Evaluating the Use of Genetics in Brugada Syndrome Risk Stratification

Michelle M. Monasky 1†, Emanuele Micaglio 1†, Emanuela T. Locati 1 and Carlo Pappone 1,2*

1 Arrhythmology Department, IRCCS Policlinico San Donato, Milan, Italy, 2 Vita-Salute San Raffaele University, Milan, Italy

The evolution of the current dogma surrounding Brugada syndrome (BrS) has led to a significant debate about the real usefulness of genetic testing in this syndrome. Since BrS is defined by a particular electrocardiogram (ECG) pattern, after ruling out certain possible causes, this disease has come to be defined more for what it is not than for what it is. Extensive research is required to understand the effects of specific individual variants, including modifiers, rather than necessarily grouping together, for example, “all SCN5A variants” when trying to determine genotype-phenotype relationships, because not all variants within a particular gene act similarly. Genetic testing, including whole exome or whole genome testing, and family segregation analysis should always be performed when possible, as this is necessary to advance our understanding of the genetics of this condition. All considered, BrS should no longer be considered a pure autosomal dominant disorder, but an oligogenic condition. Less common patterns of inheritance, such as recessive, X-linked, or mitochondrial may exist. Genetic testing, in our opinion, should not be used for diagnostic purposes. However, variants in SCN5A can have a prognostic value. Patients should be diagnosed and treated per the current guidelines, after an arrhythmologic examination, based on the presence of the specific BrS ECG pattern. The genotype characterization should come in a second stage, particularly in order to guide the familial diagnostic work-up. In families in which an SCN5A pathogenic variant is found, genetic testing could possibly contribute to the prognostic risk stratification.

Keywords: Brugada syndrome, sudden cardiac death, genetic testing, mutation, variant, SCN5A, sodium channel, arrhythmia

INTRODUCTION

The first description of Brugada syndrome (BrS) included eight unrelated patients with recurrent aborted sudden cardiac death due to ventricular fibrillation (VF) (1), in whom basal ECG showed persistent ST-segment elevation in precordial leads V1 to V2-V3. However, the genetic background was not discussed. Thus, no genotype-phenotype relationship was established. Meanwhile, Gellens and coworkers characterized SCN5A for the first time (2). Later, SCN5A was described in two unrelated families with long QT syndrome (LQTS) type-3 (LQT3) (3) (timeline, Figure 1).

BrS was first considered a form of idiopathic VF, resulting from abnormal electrophysiologic activity in right ventricular epicardium (4). It was described to lie on the same spectrum of cardiac
with coved morphology, specifically the type-1 BrS pattern, an ST-segment elevation ≥ 2 mm, often associated with a sharp transition from elevated ST-segment to negative T-wave, among right precordial leads V1-V2, positioned in the 2nd, 3rd, or 4th intercostal space (13). This type-1 BrS pattern can occur either spontaneously or be unmasked with intravenous administration of Class 1c antiarrhythmic drugs, such as ajmaline or flecainide (13). Recently, it was hypothesized that BrS might actually be a heterogeneous disease with a common ECG phenotype (14). While this phenotype has been commonly attributed to loss-of-function of the Nav1.5 cardiac sodium channel, such phenotype could result from a number of molecular origins, not only SCN5A variants, but also alterations in proteins that modify the channel, or even environmental influences. Regarding the environmental influences, “true BrS” is diagnosed by ruling out such causes as electrolyte disturbances or myocardial ischemia. BrS patterns in these cases are said to be “BrS phenocopies” (15, 16). We disagree with the definition of “phenocopy,” because it is based upon what BrS is not rather than providing a clear picture of what BrS is. This is especially concerning since environmental influences can have a pivotal role in BrS (17). Perhaps a better view would be to consider the “BrS pattern” as a warning of risk for sudden cardiac death, regardless of the underlying cause (18). We are aware that this concept challenges the autosomal dominant model of BrS, largely based on the accepted etiologic role of SCN5A.

BrS has also been attributed to an increase in potassium current (19, 20). Furthermore, several studies have suggested BrS may be similar to a cardiomyopathy (21–26). Thus, it is likely that the ECG pattern used to define “BrS” is actually a common clinical manifestation, resulting from a multitude of different molecular causes. Further development of this concept may lead to a new paradigm for BrS, which may be considered not only as a Mendelian disorder, but as a complex condition, which might be caused by a huge variety of genetic variants, interacting with environmental factors (14, 27). In any case, since our current understanding of BrS genetics is still elementary, today BrS should be diagnosed by the type-1 ECG pattern (see Figure 2), not by genetic findings, especially additional findings during screening for other diseases.

Genotype-Phenotype Relationships
Genotype-phenotype relationships are difficult to establish in BrS patients, because the clinical manifestations can be very subtle, and because the differential diagnosis can be extremely complex (28). Additionally, SCN5A variants have since been associated with a variety of pathologies (29, 30). Other works (31, 32) demonstrated both rare mutations and common variants in SCN5A can be considered phenotype modulators in myocardial infarction (33), arrhythmic storm (34), epilepsy (35), and even colon (36) and breast cancer (37). Thus, although SCN5A is
the only undisputed gene in which mutations are thought to cause BrS, genetic testing alone is insufficient to diagnose BrS, as mutations in this gene could result in a number of different phenotypes. Instead, BrS must be diagnosed only in the presence of a diagnostic type 1 BrS ECG pattern (spontaneous or drug-induced), not due to secondary causes, such as electrolyte disturbances or myocardial ischemia.

**Other Candidate Genes**

A recent study (9) concluded that only the SCN5A gene should be analyzed in BrS patients. We agree that mutations in SCN5A could be the cause of BrS in some patients. However, the study did not address what should be done in the majority of BrS patients, who test negative for any SCN5A mutations, nor provide clarity of the disease mechanism in those patients negative...
for SCN5A mutations, especially regarding the role of copy number variations and mitochondrial DNA. London expressed his disagreement, arguing that eliminating other genes from testing panels could stifle scientific advancement (10). Wilde and Gollob (38), however, countered by arguing that undue harm from incorrect interpretation could result in a life-changing diagnosis, require intervention, create long-term anxiety, and impact asymptomatic family members. We believe that suspected candidate genes should be tested and studied so that we can better understand their effects. However, all suspected cases should be confirmed by the presence of the BrS pattern, including patients found to have mutations in SCN5A, as single mutations in this gene are responsible for a variety of phenotypes, not only BrS found to have mutations in SCN5A, as single mutations in this gene are responsible for a variety of phenotypes, not only BrS (39, 40), and may not even cause BrS on their own (41).

Many other genes such as SCN10A (42, 43), SCN4A (44), SCN1B (45), KCNH2 (46), RANGRF (47), PKP2 (48), TPM1 (49), and several calcium channels genes (50–53) have been described in patients clinically affected by BrS. Whole exome sequencing with a high coverage was performed in a family with both hypertrophic cardiomyopathy and type-1 BrS, apparently caused by the same heterozygous TPM1 mutation (49). Thus, several candidate genes exist and should be further studied. Physiologic studies should follow the discovery of candidate mutations in the clinic, as abnormal effects in the physiology laboratory can provide useful insights to understanding particular new mutations.

**Modes of Inheritance**

In spite of recent developments in the field of genetics, BrS is often still considered a monogenic Mendelian disease (54) inherited in an autosomal dominant fashion with incomplete penetrance (55–58). This is mainly due to the description of BrS in a family in which the genetics were consistent with this kind of transmission (59), making SCN5A the only accepted BrS gene (9). Another reason why SCN5A is so “popular” is because the segregation of variants in this gene show incomplete penetrance and marked variability in a significant percentage of patients (60). However, increasing evidence suggests that BrS in some patients might be actually caused by a digenic inheritance (61) or a combined effect of multiple variants (62), including polymorphisms (63). In this subset of patients, it is difficult to identify the real molecular cause of BrS, making it difficult to understand, using only genetic testing, which family members have inherited the syndrome and which have not. Additionally, since BrS may be due to a combined effect of multiple variants, the severity can often be different between family members (40). Furthermore, there might be other cases in which some family members have the syndrome but others do not, despite sharing certain variants, because of differences in modifier genes.

Although autosomal dominant inheritance with incomplete penetrance is the most commonly accepted mode of transmission of BrS, other forms of transmission have been suggested, such as recessive (64) and X-linked (19, 20). It is also possible that yet-undiscovered somatic mutations could have an effect on the heart. Furthermore, an autosomal dominant inheritance pattern could imply that the disease is Mendelian in nature, caused by a single mutation in a single gene. However, several studies have demonstrated an oligogenic mode of inheritance (7).

Therefore, likely, in some families, a particular variant causes BrS in a Mendelian fashion, while in other families, the pattern of inheritance is more complicated to understand, because the disease is caused by a combination of factors, resulting in different phenotypes even between family members (65). Tadros et al. calculating polygenic risk scores (PRSs) for PR interval, QRS duration, and BrS, reported that 44 common variants associated with PR, and 26 common variants associated with QRS, in the general population, were associated with ajmaline-induced PR and QRS prolongation, respectively. Also, a 3-single-nucleotide-polymorphism PRS derived from a case-control BrS GWAS was independently associated with ajmaline-induced type-1 BrS ECG (66). This demonstrates the importance of polymorphisms that might predispose to arrhythmias and create a pathological effect, especially in the presence of other variants in the same patient.

**Overlap Syndromes**

Since variants in SCN5A can be found in several cardiogenetic disorders, it is not surprising to observe an overlap between BrS and other pathologies. For example, BrS can be diagnosed in the proband while LQTS, epilepsy, febrile seizures, or complete bundle branch block can be present in the family members (67–70).

Overlap between arrhythmogenic right ventricular (RV) dysplasia/cardiomyopathy (ARVD/C) and BrS has been described by many groups (71), the mechanism of which may involve cell-cell junctions (24). Both ARVC and BrS can originate from mutations in the connexome, and the phenotype that emerges depends on the type of connexome mutation (72, 73). PKP2 may be an important gene in this regard, as mutations in PKP2 can result in loss of desmosomal integrity, cause sodium current deficit, and be found in patients with BrS (74, 75). The presence of ARVC in BrS patients has been associated with higher arrhythmic risk (76). The genetics of families with overlap syndromes should be carefully considered, as these genetic causes may be different than other families in which BrS is the only phenotype observed. This is yet another example of the need for personalized medicine and to consider the genetics of BrS on a family-by-family basis.

**Mitochondrial Considerations**

Many recent studies have related cardiac arrhythmias, and particularly BrS, to mitochondrial function, or the effect of mitochondrial products on the sodium channel. Heart arrhythmias can originate from pathophysiology of the mitochondria, which produce adenosine triphosphate, a compound required for normal ion channel function (77). Aiba et al. described a family with BrS and the SCN5A mutation R526H, which is a PKA consensus phosphorylation site and might predispose to arrhythmias and create a pathological effect, especially in the presence of other variants in the same patient. Therefore, likely, in some families, a particular variant causes BrS in a Mendelian fashion, while in other families, the pattern of inheritance is more complicated to understand, because the disease is caused by a combination of factors, resulting in different phenotypes even between family members (65). Tadros et al. calculating polygenic risk scores (PRSs) for PR interval, QRS duration, and BrS, reported that 44 common variants associated with PR, and 26 common variants associated with QRS, in the general population, were associated with ajmaline-induced PR and QRS prolongation, respectively. Also, a 3-single-nucleotide-polymorphism PRS derived from a case-control BrS GWAS was independently associated with ajmaline-induced type-1 BrS ECG (66). This demonstrates the importance of polymorphisms that might predispose to arrhythmias and create a pathological effect, especially in the presence of other variants in the same patient.

**Overlap Syndromes**

Since variants in SCN5A can be found in several cardiogenetic disorders, it is not surprising to observe an overlap between BrS and other pathologies. For example, BrS can be diagnosed in the proband while LQTS, epilepsy, febrile seizures, or complete bundle branch block can be present in the family members (67–70).

Overlap between arrhythmogenic right ventricular (RV) dysplasia/cardiomyopathy (ARVD/C) and BrS has been described by many groups (71), the mechanism of which may involve cell-cell junctions (24). Both ARVC and BrS can originate from mutations in the connexome, and the phenotype that emerges depends on the type of connexome mutation (72, 73). PKP2 may be an important gene in this regard, as mutations in PKP2 can result in loss of desmosomal integrity, cause sodium current deficit, and be found in patients with BrS (74, 75). The presence of ARVC in BrS patients has been associated with higher arrhythmic risk (76). The genetics of families with overlap syndromes should be carefully considered, as these genetic causes may be different than other families in which BrS is the only phenotype observed. This is yet another example of the need for personalized medicine and to consider the genetics of BrS on a family-by-family basis.

**Mitochondrial Considerations**

Many recent studies have related cardiac arrhythmias, and particularly BrS, to mitochondrial function, or the effect of mitochondrial products on the sodium channel. Heart arrhythmias can originate from pathophysiology of the mitochondria, which produce adenosine triphosphate, a compound required for normal ion channel function (77). Aiba et al. described a family with BrS and the SCN5A mutation R526H, which is a PKA consensus phosphorylation site and associated with reduced basal I_Na due to the inability of PKA to act on the sodium channel to increase the sodium current (78). A mutation in the GPD1L protein reduces I_Na by raising intracellular NADH levels and inducing reactive oxygen species (ROS) (79). This process of ROS production, its release from mitochondria, and thus its detrimental effect on the sodium current can be reversed in several ways, namely by NAD+, inhibition of mitochondrial electron transport, a mitochondrial targeted antioxidant, and an inner membrane...
anion channel modulator (80). A specific mitochondrial DNA (mtDNA) allelic combination and a high number of mtDNA single nucleotide polymorphisms (SNPs) have been reported in association with more severe cases of BrS, suggesting that these are important cofactors in the expression of the clinical phenotype (81, 82). Tafti et al. suggested that BrS may be caused by mutations in mitochondrial transfer RNA (tRNA) genes, leading to deficiencies in the translational process of critical proteins of the respiratory chain (83). Reports have demonstrated that tRNAMet, tRNAlle, tRNATrp and tRNAGln genes are hot spots for cardiovascular diseases (83, 84). Thus, mitochondrial function, or malfunction, contributes to sodium channel function and to cardiac rhythm.

**Risk Stratification**

Risk stratification in BrS has previously relied on clinical scores (85), including familial history of sudden cardiac death, personal history of syncope, aborted cardiac arrest, spontaneous type-1 BrS pattern, or male gender. It was also reported that proband status, inducibility toward ventricular arrhythmias (86), arrhythmogenic substrate area, and late potentials (87) were predictors of higher risk. Our group recently proposed the SCN5A genetic status as a prognostic factor for BrS patients (12, 88). In particular, SCN5A mutation carriers exhibited more pronounced epicardial electrical abnormalities and a more aggressive clinical presentation. In at least a subgroup of patients, the mutated SCN5A gene acts more like a phenotype modulator than a real Mendelian dominant cause of the displayed phenotype, possibly calling into question the autosomal dominant inheritance of BrS. This is true also for variants of “unknown significance” (VUS), which are generally treated as “benign.” However, in our experience, several of these VUS are later reclassified as pathogenic. We believe that, in time, many other VUS, especially in the SCN5A gene, will be determined to be pathogenic, considering also that the oligogenic model is likely to be accepted in the near future.

**DISCUSSION**

The genetics of BrS have likely remained elusive because of how the disease has been considered only an autosomal dominant Mendelian disorder. However, when BrS is considered an oligogenic disorder, it may be possible to use genetics to predict the BrS phenotype. Besides direct modifications in the Nav1.5 protein, its function can be altered by many regulatory proteins like Hey2, Mog1, Gpd1-L, and others. According to us, studies should expand to better understand any possible role for mitochondrial involvement, including the analysis of mitochondrial genes, their products, and their functional effects on the cells. Environmental factors should also be studied, including anything to which families may be exposed, resulting in post-translational effects, especially when probands test negative for variants in all BrS candidate genes. Environmental factors could be mistaken as a genetic condition when several family members living in the same environment are affected.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.
AUTHOR CONTRIBUTIONS
MM and EM drafted the paper. EL and CP provided revisions and useful feedback. CP secured funding for the project. All authors approved the final version of the manuscript.

REFERENCES

1. 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) 20:1391–6. doi: 10.1016/0735-1097(92)90253-J
2. Gellens ME, George AL Jr, Chen LQ, Chahine M, Horn R, Barchi RL, et al. Primary structure and functional expression of the human cardiac tetrodotoxin-insensitive voltage-dependent sodium channel. Proc Natl Acad Sci U S A. (1992) 89:554–8. doi: 10.1073/pnas.89.2.554
3. Wang Q, Shen J, Sjolawski I, Atkinson D, Li Z, Robinson JL, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. Cell. (1995) 80:805–11. doi: 10.1016/0092-8674(95)30359-3
4. Gussak I, Antzelevitch C, Bjerrum A, Towbin JA, Chaitman BR. The Brugada syndrome: clinical, electrophysiologic and genetic aspects. J Am Coll Cardiol. (1999) 33:5–15. doi: 10.1016/S0735-1097(98)00528-2
5. Bezzina C, Volkmann MW, Van Den Berg MP, Postma AV, Rook MB, Vierשמו JW, et al. A single Na(+) channel mutation causing both long-QT and Brugada syndromes. Circ Res. (1999) 85:1206–13. doi: 10.1161/01..RES.85.12.1206
6. Campuzano O, Sarquella-Brugada G, Cesar S, Arbelo E, Brugada J, Brugada R. Update on genetic basis of Brugada syndrome: monogenic, polygenic or oligogenic? Int J Mol Sci. (2020) 21:7155. doi: 10.3390/ijms21191755
7. Monasky MM, Micaglio E, Cicone G, Pappone C. Brugada syndrome: oligogenic or mendelian disease? Int J Mol Sci. (2020) 21:1687. doi: 10.3390/ijms21051687
8. Kaplinger JD, Tester DJ, Alders M, Benito B, Berthet M, Brugada J, et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. Heart Rhythm. (2010) 7:33–46. doi: 10.1016/j.hrthm.2009.09.069
9. Hosseini SM, Kim R, Udupa S, Costain G, Jobling R, Liston E, et al. Reappraisal of reported genes for sudden arrhythmic death. Circulation. (2018) 138:1195–205. doi: 10.1161/CIRCULATIONAHA.118.035700
10. London B. Letter by london regarding article, “reappraisal of reported genes for sudden arrhythmic death: evidence-based evaluation of gene validity for Brugada syndrome”. Circulation. (2019) 139:1758–9. doi: 10.1161/CIRCULATIONAHA.118.036889
11. Wijeyeratne YD, Tanck MW, Mizusawa Y, Batchvarov V, Barc J, Crotti L, et al. SCN5A mutation type and a genetic risk score associate variably with brugada syndrome phenotype in SCN5A families. Circ Genom Precis Med. (2020) 3:e002911. doi: 10.1177/2042909120912355
12. Cicone G, Monasky MM, Santinelli V, Micaglio E, Vicedomini G, Anastasia L, et al. Brugada syndrome genetics is associated with phenotype severity. Eur Heart J. (2020) 42:1082–90. doi: 10.1093/eurheartj/ehaa942
13. Antzelevitch C, Van GX, Ackerman MJ, Borggreve M, Corrado D, Guo J, et al. J-Wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. J Arrhythm. (2016) 32:315–39. doi: 10.1016/j.joa.2016.07.002
14. Gray B, Semsarian C, Sy RW. Brugada syndrome: a heterogeneous disease with a common ECG phenotype? J Cardiovasc Electrophysiol. (2014) 25:450–6. doi: 10.1111/jce.12366
15. Genaro NR, Anselm DD, Cervino N, Estevez AO, Perona C, Villamil AM, et al. Brugada phenocopy clinical reproducibility demonstrated by recurrent hypokalemia. Ann Noninvasive Electrocardiol. (2014) 19:387–90. doi: 10.1111/anec.12101
16. Maheshwari A, Von Wald L, Krishnan B, Benditt DG. Hyperkalemia-induced brugada phenocopy. JACC Clin Electrophysiol. (2017) 3:1058–9. doi: 10.1016/j.jcpe.2016.12.012

FUNDING
This study was partially supported by Ricerca Corrente funding from Italian Ministry of Health to IRCCS Policlinico San Donato.
development during acute myocardial infarction. *Heart Rhythm.* (2007) 4:1072–80. doi: 10.1016/j.hrthm.2007.03.040

35. Auftin D, Leren TP, Taubell E, Gjerstad L. New SCN5A mutation in a SUDEP victim with idiopathic epilepsy. *Seizure.* (2009) 18:158–60. doi: 10.1016/j.seizure.2007.08.008

36. House CD, Vanke CJ, Schwartz AM, Obias V, Frank R, Luu T, et al. Voltage-gated Na+ channel SCN5A is a key regulator of a gene transcriptional network that controls colon cancer invasion. *Cancer Res.* (2010) 70:6957–67. doi: 10.1158/0008-5472.CAN-10-1169

37. Luo Q, Wu T, Wu W, Chen G, Luo X, Jiang L, et al. The functional role of voltage-gated sodium channel Nav1.5 in metastatic breast cancer. *Front Pharmacol.* (2020) 11:1111. doi: 10.3389/fphar.2020.01111

38. Wilde AA, Gollob MH. Response by Wilde and Gollob to letter regarding article, “reappraisal of reported genes for sudden arrhythmic death: evidence-based evaluation of gene validity for brugada syndrome”. *Circulation.* (2019) 139:1760–1. doi: 10.1161/CIRCULATIONAHA.119.039065

39. Yagihiara N, Watanabe H, Barnett P, Duboscq-Bidot L, Thomas AC, et al. Role of SCN5A in the pathogenesis of Brugada syndrome: a study of 145 SCN5A-negative patients. *Cardio J.* (2017) 21:121–127. doi: 10.5603/CJ.a2013.0125

40. Antzelevitch C, Pollevick GD, Wilber DJ. Cardiac sodium channel dysfunction and proarrhythmia in Brugada syndrome. *Epilepsy Res.* (2010) 96:15–27. doi: 10.1016/j.eplepsyres.2010.08.008

41. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, et al. Mutation load of multiple ion channel gene mutations in brugada syndrome. *Circ J.* (2017) 81:2718–26. doi: 10.1253/circj.CJ-17-0621

42. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, et al. Further insights in the most common SCN5A variant R1632C. *Circ J.* (2018) 82:703–9. doi: 10.1253/circj.CJ-17-0248

43. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, et al. Further insights in the most common SCN5A variant R1632C. *Circ J.* (2018) 82:703–9. doi: 10.1253/circj.CJ-17-0248

44. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, et al. Further insights in the most common SCN5A variant R1632C. *Circ J.* (2018) 82:703–9. doi: 10.1253/circj.CJ-17-0248

45. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, et al. Further insights in the most common SCN5A variant R1632C. *Circ J.* (2018) 82:703–9. doi: 10.1253/circj.CJ-17-0248

46. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, et al. Further insights in the most common SCN5A variant R1632C. *Circ J.* (2018) 82:703–9. doi: 10.1253/circj.CJ-17-0248

47. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, et al. Further insights in the most common SCN5A variant R1632C. *Circ J.* (2018) 82:703–9. doi: 10.1253/circj.CJ-17-0248

48. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, et al. Further insights in the most common SCN5A variant R1632C. *Circ J.* (2018) 82:703–9. doi: 10.1253/circj.CJ-17-0248

49. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, et al. Further insights in the most common SCN5A variant R1632C. *Circ J.* (2018) 82:703–9. doi: 10.1253/circj.CJ-17-0248

50. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, et al. Further insights in the most common SCN5A variant R1632C. *Circ J.* (2018) 82:703–9. doi: 10.1253/circj.CJ-17-0248

51. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, et al. Further insights in the most common SCN5A variant R1632C. *Circ J.* (2018) 82:703–9. doi: 10.1253/circj.CJ-17-0248
71. Peters S, Trummel M, Denecke S, Koehler B. Results of ajmaline testing in patients with arrhythmogenic right ventricular dysplasia-cardiomyopathy. Int J Cardiol. (2004) 95:207–10. doi: 10.1016/j.ijcard.2003.04.032
72. Agullo-Pascual E, Cerrone M, Delmar M. Arrhythmogenic cardiomyopathy and Brugada syndrome: diseases of the connexome. FEBS Lett. (2014) 588:1322–30. doi: 10.1016/j.febslet.2014.02.008
73. Corrado D, Zorzi A, Cerrone M, Rigato I, Mongillo M, Bauce B, et al. Relationship between arrhythmogenic right ventricular cardiomyopathy and brugada syndrome: new insights from molecular biology and clinical implications. Circ Arrhythm Electrophysiol. (2016) 9:e003631. doi: 10.1161/CIRCEP.115.003631
74. Cerrone M, Delmar M. Desmosomes and the sodium channel complex: implications for arrhythmogenic cardiomyopathy and Brugada syndrome. Trends Cardiovasc Med. (2014) 24:184–90. doi: 10.1016/j.tcm.2014.02.001
75. Cerrone M, Lin X, Zhang M, Agullo-Pascual E, Pfenniger A, Chkourko Gusky H, et al. Missense mutations in plakophilin-2 cause sodium current deficit and associate with a Brugada syndrome phenotype. Circulation. (2014) 129:1092–103. doi: 10.1161/CIRCULATIONAHA.113.003077
76. Scheirlynck E, Chivulescu M, Lie OH, Motoc A, Koulalis J, De Asmundis C, et al. Worse prognosis in brugada syndrome patients with arrhythmogenic cardiomyopathy features. JACC Clin Electrophysiol. (2020) 6:1353–63. doi: 10.1016/j.jaccep.2020.05.026
77. Doenst T, Nguyen TD, Abel ED. Cardiac metabolism in heart failure: implications beyond ATP production. Circ Res. (2013) 113:709–24. doi: 10.1161/CIRCRESAHA.113.300376
78. Alba T, Farinelli F, Kostecki G, Hesketh GG, Edwards D, Biswas S, et al. A mutation causing Brugada syndrome identifies a mechanism for altered autonomic and oxidant regulation of cardiac sodium currents. Circ Cardiovasc Genet. (2014) 7:249–56. doi: 10.1161/CIRCGENETICS.113.000480
79. Liu M, Sanyal S, Gao G, Gurung IS, Zhu X, Gacconnet G, et al. Cardiac Na+ current regulation by pyridine nucleotides. Circ Res. (2009) 105:737–45. doi: 10.1161/CIRCRESAHA.109.197277
80. Liu M, Liu H, Dudley SC Jr. Reactive oxygen species originating from mitochondria regulate the cardiac sodium channel. Circ Res. (2010) 107:967–74. doi: 10.1161/CIRCRESAHA.110.220673
81. Stocchi L, Polidori E, Potenza L, Rocchi MB, Calabrini C, Busacca P, et al. Mutational analysis of mitochondrial DNA in Brugada syndrome. Cardiovasc Pathol. (2016) 25:47–54. doi: 10.1016/j.carpath.2015.10.001
82. Polidori E, Stocchi L, Potenza D, Cucchiari L, Stocchi V, Potenza L. A high number of ‘natural’ mitochondrial DNA polymorphisms in a symptomatic Brugada syndrome type 1 patient. J Genet. (2020) 99:66. doi: 10.1007/s12041-020-01228-4
83. Tafiri MF, Khatami M, Rezaei S, Heidari MM, Hadadzadeh M. Novel and heteroplasmic mutations in mitochondrial tRNA genes in Brugada syndrome. Circ J. (2018) 25:113–9. doi: 10.1253/circj.a2017.0104
84. Zhu HY, Wang SW, Liu L, Chen R, Wang L, Gong XL, et al. Genetic variants in mitochondrial tRNA genes are associated with essential hypertension in a Chinese Han population. Clin Chim Acta. (2009) 410:64–9. doi: 10.1016/j.cca.2009.09.023
85. Sieira J, Conte G, Ciconte G, Chierchia GB, Casado-Arroyo R, Baltogiannis G, et al. A score model to predict risk of events in patients with Brugada syndrome. Eur Heart J. (2017) 38:1756–63. doi: 10.1093/eurheartj/ehx119
86. Sieira J, Ciconte G, Conte G, De Asmundis C, Chierchia GB, Baltogiannis G, et al. Long-term prognosis of drug-induced Brugada syndrome. Heart Rhythm. (2017) 14:1427–33. doi: 10.1016/j.hrthm.2017.04.044
87. Ciconte G, Santinelli V, Vicedomini G, Borrelli V, Monasky MM, Micaglio E, et al. Non-invasive assessment of the arrhythmogenic substrate in Brugada syndrome using signal-averaged electrocardiogram: clinical implications from a prospective clinical trial. Europace. (2019) 21:1900–10. doi: 10.1093/europace/euz295
88. Pappone C, Ciconte G, Micaglio E, Monasky MM. Common modulators of Brugada syndrome phenotype do not affect SCN5A prognostic value. Eur Heart J. (2021) 42:1273–4. doi: 10.1093/eurheartj/ehab071
89. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggreve M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. (2015) 36:2793–867. doi: 10.1093/eurheartj/ehv316

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Monasky, Micaglio, Locati and Pappone. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.