J-wave syndromes: a genetic update summary

“We are in love when we realize that the other person is unique”

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The definition of the Brugada syndrome: Point of view

Brugada syndrome (BrS) is a hereditary arrhythmic entity with a low and incomplete worldwide prevalence (0.5 per 1,000 or 5 to 20 per 10,000 individuals), predominant in Southeast Asia (prevalence of 3.7 per 1,000) and in general much more frequent in Asians in relation to other ethnic groups: nine times more common in relation to Caucasians, 36 times more common than in Hispanics and almost non-existent in the north of the African continent Denmark. The entity is also highly prevalent in males (male / female ratio 9: 1 in Southeast Asia and 3: 1 male/female ratio in Caucasians), caused by alterations in the structure and function of certain cardiac ion channels and less expression of connexin 43 (Cx43) in the right ventricle predominantly in ventricular outflow tract (RVOT) causing electromechanical abnormalities. The lower and heterogeneous expression of Cx43 produces functionally significant electrophysiological heterogeneity in the thickness of the ventricular wall and may be a mechanism to promote transmural dispersion of repolarization. Until recently, it was considered an autosomal dominant Mendelian entity in ≈ 25% of cases or sporadic, although it is currently thought to be most likely an oligogenic disorder, rather than a Mendelian condition *, affecting several loci, influenced by environmental factors and whose Diagnosis is based on the presence of a spontaneous or drug-induced coved-type ST segment 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 1A) followed by a symmetric negative T wave in ≥ 1 high right and / or right precordial lead; with (Subtype 1C) or without associated early repolarization pattern in the inferior or inferolateral wall with an increased risk of syncope (fainting), palpitations, precodial pain, seizures, difficulty breathing (nocturnal agonal respiration), and / or sudden cardiac death (SCD) secondary to polymorphic ventricular tachycardia / ventricular fibrillation (PVT/VF) unexplained cardiac arrest or documented VF/polymorphic VT or paroxysmal atrial fibrillation in the absence of **macroscopic** or **apparent** structural heart disease, electrolyte disturbance, use of certain drugs or coronary heart and fever. and that typically occurs midnight-to-early-morning period at rest (≈80% of cases) or or at a low level of physical activity especially during sleep, which suggests

that the parasympathetic is a determining factor in, arrhythmogenesis: Higher level of vagal tone and higher levels of Ito at the slower heart rates. Although it is considered a genetic disease, its mechanism remains unknown in≈70-75% of cases and a single mutation is not sufficient to cause the BrS phenotype cases. Although ≈20% of patients with BrS carry mutations in *SCN5A*, the molecular mechanisms underlying this condition are still largely unknown.. BrS is associated in with mutations in the SCN5A gene, which encodes for the pore-forming α subunit of the cardiac Na^+ channels. *SCN5A*, which was identified as the first BrS-associated gene in 1998, has emerged as the most common gene associated with BrS, Only the *SCN5A* gene is classified as having definitive evidence as a cause for BrS. The role of genetics in the approach to the arrhythmic patient, progressing beyond the concept of "one mutation, one disease", and raising concerns about the most appropriate approach to patients affected by structural/electrical cardiomyopathy. Currently, the best model is the human patient population and probably BrS is an oligogenic disease (1). There have been more than 400 mutations in SCN5A gene that have been associated with BrS. This evidence-based review of genes reported to cause (BrS) and routinely clinically tested in patients indicates that 20 of 21 genes lack sufficient genetic evidence to support their causality for BrS. Type 2 pattern has also been associated with mutations in SCN5A, glycerol-3-phosphate dehydrogenase 1-like (GPD1L), 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 (LTCC) Mutations of 21 genes other than SCN5A have been implicated in the pathogenesis of BrS to date. Multiple pathogenic variants of genes have been shown to alter the normal function of Na+, K^+ Gain-of-function mutations in genes encoding for potassium channels have also been implicated in BrS. Genes influencing Ito include KCNE3, KCND3 and SEMA3A (semaphoring, an endogenous K+ channel inhibitor) while KCNJ8 and ABCC9 (encoding for SUR2A, the ATP-binding cassette transporter for the KATP channel) mutations affected the IK,ATP.

1. Michelle M. et al.Brugada Syndrome: Oligogenic or Mendelian Disease? Int J Mol Sci. 2020 Mar; 21(5): 1687.Published online 2020 Mar 1. doi: 10.3390/ijms21051687

KCNH2, which encodes for IKr was proposed by Wang et al.(1) to be involved in BrS development.

Dysfunction in the KCNAB2, which encodes the voltage-gated K^+ 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 electrocardiographic pattern.(2)

Classification of hereditary diseases

- ***Monogenic or Mendelian,*** to be transmitted to the offspring according to Mendel's laws. They can be
    1. Autosomal Dominant,
    2. Autosomal Recessive, 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.
- ***Multifactorial or polygenic:*** produced by mutations in several genes, generally of different chromosomes and the combination of multiple environmental factors (age, sex, bad habits (obesity, tobacco, alcohol), toxic environments or a limited childhood.) And
- ***Polygenic Oligogenic*,*** where there are a few genes that have more influence than the rest. In the case of BrS, the SCN5A gene and that depending on its presence other mutations are expressed (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.

1. Q Wang 1, Seiko Ohno , Wei-Guang Ding , Megumi Fukuyama , Akashi Miyamoto, Hideki Itoh , Takeru Makiyama ,et al Gain-of-Function KCNH2 Mutations in Patients with Brugada Syndrome. J Cardiovasc Electrophysiol . 2014 May;25(5):522-530. doi: 10.1111/jce.12361.
2. Vincent Portero, Solena Le Scouarnec, Zeineb Es-Salah-Lamoureux, Sophie Burel, Jean-Baptiste Gourraud, Stéphanie Bonnaud, Pierre Lindenbaum, et al. Dysfunction of the Voltage-Gated K+ Channel β2 Subunit in a Familial Case of Brugada Syndrome,J Am Heart Assoc. 2016 Jun; 5(6): e003122. doi: 10.1161/JAHA.115.003122

Hosseini et al.'s evidence-based review of genes reported to cause BrS and routinely clinically tested in patients indicated that 20 of 21 genes lacked sufficient genetic evidence to support their causality for BrS (1). Furthermore, ancestral differences also impact the interpretation of classification of pathogenicity of variants identified from BrS patients (2). The causality of BrS-associated genes is much disputed; many of these genes demand further research but may be clinically validated in the future. 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 (3). New technologies such as microarrays, whole-exome sequencing, and whole genome sequencing, which are able 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 cost (4). Therefore, it is only a matter of time before the puzzle of genetics in BrS is solved(5;6)

1. **Hosseini SM, Kim R, Udupa S, et al. Reappraisal of Reported Genes for Sudden Arrhythmic Death: An Evidence-Based Evaluation of Gene Validity for Brugada Syndrome. Circulation 2018;138:1195-205.**
2. **Chen CJ, Lu TP, Lin LY, et al. Impact of Ancestral Differences and Reassessment of the Classification of Previously Reported Pathogenic Variants in Patients With Brugada Syndrome in the Genomic Era: A SADS-TW BrS Registry. Front Genet 2018;9:680.**
3. **Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. Proc Natl Acad Sci U S A 1977;74:5463-7**
4. **Juang JJ, Liu YB, Chen CJ, et al. Validation and Disease Risk Assessment of Previously Reported Genome-Wide Genetic Variants Associated with Brugada Syndrome: SADS-TW BrS Registry. Circ Genom Precis Med 2020;13:e002797.**
5. **Ching-Yu Julius Chen 1, Eric Y Chuang 2The puzzle of genetics in Brugada syndrome: a disease with a high risk of sudden cardiac death in young people. Ann Palliat Med. 2020 Sep 10;apm-20-1510. doi: 10.21037/apm-20-1510.**
6. **Chen CJ, Juang JJ, Lin LY, et al. Gender Difference in Clinical and Genetic Characteristics of Brugada Syndrome: SADS-TW BrS Registry. QJM 2019;112:343-50.**

A microarray is a multiplex lab-on-a-chip. It is a two-dimensional array on a solid substrate—usually a glass slide or silicon thin-film cell—that assays (tests) large amounts of biological material using high-throughput screening miniaturized, multiplexed and parallel processing and detection methods.Microarrays was first introduced and illustrated in antibody microarrays by Tse Wen Chang in 1983 (1) and a series of patents (2). The "gene chip" industry started to grow significantly after the 1995 Science Paper by the Ron Davis and Pat Brown labs at Stanford University. (3) With the establishment of companies, such as Affymetrix,, the technology of DNA microarrays has become the most sophisticated and the most widely used, while the use of protein, peptide and carbohydrate microarrays (4) is expanding. Types of microarrays include: DNA microarrays, such as cDNA microarrays, oligonucleotide microarrays, BAC microarrays and SNP microarrays, MM Chips, for surveillance of microRNA populations, protein microarrays, peptide microarrays, for detailed analyses or optimization of protein–protein interactions, tissue microarrays, cellular microarrays or transfection microarrays, chemical compound microarrays, antibody microarrays, glycan arrays, phenotype microarrays, averse phase protein lysate microarrays, microarrays of lysates or serum, interferometric reflectance imaging sensor (IRIS). People in the field of CMOS biotechnology are developing new kinds of microarrays. Once fed magnetic nanoparticles, individual cells can be moved independently and simultaneously on a microarray of magnetic coils. A microarray of nuclear magnetic resonance micro coils is under development. (5)

1. **Tse-Wen Chang, TW (1983). "Binding of cells to matrixes of distinct antibodies coated on solid surface". Journal of Immunological Methods. 65 (1–2): 217–23. doi:10.1016/0022-1759(83)90318-6.**
2. **Schena, M.; Shalon, D.; Davis, R. W.; Brown, P. O. (1995). "Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray". Science. 270 (5235): 467–70. doi:10.1126/science.270.5235.467.**
3. **Wang, D; Carroll, GT; Turro, NJ; Koberstein, JT; Kovác, P; Saksena, R; Adamo, R; Herzenberg, LA; Herzenberg, LA; Steinman, L (2007). "Photogenerated glycan arrays identify immunogenic sugar moieties of Bacillus anthracis exosporium". Proteomics. 7 (2): 180–184. doi:10.1002/pmic.200600478.Ham, Donhee; Westervelt, Robert M. (2007). "The silicon that Moves and Feels Small Living Things". IEEE Solid-State Circuits Newsletter. 12 (4): 4–9. doi:10.1109/N-SSC.2007.**
4. **Wang, D; Carroll, GT; Turro, NJ; Koberstein, JT; Kovác, P; Saksena, R; Adamo, R; Herzenberg, LA; Herzenberg, LA; Steinman, L (2007). "Photogenerated glycan arrays identify immunogenic sugar moieties of Bacillus anthracis exosporium". Proteomics. 7 (2): 180–184. doi:10.1002/pmic.200600478.**
5. **Ham, Donhee; Westervelt, Robert M. (2007). "The silicon that Moves and Feels Small Living Things". IEEE Solid-State Circuits Newsletter. 12 (4): 4–9. doi:10.1109/N-SSC.2007.4785650**

Whole-exome sequencing (WES)

It 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.(1) 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 these variants can be responsible for both Mendelian and common polygenic diseases, whole exome sequencing has been applied both in academic research and as a clinical diagnostic. 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;(2) by contrast, techniques such as SNP arrays can only detect shared genetic variants that are common to many individuals in the wider population.(3) Furthermore, because severe disease-causing variants are much more likely (but by no means exclusively) to be in the protein coding sequence[citation needed], focusing on this 1% costs far less than whole genome sequencing but still detects a high yield of relevant variants. In the past, 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 only certain types of variation (e.g. comparative genomic hybridization) but provided definitive genetic diagnoses in fewer than half of all patients.(4) 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 features

1. Ng SB, Turner EH, Robertson PD, Flygare SD, Bigham AW, Lee C, Shaffer T, Wong M, Bhattacharjee A, Eichler EE, Bamshad M, Nickerson DA, Shendure J (10 September 2009). "Targeted capture and massively parallel sequencing of 12 human exomes". Nature. 461 (7261): 272–276. Bibcode:2009Natur.461..272N. doi:10.1038/nature08250.

2. Sarah B Ng; Kati J Buckingham; Choli Lee; Abigail W Bigham; Holly K Tabor; Karin M Dent; Chad D Huff; Paul T Shannon; Ethylin Wang Jabs; Deborah A Nickerson; Jay Shendure; Michael J Bamshad (2010). "Exome sequencing identifies the cause of a mendelian disorder". Nature Genetics. 42 (1): 30–35. doi:10.1038/ng.499.
3. Wang, D. G.; Fan, J. B.; Siao, C. J.; Berno, A.; Young, P.; Sapolsky, R.; Ghandour, G.; Perkins, N.; Winchester, E. (1998-05-15). "Large-scale identification, mapping, and genotyping of single-nucleotide polymorphisms in the human genome". Science. 280 (5366): 1077–1082. Bibcode:1998Sci...280.1077W. doi:10.1126/science.280.5366.1077.
4. Rauch, A; Hoyer, J; Guth, S; Zweier, C; Kraus, C; Becker, C; Zenker, M; Hüffmeier, U; Thiel, C; Rüschendorf, F; Nürnberg, P; Reis, A; Trautmann, U (Oct 1, 2006). "Diagnostic yield of various genetic approaches in patients with unexplained developmental delay or mental retardation". American Journal of Medical Genetics Part A. 140 (19): 2063–74. doi:10.1002/ajmg.a.31416.

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.(1)

Whole genome sequencing has largely been used as a research tool, but was being introduced to clinics in 2014(**2-4**)

1. Definition of whole-genome sequencing - NCI Dictionary of Cancer Terms". National Cancer Institute. 2012-07-20. Retrieved 2018-10-13.

]In the future of personalized medicine, whole genome sequence data may be an important tool to guide therapeutic intervention.(5) The tool of gene sequencing at 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.(6)

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.(7)

5. **Mooney, Sean (Sep 2014). "Progress towards the integration of pharmacogenomics in practice". Human Genetics. 134 (5): 459–65. doi:10.1007/s00439-014-1484-7. PMC 4362928**
6. **van El, CG; Cornel, MC; Borry, P; Hastings, RJ; Fellmann, F; Hodgson, SV; Howard, HC; Cambon-Thomsen, A; Knoppers, BM; Meijers-Heijboer, H; Scheffer, H; Tranebjaerg, L; Dondorp, W; de Wert, GM (June 2013). "Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics". European Journal of Human Genetics. 21 Suppl 1: S1–5. doi:10.1038/ejhg.2013.46. PMC 3660957. PMID 23819146**
7. **Psst, the human genome was never completely sequenced". STAT. 2017-06-20. Archived from the original on 2017-10-23. Retrieved 2017-10-23.**

Genes associated with Brugada syndrome and Early Repolarization Syndrome				
Gene/ OMIM	**BrS**	**ERS**	**Protein /Locus**	**Functional effect/author**
SCN5A/ # 601144	Yes BrS1	Yes	Cardiac sodium channel alpha subunit (Nav1.5) / Locus on chromosome 3p21	Loss of function, reduced Na1 current (**Chen Q et al 1998**). 20-30% of all cases.
GPD1-L/ # 911778	Yes BrS2	No	Glycerol-6-phosphatedehydrogenase / Locus on chromosome 3p22.3	Loss of function, reduced Na1 current (**London B et al 2007**)
CACNA1c/ # 114205	Yes BrS3	Yes	L-type calcium channel α subunit (Cav1.2) / Locus on chromosome 12p13.3	Loss of function, reduced Ca21 current (**Antzelevitch C et al 2007**)
CACNB2/ 114205	Yes BrS4	Yes	L-type calcium channel β subunit (Cav1.2) / Locus on chromosome 10p12.33-p12.31	Loss of function, reduced Ca21 current(**Antzelevitch C et al 2007**)
SCN1B/ # 612838	Yes BrS5	No	Cardiac sodium channel beta1 subunit /19q13.1	Loss of function, reduced Na1 current (**Watanabe H et al 2008**)
KCNE3/ # 613119	Yes BrS6	No	Transient outward current beta subunit-transient outward current /11q13-14	Gain of function, increased K1 Ito current (**Delpon E et al 2008**)
SCN3B/ # 6081214	Yes BrS7	No	Cardiac sodium channel beta-3 subunit / 11q23.3	Loss of function, reduced Na1 current (**Hu D et al** 2009)
HCN4 # 613123	Yes BrS8	Yes	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4/ Locus on chromosome 15q24.1	↑$\mathbf{I_{K=ATP}}$ 2% (**Ueda K, et al 2009**.) (**Crotti, L, et al.2012**) (**Barajas-Martinez H, et al. 2012**)
KCND3 # 616399	Yes BrS9	Yes	Potassium voltage-gated channel subfamily D member 3 or K_v4.3/Locus on chromosome 1p13.	Transient outward current or ↑Ito gain-of-function (**Giudicessi, J. R., et al 2011**.)

Gene/ OMIM	BrS	ERS	Protein /Locus	Functional effect/author
CACNA2D1	Brs 10		Cavα2δ−1/Locus on chromosome 7q21-22	Loss-of-function LOF
RANGRF	BrS11		MOGI/17p13.1	Loss-of-function LOF Rare (Olesen MS, et al, 2011)
KCNE5(*KCNE 1L*)	BrS12		MiRP4/Locus on chromosome Xq22.3	Kv4.3, I_{to} Gain-of-function (GOF) (Ohno S, et al, 2011)
KCND3	BrS13? Or BrS9		Potassium Voltage-gated Channel, Shal-related Subfamily, Member 3/Locus on chromosome: 1p13.2	↑I_{to} Gain-of-function (GOF) (Postma,A.V 2000) (Giudicessi, J. R et al 2012)
HCN4	BrS14		Hyperpolarization-activated Cyclic Nucleotide-gated Potassium Channel 4 /Locus on chromosome 15q24.1	GOF ↑IK^+Rare (Crotti, L, et al 2012)
SLMAP	BrS15 and Cerebral Cavernous Malformations, 3		Sarcolemma Menbrane Associated Protein /Locus on chromosome 3p21.2-p14.3	↓INa^+modulating the intracell, ular trafficking of hNav1.5 channel. (Ishikawa T, et al. 2012)
TRPM4	BrS16		NSCCa/Locus on chromosome 19q13.33	Abnormal resting potential. Rare (Hui Liu, et al 2013)
SCN2B * 601327	BrS17		Sodium Voltage-gated Channel, Beta Subunit 2Navβ3/Locus on chromosome 11q23.3	Loss-of-function(LOF)↓INa^+ Rare (Riuro, H et al 2013)
SCN10A * 604427	BrS18		Sodium Voltage-gated Channel, Alpha Subunit 10Nav1.8/Locus on chromosome 3p22.2	↓INa^+ Loss-of-function(LOF) Rare (Fukuyama M 2016)
HEY2 * 604674	Yes BrS19	No	Hes related family bHLH transcription factor with YRPW motif 2Nav1.5/Locus on chromosome 6q22.31	Loss-of-function(LOF) (Christiaan C Veerman, et al 2017)
PKP2	Yes BrS20	No ARV C9	Plakophilin-2 PKP2/Locus on chromosome 12p11.21 12p13	Loss-of-function (LOF) ↓INa^+ (**Cerrone M et al, 2013, 2014**)

Gene/ OMIM	BrS	ERS	Protein /Locus	Functional effect/author
ABCC9 * 601439	Yes Brs 21	Yes	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9 *SUR2A* (sulfonylurea receptor subunit 2 A), IK-ATP)/ /Locus on chromosome *12p12.1*	GOF/ (**Hu D et al 2014**)

Genetic basis of Brugada syndrome

Gene	Frequency	Functional abnormalities
INa^+ channel dysfunction		
SCN5A	20-30%	LOF $\downarrow INa^+$
SCN10A	Rare	LOF $\downarrow INa^+$
SCN1B	Rare	LOF $\downarrow INa^+$
SCN2B	Rare	LOF $\downarrow INa^+$
SCN3B	Rare	LOF $\downarrow INa^+$
GPD1L	Rare	LOF $\downarrow INa^+$
MOGI1	Rare	LOF $\downarrow INa^+$
SLMAP	Rare	LOF $\downarrow INa^+$
PKP2	Rare	LOF $\downarrow INa^+$

Gene	Frequency	Functional abnormalities
Ca^{++} channel dysfunction		
CACNA1C	1-3%	LOF $\downarrow Ca^{++}$
CACNB2	1-3%	LOF $\downarrow Ca^{++}$
CACNA2D1	1-3%	LOF $\downarrow Ca^{++}$
K^+ channel dysfunction		
HCN4	Rare	GOF $\uparrow IK^+$
KCNE3	Rare	GOF $\uparrow IK^+$
KCNE5	Rare	GOF $\uparrow IK^+$
ABCC9	Rare	GOF $\uparrow IK^+$
KCNJ8	Rare	GOF $\uparrow IK^+$
KCNH2	Rare	GOF $\uparrow IK^+$
PKP2	Rare	GOF $\uparrow IK^+$
Others TRPM4	Rare	Abnormal resting potential

LOF: Loss of function; GOF: Gain of function

Gene	Yes	No	Protein/lLocus	Functional deffect
KCNH2	Yes	No	Rapid component of the cardiac delayed rectifier current	Increased repolarizing current (gain of function)
KCNJ8	Yes	Yes	Acetylcholine-dependent potassium current / 12p11.23	Incomplete closing of the ATP-sensitive potassium channels
CACNA2D1	Yes	No	L-type calcium channel delta 2 subunit	Loss of function, reduced Ca21 current
RANGRF	Yes	No	RAN protein GTP releasing factor	Unknown (possible effect on sodium current)
KCNE5	Yes	No	Potassium channel β 5 subunit transient outward current	Gain of function, increased K1 Ito current
KCND3	Yes	No	SHAL potassium channel isoform 3-transient outward current	Gain of function, increased K1 Ito current
HCN4	Yes	No	Hyperpolarization activated potassium channel (If)	No functional studies available
SLMAP	Yes **BrS 12**	No	Sarcolemmal membrane–associated protein	Reduced Na^+current (impaired NaV 1.5 trafficking) **↓INa. Rare** Ishikawa T,et al. 2012)
TRPM4	Yes	No	Calcium-activated cationic channel subfamily M isoform 4	Reduced sodium current
SCN2B	Yes	No	Cardiac sodium channel Beta 2 subunit	Loss of function, reduced Na1 current
SCN10A	Yes	Yes	Voltage-gated sodium channel alpha subunit 10	Reduced NaV1.8 current
MOG1	Yes **BrS 11**	No	Guanine nucleotide release factor, control of NaV1.5 trafficking Locus **17p13.1**	Loss of function, **↓INa^+** reduced Na current (**Olsen MS, et al. 2011**) Rare.
TRPM4	Yes	No	Calcium-activated cationic channel subfamily M isoform 4	Reduced sodium current
SCN2B	Yes	No	Cardiac sodium channel Beta 2 subunit	Loss of function, reduced Na1 current

	Brugada Syndrome	Early Repolarization Syndrome	Possible Mechanism(s)
Ameliorative response to cilostazol	Yes	Yes	Increased ICa, reduced Ito and faster heart rat
Ameliorative response to pacing	Yes	Yes	Reduced availability of Ito due to slow recovery from inactivation
Vagally mediated accentuation of ECG pattern	Yes	Yes	Direct effect to inhibit ICa and indirect effect to increase Ito (due to slowing of heart rate)
Effect of sodium channel blockers on unipolar epicardial electrogram	Augmented J waves	Augmented J waves	Outward shift of balance of current in the early phases of the epicardial AP
Fever	Augmented J waves	Augmented J waves	Accelerated inactivation of INa and accelerated recovery of Ito from inactivation
Hypothermia	Augmented J waves mimicking BrS	Augmented J waves	Slowed activation of ICa, leaving Ito unopposed. Increased phase 2 reentry but reduced pVT due to prolongation of APD (Morita et al 2007)

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Genetic defects associated with Early Repolarization Syndrome and genetic mutation shared with BrS

	Locus	Gene/protein	Gene shared with BrS	Ion channel	% of probands
ERS1	12p11.23	KCNJ8, Kir6.1	BrS8	↑ $I_{K\text{-}ATP}$	Rare
ERS2	12p13.3	CACNA1C, $Ca_v1.2$	BrS3	↓ I_{Ca}	4.1%
ERS3	10p12.33	CACNB2b, $Ca_v\beta2b$	BrS4	↓ I_{Ca}	8.3%
ERS4	7q21.11	CACNA2D1, $Ca_v\alpha2\delta1$	BrS9	↓ I_{Ca}	4.1%
ERS5	12p12.1	ABCC9, SUR2A	Brs13	↑ $I_{K\text{-}ATP}$	Rare
ERS6	3p21	SCN5A, $Na_v1.5$	BrS1	↓I_{Na}	Rare
ERS7	3p22.2	SCN10A, $Na_v1.8$	BrS17	↓ I_{Na}	Rare
ERS8	1p13.2	KCND3, $K_v4.3$	BrS10	↑I_{TO}	Rare
ERS9 or IVF	7q36.2	DPP6/Dipeptidyl aminopeptidase-like protein 6	Familial idiopathic VF (1)	↑I_{TO}	Rare
ERS10 (2) (2020)	3p24	GPD1L/ glycerol-3-phosphate dehydrogenase 1-like	BrS2 (3) 2007 + SIDS (4) 2007	↓ I_{Na}	Rare

Alders, M., et al, 2009.; Jun Fan,et al 2020.; London B,et al.2007.; Van Norstrand DW, et al.2007)