About the genetic and phenotypes of the Brugada Syndrome - 2020

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The genetics of BrS is not well understood, with about half of cases lacking molecular confirmation, and possible new genes are an active area of research.(Brugada, Campuzano, Arbelo, Sarquella-Brugada, & Brugada, 2018; Monasky et al., 2019) About 15–30% of cases are thought to be caused by variants in the gene *SCN5A*, which is the most commonly associated gene with BrS. Currently, the literature strongly suggests that the concept of a single causative gene with autosomal dominant inheritance may not be the case of BrS. BrS probably is a multifactorial disease, which is affected by several loci, each of which are influenced by the environment. Variants occurring in at least 21 different genes have been previously considered causative, although the causative effect of all but the *SCN5A* gene has been recently challenged, due to the lack of systematic, evidence-based evaluations, such as a variant's frequency among the general population, family segregation analyses, and functional studies. Also, variants within a particular gene can be associated with an array of different phenotypes, even within the same family, preventing a clear genotype–phenotype correlation. Moreover, an emerging concept is that a single mutation may not be enough to cause the BrS phenotype, due to the increasing number of common variants now thought to be clinically relevant. Thus, not only the complete list of genes causative of the BrS phenotype remains to be determined, but also the interplay between rare and common multiple variants. This is particularly true for some common polymorphisms whose roles have been recently re-evaluated by outstanding works, including considering for the first time ever a polygenic risk score derived from the heterozygous state for both common and rare variants. The more common a certain variant is, the less impact this variant might have on the heart function. We are aware that further studies are warranted to validate a polygenic risk score, because there is no mutated gene that connects all, or even a majority of BrS cases. For the same reason, it is currently impossible to create animal and cell line genetic models that represent all BrS cases, which would enable the expansion of studies of this syndrome. Thus, the best model at this point is the human patient population. Further studies should first aim to uncover genetic variants within individuals, as well as to collect family segregation data to identify potential genetic causes of BrS.

The main gene is SCN5A. Additional variants in 42 other genes have been reported as deleterious, although these variants have not received comprehensive pathogenic analysis. Accurate interpretation of rare genetic variants is a challenge for clinical translation. Updates in recommendations for rare variant classification require the

reanalysis and reclassification. Campuzano et al. aim to perform an exhaustive re-analysis of rare variants associated with inherited arrhythmogenic syndromes, which were classified in 2010, to determine whether their classification aligns with current standards and research findings. The rare variants identified through genetic analysis were classified following recommendations available at that time. Nowadays, the same variants have been reclassified following current American College of Medical Genetics and Genomics recommendations. The authors' cohort included 104 cases diagnosed with inherited arrhythmogenic syndromes and 17 post-mortem cases in which inherited arrhythmogenic syndromes was cause of death. 71.87% of variants change their classification. While 65.62% of variants were classified as likely pathogenic in 2010, after reanalysis, only 17.96% remain as likely pathogenic. In 2010, 18.75% of variants were classified as uncertain role but nowadays 60.15% of variants are classified of unknown significance. Reclassification occurred in more than 70% of rare variants associated with inherited arrhythmogenic syndromes. These results support the periodical reclassification and personalized clinical translation of rare variants to improve diagnosis and adjust treatment.(Campuzano et al., 2020) This research group clarified the role of all currently reported variants in minor genes associated with BrS. The authors performed a comprehensive analysis according to the American College of Medical Genetics and Genomics guidelines of published clinical and basic data on all genes (other than SCN5A) related to BrS. Their results identified 133 rare variants potentially associated with BrS. After applying current recommendations, only six variants (4.51%) show a conclusive pathogenic role. In total, 33.83% of variants in 19 additional genes were potentially pathogenic. Beyond SCN5A, the authors concluded definitive pathogenic variants associated with BrS in four minor genes: SCN5A, SLMAP, SEMA3A, SCNN1A, and SCN2B.(Campuzano et al., 2020)

Currently, BrS is not considered a pure Mendelian disorder, but rather a common ECG pattern that results from a vast number of diverse molecular pathologies. Thus, genetic testing alone, are not sufficient to understand this complex syndrome. Perhaps additional omics approaches, such as epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, and glycomics, could shed light on this complex pathology. (Monasky, Micaglio, Ciconte, & Pappone, 2020). Additionally, abnormalities in the function of the sodium channels may induce structural abnormalities and cell death. The type 1 Brugada ECG pattern is not exclusively a marker of a specific syndrome; rather, it is a common ECG manifestation of structural abnormalities in the right ventricle that may have genetic (ARVD/C), infective, and inflammatory origins(Frustaci et al., 2005), or the so called Brugada phenocopies (BrP), which are elicited by various underlying clinical conditions such as myocardial ischemia,(Perez-Riera, Barbosa-Barros, Daminello-Raimundo, de Abreu, & Baranchuk, 2017; Xu et al., 2019) left ventricular aneurism,(Gul, Haseeb, Al Amoudi, & Baranchuk, 2018) takattsubo cardiomyopathy, (Kirbas et al., 2016) coronary anomalies,(Dendramis, 2015) pulmonary embolism, (Zhan, Wang, Nikus, Perez-Riera, & Baranchuk, 2014) myocardial a pericardial disease such s pericardial effusion,(Lazaros, Lazarou, & Tousoulis, 2019) acute pericarditis,(Yu, Zhang, Huang, & Zhao, 2018) compressive mediastinal tumor,(Perez-Riera, Barbosa Barros, Daminello-Raimundo, Resende Barbosa, & de Abreu, 2018) pectus excavatum, (Siniorakis et al., 2017) tension pneumothorax,(Lancini & Shetty, 2019) ECG

modulation, metabolic imbalance, electrolyte disturbances (hyper and hypokalemia, hyponatremia), diabetic ketoacidosis,(Alanzalon, Burris, & Vinocur, 2018) phosphine poisoning,(Gottschalk, Anselm, & Baranchuk, 2016) yellow phosphorus intoxication, (Dharanipradab, Viswanathan, Kumar, Krishnamurthy, & Stanley, 2018) methanol intoxication,(Monterrubio-Villar & Llinares-Moya, 2020) cocaine, heroin, and cannabis abuse,(Akinlonu et al., 2018) or poor ECG filters and other miscellaneous.

BrS Genetic types from the Mendelian point of view (The classification of both BrS-associated mutations and common variants requires a complete functional study with patch clamp and/or the voltage clamp technique).

Genes implicated in Brugada syndrome following Mendelian with the first Manuscript sequential

- *SCN5A (BrS-1)*. (**Chen Chen 1, Zhaochong Tan 1, Wengen Zhu 1, Linghua Fu 1, Qiling Kong 1, Qinmei Xiong 1, Jianhua Yu 1, Kui Hong 1 2 3Brugada Syndrome With SCN5A Mutations Exhibits More Pronounced Electrophysiological Defects and More Severe Prognosis: A Meta-Analysis.Clin Genet. 2020 Jan;97(1):198-208. doi: 10.1111/cge.13552**)
- *GPD1L(BrS-2),* (**Weiss, R., Barmada, M. M., Nguyen, T., Seibel, J. S., Cavlovich, D., Kornblit, C. A., Angelilli, A., Villanueva, F., McNamara, D. M., London, B. Clinical and molecular heterogeneity in the Brugada syndrome: a novel gene locus on chromosome 3. Circulation 105: 707-713, 2002.**).
- *CACNA1C(BrS3)*, (**Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, 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**):
- *CACNB2(BsS-4)*, (**Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, 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.**)
- *SCN1B (BsS-5)*, (**Watanabe, H., Koopmann, T. T., Le Scouarnec, S., Yang, T., Ingram, C. R., Schott, J.-J., Demolombe, S., Probst, V., Anselme, F., Escande, D., Wiesfeld, A. C. P., Pfeufer, A., Kaab, S., Wichmann, H.-E., Hasdemir, C., Aizawa, Y., Wilde, A. A. M., Roden, D. M., Bezzina, C. R. Sodium channel beta-1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. J. Clin. Invest. 118: 2260-2268, 2008.**
- *KCNE3 MiRP2(BrS-6)*, **(Delpón E, Cordeiro JM, Núñez L, Thomsen PE, Guerchicoff A, Pollevick GD, Wu Y, Kanters JK, Larsen CT, Hofman-Bang J, Burashnikov E, Christiansen M, Antzelevitch C (Aug 2008). "Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome". Circulation: Arrhythmia and Electrophysiology. 1 (3): 209–18. doi:10.1161/ CIRCEP.107.748103. PMC 2585750. PMID 19122847**.)
- *SCN3B(BRs-7)*, (**Hu D, Barajas-Martinez H, Burashnikov E, Springer M, Wu Y, Varro A, et al. A mutation in the beta 3 subunit of the cardiac sodium channel associated with Brugada ECG phenotype. Circulation Cardiovascular genetics. 2009;2(3):270-8**)

- *HCN4(*BrS8*)*(**Ueda K1, Hirano Y, Higashiuesato Y, Aizawa Y, Hayashi T, Inagaki N, Tana T, Ohya Y, Takishita S, Muratani H, Hiraoka M, Kimura A.Role of HCN4 channel in preventing ventricular arrhythmia.J Hum Genet. 2009 Feb; 54(2):115-21. doi: 10.1038/jhg.2008.16. Epub 2009 Jan 23DOI: 10.1038/jhg. 2008.16**)
- *KCNJ8* potassium inwardly rectifying channel subfamily J member 8 *Kir6.1(BrS-8)*, (.**Medeiros-Domingo A1, Tan BH, Crotti L, Tester DJ, Eckhardt L, Cuoretti A, Kroboth SL, Song C, Zhou Q, Kopp D, Schwartz PJ, Makielski JC, Ackerman MJ.Gain-of-function mutation S422L in the KCNJ8-encoded cardiac K(ATP) channel Kir6.1 as a pathogenic substrate for J-wave syndromes.Heart Rhythm. 2010 Oct;7(10):1466-71. doi: 10.1016/j.hrthm.2010.06.016.**)
- *CACNA2D1.Ca*a2d *(BsS-9)*, (**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**).
- KCND3, Kv4.3 (BrS-10), (**Giudicessi JR, Ye D, Tester DJ, Crotti L, Mugione A, Nesterenko VV, Albertson RM, Antzelevitch C, Schwartz PJ, Ackerman MJ. Transient outward current (I(to)) gain-of-function mutations in the KCND3-encoded Kv4.3 potassium channel and Brugada syndrome. Heart rhythm. 2011 Jul;8(7):1024-32. doi: 10.1016/j.hrthm.2011.02.021**.).
- RANGRF, MOGI (BrS-11), (**Darouna Kattygnarath 1, Svetlana Maugenre, Nathalie Neyroud, Elise Balse, Carole Ichai, Isabelle Denjoy, Gilles Dilanian, Raphaël P Martins, Véronique Fressart, Myriam Berthet, Jean Jacques Schott, Antoine Leenhardt, Vincent Probst, Hervé Le Marec, Bernard Hainque, Alain Coulombe, Stéphane N Hatem, Pascale Guicheney. MOG1: A New Susceptibility Gene for Brugada Syndrome. Circ Cardiovasc Genet. 2011 Jun;4(3):261-8. doi: 10.1161/CIRCGENETICS.110.959130**.) (**Olesen MS, Jensen NF, Holst AG, Nielsen JB, Tfelt-Hansen J, Jespersen T, et al. A novel nonsense variant in Nav1.5 cofactor MOG1 eliminates its sodium current increasing effect and may increase the risk of arrhythmias. The Canadian journal of cardiology. 2011;27(4):523 e17-23**):
- SLMAP (BrS-12.) (**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**):
- *ABCC9, SUR2A(BrS-13)*, : (**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**)
- SCN2B, Na_vb2(BrS-14), (**Plummer NW, Meisler MH (May 1999). "Evolution and diversity of mammalian sodium channel genes". Genomics. 57 (2): 323–31. doi:10.1006/geno.1998.5735. PMID 10198179**.).
- PKP2, plakophilin-2*(BrS-15)*, (**Huang L, Tang S, Peng L, Chen Y, Cheng J. Molecular Autopsy of Desmosomal Protein Plakophilin-2 in Sudden Unexplained Nocturnal Death Syndrome. Journal of forensic sciences. 2016;61(3):687-91**).

- *FGF12, (BrS-16)* (**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**) (**Hennessey JA1, Marcou CA, Wang C, Wei EQ, Wang C, Tester DJ, Torchio M, Dagradi F, Crotti L, Schwartz PJ, Ackerman MJ, Pitt GS.FGF12 is a candidate Brugada syndrome locus.Heart Rhythm. 2013 Dec; 10(12):1886-94. doi: 10.1016/j.hrthm.2013.09.064**.)
- *FHAF1. (BrS-17)* (**Garcia-Elias A, Benito B (February 2018). "Ion Channel Disorders and Sudden Cardiac Death". International Journal of Molecular Sciences. 19 (3): 692. doi:10.3390/ijms19030692. PMC 5877553. PMID 29495624**)
- *SCN10A, (BrS-18)* (**Connie R Bezzina 1, Julien Barc, Yuka Mizusawa, Carol Ann Remme, Jean-Baptiste Gourraud, Floriane Simonet, Arie O Verkerk, Peter J Schwartz, Lia Crotti, Federica Dagradi, Pascale Guicheney, Véronique Fressart, Antoine Leenhardt, Charles Antzelevitch, Susan Bartkowiak, Martin Borggrefe, Rainer Schimpf, Eric Schulze-Bahr, Sven Zumhagen, Elijah R Behr, Rachel Bastiaenen, Jacob Tfelt-Hansen, Morten Salling Olesen, Stefan Kääb, Britt M Beckmann, Peter Weeke, Hiroshi Watanabe, Naoto Endo, Tohru Minamino, Minoru Horie, Seiko Ohno, Kanae Hasegawa, Naomasa Makita, Akihiko Nogami, Wataru Shimizu, Takeshi Aiba, Philippe Froguel, Beverley Balkau, Olivier Lantieri, Margherita Torchio, Cornelia Wiese, David Weber, Rianne Wolswinkel, Ruben Coronel, Bas J Boukens, Stéphane Bézieau, Eric Charpentier, Stéphanie Chatel, Aurore Despres, Françoise Gros, Florence Kyndt, Simon Lecointe, Pierre Lindenbaum, Vincent Portero, Jade Violleau, Manfred Gessler, Hanno L Tan, Dan M Roden, Vincent M Christoffels, Hervé Le Marec, Arthur A Wilde, Vincent Probst, Jean-Jacques Schott, Christian Dina, Richard Redon. Common Variants at SCN5A-SCN10A and HEY2 Are Associated With Brugada Syndrome, a Rare Disease With High Risk of Sudden Cardiac Death. Nat Genet. 2013 Sep;45(9): 1044-9. Epub 2013 Jul 21. PMID: 23872634 PMCID: PMC3869788 DOI: 10.1038/ ng.2712**)
- SEMA3A *(BrS-19)*, (**Nicole J Boczek 1, Dan Ye 1, Eric K Johnson 1, Wei Wang 1, Lia Crotti 1, David J Tester 1, Federica Dagradi 1, Yuka Mizusawa 1, Margherita Torchio 1, Marielle Alders 1, John R Giudicessi 1, Arthur A M Wilde 1, Peter J Schwartz 1, Jeanne M Nerbonne 1, Michael J Ackerman 2. Characterization of SEMA3A-encoded Semaphorin as a Naturally Occurring Kv4.3 Protein Inhibitor and Its Contribution to Brugada Syndrome.2014 Aug 1;115(4):460-9. doi:10.1161/CIRCRESAHA.115.303657**..)(The gene *SEMA3A*(**Boczek NJ1, Ye D1, Johnson EK1, Wang W1, Crotti L1, Tester DJ1, Dagradi F1, Mizusawa Y1, Torchio M1, Alders M1, Giudicessi JR1, Wilde AA1, Schwartz PJ1, Nerbonne JM1, Ackerman MJ2.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**.) (**Antzelevitch C, Patocskai B (January 2016). "Brugada Syndrome: Clinical, Genetic, Molecular, Cellular, and Ionic Aspects". Current Problems in Cardiology. 41 (1): 7–57. doi:10.1016/j.cpcardiol.2015.06.002. PMC 4737702. PMID 26671757**) (**Brugada R., Campuzano O., Sarquella-Brugada**

G., Brugada J., Brugada P. Brugada syndrome. Methodist Debakey Cardiovasc J. 2014;10:25–28. doi: 10.14797/mdcj-10-1-25.)

- *KCND2KCNE5*, *KCNH2*, *SLMAP*, The gene *SLMAP* Brugada syndrome and sarcomeropathies The sarcolemmal membrane (**Ishikawa T1, Sato A, Marcou CA, Tester DJ, Ackerman MJ, Crotti L, Schwartz PJ, On YK, Park JE, Nakamura K, Hiraoka M, Nakazawa K, Sakurada H, Arimura T, Makita N, Kimura A.A novel disease gene for Brugada syndrome: sarcolemmal membrane-associated protein gene mutations impair intracellular trafficking of hNav1.5.Circ Arrhythm Electrophysiol. 2012 Dec;5(6):1098-107. doi: 10.1161/CIRCEP.111.969972**.)
- *HEY2 transcriptional factor (**Weber D1, Wiese C1, Gessler M2.Hey bHLH transcription factors.Curr Top Dev Biol. 2014;110:285-315. doi: 10.1016/B978-0-12-405943-6.00008-7**.)*
- Mitochondrial mutation BrS **(Tafti M.F., Khatami M., Rezaei S., Heidari M.M., Hadadzadeh M. Novel and heteroplasmic mutations in mitochondrial tRNA genes in Brugada syndrome. Cardiol. J. 2018;25:113–119. doi: 10.5603/CJ.a2017.0104.**).
- *TRPM4* Autossomal recessive BrS (TRPM4) (**Janin A1, Bessière F2, Georgescu T3, Chanavat V1, Chevalier P2, Millat G4.TRPM4 mutations to cause autosomal recessive and not autosomal dominant Brugada type 1 syndrome.Eur J Med Genet. 2019 Jun;62(6):103527. doi: 10.1016/j.ejmg.2018.08.008**.)