Brugada syndrome and Inheritance patterns and ARVC or AC relationship

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Brugada syndrome (BrS) is transmitted in an autosomal-dominant manner with incomplete penetrance. Very rarely, BrS is transmitted in an autosomal-recessive manner (**Alexandre Janin 1, Francis Bessière 2, Tudor Georgescu 3, Valérie Chanavat 1, Philippe Chevalier 2, Gilles Millat 4. TRPM4 Mutations to Cause Autosomal Recessive and Not Autosomal Dominant Brugada Type 1 Syndrome. Meta-Analysis Eur J Med Genet. 2019 Jun;62(6):103527. doi: 10.1016/j.ejmg. 2018.08.008.).**

KCNE5-related BrS, has inherited in an X-linked manner. (**Brugada R, Compuzano O, Brugada P, Brugada J, Hong K. Brugada Syndrome. (Updated Nov 11 2016) In GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle, 1993-2019: Available at: http://www.ncbi.nlm.nih.gov/books/NBK1517/.**)

This means that an individual has a 50% chance of passing on a mutation to their children. Additionally, parents and siblings of known carriers have a 50% chance of being carriers of the same mutation. When a mutation in a child is not found in the parents, it is assumed that there is a de novo mutation in the child. De novo mutations are estimated to occur in approximately 1% of cases. (**Brugada R, Compuzano O, Brugada P, Brugada J, Hong K. Brugada Syndrome. (Updated Nov 11 2016) In GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle, 1993-2019: Available at: http://www.ncbi.nlm.nih.gov/books/NBK1517/.**)

Siblings would still need to be tested to rule out germline mutations. A DNA test for BrS should be offered to the person who has the most obvious disease, as that individual will more likely test positive than someone without disease. At this time, population wide carrier screening for BrS is not recommended. (**Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace. 2011;13(8):1077-1109.**)

Although BrS is considered a genetic disease, its molecular mechanism remains unknown in » 70- 75% of clinically-confirmed cases. A single

mutation **is not enough to cause the BrS phenotype**. Not only the numerous genes causative of the BrS phenotype remains to be determined, but also the interplay between rare and common multiple variants. Some common polymorphisms whose roles have been 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 heart function. Geneticists 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.

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 (**Michelle M. Monasky,† Emanuele Micaglio,† Giuseppe Ciconte, and Carlo Pappone*Brugada Syndrome: Oligogenic or Mendelian Disease? Int J Mol Sci. 2020 Mar; 21(5): 1687.Published online 2020 Mar 1. doi: 10.3390/ijms21051687)**

https://www.evicore.com/-/media/files/evicore/clinical-guidelines/solution/lab-management/healthplan/2020-guidelines/brugada_syndrome_genetic_2020.pdf

The *PKP-2* p.S183N mutation was found in a patient affected by BrS, Persampieri et al. describe a case of a patient carrier of the same BrS-related *PKP2* p.S183N mutation but with a clear diagnosis of AC (or ARVC). Specifically, these authors report how clinical and molecular investigations can be integrated for diagnostic purposes, distinguishing between AC and BrS, which are increasingly recognized as syndromes with clinical and genetic overlaps. This relevant observation redefines 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. (**Simone Persampieri,1,† Chiara Assunta Pilato,2,† Elena Sommariva,2,* Angela Serena Maione,2 Ilaria Stadiotti,2 Antonio Ranalletta,1 Margherita Torchio,3 Antonio Dello Russo,1,4 Cristina Basso,5 Giulio Pompilio,2,6 Claudio Tondo,1,6 and Michela Casella1,4Clinical and Molecular Data Define a Diagnosis of Arrhythmogenic Cardiomyopathy in a Carrier of a Brugada-Syndrome-Associated PKP2 Mutation. Genes (Basel). 2020 May; 11(5): 571.doi: 10.3390/genes11050571**).

The table 1 shows the mutations that are likely to share BrS and AC

Table 1 Mutations that are likely to share BrS and AC.

	BrS	AC (or ARVC)
SCN5A mutation	1. BrS-1. » 25% of cases. Patient with this mutation exhibit more conduction abnormalities on ECG and have higher risk for cardiac events (**Kenichiro Yamagata 1, Minoru Horie 1, Takeshi Aiba 1, Satoshi Ogawa 1, Yoshifusa Aizawa 1, Tohru Ohe 1, Masakazu Yamagishi 1, Naomasa Makita 1, Harumizu Sakurada 1, Toshihiro Tanaka 1, Akihiko Shimizu 1, Nobuhisa Hagiwara 1, Ryoji Kishi 1, Yukiko Nakano 1, Masahiko Takagi 1, Takeru Makiyama 1, Seiko Ohno 1, Keiichi Fukuda 1, Hiroshi Watanabe 1, Hiroshi Morita 1, Kenshi Hayashi 1, Kengo Kusano 1, Shiro Kamakura 1, Satoshi Yasuda 1, Hisao Ogawa 1, Yoshihiro Miyamoto 1, Jamie D Kapplinger 1, Michael J Ackerman 1, Wataru Shimizu 2). Genotype-Phenotype Correlation of SCN5A Mutation for the Clinical and Electrocardiographic Characteristics of Probands With Brugada Syndrome: A Japanese Multicenter Registry Circulation. 2017 Jun 6;135(23):2255-2270. doi: 10.1161/CIRCULATIONAHA. 117.027983**.). Mutations on SCN5A gene is present in »25% of cases. and is more frequently found in females (48% vs 28% in males). **Zou P, Pinotsis N, Lange S, Song YH, Popov A, Mavridis I, Mayans OM, Gautel M, Wilmanns M (Jan 2006). "Palindromic assembly of the giant muscle protein titin in the sarcomeric Z-disk". Nature. 439 (7073): 229–33. doi:10.1038/nature04343. PMID 16407954**.)	1% (**Damir Erkapic 1, Thomas Neumann, Jörn Schmitt, Johannes Sperzel, Alexander Berkowitsch, Malte Kuniss, Christian W Hamm, Heinz-Friedrich Pitschner. Electrical Storm in a Patient With Arrhythmogenic Right Ventricular Cardiomyopathy and SCN5A Mutation. Europace. 2008 Jul;10(7): 884-7. doi: 10.1093/ europace/eun065. Epub 2008 Mar 29. 18375968 DOI: 10.1093/europace/ eun065**) Loss-of-function mutation in the cardiac Na^+ channel gene SCN5A,
Nondesmosomal cell signaling, providing structure and stability to heart muscle cells, and helping to maintain a normal heart rhythm.	TMEM43 variant + 2 missense variants in the SCN5A gene manifested by syncope, bradycardia, trifascicular block: first degree AV block, left posterior fascicular block complete right bundle branch block (RBBB) without structural heart disease. An epsilon wave in V2 can be suspected normal magnetic resonance imaging. A monomorphic ventricular tachycardia was induced (**J Shaffu 1, P Goethals 1, L Jordaens 2 3Funny Waves in Repolarisation and Tachycardia in a Patient Suspected for Brugada Syndrome. Neth Heart J. 2019 Sep;27(9):451-452. doi: 10.1007/s12471-019-1291-9.PMID: 31115760 PMCID: PMC6712179 DOI: 10.1007/ s12471-019-1291-9**)	Very unusual mutation TMEM43-p.S358L missense mutation ARVC Type 5 (42-43) OMIM: 604400; Gene *TMEM43*; #Cytogenetic Location: 3p25.1, which is the short (p) arm of chromosome 3 at position 25.1. s. A very rare mutation in TMEM 43 has a definite connection with desmosomal proteins (plakoglobin) (52)(51) (45)

Desmosome genes	BrS-15 Plakophilin-2 (*PKP2*) p.S183N mutation (**Simone Persampieri,1,† Chiara Assunta Pilato,2,† Elena Sommariva,2,* Angela Serena Maione,2 Ilaria Stadiotti,2 Antonio Ranalletta,1 Margherita Torchio,3 Antonio Dello Russo,1,4 Cristina Basso,5 Giulio Pompilio,2,6 Claudio Tondo,1,6 and Michela Casella1,4Clinical and Molecular Data Define a Diagnosis of Arrhythmogenic Cardiomyopathy in a Carrier of a Brugada-Syndrome-Associated PKP2 Mutation. Genes (Basel). 2020 May; 11(5): 571.doi: 10.3390/genes11050571**) (**Marina Cerrone 1, Xianming Lin, Mingliang Zhang, Esperanza Agullo-Pascual, Anna Pfenniger, Halina Chkourko Gusky, Valeria Novelli, Changsung Kim, Tiara Tirasawadichai, Daniel P Judge, Eli Rothenberg, Huei-Sheng Vincent Chen, Carlo Napolitano, Silvia G Priori, Mario Delmar. Missense Mutations in plakophilin-2 Cause Sodium Current Deficit and Associate With a Brugada Syndrome Phenotype 2014 Mar 11;129(10):1092-103. doi: 10.1161/CIRCULATIONAHA. 113.003077**.). This is a typical example of connexome: an association between desmosomal proteins, jap junctions and Na^+ channel complexes (48)(51). In typical BrS plakophilin-2 is in about 2.5% of cases of the gene mutation of interest after exclusion of any relevant BrS genes. Plakophilin-2 produces Na^+ deficit thus producing typical features of BrS. Mutations of PKP2 gene present in patients diagnosed with BrS and consecutive loss of desmosomal integrity could lead to reduced Na^+ current and hereby arrhythmogenic state through delayed depolarization. Epicardial VT ablation in a patient with Brugada ECG pattern, mutation of PKP2 and DSP Genes could be effective (55). BrS plakophilin-2 represent » 2.5% of cases of the gene mutation of interest after exclusion of any relevant BrS genes. Plakophilin-2 produces Na^+ deficit thus producing BrS phenotype (**Peters S. Is Brugada syndrome a variant of arrhythmogenic cardiomyopathy? Int J Cardiol. 2015;189: 88-90. doi: 10.1016/ j.ijcard.2015.03.394. Epub 2015 Mar 28. PMID: 25889434**.).	The most important protein is plakophilin-2, found in » 25–40% of cases (57) Plakophilin-2 (*PKP2*) Mutations in PKP2 are most frequently identified in AC patients. (47) Stefan Peters held the first description of AC and BrS caused by missense mutation in plakophilin-2. In all cases described no one had both — AC and BrS in one case. (**Peters S. Arrhythmogenic cardiomyopathy and provocable Brugada ECG in a patient caused by missense mutation in plakophilin-2. Int J Cardiol. 2014 May 1;173(2):317-8. doi: 10.1016/j.ijcard. 2014.03.071. Epub 2014 Mar 19. PMID: 24681023**.)

Desmoglein-2 mutations	Can be the cause (**DiResta C, Pietrelli A, Sala S, Della Bella P, DeBellis G, Ferrari M, et al. High-throughput characterization of a cohort of Brugada syndrome patients. Hum Nol Genet 2015: 24: 5828 – 35**,)	Can be the cause (**DiResta C, Pietrelli A, Sala S, Della Bella P, DeBellis G, Ferrari M, et al. High-throughput characterization of a cohort of Brugada syndrome patients. Hum Nol Genet 2015: 24: 5828 – 35**,)
TCAP gene	Recently identified (**Isik Turker 1, Takeru Makiyama 2, Takeshi Ueyama 3, Akihiko Shimizu 3, Masaru Yamakawa 4, Peng-Sheng Chen 1, Matteo Vatta 5, Minoru Horie 6, Tomohiko Ai 1 7 Telethonin Variants Found in Brugada Syndrome, J-wave Pattern ECG and ARVC Reduce Peak Na v 1.5 Currents in HEK-293 Cells.Pacing Clin Pacing Clin Electrophysiol. 2020 Jun 25.doi: 10.1111/pace.13996**.)	Recently identified (**Isik Turker 1, Takeru Makiyama 2, Takeshi Ueyama 3, Akihiko Shimizu 3, Masaru Yamakawa 4, Peng-Sheng Chen 1, Matteo Vatta 5, Minoru Horie 6, Tomohiko Ai 1 7 Telethonin Variants Found in Brugada Syndrome, J-wave Pattern ECG and ARVC Reduce Peak Na v 1.5 Currents in HEK-293 Cells.Pacing Clin Pacing Clin Electrophysiol. 2020 Jun 25.doi: 10.1111/pace. 13996**.)

transmembrane flow and disrupted integrity of the desmosome with resulting fatty infiltration have been identified, corresponding to BrS and AC, respectively. BrS patients could represent a rather heterogenic group comprising of individuals with mutations of desmosomal genes in as much as 3% of cases. (47) **#**ARVC-5 is the most aggressive heterozygous form of AC. It is predominantly caused by a fully penetrant mutation (p.S358L) in the nondesmosomal gene TMEM43-endemic to Newfoundland, Canada. To date, all familial cases reported worldwide share a common ancestral haplotype. It is unknown whether the p.S358L mutation by itself causes ARVC-5 or whether the disease is influenced by genetic or environmental factors. This gene contains a response element for PPAR gamma (an adipogenic transcription factor), which may explain the fibrofatty replacement of the myocardium, a characteristic pathological finding in AC. The presence of multiple mutations or a mutation in TMEM43; and the patient's willingness to restrict exercise and to eliminate participation in competitive or endurance exercise. (**Hugh Calkins, M.D.,1 Domenico Corrado, M.D., PhD,2 and Frank Marcus, M.D.3. Risk Stratification in Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Circulation. 2017 Nov 21; 136(21): 2068–2082. doi:10.1161/ CIRCULATIONAHA.117.030792**) “nondesmosomal” TMEM43-p.S358L missense

mutation, which is rare, observed almost exclusively in individuals in Newfoundland Canada, fully penetrant, and has ominous prognosis.