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ORIGINAL ARTICLE

Brugada syndrome: current concepts and genetic background

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Abstract

Backgroung: Brugada syndrome (BrS) is a hereditary clinical-electrocardiographic arrhythmic entity with low worldwide prevalence. The syndrome is caused by changes in the structure and function of certain cardiac ion channels and reduced expression of Connexin 43 (Cx43) in the Right Ventricle (RV), predominantly in the Right Ventricular Outflow Tract (VSVD), causing electromechanical abnormalities. The diagnosis is based on the presence of spontaneous or medicated ST elevation, characterized by boost of the J point and the ST segment ≥2 mm, of superior convexity "hollow type" (subtype 1A) or descending rectilinear model (subtype 1B). BrS is associated with an increased risk of syncope, palpitations, chest pain, convulsions, difficulty in breathing (nocturnal agonal breathing) and/or Sudden Cardiac Death (SCD) secondary to PVT/VF, unexplained cardiac arrest or documented PVT/VF or Paroxysmal atrial fibrillation (AF) in the absence of apparent macroscopic or structural heart disease, electrolyte disturbance, use of certain medications or coronary heart disease and fever. In less than three decades since the discovery of Brugada syndrome, the concept of Mendelian heredity has come undone. The enormous variants and mutations found mean that we are still far from being able to concretely clarify a genotype-phenotype relationship. There is no doubt that the entity is oligogenetic, associated with environmental factors, and that there are variants of uncertain significance, especially the rare variants of the SCN5A mutation, with European or Japanese ancestors, as well as a spontaneous type 1 or induced pattern, thanks to gnomAD (coalition) researchers who seek to aggregate and harmonize exome and genome sequencing data from a variety of large-scale sequencing projects and make summary data available to the scientific community at large). Thus, we believe that this in-depth analytical study of the countless mutations attributed to BrS may constitute a real cornerstone that will help to better understand this intriguing syndrome.

Keywords: Brugada Syndrome, arrhythmic, environmental, genotype, phenotyp..

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Authors summary

Why was this study done?
In less than three decades since the discovery of Brugada syndrome, the concept of Mendelian heredity has fallen apart. There is no doubt that the entity is oligogenetic associated with environmental factors.

What did the researchers do and find?
Recent research by the American College of Medical Genetics and Genomics / Association for Molecular Pathology (ACMG/AMP) has shown us that variants of uncertain significance, especially the rare variants of the SCN5A mutation, with European or Japanese ancestors, as well as spontaneous type 1 pattern or induced, thanks to Genome Aggregation Database (gnomAD) (coalition of researchers who seek to aggregate and harmonize exome and genome sequencing data from a variety of large-scale sequencing projects and make summary data available to the scientific community in generall).

What do these findings mean?
The enormous variants and mutations found mean that we are still far from being able to concretely clarify a genotype-phenotype relationship. Thus, we believe that this in-depth analytical study of the numerous mutations attributed to BrS can constitute a truly cornerstone that will help to better understand this intriguing syndrome.

INTRODUCTION

The Brugada Syndrome (BrS) is a hereditary clinical-electrocardiographic arrhythmic entity with a low prevalence worldwide (0.5 per 1,000 or 5 to 20 per 10,000 individuals), however, endemic in Southeast Asia (prevalence of 3.7 per 1,000). BrS clearly has male preponderance with a male/female ratio of 9:1 in Southeast Asia and 3:1 among Caucasians.

The syndrome is caused by alterations in the structure and function of certain cardiac ion channels and reduced expression of Connexin 43 (Cx43) in the Right Ventricle (RV), predominantly in the Right Ventricular Outflow Tract (RVOT) causing electromechanical abnormalities. The reduced and heterogeneous expression of Cx43 produces functionally significant electrophysiological heterogeneity in the ventricular wall and may promote transmural dispersion of repolarization. Until recently, BrS was considered an Autosomal Dominant (AD) Mendelian entity in ≈25% of cases or alternatively, sporadic.

It is currently thought that BrS most likely is an oligogenic disorder, rather than a Mendelian condition*, affecting several loci, and influenced by environmental factors. The diagnosis is based on the presence of a spontaneous or drug-induced ST elevation characterized by elevation of the J point and the ST segment of ≥2 mm, of superior convexity "coved type" (Subtype 1A) or descending rectilinear (Subtype 1B) type. The ST elevation is followed by a symmetric negative T wave in ≥1 right and/or high right precordial leads.

In the Subtype 1C, the J-point elevation is located to the inferior or inferolateral leads, with or without association with the early repolarization pattern. Brs is associated with an increased risk of syncope, palpitations, precordial pain, seizures, difficulty in breathing (nocturnal agonal respiration), and/or Sudden Cardiac Death (SCD) secondary to PVT/VF, unexplained cardiac arrest or documented PVT/VF or paroxysmal Atrial Fibrillation (AF) in the absence of macroscopic or apparent structural heart disease, electrolyte disturbance, use of certain drugs or coronary heart and fever.

The event typically occurs during the midnight-to-early-morning period at rest (≈80% of cases) or at a low level of physical activity especially during sleep, which suggests that parasympathetic tone is a determining factor in arrhythmogenesis: higher level of vagal tone and higher levels of Ito (cardiac transient outward potassium current) is evident during slower heart rates. Although BrS is considered a genetic disease, its mechanism remains unknown in ≈70-75% of cases and no single mutation is sufficient to cause the BrS phenotype. Although ≈20% of patients with BrS carry mutations in SCN5A, which encodes for the pore-forming α subunit of the cardiac sodium channels, the molecular mechanisms underlying this condition are still largely unknown. SCN5A, that was identified as the first BrS-associated gene in 1998, has emerged as the most common gene associated with the syndrome. The SCN5A gene is considered as the only gene definitely associated with BrS.

Currently, the oligogenic disease model is the accepted model[1]. More than 400 mutations in the SCN5A gene have been associated with SB. In an evidence-based review of genes reported to cause BS, which are in clinical use, 20 of the 21 genes did not have enough genetic evidence to support their causality for BS.

Type 2 Brugada ECG (Electrocardiographic/ Electrocardiogram) pattern has also been associated with mutations in SCN5A (glycerol-3-phosphate dehydrogenase 1-like (GPD1L) protein), which is the domain responsible for a site homologous to SCN5A, and CACNA1C, the gene responsible for the α-subunit of cardiac L-type calcium channels.

To date, mutations of more than 20 genes, other than SCN5A, have been implicated in the pathogenesis of BrS. Multiple pathogenic variants of genes have been shown to alter the normal function of sodium ↓Loss- Of-Function (↓LOF), potassium Gain-Of-Function (↑GOF), and mutations in genes encoding for potassium channels have also been implicated.

Genes influencing I_{to}, include KCNE3, KCND3 and SEMA3A (semaphoring, an endogenous potassium channel inhibitor) while KCNJ8, HCN4, KCN5 and ABCC9 (encoding for SUR2A, the ATP-binding cassette transporter for the KATP channel) mutations affected the ATP-sensitive potassium channel (or KATP channel). KCNH2, which encodes for IKr was proposed by Wang *et al*[2] to be associated with the BrS.

Dysfunction in the KCNAB2, which encodes the voltage-gated potassium channel β2-subunit, was associated with increased Ito activity and identified as a putative gene involved in BrS. Kvβ2 dysfunction can contribute to the Brugada ECG pattern[3].

Classification of hereditary diseases

o Monogenic or Mendelian: to be transmitted to the offspring according to Mendel's laws. They can be: 1) AD, 2) Autosomal Recessive (AR), or 3) X-linked. Mendelian inheritance refers to the patterns of inheritance that are characteristic of organisms that reproduce sexually. It refers to the type of inheritance that can be easily understood as a consequence of a single gene.

o Multifactorial or polygenic: produced by mutations in several genes, generally of different chromosomes and the combination of multiple environmental factors (age, sex, obesity, tobacco or alcohol use, toxic environments or a limited childhood).

o Oligogenic*: there are a few genes that have more influence than the rest. In the case of BrS, this is the case for the SCN5A gene. The inheritance also depends on the expression of other mutations (epistasis: https://academic.oup.com/hmg/article/11/20/2463/616080). Despite their importance, mutations in the SCN5A gene are present in ≈20 to 30% of cases.

Ancestral differences also have impact on the classification of pathogenicity of variants identified from BrS patients[4]. The causality of BrS-associated genes is much disputed; many of these genes demand further research, but may be clinically valid. Although controversies still exist, more than two decades of extensive research in BrS has helped researchers to gain a better understanding of the overall spectrum of the condition, including its molecular pathophysiology, genetic background, and management.

Sanger sequencing was considered as the gold standard for DNA sequencing, applied for the mutation screening of BrS[5]. With newtechnologies, such as microarrays, whole-exome sequencing, and whole genome sequencing, it is possible to identify a variant at a single nucleotide resolution in relatively medium- to large-sized genomic regions. These technological genomic advancements enable the detection of genetic variations in patients, with high accuracy and reduced cost6. Therefore, it is probably only a matter of time before the puzzle of genetics in BrS is solved[7,8].

Whole-exome sequencing

This is a genomic technique for sequencing all of the protein-coding regions of genes in a genome (known as the exome). It consists of two steps: the first step is to select only the subset of DNA that encodes proteins. These regions are known as exons – humans have about 180,000 exons, constituting about 1% of the human genome, or approximately 30 million base pairs.

The second step is to sequence the exonic DNA using any high-throughput DNA sequencing technology[9]. The goal of this approach is to identify genetic variants that alter protein sequences, and to do this at a much lower cost than whole-genome sequencing. Since gene variants can be responsible for both Mendelian and common polygenic diseases, whole exome sequencing has been applied both in academic research and clinical practice.

Exome sequencing is especially effective in the study of rare Mendelian diseases, because it is an efficient way to identify the genetic variants in all of an individual's genes. These diseases are most often caused by very rare genetic variants that are only present in a tiny number of individuals[10]. By contrast, techniques such as SNP arrays, can only detect shared genetic variants that are common to many individuals in the wider population[11].

Furthermore, because severe disease-causing variants are much more likely (but by no means exclusively) to be in the protein coding sequence[12], focusing on this 1% costs far less than whole-genome sequencing but still detects a high yield of relevant variants. The traditional way of genetic diagnostics, where clinical genetic tests were chosen based on the clinical presentation of the patient (*i.e.* focused on one gene or a small number known to be associated with a particular syndrome), or surveyed based only on certain types of variation (*e.g.* comparative genomic hybridization), provided definitive genetic diagnoses in fewer than half of all patients[13].

Exome sequencing is now increasingly used to complement these other tests: both to find mutations in genes already known to cause disease as well as to identify novel genes by comparing exomes from patients with similar clinical features.

Whole genome sequencing

Whole genome sequencing is ostensibly the process of determining the complete DNA sequence of an organism's genome at a single time. This entails sequencing all of an organism's chromosomal DNA as well as DNA contained in the mitochondria and, for plants, in the chloroplast. In practice, genome sequences that are nearly complete are also called whole genome sequences.

Whole genome sequencing has largely been used as a research tool, but was introduced into the clinics in 2014[10,11,13].

In the future of personalized medicine, whole genome sequence data may be an important tool to guide therapeutic approach[14]. The tool of gene sequencing at single nucleotide polymorphism (SNP) level is also used to pinpoint functional variants from association studies and improve the knowledge available to researchers interested in evolutionary biology, and hence may lay the foundation for predicting disease susceptibility and drug response.

Whole genome sequencing should not be confused with DNA profiling, which only determines the likelihood that genetic material came from a particular individual or group, and does not contain additional information on genetic relationships, origin or susceptibility to specific diseases[15]. In addition, whole genome sequencing should not be confused with methods that sequence specific subsets of the genome - such methods include whole exome sequencing (1-2% of the genome) or SNP genotyping (<0.1% of the genome).

As of 2017, there were no complete genomes for any mammals, including humans. Between 4% to 9%

of the human genome, mostly satellite DNA, had not been sequenced (https://www.statnews.com/2017/06/20/human-genome-not-fully-sequenced/).

Stringent variant interpretation guidelines can lead to high rates of Variants of Uncertain Significance (VUS) for genetically heterogeneous disease like LQTS and BrS. Quantitative and disease-specific customization of American College of Medical Genetics and Genomics/ Association for Molecular Pathology (ACMG/AMP) guidelines can address this false negative rate.

The authors compared rare variant frequencies from 1847 LQTS (KCNQ1/KCNH2/SCN5A) and 3335 BrS (SCN5A) cases from the International LQTS/BrS Genetics Consortia to population-specific Genome Aggregation Database (gnomAD) data and developed disease-specific criteria for ACMG/AMP evidence classes-rarity (PM2/BS1 rules) and case enrichment of individual (PS4) and domain-specific (PM1) variants.

Rare SCN5A variant prevalence differed between European (20.8%) and Japanese (8.9%) BrS patients and diagnosis with spontaneous (28.7%) versus induced (15.8%) Brugada type 1 ECG (Electrocardiographic/ Electrocardiogram). Ion channel transmembrane regions and specific N-terminus (KCNH2) and C-terminus (KCNQ1/KCNH2) domains were characterized by high enrichment of case variants and >95% probability of pathogenicity. Applying the customized rules, 17.4% of European BrS and 74.8% of European LQTS cases had (likely) pathogenic variants, compared with estimated diagnostic yields (case excess over gnomAD) of 19.2%/82.1%, reducing VUS prevalence to close to background rare variant frequency.

The authors concluded that large case-control data sets enable quantitative implementation of ACMG/AMP guidelines and increased sensitivity for inherited arrhythmia genetic testing[16].

Table 1: Lists common definitions used in genetics

Word	Meaning
Genetic testing	Process of sequencing DNA.
Genome sequencing	Sequencing of entire genome (including coding and non-coding regions)
Exome sequencing	Sequencing of just the coding regions (exons), including approximately 22,000 genes
Proband	The index case in the family, usually the first or the most severely affected.
Genetic diagnosis	When a genetic variant can be confidently attributed to a disease in an individual.
Phenotype	The clinical manifestations of a genetic trait.
Variant	A change in the DNA sequence. This may be disease-causing or just part of normal variation.
Pathogenic	Describes a variant with 0.99% confidence to be disease causing. There is sufficient evidence to offer cascade genetic testing to family members.
Likely pathogenic	Describes a variant with 90–95% confidence to be disease causing. There is sufficient evidence to offer cascade genetic testing to family members.
VUS	There is insufficient or conflicting evidence for pathogenicity and the variant is therefore considered uncertain. Cascade genetic testing cannot be offered to family members.
Likely benign/benign	Describes a variant with sufficient evidence to state that the variant is not the cause of the disease.
Cascade genetic testing	Genetic testing of asymptomatic relatives to determine the presence or absence of the causative variant in their family.
Pathogenicity	The process of determining whether a variant is causative or not, most often involves collating evidence against systematic criteria.
Penetrance	Penetrance in genetics is the proportion of individuals carrying a particular variant (or allele) of a gene (the genotype) that also express an associated trait (the phenotype).
Variable expression	Variation in the manner in which a trait is manifested. When there is variable expressivity, the trait may vary in clinical expression from mild to severe. This can include variation in disease severity, age at onset, but also difference in disease characteristics. For example, the condition neurofibromatosis type 1 may be mild, presenting with café-au-lait spots only, or may be severe, presenting with neurofibromas and brain tumors.
Copy number variant/ variation	When the number of copies of a particular gene varies from one individual to the next. Following the completion of the Human Genome Project, it became apparent that the genome experiences gains and losses of genetic material.

Continuation - Table 1: Lists common definitions used in genetics

Word	Meaning
Proband or propositus. From Latin probandus, gerundive of probāre to test	An individual being studied or reported on. A patient who is the initial member of a family to come under study. Usually it is the first affected individual in a family who brings a genetic disorder to the attention of the medical community.
Cytogenetic location	Geneticists use maps to describe the location of a particular gene on a chromosome. One type of map uses the cytogenetic location to describe a gene's position. The cytogenetic location is based on a distinctive pattern of bands created when chromosomes are stained with certain chemicals.
Paralogs or Paralogous genes	Paralogs are gene copies created by a duplication event within the same genome. While orthologous genes keep the same function, paralogous genes often develop different functions due to missing selective pressure on one copy of the duplicated gene.
SNP	SNPs are the most common type of genetic variation among people. Each SNP represents a difference in a single DNA building block, called a nucleotide. Most commonly, these variations are found in the DNA between genes.
gnomAD	It is a coalition of investigators seeking to aggregate and harmonize exome and genome sequencing data from a variety of large-scale sequencing projects, and to make summary data available for the wider scientific community.

SNP: single nucleotide polymorphism

Brugada syndrome -susceptibility genes
Brs-1 brugada syndrome 1; brgda1[17]

Locus: 3p21-23; OMIM: 601144; Gene: SCN5A. Only the SCN5A gene is classified as having definitive evidence as a cause for BrS[18]; Ion channel and effect: INa^+↓LOF; Protein: $Na_v1.5$- α subunit of the cardiac sodium channel carrying the sodium current INa^+; Proportion of BrS attributed to this genetic variant: 11-28%. Phenotypes: 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[19]. Figure 1 shows the numerous phenotypes with SCN5A mutations.

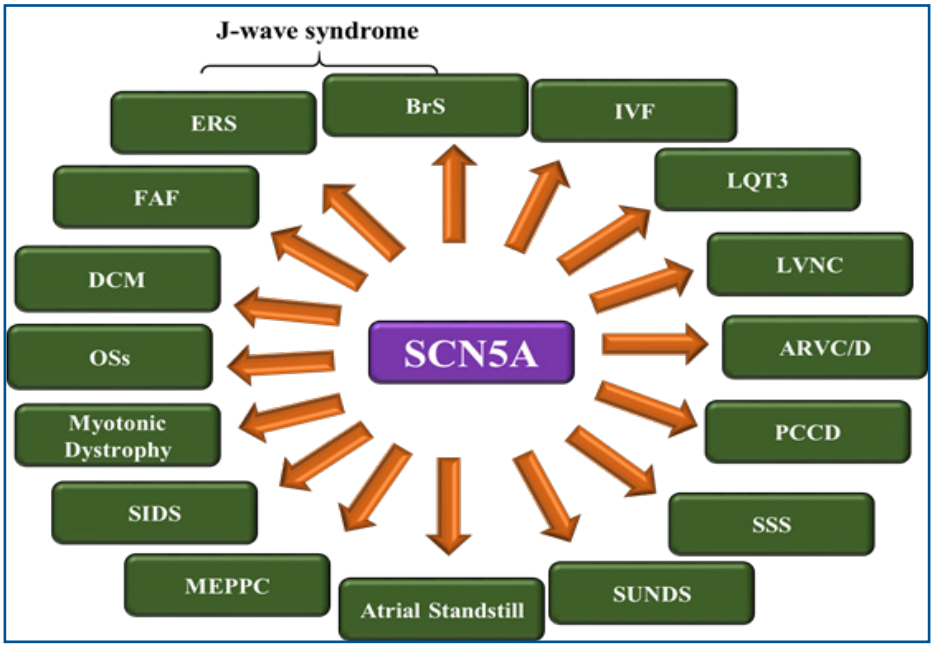

Figure 1: Representation of numerous phenotypes consequence of SCN5A gene mutations: ERS: Early repolarization syndrome; BrS: Brugada syndrome; LQT3: Congenital long QT syndrome variant 3; PCCD: Progressive Cardiac Conduction Disease or Lenègre disease; SSS: Sick Sinus Syndrome; SUNDS: Sudden Unexplained Nocturnal Death Syndrome; MEPPC: Multifocal Ectopic Purkinje-related Premature Contractions; SIDS: Sudden Infant Death Syndrome; OSs: Overlap syndromes; DCM: Dilated Cardiomyopathy; IVF: Idiopathic Ventricular Fibrillation; ARVD/C: Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy; LVNC: Left Ventricular Noncompaction; FAF: Familial Atrial Fibrillation.

↑GOF mutations in SCN5A lead to more sodium influx into the cardiomyocytes through aberrant channel gating and cause Congenital long QT syndrome variant 3 (LQT3)[20-22].

↓LOF mutations in SCN5A lead to lower levels of expression of SCN5A or production of defective $Na_v1.5$ proteins, thereby causing BrS.

↓LOF and ↑GOF mutations may cause Dilated Cardiomyopathy (DCM).

Other SCN5A-related diseases are: Multifocal Ectopic Purkinje-related Premature Contractions (MEPPC) (↑GOF mutations)23, isolated cardiac conduction defect (↓LOF mutations)24, Sick Sinus Syndrome (SSS) (↓LOF mutations), Familial Atrial Fibrillation (FAF) (↓LOF or ↑GOF mutations), and overlap syndromes (both ↓LFO and ↑GOF mutations). Growing insights into the role of SCN5A in health and disease has enabled clinicians to lay out gene-specific risk stratification schemes and mutation-specific diagnostic and therapeutic strategies in the management of patients with a SCN5A mutation[25].

Based on a study of AF in a large cohort of BrS patients, Amin *et al.*,[26] hypothesized that a reduced number of potentially triggering Premature Atrial Contractions (PACs) in the presence of a more extensive substrate in SCN5A mutation carriers may explain the fact that AF is not 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.

Figure 2 shows the sarcolemma cytoplasmic membrane crossed by the sodium channel, the components of this channel and the temporal correlation between the AP and the surface ECG (Electrocardiographic/ Electrocardiogram).

Mutations in the SCN5A gene can produce ↑GOF, ↓LOF or both in the sodium channel (figure 3).

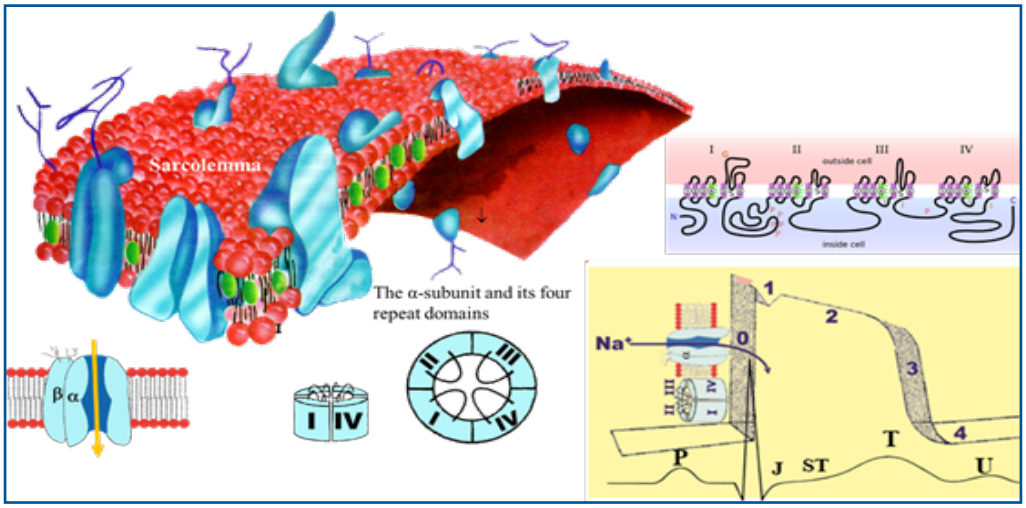

Figure 2: Representation of sodium channel structure across sarcolemma cytoplasmic membrane and fast AP with surface ECG (Electrocardiographic/Electrocardiogram) temporal correlation. Note sodium channel opening during phase 0 of monophasic AP in rapid fibers.

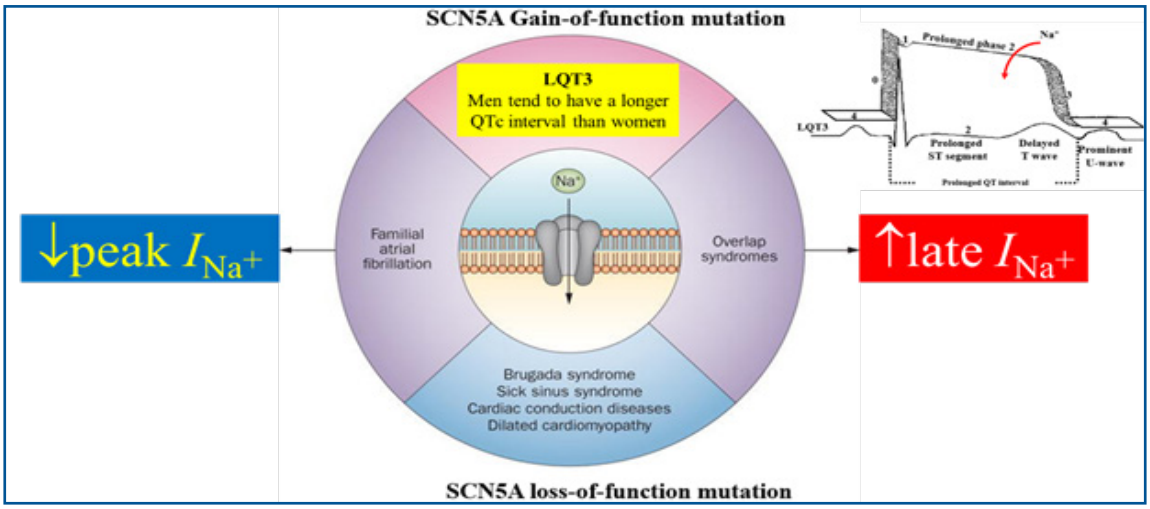

Figure 3: Mutations in SCN5A can produce various clinical phenotypes. SCN5A ↑GOF mutations can result in increased late I_{Na}, leading to LQT3. SCN5A ↓LOF mutations can lead to decreased ↓peak I_{Na}, which is associated with BrS, SSS, Progressive Cardiac Conduction Disease (Lenègre disease) (PCCD), and possibly DCM. Moreover, SCN5A mutations that cause both a gain in late I_{Na} and a loss of peak INa can be associated with a mixed phenotype or overlap syndromes (for example, BrS and LQT3). Similarly, both ↑GOF and ↓LOF mutations have been associated with FAF.

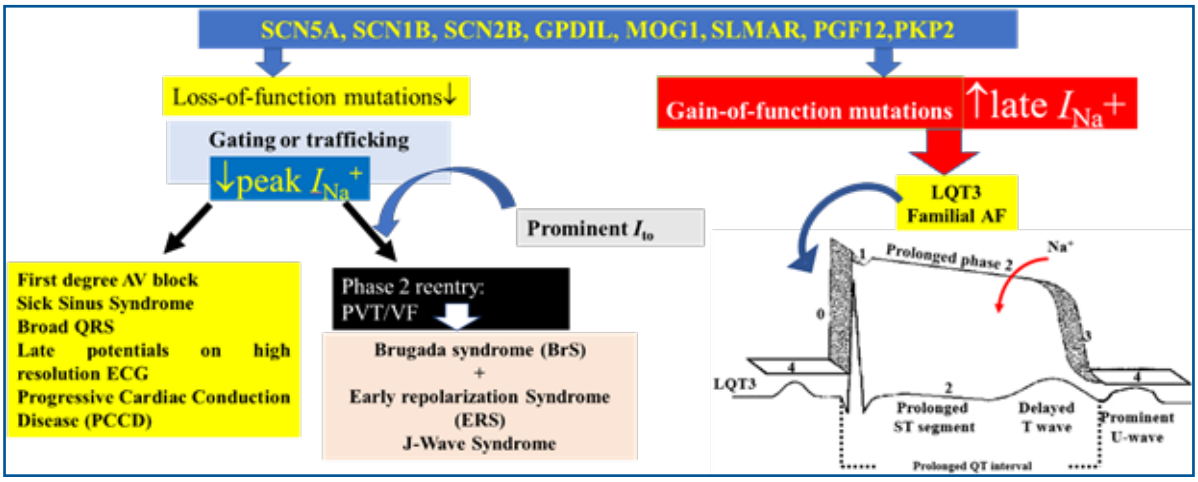

Figure 4: Shows the effect of SCN5A, SCN2B, GPDH, SLMAR, PGF12, and PKP2 mutations.

Overlap syndromes resulting from genetic defects caused by ↓LOF of sodium channel current (I_{Na}) or ↑GOF Late INa. In the absence of prominent Ito or IK-ATP, ↓LOF mutations in the inward currents result in various manifestations of PCCD. In the presence of prominent Ito or IK-ATP, ↓LOF mutations in inward currents cause conduction disease as well as J-wave syndromes (BrS and ERS). ↓LOF mutations of inward current in the presence of prominent ITO in certain regions of the Left Ventricle (LV), particularly the inferior wall, are considered etiologic factors of ERS (Early Repolarization Syndrome). The genetic defects that contribute to BrS and ERS can also contribute to the development of LQT3 and PCCD, in some cases causing multiple expressions of these overlap syndromes. In some cases, structural defects contribute to the phenotype, such as DCM, Left Ventricular Non compaction (LVNC).

More than 400 mutations have been identified in the SCN5A gene. Although the mechanisms of SCN5A mutations leading to a variety of channelopathies can be classified according to the alteration of INa-P and INa-L acting thorugh ↑GOF or ↓LOF, few researchers have summarized the mechanisms in this way[27]. ↑GOF mutations in *SCN5A* lead to more sodium influx into the cardiomyocytes through aberrant channel gating causing LQT3. Slowed or incomplete inactivation of the N*aV*1.5 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[20]. Carriers of this mutation may not only present with LQT3, but also with ECG (Electrocardiographic/ Electrocardiogram) features of sinus bradycardia, PCCD, and BrS, thus creating the first described arrhythmic 'overlap syndrome[28].

SCN5A 1795insD is supposed to be a ↑GOF mutation in light of the QT prolongation. A ↓LOF mutation cause sinus bradycardia, PCCD, and BrS. MEPPC is caused by both ↓LOF and ↑GOF mutations. ↓LOF in *SCN5A* result in amplitude reduction in the peak sodium current, leading to channel protein dysfunction or PCCD an entity with minor structural heart disease. Both↓LOF and ↑GOF mutations may cause DCM and/or AF[25]. ↑GOF MEPPC is a rare cardiac syndrome combining Polymorphic Ventricular Tachycardia (PVT) with DCM[23].

Experimental animal models have shown that there is a potential role for Purkinje fibers in the initiation of arrhythmias in different disease entities, such as LQT3 (SCN5A), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) (RyR2), and Idiopathic Ventricular Fibrillation (IVF) (DPP6). This is also the case in experimental clinical scenarios in MEPPC (SCN5A), IVF (DPP6)[29]. Recently, Haïssaguerre *et al.,*[30] found two potential explanations in arrhythmic SCD without apparent structural heart disease: a microstructural background (fibrosis, inflammation, fat infiltration, dysplasia, etc) or truly electrical heart disease in the myocardium or the Purkinje fibers. They highlighted three possible mechanisms: 1) focal excitation abnormality (IVF, CPVT, MEPPC); 2) dromotropic disturbance (BrS, J wave syndrome, IVF); and 3) repolarization abnormality (Long QT syndrome [LQTS], short QT syndrome [SQTS], ERS)[30].

In the ECG (Electrocardiographic/ Electrocardiogram), PR interval prolongation is the only parameter that predicted the presence of a SCN5A mutation in BrS.

Late potentials in high resolution ECG were more frequently observed in SCN5A mutation carriers[31].

SCN5A mutation is associated with an increased risk of drug-induced ventricular arrhythmia in patients without baseline type-1 BrS ECG. In particular, Snon-missense and Smissense-TP represent high risk[32].

The genetic basis of BrS is poorly understood, and there is growing evidence that many cases are polygenic, with familial inheritance rarely reported. Genetic testing in the clinical setting should be carefully considered and confined to *SCN5A*. Patients with a positive family history of disease, a spontaneous type 1 ECG pattern and symptomatic presentations may have a greater genetic yield though this is an area requiring further research.

Polygenic diseases are caused by numerous genetic and non-genetic factors, with coronary artery

disease being a well-described example. By performing genome-wide association studies (GWAS), thousands of single nucleotide variants which each provide a small incremental increased risk of disease can be identified[33]. A polygenic risk score (PRS) is the predicted additive effect of these variants which can be used to predict the risk of developing disease. While not currently in clinical practice, the study reported by Khera and colleagues illustrated the potential for PRS to provide important prognostic value in the management of patients with coronary artery disease[34]. By combining millions of common variants, a PRS was calculated showing better prediction of coronary artery disease than any single traditional risk factor. While promising, these findings are yet to be associated with clear clinical interventions, and to date have the greatest predictive power in European individuals. In the future, used in tandem with clinical investigations and information, PRS may enhance our ability to predict those at greater risk of complex diseases or adverse outcomes, even further necessitating access to specifically trained genetic counsellors.

Mutations in *SCN5A*, *GPDIL, KCND3* and *KCNJ8*, Kir6.1 genes s cause ↓LOF on Na^{+}↓INa^{+}/and ↓Ca^{++} and ↑GOF in ↑I_{TO} ↑$I_{K=ATP}$ channels affecting epi-/endomyocardial APs, resulting in the type 1 BrS ECG) pattern, triggers of short coupled PVCs and eventually VT/VF (figure 5).

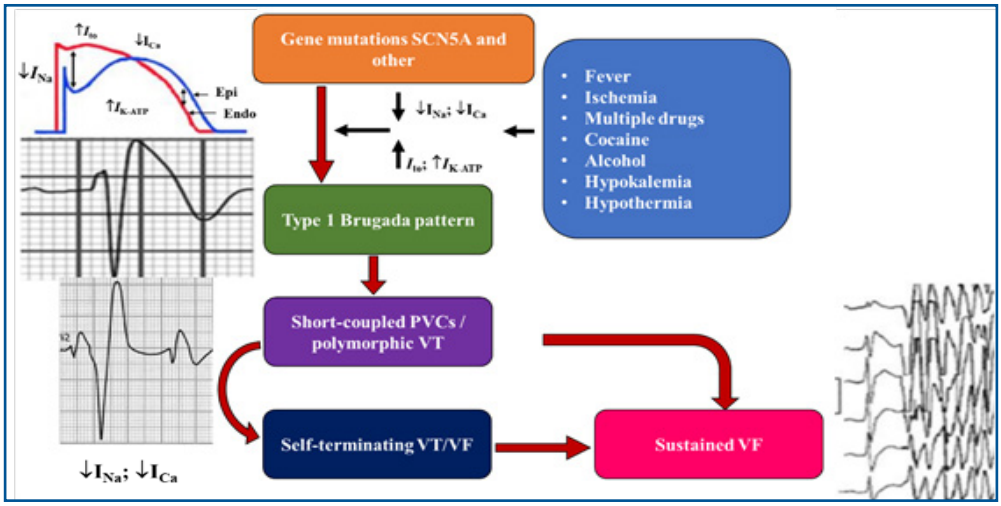

Figure 5: Effect of SCN5A mutation on epi-/endomyocardial action potentials, ECG type 1 Brugada pattern, triggers of short coupled PVCs and VT/VF.

Micaglui *et al.*, presented a case report, with a novel inherited frameshift mutation (c.4700_4701del (p. Phe1567Cysfs*221) in a single copy of the *SCN5A* gene associated with BrS. The proband experienced ventricular events successfully treated with DC-shock and he also suffered from supraventricular tachycardia. An ajmaline test confirmed the BrS diagnosis. The same mutation was found in the father and sister, who were both diagnosed with BrS. The authors hypothesize that this SCN5A frameshift mutation could be responsible for BrS and potentially linked to supraventricular tachycardias[35].

Monaski *et al.,* reported the novel NM_198056.2:c.1111C>T (p.Gln371*) heterozygous variant in the SCN5A gene, as well as its segregation with BrS in a large family. The proband was an Italian young adult woman, who had previously performed genetic counseling elsewhere with a positive test for the familial heterozygous variant in the *SCN5A* gene. She complained of palpitations. She underwent an ajmaline challenge, which was positive. Later on, she had PVT, underwent an Electrophysiological Study (EPS), which was positive, and received an Implantable Cardioverter Defibrillator (ICD). The proband then underwent RF of the AS, which was found in the epicardium of the RVOT. Ajmaline was administered prior to ablation, suggesting a pathogenic effect of this variant[36].

Monaski *et al.,* reported the largest family to-date with the segregation of the heterozygous variant NM 198056:c.4894C>T (p.Arg1632Cys) in the *SCN5A* gene. The genotype-phenotype relationship observed suggests a likely pathogenic effect of this variant. Functional studies to better understand the molecular effects of this variant are necessary[37].

Micaglio *et al.,* reported for the first time a family in which the inherited nonsense mutation [c. 3946C > T (p.Arg1316*)] in the SCN5A gene segregated in association with BrS. Moreover, they also reported, for the first time, the frameshift mutation [c.7686delG (p.Ile2563fsX40)] in the NF1 gene, as well as its association with type 1 neurofibromatosis (NF1). Both of these mutations and associated phenotypes were discovered in the same family. This genetic association may identify a subset of patients at higher risk of SCD. This case series highlights the importance of genetic testing not only to confirm the molecular pathology but also to identify asymptomatic family members, who need clinical examinations and preventive interventions, as well as to advise about the possibility of avoiding recurrence risk with medically assisted reproduction[38].

Micaglio *et al.,* presented a 30-year-old Italian male proband with a history of palpitations and syncope since puberty. He received a diagnosis of BrS elsewhere due to a spontaneous type 1 BrS ECG pattern. His brother had also been diagnosed with BrS, and had an ICD implanted. Prior to radiofrequency ablation of the arrhythmogenic substrate, genetic testing revealed the

variant NM_198056.2:c.2091G>A (p.Trp697X) in the SCN5A gene (Leiden Open Variation. A spontaneous type 1 ECG was observed. The novel heterozygous variant NM_198056.2:c.2091G>A (p.Trp697X) in the SCN5A gene segregates with BrS in the family presented, providing crucial human data relevant to understanding the pathology of BrS for patients with this variant. The study results suggested a likely pathogenic effect of the variant and could be used as a stepping stone for functional studies to better understand the molecular pathways involved[39].

Smani *et al.,* reported the *SCN5A* mutation L1393X, identified in a patient with overlap phenotypes PCCD and BrS and *SCN5A*-E1784K and SCN5A-H558R polymorphism causing Overlapping Phenotype of Long QT Syndrome, BrS, and Conduction Defect[40].

Eight *SCN5A* nonsense mutations were identified in BrS patients, L1393X[41] did not form functional channels, which may severely affect the electrophysiological properties of the heart. Interestingly, none of those eight nonsense mutations have been reported to cause PCCDs. Also, the proband patient did not show severe BrS phenotypes (*i.e.*, no syncope or aborted SCD) despite the severe functional defects of sodium channels. However, this might be due to the timing of diagnosis. Probst reported that conduction defects can be developed over time in the patients who carry the SCN5A mutations[42]. In addition, some patients with the spontaneous type 1 Brugada ECG pattern at rest or during drug-challenge tests experience severe ventricular events, whereas other patients or family members carrying the same mutations sometimes remain asymptomatic[43]. Since this is a single case report, there is a limitation in linking this experimental data to the clinical scenario[41].

There are four known common polymorphisms of the SCN5A gene related to BrS, including R34C, H558R, S1103Y, and R1193Q[44,45]. These polymorphisms could decrease expression of sodium-channel proteins and alter gating properties resulting in prolonged QRS duration and slow conduction in the heart[46]. The *SCN5A* mutations may be associated with early and frequent Ventricular Fibrillation (VF) recurrence or Sudden Cardiac Arrest (SCA) in BrS patients, which may be related to fibrosis in the epicardial surface of the right ventricular outflow tract[47]. SCN5A-R1193Q is a genetic marker associated with cardiac conduction defects and VF in symptomatic BrS patients.

Table 2 shows inherited cardiomyopathies and inherited arrhythmia syndromes with robust evidence for disease causation and figure 1 assesses the weight of evidence for pathogenicity using Gnomad: Genome Aggregation Database.

Table 2: Genes with robust evidence for disease causation

Phenotype	Key genes	Diagnostic yield of genetic testing
Inherited cardiomyopathies		
Hypertrophic cardiomyopathy	ACTC1, MYBPC3, MYH7, MYL2, MYL3, TNNI3, TNNT2, TPM1	30–50%
Isolated LV hypertrophy	ACTN2, FLNC, GLA, LAMP2, PLN, PRKAG2, TTR	<5%
Dilated cardiomyopathy	BAG3, DES, DMD, DSP, EYA4, FLNC, LMNA, MYH7, PLN, RBM20, SCN5A, TNNC1, TNNI3, TNNT2, TTN, TPM1, VCL	20-30%
AC	DSC2, DSG2, DSP, JUP, PKP2, PLN, TMEM43	50%
Inherited arrhythmia syndromes		
Long QT syndrome	KCNQ1, KCNH2, SCN5A	60-70%
CPVT	RYR2, CASQ2	50-60%
BrS	SCN5A	≈20%
Familial hypercholesterolemia		
Familial hypercholesterolemia	LDLR, APOB, PCSK9	30-40%
Familial aortopathies		
Thoracic aortic aneurysms; Loey-Deitz; Marfan syndrome	ACTA2, COL3A1, FBN1, LOX, MYH11, MYLK, PRKG1 SMAD3, TGFB2, TGFBR1, TGFBR2.	≈20%

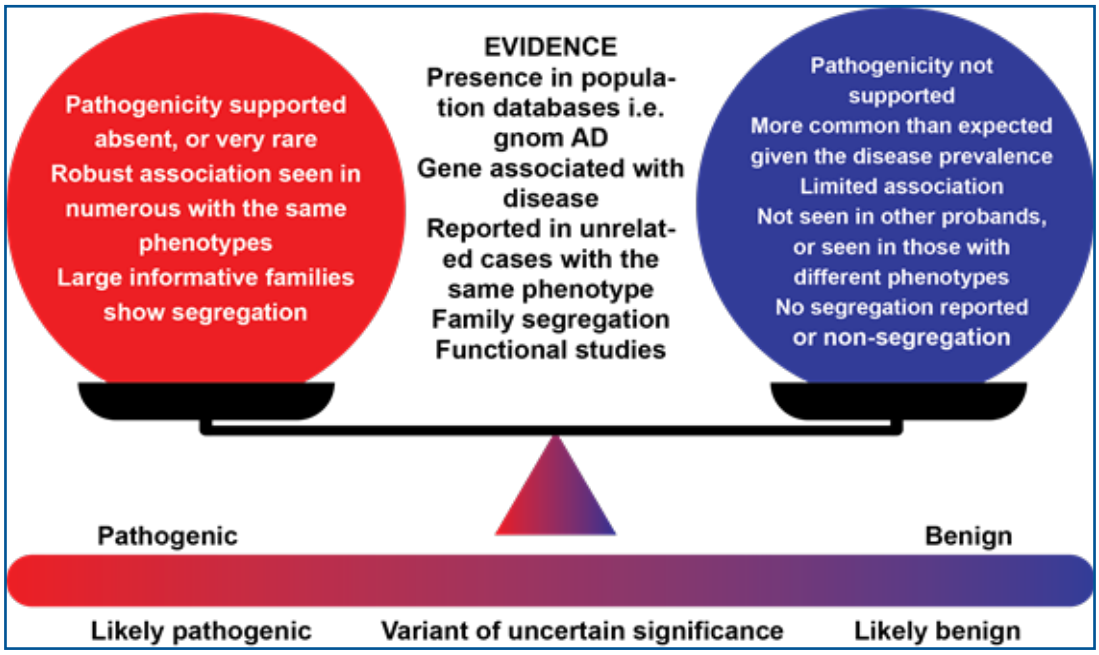

Figure 6: Shows the presence or absence of pathogenicity support

BrS-2 BRUGADA SYNDROME 2; BRGDA2

Locus: 12p13.3; OMIM: #611777; Gene: GPD1L; Ion channel and effect: ↓INa^+ LOF; Protein: Glycerol-3phosphate dehydrogenase 1-like protein. Peptide-reduced GPD1-L activity leads to phosphorylation of $N_a v1.5$ and decreased ↓INa^+ Channels affected and effect: ↓INa+ LOF. Amino acid substitution A280V[49]; Proportion of BrS attributed to this variant: Rare <1%[50]. Other Phenotypes: Defects in this gene may also cause Sudden Infant Death Syndrome sometimes known as "cot death" (SIDS), sometimes known as "cot death" - sudden, unexpected and unexplained death of an apparently healthy infant less than one year old despite thorough case investigation, including complete autopsy, examination of the death scene, and review of clinical history[51].

BrS-3 BRUGADA SYNDROME 3; BRGDA3

Locus: 12p13.33, which is the short (p) arm of chromosome 12 at position 13.33; OMIM: 114205; Gene: CACNA1C, Cav1.2; Ion channel and effect: ↓Ica^{2+} LOF; Protein: Voltage-dependent L-type calcium channel subunit α-1C/Cav1.2- a-subunit of the voltage-gated calcium channel carrying the L-type Ca2+ current ICa(L); Proportion of BrS attributed to this genetic variants: 6.6%; Amino acid Substitution: A39V, G490R; Other phenotypes: Timothy syndrome (TS1), SN5A and CACNA1C, complex BrS[52], congenital cardiac anomalies, cardiomyopathy, neonatal onset epileptic encephalopathy[53], bipolar type I disorder[54], schizophrenia[55].

BrS-4 BRUGADA SYNDROME 4; BRGDA4

Locus: 10p12.33; OMIM: 600003; Gene: CACNB2b, Cavβ2b; Ion channel and effect: ↓ICa^{++} LOF; Protein: Voltage-dependent L-type calcium channel subunit β-2 or 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; Proportion of BrS attributed to this genetic variants: 4.8%.

Note: 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[56] protein is required in the heart for control of cell proliferation and heart tube integrity[56].

BrS-5 BRUGADA SYNDROME 5; BRGDA5

Locus: 19q13,1; OMIM: 600235; Gene: SCN1B, Na↓1; Ion channel and effect: ↓INa+ ↓LOF. Heterologous expression assays illustrate that reported SCN1B mutations are ↓LOF and appear to interfere with modulation of channel gating[57]; Protein: Navβ1. Sodium channel subunit β-1 is a protein that in humans is encoded by the SCN1B gene: INa+.

This is proportion of BrS attributed to this genetic variants: 4.8%: 1.1%; Phenotypes: Mutation in the SCN1B gene are associated with BrS and generalized epilepsy with febrile seizures plus (GEFS+). GEFS+ is a syndromic autosomal dominant disorder where afflicted individuals can exhibit numerous epilepsy phenotypes. GEFS+ can persist beyond early childhood (*i.e.*, 6 years of age). GEFS+ is also now believed to encompass three other epilepsy disorders: severe myoclonic epilepsy of infancy (SMEI) or Dravet's syndrome, borderline SMEI (SMEB), and intractable epilepsy of childhood (IEC)[58]. ↓LOF mutations in the β-subunits (encoded by C) have also been described for AF[59].

OMIN: # 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. Other non-cardiac entities related to SCN1B mutations:

The mutation C121W occurred in temporal lobe epilepsy[60], and a single SCN1B mutation has been reported in Dravet syndrome (a rare, catastrophic, lifelong form of epilepsy that begins in the first year of life with frequent and/or prolonged seizures)[61].

BrS-6 BRUGADA SYNDROME 6; BRGDA6

Locus: 11q13-14; OMIM: 604433; Gene: KCNE3, MiRP2; Ion channel and affect: ↑I_{to} in phase 1 of the action potential. ↑GOF; Protein: Potassium voltage – gated channel subfamily E member 3 MiRP2- β subunit to voltage potassium channels. Modulates the transient outward potassium current I_{to}; Proportion of BrS attributed to this genetic variants: <1% (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.

Delpont *et al.,* studied 105 probands with the BrS, who were screened for ion channel gene mutations using single-strand conformation polymorphism electrophoresis and direct sequencing. A missense mutation (R99H) in KCNE3 (MiRP2) was detected in one proband. The R99H mutation was found 4/4 phenotype-positive and 0/3 phenotype-negative family members. Chinese hamster ovary-K1 cells were cotransfected using wild-type (WT) or mutant KCNE3 and either WT KCND3 or KCNQ1. Whole-cell patch clamp studies were performed after 48 hours. Interactions between Kv4.3 and KCNE3 were analyzed in coimmunoprecipitation experiments in human atrial samples.

Cotransfection of R99H-KCNE3 with KCNQ1 produced no alteration in tail current magnitude or kinetics. However, cotransfection of R99H KCNE3 with KCND3 resulted in a significant increase in the Ito intensity (↑GOF I_{to}) compared with WT KCNE3KCND3.

Using tissues isolated from the left atrial appendages of human hearts, the authors also demonstrated that Kv4.3 and KCNE3 can be coimmunoprecipitated. These results provide evidence for a functional role of KCNE3 in the modulation of Ito in the human heart and suggest that mutations in KCNE3 can underlie the development of the BrS[62]. A KCNE3 T4A mutation was identified in a Japanese patient presenting with the Brugada ECG-pattern and neurally mediated syncope (NMS). Its functional consequence was the ↑GOF of Ito, which could underlie the pathogenesis of this ECG pattern. The data provide novel insights into the genetic basis of Japanese BrS[63].

BrS-7 BRUGADA SYNDROME 7; BRGDA7

Locus: 11q23.3; OMIM: 6081214; Gene: SCN3B; Ion channel and affected: ↓INa ↓LOF[64,65]; Protein: Ran guanine nucleotide release factor; Proportion of BrS attributed to this genetic variants: <1% (rare).

Note: Navb-3 subunit of the cardiac sodium channel carrying the sodium current INa+; # 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.

The Val110Ile mutation of SCN3B is a relatively common cause of SCN5A-negative BrS in Japan, and has a reduced ↓ INa current because of the loss of cell surface expression of $N_a v1.5$[66].

BrS-8 BRUGADA SYNDROME 8; BRGDA8

Locus: 12q11. 23; OMIM: 600935, Gene: KCNJ8; Protein: Kir6.1; Ion channel and effect: ↑$I_{K=ATP}$ ↑GOF; Protein: ATP-sensitive inward rectifier potassium channel 8 Kir6, carries the inward rectifier potassium current.

This is proportion of BrS attributed to this genetic variants: 2%. # 613123. A number sign (#) is used with this entry because of evidence that BrS-8 is caused by heterozygous mutation in the HCN4 gene on chromosome 15q2467; Authors: KCNJ8 is a susceptibility gene for BrS and ERS (Early Repolarization Syndrome) and point to S422L as a possible hotspot mutation. The S422Linduced ↑GOF in ↑$I_{K=ATP}$ sensitive potassium channel current is due to reduced sensitivity to intracellular ATP[68].

BrS-9 BRUGADA SYNDROME 9; BRGDA9

Locus: 7q21.11; OMIM: 114204; Gene: CACNA2D1, Cavα2δ; Ion channel and effect: ↓ICa++ LOF; Protein: Voltage-dependent calcium channel subunit α2/δ1 subunit of the voltage-gated calcium channel carrying the L-type calcium current ICaL; Proportion of BrS attributed to this genetic variants: 1.8%. # 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[69].

Other phenotypes: Short QT syndrome type 6 (SQT6) was identified in a 17-year-old female who suddenly lost consciousness. VF was terminated by defibrillation. In hospital, her ECG showed a short QTc interval (329 ms) and tall, narrow T waves70. Programmed electrical stimulation could elicit AF and Ventricular Tachycardia (VT). Genetic screening revealed a S755T substitution CACNA2D1 encoded Cavα2δ-1 subunit of the L-type Ca2+ channel. Coexpression of the mutant Cavα2δ-1 subunit with Cav1.2α1 and Cavβ2b led to reduced ICa,L (using Ba2+ ions as charge carrier) compared to the WT control, without an obvious effect on surface expression, suggestive of a modification of single channel properties by the S755T Cavα2δ-171 and malignant hyperthermia susceptibility[72].

BrS-10 BRUGADA SYNDROME 10; BRGDA10

Locus:1p13.2; OMIM: 605411; Gene: KCND3, Kv4.3; Ion channel and effect: ↑I_{to} ↑GOF for the phase-1 repolarization of the action potential; Protein: Potassium voltage-gated channel subfamily D member 3. Kv4.3, α-subunit of the transient outward potassium channel Ito. An increased Ito may directly affect cardiac conduction. However, the effects of an increased Ito on AP upstroke velocity or sodium current at the cellular level remain unknown.

This is proportion of BrS attributed to this genetic variants: <1%. There is a prominent role of the Ito in BrS pathogenesis, the rare ↑GOF mutations in KCND3 serve as a pathogenic substrate for BrS. Giudicessi et al, provided the first molecular and functional evidence implicating novel KCND3 ↑GOF 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 highest[69].

Portero *et al.,*[73] investigated the consequences of KV4.3 overexpression on NaV1.5 current and consequent sodium channel availability. They found that overexpression of KV4.3 protein in HEK293 cells stably expressing NaV1.5 (HEK293-NaV1.5 cells) significantly reduced NaV1.5 current density without affecting its kinetic properties. In addition, KV4.3 overexpression decreased AP upstroke velocity in HEK293-NaV1.5 cells, as measured with the alternating voltage/current clamp technique.

These effects of KV4.3 could not be explained by alterations in total NaV1.5 protein expression. Using computer simulations employing a multicellular in silico model, the authors demonstrated that the experimentally observed increase in KV4.3 current and concurrent decrease in NaV1.5 currents may result in a dromotropic disturbance, underlining the potential functional relevance. This study gives the first proof of concept that KV4.3 directly impacts on NaV1.5 currents[73].

Giudicessi *et al.,*[69]. provided the first molecular and functional evidence implicating novel KCND3 ↑GOF mutations in the pathogenesis and phenotypic expression of BrS, with the potential for a lethal arrhythmia being precipitated by a genetically $\uparrow I_{to}$ current gradient within the RV where KCND3 expression is the highest[69].

BrS-11 BRUGADA SYNDROME 11; BRGDA11

Locus: 17p13.1; OMIM: 607954; Gene: RANGRF; Ion channel and effect: ↓INa+ ↓LOF; Protein: Sodium channel subunit beta 3that 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

This is proportion of BrS attributed to this genetic variants: <1% (rare)[74]; Olesen et al., while screening for the Nav1.5 cofactor MOG1, uncovered a novel nonsense variant, that appeared to be present more frequently among patients than in control subjects[75].

In cardiomyocytes, MOG1 is mostly localized in the cell membrane and co-localized with Nav1.5. MOG1 is a critical regulator of cardiac sodium channel function. Wu et al, demonstrated the functional diversity of Nav1.5-binding proteins, which have important functions for Nav1.5 under different cellular conditions[76].

Chakrabarti *et al.,*[75,77], screening for the Nav1.5 cofactor MOG1, uncovered a novel nonsense variant that appeared to be more frequent among patients than control subjects. This variant causes MOG1 ↓LOF and therefore, it might be disease causing or modifying under certain conditions[75,77].

BrS-12 BRUGADA SYNDROME 12; BRGDA12

Locus: 3p21.2-2-p14.3; OMIM: 602701; Gene: SLMAP; Ion channel and effect: $\downarrow INa^{+}$ ↓LOF; Protein: Sarcolemma membrane-associated protein (SLMAP), a component of T-tubes and the sarcoplasmic reticulum – influences trafficking of Nav1.5;

The proportion of BrS attributed to this genetic variants: Rare. T-tubules and sarcoplasmic reticulum are essential in excitation of cardiomyocytes, and SLMAP is a protein of unknown function localizing at T-tubules and sarcoplasmic reticulum. This protein belongs to the super family of tail anchored membrane proteins which serve diverse roles including cell growth, protein trafficking and ion channel regulation. Three main SLMAP isoforms (SLMAP1 (35 kDa), SLMAP2 (45 kDa), and SLMAP3 (91 kDa)) are expressed in the myocardium but their precise role is unknown[78].

The mutations in SLMAP may cause BrS via modulating the intracellular trafficking of hNav1.5 channel[79].

BrS-13 BRUGADA SYNDROME 13; BRGDA13

Locus:12p12.1; OMIM: 601439; Gene: ABCC9 SUR2A; Ion channel and effect: $\uparrow I_{K(ATP)}$ ↑GOF; Protein: SUR2A, the adenosine triphosphate (ATP) binding cassette transporter of the $I_{K(ATP)}$ channel; Proportion of BrS attributed to this genetic variants: 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 ERS (Early Repolarization Syndrome) and point to S422L as a possible hotspot mutation.

The S422L-induced ↑GOF in ATP-sensitive potassium channel current is due to reduced sensitivity to intracellular ATP. ABCC9 has ERS and BrS susceptibility genes. A ↑GOF in IK-ATP when coupled with a ↓LOF in SCN5A may underlie type 3 ERS, which is associated with a severe arrhythmic phenotype[68,80].

BrS-14 BRUGADA SYNDROME 14; BRGDA14

Locus: 11q23; OMIM: 601327; Gene: SCN2B, Navβ2; Ion channel and effect: ↓INa+ LOF; Protein: Sodium channel subunit β-2. Navβ2β -2subunit of the cardiac sodium channel carrying the sodium current ↓INa+; Proportion of BrS attributed to this genetic variants: <1% (rare).

Riuró *et al.,*[59] 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[81].

Other phenotypes: FAF[59]. Genetic deletion of SCN2B in mice resulted in ventricular (VAs) and atrial arrhythmias, consistent with reported SCN2B mutations

in human patients[82]. ↓INa+ LOF mutations were identified in patients with FAF and were associated with a distinctive ECG phenotype. Decreased Na+ current enhances AF susceptibility.

BRUGADA15 BRUGADA SYNDROME 15; BRGDA15

BrS15: Locus: 12p11; OMIM: 602861; Gene: PKP2; Protein: Desmosome protein Plakophillin-2; Ion channel and effect: ↓INa+ LOF; Proportion of BrS attributed to this genetic variants: <1% (rare).

Desmosome protein Plakophillin-2 interacts with INa+. Plakophilin-2 (PKP2) variants could produce a BrS phenotype, which is the same allelic disorder as some Sudden Unexplained Nocturnal Death Syndromes (SUNDS) variants.

All coding regions of the 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 eight 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 the PKP2 genetic phenotype in SUNDS was 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[83]. Mutations in proteins of the desmosome are associated with Arrhythmogenic Cardiomyopathy (AV). Life-threatening VAs often occur in the concealed forms/phases of the AC before the onset of structural changes.

It was suggested 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[84].

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 RV. Although BrS was initially described as a purely electric condition in intact hearts, it is now recognized that structural changes occur mainly at the RVOT[85].

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 current86 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[47].

BrS-16 BRUGADA SYNDROME 16; BRGDA16

Locus: 3q28-q29; OMIM: 601513; Gene: FGF12 (Fibroblast Growth Factor); Ion channel and effect: ↓INa+ LOF; Protein: FHAF1 Fibroblast growth factor homologues factor-1- mutation decreases ↓INa+; Proportion of BrS attributed to this genetic variants: <1% (rare)[87]. Multilevel investigations strongly suggest that Q7R-FGF12 is a disease-associated BrS mutation. FHF effects on↓INa+and ↓ICa++channels are separable.

Most significantly, a study by Hennessey et established 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 ↓INa+ and ↓ICa++channel currents, FHFs are candidate BrS loci[88]. Mutation FGF12 also causes neonatal-onset epilepsy[89].

BrS-17 BRUGADA SYNDROME 17; BRGDA17

Locus: 3p22.22; OMIM: 604427; Gene: SCN10A, Nav1.8; Ion channel and effect: ↓INa+ LOFβ; Protein: Nav1.8-α subunit of the neural sodium channel; Proportion of BrS attributed to this genetic variants: 5-16.7%.

Hu *et al.,*[90] 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[90], and is expressed in the myocardium and the conduction system, suggesting a possible role in the electrical function of the heart[91].

Mutations in the SCN10A gene cause ↓LOF in INa: Co-expression of SCN5A-WT with SCN10A-mutant cause a major ↓LOF in INa, in BrS patient[s90]. It is necessary to conduct studies in larger populations to better understand the role of SCN10A in BrSand other genetic cardiac arrhythmias[92].

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[93].

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 sodium current.

Fukuyama *et al*[94]., 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 VF, 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[94].

El-Battrawy et al used a cellular model of BrS to study SCN10A mutations using human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs). They observed that patient-specific hiPSC-CMs are able to recapitulate single-cell phenotype features of with SCN10A mutations and may provide novel opportunities to further elucidate the cellular disease mechanism95.

Gray *et al*[94]., observed that the lack of genotype-phenotype concordance among families, combined with the high frequency of previously reported mutations in the Genome Aggregation Database browser, suggests that SCN1B is not a monogenic cause of BrS or SADS[96].

SCN10A mutation phenotypes: possible association between variants in the SCN5A (600163), SCN10A, and HEY2 (604674) genes and BrS, see 601144. Associations Pending Confirmation; BrS+ERS3, SCN10A is an important susceptibility gene for BrS and for other cardiac syndromes, including cardiac conduction defect, ERS (Early Repolarization Syndrome), AF, VT/VF, RBBB, and bradycardia. SCN10A is known to be involved in nociception[97].

BrS-18 BRUGADA SYNDROME 18; BRGDA18

Locus: 6q22.3; OMIM: 604674; Gene: helix-loop-helix transcription factor HEY2 (transcriptional factor). Hey2 is specifically expressed in the embryonic mouse ventricles and is indispensable for ventricular myocyte differentiation, compartment identity and morphogenesis of the heart[98].

However, how Hey2 transcription is precisely regulated in the heart remains unclear; Ion channel and effect: ↓INa^+ LOF; Protein: Transcription factor identified in GWAS; Proportion of BrS attributed to this genetic variants: Rare.

Common variants of *SCN5A, SCN10A*, and HEY2 are associated with BrS[99].

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 this gene regulates cardiac electrical activity, shows that BrS may originate from altered transcriptional programming during cardiac development[99].

The study by Veerman *et al.*, uncovered a role of HEY2 in the normal transmural electrophysiological gradient in the ventricle and provided compelling evidence that genetic variation at 6q22.31 (rs9388451) is associated with BrS through a HEY2-dependent alteration of ion channel expression across the cardiac ventricular wall[100].

Andreasen *et al.,*[101] investigated whether three single-nucleotide polymorphisms (SNPs) (rs11708996; G>C located intronic to *SCN5A*, rs10428132; T>G located in *SCN10A*, and rs9388451; T>C located downstream to *HEY2*) at loci associated with BrS in a GWAS also were associated with AF. They concluded that the prevalence of three risk alleles previously associated with BrS was lower in AF patients than in patients free of AF, suggesting a protective role of these loci in developing AF[101].

Nakano *et al.,*[102] investigated relationships between genotypes of 3 single-nucleotide polymorphisms reported in a recent GWAS and BrS phenotypes. Their findings suggest that the *HEY2 CC* genotype may be a favorable prognostic marker for BrS, protectively acting to prevent VF presumably by regulating the repolarization current[102].

BrS-19 BRUGADA SYNDROME 19; BRGDA19

Locus: 7p12.1; OMIM: 603961; Gene: SEMA3A, semaphoring; Ion channel and effect: Ito ↑GOF; Protein: NaV1.5 - α subunit of the cardiac sodium channel carrying the sodium current INa; Proportion of BrS attributed to this genetic variants: <1% (rare). Boczek et al.103 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 ↑GOF mechanism[103].

The portion of *SEMA3A* is analogous to the Hanatoxin toxin, which binds to and inhibits potassium channels. ↑GOF of *Kv4.3* potassium channels in the heart can lead to a BrS phenotype that may be associated with SCD.

Boczek *et al.,* [103] identified a novel function for SEMA3A as a Kv4.3-specific channel blocker. Specifically, SEMA3A reduces Kv4.3 channel current density in a dose dependent manner, alters Kv4.3 channel kinetics, yet has no effect on other cardiac ion channels. SEMA3A co-immunoprecipitated with Kv4.3, suggesting a direct binding interaction between these two proteins. With the identification of rare SEMA3A mutations, leading to an overall ↑GOF in Kv4.3 current, genetic perturbations in SEMA3A may contribute to BrS[103].

BrS-20 BRUGADA SYNDROME 20; BRGDA20

Locus: 1P36.3; OMIM: 601142; Gene: *KCNAB2*; Protein: voltage-gated K(+) channel β2-subunit (Kvβ2-R12Q) subfamily A; Proportion of BrS attributed to this genetic variants: <1% (rare). Dysfunction in the *KCNAB2*, which encodes the voltage-gated potassium channel β2-subunit, was associated with increased Ito activity and identified as a putative gene involved in BrS. Kvβ2 dysfunction can contribute to the Brugada ECG pattern[3].

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 regulation of neurotransmitter release, heart rate, insulin secretion, neuronal excitability, epithelial electrolyte transport, smooth muscle contraction,

and cell volume. Four sequence-related potassium channel genes - shaker, shaw, shab, and shal - have been identified in Drosophila, and each has been shown to have human homolog(s).

This gene encodes a member of the potassium channel, voltage-gated, shaker-related subfamily. This member is one of the β subunits, which are auxiliary proteins associating with functional Kv-α subunits. This member alters functional properties of the *KCNA4* gene product. Alternative splicing of this gene results in multiple transcript variants encoding distinct isoforms.

Portero *et al*., [3] combined whole-exome sequencing and linkage analysis to identify the genetic variant likely causing BrS in a pedigree for which *SCN5A* mutations had been excluded. This approach identified six genetic variants cosegregating with the Brugada ECG pattern within the pedigree. In silico gene prioritization pointed to one variant residing in *KCNAB2*, which encodes the voltage-gated K(+) channel β2-subunit (Kvβ2-R12Q)[3].

Kvβ2 is widely expressed in the human heart and has been shown to interact with the fast Ito channel subunit Kv4.3, increasing its current density. By targeted sequencing of the *KCNAB2* gene in 167 unrelated patients with BrS, the authors found two additional rare missense variants (L13F and V114I). They then investigated the physiological effects of the three *KCNAB2* variants by using cellular electrophysiology and biochemistry[3].

Patch-clamp experiments performed in COS-7 cells expressing both Kv4.3 and Kvβ2 revealed a significant increase in the current density in presence of the R12Q and L13F Kvβ2 mutants. Although biotinylation assays showed no differences in the expression of Kv4.3, the total and submembrane expression of Kvβ2-R12Q were significantly increased in comparison with wild-type Kvβ2. Altogether, their results indicate that Kvβ2 dysfunction can contribute to the Brugada ECG pattern3.

BRGDA number?

Locus: 3p25.1; OMIM: *612048; Gene: Telethonin (TCAP) TITIN-CAP. This gene belongs to the TMEM43 family[104]; Protein: TMEM43 transmembrane protein 43. A missense mutation, c.1073C>T (p.S358L) in the transmembrane protein 43 (TMEM43) are the cause of familial Arrhythmogenic Right Ventricular Dysplasia (ARVD) type 5 (ARVD5), also known as Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) type 5 (ARVC5)[105], currently named AC.

It is an inherited disorder, often involving both ventricles, and is characterized by VT, heart failure, SCD, and fibrofatty replacement of cardiomyocytes.

This gene contains a response element for the Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) (an adipogenic transcription factor), which may explain the fibrofatty replacement of the myocardium, a characteristic pathological finding in AC. Using a positional cloning approach in a study of 15 families with ARVD/C mapping to chromosome 3 (ARVD5; 604400)[106].

Merner *et al.,*[106] identified TMEM43 as the gene mutated in this disorder. A very rare mutation in TMEM43 for the development of AC has a definite connection with desmosomal proteins (plakoglobin)[107] and results in a highly arrhythmogenic form of the disease with need for ICD implantation in all male patients and in a significant number of female patients.

BrS: number?

Locus: 12q15. By genomic sequence analysis, Nakane et al. (2004) mapped the Leucine-rich repeat containing 10 (LRRC10) gene.

They mapped the mouse Lrrc10 gene to chromosome 15[108]; OMIM: *610846; Gene: LRRC10. Together with Receptor Accessory Protein 5, LRRC10 is a Novel Regulators of Cardiac Excitation-Contraction Coupling Structure and Function[109]; Ion channel and effect: INa^{+}↓LOF; Protein: LRRC10 that is a cardiac-specific protein exclusively expressed in embryonic and adult cardiomyocytes[110].

The Proportion of BrS attributed to this genetic variant: Unknown %. Phenotypes: MGI Mutant phenotypes for LRRC10: inferred from 2 alleles cardiovascular system. The first report of genetic screening of LRRC10 was published in 2016 in Chinese SUNDS victims and BrS patients. LRRC10 may be a new susceptible gene for SUNDS, and an LRRC10 variant was initially and genetically linked to BrS-associated arrhythmia[111].

Silico-predicted malignant LRRC10 mutation p.E129K was detected in one SUNDS victim without pathogenic rare variants in a panel of 80 arrhythmia/cardiomyopathy-related genes. It was also shown that the rare variant p.P69L might contribute to the genetic cause for one SUNDS victim and two BrS family members. This was the first report of genetic screening of LRRC10 in Chinese SUNDS victims and BrS patients.

LRRC10 may be a new susceptible gene for SUNDS, and the LRRC10 variant was initially and genetically linked to BrS-associated arrhythmia[111].

Other phenotypes: human idiopathic DCM[112] and Anomalous Left Coronary Artery From The Pulmonary Artery. Gene Ontology annotations related to this gene include actin binding and alpha-actinin binding. Additionally, behavior/neurological phenotype mortality/aging muscle phenotype.

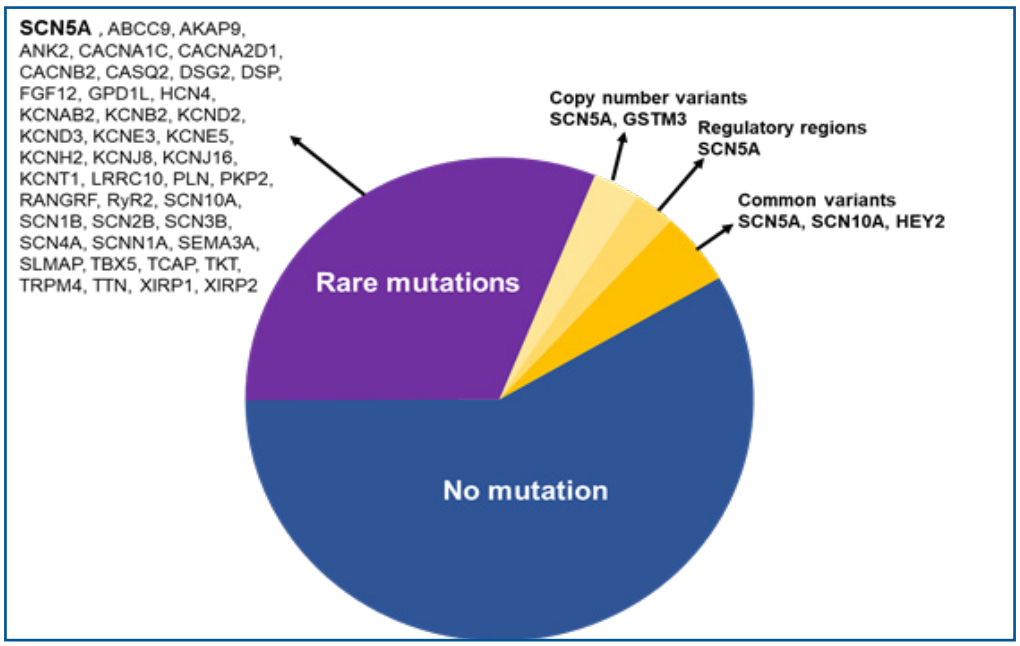

Figure 7: Illustrates percentages of genetic mutations in the BrS.

Table 3: Shows calcium channel mutations in BrS.

Channel	Gene	Protein	Proportion of BrS attributed to genetic variants %
Calcium	CACNA1C	Voltage-dependent L-type calcium channel subunit alpha 1C	6.6%
Calcium	CACNB2B	Voltage-dependent L-type calcium channel subunit beta 2	4.8%
Calcium	CACNA2D1	Voltage-dependent L-type calcium channel subunit α-2 delta 1	1.8%
Calcium	TRPM4	Transient receptor potential cation channel subfamily M member 4	<1%

Mutations in LTCC genes, including CACNA1C, CACNA1D, CACNB2 and CACNA2D, will induce dysfunctions of calcium channels, which result in the abnormal excitations of cardiomyocytes, and finally lead to cardiac arrhythmias. Nevertheless, the newly found mutations in LTCC and their functions are continuously being elucidated. These mutations are associated with long QT syndromes, Timothy syndrome (TS, OMIM 601005)[114], Brugada syndromes 3 BRGDA3, OMIM 611875)[115], overlap hypertrophic cardiomyopathy, SQTSs, ERP[116], CACNA1C cardiac arrhythmias, and a variety of neuropsychiatric disorders (bipolar disorder, major depression, schizophrenia, autism spectrum disorder, psychotic manifestations)[124].

Table 4: Shows sodium channel mutations in BrS.

Channel	Gene	Protein	Proportion of BrS attributed to genetic variants %
Sodium	SCN5A	Sodium channel protein type 5 subunit alpha	11-28%
Sodium	SCN10A	Neuronal sodium channel Nav 1.8	5-16.7%
Sodium	GD1-L	Glicerol-3phosphate dehydrogenase 1-lile protein	<1%
Sodium	SCN1B	Sodium channel subunit beta-1	1.1%
Sodium	SCN2B	Sodium channel subunit beta-2	<1%
Sodium	SCN3B	Ran guanine nucleptide release factor	<1%
Sodium	SLMAP	Sarcolemmal membrane-associated protein	<1%
Sodium	PKP2	Desmosome Protein Plakophilin-2	<1%
Sodium	RANGRF	Sodium channel subunit beta 3	<1%

SCN5A mutations phenotypes: Cardiac Phenotypes: Long QT Syndrome Type 3, Brugada Syndrome, Progressive Cardiac Conduction Disease (PCCD) or Lenègre Disease; Idiopathic Ventricular Fibrillation; Early Repolarization Syndrome (ERS); Sick Sinus Syndrome (SSS); Sudden Unexplained Nocturnal Death Syndrome (SUNDS); Multifocal Ectopic Purkinje-Related Premature Contractions (MEPPE); SIDS; Overlapping Syndromes (OSs); Dilated Cardiomyopathy (DCM); Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC); Left Ventricular Noncompaction (LVNC)[117]; Familial Atrial Fibrillation (FAF); Gastrointestinal: Irritable Bowel Syndrome.

Table 5: Shows potassium channel mutations in BrS.

Channel	Gene	Protein	Proportion of BrS attributed to genetic variants %
Potassium	KCND3	Potassium voltage-gated channel subfamily D member 3	<1%
Potassium	KCNE3	Potassium voltage-gated channel subfamily E member 3	<1%
Potassium	KCNJ8	ATP-sensitive inward rectifier potassium channel B	2
Potassium	HCN4	Hyperpolarization –activated cyclic nucleotide gated channel 4	<1%
Potassium	KCN5	Potassium voltage-gated channel subfamily E member 1-like protein	<1%

The cardiac potassium channels[118]

Cardiac potassium channels are membrane-spanning proteins that allow the passive movement of potassium ions across the cell membrane along its electrochemical gradient. They regulate the resting membrane potential, the frequency of pacemaker cells and the shape and duration of the cardiac APl. Normal potassium channel function is essential to maintain electrical stability in the heart. Gene mutations that alter the assembly, trafficking, turnover or gating of cardiac potassium channels can cause LQTS, SQTS, J-wave syndromes and AF.

1. Delayed Rectifier Potassium Currents/Channels

a) Rapid delayed rectifier potassium current (I_{Kr}) or The rapidly activating component of the delayed rectifier potassium current, I_{Kr}, rapid-rates of activation onset. Name: Kv11.1 (HERG), Gene: KCNH2, Human Chromosomal location:7q35–36 I_{Kr} and I_{NaL} are counterbalancing currents during the physiological ventricular AP and their integrals covary in individual myocytes. Targeting these ionic currents to normalize their balance may have significant therapeutic potential in heart diseases with repolarization abnormalities[119].

b) The slowly activating component of the delayed rectifier potassium current, IKs, slow-rates of activation onset: Name: Kv7.1 (KVLQT1), Gene: *KCNQ1*. Human Chromosomal location 11p15.5. A weaker IKs contributes to the longer action potential of the M cell[120].

c) The ultrarapid (I_{Kur}) ultra-rapid rates of activation onset. Name: *KCNA5*, Gene:12p13.3; Human chromosomal location: 12p13.3. In humans, chronic AF decreases the transient outward current and ultrarapid component of the delayed rectifier current differentially in both atria and increases the slow component of the delayed rectifier current in both[121].

2. Inward rectifying potassium channels

a) I_{K1}, "The transient outward current". Name: Kir2.1 (IRK1); Gene: *KCNJ2*; Human chromosomal location: 17q23.1–24.2.

b) I_{KATP} ATP-sensitive potassium channels, KATP. Name: Kir6.2 (BIR); Gene: KCNJ11; Human chromosomal location:11p15.1.

c) I_{KAch}: The acetylcholine-activated potassium current, I_{KAch}. Name: Kir3.1 (GIRK1); Gene: *KCNJ3*; Human chromosomal location: 2q24.111p15.1.

Inward rectifier potassium (Kir) channels typically conduct larger inward currents than outward currents, resulting in an inwardly rectifying current versus voltage relationship.

This property of inward rectification results from the voltage-dependent block of the channels by intracellular polyvalent cations and makes these channels uniquely designed for maintaining the resting potential near the potassium equilibrium potential (E_K). The Kir family of channels consist of seven subfamilies of channels (Kir1.x through Kir7.x) that include the classic inward rectifier (Kir2.x) channel, the G-protein-gated inward rectifier potassium (GIRK) (Kir3.x), and the adenosine triphosphate (ATP)-sensitive (K_{ATP}) (Kir 6.x) channels as well as the renal Kir1.1 (ROMK), Kir4.1, and Kir7.1 channels.

These channels not only function to regulate electrical/electrolyte transport activity, but also serve as effector molecules for G-protein-coupled receptors (GPCRs) and as molecular sensors for cell metabolism. Of significance, Kir channels represent promising pharmacological targets for treating a number of clinical

conditions, including cardiac arrhythmias, anxiety, chronic pain, and hypertension[122,123].

Transient outward currents

d) I_{tof} I_{to1} 4-aminopyridine (4-AP)-sensitive, calcium-independent potassium current (I_{to1}) is rapidly activated and inactivated in response to depolarization

e) I_{to2} I_{to2} 4-AP-insensitive, Ca^{2+}-activated Cl^- or potassium current (I_{to2})

3. Intracellular cation activated currents

a) IKNa,

b) IKCa and at least one

c) "background leak" current (IKleak)

Thus, we believe that this in-depth analytical study of the numerous mutations attributed to BrS can constitute a truly cornerstone that will help to better understand this intriguing syndrome.

CONCLUSION

- In less than three decades since the discovery of Brugada syndrome, the concept of Mendelian heredity has fallen apart. There is no doubt that the entity is oligogenetic associated with environmental factors.

- us that variants of uncertain significance, especially the rare variants of the SCN5A mutation, with European or Japanese ancestors, as well as spontaneous type 1 pattern or induced, thanks to gnomAD (coalition of researchers who seek to aggregate and harmonize exome and genome sequencing data from a variety of large-scale sequencing projects and make summary data available to the scientific community in general).

- The enormous variants and mutations found mean that we are still far from being able to concretely clarify a genotype-phenotype relationship.

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Resumo

Introdução: A Síndrome de Brugada (SBr) é uma entidade arrítmica clínico-eletrocardiográfica hereditária com baixa prevalência mundial. A síndrome é causada por alterações na estrutura e função de certos canais iônicos cardíacos e redução da expressão da Connexina 43 (Cx43) no Ventrículo Direito (VD), predominantemente no Trato de Saída do Ventricular Direito (VSVD), causando anormalidades eletromecânicas. O diagnóstico é baseado na presença de supradesnivelamento de ST espontâneo ou medicamentoso caracterizado por supradesnivelamento do ponto J e do segmento ST ≥2 mm, de convexidade superior "tipo covado" (subtipo 1A) ou modelo retilíneo descendente (subtipo 1B). A SBr está associado a um risco aumentado de síncope, palpitações, dor precordial, convulsões, dificuldade em respirar (respiração agonal noturna) e/ou Morte Cardíaca Súbita (MSC) secundária a PVT/VF, parada cardíaca inexplicada ou PVT/VF documentado ou Fibrilação atrial paroxística (FA) na ausência de doença cardíaca macroscópica ou estrutural aparente, distúrbio eletrolítico, uso de certos medicamentos ou coração coronário e febre. Em menos de três décadas desde a descoberta da síndrome de Brugada, o conceito de hereditariedade mendeliana se desfez. As enormes variantes e mutações encontradas significam que ainda estamos longe de sermos capazes de esclarecer concretamente uma relação genótipo-fenótipo. Não há dúvida de que a entidade é oligogenética associada a fatores ambientais, e que há variantes de significado incerto, principalmente as raras variantes da mutação SCN5A, com ancestrais europeus ou japoneses, bem como padrão espontâneo tipo 1 ou induzido, graças ao gnomAD (coalizão de pesquisadores que buscam agregar e harmonizar dados de sequenciamento de exoma e genoma de uma variedade de projetos de sequenciamento em grande escala e disponibilizar dados resumidos para a comunidade científica em geral). As enormes variantes e mutações encontradas significam que ainda estamos longe de sermos capazes de esclarecer concretamente uma relação genótipo-fenótipo. Assim, acreditamos que este estudo analítico em profundidade das inúmeras mutações atribuídas à BrS pode constituir uma verdadeira pedra angular que ajudará a compreender melhor esta síndrome intrigante.

Palavras-chave: Síndrome de Brugada, arrítmica, ambiental, genótipo, fenótipo.