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Genetic Basis of Brugada Syndrome

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Abstract

Brugada syndrome is a rare cardiac disorder described as a clinical entity in 1992. It is characterized by typical electrocardiographic alteration in a structurally normal heart, and associated with a high risk of sudden cardiac death. Brugada syndrome affects mainly young adult males and patients can present a wide range of symptoms or even remain asymptomatic. The first genetic basis responsible for the syndrome was described in 1998 in SCN5A. Since then, several pathogenic mutations have been identified in 16 genes, encoding mainly subunits of cardiac sodium, potassium, and calcium channels, or genes involved in the trafficking/regulation of these channels. All these genes together are responsible for 35% of total cases, remaining 2/3 parts of Brugada syndrome cases without genetic cause identified. In this review, we focus on recent advances in genetics of Brugada Syndrome.

Keywords: Sudden cardiac death; Channelopathies; Brugada syndrome; Genetics

Abbreviations: AF: Atrial Fibrillation; BrS: Brugada Syndrome; CNV: Copy Number Variations; DCM: Dilated cardiomyopathy; ECG: Electrocardiogram; GVUS: Genetic Variant Unknown Significance; HCM: Hypertrophic cardiomyopathy; ICD: Implantable Cardioverter Defibrillator; LQTS: Long QT Syndrome; NGS: Next Generation Sequencing; PCCD: Progressive Conduction Cardiac Disease; PFHB1B: Progressive Familial Heart Block type 1B; PVT: Polymorphic Ventricular Tachycardia; RBBB: Right Bundle Branch Block; RVOT: Right ventricular outflow tract; SCD: Sudden Cardiac Death; SIDS-Sudden Infant Death Syndrome; SNP: Single Nucleotide Polymorphism; SQTS: Short QT Syndrome; SSS: Sick Sinus Syndrome; VF: Ventricular Fibrillation

Introduction

In 1992, Brugada et al. [1] described a new clinical entity: "*the ECG during sinus rhythm showed right bundle branch block (RBBB), normal QT interval and persistent ST segment elevation in precordial leads V1 to V2-V3 not explainable by electrolyte disturbances, ischemia or structural heart disease*", later named the Brugada Syndrome (BrS) -ORPHA130- by the scientific community. Since then, there have been two consensus conferences about BrS, the first outlining the diagnostic criteria [2], and the second addressing risk stratification guidelines and approaches to clinical therapy [3]. Despite originally reported as "*persistent ST elevation and with right bundle branch block*", both criteria are no longer necessary for its diagnosis. Three types of ECG patterns were described in BrS (Figure 1): the ECG type I is characterized by ST-segment elevation followed by a negative T wave, with little or no isoelectric separation, with a 'coved morphology' [2]. This pattern may be spontaneous or induced by a pharmacological test using Class I AAD -antiarrhythmic drug- (Flecainide, Ajmaline, Procainamide, and Pilsicainide) [4]. Type II and type III are saddleback-shaped patterns, with a high initial augmentation followed by an ST elevation greater than 2 mm for type II and less than 2 mm for type III. Currently, only type I is accepted as diagnostic of BrS. Other ECG patterns are suggestive of but not diagnostic for BrS [5].

Despite continuous advances, BrS is often difficult to diagnose due to incomplete penetrance and dynamic ECG manifestations. Thus, the BrS diagnostic pattern could be documented in only approximately 25% of the tracings. Some patients can suffer syncope or sudden cardiac death (SCD), secondary to polymorphic ventricular tachycardia (PVT)/ventricular fibrillation (VF) while other may remain completely asymptomatic [4]. It is believed to be responsible for 12% of SCD cases and approximately 20% of SCD in patients with structurally normal hearts [6]. However, it has been recently published scattered fibrosis in the myocardium of BrS patients but the cause is yet to be well elucidated [7]. The global prevalence of the disease varies from 5 to 20 in every 10.000. In some geographic areas, like Southeast Asia, BrS is considered endemic and believed to be the second cause of death among young men after car accidents, with a prevalence reaching 60 in 10000 [5]. In addition, males are more often symptomatic than females (8:1), probably by the influence of hormones and gender distribution of ion channels in the heart. European series show a strong gender disequilibrium ratio of 3:1 and up to 9:1 in a South-Asian cohort [8]. The first arrhythmias normally occur around age 40 (1-77 years), and often during rest or while sleeping, believed due to high vagal tone [4]. The phenotype is also age dependent. Thus, adults show more abnormalities (0.05–0.28%) than adolescents (0.005–0.06%) [9]. In the pediatric population there is little information, but studies performed in children have failed to indicate a male predominance, perhaps due to low levels of testosterone in children of both genders [4]. The implantation of ICD is the only treatment option shown to be. However there are important discussions on the patient subgroups which may benefit from an ICD [10].

The BrS is a genetic disease with an autosomal dominant pattern of inheritance [11]. So far, several pathogenic mutations in 16 genes have been associated with BrS. Though, all these genes account only for 35% of total cases.

Brugada syndrome has being deeply investigated at the clinical, molecular and cellular levels but there are still main controversies in the electrophysiological mechanisms underlying the syndrome, risk

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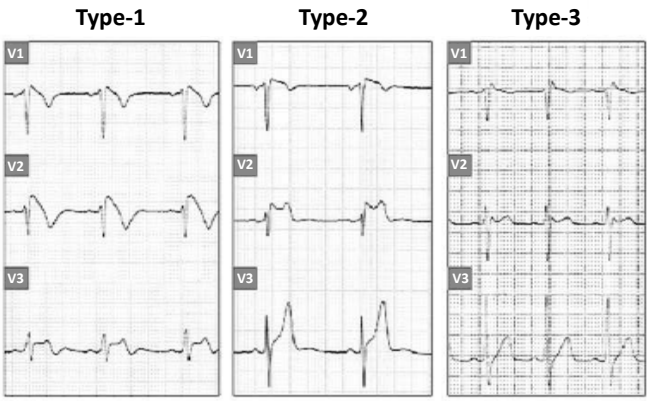

Figure 1: Three different ECG patterns in right precordial leads frequently observed in patients with BrS. Type-1 or otherwise called coved-type ECG pattern, in which a descendant ST-segment elevation is followed by negative T waves. Type-2 or saddle-back pattern, a ST-segment elevation followed by positive or biphasic T waves. Type-3, either a coved-type or saddle-back morphology with ST-segment elevation less than 1mm. A type-1 ECG pattern is required to establish the definite diagnosis of BrS. Adapted from Chapter entitled *Brugada Syndrome and related Cardiac Diseases* (Book: Clinical Genomics: Practical Applications in Adult Patient Care) American College of Physicians, 2011.

stratification, and treatment, mainly of asymptomatic patients. This review provides a genetic update of molecular basis responsible for BrS.

Molecular Mechanisms

Brugada syndrome is a channelopathy caused by a dysfunction in channels involved in the generation of the cardiac action potential. In general, pathogenic mutations induce a loss-of-function to inward depolarizing sodium and calcium currents or gain-of-function in outward repolarizing potassium current [12]. The pathophysiological mechanisms remain to be clarified and it has been proposed that several key players, including genetic predisposition, are needed to induce the BrS phenotype. So far, two mechanisms have been proposed as responsible for ST elevation identified in the ECG, the repolarization and depolarization theories, despite none have been conclusively confirmed [13]. Repolarization theory [14] focuses on disequilibrium between I_{Na} and I_{to}. This disequilibrium generates transmural dispersion of repolarization and the substrate for arrhythmias. Depolarization theory [15] focuses on conduction slowing in the right ventricular outflow tract (RVOT), leading to ST segment elevation in right precordial leads. Recently, a third hypothesis has been proposed, suggesting that the embryological development of the RV could explain the electrophysiological heterogeneity in the ventricular myocardium, including the RV outflow tract, which could provide the arrhythmogenic substrate [16]. These models are not mutually exclusive, and it is possible that BrS could be a mechanistically heterogeneous disease [17].

Genetics

Brugada syndrome (Online Mendelian Inheritance in Man – OMIM601144-) is a channelopathy with an autosomal dominant pattern of transmission. To date, more than 350 pathogenic mutations (Human Genetic Mutation Database -HGMD-) has been identified in 16 genes (Table1). These genes codify for sodium channels or its associated proteins (*SCN5A, GPD1L, SCN1B, SCN2B, SCN3B, RANGRF,* and *SLMAP*), potassium channels or its associated proteins (*KCNE3, KCNj8, HCN4, KCNE5*, and *KCND3*), and calcium channels or its associated proteins (*CACNA1C, CACNB2B, CACNA2D1,* and *TRPM4*). The associated proteins are involved in the trafficking/regulation of sodium, potassium and calcium channels, respectively. All these 16 gens together are only responsible for nearly 35% of all BrS patients [4,12]. Therefore, 65% of clinically diagnosed BrS patients remain without an identified genetic cause.

SCN5A

This gene (ID: 6331-, OMIM: 600163) encodes the alpha subunit of the cardiac voltage-gated sodium channel, $Na_v1.5$ (Q145243, CCDS: 46797.1). It is located in chromosome 3p21 minus strand (38589553 – 38691163) (GCID: GC03M038589). The protein has a size of 101617 bases (2016 aminoacids) with a weight of 226940Da. The α-subunit protein Nav1.5 is made up of a cytoplasmic N terminus, four internal homologous domains (DI-DIV, each with 5 hydrophobic segments (S1, S2, S3, S5, and S6) and one positively charged segment (S4), interconnected by cytoplasmic linkers, and a cytoplasmic C terminal domain. Segments S4 are probably the voltage-sensors and are characterized by a series of positively charged aminoacids at every third position [18]. The Nav1.5 protein mediates the voltage-dependent sodium ion permeability of excitable membranes. The Nav1.5 is responsible for the initial upstroke of the action potential, and its inactivation is regulated by intracellular calcium levels [19]. Pathogenic mutations in the *SCN5A* gene have been associated with several diseases, such as Long QT Syndrome (LQTS), Atrial Fibrillation (AF), Sick Sinus Syndrome (SSS), Progressive Conduction Cardiac Disease (PCCD) and Sudden Infant Death Syndrome (SIDS) [20]. Despite most of these diseases belong to the group of channelopathies without structural heart alterations, *SCN5A* mutations have also been reported with dilated cardiomyopathy (DCM) [21] (Figure 2). *SCN5A* mutations were identified in BrS in 1998 [22], being this the first gene associated with the disease. Last compendium of *SCN5A* genetic variations was published in 2010 [23]. It is suggested that *SCN5A* account for 25-30% of total BrS mutations. Nowadays, nearly 330 pathogenic mutations have been reported (226 *missense,* 22 *nonsense*, 20 splicing, 44 small deletions, 14 small insertions, 3 small *indels* –insertion/deletion-, and 1 gross deletion) resulting in loss of function of the sodium channel. The distribution towards the gene is homogeneous, without clear associated spot-hot zones [23]. All these pathogenic mutations were point mutations or a small number of nucleotides changes in the genomic sequence. However, in 2011 a large *SCN5A* deletion of all one exon was identified for the first time in BrS (CG1111456) [24].

GPD1L

This gene (ID: 23171+, OMIM: 611778) encodes the glycerol-3-phosphate dehydrogenase 1-like, G3PD1L (Q8N335, CCDS 33729.1). It is located in chromosome 3p22.3 plus strand (32,147,181 – 32,210,207) (GCID: GC03P032123). The protein has a size of 63027 bases (351 amino acids) with a weight of 38419Da. The encoded protein is found in the cytoplasm, associated with the plasma membrane, where it binds the Nav1.5. The protein plays a role in trafficking of the cardiac sodium channel to the cell surface, thus regulating cardiac sodium current [19]. It catalyzes the conversion of sn-glycerol 3-phosphate to glycerone phosphate (sn-glycerol 3-phosphate + NAD^+ = glycerone phosphate + NADH) [25]. Decreased enzymatic activity induces increased levels of glycerol 3-phosphate which activate the DPD1L-dependent Nav1.5 phosphorylation pathway, leading to a decrease of sodium current. In addition, cardiac sodium current may also be reduced due to alterations of NAD(H) balance, mainly induced by DPD1L [26] Pathogenic

Channel	Inheritance	Locus	Gene	Protein	Function	Percentage	Reference
SODIUM	AD	3p21-p24	*SCN5A*	Nav1.5	Loss	25%-30%	[22]
	AD	3p22.3	*GPD1-L*	glycerol-3-P-DH-1	Loss	<1%	[27]
	AD	19q13.1	*SCN1B*	Navb1	Loss	<1%	[28]
	AD	11q24.1	*SCN3B*	Navb3	Loss	<1%	[30]
	AD	11q23.3	*SCN2B*	Navb2	Loss	<1%	[29]
	AD	17p13.1	*RANGRF*	RAN-G-release factor	Loss	<1%	[32]
	AD	3p14.3	*SLMAP*	sarcolemma associated protein	Loss	<1%	[34]
POTASSIUM	AD	11q13-q14	*KCNE3*	MiRP2	Gain	<1%	[36]
	AD	12p12.1	*KCNJ8*	Kv6.1 Kir6.1	Gain	<1%	[39]
	AD	15q24.1	*HCN4*	hyperpolarization cyclic nucleotide-gated 4	NA	<1%	[45]
	Sex-related	Xq22.3	*KCNE5*	potassium voltage-gated channel subfamily E member 1 like	Gain	<1%	[46]
	AD	1p13.2	*KCND3*	Kv4.3 Kir4.3	Gain	<1%	[47]
CALCIUM	AD	2p13.3	*CACNA1C*	Cav1.2	Loss	1%	[50]
	AD	10p12.33	*CACNB2B*	voltage-dependent b-2	Loss	1%	[50]
	AD	7q21-q22	*CACNA2D1*	voltage-dependent a2/d1	NA	1%	[52]
	AD	19q13.33	*TRPM4*	transient receptor potential M4	Loss/Gain	<1%	[54]

Table 1: Genes related to Brugada Syndrome. AD, Autosomic Dominant; AR, Autosomic Recessive, NA, Not Available. (*) Asterisk means that BrS type 3 and 4 were described also associated to shorter QT.

mutations in *GPD1L* have been associated with SIDS and BrS (Figure 2). This gene is suggested as responsible only for a minimum number of BrS cases because, so far, only one *missense* pathogenic mutation has been reported (p.A280V –p.Ala280Val, c.839C>T) (CM074892). This pathogenic mutation causes abnormal trafficking of the cardiac sodium channel to the cell surface and a reduction of nearly 50% of the inward sodium current [27].

SCN1B

This gene (ID: 6324+, OMIM: 612838) encodes the beta subunit type I of the cardiac voltage-gated sodium channel (Q07699, CCDS: 12441.1). It is located in chromosome 19q13.1 plus strand (35521592 - 35531353) (GCID: GC19P035521). The protein has a size of 9762 bases (218 amino acids) with a weight of 24707Da. Voltage-gated sodium channels are heteromeric proteins that function in the generation and propagation of action potentials in excitable cells, including nerve, muscle, and neuroendocrine cell types. Structurally, Nav channels are composed of one pore-forming alpha-subunit, which may be associated with either one or more beta-subunits, where the alpha subunit provides channel activity and the beta-1 subunit modulates the kinetics of channel inactivation. Hence, the *SCN1B* gene is crucial in the heterotrimeric complex of the sodium channel [19]. Pathogenic mutations in this gene have been associated to epilepsy plus febrile seizures, AF, defects in cardiac conduction and BrS (Figure 2). So far, only one pathogenic mutation has been associated with BrS, the p.Glu87Gln (c.259G>C, p.E87Q) (CM081777). Sodium current decrease when Nav1.5 was coexpressed with mutant beta1/beta1B subunits due to sodium channel trafficking alterations [28]. This gene is responsible for a low number of cases (<1%) of total BrS patients.

SCN2B

This gene (ID: 6327-, OMIM: 601327) encodes the beta subunit type 2 of the cardiac voltage-gated sodium channel (Q060939, CCDS: 8390.1). It is located in chromosome 11q23.3 minus strand (118,032,666 - 118,047,388) (GCID: GC11M118033). The protein has a size of 14723 bases (215 amino acids) with a weight of 24326Da. The sodium channel consists of a pore-forming alpha subunit, beta-1 and beta-2 subunits. Beta-1 is non-covalently associated with alpha, while beta-2 is covalently linked by disulfide bonds. The subunit beta-2 causes an increase in the plasma membrane surface area and in its folding into microvilli [19]. Pathogenic mutations in *SCN2B* have been associated with epilepsy, SIDS, AF and BrS (Figure 2). This gene has been recently associated with BrS by our group [29]. The *missense* pathogenic mutation identified, p.Asp211Gly (p.D211G, c.632A>G) decreases the Nav1.5 cell surface expression. So far, no more pathogenic variations have been associated with BrS in this gene. Therefore, this gene is responsible for a minor number of cases (<1%) of total BrS patients.

SCN3B

This gene (ID: 20665-, OMIM: 608214) encodes the beta subunit type 3 of the cardiac voltage-gated sodium channel (Q9NY72, CCDS: 8442.1). It is located in chromosome 11q24.1 minus strand (123,499,895 - 123,525,952) (GCID: GC11M123533). The protein has a size of 26058 bases (215 amino acids) with a weight of 24702Da. The voltage-sensitive sodium channel consists of an ion conducting pore forming alpha-subunit regulated by one or more beta-1, beta-2 and/or beta-3 subunits. Beta-1 and beta-3 are non-covalently associated with alpha, while beta-2 is covalently linked by disulfide bonds [19]. Pathogenic mutations in *SCN3B* have been associated with SIDS, AF and BrS (Figure 2). There are two pathogenic mutations associated with BrS, both *missense* mutations: p.Leu10Pro (c.29T>C, p.L10P) (CM093686) [30] and p.Val110Ile (c.328G>A, p.V110I) (CM1212171), recently identified [31]. Pathogenic mutations in this gene lead to a loss of function of the sodium cardiac channel. It is suggested as responsible only for a reduced number of BrS cases (<1%).

RANGRF

This gene (ID: 29098+, OMIM: 607954) encodes the RAN guanine nucleotide release factor (Q9HD47, CCDS: 11137.1). It is located in chromosome 17p13 plus strand (8,191,815 - 8,193,410) (GCID: GC17P008191). The protein has a size of 1596 bases (186 amino acids) with a weight of 20448Da. This gene encodes a protein that regulates the expression, function and cell surface localization of the Nav1.5 cardiac sodium channel in human cardiac cells. It interacts with the cytoplasmic loop 2 of the Nav1.5, playing a key role in intracellular trafficking of RAN between the nucleus and cytoplasm [19]. Recently, Kattygnarath et al. [32] published a study supporting that *RANGRF* can impair the trafficking of Nav1.5 to the membrane, leading to I_{Na} reduction and clinical manifestation of BrS. This was the first BrS-related pathogenic mutation identified in this gene, p.Glu83Asp (p.E83D, c.249G>C)

(CM114693). The second genetic variation identified in this gene was the *nonsense* p.E61X (p.Glu61STOP, c.181G>T) [33]. However, a current argument exist about the deleterious effect of this last variation because of 2/488 healthy individuals (0,4%) carry the same variation. This fact suggests p.E61X as a genetic variation of unknown significance (GVUS). Thus, *RANGRF* is suggested as responsible for a minor number of cases (<1%) of total BrS patients.

SLMAP

This gene (ID: 7871+, OMIM: 602701) encodes the sarcolemmal associated protein (Q14BN4, CCDS: 33774.1). It is located in chromosome 3p21.2-p14.3 plus strand (57,741,177 - 57,914,895) (GCID: GC03P057802). The protein has a size of 173719 bases (828 amino acids) with a weight of 95198Da. This gene encodes a homodimer that interacts with myosin protein, playing a role during myoblast fusion. Sarcolemmal membrane-associated protein is a protein of unknown function localizing at T-tubules and near the junctional sarcoplasmic reticulum membrane-associated (along the Z- and M-lines). This gene has been associated with BrS in 2012, via modulating the intracellular trafficking of Nav1.5 but no direct interaction between SLMAP and hNaV1.5 was observed [34]. So far, only two pathogenic *missense* mutations have been associated with BrS, the p.Val269Ile (c.805G>A, p.V269I) (CM129586), and p.Glu710Ala (c.2129A>C, p.E710A) (CM129587). Therefore, this gene is also suggested as responsible for a reduced number of cases (<1%) of total BrS patients.

KCNE3

This gene (ID: 10008-, OMIM: 613119) encodes the β-subunit that regulates the potassium channel I_{to}, MIRP2 (Q9Y6H6, CCDS: 8232.1). It is located in chromosome 11q13.4 minus strand (74,165,886 - 74,178,774) (GCID: GC11M074165). The protein has a size of 12889 bases (103 amino acids) with a weight of 11710Da. Voltage-gated potassium (Kv) channels represent the most complex class of voltage-gated ion channels from both functional and structural standpoints. Their diverse functions include regulating neurotransmitter release, heart rate, insulin secretion, neuronal excitability, epithelial electrolyte transport, smooth muscle contraction, and cell volume. The MIRP2 assembles with a potassium channel alpha-subunit to modulate the gating kinetics and enhance stability of the multimeric channel complex [35]. Pathogenic mutations in this gene have been associated with LQTS, AF and BrS (Figure 2). Currently, two *missense* pathogenic mutations have been reported in BrS; the first one was p.Arg99His (c.296G>A, p.R99H) (CM086422), resulting in an increase of I_{to} magnitude and density [36]. In addition, in 2012 [37] the p.T4A (c.10A>G) *missense* pathogenic mutation was identified in a Japanese patient presenting Brugada-pattern ECG and neurally mediated syncope (NMS). Its functional consequence was the gain of function of I_{to}, which could underlie the pathogenesis of BrS-pattern ECG. So, this gene is responsible for a minor number of cases (<1%) of total BrS patients.

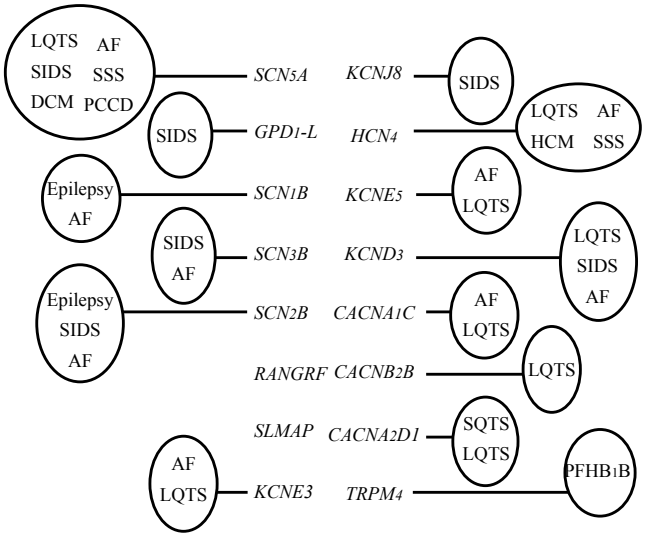

Figure 2: Brugada Syndrome genes and main related arrhythmogenic diseases. LQTS, Long QT Syndrome; SQTS, Short QT Syndrome; AF, Atrial Fibrillation; SSS, Sick Sinus Syndrome; PCCD, Progressive Conduction Cardiac Disease; DCM, Dilated cardiomyopathy; HCM, Hypertrophic cardiomyopathy; SIDS, Sudden Infant Death Syndrome; PFHB1B, Progressive Familial Heart Block type 1B.

KCNJ8

This gene (ID: 3764-, OMIM: 600935) encodes the ATP-sensitive inward rectifier potassium channel eight –Kir6.1- (Q15842, CCDS: 8692.1). It is located in chromosome 12p12.1 minus strand (21,917,889-21,928,515) (GCID: GC12M021818). The protein has a size of 10627 bases (424 amino acids) with a weight of 47968Da. This potassium channel is controlled by G proteins. Inward rectifier potassium channels are characterized by a greater tendency to allow potassium to flow into the cell rather than out of it. Their voltage dependence is regulated by the concentration of extracellular potassium; as external potassium is raised, the voltage range of the channel opening shifts to more positive voltages [38]. Pathogenic mutations in this gene have been associated to SIDS, J-wave syndromes and BrS (Figure 2). The first BrS genetic variation was published in 2010 (p.Ser422Leu, p.S422L, c.1265C>T), conferring predisposition to dramatic repolarization changes and ventricular vulnerability [39]. However, it was in 2012 when a pathogenic role was associated with p.S422L (CM091549). This deleterious role is due to gain of function in ATP-sensitive potassium channel current, induced by a sensitivity reduction to intracellular ATP [40]. Despite this fact, few months ago it was found that the p.S422L allele was at a significantly higher frequency in Ashkenazi Jews (>4%) compared with other populations, suggesting that either previous studies implicating p.S422L as pathogenic for J-wave syndromes failed to appropriately account for European population structure and the variant is likely benign, or that Ashkenazi Jews may be at significantly increased risk of J-wave syndromes and ultimately SCD [41]. Thus, *KCNJ8* is suggested as responsible for a minor number of cases (<1%) of total BrS patients.

HCN4

This gene (ID: 10021-, OMIM: 613123) encodes the hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 or If channel (Q9Y3Q4, CCDS: 10248.1). It is located in chromosome 15q24.1 minus strand (73,612,200 - 73,661,605) (GCID: GC15M073612). The protein has a size of 49406 bases (1203 amino acids) with a weight of 129042Da. The hyperpolarization-activated ion channel with very slow activation and inactivation exhibits weak selectivity for potassium over sodium. It contribute to the native pacemaker currents in heart (If), and activated by cAMP mediates responses to sour stimuli [42]. Pathogenic mutations in this gene have been associated to SSS, LQTS associated with bradycardia, AF and BrS. It was also associated with hypertrophic cardiomyopathy

(HCM) [43] (Figure 2). The first association with BrS was obtained in 2009 with the identification of an *HCN4* mutation in heterozygous state in a symptomatic BrS patient [44]. This mutation (IVS2DS) was an insertion of four bases (GTGA) at a splicing junction donor site of exon 2 and intron 2, predicted to cause a frameshift and the addition of 44 no relevant C-terminal residues and premature truncation. Recently, other BrS pathogenic mutation has been reported in *HCN4*, p.Ser841Leu (c.2522C>T, p.S841L) (CM127063) [45]. Thus, this gene is responsible for a small number of cases (<1%) of all BrS cases.

KCNE5

This gene (ID: 23630-, OMIM: 300328) encodes the potassium voltage-gated channel, Isk-related family, member 1-like –KCNE1L- (Q5JWV7, CCDS: 14547.1). It is located in chromosome Xq22.3 minus strand (108,866,929 - 108,868,393) (GCID: GC0XM108866). The protein has a size of 1465 bases (142 amino acids) with a weight of 14993Da. This gene encodes a membrane protein which has sequence similarity to the *KCNE1* gene product, a member of the potassium channel, voltage-gated, isk-related subfamily. Pathogenic mutations in this gene have been associated with LQTS, AF and BrS (Figure 2). Concerning to BrS, only two pathogenic mutations have been published: a novel *missense* variant causing gain-of-function effects on I_{to} p.Tyr81His (c.241T>C, p.Y81H) (CM113001)-, and an insertion c.276_277delCGinsAT (CX113002) [46]. Thus, *KCNE5 (KCNE1L)* is suggested as responsible for a minor number of BrS cases (<1%).

KCND3

This gene (ID: 3752-, OMIM: 605411) encodes the potassium voltage-gated channel, Shal-related subfamily, member 3 –Kv4.3- (Q9UK17, CCDS: 843.1). It is located in chromosome 1p13.3 minus strand (112,313,284 - 112,531,777) (GCID: GC01M112313). The protein has a size of 218494 bases (655 amino acids) with a weight of 73451Da. It is a pore-forming (alpha) subunit of voltage-gated rapidly inactivating A-type potassium channels that contribute to I_{to} current. Channel properties are modulated by interactions with other alpha subunits and with regulatory subunits. Pathogenic mutations in this gene have been associated with LQTS, SIDS, AF and BrS (Figure 2). In 2011, Giudicessi et al. [47] provide the first molecular and functional evidence implicating novel *KCND3* gain-of-function mutations (Kir4.3 protein) in the pathogenesis and phenotypic expression of BrS, with enhanced I_{to} current gradient within the right ventricle where the *KCND3* gene expression is the highest. Currently, two pathogenic mutations have been associated with BrS, p.Leu450Phe (c.1348C>T, p.L450F) (CM111334), and p.Gly600Arg (c.1798G>C, p.G600R) (CM1110945) [48] despite this last variation was reported in a SUDS case with no confirmed BrS, so far. This gene is also responsible for a minor number of all BrS cases (<1%).

CACNA1C

This gene (ID: 775+, OMIM: 611875) encodes the voltage-dependent L-type calcium channel subunit alpha-1C (Q13936, CCDS: 44787.1). It is located in chromosome 12p13.33 plus strand (2,079,952 - 2,807,115) (GCID: GC12P002032). The protein has a size of 727164 bases (2221 amino acids) with a weight of 248977Da. Voltage-sensitive calcium channels (VSCC) mediate the entry of calcium ions into excitable cells upon membrane polarization and are also involved in a variety of calcium-dependent processes, including muscle contraction. The calcium channel is a multisubunit complex consisting of alpha-1, alpha-2/delta, beta, and gamma subunits in a 1:1:1:1 ratio [49]. Pathogenic mutations in the *CACNA1C* gene are responsible for a defective α unit of the type-L calcium channel ($Ca_v1.2$), inducing a loss of channel function. It is responsible for LQTS, AF and a syndrome overlapping the BrS ECG pattern with a shorter than normal QT interval [50,51] (Figure 2). So far, 7 pathogenic mutations have been reported: 6 *missense* (CM070048, CM070047, CM109282, CM109283, CM109284, and CM109285), and one duplication (c.5487_5501dup15) (CI109286) [52]. Despite number of pathogenic mutations reported, this gene is suggested as responsible for a number of cases nearly 1%.

CACNB2B

This gene (ID: 783+, OMIM: 611876) encodes the calcium channel, voltage-dependent, beta 2 subunit (Q08289, CCDS: 7125.1). It is located in chromosome 10p12.3 plus strand (18,429,606 - 18,830,798) (GCID: GC10P018469). The protein has a size of 401193 bases (660 amino acids) with a weight of 73581Da. The protein is a member of the voltage-gated calcium channel superfamily. It contributes to the function of the calcium channel by increasing peak calcium current, shifting the voltage dependencies of activation and inactivation, modulating G protein inhibition and controlling the alpha-1 subunit membrane targeting [49]. Pathogenic mutations in the *CACNB2B* gene are responsible for a defective β-subunit (Ca_vb2b) inducing a loss of channel function. It is responsible for LQTS and a syndrome overlapping the BrS ECG pattern with a shorter than normal QT interval [50,51] (Figure 2). So far, 7 *missense* pathogenic mutations have been reported (CM095258, CM109288, CM127056, CM109291, CM109289, CM127057, and CM109290). Despite number of pathogenic mutations reported, this gene is suggested as responsible for a number of cases nearing 1%.

CACNA2D1

This gene (ID: 781-, OMIM: 114204) encodes the calcium channel, voltage-dependent, alpha 2/delta subunit 1 (P54289, CCDS: 5598.1). It is located in chromosome 7q21-q22 minus strand (81,575,760 - 82,073,114) (GCID: GC07M081575). The protein has a size of 497355 bases (1103 amino acids) with a weight of 124568Da. The protein is a dimer formed of alpha-2-1 and delta-1 chains disulfide-linked. The alpha-2/delta subunit of voltage-dependent calcium channels regulates calcium current density and activation/inactivation kinetics of the calcium channel. It plays an important role in excitation-contraction coupling [49]. Pathogenic mutations in this gene have been associated with LQTS, SQTS and BrS [52] (Figure 2). So far, 4 *missense* pathogenic mutations have been reported (CM109296, CM109295, CM109297, and CM109434). Despite number of pathogenic mutations reported, this gene is suggested as responsible for a number of cases nearing 1%.

TRPM4

This gene (ID: 54795+, OMIM: 604559) encodes the transient receptor potential cation channel, subfamily M, member 4 (Q8TD43, CCDS: 843.1). It is located in chromosome 19q13.33plus strand (49,661,052 - 49,715,093) (GCID: GC19P049661). The protein has a size of 54042 bases (1214 amino acids) with a weight of 134301Da. The protein encoded by this gene is a homomultimer that mediates transport of monovalent cations ($Na^+>K^+>Cs^+>Li^+$) across membranes, thereby depolarizing the membrane of cardiomyocytes. The activity of the encoded protein increases with increasing intracellular calcium concentration, but this channel does not transport calcium [53]. Pathogenic mutations in this gene have been associated to Progressive Familial Heart Block type 1B (PFHB1B), and BrS [54] (Figure 2). So far, 9 *missense* pathogenic mutations have been reported (CM120320, CM105352, CM120323, CM105353, CM120321, CM120324,

CM105354, CM120325 and CM120322). Consequences of these mutations alters the resting membrane potential, and a reduction or increase of TRPM4 channel function may both reduce the availability of sodium channel and thus lead to BrS. Despite number of pathogenic mutations, this gene is suggested as responsible for a reduced number of BrS cases.

Genetic Causality and Phenotype Modulation

Continuous both clinical and basic investigations have reported several genetic and environmental candidate and modulators which could explain, in part, the presence of incomplete penetrance, as well as the variable expressivity in BrS [55,56]. As mentioned before, nearly 65% of BrS patients remain without genetic cause identified. Epigenetic factors such as DNA methylation, post-translational modifications of histone proteins, and RNA-based mechanisms that operate in the nucleus could be responsible for the disease. Though the knowledge about the function of epigenetic signatures in cardiovascular disease is still largely unexplored [57,58]. Genetic variants in the *SCN5A* promoter region gene could play a pathophysiological role in BrS population, functionally linked to a reduced expression of the sodium current [59,60]. In addition, our group showed that post-translational arginine methylation in the *SCN5A* gen could be a potential cause of a phenotype of BrS [61].

Finally, this high % of BrS patients without genetic diagnosis could carry pathogenic mutations in other yet to be identified genes so far. In this regard, recent genetic technologies, named Next Generation Sequencing (NGS), allow the performance of exhaustive genetic studies including large number of candidate genes, even whole exome and/or full genome analysis [62]. However, no genetic reports have yet been published using NGS technology in BrS families [63].

Several triggering factors have been identified which can unmask or modulate the BrS type I ECG pattern, such as sodium channel blockers, a febrile state, vagotonic agents, autonomic nervous system changes, tricyclic/tetracyclic antidepressants, first-generation antihistamines, a combination of glucose and insulin, hyperkalemia, hypokalemia, hypercalcemia, and alcohol or cocaine toxicity (www.brugadadrugs.org) [12]. In addition to environmental factors, single nucleotide polymorphisms (SNPs) have been described as modulators of electrical current in myocytes. The polymorphism p.H558R_*SCN5A* -c.1673A>G- (rs1805124) localized in 3:38645420 (GRCh37/hg19) has a Minor Allele Frequency (MAF) of 23.2092/27.4833/24.6276 in European American (EA), African American (AA) and all populations, respectively -NHLBI GO Exome Sequencing Project (ESP)- (http://evs.gs.washington.edu/EVS/). This common genetic variant partially restores the sodium current impaired by the deleterious mutation, thus is a genetic modulator of BrS phenotype among carriers of pathogenic mutations in the *SCN5A* gene [64].

Genetic Risk Stratification

Currently, some clinical features have been identified as markers of high risk in BrS patients, but there is still controversy on how to stratify arrhythmogenic risk and potential treatment, mainly among asymptomatic patients [12]. Several series reported no differences in arrhythmic events when BrS patients were classified according to the presence of pathogenic mutations in the *SCN5A* gene. However, other studies have reported a higher rate of syncope among BrS with *nonsense* or *frame-shift* pathogenic mutations [5]. Regarding *missense* pathogenic mutations in *SCN5A*, some reports have identified differences mainly in those carrying *SCN5A missense* pathogenic mutations resulting in a decrease of more than 90% of the I_{Na} (non-functional Na^+ channels), compared to patients carrying *SCN5A missense* pathogenic mutations but that produce a decrease of sodium current ≤ 90% [4]. In addition, more recent studies have identified compound pathogenic mutations in BrS patients, causing a more severe phenotype [65,66]. Finally, a recent study performed in a BrS cohort corroborates the emerging 'Multi-Hit Hypothesis' in arrhythmogenic syndromes associated to SCD. This study reports that the presence of pathogenic mutations in the *SCN5A* gene in combination with common genetic variations in other genes not BrS-associated can increase the arrhythmogenic risk in BrS patients [67].

Conclusions

Twenty years after the first description of BrS, and despite continuous improvement both in clinical and molecular basis, several key features remain still to be clarified. The etiology of the BrS is multifactorial, with several players modulating the disease progression and outcome. Thus, epigenetic mechanisms should be considered as key factors in families showing incomplete penetrance and variable expressivity. In addition, to clarify the role of rare genetic variants in BrS phenotype, familial cosegregation, *in vitro* studies, and *in silico* predictions are crucial. Despite association of several genes with BrS, nearly 65% of total cases remain without an identified genetic cause. So far, given our limited knowledge on the genetic of BrS, its management and risk stratification should be performed always under a clinical context. Nonetheless, genetic testing allows confirmation of the diagnosis in borderline cases and identification of asymptomatic genetic carriers that may be at risk of SCD, enabling the undertaking of preventive strategies. New genetic technologies now allow to performing wide-ranging genetic analysis in BrS patients, improving the identification of pathogenic variations, and the complexity of their clinical interpretation.

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