Tres preguntas

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1. **¿Ahora, si tiene un bloqueo tetrafascicular, AV de 1° + BRD + LAFB + LSBF algo enfermedad estructural tiene??**

Respuesta: actualmente no cabe duda que el síndrome de Brugada tiene enfermedad estructural mínima subyacente.

A lo largo de los años, se ha propuesto que tanto la dispersión transmural mejorada en la repolarización como los disturbios de la despolarización con enlentecimiento de la conducción, en particular dentro del VD/ y en especial en el tracto de salida del VD (TSVD) mejor registrado en la odiosamente denominada **"the forgotten lead"** (aVR) la cual se posiciona al frente de esta estructura , son la base del patrón de ECG y la arritmogénesis en el SBr. Sin embargo, aunque originalmente se definió como un trastorno puramente eléctrico, las anomalías estructurales cardíacas ahora se consideran cada vez más relevantes.

Aunque la ecocardiografía cardíaca convencional transtorácica a menudo muestra un corazón normal, se han observado anomalías sutiles mediante resonancia nuclear magnética cardiaca y la tomografía computarizada, como:

1) Dilatación del TSVD,
2) Reducción de la fracción de eyección del VD y
3) Anomalías en el movimiento de la pared del VD. Estas últimas pueden representar deformidades estructurales y/o el enlentecimiento de la conducción eléctrica con el consiguiente retraso de la contracción del miocardio.

Los estudios de biopsia han encontrado alteraciones miocardiopatías sutiles en los pacientes Brugada (después de excluir displasia), además de mayor de fibrosis y expresión reducida de la proteína de unión comunicante conexina-43 en el VD/TSVD. Estos cambios estructurales tanto pueden ser causa como consecuencia de perturbaciones eléctricas y/o disfunción de los canales iónicos. Por ejemplo, un número reducido de canales de sodio puede afectar a otras proteínas (estructurales) que colocan y/o interactúan con el SCN5A NaV1.5 en la unión célula-célula (disco intercalado: "Gap junction"); lo que puede explicar el vínculo observado entre las mutaciones SCN5A y la displasia arritmgénica. Sin embargo, dado que la mayoría de los pacientes con BrS no tienen mutaciones SCN5A, con certeza está involucrados otros mecanismos aún desconocidos. Las anomalías estructurales podrían explicar la aparición de los síntomas de BrS en la mediana edad (entre 30 y 40 años), lo que indica que la patología subyacente necesita tiempo para desarrollarse. Por el contrario, las alteraciones eléctricas pueden ser las principales responsables de los síntomas de aparición precoz en

bebés y niños con SBr, como sugiere la alta prevalencia de mutaciones en el gen SCN5A en esta faja de edad como el caso presentado Independientemente de su origen, las anomalías estructurales pueden causar bloqueo de conducción como lo menciona Pedrito en su magnífico trabajo pionero donde comenta la existencia **bloqueo en el haz de His y hasta "Split His"** y facilitar la reentrada arritmias.
De hecho, la ablación con catéter del miocardio sobreviviente entre el tejido fibrocito puede eliminar este sustrato arritmogénico, borrando así el patrón electrocardiográfico de Brugada reduciendo así la carga arrítmica.

2. **Segunda pregunta de Juan ¿Puede ser Lenegre?**

Respuesta: en ingles

Both entities, called Progressive Cardiac Conduction Defects (PCCD), are grouped together as primary conduction diseases (Lev-Lenègre). Both Lenègre disease—known as "primary" PCCD[1] —as well as the secondary mechanic lesion—sclerosis of the left "cardiac skeleton" or Lev disease[2] —usually cause LBBB or RBBB, frequently associated with divisional or fascicular blocks. Occasionally, they develop into more advanced degrees of block with a potential to cause SCD due to total AV block, to the extent that they represent the most important cause of pacemaker implantation in the first world: 0.15 per 1,000 inhabitants a year. The same mutation in novel single SCN5A missense mutation can lead either to Brugada syndrome or to a PCCD. Modifier gene(s) may influence the phenotypic consequences of a SCN5A mutation. A G-to-T mutation at position 4372 was identified by direct sequencing and was predicted to change a glycine for an arginine (G1406R) between the DIII-S5 and DIII-S6 domain of the Na+ channel protein[3].

DIFFERENCES BETWEEN LENÈGRE AND LEV DISEASE[4]

	LEV DISEASE	LENÈGRE DISEASE

Pathologic anatomy	Mechanical progressive fibrosis of the left "cardiac skeleton." Calcification of the mitral valve ring, fibrous central body, membranous part of the aorta base, apex muscular septum, and direct Hisian system and antero-superior fasciculus of the left branch.	Progressive sclerosis of the intraventricular His-Purkinje conduction system.
Etiology	Idiopathic. Mechanical acceleration of the aging process.	Allelic heterozygotic mutation with Brugada syndrome located in the alpha subunit of the sodium channel in the SCN5A gene.
Identified genetic defect		1) Substitution of the serine amino acid by glycine (G298S) in the domain of the I S5-S6 loop. 2) Substitution of asparagine by aspartic acid within the IV domain of S3 (D1595N). 3) Substitution of 514 cysteine by glycine (G514C). 4) Substitution of glycine by threonine in the 4372 position and glycine by arginine (G1405R) between the DIII-S5 domains of the sodium channel.

BRUGADA SYNDROME AND LENÈGRE DISEASE

Tan et al[5] identified a single mutation in five affected family members; this mutation results in the substitution of cysteine 514 for glycine (G514C) in the channel protein.

Biophysical characterization of the mutant channel shows that there are abnormalities in voltage-dependent 'gating' behaviour that can be partially corrected by dexamethasone, consistent with the salutary effects of glucocorticoids on the clinical phenotype. Computational analysis predicts that the gating defects of G514C selectively slow myocardial conduction, but do not provoke the rapid cardiac arrhythmias associated previously with SCN5A mutations.

A two new allelic heterozygotic mutations with Brugada syndrome, located in the alpha subunit of the Na+ channel in the SCN5A gene, what has been clinically translated into AV block. They are the result of the substitution of the serine amino acid by glycine (G298S) in the domain of the I S5-S6 loop, and asparagine by aspartic acid within the S3 of the IV domain (D1595N). Both mutations prevent fast inactivation, reduce sodium channel density, and accentuate the slow component of inactivation. This combination causes a decrease in conduction velocity and leads to AV block**.**

A mutation was identified, which causes intraventricular dromotropic disorder secondary to substitution of the cysteine amino acid by glycine (G514C) in the Na+ proteic fast channel[6]**.** In Brugada syndrome, the PR interval and the HV of the electrogram are prolonged in nearly 50% of cases. HV can reach a duration of approximately twice its maximal normal limit.Lenègre disease should not continue to be classified as an idiopathic progressive disease of the His-Purkinje system. It should be called a Progressive Cardiac Conduction Defect or PCCD. It has been identified as a disease of the Na+ fast channel or channelopathy by mutation in the SCN5A gene, and as allele of Brugada syndrome with a different phenotypic expression, in a similar fashion to the LQT3 variant of the hereditary-familial LQTS. The same missense mutation in the SCN5A gene can cause both phenotypes: Brugada disease and Lenègre disease[7].

1. **ReferencesLenègre J.The pathology of complete atrioventricular block. Progr Cardiovasc Dis 1964; 6:317-323.**
2. **Lev M. Anatomic basis of atrioventricular block. Am J Med 196437:742.**
3. **Kyndt F, Probst V, Potet F, et. al. Novel SCN5A Mutation Leading Either to Isolated Cardiac Conduction Defect or Brugada Syndrome in a Large French Family. Circulation 2001; 104: 3081-3086.**
4. **Van Der Merwe PJ, Weimar HW, Torrington M et al. Progressive familial heart block (type I): A follow up study after ten years S Med J 1988; 73: 275**
5. **Torrington M, Weimar HW, Van Der Merwe P. Progressive familial heart block: PtI. Extent of the disease. 1986; 70:354.**
6. **Wang DW, Viswanathan PC, Balser JR, et al. Clinical, Genetic, and Biophysical Characterization of SCN5A Mutations Associated With Atrioventricular Conduction Block.Circulation 2002; 105:341-346.**
7. **Tan HL, Bink-Boelkens MT, Bezzina CR, et al. A sodium-channel mutation causesIsolated cardiac conduction disease. Nature 2001; 409:1043-1047**

3. **¿Es diagnóstico inobjetable S° Brugada con SCN5A? Si**

Para eso debemos analizar la genética de este gen polivalente responsable por el Brugada tipo 1 con mutacion en el Gen: SCN5A

Paso al English

BrS types, locus, OMIM, gene, channels affected and percentage

I. BrS-1 [54]: Locus: 3p21-23; OMIM: 601144; Gene: SCN5A; Ion channel and effect: INa+ loss-of-function; Protein: NaV1.5 - α subunit of the cardiac sodium channel carrying the sodium current INa+; % of probands: 11-28%. Amin et al [55] hypothesized based on a study of AF in a large cohort of BrS patients, that a reduced number of potentially triggering premature atrial contractions (PACs) in the presence of a more extensive substrate in SCN5A mutation carriers may account for AF being no more prevalent in patients with SCN5A mutations than in those without. Given the polemic and complex issues underlying the pathophysiology of BrS, one should regard this hypothesis as one potential mechanism of many that influence the prevalence of AF in BrS. Mutations in SCN5A lead to a broad spectrum of phenotypes, however the SCN5A gene is not commonly involved in the pathogenesis of BrS and associated disorders. Studies have revealed significant overlap between aberrant rhythm phenotypes, and single mutations have been identified that evoke multiple rhythm disorders with common gating lesions. Nav1.5 consists of peak and late components (INa-P and INa-L). Mutant Nav1.5 causes alterations in the peak and late Na+ current and is associated with an increasingly wide range of genetic arrhythmias. More than 400 mutations have been identified in the SCN5A gene. Although the mechanisms of SCN5A mutations leading to a variety of channelopaties can be classified according to the alteration of INa-P and INa-L as gain-of-function, loss-of-function and both, few researchers have summarized the mechanisms in this way [56]. Gain-of-function mutations in SCN5A lead to more Na+ influx into cardiomyocytes through aberrant channel gating causing LQT3. Slowed or incomplete inactivation of the NaV1.5 channel results in an additional inward current, known as the late or persistent sodium current (Ipst), during the plateau phase of the ventricular action potential with ST segment prolongation and late T occurrence. Among the mutations in SCN5A associated with LQT3 is 1795insD, which is characterized by the insertion of 3 nucleotides (TGA) at position 5537 C-terminal domain of the NaV1.5 protein [57]. Carriers of this mutation may not only present with LQT3, but also with ECG features of sinus

bradycardia, progressive cardiac conduction disease, and Brugada syndrome, thus creating the first described arrhythmic 'overlap syndrome' [58]. Interestingly, 1795insD is supposed to be a gain-of-function mutation in light of the QT prolongation, but a loss-of-function mutation in light of the sinus bradycardia, progressive cardiac conduction disease, and Brugada syndrome Additionally , and multifocal ectopic premature Purkinje-related complexes; loss-of-function mutations in SCN5A result in amplitude reduction in peak Na+ current, further leading to channel protein dysfunction. i or cardiac conduction defect an entity with minor structural heart disease. In addition, both loss- and gain-of-function mutations may cause dilated cardiomyopathy and/or atrial fibrillation. [59]. On ECG PR interval prolongation is the only parameter that predicted the presence of a SCN5A mutation in BrS, additionally, late potentials on high resolution ECG LP were more frequently observed in SCN5A mutation carriers [60]. SCN5A mutation is associated with an increased risk of drug-induced ventricular arrhythmia in patients without baseline type-1 ECG. In particular, Snon-missense and Smissense-TP are at high risk [61].

II. BrS-2 [62]: Locus: 12p13.3; OMIM: 911778; Gene: GPDIL; Ion channel and effect: INa+ loss-of-function; Protein: Glycerol-3phosphate dehydrogenase like peptide-reduced GPD1-L activity leads to phosphorylation of Nav1.5 and decreased INa+; % probands: Rare. Defects in this gene are also a cause of sudden infant death syndrome (SIDS). SIDS is the SCD of an infant younger than 1 year that remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of clinical history.

III. BrS-3 [63]: Locus: 12p13.3; OMIM: 114205; Gene: CACNA1C, Cav1.2; Ion channel and effect: ICa loss-of-function; Protein: e: Cav1.2- a-subunit of the voltage-gated calcium channel carrying the L-type calcium current ICa(L); % probands: 6.6%. Chromosomal location: 12p13.33, which is the short (p) arm of chromosome 12 at position 13.33. Shared with Timothy syndrome. SN5A and CACNA1C: complex BrS [64].

IV. BrS-4 [63]: Locus: 10p12.33; OMIM: 600003; Gene: CACNB2b, Cavβ2b; Ion channel and effect: ICa loss-of-function; Protein: Cavβ2B- β-2 subunit of the voltage-gated calcium channel carrying the L-type calcium current ICaL.(LTCC) regulates calcium entry into cardiomyocytes. CACNB2 (β2) LTCC auxiliary subunits traffic the pore-forming CACNA subunit to the membrane and modulate channel kinetics. β2 is a membrane associated guanylate kinase (MAGUK) protein. A major role of MAGUK proteins is to scaffold cellular junctions and multiprotein complexes. β2.1 may also function in the heart as a

MAGUK scaffolding unit to maintain N-cadherin-based adherens junctions and heart tube integrity [65]; % probands: 4.8%.

V. BrS-5 [66]: Locus: 19q13,1; OMIM: 600235; Gene: SCN1B, Naβ1; Ion channel and effect: INa+ loss-of-function; Protein: Nav β 1- β 1 subunit of the sodium channel carrying the sodium current: INa+; % probands: 1.1%. Loss-of-function mutations in the β-subunits (encoded by C) have also been described for AF [67]. # 612838 A number sign (#) is used with this entry because of evidence that BrS-5 and a nonspecific cardiac conduction defect are caused by heterozygous mutation in the SCN1B gene on chromosome 19q13,1.

VI. BrS-6. [68]: Locus: 11q13-14; OMIM: 604433; Gene: KCNE3, MiRP2; Ion channel and affect: Ito gain-of-function; Protein: MiRP2- β subunit to voltage potassium channels. Modulates the transient outward potassium current Ito; % probands: Rare. # 613119 A number sign (#) is used with this entry because of evidence that BrS-6 is caused by heterozygous mutation in the KCNE3 gene on chromosome 11q13.

VII. BrS7 [69]: Locus: 11q23.3; OMIM: 6081214; Gene: SCN3B; Ion channel and affected: INa+ loss-of-function; Note: Navb-3 subunit of the cardiac sodium channel carrying the sodium current INa+; % probands: Rare. # 613120 A number sign (#) is used with this entry because of evidence that BrS-7and AF-16 (18, 19) are caused by heterozygous mutation in the SCN3B gene on chromosome 11q24. BrS8: Locus: 12q11.23; OMIM: 600935; Gene: KCNJ8, Kir6.1; Ion channel and effect: Ik-ATP gain-of-function; Protein: Kir6., carries the inward rectifier potassium current Ikr; % probands: 2%. # 613123A number sign (#) is used with this entry because of evidence that BrS-8 is caused by heterozygous mutation in the HCN4 gene on chromosome 15q24 [70].

VIII. BrS-8 is caused by heterozygous mutation in the HCN4 gene on chromosome 15q24 [70]. Locus: 12q11.23; OMIM: 600935; Gene: KCNJ8, Kir6.1; Ion channel and effect: Ik-ATP gain-of-function; Protein: Kir6., carries the inward rectifier potassium current Ikr; % probands: 2%. # 613123A number sign (#) is used with this entry because of evidence that BrS-8 is caused by heterozygous mutation in the HCN4 gene on chromosome [70].

IX. BrS9: Locus: 7q21.11; OMIM: 114204; Gene: CACNA2D1, Ca, α2δ; Ion channel and effect: ICa loss-of-function; Protein: α2δ subunit of the voltage-gated calcium channel carrying the L-type calcium current ICa(L); % probands: 1.8%. Rare.# 616399 A number sign (#) is used with this entry because of evidence that BrS-9 is caused by heterozygous mutation in the KCND3 gene on chromosome 1p13 [71].

X. BrS10: Locus:1p13.2; OMIM:605411; Gene: KCND3, Kv4.3; Ion channel and effect: Ito gain-of-function; Protein: Kv4.3, a-subunit of the transient outward potassium channel Ito; % probands: Rare. The prominent role of the Ito in BrS pathogenesis, the rare gain-of-function mutations in KCND3 serve as a pathogenic substrate for BrS. Giudicessi et al provided the first molecular and functional evidence implicating novel KCND3 gain-of-function mutations in the pathogenesis and phenotypic expression of BrS, with the potential for a lethal arrhythmia being precipitated by a genetically enhanced I(to) current gradient within the right ventricle where KCND3 expression is the highest [71].

XI. BrS11 [72]: Locus: 17p13.1; OMIM: 607954; Gene: RANGRF; Ion channel and effect: INa+ loss-of-function; Protein: Encodes MOG1 – influences trafficking of Nav 1.5. The protein MOG1 is a cofactor of the cardiac sodium channel, Nav1.5. Overexpression of MOG1 in Nav1.5-expressing cells increases sodium current markedly. Mutations in the genes encoding Nav1.5 and its accessory proteins have been associated with cardiac arrhythmias of significant clinical impact; % Probands: Rare [73]. Olesen et al. screening of Nav1.5 cofactor MOG1 uncovered a novel nonsense variant that appeared to be present at a higher frequency among patients than in control subjects.

XII. BrS12 [74]: Locus: 3p21.2-2-p14.3; OMIM: 602701; Gene: SLMAP; Ion channel and effect: INa+ loss-of-function; Protein: Sarcolemma membrane-associated protein, a component of T-tubes and the sarcoplasmic reticulum – influences trafficking of Nav1.5; % Probands: Rare. T-tubules and sarcoplasmic reticulum are essential in excitation of cardiomyocytes, and sarcolemmal membrane-associated protein (SLMAP) is a protein of unknown function localizing at T-tubules and sarcoplasmic reticulum. The mutations in SLMAP may cause BrS via modulating the intracellular trafficking of hNav1.5 channel.

XIII. BrS13: Locus [75]: 12p12.1; OMIM: 601439; Gene: ABCC9 SUR2A; Ion channel and effect: Ik(ATP) gain-of-function; Protein: SUR2A, the adenosine triphosphate (ATP) binding cassette transporter of the Ik(ATP) channel.; % Probands: Rare. The ABCC9 is an ion channels/ion channel-related AF. Adenosine triphosphate (ATP)-sensitive potassium cardiac channels consist of inward-rectifying channel subunits Kir6.1 or Kir6.2 (encoded by KCNJ8 or KCNJ11) and the sulfonylurea receptor subunits SUR2A (encoded by ABCC9). KCNJ8 is a susceptibility gene for BrS and early repolarization syndrome (ERS and point to S422L as a possible hotspot mutation. The S422L-induced gain of function in ATP-sensitive potassium channel current is due to reduced sensitivity to intracellular ATP. ABCC9 has ERS and BrS susceptibility genes. A gain-of-function in IK-ATP when coupled with a loss-of-function in SCN5A may underlie type 3 ERS, which is associated with a severe arrhythmic phenotype [76].

XIV. BrS14 [77]: Locus: 11q23; OMIM: 601327; Gene: SCN2B, Navβ2; Ion channel and effect: INa+ loss-of-function; Protein: Navβ2-β -2subunit of the cardiac sodium channel carrying the sodium current INa; % Probands: Rare. Riuró et al. identified a novel missense mutation in the sodium β2 subunit encoded by SCN2B, in a woman diagnosed with BrS. They studied the sodium current from cells coexpressing Nav 1.5 and wild-type (β2WT) or mutant (β2D211G) β2 subunits. Electrophysiological analysis showed a reduction in INa density when Nav 1.5 was coexpressed with β2D211G. Single channel analysis showed that the mutation did not affect the Nav 1.5 unitary channel conductance. Instead, protein membrane detection experiments suggested that β2D211G decreases Nav 1.5 cell surface expression. The effect of the mutant β2 subunit on the INa strongly suggests that SCN2B is a candidate gene associated with BrS.

XV. BrS15: Locus: 12p11; OMIM: 602861; Gene: PKP2, Plakophillin-2; Ion channel and effect: INa+ loss-of-function; Protein: Plakophillin-2 – interacts with INa+; % probands: Rare. Plakophilin-2 (PKP2) variants could produce a BrS phenotype, which is the same allelic disorder as some sudden unexplained nocturnal death syndromes (SUNDS). All coding regions of PKP2 gene in 119 SUNDS victims were genetically screened using PCR and direct Sanger sequencing methods. Three novel mutations (p.Ala159Thr, p.Val200Val, and p.Gly265Glu), one novel rare polymorphism (p.Thr723Thr), and 8 polymorphisms were identified. A compound mutation (p.Ala159Thr and p.Gly265Glu) and a rare polymorphism (p.Thr723Thr) were found in one SUNDS case with absence of the apparent structural heart disease. The detected compound mutation identified in this first investigation of PKP2 genetic phenotype in SUNDS is regarded as the plausible genetic cause of this SUNDS case. The rare incidence of PKP2 mutation in SUNDS (1%) supports the previous viewpoint that SUNDS is most likely an allelic disorder as BrS [78]. Mutations in proteins of the desmosome are associated with arrhythmogenic cardiomyopathy (AC). Life-threatening ventricular arrhythmias (VAs) often occur in the concealed forms/phase of the AC before the onset of structural changes. Evidence indicating that loss of desmosomal integrity (including mutations or loss of expression of plakophilin-2; PKP2) leads to reduced sodium current, the PKP2-INa relation could be partly consequent to the fact that PKP2 facilitates proper trafficking of proteins to the intercalated disc, and, PKP2 mutations can be present in XV patients diagnosed with BrS, thus supporting the previously proposed notion that AC and BrS are not two completely separate entities [79]. Mutations on PKP2 account for the majority of AC cases, a disease characterized by high incidence of VAs and a progressive cardiomyopathy with fibrofatty infiltration involving predominantly the right ventricle. Although BrS was initially described as a purely electric condition in intact hearts, it is now

recognized that structural changes occur mainly at the right ventricular outflow tract (RVOT) [80]. These findings support the hypothesis, suggested in the past by some clinicians, that the two conditions could be at the bookends of a phenotypical common spectrum. PKP2 is a structural protein of the desmosome whose principal role is to maintain tissue integrity and cell-to-cell stability. However, data from cellular and mouse models demonstrated that loss of PKP2 could facilitate arrhythmias by decreasing sodium current [81], thus through an electrophysiological effect. Indeed, in vitro characterization of the PKP2 mutations detected in patients with a BrS phenotype showed a decreased sodium current, consistent with the clinical phenotype. Super-resolution microscopy data showed that loss of PKP2 could affect proper trafficking of the sodium channel at the membrane, thus supporting the concept that proteins could have accessory roles aside from the primary one ascribed to them. The role of the cardiac intercalated disc as a functional unit with both structural and electric regulatory functions has been opening new paths of investigations on the possible arrhythmogenic substrate in BrS [82].

XVI. BrS-16: Locus: 3q28; OMIM: 601513; Gene: FGF12, FHAF1; Ion channel and effect: INa+ loss-of-function; Protein: Fibroblast growth factor homologues factor-1- mutation decreases INa+; Cytogenetic location: 3q28-q29; % Probands: Rare. Multilevel investigations strongly suggest that Q7R-FGF12 is a disease-associated BrS mutation. FHF effects on Na(+) and Ca(2+) channels are separable. Most significantly, the Hennessey study establishes a new method to analyze effects of human arrhythmogenic mutations on cardiac ionic currents. On the basis of the recent demonstration that FGF homologous factors (FHFs; FGF11-FGF14) regulate cardiac Na(+) and Ca(2+) channel currents, FHFs are candidate BrS loci [83]. Mutation FGF12 also causes neonatal-onset epilepsy.

XVII. BrS-17 [84] Locus: 3p22.22; OMIM: 604427; Gene: SCN10A, Nav1.8; Ion channel and effect: INa+ loss-of-function; Protein: Nav1.8-αsubunit of the neural sodium channel.; % Probands: 16.7%. Hu et al identified SCN10A as a major susceptibility gene for BrS, thus greatly enhancing our ability to genotype and risk stratify probands and family members. The SCN10A SNP V1073 is strongly associated with BrS. Rare variants in the screened QRS-associated genes (including SCN10A) are not responsible for a significant proportion of SCN5A mutation negative BrS. The common SNP SCN10A V1073 was strongly associated with BrS and demonstrated loss of NaV1.8 function, as did rare variants in isolated patients [85]. The expression of sodium channel Nav1.8 in cardiac nervous systems has been identified, and variants of SCN10A that encodes Nav1.8 contribute to the development of BrS by modifying the function of Nav1.5 or directly reducing the Na+ current. Fukuyama et al screened for the

SCN10A gene using a high-resolution melting method and direct sequencing. and compared the clinical characteristics among the probands with gene mutations in SCN10A, 6 probands with CACNA1C and 17 probands with SCN5A. They identified six SCN10A variant carriers (2.5%): W189R, R844H (in two unrelated probands), N1328K, R1380Q, and R1863Q. Five were male. Four were symptomatic: one died following SCD age 35, one suffered ventricular fibrillation, and two had recurrent syncope. Compared with BrS patients carrying SCN5A or CACNA1C mutations, although there were no significant differences among them, symptomatic patients in the SCN10A group tended to be older than those in the other gene groups [86].

XVIII.BrS-18 [87]: Locus: 6q; OMIM: 604674; Gene: HEY2 (transcriptional factor); Ion channel and effect: INa+ loss-of-function; Protein: Transcription factor identified in GWAS; % Probands: Rare. The association signals at SCN5A-SCN10A demonstrate that genetic polymorphisms modulating cardiac conduction can also influence susceptibility to cardiac arrhythmia. The implication of association with HEY2, supported by new evidence that Hey2 regulates cardiac electrical activity, shows that BrS may originate from altered transcriptional programming during cardiac development.

XIX.BrS-19 [88] Locus: 7p12.1; OMIM: 603961; Gene: SEMA3A, Semaphoring; Ion channel and effect: Ito gain-of-function; Protein: NaV1.5 - α subunit of the cardiac sodium channel carrying the sodium current INa; % of Probands: Rare. Boczek et al were the first to demonstrate SEMA3A as a naturally occurring protein that selectively inhibits Kv4.3 and SEMA3A as a possible BrS susceptibility gene through a Kv4.3 Ito gain-of-function mechanism

Some mutations associated with BrS can also cause other heart conditions. Those who show more than one cardiac condition at the same time caused by a single mutation are described as having an overlap syndrome [89].

REFERENCES

1. Bayes de Luna A, Brugada J, Baranchuk A*, et al.* Current electrocardiographic criteria for diagnosis of Brugada pattern: a consensus report. J Electrocardiol. 2012;45:433-442.
2. Peritz DC, Chung EH. Criteria for evaluating rSr' patterns due to high precordial ECG lead placement accurately confirm absence of a Brugada ECG pattern. J Electrocardiol. 2016;49:182-186.
3. Ohkubo K, Watanabe I, Okumura Y*, et al.* A new criteria differentiating type 2 and 3 Brugada patterns from ordinary incomplete right bundle branch block. Int Heart J. 2011;52:159-163.

4. Chevallier S, Forclaz A, Tenkorang J*, et al.* New electrocardiographic criteria for discriminating between Brugada types 2 and 3 patterns and incomplete right bundle branch block. J Am Coll Cardiol. 2011;58:2290-2298.
5. Serra G, Baranchuk A, Bayes-De-Luna A*, et al.* New electrocardiographic criteria to differentiate the Type-2 Brugada pattern from electrocardiogram of healthy athletes with r'-wave in leads V1/V2. Europace. 2014;16:1639-1645.
6. Serra G, Baranchuk A, Bayes-De-Luna A*, et al.* Base of the triangle to determine a Brugada electrocardiogram pattern. Europace. 2015;17:505.
7. Crea P, Rivetti L, Bitto R*, et al.* Diagnosis of type 2 Brugada pattern: insights from a pilot survey. Minerva Cardioangiol. 2020.
8. Sciarra L, Moriya M, Robles AG*, et al.* Type 2 Brugada pattern: more doubts than certainties. Minerva Cardioangiol. 2020.
9. Priori SG, Wilde AA, Horie M*, et al.* Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Europace. 2013;15:1389-1406.
10. Calo L, Giustetto C, Martino A*, et al.* A New Electrocardiographic Marker of Sudden Death in Brugada Syndrome: The S-Wave in Lead I. J Am Coll Cardiol. 2016;67:1427-1440.
11. Babai Bigi MA, Aslani A, Shahrzad S. aVR sign as a risk factor for life-threatening arrhythmic events in patients with Brugada syndrome. Heart Rhythm. 2007;4:1009-1012.
12. Rattanawong P, Riangwiwat T, Prasitlumkum N*, et al.* Baseline fragmented QRS increases the risk of major arrhythmic events in Brugada syndrome: Systematic review and meta-analysis. Ann Noninvasive Electrocardiol. 2018;23:e12507.
13. Kataoka N, Mizumaki K, Nakatani Y*, et al.* Paced QRS fragmentation is associated with spontaneous ventricular fibrillation in patients with Brugada syndrome. Heart Rhythm. 2016;13:1497-1503.
14. Francis J, Antzelevitch C. Atrial fibrillation and Brugada syndrome. J Am Coll Cardiol. 2008;51:1149-1153.
15. Migliore F, Testolina M, Zorzi A*, et al.* First-degree atrioventricular block on basal electrocardiogram predicts future arrhythmic events in patients with Brugada syndrome: a long-term follow-up study from the Veneto region of Northeastern Italy. Europace. 2019;21:322-331.
16. Pranata R, Yonas E, Chintya V*, et al.* Association between PR Interval, First-degree atrioventricular block and major arrhythmic events in patients with Brugada syndrome - Systematic review and meta-analysis. J Arrhythm. 2019;35:584-590.
17. Aro AL. First-degree atrioventricular block: risk marker or innocent finding? Heart. 2016;102:655-656.
18. Kamakura T, Sacher F, Katayama K*, et al.* High-risk atrioventricular block in Brugada syndrome patients with a history of syncope. J Cardiovasc Electrophysiol. 2021;32:772-781.
19. Ragab AAY, Houck CA, van der Does L*, et al.* Usefulness of the R-Wave Sign as a Predictor for Ventricular Tachyarrhythmia in Patients With Brugada Syndrome. Am J Cardiol. 2017;120:428-434.

20. Pérez-Riera AR, Yanowitz F, Barbosa-Barros R, *et al.* Electrocardiographic "Northwest QRS Axis" in the Brugada Syndrome: A Potential Marker to Predict Poor Outcome. J Am Coll Cardiol Case Rep. 2020 2:2230-2234.
21. Miyamoto A, Hayashi H, Makiyama T, *et al.* Risk determinants in individuals with a spontaneous type 1 Brugada ECG. Circ J. 2011;75:844-851.
22. Take Y, Morita H, Wu J, *et al.* Spontaneous electrocardiogram alterations predict ventricular fibrillation in Brugada syndrome. Heart Rhythm. 2011;8:1014-1021.
23. Kawata H, Morita H, Yamada Y, *et al.* Prognostic significance of early repolarization in inferolateral leads in Brugada patients with documented ventricular fibrillation: a novel risk factor for Brugada syndrome with ventricular fibrillation. Heart Rhythm. 2013;10:1161-1168.
24. Takagi M, Aonuma K, Sekiguchi Y, *et al.* 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;10:533-539.
25. Conte G, de Asmundis C, Sieira J, *et al.* Prevalence and Clinical Impact of Early Repolarization Pattern and QRS-Fragmentation in High-Risk Patients With Brugada Syndrome. Circ J. 2016;80:2109-2116.
26. Tokioka K, Kusano KF, Morita H, *et al.* Electrocardiographic parameters and fatal arrhythmic events in patients with Brugada syndrome: combination of depolarization and repolarization abnormalities. J Am Coll Cardiol. 2014;63:2131-2138.
27. Junttila MJ, Brugada P, Hong K, *et al.* Differences in 12-lead electrocardiogram between symptomatic and asymptomatic Brugada syndrome patients. J Cardiovasc Electrophysiol. 2008;19:380-383.
28. Ohkubo K, Watanabe I, Okumura Y, *et al.* Prolonged QRS duration in lead V2 and risk of life-threatening ventricular Arrhythmia in patients with Brugada syndrome. Int Heart J. 2011;52:98-102.
29. Nagase S, Kamakura T, Kataoka N, *et al.* Low-Voltage Type 1 ECG Is Associated With Fatal Ventricular Tachyarrhythmia in Brugada Syndrome. J Am Heart Assoc. 2018;7:e009713.
30. Pitzalis MV, Anaclerio M, Iacoviello M, *et al.* QT-interval prolongation in right precordial leads: an additional electrocardiographic hallmark of Brugada syndrome. J Am Coll Cardiol. 2003;42:1632-1637.
31. Castro Hevia J, Antzelevitch C, Tornes Barzaga F, *et al.* Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol. 2006;47:1828-1834.
32. Naseef A, Behr ER, Batchvarov VN. Electrocardiographic methods for diagnosis and risk stratification in the Brugada syndrome. J Saudi Heart Assoc. 2015;27:96-108.
33. Makimoto H, Nakagawa E, Takaki H, *et al.* Augmented ST-segment elevation during recovery from exercise predicts cardiac events in patients with Brugada syndrome. J Am Coll Cardiol. 2010;56:1576-1584.
34. Yoshioka K, Amino M, Zareba W, *et al.* Identification of high-risk Brugada syndrome patients by combined analysis of late potential and T-wave amplitude variability on ambulatory electrocardiograms. Circ J. 2013;77:610-618.
35. Garcia-Fuertes D, Villanueva-Fernandez E, Crespin-Crespin M, *et al.* Type 1 Brugada Pattern Unmasked During the Recovery Period of an Exercise Stress Test. Arq Bras Cardiol. 2016;106:447-449.

36. Morita H, Fukushima-Kusano K, Nagase S*, et al.* Sinus node function in patients with Brugada-type ECG. Circ J. 2004;68:473-476.
37. Batchvarov VN, Govindan M, Camm AJ*, et al.* Brugada-like changes in the peripheral leads during diagnostic ajmaline test in patients with suspected Brugada syndrome. Pacing Clin Electrophysiol. 2009;32:695-703.
38. Bonakdar H, Haghjoo M, Sadr-Ameli MA. Brugada syndrome manifested by the typical electrocardiographic pattern both in the right precordial and the high lateral leads. Indian Pacing Electrophysiol J. 2008;8:137-140.
39. Chinushi M, Izumi D, Furushima H*, et al.* Multiple premature beats triggered ventricular arrhythmias during pilsicainide infusion in a patient with inferior ST-segment elevation. Pacing Clin Electrophysiol. 2006;29:1445-1448.
40. Kalla H, Yan GX, Marinchak R. Ventricular fibrillation in a patient with prominent J (Osborn) waves and ST segment elevation in the inferior electrocardiographic leads: a Brugada syndrome variant? J Cardiovasc Electrophysiol. 2000;11:95-98.
41. Rollin A, Sacher F, Gourraud JB*, et al.* Prevalence, characteristics, and prognosis role of type 1 ST elevation in the peripheral ECG leads in patients with Brugada syndrome. Heart Rhythm. 2013;10:1012-1018.
42. Takagi M, Aihara N, Takaki H*, et al.* Clinical characteristics of patients with spontaneous or inducible ventricular fibrillation without apparent heart disease presenting with J wave and ST segment elevation in inferior leads. J Cardiovasc Electrophysiol. 2000;11:844-848.
43. van den Berg MP, Wiesfeld AC. Brugada syndrome with ST-segment elevation in the lateral leads. J Cardiovasc Electrophysiol. 2006;17:1035.
44. Honarbakhsh S, Providencia R, Garcia-Hernandez J*, et al.* A Primary Prevention Clinical Risk Score Model for Patients With Brugada Syndrome (BRUGADA-RISK). JACC Clin Electrophysiol. 2021;7:210-222.
45. Deliniere A, Baranchuk A, Giai J*, et al.* Prediction of ventricular arrhythmias in patients with a spontaneous Brugada type 1 pattern: the key is in the electrocardiogram. Europace. 2019;21:1400-1409.
46. Pablo Florez J, Garcia D, Valverde I*, et al.* Role of syncope in predicting adverse outcomes in patients with suspected Brugada syndrome undergoing standardized flecainide testing. Europace. 2018;20:f64-f71.
47. Letsas KP, Efremidis M, Gavrielatos G*, et al.* Neurally mediated susceptibility in individuals with Brugada-type ECG pattern. Pacing Clin Electrophysiol. 2008;31:418-421.
48. Garcia Iglesias D, Roqueni Gutierrez N, De Cos FJ*, et al.* Analysis of the High-Frequency Content in Human QRS Complexes by the Continuous Wavelet Transform: An Automatized Analysis for the Prediction of Sudden Cardiac Death. Sensors (Basel). 2018;18.
49. Garcia-Iglesias D, de Cos FJ, Romero FJ*, et al.* Spectral Analysis of the QT Interval Increases the Prediction Accuracy of Clinical Variables in Brugada Syndrome. J Clin Med. 2019;8.
50. Gehi AK, Duong TD, Metz LD*, et al.* Risk stratification of individuals with the Brugada electrocardiogram: a meta-analysis. J Cardiovasc Electrophysiol. 2006;17:577-583.

51. Paul M, Gerss J, Schulze-Bahr E*, et al.* Role of programmed ventricular stimulation in patients with Brugada syndrome: a meta-analysis of worldwide published data. Eur Heart J. 2007;28:2126-2133.
52. Priori SG, Gasparini M, Napolitano C*, et al.* Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol. 2012;59:37-45.
53. Shinohara T, Takagi M, Kamakura T*, et al.* Risk stratification in asymptomatic patients with Brugada syndrome: Utility of multiple risk factor combination rather than programmed electrical stimulation. J Cardiovasc Electrophysiol. 2021;32:507-514.
54. Chen Q, Kirsch GE, Zhang D*, et al.* Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature. 1998;392:293-296.
55. Amin AS, Boink GJ, Atrafi F*, et al.* Facilitatory and inhibitory effects of SCN5A mutations on atrial fibrillation in Brugada syndrome. Europace. 2011;13:968-975.
56. Han D, Tan H, Sun C*, et al.* Dysfunctional Nav1.5 channels due to SCN5A mutations. Exp Biol Med (Maywood). 2018;243:852-863.
57. Bezzina C, Veldkamp MW, van Den Berg MP*, et al.* A single Na(+) channel mutation causing both long-QT and Brugada syndromes. Circ Res. 1999;85:1206-1213.
58. Remme CA, Wilde AA, Bezzina CR. Cardiac sodium channel overlap syndromes: different faces of SCN5A mutations. Trends Cardiovasc Med. 2008;18:78-87.
59. Wilde AAM, Amin AS. Clinical Spectrum of SCN5A Mutations: Long QT Syndrome, Brugada Syndrome, and Cardiomyopathy. JACC Clin Electrophysiol. 2018;4:569-579.
60. Robyns T, Nuyens D, Vandenberk B*, et al.* Genotype-phenotype relationship and risk stratification in loss-of-function SCN5A mutation carriers. Ann Noninvasive Electrocardiol. 2018;23:e12548.
61. Amin AS, Reckman YJ, Arbelo E*, et al.* SCN5A mutation type and topology are associated with the risk of ventricular arrhythmia by sodium channel blockers. Int J Cardiol. 2018;266:128-132.
62. London B, Michalec M, Mehdi H*, et al.* Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias. Circulation. 2007;116:2260-2268.
63. Antzelevitch C, Pollevick GD, Cordeiro JM*, et al.* Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation. 2007;115:442-449.
64. Beziau DM, Barc J, O'Hara T*, et al.* Complex Brugada syndrome inheritance in a family harbouring compound SCN5A and CACNA1C mutations. Basic Res Cardiol. 2014;109:446.
65. Chernyavskaya Y, Ebert AM, Milligan E*, et al.* Voltage-gated calcium channel CACNB2 (beta2.1) protein is required in the heart for control of cell proliferation and heart tube integrity. Dev Dyn. 2012;241:648-662.
66. Tada T, Kusano KF, Nagase S*, et al.* Clinical significance of macroscopic T-wave alternans after sodium channel blocker administration in patients with Brugada syndrome. J Cardiovasc Electrophysiol. 2008;19:56-61.

67. Watanabe H, Darbar D, Kaiser DW*, et al.* Mutations in sodium channel beta1- and beta2-subunits associated with atrial fibrillation. Circ Arrhythm Electrophysiol. 2009;2:268-275.
68. Delpon E, Cordeiro JM, Nunez L*, et al.* Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome. Circ Arrhythm Electrophysiol. 2008;1:209-218.
69. Hu D, Barajas-Martinez H, Burashnikov E*, et al.* A mutation in the beta 3 subunit of the cardiac sodium channel associated with Brugada ECG phenotype. Circ Cardiovasc Genet. 2009;2:270-278.
70. Ueda K, Hirano Y, Higashiuesato Y*, et al.* Role of HCN4 channel in preventing ventricular arrhythmia. J Hum Genet. 2009;54:115-121.
71. Giudicessi JR, Ye D, Tester DJ*, et al.* Transient outward current (I(to)) gain-of-function mutations in the KCND3-encoded Kv4.3 potassium channel and Brugada syndrome. Heart Rhythm. 2011;8:1024-1032.
72. Olesen MS, Jensen NF, Holst AG*, et al.* A novel nonsense variant in Nav1.5 cofactor MOG1 eliminates its sodium current increasing effect and may increase the risk of arrhythmias. Can J Cardiol. 2011;27:523 e517-523.
73. Campuzano O, Berne P, Selga E*, et al.* Brugada syndrome and p.E61X_RANGRF. Cardiol J. 2014;21:121-127.
74. Ishikawa T, Sato A, Marcou CA*, et al.* A novel disease gene for Brugada syndrome: sarcolemmal membrane-associated protein gene mutations impair intracellular trafficking of hNav1.5. Circ Arrhythm Electrophysiol. 2012;5:1098-1107.
75. Barajas-Martinez H, Hu D, Ferrer T*, et al.* Molecular genetic and functional association of Brugada and early repolarization syndromes with S422L missense mutation in KCNJ8. Heart Rhythm. 2012;9:548-555.
76. Hu D, Barajas-Martinez H, Terzic A*, et al.* ABCC9 is a novel Brugada and early repolarization syndrome susceptibility gene. Int J Cardiol. 2014;171:431-442.
77. Riuro H, Beltran-Alvarez P, Tarradas A*, et al.* A missense mutation in the sodium channel beta2 subunit reveals SCN2B as a new candidate gene for Brugada syndrome. Hum Mutat. 2013;34:961-966.
78. Huang L, Tang S, Peng L*, et al.* Molecular Autopsy of Desmosomal Protein Plakophilin-2 in Sudden Unexplained Nocturnal Death Syndrome. J Forensic Sci. 2016;61:687-691.
79. Cerrone M, Delmar M. Desmosomes and the sodium channel complex: implications for arrhythmogenic cardiomyopathy and Brugada syndrome. Trends Cardiovasc Med. 2014;24:184-190.
80. Papavassiliu T, Wolpert C, Fluchter S*, et al.* Magnetic resonance imaging findings in patients with Brugada syndrome. J Cardiovasc Electrophysiol. 2004;15:1133-1138.
81. Cerrone M, Noorman M, Lin X*, et al.* Sodium current deficit and arrhythmogenesis in a murine model of plakophilin-2 haploinsufficiency. Cardiovasc Res. 2012;95:460-468.
82. Nademanee K, Raju H, de Noronha SV*, et al.* Fibrosis, Connexin-43, and Conduction Abnormalities in the Brugada Syndrome. J Am Coll Cardiol. 2015;66:1976-1986.

83. Hennessey JA, Marcou CA, Wang C*, et al.* FGF12 is a candidate Brugada syndrome locus. Heart Rhythm. 2013;10:1886-1894.
84. Hu D, Barajas-Martinez H, Pfeiffer R*, et al.* Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. J Am Coll Cardiol. 2014;64:66-79.
85. Behr ER, Savio-Galimberti E, Barc J*, et al.* Role of common and rare variants in SCN10A: results from the Brugada syndrome QRS locus gene discovery collaborative study. Cardiovasc Res. 2015;106:520-529.
86. Raatikainen MJ, Arnar DO, Merkely B*, et al.* Access to and clinical use of cardiac implantable electronic devices and interventional electrophysiological procedures in the European Society of Cardiology Countries: 2016 Report from the European Heart Rhythm Association. Europace. 2016;18 Suppl 3:iii1-iii79.
87. Bezzina CR, Barc J, Mizusawa Y*, 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;45:1044-1049.
88. Boczek NJ, Ye D, Johnson EK*, et al.* Characterization of SEMA3A-encoded semaphorin as a naturally occurring Kv4.3 protein inhibitor and its contribution to Brugada syndrome. Circ Res. 2014;115:460-469.
89. Antzelevitch C. Brugada syndrome: clinical, genetic, molecular, cellular and ionic aspects. Expert Rev Cardiovasc Ther. 2003;1:177-185.
90. Wilde AA, Antzelevitch C, Borggrefe M*, et al.* Proposed diagnostic criteria for the Brugada syndrome. Eur Heart J. 2002;23:1648-1654.
91. Wilde AA, Antzelevitch C, Borggrefe M*, et al.* Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation. 2002;106:2514-2519.
92. Riera AR, Ferreira C, Schapachnik E*, et al.* Brugada syndrome with atypical ECG: downsloping ST-segment elevation in inferior leads. J Electrocardiol. 2004;37:101-104.
93. Kukla P, Jastrzebski M, Bacior B*, et al.* [Variant Brugada syndrome--mild ST segment elevation in inferior leads and aborted sudden cardiac death]. Kardiol Pol. 2007;65:1494-1498.
94. Pastore CA, Moffa PJ, Spiritus MO*, et al.* [Fascicular blocks of the right branch. Standardization of vectorelectrocardiographic findings]. Arq Bras Cardiol. 1983;41:161-166.
95. Luna Filho B, Bocanegra JA, Pfeferman A*, et al.* [Fascicular block of the His bundle: critical approach for its identification]. Arq Bras Cardiol. 1989;53:261-265.
96. Butz T, Vogt J, Vielhauer C*, et al.* Detection of a type 1 Brugada ECG by ECG recording at a higher intercostal space of leads V(1) and V (2). Herz. 2010;35:112.
97. Casini S, Tan HL, Bhuiyan ZA*, et al.* Characterization of a novel SCN5A mutation associated with Brugada syndrome reveals involvement of DIIIS4-S5 linker in slow inactivation. Cardiovasc Res. 2007;76:418-429.
98. Veldkamp MW, Viswanathan PC, Bezzina C*, et al.* Two distinct congenital arrhythmias evoked by a multidysfunctional Na(+) channel. Circ Res. 2000;86:E91-97.
99. Morita H, Zipes DP, Morita ST*, et al.* Temperature modulation of ventricular arrhythmogenicity in a canine tissue model of Brugada syndrome. Heart Rhythm. 2007;4:188-197.

100. Morita H, Zipes DP, Morita ST, *et al.* Differences in arrhythmogenicity between the canine right ventricular outflow tract and anteroinferior right ventricle in a model of Brugada syndrome. Heart Rhythm. 2007;4:66-74.
101. Letsas KP, Weber R, Astheimer K, *et al.* Predictors of atrial tachyarrhythmias in subjects with type 1 ECG pattern of Brugada syndrome. Pacing Clin Electrophysiol. 2009;32:500-505.
102. Kamakura S, Ohe T, Nakazawa K, *et al.* Long-term prognosis of probands with Brugada-pattern ST-elevation in leads V1-V3. Circ Arrhythm Electrophysiol. 2009;2:495-503.
103. Junttila MJ, Gonzalez M, Lizotte E, *et al.* Induced Brugada-type electrocardiogram, a sign for imminent malignant arrhythmias. Circulation. 2008;117:1890-1893.
104. Sangawa M, Morita H, Nakatsu T, *et al.* Abnormal transmural repolarization process in patients with Brugada syndrome. Heart Rhythm. 2009;6:1163-1169.
105. Kusano KF, Taniyama M, Nakamura K, *et al.* Atrial fibrillation in patients with Brugada syndrome relationships of gene mutation, electrophysiology, and clinical backgrounds. J Am Coll Cardiol. 2008;51:1169-1175.
106. Ikeda T, Sakurada H, Sakabe K, *et al.* Assessment of noninvasive markers in identifying patients at risk in the Brugada syndrome: insight into risk stratification. J Am Coll Cardiol. 2001;37:1628-1634.
107. Doi A, Takagi M, Maeda K, *et al.* Conduction delay in right ventricle as a marker for identifying high-risk patients with Brugada syndrome. J Cardiovasc Electrophysiol. 2010;21:688-696.
108. Coronel R, Casini S, Koopmann TT, *et al.* Right ventricular fibrosis and conduction delay in a patient with clinical signs of Brugada syndrome: a combined electrophysiological, genetic, histopathologic, and computational study. Circulation. 2005;112:2769-2777.
109. Hayashi H, Sumiyoshi M, Yasuda M, *et al.* Prevalence of the Brugada-type electrocardiogram and incidence of Brugada syndrome in patients with sick sinus syndrome. Circ J. 2010;74:271-277.
110. Morita H, Kusano KF, Miura D, *et al.* Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. Circulation. 2008;118:1697-1704.
111. Das MK, Zipes DP. Fragmented QRS: a predictor of mortality and sudden cardiac death. Heart Rhythm. 2009;6:S8-14.
112. Das MK, El Masry H. Fragmented QRS and other depolarization abnormalities as a predictor of mortality and sudden cardiac death. Curr Opin Cardiol. 2010;25:59-64.
113. Tigen K, Karaahmet T, Gurel E, *et al.* The utility of fragmented QRS complexes to predict significant intraventricular dyssynchrony in nonischemic dilated cardiomyopathy patients with a narrow QRS interval. Can J Cardiol. 2009;25:517-522.
114. Peters S, Trummel M, Koehler B. QRS fragmentation in standard ECG as a diagnostic marker of arrhythmogenic right ventricular dysplasia-cardiomyopathy. Heart Rhythm. 2008;5:1417-1421.
115. Homsi M, Alsayed L, Safadi B, *et al.* Fragmented QRS complexes on 12-lead ECG: a marker of cardiac sarcoidosis as detected by gadolinium cardiac magnetic resonance imaging. Ann Noninvasive Electrocardiol. 2009;14:319-326.

116. Moss AJ. Fragmented QRS: the new high-risk kid on the block in acquired long QT syndrome. Heart Rhythm. 2010;7:1815-1816.
117. Cheema A, Khalid A, Wimmer A*, et al.* Fragmented QRS and mortality risk in patients with left ventricular dysfunction. Circ Arrhythm Electrophysiol. 2010;3:339-344.
118. Yuce M, Davutoglu V, Ozbala B*, et al.* Fragmented QRS is predictive of myocardial dysfunction, pulmonary hypertension and severity in mitral stenosis. Tohoku J Exp Med. 2010;220:279-283.
119. McIntyre WF, Perez-Riera AR, Femenia F*, et al.* Coexisting early repolarization pattern and Brugada syndrome: recognition of potentially overlapping entities. J Electrocardiol. 2012;45:195-198.
120. Calvo D, Florez JP, Valverde I*, et al.* Surveillance after cardiac arrest in patients with Brugada syndrome without an implantable defibrillator: An alarm effect of the previous syncope. Int J Cardiol. 2016;218:69-74.
121. Nakagawa K, Nagase S, Morita H*, et al.* Left ventricular epicardial electrogram recordings in idiopathic ventricular fibrillation with inferior and lateral early repolarization. Heart Rhythm. 2014;11:314-317.
122. Bigi MA, Aslani A, Shahrzad S. Clinical predictors of atrial fibrillation in Brugada syndrome. Europace. 2007;9:947-950.
123. Nam GB, Kim YH, Antzelevitch C. Augmentation of J waves and electrical storms in patients with early repolarization. N Engl J Med. 2008;358:2078-2079.
124. Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. Circulation. 1996;93:372-379.
125. Antzelevitch C. Modulation of transmural repolarization. Ann N Y Acad Sci. 2005;1047:314-323.
126. Baranchuk A, Nguyen T, Ryu MH*, et al.* Brugada phenocopy: new terminology and proposed classification. Ann Noninvasive Electrocardiol. 2012;17:299-314.
127. Anselm DD, Evans JM, Baranchuk A. Brugada phenocopy: A new electrocardiogram phenomenon. World J Cardiol. 2014;6:81-86.
128. Anselm DD, Baranchuk A. Brugada Phenocopy in the context of pulmonary embolism. Int J Cardiol. 2013;168:560.
129. Anselm DD, Baranchuk A. Brugada phenocopy: redefinition and updated classification. Am J Cardiol. 2013;111:453.
130. Recasens L, Merono O, Ribas N. Hyperkalemia mimicking a pattern of Brugada syndrome. Rev Esp Cardiol (Engl Ed). 2013;66:309.
131. Dogan M, Ertem AG, Cimen T*, et al.* Type-1 Brugada-like ECG pattern induced by adrenal crisis. Herz. 2015;40:304-306.
132. Mok NS, Tong CK, Yuen HC. Concomitant-acquired Long QT and Brugada syndromes associated with indapamide-induced hypokalemia and hyponatremia. Pacing Clin Electrophysiol. 2008;31:772-775.
133. Nayyar S, Nair M. Brugada pattern in toxic myocarditis due to severe aluminum phosphide poisoning. Pacing Clin Electrophysiol. 2009;32:e16-17.
134. Kovacic JC, Kuchar DL. Brugada pattern electrocardiographic changes associated with profound electrolyte disturbance. Pacing Clin Electrophysiol. 2004;27:1020-1023.

135. Gazzoni GF, Borges AP, Bergoli LC, *et al.* Brugada-like electrocardiographic changes induced by hypokalemia. Arq Bras Cardiol. 2013;100:e35-37.
136. Kaneko Y, Nakajima T, Irie T, *et al.* Brugada-type ST-elevation associated with writhing of a reconstructed esophagus. Intern Med. 2013;52:2287-2288.
137. Rollin A, Maury P, Guilbeau-Frugier C, *et al.* Transient ST elevation after ketamine intoxication: a new cause of acquired brugada ECG pattern. J Cardiovasc Electrophysiol. 2011;22:91-94.
138. Daccarett M, Freih M, Machado C. Acute cannabis intoxication mimicking brugada-like ST segment abnormalities. Int J Cardiol. 2007;119:235-236.
139. Awad SF, Barbosa-Barros R, Belem Lde S, *et al.* Brugada phenocopy in a patient with pectus excavatum: systematic review of the ECG manifestations associated with pectus excavatum. Ann Noninvasive Electrocardiol. 2013;18:415-420.
140. Ortega-Carnicer J, Benezet J, Ruiz-Lorenzo F, *et al.* Transient Brugada-type electrocardiographic abnormalities in renal failure reversed by dialysis. Resuscitation. 2002;55:215-219.
141. Ozeke O, Selcuk MT, Topaloglu S, *et al.* Brugada-like early repolarisation pattern associated with acute pericarditis. Emerg Med J. 2006;23:e64.
142. Wang JG, McIntyre WF, Kong W, *et al.* Electrocution-induced Brugada phenocopy. Int J Cardiol. 2012;160:e35-37.
143. Tsai CF, Wu DJ, Lin MC, *et al.* A Brugada-pattern electrocardiogram and thyrotoxic periodic paralysis. Ann Intern Med. 2010;153:848-849.
144. Genaro NR, Anselm DD, Cervino N, *et al.* Brugada phenocopy clinical reproducibility demonstrated by recurrent hypokalemia. Ann Noninvasive Electrocardiol. 2014;19:387-390.
145. Riera AR, Uchida AH, Schapachnik E, *et al.* Propofol infusion syndrome and Brugada syndrome electrocardiographic phenocopy. Cardiol J. 2010;17:130-135.
146. Nguyen T, Smythe J, Baranchuk A. Rhabdomyoma of the interventricular septum presenting as a Brugada phenocopy. Cardiol Young. 2011;21:591-594.
147. Arce M, Riera AR, Femenia F, *et al.* Brugada electrocardiographic phenocopy in a patient with chronic Chagasic cardiomyopathy. Cardiol J. 2010;17:525-527.
148. Kataoka H. Electrocardiographic patterns of the Brugada syndrome in 2 young patients with pectus excavatum. J Electrocardiol. 2002;35:169-171.