Familial Atrial fibrillation/atrial flutter in BrS and channelopathies

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Familial atrial fibrillation (FAF) is an inherited abnormality of the heart's normal rhythm. AF is characterized by episodes of uncoordinated electrical activity (fibrillation) in the heart's upper chambers (the atria), which cause a fast and irregular heartbeat. If untreated, this abnormal heart rhythm (arrhythmia) can lead to dizziness, chest pain, a sensation of fluttering or pounding in the chest (palpitations), shortness of breath, or fainting (syncope). AF also increases the risk of stroke and SCD. Complications of AF can occur at any age, although some people with this heart condition never experience any health problems associated with the disorder.The arrhythmogenic substrate in BrS may not be restricted to the ventricular level. Palpitations in this syndrome should raise the possibility of AF. Conversely, in patients with SVT and aborted CA or syncope not related to SVT, the BrS should be considered a possible additional electrophysiologic abnormality. (**L Eckardt 1, P Kirchhof, P Loh, E Schulze-Bahr, R Johna, T Wichter, G Breithardt, W Haverkamp, M BorggrefeBrugada syndrome and supraventricular tachyarrhythmias: a novel association Brugada syndrome and supraventricular tachyarrhythmias: a novel association. J Cardiovasc Electrophysiol. 2001 Jun;12(6):680-5. doi: 10.1046/j.1540-8167.2001.00680.x**.).

Type 1 ECG Brugada pattern may be associated not only with an increased risk of ventricular tachyarrhythmias but also with an increased risk of paroxysmal AF, and that the arrhythmogenesis may be related to the pronounced ST-segment elevation. (**H Itoh 1, M Shimizu, H Ino, K Okeie, M Yamaguchi, N Fujino, H Mabuchi, Hokuriku Brugada Study Group. Arrhythmias in patients with Brugada-type electrocardiographic findings. Jpn Circ J. 2001 Jun;65(6):483-6. doi: 10.1253/jcj.65.483**.)

In young patients with AF without structural heart disease (SHD) and/or known risk factors, latent BrS should be suspected. Syncope

and a family history of BrS emerge as easily identifiable factors related to BrS. Long-term sinus rhythm maintenance appears satisfactory, either in the presence or not of BrS.

AF is the most common type of recurrent arrhythmia, affecting more than 3 million people in the United States. The risk of developing this irregular heart rhythm increases with age. The incidence of the familial form of AF is unknown; however, recent studies suggest that up to 30% p of all people who have AF without an identified “Lone AF” cause have a history of the condition in their family.

Causes: multiple factors, genetic or acquired, that may impact upon autonomic function, atrial structure, and conduction velocities or other unknown factors.

Estimated incidence of AF in BrS

	Incidence of AF in BrS
Sacher F, et al. Remote implantable cardioverter defibrillator monitoring in a Brugada syndrome population. *Europace. 2009 Apr;11(4): 489-94. doi: 10.1093/europace/eup034..*	**10 %**
Schimpf R, et al. Clinical and molecular genetics of the short QT syndrome. *Curr Opin Cardiol.* 2008;23:192.	**11 %**
Kusano, et al. Atrial Fibrillation in Patients With Brugada Syndrome. *JACC.* 2008 Mar 25;51(12): 1169-75. doi: 10.1016/j.jacc.2007.10.060..	**13.7%**
Morita H, et al. Atrial Fibrillation and Atrial Vulnerability in Patients With Brugada Syndrome. J Am Coll Cardiol. 2002 Oct 16;40(8):1437-44. doi: 10.1016/s0735-1097(02)02167-8.	**29 %**
Bigi MA, et al. Clinical predictors of atrial fibrillation in Brugada syndrome. *Europace.* 2007 Oct;9(10): 947-50. doi: 10.1093/europace/eum110.	**53 %**

Pathophysiology factors

Triggers: high density Ito contractions in atrial tissue cause Premature Atrial Contraction(PCA) with short wavelength due to conduction delay or shortened refractoriness, regions of conduction block leading to Phase 2 Reentry

SCN5A mutation: cause intra-atrial conduction delay, increase LA volume, LA electroanatomical remodeling, and propension to fibrosis

Imbalance in the intracardiac ganglia activity predominance of vagal tonus as factor of modulating factor

inflammation

The pathophysiology of AF in BrS includes an interplay of triggers, arrhythmogenic substrate, and modulating factors such as the autonomic nervous system or inflammation.

Predictors of atrial fibrillation in Brugada syndrome

Kusano, et al. Atrial Fibrillation in Patients with Brugada Syndrome. Am Coll Cardiol. 2008 Mar 25;51(12):1169-75. doi: 10.1016/j.jacc. 2007.10.060.	· **Syncopal episodes** · **Documented VF** · **Spontaneous Type 1 Brugada pattern** · **Prolonged intraatrial conduction time** · **Prolonged sinus node recovery time**

Letsas KP, et al. Predictors of atrial tachyarrhythmias in subjects with type 1 ECG pattern of Brugada syndrome. *Pacing Clin Electrophysiol. 2009 Apr;32(4):500-5. doi: 10.1111/j. 1540-8159.2009.02311.x.*	**12-lead ECG** · **Prolonged P-wave duration in II** · **Prolonged P-wave dispersion** · **Prolonged PR interval in lead II** · **Prolonged QRS duration in II and V2(not an independent preditor)** · **Increase T-peak end interval in lead II** · **Increase T-peak end dispersion in lead IIin 12-l** · **EP parameters** · **Increase AH interval** · **Increase HV interval**
Bigi MA, et al. Clinical predictors of atrial fibrillation in Brugada syndrome. *Europace. 2007 Oct;9(10):947-50. doi: 10.1093/europace/ eum110.*	· **Syncope** · **Polymorphic VT** · **VF** · **ACA** (Aborted Cardiac Arrest)

Familial Atrial Fibrillation

	Chromosome Locus	OMIN	Inheritance Gene	Protein	Reference
FAF1	10q22-q24	60858	AD ?	´´	**Brugada R, et al. Identification of a genetic locus for familial atrial fibrillation. *N Engl J Med.* 1997 Mar 27;336(13):905-11. doi: 10.1056/ NEJM199703273361302.**

F A F 2	6 q 1 4 - q16	KCN Q1 6089 88	AD	´´	**Ellinor PT, et al. Locus for atrial fibrillation maps to chromosome 6q14– 16. *Circulation.* 2003 Jun 17;107(23): 2880-3.doi: 10.1161/01.CIR. 0000077910.80718.49.**
F A F 3	11q15.5	60755	AD	α- subu nit of Iks	**Chen YH, Xu SJ, Bendahhou S, Wang XL, Wang Y, Xu WY, Jin HW, Sun H, Su XY, Zhuang QN, Yang YQ, Li YB, Liu Y, Xu HJ, Li XF, Ma N, Mou CP, Chen Z, Barhanin J, Huang W. KCNQ1 gain-of-function mutation in familial atrial fibrillation. Science. 2003 Jan 10;299(5604):251-4.**
F A F 4	21q22.1	KCN E2	AD	MIRP 1	**Yang Y, et al. Identi? cation of a KCNE2 gain-of-function mutation in patients with familial atrial? brillation. *Am J Hum Genet.* 2004;75:899, doi: 10.1086/425342**
F A F 5	4q25	´´	AD		**Gudbjartsson DF, et al. Variants conferring risk of atrial? brillation on chromosome 4q25. *Nature.* 2007; 448:353.doi: 10.1038/ nature06007.**

F A F 6	1p36,2	NPPA	AD	Atrial Natriuretic Peptide	**Hodgson-Zingman DM, et al. Atrial natriuretic peptide frameshift mutation in familial atrial fibrillation. *New Eng. J. Med.* 2008;359:158.**
F A F 7	12q13	KCNAS	AD	Kv1.5	
					Olson T, et al. Kv1.5 channelopathy due to KCNA5 loss-of-function mutation causes human atrial fibrillation. *Hum. Molec. Genet.* 2006; 15:2185. (Yang Y, et al. Novel KCNA5 loss-of-function mutations responsible for atrial fibrillation. *J. Hum. Genet.* 2008; 54:277 2009 May;54(5): 277-83. doi: 10.1038/ jhg.2009.26..)
F A F 8		16q22 613055			

Others important references

· Fatkin D, Santiago CF, Huttner IG, Lubitz SA, Ellinor PT. Genetics of Atrial Fibrillation: State of the Art in 2017. Heart Lung Circ. 2017 Sep;26(9):894-901. doi: 10.1016/j.hlc.2017.04.008. Epub 2017 May 11. Review. Citation on PubMed

· Gutierrez A, Chung MK. Genomics of Atrial Fibrillation. Curr Cardiol Rep. 2016 Jun;18(6):55. doi: 10.1007/s11886-016-0735-8. Review. Citation on PubMe or Free article on PubMed Central

· Hucker WJ, Saini H, Lubitz SA, Ellinor PT. Atrial Fibrillation Genetics: Is There a Practical Clinical Value Now or in the Future? Can J Cardiol. 2016 Nov;32(11):1300-1305. doi: 10.1016/j.cjca.2016.02.032. Epub 2016 Feb 12. Review. Citation on PubMed or Free article on PubMed Central
· Xiao J, Liang D, Chen YH. The genetics of atrial fibrillation: from the bench to the bedside. Annu Rev Genomics Hum Genet. 2011;12:73-96. doi: 10.1146/annurev-genom-082410-101515. Review.

Genes affected in BrS and AF: BrS has autosomal dominant pattern of transmission with variable penetrance. SCN5A on chromosome 3p21 (with more than 100 mutations), can be found in »25% of cases. The presence of an SCN5A mutation is associated with intra-atrial dromotropic disturbance slowing, manifested in surface ECG by a prolonged P-wave duration, providing a substrate for AF maintenance. Loss-of-function (LOF) mutations in SCN5A generates an imbalance in the intracardiac ganglia activity and increases arrhythmogenic augmentation vagal tone. Prolongation of atrio His and HV interval; occur in patients with SCN5A mutations (**Smits JP, Eckardt L, Probst V, et al. Genotype-phenotype relationship in Brugada syndrome: electrocardiographic features differentiate SCN5A-related patients from non-SCN5A-related patients. *J Am Coll Cardiol.* 2002;40:350–6**.) Intraatrial conduction delay and its heterogeneity may be present in BrS patients, especially those showing -type 1 ECG Brugada pattern. These atrial electrical abnormalities could be a substrate for atrial reentrant tachycardia such as AF. (**Yoshio Furukawa 1, Takahisa Yamada, Yuji Okuyama, Takashi Morita, Koji Tanaka, Yusuke Iwasaki, Hiromichi Ueda, Takeshi Okada, Masato Kawasaki, Yuki Kuramoto, Masatake FukunamiIncreased intraatrial conduction abnormality assessed by P-wave signal-averaged electrocardiogram in patients with Brugada syndrome. Pacing Clin Electrophysiol. 2011 Sep;34(9): 1138-46. doi: 10.1111/j.1540-8159.2011.03122. x.**) Conduction slowing are more marked and more progressively accentuated in Brugada probands with SCN5A mutation than in those without SCN5A mutation. (**Miki Yokokawa 1, Takashi Noda, Hideo Okamura, Kazuhiro Satomi, Kazuhiro Suyama, Takashi Kurita, Naohiko Aihara, Shiro Kamakura, Wataru Shimizu. Comparison of long-term follow-up of electrocardiographic features in Brugada syndrome between the SCN5A-positive probands and the SCN5A-negative probands. Am J Cardiol. 2007 Aug 15;100(4):649-55. doi: 10.1016/j.amjcard. 2007.03.078**.) Common genetic variation is associated with variable expressivity of BrS phenotype in *SCN5A* families, explaining in part incomplete penetrance and genotype-negative phenotype-positive

individuals. *SCN5A* mutation genotype and a BrS-GRS(genetic risk score) associate with BrS phenotype, but the strength of association varies according to presence of a *SCN5A* mutation and severity of loss of function.
Additionally, rare variants in genes affecting the sodium current (SCN1B (**London B, Sanyal S, Michalec M, et al. A mutation in the C(abstr) *Heart Rhythm.* 2006;3: S32.), SCN10A**) and calcium current (CACNA1C, CACNA2D1, and CACNB2B) have been described in BrS patients. Mutations mostly result in qualitative or quantitative alteration of sodium channels. A high Ito density in the atria and the observation that AF episodes may be triggered by closely PACs suggest that the substrate that underlies the onset of AF may be similar to that malignant arrhythmogenesis in ventricles. The presence of SCN3B mutation and its association with the L10P missense mutation has also been associated with lone AF. (**Olesen MS, Jespersen T, Nielsen JB, Liang B, Møller DV, Hedley P, Christiansen M, Varró A, Olesen SP, Haunsø S, Schmitt N, Svendsen JH.Mutations in sodium channel beta-subunit SCN3B are associated with early-onset lone atrial fibrillation. Cardiovasc Res. 2011 Mar 1;89(4):786-93. doi: 10.1093/cvr/cvq348**.). GPD1-L is a novel gene that may affect trafficking of the cardiac Na+ channel to the cell surface. A GPD1-L mutation decreases SCN5A surface membrane expression, reduces inward Na+ current, and causes BrS
(Barry London 1, Michael Michalec, Haider Mehdi, Xiaodong Zhu, Laurie Kerchner, Shamarendra Sanyal, Prakash C Viswanathan, Arnold E Pfahnl, Lijuan L Shang, Mohan Madhusudanan, Catherine J Baty, Stephen Lagana, Ryan Aleong, Rebecca Gutmann, Michael J Ackerman, Dennis M McNamara, Raul Weiss, Samuel C Dudley Jr Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias. Circulation. 2007 Nov 13;116(20):2260-8. doi: 10.1161/CIRCULATIONAHA.107.703330. Epub 2007 Oct 29.).
Autonomic tone: A circadian pattern for AF has been described such as for ventricular arrhythmias, where most episodes occur at night, suggesting a potential role of nocturnal vagal activity and withdrawal of sympathetic activity in arrhythmogenesis. Acetylcholine activation of the K+ current I KACh abbreviates action potential duration (APD) and effective refractory period(ERP). Moreover, ERP heterogeneity may correlate with the duration of inducible AF. Electroanatomical abnormalities in the atrium: Gain-of-function mutation in SCN5A increases inward Na+ currents leading to might cause to failure of repolarization or early after-depolarizations (EADs), thereby inducing triggered activities, PACs, and AF. Prolonged atrial conduction times and increased LA volumes and increased atrial electroanatomical structural

remodeling in BrS patients with SCN5A mutations compared with those without. 50 percent reduction in the expression of atrial connexin 40, in addition to reduced sodium current is responsible for atrial conduction slowing. Structural abnormalities such as interstitial fibrosis and functional changes in connexins/ cardiac ion channels promote the perfect substrate for anatomical and functional re-entrant activities, facilitating AF maintenance. Lone AF may be the first clinical manifestation of latent BrS, preceding the onset of VA and representing the most common atrial arrhythmia in BrS. (**Konstantinos Vlachos 1, Giuseppe Mascia 2, Claire A Martin 1 3, George Bazoukis 4, Antonio Frontera 1, Ghassen Cheniti 1, Konstantinos P Letsas 4, Micheal Efremidis 4, Stamatis Georgopoulos 4, Charis Gkalapis 5 6, Josselin Duchateau 1, Thomas Parmbrun 1, Nicholas Derval 1, Mélèze Hocini 1, Michel Haissaguerre 1, Pierre Jais 1, Frédéric Sacher 1 Atrial fibrillation in Brugada syndrome: Current perspectives J Cardiovasc Electrophysiol. 2020 Apr;31(4): 975-984. doi: 10.1111/jce.14361**.)

Management: Young BrS patients with arrhythmic events represent a very arrhythmogenic group. Current management after the first arrhythmia episode is associated with a high recurrence rate. Alternative therapies, besides defibrillator implantation, should be considered. antiarrhythmic drugs effective in preventing malignant arrhythmias in BrS such as quinidine or invasive treatment with pulmonary vein isolation (PVI) (**Yoav Michowitz 1, Anat Milman 2, Antoine Andorin 3, Georgia Sarquella-Brugada 4, M Cecilia Gonzalez Corcia 5, Jean-Baptiste Gourraud 3, Giulio Conte 6, Frederic Sacher 7, Jimmy J M Juang 8, Sung-Hwan Kim 9, Eran Leshem 10, Philippe Mabo 11, Pieter G Postema 12, Aviram Hochstadt 13, Yanushi D Wijeyeratne 14, Isabelle Denjoy 15, Carla Giustetto 16, Yuka Mizusawa 12, Zhengrong Huang 17, Camilla H Jespersen 18, Shingo Maeda 19, Yoshihide Takahashi 19, Tsukasa Kamakura 20, Takeshi Aiba 20, Elena Arbelo 21, Andrea Mazzanti 22, Giuseppe Allocca 23, Ramon Brugada 24, Ruben Casado-Arroyo 25, Jean Champagne 26, Silvia G Priori 22, Christian Veltmann 27, Pietro Delise 23, Domenico Corrado 28, Josep Brugada 21, Kengo F Kusano 20, Kenzo Hirao 19, Leonardo Calo 29, Masahiko Takagi 30, Jacob Tfelt-Hansen 18, Gan-Xin Yan 31, Fiorenzo Gaita 16, Antoine Leenhardt 15, Elijah R Behr 14, Arthur A M Wilde 12, Gi-Byoung Nam 32, Pedro Brugada 33, Vincent Probst 3, Bernard Belhassen 34 Characterization and Management of Arrhythmic Events in Young Patients With Brugada Syndrome. J Am Coll Cardiol. 2019 Apr 16;73(14): 1756-1765. doi: 10.1016/j.jacc.2019.01.048.)**