Brugada syndrome: etyological, forms and genetic basis- 2008

Dr. Andrés R. Pérez Riera

1) Sporadic forms without genetic mutation: » 70% to 82% of the cases.

2) With genetic mutation: » 18% to 30% of cases

(2-1) Brugada syndrome type 1 or B1: OMIN number: 601144, Locus: 3p21; Gene: mutation in alpha subunit of the sodium channel (SCN5A Nav1.5) gene[1].

(2-2) Brugada syndrome type 2 or B2: Locus: 3p24, gene loss-of-function mutations in gene encoding the cardiac L-type calcium channel: Mutation in glycerol-3 phosphate dehydrogenase-1 like (GPD1L [2; 3]). The entity is associated with progressive conduction disease, a low sensitivity to procainamide, and a relatively good prognosis[4].

(2-3) Brugada syndrome type 3or B3: Locus: 12.p 13.3 Gene: mutation in CACNA1C.Ca_v1.2 gene[5].

(2-4) Brugada syndrome type 4 or B4: Locus: 10p12.33, Gene: loss-of-function mutations in gene encoding the cardiac L-type calcium channel: The CACNB2b.CAvb2b gene. The entity consists of an ST-segment elevation in the right precordial ECG leads, a shorter-than-normal QT interval (≤370 ms), and a familial history of sudden cardiac death[5].

Observation: Types 3 and 4 are very rare, and probably have and overlap genotype (horter-than-normal QT interval (≤370 ms) interval + Brugada syndrome ECG phenotypes)

(2-5) Brugada syndrome type 5 or B5: OMIN number: 604433, *KCNE3* which coassembles with KCND2 beta subunit act in

the modulation of I_{to} potassium outward current in the human heart. Mutations in *KCNE3* can underlie the development of the Brugada syndrome[6]

(2-6) Brugada syndrome type 6 or B6: OMIN number: 600235, SCN1B beta 2 subunit of the sodium channel SCN5A. Watanabe et al[7] investigated SCN1B, which encodes the function-modifying sodium channel beta1 subunit, in 282 probands with Brugada syndrome and in 44 patients with conduction disease, none of whom had SCN5A mutations. The authors identified 3 mutations segregating with arrhythmia in 3 kindreds. Two of these mutations were located in a newly described alternately processed transcript, beta1B. Both the canonical and alternately processed transcripts were expressed in the human heart and were expressed to a greater degree in Purkinje fibers than in heart muscle, consistent with the clinical presentation of conduction disease. Sodium current was lower when NaV1.5 was coexpressed with mutant beta1 or beta1B subunits than when it was coexpressed with WT subunits. These findings implicate SCN1B as a disease gene for human arrhythmia susceptibility.

3) Atypical Brugada syndrome or idiopathic ventricular fibrillation with J waves in inferior, lateral or inferior lateral leads
Until to day, two identified mutations

(3-1) SCN5A[9]

(3-2) KCNJ8 $_{KATP}$[10; 11] The ECGs have an elevation of the QRS-ST junction of at least 0.1 mV from baseline in the inferior or lateral lead, manifested as QRS slurring or notching. Among patients with a history of idiopathic ventricular fibrillation, there is an increased prevalence of early repolarization.

4) “Acquired” or secondary forms[12]
(4-1) Drug-induced like congenital LQTS
(4-2) Electrolytes abnormities-induced
(4-3) Acute ischemia-induced
(4-4) Fever-induced
(4-5) Hypothermic-induced

(4-6) Mechanical compression of right ventricle outflow tract - induced

(4a) without genetic background

(4b) with genetic background

References

1) Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Ortiz-Lopez R, Wang Z, Antzelevitch C, O'Brien RE, Schulze-Bahr E, Keating MT, Towbin JA, Wang Q.Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature. 1998; 392(6673):293-296.

2) London B, Michalec M, Mehdi H, Zhu X, Kerchner L, Sanyal S, Viswanathan PC, Pfahnl AE, Shang LL, Madhusudanan M, Baty CJ, Lagana S, Aleong R, Gutmann R, Ackerman MJ, McNamara DM, Weiss R, Dudley SC Jr.Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias. Circulation. 2007;116:2260-22608.

3) Makiyama T, Akao M, Haruna Y, Tsuji K, Doi T, Ohno S, Nishio Y, Kita T, Horie M.Mutation analysis of the glycerol-3 phosphate dehydrogenase-1 like (GPD1L) gene in Japanese patients with Brugada syndrome. Circ J. 2008; 72:1705-1706.

4) Weiss, R; Barmada, MM; Nguyen, T; Seibel, JS; Cavlovich, D; Kornblit, CA; Angelilli, A; Villanueva, F; McNamara, DM; London, B. Clinical and molecular heterogeneity in the Brugada syndrome. A novel gene locus on chromosome 3. Circulation. 2002;105:707–71

5) Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, Guerchicoff A, Pfeiffer R, Oliva A, Wollnik B, Gelber P, Bonaros EP Jr, Burashnikov E, Wu Y, Sargent JD, Schickel S, Oberheiden R, Bhatia A, Hsu LF, Haïssaguerre M, Schimpf R, Borggrefe M, Wolpert C.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;115:442-449.

6) Postma AV, Bezzina CR, de Vries JF, Wilde AA, Moorman AF, Mannens MM.Genomic organisation and chromosomal localisation of two members of the KCND ion channel family, KCND2 and KCND3. Hum Genet. 2000 Jun;106(6):614-619.

7) Delpón E, Cordeiro JM, Núñez L, Bloch Trhomsen PE, Guerchicoff A, Pollevick GD, Wu Y, Kanters JK, Larsen CT, Burashnikow E, Christiansen M, Antzelevitch C. "Functional Effects of KCNE3 Mutation and Its Role in the Development of Brugada Syndrome". *Circulation Arrhythmia and Electrophysiology* 1 (3): 209-218

8) Watanabe H, Koopmann TT, Le Scouarnec S, Yang T, Ingram CR, Schott JJ, Demolombe S, Probst V, Anselme F, Escande D, Wiesfeld AC, Pfeufer A, Kääb S, Wichmann HE, Hasdemir C, Aizawa Y, Wilde AA, Roden DM, Bezzina CR. "Sodium channel beta1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans". *J. Clin. Invest.* 118: 2260–2268.

9) Potet F, Mabo P, Le Coq G, Probst V, Schott JJ, Airaud F, Guihard G, Daubert JC, Escande D, Le Marec H Novel brugada SCN5A mutation leading to ST segment elevation in the inferior or the right precordial leads. J Cardiovasc Electrophysiol. 2003;14:200-203

10) Haissaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mayry S, De Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, Le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O'Neill M, Hocini M, Lim KT, Knecht S, Veenhuyzen GD, Bordachar P, Chauvin M, Jais P, Coureau G, Chene G, Klein GJ, Clémenty J. Sudden cardiac arrest associated with early repolarization. N Engl J Med. 2008 May 8; 358:2016-2023.

11) Haissaguerre M, Chatel S, Sacher F, Weerasooriya R, Probst V, Loussauarn G, Horlitz M, Liershch R, Shulze-Bahr E, Wilde A, Kaab S, Koster J, Rudy Y, Le Marec H, Shott JJ Ventricular Fibrillationwith Prominet Early Repolarization Associted with a Rare Variant of KCNJ8/K_{ATP} Channel Journal of Cardiovascular Electrophysiology 2008?????

12) Shimizu W. Acquired forms of the Brugada syndrome. J Electrocardiol. 2005; 38: 22-25.