risk for developing the condition.27 Interestingly, the odds ratios for these variants, ranging from 1.58 to 2.55, align with the notion that though they are predisposing, they are not sufficient in isolation to give rise to a BrS phenotype. Given that BrS is a rare condition, the presumption has been that rare, rather than common, genetic variants are responsible for its development. It is likely then that the development of a BrS phenotype is dependent upon a combination of common and rare variants, accounting for the complex inheritance patterns that are observed in the clinic, and the challenging nature of gene discovery.

Pathophysiology

Mirroring the genetic landscape and partly guided by its continued progress, major strides have been made towards clarifying BrS pathophysiology, but many questions still remain. Although there is a consensus that BrS’s pathophysiology localizes to the right ventricular outflow tract (RVOT), there is still some debate that continues to persist regarding whether BrS is a disorder of depolarization, repolarization, or both.28 The repolarization hypothesis posits that the arrhythmogenic substrate develops secondary to either a pathologic reduction in $I_{Na}$, an increase in $I_{to}$, or both.29 $I_{to}$, being most prominent on the epicardial surface of the RVOT, is hypothesized to account for its pathophysiology localizing to that region.29 The pathologic alteration in either $I_{Na}$ or $I_{to}$ leads to the loss of the Phase 2 action potential dome within the epicardium; the resultant transmural repolarizing voltage gradient across the RVOT is hypothesized then to account for the characteristic type 1 Brugada ECG pattern.29,31 In addition, this transmural dispersion of repolarization is felt to provide a substrate sufficient for phase 2 re-entry, which may subsequently trigger and/or manifest clinically as polymorphic ventricular tachycardia (VT). Notably, a similar mechanism has been hypothesized to be responsible for the early repolarization syndrome, leading investigators to collectively refer to both conditions as J-wave syndromes.32

The other primary competing hypothesis contends that the BrS phenotype develops secondary to a depolarization abnormality associated with conduction slowing within the RVOT.30 The proposed mechanism of arrhythmogenesis is the production of a gradient between the RVOT and the adjacent right ventricular (RV) myocardium secondary to this conduction delay, and potentially secondary to fibrosis. Support for the depolarization hypothesis has been bolstered by intriguing findings from Nadamanee et al.,10 who identified low-voltage regions along the anterior aspect of the epicardial RVOT that possessed late potentials and fractionated electrograms in BrS patients. Perhaps most strikingly, ablation of these signals rendered ventricular fibrillation non-inducible with programmed extra-stimulation, resulted in the normalization of the type 1 Brugada ECG pattern, and led to the effective clinical suppression of arrhythmias during long-term follow-up. Subsequent investigations performed on autopsies of whole hearts, as well as biopsies obtained at the time of ablation via thoracotomy, revealed that the RVOT of BrS patients had increased collagen deposition and fibrosis, coupled with reduced connexin-43 expression compared with the controls.34

Although in apparent direct opposition to one another, it is possible that both depolarization and repolarization abnormalities may be operative in BrS pathogenesis. Utilizing non-invasive ECG imaging (ECGI), a technology that records surface ECG potentials using 250 electrodes, investigators identified delayed RVOT activation, along with low amplitude and fractionated electrograms, in BrS patients, which are findings consistent with a depolarization abnormality.35 Concurrently, however, the patients included in the study were also observed to have prolonged recovery times and sleep repolarization gradients, leading the authors to conclude that abnormalities in both depolarization and repolarization contribute to the BrS phenotype.

Diagnosis

The criteria for diagnosing BrS have evolved since the condition’s initial description, and debate continues regarding the need for additional identifiable clinical features beyond the distinctive electrocardiographic pattern, particularly in cases in which a type 1 pattern is only observed during provocative drug challenge. Criteria for concluding a type 1 ECG pattern require J-point elevation ≥ 2 mm in one or more lead among V1 or V2 positioned in the second, third, or fourth
intercostal space, in association with a coved ST-segment morphology, whereas the type 2 pattern requires ≥2 mm of J-point elevation in similar lead positions in association with a saddleback ST-segment morphology. The most recent Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society (HRS/EHRA/APHRS) expert consensus statement indicates that a type 1 Brugada ECG pattern, either spontaneous, fever, or drug induced, is sufficient to satisfy a diagnosis of BrS (Figure 1a). Recent studies have highlighted concern regarding the possibility of a high false-positive rate with provocative drug challenge, particularly in the case of ajmaline use, although the lack of a gold standard renders this concern challenging to assess in an objective manner. Driven by concern for over-diagnosis, experts have proposed the Shanghai Score System that, beyond the ECG analysis, also accounts for clinical and family history and genetic testing results (Figure 1b). The distinctive feature of this scoring system, relative to the recent HRS/EHRA/APHRS

### HRS/EHRA/APHRS Expert Consensus Diagnostic Criteria for the Brugada Syndrome (2013)

1. Brugada syndrome is diagnosed in patients with ST-segment elevation with type 1 morphology ≥2 mm to ≥1 lead among the right precordial leads V1, V2, positioned in the 2nd, 3rd, or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.

2. Brugada syndrome is diagnosed in patients with type 2 or type 3 ST-segment elevation with ≥1 lead among the right precordial leads V1, V2, positioned in the 2nd, 3rd, or 4th intercostal space occurring when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type 1 ECG morphology.

### Proposed Shanghai Score System for Brugada Syndrome (2016)

| Score (requires ECG finding) | Points |
|------------------------------|--------|
| ≥3.5 points = Probable/definite Brugada Syndrome | 2-3 points = Possible Brugada Syndrome, < 2 points = Non-diagnostic |

(Points awarded for highest in each category)

1. **ECG (12-lead/ambulatory)**
   - Spontaneous type 1 Brugada ECG pattern at nominal or high leads (3.5 points)
   - Fever-induced type 1 Brugada ECG pattern at nominal or high leads (3 points)
   - Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge (2 points)

2. **Clinical History**
   - Unexplained arrest or documented VF/polymorphic VT (3 points)
   - Nocturnal agonal respirations (2 points)
   - Suspected arrhythmic syncope (2 points)
   - Syncope of unclear mechanism/unclear etiology (1 point)
   - Atrial flutter/fibrillation in patients < 30 years without alternative etiology (0.5 points)

3. **Family History**
   - First- or second-degree relative with definite Brugada Syndrome (2 points)
   - Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in first- or second-degree relative (1 point)
   - Unexplained SCD < 45 years in first- or second-degree relative with negative autopsy (0.5 points)

4. **Genetic Test Result**
   - Probable pathogenic mutation in Brugada Syndrome susceptibility gene (0.5 points)

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**Figure 1:** Alternate contemporary criteria for the diagnosis of Brugada syndrome. (a) HRS/EHRA/APHRS Expert Consensus Diagnostic Criteria for the Brugada Syndrome; (b) Shanghai Score System for Diagnosis of Brugada Syndrome. HRS: Heart Rhythm Society; EHRA: European Heart Rhythm Association; APHRS: Asia Pacific Heart Rhythm Society; VF: ventricular fibrillation; VT: ventricular tachycardia; SCD: sudden cardiac death.
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ablation. This approach, which appears to permit for a more complete identification of the BrS arrhythmogenic substrate, has resulted in improved long-term clinical results, and will hopefully be sufficient to overcome prior treatment failures. In order to further clarify the efficacy of catheter ablation, a randomized controlled trial, called the Ablation in Brugada Syndrome for Prevention of VF (BRAVE) study, is being initiated. BrS patients who have suffered an ICD shock will be randomized to either receive catheter ablation or no additional therapy, and will be followed for up to three years for recurrent malignant arrhythmias.

**Arrhythmic risk**

Insight into the risk of arrhythmic events among individuals with a type 1 Brugada pattern has markedly evolved over the last two decades. The initial report from the Brugada group in 1998 reported a 32% incidence for ventricular fibrillation and sudden cardiac death during a 3-year follow-up period. Reflecting a pattern observed in many newly discovered syndromes, the initially reported alarmingly high event rate is now felt to have been likely secondary to the cohort being comprised of cases with more severe phenotypes. Following improved recognition of BrS among physicians and the establishment of registries that include a broader spectrum of phenotypic severities, it has become apparent that the risk of events in asymptomatic individuals is in fact quite low, accounting for the recommendations regarding management being restricted to observation in the majority of these individuals.

The FINGER Brugada Syndrome Registry was a multicenter study involving 1,029 European patients who exhibited spontaneous or drug-induced type 1 ECG patterns with a mean follow-up period of 32 months. In this study, the annual cardiac event rate identified was highest among those with a history of aborted cardiac arrest (7.7%), while patients with a history of presumed cardiac syncope and asymptomatic patients had event rates of 1.9% and 0.5%, respectively. Comparable findings were also observed in the PRELUDE study, which prospectively followed 308 BrS patients with no prior history of cardiac arrest. An overall annual event rate of 1.5% was observed in this study during a mean follow-up period of 36 months, which corresponded to event rates of 3.6% and 1.0% among patients with prior instances of cardiac syncope and asymptomatic individuals, respectively. A more recent report from the Brugada group has revealed similar findings, with a notable temporal dichotomy present within their cohort among individuals enrolled from 1986 to 2002 and from 2003 to 2014. The annual event rate was 2.5% in the earlier cohort, as compared with 1.8% in the later cohort (p < 0.001). Notably, asymptomatic patients with a drug-induced type 1 pattern had a 0.51% annual event rate, consistent with findings from other contemporary studies.

**Risk stratification in asymptomatic individuals**

Although ICD therapy is justified for individuals with episodes of prior aborted cardiac arrest or cardiac syncope given their high risk for fatal arrhythmias, asymptomatic patients have a low incidence of events, rendering treatment challenging given the risks associated with long-term ICD therapy. Widespread ICD implantation in asymptomatic BrS patients has had an unfavorable risk–benefit profile; however, a watchful waiting strategy is inevitably expected to witness incident cases of SCD, an occurrence that is unacceptable in young, otherwise healthy individuals. This conundrum highlights a critical need to develop more effective risk stratification tools in asymptomatic individuals to facilitate targeted ICD therapy in the small minority of individuals who will succumb to SCD during follow-up.

Various clinical features have been evaluated in asymptomatic BrS patients in an attempt to identify those at increased risk for malignant arrhythmic events, including age, sex, and family history of SCD. Mounting evidence suggests that asymptomatic BrS patients >60 years of age, and particularly those >70 years of age, have very low event rates, implying that ICD therapy may be largely unnecessary in this elderly patient subgroup. Although BrS is more prevalent among males, perhaps secondary to the influence of testosterone on Io, a reduced risk of arrhythmic events in females has not yet been clearly established. Similarly, a positive family history of SCD has not yet been shown to confer a worse prognosis for BrS patients. The role of genetic testing for informing prognosis has also been evaluated and, and although mixed results have been observed, there is no strong evidence to date to suggest that genotype can serve as a reliable predictor of arrhythmic events.

**ECG features**

A series of surface ECG features (Figure 2) has been suggested to predict an increased risk of arrhythmic events in BrS, including QRS fragmentation, early repolarization and/or a prominent S-wave in lead I. QRS fragmentation, referring to multiple sharp deflections observed during depolarization, has been variably defined in the BrS literature based on the number of “spikes” observed. Despite the different definitions, however, multiple studies have identified an association between QRS fragmentation and a risk of incident events. When prospectively evaluated in the PRELUDE registry and defined as ≥ two spikes within the QRS complex in leads V1 to V3, the presence of QRS fragmentation was associated with a statistically significant 8.9-fold increased hazard of arrhythmia.

The S-wave in lead I, partially mediated by depolarization of the RVOT, has recently been suggested to serve as a powerful marker for arrhythmic risk in BrS. Among 347 asymptomatic patients with a spontaneous type 1 Brugada pattern, the presence of a significant S-wave in lead I, defined as ≥ 0.1 mV and/or ≥ 40 ms, was associated with a staggering 39.1-fold increased hazard of ventricular fibrillation or SCD on multivariate analysis. Although this finding will need to be replicated in additional studies, the magnitude of association observed...
suggests it could serve as a critical tool for risk stratification. Mirroring numerous other cardiac conditions, the presence of an inferolateral early repolarization pattern has been shown to confer an increased risk of events among BrS patients. This finding has been replicated in multiple studies and has been further reinforced by a recent meta-analysis, consistent with its being a reliable marker of arrhythmic risk. The concomitant presence of atrial arrhythmias, including sinus node dysfunction and atrial fibrillation, has also been suggested to confer an increased risk of malignant arrhythmic events.

Electrophysiology study

The role of invasive electrophysiology study in identifying BrS has been controversial, with disagreement regarding its clinical utility, a notion currently reflected in that it has a class IIb indication as a tool for risk stratification. Debate surrounding its utility partially stems from variable results having been described in the literature, with certain reports from the Brugada group suggesting that it is highly predictive of events, although other studies have found no association.

Reasons for the conflicting results have been hypothesized to be secondary to both heterogeneous patient populations having been evaluated and variations being present within the programmed extra-stimulation protocols used for the induction of polymorphic ventricular tachycardia/ventricular fibrillation.

In an effort to provide clarity, Priori and colleagues conducted the PRELUDE study, a multicenter prospective registry involving 308 BrS patients with no prior history of SCD. A pre-specified induction protocol was used consisting of 600 and 400 ms drive trains with the addition of up to three extra-stimuli from both the RVOT and RV apex. Consistent with their prior work, the investigators found no association between inducibility at electrophysiology study and subsequent arrhythmic events during a mean follow-up period of 36 months. The sensitivity and specificity of programmed extra-stimulation for predicting subsequent arrhythmic events with up to three extra-stimuli was determined to be 35.7% and 58.8%, respectively. Limiting programmed extra-stimulation to one to two extra-stimuli improved specificity to 74.2%, but lowered sensitivity to 25%. Highlighting additional concern for reproducibility of the test, only 34% of inducible patients could be re-induced at the time of a second electrophysiology study. Although ventricular fibrillation inducibility was not predictive of events, a large magnitude association was observed between a ventricular refractory period <200 ms and subsequent arrhythmic events (hazard ratio = 3.91, 95% CI 1.03–12.79) (Figure 2). A subsequent pooled analysis with individual-level data that combined eight prior studies and a total of 1,312 patients, though not involving prior work from the Brugada group, found that inducibility at the time of invasive electrophysiology study was associated with an
increased risk of events, with a hazard ratio of 2.66 (95% CI 1.44–4.92) and a higher risk observed among those induced with single or double extra-stimuli.56 Perhaps equally important, however, was that the lack of induction exhibited a modest negative predictive value, leading the authors to caution that a negative electrophysiology study should not be used as evidence to avoid ICD implantation, especially when measured in relation to other high-risk features like a spontaneous type 1 pattern or syncope presumed to be cardiac in origin. These important findings have led to a resurgence of interest in the role of invasive electrophysiology study as a tool for risk stratification in BrS.

**Multivariable risk prediction model**

Consistent with most medical conditions, it is unlikely that a single factor in isolation will be sufficient as a means for accurately predicting arrhythmic risk in asymptomatic BrS individuals. Composite risk scores that account for multiple variables may ultimately yield more accurate measures of risk prediction, in a manner similar to that of the Framingham Risk Score for coronary artery disease. A series of studies has evaluated this concept in BrS and suggested promising results, though their relatively small size, compounded by the low observed event rates, highlight the need for larger scale studies prior to incorporation of such models into widespread clinical practice.67,68

**Conclusions**

Since its original description approximately 25 years ago, major strides have been made towards unraveling the mechanisms underlying BrS. In a similar manner, our treatment of BrS patients has progressively evolved during this period, with gradually improved insight into the benefits and risks of different treatment strategies. Exciting new therapeutic options hold significant promise, though deciding when and how to intervene in asymptomatic patients will likely remain a vexing challenge. Provided that the risk of events in BrS is not truly stochastic, distinct sub-phenotypes of the condition possessing variable levels of arrhythmic risk are presumably operative. It is hoped that our rapidly progressing knowledge of the genetic and pathophysiologic underpinnings may yield insight into the existence of these sub-phenotypes, leading to improved care of BrS patients and their families.

**References**

1. Sieira J, Dendramis G, Brugada P. Pathogenesis and management of Brugada syndrome. *Nat Rev Cardiol*. 2016;13(12):744–756.
2. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome: A multicenter report. *J Am Coll Cardiol*. 1992;20(6):1391–1396.
3. Mizusawa Y, Wilde AAM. Brugada Syndrome. *Circ Arrhythm Electrophysiol*. 2012;5(3):606–616.
4. Martini B, Nava A, Thiene G, Buja GF, Canciani B, Scognamiglio R, et al. Ventricular fibrillation without apparent heart disease: description of six cases. *Am Heart J*. 1989;118(6):1203–1209.
5. Gourraud JB, Barc J, Thollet A, Le Scouarne S, Le Marec H, Schott JJ, et al. The Brugada syndrome: A rare arrhythmia disorder with complex inheritance. *Front Cardiovasc Med*. 2016;3:9.
6. Roberts JD, Klein GJ. Rare disease and low event rates: challenges for refining risk stratification in Brugada syndrome. *Can J Cardiol*. 2016;32(11):1294.e1-1294.e3.
7. Tse G, Liu T, Li KHC, Laxton V, Chan YWF, Keung W, et al. Electrophysiological mechanisms of Brugada syndrome: Insights from pre-clinical and clinical studies. *Front Physiol*. 2016;7:467.
8. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;10(12):1932–1963.
9. Bardy GH, Smith WM, Hood MA, Crotzer IG, Melton IC, Jordaens L, et al. An entirely subcutaneous implantable cardioverter-defibrillator. *N Engl J Med*. 2010;363(1):36–44.
10. Nademanee K, Veerakul G, Chandanamatthua P, Chaothawee L, Artyachaipanich A, Jirastirojnakorn K, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. *Circulation*. 2011;123(12):1270–1279.
11. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature*. 1998;392(6673):293–296.
12. Voerman CC, Wilde AAM, Lodder EM. The cardiac sodium channel gene SCN5A and its gene product NaV1.5: Role in physiology and pathophysiology. *Gene*. 2015;573:177–187.
13. Crotti L, Marcou CA, Tester DJ, Castelli S, Giudicessi JR, Torchio M, et al. Spectrum and prevalence of mutations involving BrS1- through BrS12-susceptibility genes in a cohort of unrelated patients referred for Brugada syndrome genetic testing: implications for genetic testing. *J Am Coll Cardiol*. 2012;60:1410–1418.
14. Hu D, Barajas-Martinez H, Pfeiffer R, Dezi F, Pfeiffer J, Buch T, et al. Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. *J Am Coll Cardiol*. 2014;64(1):66–79.
15. Hu D, Barajas-Martinez H, Medeiros-Domingo A, Crotti L, Veltmann C, Schimpf R, et al. A novel rare variant in SCN1B linked to Brugada syndrome and SIDS by combined modulation of Na(v)1.5 and K(v)4.3 channel currents. *Heart Rhythm*. 2012;9(5):760–769.
16. Ruiu H, Beltran-Alvarez P, Tarradas A, Selga E, Campuzano O, Verges M, et al. A nonsense mutation in the sodium channel β2 subunit reveals SCN2B as a new candidate gene for Brugada syndrome. *Hum Mutat*. 2013;34(7):961–966.
17. Hu D, Barajas-Martinez H, Burashnikov E, Springer M, Wu Y, Varro A, et al. A mutation in the beta 3 subunit of the cardiac sodium channel associated with Brugada ECG phenotype. *Circ Cardiovasc Genet*. 2009;2(3):270–278.
18. Delpón E, Cordeiro JM, Núñez L, Thomsen PEB, Guercichoff A, Pollevick GD, et al. Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome. *Circ Arrhythm Electrophysiol*. 2008;1(3):209–218.
19. Giudicessi JR, Ye D, Tester DJ, Crotti L, Mugione A, Nesterenko VV, et al. Transient outward current (Ito) gain-of-function mutations in the KCNQ3-encoded Kv4.3 potassium channel and Brugada syndrome. *Heart Rhythm*. 2011;8(7):1024–1032.
20. Antzedeitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, et al. Loss-of-function mutations

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in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation.* 2007;115(4):442–449.

21. Burashnikov E, Pfeiffer R, Barajas-Martinez H, Delpoin E, Hu D, Desai M, et al. Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death. *Heart Rhythm.* 2010;7(12):1872–1882.

22. Medeiros-Domingo A, Tan B-H, Crotti L, Tester DJ, Eckhardt L, Cucetti A, et al. Gain-of-function mutation S422L in the KCNJ8-encoded cardiac K(ATP) channel Kir6.1 as a pathogenic substrate for J-wave syndromes. *Heart Rhythm.* 2010;7(10):1466–1471.

23. Hu D, Barajas-Martinez H, Terzic A, Park S, et al. ABCG9 is a novel Brugada and early repolarization syndrome susceptibility gene. *Int J Cardiol.* 2014;171(3):431–442.

24. London B, Michalec M, Mehdi H, Zhu X, Kerchner L, Sanyal S, et al. Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias. *Circulation.* 2007;116(20):2260–2268.

25. Probst V, Wilde AAM, Barc J, Sacher F, Babuty D, Mabo P, et al. SCN5A mutations and the role of genetic background in the pathophysiology of Brugada syndrome. *Circ Cardiovasc Genet.* 2009;2(6):552–557.

26. Rigaarda B, Jabbari B, Refsgaard L, Holst AG, Haunso S, Sadjadiieh A, et al. High prevalence of genetic variants previously associated with Brugada syndrome in new exome data. *Clin Genet.* 2013;84(5):489–495.

27. Bezzina CR, Barc J, Mizusawa Y, Remmee CA, Gourraud JB, Simonet F, et al. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. *Nat Genet.* 2013;45(9):1044–1049.

28. Hoogendijk MG, Opthof T, Postema PG, Wilde AAM, Bakker JMT de, Coronel R. The Brugada ECG pattern: a marker of channelopathy, structural heart disease, or neither? Toward a unifying mechanism of the Brugada syndrome. *Circ Arrhythm Electrophysiol.* 2010;3(3):283–290.

29. Yan G-X, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. *Circulation.* 1999;100(15):1660–1666.

30. Antzelevitch C, Patocskai B. Brugada syndrome: Clinical, genetic, molecular, cellular, and ionic aspects. *Curr Probl Cardiol.* 2016;41(1):7–57.

31. Yan G-X, Antzelevitch C. Cellular basis for the electrocardiographic J wave. *Circulation.* 1996;93(2):372–379.

32. Antzelevitch C, Yan G-X. J wave syndromes. *Heart Rhythm.* 2010;7(4):549–556.

33. Postema PG, van Dessel PFHM, Kors JA, Linnenbank AC, van Herpen G, Ritsema van Eck HJ, et al. Local depolarization abnormalities are the dominant pathophysiological mechanism for type 1 electrocardiogram in brugada syndrome a study of electrocardiograms, vectorcardiograms, and body surface potential maps during ajmaline provocation. *J Am Coll Cardiol.* 2010;55(8):789–797.

34. Nademanee K, Raju H, de Noronha SV, Papadakis M, Robinson L, Rothery S, et al. Fibrosis, connexin-43, and conduction abnormalities in the Brugada syndrome. *J Am Coll Cardiol.* 2015;66(18):1976–1986.

35. Zhang J, Sacher F, Hoffmayer K, O’Hara T, Strom M, Cuculich P, et al. Cardiac electrophysiological substrate underlying the ECG phenotype and electrogram abnormalities in Brugada syndrome patients. *Circulation.* 2015;131(22):1950–1959.

36. Antzelevitch C, Brugada P, Borggreve M, Brugada J, Brugada R, Corrado D, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Association. *Circulation.* 2005;111(5):659–670.

37. Hasdemir C, Payzin S, Kocabas U, Sahin H, Yildirim N, Alp A, et al. High prevalence of concealed Brugada syndrome in patients with atrioventricular nodal reentrant tachycardia. *Heart Rhythm.* 2015;12(7):1584–1594.

38. Viskin S, Rosso R, Friedensohn L, Havakuk O, Wilde AAM. Everybody has Brugada syndrome until proven otherwise? *Heart Rhythm.* 2015;12(7):1595–1598.

39. Antzelevitch C, Yan GX, Ackerman MJ, Borggreve M, Corrado D, Guo J, et al. J-wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. *Heart Rhythm.* 2016;13(10):e295-324.

40. Brachuk A, Nguyen T, Ryu MH, Femenia F, Zarewa B, Wilde AAM, et al. Brugada phenocopy: new terminology and proposed classification. *Ann Noninvasive Electrocardiol.* 2012;17(4):299–314.

41. Olde Nordkamp LRA, Postema PG, Knops RE, van Dijk N, Limpens J, Wilde AAM, de Groot JR. Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: A systematic review and meta-analysis of inappropriate shocks and complications. *Heart Rhythm.* 2016;13(2):443–454.

42. Brouwer TF, Yilmaz D, Lindeboom R, Buiten MS, Olde Nordkamp LRA, Schalij MJ, et al. Long-term clinical outcomes of subcutaneous versus transvenous implantable defibrillator therapy. *J Am Coll Cardiol.* 2016;68(19):2047–2055.

43. Olde Nordkamp LRA, Conte G, Rosenmoller B, Warnaars JLF, Tan HL, Caputo ML, et al. Brugada syndrome and the subcutaneous implantable cardioverter-defibrillator. *J Am Coll Cardiol.* 2016;68(6):665–671.

44. Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with brugada syndrome. *Circulation.* 2004;110(13):1731–1737.

45. Belhassen B, Rahkovich M, Michowitz Y, Glick A, Viskin S. Management of Brugada syndrome: Thirty-three-year experience using electrophysiologically guided therapy with class 1A antiarrhythmic drugs. *Circ Arrhythm Electrophysiol.* 2015;8(6):1393–1402.

46. Belhassen B. Management of Brugada syndrome 2016: Should all high risk patients receive an ICD? Alternatives to implantable cardiac defibrillator therapy for Brugada syndrome. *Circ Arrhythm Electrophysiol.* 2016;9(11).

47. Haissaguerre M, Extramiana F, Hocini M, Haissaguerre M. Epicardial substrate ablation of Brugada syndrome. *Heart Rhythm.* 2015;12(7):1595–1598.

48. Brugada J, Pappone C, Berruezo A, Vicedomini G, Manguso F, Cicone G, et al. Brugada syndrome phenotype elimination by epicardial substrate ablation. *Circ Arrhythm Electrophysiol.* 2015;8(6):1373–1381.

49. Zhang P, Tung R, Zhang Z, Sheng X, Liu Q, Jiang R, et al. Characterization of the epicardial substrate for catheter ablation of Brugada syndrome. *Heart Rhythm.* 2016;13(11):2151–2158.

50. Nademanee K, Hocini M, Haissaguerre M. Epicardial substrate ablation for Brugada syndrome. *Heart Rhythm.* 2017;14(3):457–461.

51. Wilde AAM, Nademanee K. Epicardial substrate ablation in Brugada syndrome: Time for a randomized trial? *Circ Arrhythm Electrophysiol.* 2015;8(6):1306–1308.

52. Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in patients without demonstrable structural heart disease. *Circulation.* 1998;97(5):457–460.
53. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, et al. Long-term prognosis of patients diagnosed with Brugada Syndrome Registry. *Circulation*. 2010;121(5):635–643.

54. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, et al. Risk stratification in Brugada syndrome: results of the PRELUDE (Programmed Electrical stimulation predictive value) registry. *J Am Coll Cardiol*. 2012;59(1):259–265.

55. Casado-Arroyo R, Berne P, Rao JY, Rodriguez-Manero M, Levinstein M, Conte G, et al. Long-term trends in newly diagnosed Brugada syndrome: Implications for risk stratification. *J Am Coll Cardiol*. 2016;68(6):614–623.

56. Conte G, DE Asmundis C, Sieira J, Levinstein M, Chierchia GB, DI Giovanni G, et al. Clinical characteristics, management, and prognosis of elderly patients with Brugada syndrome. *J Cardiovasc Electrophysiol*. 2014;25(5):514–519.

57. Tokioka K, Kusano KF, Morita H, Miura D, Nishii N, Nagase S, et al. Electrocardiographic parameters and fatal arrhythmic events in patients with Brugada syndrome: combination of depolarization and repolarization abnormalities. *Am J Cardiol*. 2016;68(6):2131–2138.

58. Calo` L, Giustetto C, Martino A, Sciarra L, Cerrato N, Marziali M, et al. A new electrocardiographic marker of sudden death in Brugada syndrome: The S-wave in lead I. *J Am Coll Cardiol*. 2016;67(12):1427–1440.

59. Sroubek J, Probst V, Mazzanti A, Delise P, Castro Hevia J, Ohkubo K, et al. Programmed ventricular stimulation for risk stratification in the Brugada syndrome: A pooled analysis. *Circ Arrhythm Electrophysiol*. 2009;2(2):154–161.

60. Takagi M, Aonuma K, Sekiguchi Y, Yokoyama Y, Aihara N, Hiraoka M, Japan Idiopathic Ventricular Fibrillation Study (J-IVFS) Investigators. The prognostic value of early repolarization (J wave) and ST-segment morphology after J wave in Brugada syndrome: multicenter study in Japan. *Heart Rhythm*. 2013;10(4):533–539.

61. Georgopoulos S, Letsas KP, Liu T, Kalafateli M, Korantzopoulos P, Burkle G, et al. A meta-analysis on the prognostic significance of inferolateral early repolarization pattern in Brugada syndrome. *European*. 2017. [Epub ahead of print].

62. Giustetto C, Cerrato N, Gribaudi E, Scrocco C, Castagno D, Richiardi E, et al. Atrial fibrillation in a large population with Brugada electrocardiographic pattern: prevalence, management, and correlation with prognosis. *Heart Rhythm*. 2014;11(2):259–265.

63. Sieira J, Cicente G, Conte G, Chierchia GB, de Asmundis C, Ballogiannis G, et al. Asymptomatic Brugada syndrome: Clinical characterization and long-term prognosis. *Circ Arrhythm Electrophysiol*. 2015;8(5):1144–1150.

64. Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. *Circulation*. 2002;105(1):73–78.

65. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, et al. Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation*. 2002;105(11):1342–1347.

66. Delise P, Allioca G, Marras E, Giustetto C, Gaita F, Sciarra L, et al. Risk stratification in individuals with the Brugada type 1 ECG pattern without previous cardiac arrest: usefulness of a combined clinical and electrophysiologic approach. *Eur Heart J*. 2011;32(2):169–176.

67. Kawazoe H, Nakano Y, Ochi H, Takagi M, Hayashi Y, Uchimura Y et al. Risk stratification of ventricular fibrillation in Brugada syndrome using noninvasive scoring methods. *Heart Rhythm*. 2016;13(1):1947–1954.