Brugada Syndromes types, locus, OMIM, gene, channels affected, percentage and authors

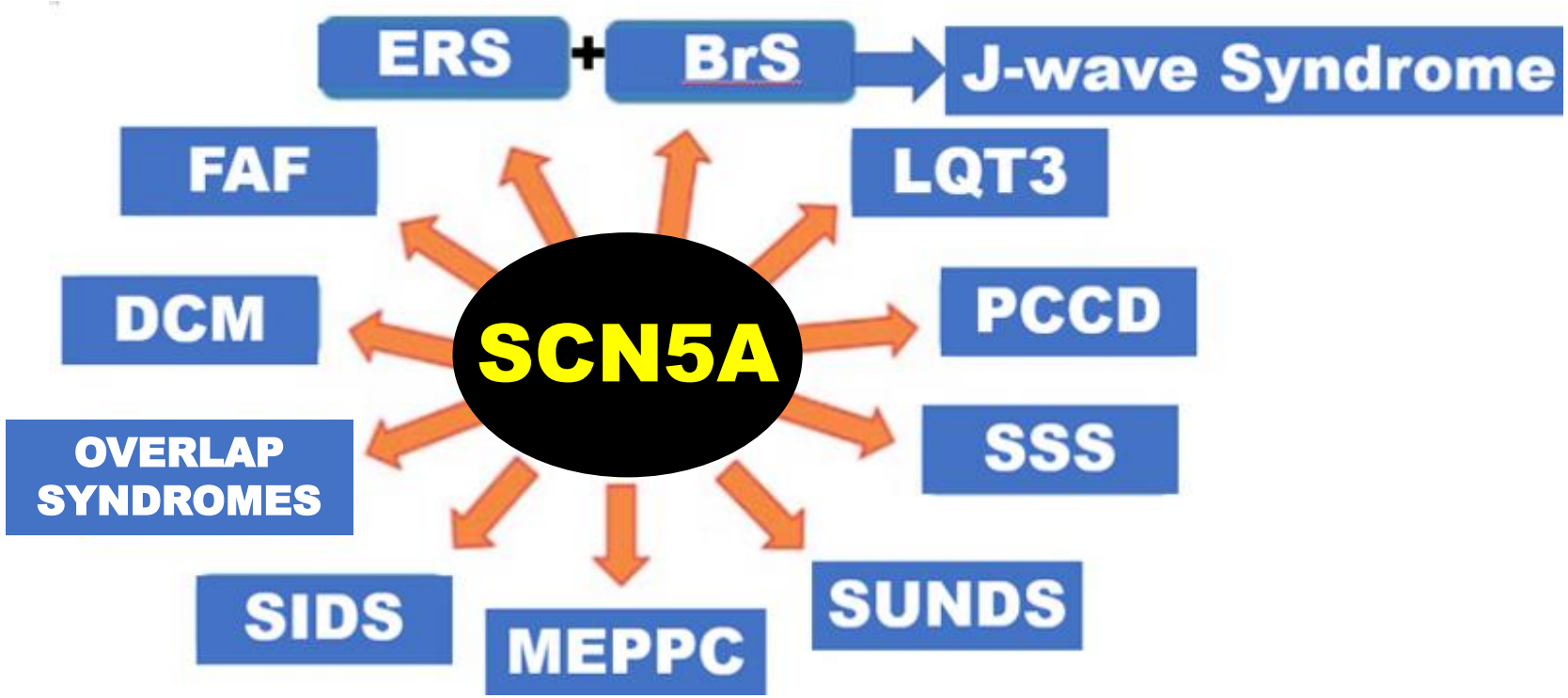
BrS-1 (**1**): **Locus:** 3p21-23; **OMIM:** 601144; **Gene:** SCN5A: Only the *SCN5A* gene is classified as having definitive evidence as a cause for BrS. (**2**) ; **Ion channel and effect**: $INa^{+}\downarrow$ loss-of-function; Protein: NaV1.5 - α subunit of the cardiac sodium channel carrying the sodium current INa^{+}; **% of probands:** 11-28%.

Amin et al (**3**) hypothesized based on a study of AF in a large cohort of BrS patients, that a reduced number of potentially triggering premature atrial contractions (PACs) in the presence of a more extensive substrate in SCN5A mutation carriers may account for AF being no more prevalent in patients with SCN5A mutations than in those without. Given the polemic and complex issues underlying the pathophysiology of BrS, one should regard this hypothesis as one potential mechanism of many that influence the prevalence of AF in BrS.

1. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature. 1998;392(6673):293-6.
2. S. Mohsen Hosseini,1 Raymond Kim,Sharmila Udupa, Gregory Costain, Rebekah Jobling, Eriskay Liston, Seema M. Jamal, Marta Szybowska, Chantal F. Morel, Sarah Bowdin, John Garcia, Melanie Care, Amy C. Sturm, Valeria Novelli, Michael J. Ackerman, James S. Ware, Ray E. Hershberger, Arthur A.M. Wilde, Michael H. Gollob, On behalf of the National Institutes of Health Clinical Genome Resource Consortium. Reappraisal of Reported Genes for Sudden Arrhythmic Death. Evidence-Based Evaluation of Gene Validity for Brugada Syndrome.Circulation. 2018 Sep 18; 138(12): 1195–1205.doi:10.1161/CIRCULATIONAHA.118.035070
3. Amin AS, Boink GJ, Atrafi F, et al. Facilitatory and inhibitory effects of SCN5A mutations on atrial fibrillation in Brugada syndrome. Europace. 2011 Jul;13(7):968-75. doi: 10.1093/europace/eur011

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 **(1)**

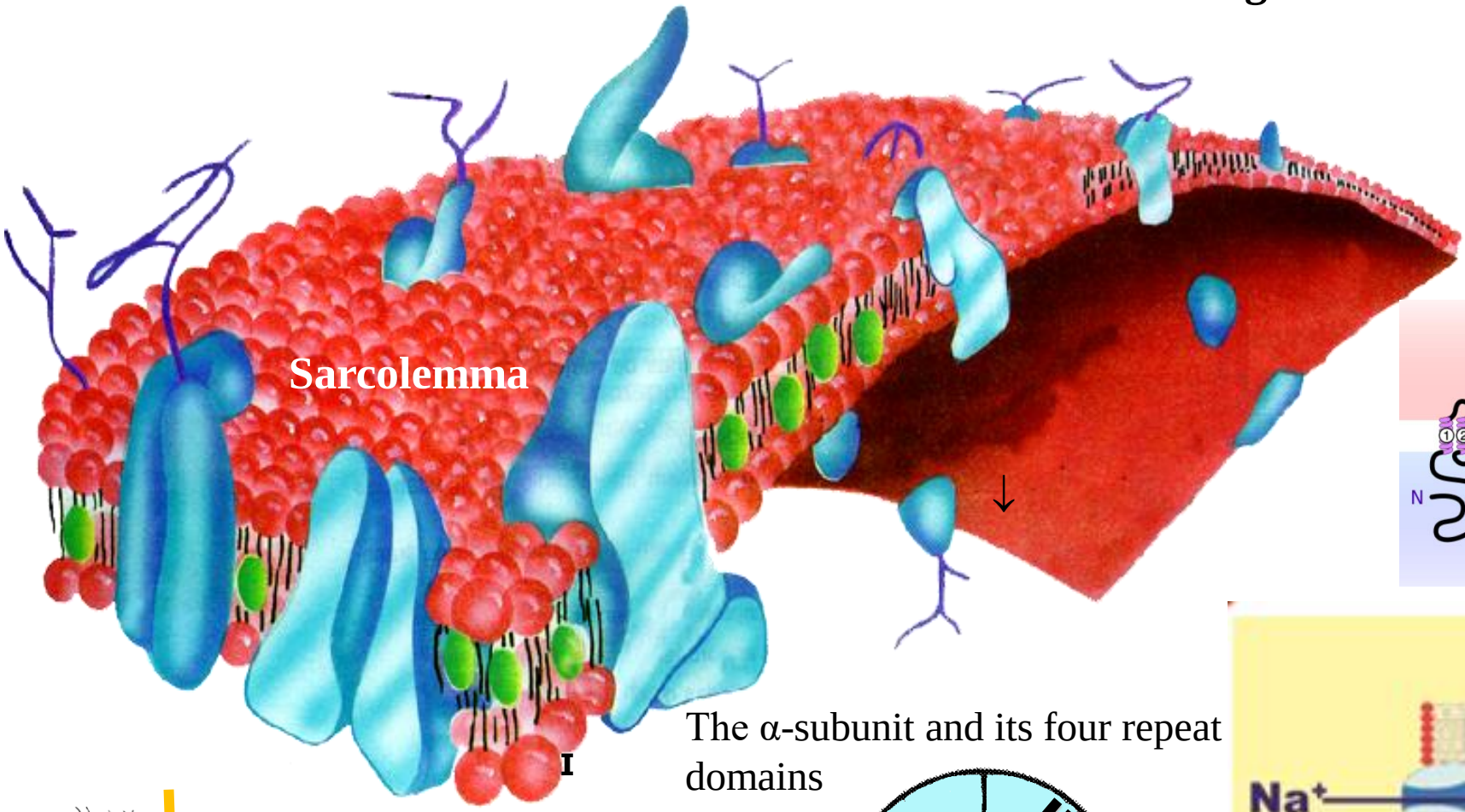
Loss-of-function mutations decrease in peak $I_{Na}\downarrow$

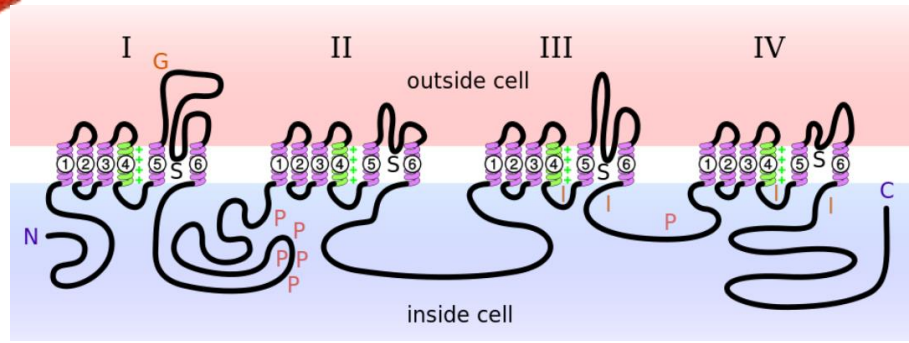


Representation of numerous phenotypes consequence of SCN5A gene mutations: Early repolarization syndrome (ERS); Brugada syndrome (BrS); Congenital long QT syndome variant 3 (LQT3); Progressive Cardiac Conduction Disease (PCCD) or Lenègre disease; Sick Sinus Syndrome (SSS); Sudden Unex- plained Nocturnal Death Syndrome(SUNDS); Multifocal Ectopic Purkinje-related Premature Contractions (MEPPC); Sudden Infant Death Syndrome (SIDS); Overlapping syndromes; Dilated Cardiomyopathy (DCM) Modified from

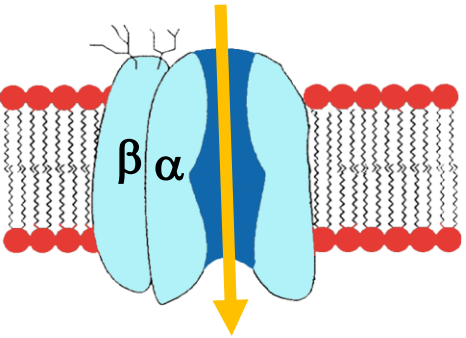
1. **Pérez-Riera AR, Daminello Raimundo R, Akira Watanabe R, Figueiredo JL, de Abreu LC. Cardiac sodium channel, its mutations and their spectrum of arrhythmia phenotypes. J Hum Growth Dev. 2016;26(3):277-80.**

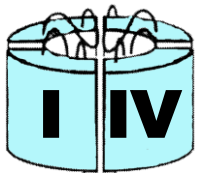
Sodium channel mutations on gene SCN5A

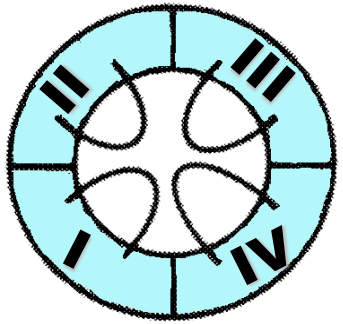


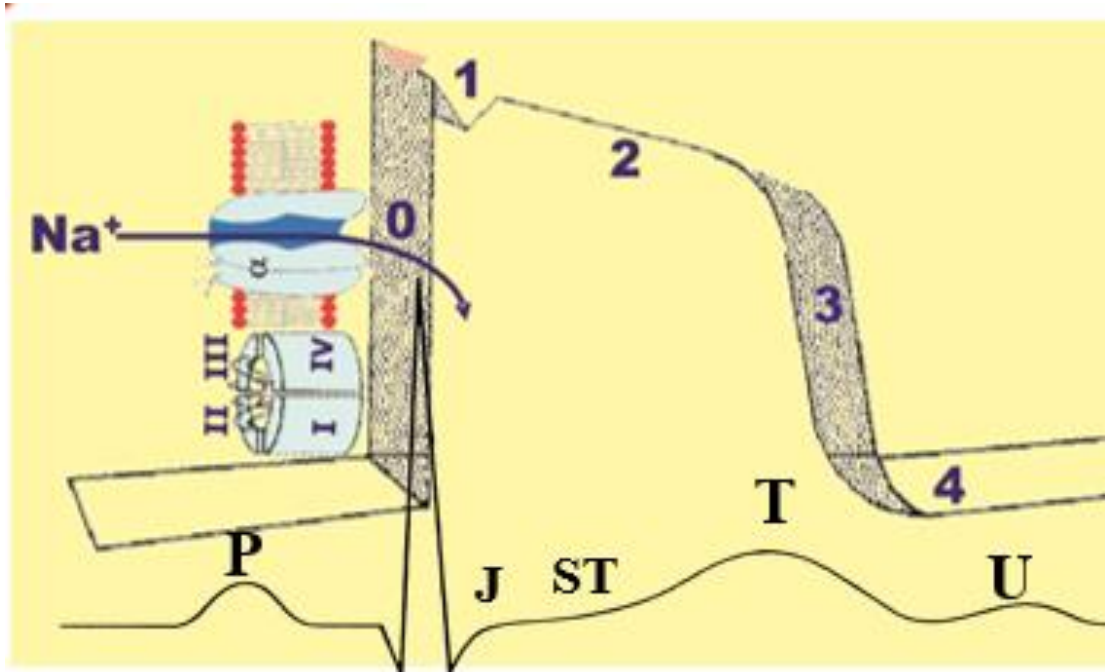


The α-subunit and its four repeat domains



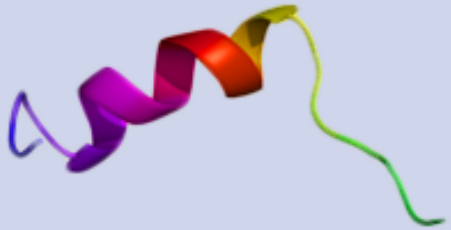


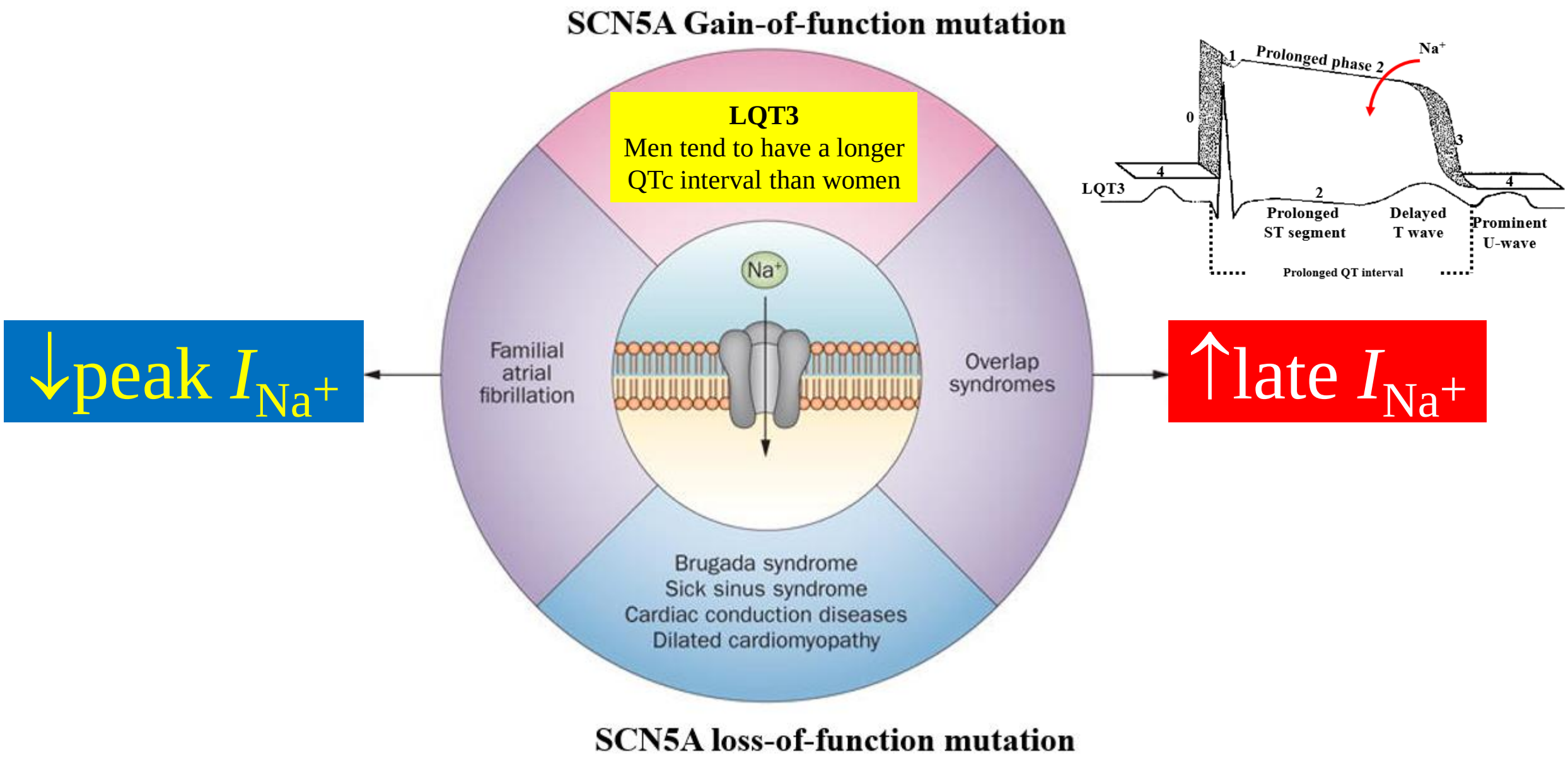




Wilde AA, et al. Circ Res. 2011 Apr 1;108:884-897

Nomenclature and some functions of voltage-gated sodium channel alpha subunits

Gene	Protein name	Associated human inherited primary arrhythmia syndromes
SCN5A ↓peak I_{Na+} ↑late I_{Na+} Locus: 3p21-23; OMIM: 601144	NaV1.5 is an integral membrane protein and tetrodotoxin-resistant voltage-gated sodium channel subunit. 	Cardiac: LQT3, BrS1, PCCD, familial AF and IVF, SSS, ERS, J-wave syndrome, SUNDS, MEPPC, SIDS, DCM, overlap
SCN1B Locus: 19q13,1; OMIM: 600235	Nav β 1- β 1 subunit of the sodium channel carrying the sodium current: INa+	BrS5, nonspecific cardiac conduction defect are caused by heterozygous mutation in the SCN1B
SCN2B Locus: 11q23; OMIM: 601327	Navβ2-β -2subunit of the cardiac sodium channel carrying the sodium current INa	BrS14
GPDIL Locus: 12p13.3; OMIM: 911778	Glycerol-3phosphate dehydrogenase like peptide-reduced GPD1-L activity leads to phosphorylation of Nav1.5 and decreased INa+	BrS2
RANGRF Locus: 17p13.1; OMIM: 607954	Encodes MOG1 – influences trafficking of Nav 1.5. The protein MOG1 is a cofactor of the cardiac sodium channel, Nav1.5	BrS11
PKP2 Locus: 12p11; OMIM: 602861	Plakophilin-2 (PKP2)	BrS15, SUNDS, arrhythmogenic cardiomyopathy (AC)



Mutations in *SCN5A* can produce various clinical phenotypes. *SCN5A* ↑gain-of-function mutations can result in increased late I_{Na}, leading to LQT3. *SCN5A* loss-of-function mutations can lead to decreased ↓peak I_{Na}, which is associated with BrS, SSS, PCCD, and possibly dilated cardiomyopathy. Moreover, *SCN5A* mutations that cause both a gain in late I_{Na} and a loss of peak I_{Na} can be associated with a mixed phenotype or overlap syndromes (for example, BrS and LQT3). Similarly, both gain-of-function and loss-of-function mutations have been associated with FAF.

SCN5A, SCN1B, SCN2B, GPDIL, MOG1, SLMAR, PGF12,PKP2

Loss-of-function mutations↓

Gating or trafficking

↓peak I_{Na}+

First degree AV block
Sick Sinus Syndrome
Broad QRS
Late potentials on high resolution ECG
Progressive Cardiac Conduction Disease (PCCD)

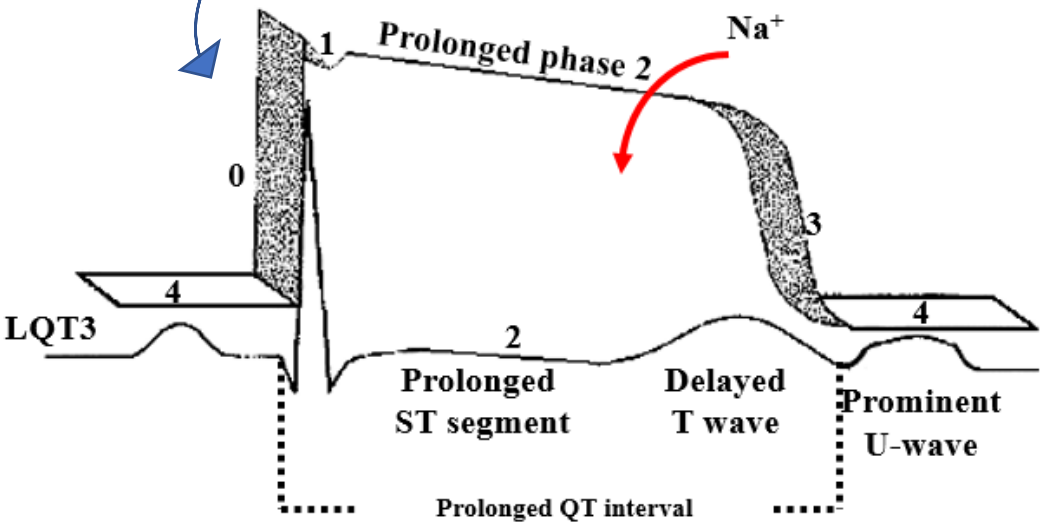
Prominent I_{to}

Phase 2 reentry:
PVT/VF

Brugada syndrome (BrS)
+
Early repolarization Syndrome (ERS)
J-Wave Syndrome

Gain-of-function mutations ↑late I_{Na}+

LQT3
Familial AF



Schematic showing overlap syndromes resulting from genetic defects consequence of loss of function of Na^+ channel current (INa) or gain of function in Late INa. In the absence of prominent Ito or IK-ATP, loss-of-function mutations in the inward currents result in various manifestations of conduction disease. In the presence of prominent Ito or IK-ATP, loss-of-function mutations in inward currents cause conduction disease as well as the J-wave syndromes (BrS and ERS). ERS is believed to be caused by loss-of-function mutations of inward current in the presence of prominent $\mathbf{I_{TO}}$ in certain regions of the left ventricle(LV), particularly the inferior wall of the LV. 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. PVT, polymorphic ventricular tachycardia; VF/ ventricular fibrillation

More than 400 mutations have been identified in the SCN5A gene. Although the mechanisms of SCN5A mutations leading to a variety of channelopaties can be classified according to the alteration of INa-P and INa-L as gain-of-function, loss-of-function and both, few researchers have summarized the mechanisms in this way (**1**). Gain-of-function mutations in SCN5A lead to more Na^+ influx into cardiomyocytes through aberrant channel gating causing LQT3. Slowed or incomplete inactivation of the NaV1.5 channel results in an additional inward current, known as the late or persistent sodium current (Ipst), during the plateau phase of the ventricular action potential with ST segment prolongation and late T occurrence. Among the mutations in SCN5A associated with LQT3 is 1795insD, which is characterized by the insertion of 3 nucleotides (TGA) at position 5537 C-terminal domain of the NaV1.5 protein (**2**). Carriers of this mutation may not only present with LQT3, but also with ECG features of sinus bradycardia, PCCD, and BrS, thus creating the first described arrhythmic ‘overlap syndrome (3).

References

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3. Remme C.A., Wilde A.A.M., Bezzina C.R. Cardiac sodium channel overlap syndromes: Different faces of SCN5A mutations. Trends Cardiovasc. Med. 2008;18:78–87. doi: 10.1016/j.tcm.2008.01.002

SCN5A 1795insD is supposed to be a gain-of-function mutation in light of the QT prolongation,

A loss-of-function mutation cause sinus bradycardia, progressive cardiac conduction disease, and BrS. Multifocal ectopic premature Purkinje-related complexes; is caused by loss-of-function mutations in SCN5A result in amplitude reduction in peak Na^+ current, further leading to channel protein dysfunction. or cardiac conduction defect an entity with minor structural heart disease.

Both loss- and gain-of-function mutations may cause DCM and/or AF. **(1).**

On ECG PR interval prolongation is the only parameter that predicted the presence of a SCN5A mutation in BrS.

Late potentials on high resolution ECG were more frequently observed in SCN5A mutation carriers **(2).**

SCN5A mutation is associated with an increased risk of drug-induced ventricular arrhythmia in patients without baseline type-1 ECG. In particular, Snon-missense and Smissense-TP are at high risk **(3).**

1. Wilde AAM1, Amin AS2. Clinical Spectrum of SCN5A Mutations: Long QT Syndrome, Brugada Syndrome, and Cardiomyopathy.JACC Clin Electrophysiol. 2018 May;4(5):569-579. doi: 10.1016/j.jacep.2018.03.006
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3. Amin AS1, Reckman YJ2, Arbelo E3, Spanjaart AM2, Postema PG2, Tadros R4, Tanck MW2, Van den Berg MP5, Wilde AAM6, Tan HL2.SCN5A mutation type and topology are associated with the risk of ventricular arrhythmia by sodium channel blockers.Int J Cardiol. 2018 Sep 1;266:128-132. doi: 10.1016/j.ijcard.2017.09.010).

Genetic Defects BrS	*Cytogenetic location* Locus	Gene/Protein	Ion Channel	Percent of Probands/ Phenotypes/Authors
BrS1 OMIM: 601144	**3p21**	**SCN5A, $Na_y1.5$**	**↓INa^+**	% probands: 11%-28% BrS, Other phenotypes: IVF Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, et al. Genetic basis and molecular mechanism for idiopathicventricularfibrillation.Nature.1998;392(6 6730:2936.
BrS2 OMIM: 911778;	**3p22.3**	**GPD1L/Glycerol-3phosphate dehydrogenase like peptide-reduced GPD1-L activity**	**↓INa^+ Glycerol phosphorylation of Nav1.5 and ↓INa^+**	Rare. Other phenotypes: Sudden Infant Death Syndrome (SIDS).London B, Michalec M, Mehdi H, et al. Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias. Circulation. 2007;116(20):2260-8
BrS3 OMIM: 114205	**12p13.3**	**CACNA1C, $Ca_V1.2$.**	**↓ICa^{2+}**	% probands: 6.6% Antzelevitch C, Pollevick GD, Cordeiro JM,, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation. 2007;115(4):442-9
BrS4 OMIM: 114205	**10p12.33-p12.31**	**CACNB2/theCavβ-2 subunit of the voltage-dependent L-type calcium channel**	**↓ICa^{2+}**	% probands: 4.8%.Antzelevitch C, Pollevick GD, Cordeiro JM, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation. 2007;115(4):442-9.

BrS8 **MIM number** # 613123	**12p11.23**	**HCN4/KCNJ8,Kir6.1** **Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4HCN4 is prominently expressed in the pace maker region of the mammalian heart**	**↑$I_{K=ATP}$**	Schulze-Bahr E, Neu A, Friederich P, Kaupp UB, Breithardt G, Pongs O, Isbrandt D (May 2003). "Pacemaker channel dysfunction in a patient with sinus node disease". The Journal of Clinical Investigation. 111 (10): 1537–452% Ueda K, Hirano Y, Higashiuesato Y, Aizawa Y, Hayashi T, Inagaki N, et al. Role of HCN4 channel in preventing ventricular arrhythmia. Journal of human genetics. 2009;54(2):115-21)(Stephanie Biel , Marco Aquila , Brigitte Hertel , Anne Berthold , Thomas Neumann, Dario DiFrancesco 5, Anna Moroni, Gerhard Thiel 6, Silke Kauferstein 1Mutation in S6 domain of HCN4 channel in patient with suspected Brugada syndrome modifies channel function. Pflugers Arch. 2016 Oct;468(10):1663-71. doi: Others phenotypes sick sinus syndrome Sinus Node disease:
BrS9 # 616399	1p13.2	**KCND3Kv4.3 K+ channel**	**↑I_{TO}** **Transient outward current (I-to) gain-of-function mutations**	1.8% Giudicessi JR, Ye D, Tester DJ, Crotti L, Mugione A, Nesterenko VV, et al. Transient outward current (I(to)) gain-of-function mutations in the KCND3-encoded Kv4.3 potassium channel and Brugada syndrome. Heart rhythm. 2011;8(7):1024-32 Giudicessi, J. R., Ye, D., Kritzberger, C. J., Nesterenko, V. V., Tester, D. J., Antzelevitch, C., Ackerman, M. J. Novel mutations in the KCND3-encoded Kv4.3 K+ channel associated with autopsy-negative sudden

BrS12	**3p21.2.p14.3**	**SLMAP**	**↓INa**	Rare. Ishikawa T, Sato A, Marcou CA, Tester DJ, Ackerman MJ, Crotti L, et al. A novel disease gene for Brugada syndrome: sarcolemmal membrane-associated protein gene mutations impair intracellular trafficking of hNav1.5. Circulation Arrhythmia and electrophysiology. 2012;5(6):1098-107
BrS13	**12p12.1**	**ABCC9, SUR2A** ATP binding cassette subfamily C member 9	**↑$I_{K=ATP}$**	Rare. Barajas-Martinez H, Hu D, Ferrer T, Onetti CG, Wu Y, Burashnikov E, et al. Molecular genetic and functional association of Brugada and early repolarization syndromes with S422L missense mutation in KCNJ8. Heart rhythm. 2012;9(4):548-55
BrS14	**11q23**	**SCN2B,Na**	**↓INavβ2**	Rare. Riuro H, Beltran-Alvarez P, Tarradas A, Selga E, Campuzano O, Verges M, et al. A missense mutation in the sodium channel beta2 subunit reveals SCN2B as a new candidate gene for Brugada syndrome. Human mutation. 2013;34(7):961-6
BrS15	**12p11**	**PKP2,Plalophillin-2**	**↓INa^+**	Rare. Cerrone M, Delmar M. Desmosomes and the sodium channel complex: implications for arrhythmogenic cardiomyopathy and Brugada syndrome. Trends in cardiovascular medicine. 2014;24(5):184-90

BrS16 OMIM: 601513	**3q28**	**FGF12, FHAF1** Protein: Fibroblast growth factor homologues factor-1-mutation decreases INa+	↓INa	Rare Wang C, Wang C, Hoch EG, Pitt GS. Identification of novel interaction sites that determine specificity between fibroblast growth factor homologous factors and voltage-gated sodium channels. The Journal of biological chemistry. 2011;286(27):24253-63
BrS17 OMIM: 604427	**3p22.2**	**SCN10A, $Na_v1.8$/** Protein: Nav1.8-αsubunit of the neural sodium channel.	**↓INa^+**	5%=16.7%Hu D, Barajas-Martinez H, Pfeiffer R,, et al. Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. Journal of the American College of Cardiology. 2014;64(1):66-79. Behr ER, Savio-Galimberti E, Barc J, Holst AG, Petropoulou E, Prins BP, et al. Role of common and rare variants in SCN10A: results from the Brugada syndrome QRS locus gene discovery collaborative study. Cardiovascular research. 2015;106(3):520-9 Behr ER, Savio-Galimberti E, Barc J, et al. Role of common and rare variants in SCN10A: results from the Brugada syndrome QRS locus gene discovery collaborative study. Cardiovascular research. 2015;106(3):520-9
BrS18 **OMIM: 604674**	**6q**	**HEY2/Transcription factor identified in GWAS (transcriptional factor)**	**↑Na**	RareBezzina CR, Barc J, Mizusawa Y, Remme CA, Gourraud JB, Simonet F, et al. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. Nature genetics. 2013;45(9):1044-9

BrS19 **OMIN 9603961**	***7q21.11***	**SEMA3A/Semaphorin 3A**	**inhibit** **K^+ channel, voltage dependent, Kv4.3Kv4.3 channels**	**Rare** **Nicole J Boczek et al Characterization of SEMA3A-encoded semaphorin as a naturally occurring Kv4.3 protein inhibitor and its contribution to Brugada syndrome. Circ Res. 2014 Aug 1;115(4):460-9. doi: 10.1161/CIRCRESAHA.115.303657.**
BrS20 **OMIM:*** 601142	***1p36.31***	**KCNAB2** **the Voltage-Gated K+ Channel β2** **subfamily A regulatory beta subunit 2**	**↑I_{TO}** **K^+**	**Rare** **Vincent Portero 1, et al.Dysfunction of the Voltage-Gated K+ Channel β2 Subunit in a Familial Case of Brugada SyndromeJ Am Heart Assoc. 2016 Jun 10;5(6):e003122. doi: 10.1161/JAHA.115.003122**

Genes associated with Brugada syndrome.

Channel	Gene	Protein
Sodium	*SCN5A,*	Nav1.5
	GPD1-L,	Gycerol-3-P-DH-1
	SCN1B,	Navβ1Nav β 1- β 1 subunit of the sodium channel carrying the sodium current: INa+
	SN3B,	Navβ3
	SN2B,	Navβ2.
	RANGRF,	RAN-G release factor(or MOGI)
	SLMAP	Sarcolemma associated protein
	SCN3B,	MiRP2
	KCNE3	K-voltage-gted subfamily E member 1 like
	KCNJ8	Kv6.1Kir6.1
Potassium	*KCN4*	Hyperpolarization cyclic nucleotide-gated 4
	KCNE5	K voltage-gated subfamily E member 1 like
	KCND3	Kv4.3 Kird4.3
Calcium	*CACNCA1C*	Cav1.2
	CANCB2B	Voltage-dependent β-2
	CACNA2D1	Voltage-dependent α 2/δ1
	TRPM4	Transient receptor potential cation channel subfamily M member 4

Reported Genes for Brugada Syndrome

Gene Symbol	Gene Name	HGNC ID	MIM Phenotype Record	Number of Core Publications
ABCC9	ATP binding cassette subfamily C member 9	60	-	1
ANK2	Ankyrin 2	493	Brugada syndrome 3-611875	2
α1 **CACNA1C**	Calcium voltage-gated channel subunit alpha 1C	1390	Brugada syndrome 3-611875	4
A2 δ **CACN A2D1**	Calcium voltage-gated channel auxiliary subunit alpha 2C delta 1	1399	-	2
β2**CACNB2**	Calcium voltage-gated channel auxiliary subunit beta 2	1402	Brugada syndrome 4-611876	4
FGF12	Fibroblast growth factor 12	3668	-	1q
GPD1L	Glicerol-3-phosphate dehydrogenase 1 like	28956	Brugada syndrome 2-617777	2
HCN4	Hyperpolarization activated cyclic nucleotide-gated potassium channel 4	16882	Brugada syndrome 8-613123	2
KCND3	Potassium voltage-gated channel subfamily D member 3 Encoding the KV4.3 K^+ -channel (the α-subunit of the Ito↑) gain-of-function phenotype	6239	Brugada syndrome 9-616399	3
KCNE3	Potassium voltage-gated channel subfamily E regulatory subunit 3	6243	Brugada syndrome 6-613119	2
KCNE5	Potassium voltage-gated channel subfamily E regulatory subunit 5	6241	-	1

Gene Symbol	Gene Name	HGNC ID	MIM Phenotype Record	Number of Core Publications
KCNAB2	K^+ Voltage-Gated Channel Subfamily A Regulatory β Subunit 2	6229	601142	
RNAGRF	RAN guanine nucleotide release factor	17679	-	3
PKP2	Pakophilin 2	9024	-	2
SCN10A	Sodium voltage-gated channel alpha subunit 10	10582		5
SCN1B	Sodium voltage-gated channel beta-subunit 1	10586	Brugada syndrome 5-612838	9
SCN28	Sodium voltage-gated channel beta subunit 2	10589	-	4
SCN3B	Sodium voltage-gated channel beta subunit 3	20665	Brugada syndrome 7-613120	4
SCN5A	Sodium voltage-gated channel alpha subunit 5	10593	Brugada syndrome 1 -601144	7
SEMA3A	Semaphoring 3A	19593	-	7
SLMAP	Sarcolemma-associated protein	16643		1
TRPM4	Transient receptor potential cation channel subfamily M member 4	17993	-	2

HGNC ID: HUGO Gene Nomenclature Committee. The recourse for approved human gene nomenclature. MIM: McKusick's Mendelian Inheritance in Man (**MIM**) (1), is the primary repository of comprehensive, curated information on **genes** and **genetic** phenotypes and the relationships between them. **MIM** was published through 12 editions between 1966 and 1998, and OMIM has been online and searchable since 1987. MIM number A numerical assignment for inherited diseases, genes and functional segments of DNA, as listed in the comprehensive catalog Mendelian Inheritance in Man (created and maintained by Victor McKusick of Johns Hopkins Medical Center, Baltimore, until his passing in 2008).The catalogue assignment for a mendelian trait in the *Mendelian Inheritance in Man* (MIM) system. If the initial digit is 1, the trait is deemed autosomal dominant; if 2, autosomal recessive; if 3, then X-linked.