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Research Article

Some Advances on Genetics Related to Brugada Syndrome

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Abstract

Brugada Syndrome (BrS) is a rare inherited arrhythmogenic disorder that exhibits ECG ST-segment elevation≥2mm with a negative T-wave in the right precordial leads (V1-V2), with normal heart structure, predisposing to Ventricular Fibrillation (VF) and Sudden Cardiac Death (SCD). Genetically BrS is autosome dominant accompanied by incomplete penetrance, and mutations in *SCN5A* gene had been identified as the main pathogenic cause of BrS. Besides, mutations of other 16 genes also link to BrS, but mutation in *SCN5A* account for approximately 30% and those in other genes 5% leaving no definitive genetic background in 65% of BrS patients. Some advances on genetics related to BrS are reviewed in this paper.

Keywords: Brugada syndrome; Genetics; *SCN5A*; Gene mutation

Introduction

BrS is a rare inherited arrhythmogenic disorder that exhibits ECG ST-segment elevation≥2mm with a negative T-wave in the right precordial leads (V1-V2), with normal heart structure, predisposing to Ventricular Fibrillation (VF) and Sudden Cardiac Death (SCD). In 1992, Brugada P and Burgada J first discovered it as a new arrhythmia. After *SCN5A* was identified as the first pathogenic gene of BrS [1-3] in 1998, it was learned that BrS is an autosomal dominant inheritance accompanied by incomplete penetrance.

Retrospect of Researches on BrS in Past Ten Years [1]

From 1998 to 2008, 6 gene mutations were found associated with BrS, in which 4 gene mutations were reported in 2008.The first gene mutation is *SCN5A* intronic mutation activated by cryptic splice site in a family with BrS, resulting loss-of-function of Na+ channel. The second site is in autosome 3 [1] (similar but different from *SCN5A*), it has been linked to a large family with BrS, accompanied by syndrome of progressive conduct disease. This gene was called glycerol-3-phophate dehydrogenase like gene (*GPDIL*). *GPDIL* mutation is at least partly caused by membrane transport defect. Afterwards, the third and the fourth genes code α_1 subunit (*CACNA1C*) and β subunit (*CANB2β*) of L type cardiac Ca^{2+} channel, respectively. The mutations in α and β subunits of cardiac Ca^{2+} channel are usually accompanied by familial sudden cardiac death syndrome. See following (Table 1).

Research Status on Brugada Syndrome in Recent 3 Years

Research advances in 2013

Hsiao et al., [4] systematically mentioned the genetic aspects related to BrS when reviewing ion channelopathies. They reported that 11 gene mutations had been identified in BrS. These mutations locate in *SCN5A* (coding Nav1.5), *SCN1B* and *SCN3B* (coding cardiac Na^+ channel β subunit) or *GPD1L* and *MOG1* (involving Nav1.5 to membrane transport). All of them cause loss-of-function of Nav1.5, thereby decreasing INa. Other mutations locate in *CACN1C, CACNB2b* and *CACNA2D1* respectively (coding α_1, β_{2b} and $\alpha_2\delta_1$ subunits of Cav1.2, respectively), leading to the decrease of L type Ca^{2+} current ($I_{Ca}L$), *KCNE3* (coding MiRP2, α and β subunits of several K^+ channels) and *KCNJ8* (coding ATP-sensitive K^+ channel). In a word, *SCN5A* mutation accounts for approximately 20% BrS patients, mutations in other genes account for only 10%, the remaining 70% BrS patients have not found definitive genetic background.

Research advances in 2014

Brugada, et al., [3] revealed that 16 genes (*SCN5A, GPDIL, SCN1B, SCN2B, SCN3B, RANGRF, SLM4P, KCNE3, KCNJ8, KCNE4, KCNE5, KCND3, CACN1C, CACNB2b, CACNA2D1 and TPPM4*) 350 mutations had been reported until 2014. These genes code cardiac Na^+, K^+ and Ca^{2+} channels, respectively, and are involved in transport or regulation of these channels. Even though the number of genes is high, they are the pathogenic cause of only about 35% BrS patients, in which mutations of *SCN5A* gene account for approximate 30%, mutations of other genes only 5%. The remaining 65% patients cannot find a genetic source. Hence, the achievement on genetic researches of BrS in 2014 is good: pathogenic genes were found 5 more than in 2013. Several factors in gene screening may account for the cause of BrS patients without genetic source, such as the change of replication number in *SCN5A*, in addition, pathogenic mutation may locate in undiscovered genes. BrS may be related to epigenetic factors, principally DNA methylation, post-translation modification and RNA mechanism. All these factors at least partly account for BrS mild incomplete penetrance and its variation expression characteristics.

Research advances in the first season of 2015

SCN10A Behr, et al., [5] studied 156 cases of Cancasus patients with *SCN5A* dominant negative BrS. They had identified 7 candidate genes *(SCN10A, Handl, PLN, Casqz, TKT, TBX3 and TBX5)* as variant in 49 cases, rare (MAF 1%) and non-synonymous in 18 cases, in which 11 cases were mostly *SCN10A*, predicting that it was pathogenic. Co-segregation showed that 4/7 cases carried new variant possibly, only 1 case had *V/G 1299A* in *SCN10A* and did not display co-segregation.

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Table 1: Genetic Basis of BrS.

Researcher	Type	Site	Ion channel	Gene	Protein	Incidence(%)
Chen,et al.,	BrS1	3p21	I_{Na}	*SCN5A*	Nav1.5	15
London,et al.,	BrS2	3p24	I_{Na}	*GPD1L*	-	Rare
Antzelevitch,et al.,	BrS3	12p13.3	I_{Ca}	*CACNA1C*	Cav1.2	6.6
Antzelevitch,et al.,	BrS4	10p12.33	I_{Ca}	*CACNB2b*	Cav$\beta_2$1	4.8
Watanabe	BrS5	19q13.1	I_{Na}	*SCN1B*	Navβ_1	1.1
Delpon,et al.,	BrS6	11q13-q14	Ito	*KCNE3*	MiPR2	Rare

However, single nucleotide polymorphism (SNP) *V1073* in *SCN10A* was closely related to BrS. In frequent variants (*V1073 and A1073*) and rare variants (*A200V and 1671V*) of *SCN10A*, voltage-clamp test was carried out. The peak value of inward current of Na^+ current (I_{Na}) decreased markedly, when compared with the ancestral allelles *A1073 (rs795970)*. They concluded that when screening rare variant of QRS related genes (including *SCN10A*), most of them did not result in *SCN10A* dominant negative BrS. Frequnet SNP *SCN10A V1073* were closely related to BrS, and Nav1.5 loss-of-function had been confirmed.

Genes coding variant burden La Souamee, et al., [6] determined rare gene coding variant burden in arrhythmia-sensitive genes of a large group of BrS patients. They captured and sequenced coding regions of arrhythmia-sensitive genes (reported previously) in 45 cases, by using customized equipment. Through burden test, they observed a large quantity of coding variant only in *SCN5A* (the frequency of minor allele<0.1%). 20.09% BrS patients and 24% controls carried rare coding variant, whereas in any other arrhythmia-sensitive genes (including *SCN10A* and *CACNA1C*), they did not found a large quantity of coding variant. These results indicated that except *SCN5A*, rare coding variant in arrhythmia-sensitive genes reported previously is related to European ancestry individuals with BrS. In case of molecular diagnosis, it should be doubly careful to explain the genetic variation, because coding variant of BrS-sensitive genes can be observed in the same number of patients and controls.

New genetic variants found in *SCN5A* Saber, et al., [7] had proposed that at least 17 genes linked to patients with BrS, although recent findings reveal its polygenic background. They found that *SCN5A* carried new genetic variant *p.P1506S* in BrS patients of a large Irish family. From clinical, genetic and expressive researches, they observed availability curve hyper polarization shift, activation curve depolarization shift and promoting rapid inactivation process. The change induced by these mutations resulted in loss-of-function of Nav1.5, in this way, *p.P1506S* variant is pathogenic. In addition, cascade familial screening discovered that BrS family members did not carry *p.P1506S* mutation within *KCNH2* gene in *SCN5A*-neative patients. These finding clarified complex genetic background as well as possible pathogenic role of new *SCN5A* genetic variant in this family. In genetic examination of *SCN5A* in 6 Polish BrS patients with ajmaline provocation test positive, Uzieblo-Zyczkowska [8] revealed 6 kinds of known polymorphism, 8 new single nucleotide points (SNP), whose variants locate in the exons, 12 new SNPs locating in the introns. Three new SNPs in *SCN5A* gene exon influenced protein sequence.

Newly Discovered Gene Mutations in *SCN5A*

Hsuch,et al., [9] reported 3 new *SCN5A* mutations in Taiwan area, ie. *p.1848fs, p. R965C* and *p.1876insM. p. 1848fs* mutation did not produce Na^+ current. The latter two mutations produced steady-state inactivation channels shifting toward negative potential (19.4mV and 8mV, respectively) as well as a slower recovery time. *p.1876insM* steadied the activation change shifting toward positive potential (7.69mV). They considered that *SCN5A* channel defect related to BrS might be different, but all gave rise to Na^+ current reduction. Zeng, et al., [10] found dominant missense mutation (*R1629Q*) locating in DIV-S4 in a Chinese Han family. They identified such mutation from DNA of proband by using *SCN5A* direct sequencing. They also identified steady-state inactivation curve hyperpolaization shift in cells expressing *R1629Q* channel. *R1629Q* channel manifested intermediate inactivation enhance as well as time extension from inactivation to recovery. Their research showed that *R1629Q* mutation lead to loss-of-function in channels due to the change of channel electrophysiological characteristics. Tarrades, et al., [11] showed that new *1890T* mutation of *SCN5A* located in pore region of Nav1.5, leading to definite loss-of-function in channels. It seemed that BrS phenotype observed in proband is most likely due to this mutation. Antzelevitch and Nof [1] reported the additional actions of 2 heterozygote missence mutations in *SCN5A:p336L* mutation in *SCN5A* resulting in I_{Na} decrease, whereas *116201* mutation terminating I_{Na}. Only in proband who carries these 2 mutations simultaneously, BrS phenotype can display, in which any one mutation alone cannot produce clinical phenotype in father or daughter of proband. Saber, et al., [12] found that *delKPQ1505-1507* mutation known in *SCN5A* gene not only showed LQTS phenotype, but also its carrier appeared LQTS and BrS simultaneously (Joint phenotype). This overlapping phenotype has high risk of sudden cardiac death. Zakzliazminskaia, et al., [13] reported 25 Russian patients with BrS. They found *SCN5A* rare genetic variants in 7/24 probands in which 2 cases involved protein splice (*eIVS16DS-5A>G* and *cIVS24A+1G>A*) 3 cases had missence mutation (*p.Y87C, p.R93H,p.S1787N*),1 case had in-frame deletion *p.del 18481*, and 1 case had nonsense mutation *pE553X*.

SCN1B and *SCN3B*

So far, there are 17 genes linked to BrS. Besides *SCN5A* has been well known, *SCN10A* and *GPDIL* were introduced just now. The remaining 14 genes can only introduce *SCN1B* and *SCN2B* here, the rest are not quite clear in the literature. Ricci, et al., [14] studied *SCN1B*, which codes voltage-gating β_1 subunit and its soluble β_{1b} isoform in Na^+ channel. They found that *SCN1B* mutation had been accompanied by BrS and other arrhythmia, familial epilepsy. They analyzed exon 3A & 3\UTR of *SCN1B* in 145 *SCN5A*-negative

patients, and found 2 new *SCN1B* variants. Their findings contribute more evidence that *SCN1B* variants occur in BrS.

Ishikawa, et al., [15] studied a total of 181 BrS patients without *SCN5A* mutation. In 3 Japanese patients, *SCN3B* mutation (*Val750lle*) was identified. *SCN3B* mutation damages cytoplasm transport. Na^+ current decreases obviously. They considered *Val750lle* mutation in *SCN3B* as a relatively common cause of Japanese *SCN5A*-negative BrS patients, because Nav1.5 cell surface expression defect leads to Na^+ current decrease. Hu, et al., [16] support the hypothesis that *SCN3B* can cause Nav1.5 protein transport function expression defect, which results in Na^+ channel current decrease and hence show clinical phenotype of BrS.

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