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REVIEW

Molecular genetics of Brugada syndrome

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Abstract Brugada syndrome (BrS) is a life-threatening cardiac rhythm disorder characterized by persistent ST-segment elevation in leads V1–V3 and right bundle branch block on electrocardiograms (ECG), and by syncope and sudden death from ventricular tachycardia (VT) and ventricular fibrillation (VF). BrS is responsible for nearly 4% of sudden cardiac deaths and considered to be the most common cause of natural death in males younger than 50 years in some Asian countries. Since the first disease-causing gene for BrS (the cardiac sodium channel gene *SCN5A*) was identified in 1998, extensive investigations on both clinical and basic aspects of BrS have occurred rapidly. *SCN5A* mutations remain the most common cause of BrS; nearly 300 *SCN5A* mutations have been identified and are responsible for 20%–30% of BrS cases. Commercial genetic testing is available for *SCN5A*. Recently, seven other disease-causing genes for BrS have been identified and include *GPD1L* (BrS2), *CACNA1C* (Cav1.2, BrS3), *CACNB2* (Cavβ2, BrS4), *SCN1B* (Navβ1, BrS5), *KCNE3* (MiRP2, BrS6), *SCN3B* (Navβ3, BrS7), and *HCN4* (BrS8). This article will briefly review the progress made over the past decade in our understanding of the clinical, genetic and molecular aspects of BrS.

Keywords Brugada syndrome, molecular genetics, arrhythmia, sudden death, *SCN5A*, ion channel

1 Introduction

Brugada syndrome (BrS) is a cardiac disorder characterized by ST-segment elevation in the right precordial leads (V1–V3) and right bundle branch block on electrocardiograms (ECG) (Fig. 1). BrS is associated with an increased risk of sudden death due to polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF). BrS was described as a distinct clinical entity by the Brugada brothers in 1992, and is now regarded as the most common cause of genetically determined cardiac VT and VF worldwide (Brugada and Brugada, 1992). To date, eight disease-causing genes have been identified (Hedley et al., 2009). In this review, we summarize the current progress made over the past decade, focusing on the clinical and genetic aspects of the syndrome, and the underlying pathophysiological mechanisms of this disease.

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2 Diagnostic criteria, epidemiology, pathogenetic mechanisms and treatment

2.1 Diagnosis and clinical symptoms

Three patterns of ECG abnormalities have been identified for BrS and differ in terms of the nature of ST segment elevation and the T wave morphology.

Type I: covered-type ST-segment elevation of $\geqslant$ 2 mm followed by negative T waves.

Type II: ST-segment elevation of $\geqslant$ 2 mm followed by positive or biphasic T waves.

Type III: any of the 2 previous types if ST-segment elevation is $\leqslant$ 1 mm (Benito et al., 2009).

Clinical BrS is diagnosed when type I ECG patterns are present in combination with at least one of the following criteria: documented VT, inducible VT during electrophysiological studies, recurrent syncope or nocturnal agonal respiration, a family history of sudden cardiac death before 45 years of age, or type I ECG patterns in other family members (Wilde et al., 2002).

Clinically, BrS manifests by syncope and sudden cardiac death (SCD) from polymorphic VT and VF (Fig. 2). BrS symptoms typically present during adulthood, and sudden death occurs at a mean age of 41±15 years (Antzelevitch

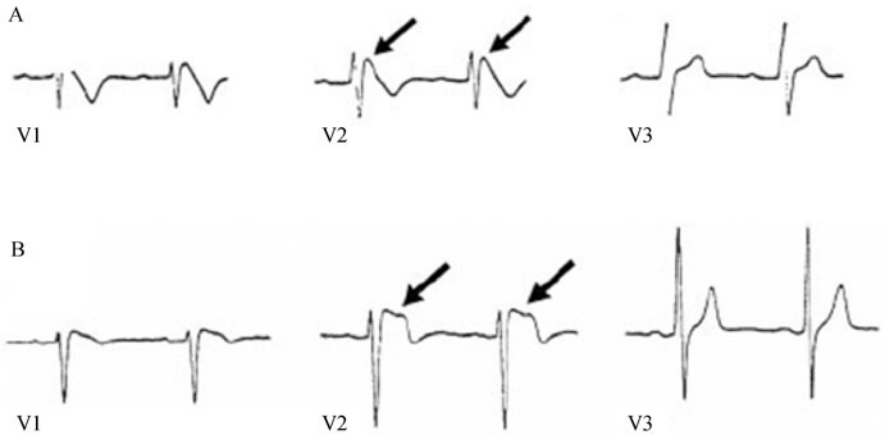

Fig. 1 Electrocardiogram (ECG) patterns in right precordial leads observed in patients with Brugada syndrome. Spontaneous ST-segment elevation is recorded in leads V2 (arrows) in patients A and B. [Modified from Chen et al. (1998). Nature, 392: 293–296 with permission.]

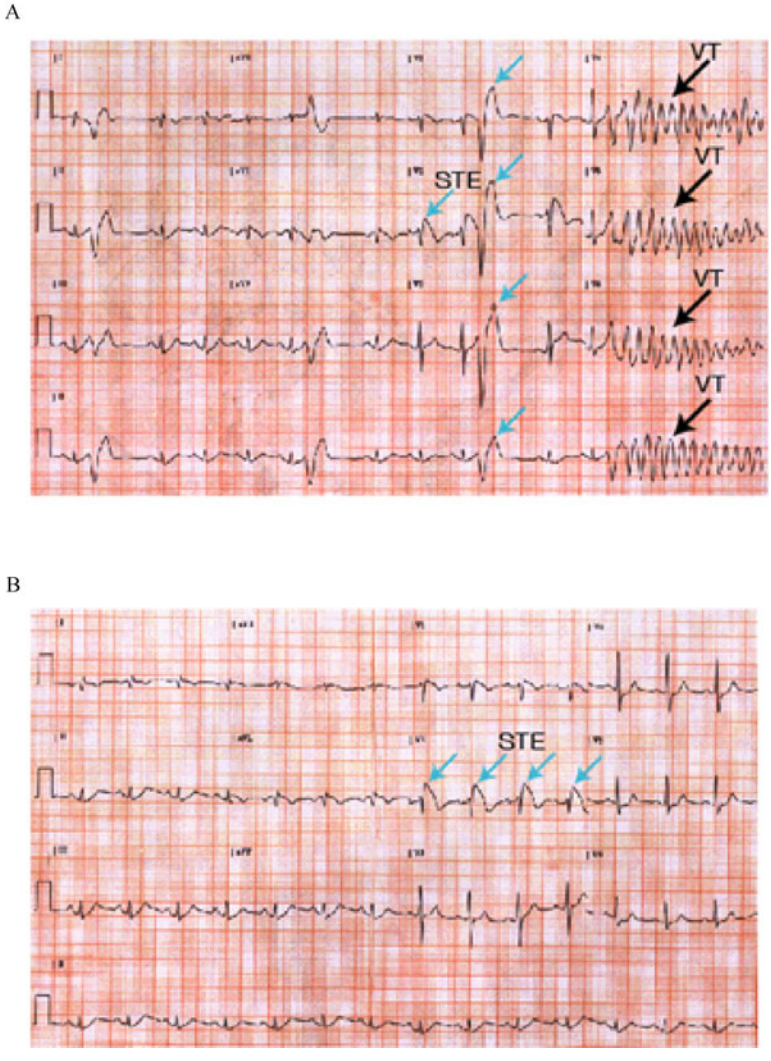

Fig. 2 Electrocardiogram (ECG) patterns showing ST-segment elevation (STE) (arrows) and ventricular tachycardia (VT) (arrows) associated with BrS in a patient immediately after the patient arrived at the Emergency Room (A) and 11 hours after the syncopal episode (B). [Modified from Wang et al. Chapter 96: Genetic Studies of Myocardial and Vascular Disease. In: Topol et al. eds. Textbook of Cardiovascular Medicine, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2007. with permission.]

et al., 2005). The arrhythmogenic substrate in BrS may not be restricted to the ventricular level, and a few cases of BrS exhibit spontaneous and induced atrial flutter/fibrillation/standstill, indicating that electrical abnormalities might exist in both atria and ventricles (Morita et al., 2002; Eleftheriadis et al., 2004; Rossenbacker and Priori, 2004; Takehara et al., 2004). In addition, the "mixed" electrocardiographic patterns including phenotypic overlap with long QT syndrome, short QT syndrome, or cardiac conduction disease have been reported (Bezzina et al., 1999; Shirai et al., 2002; Antzelevitch et al., 2007).

2.2 Epidemiology and risk factors

The incidence of BrS was initially estimated to be five cases per 10 000 inhabitants, but the real prevalence of the disease in the general population was under-estimated because the BrS ECG pattern can be intermittently present or concealed (Rossenbacker and Priori, 2007). A more recent study suggested that the prevalence of BrS reached 0.14% among adult Caucasians and Hispanics (Donohue et al., 2008). BrS causes 4% of all sudden deaths and 20% of sudden deaths in patients without structural heart disease (Antzelevitch et al., 2005).

While BrS patients have been found worldwide, a great geographical variability and ethnic differences have been reported. BrS seems to be much more common in Southeastern Asian countries than in Western Europe or North America (Hermida et al., 2000; Miyasaka et al., 2001). Of note, sudden unexplained nocturnal death syndrome (SUDS) in Southeast Asians and BrS have been shown to be phenotypically, genetically, and functionally identical. For reasons that remain elusive, the prevalence of SUDS or BrS may be as high as 3%, and it is considered to be the most common cause of sudden deaths in males younger than 50 years in these Asian countries (Vatta et al., 2002; Thomas and Grant, 2008).

Despite the even distribution of genetic autosomal dominant transmission, it has been reported that gender-related differences exist in the BrS ECG patterns. The male gender has been regarded as one of the risk factors for BrS, and there is a striking male to female ratio of approximately 8∶1 (Wilde et al., 2002). It remains unknown why men have a more penetrant form of the disease, but it was speculated that the sex distinction perhaps was due to sex-related intrinsic differences in ionic currents. For example, the transient outward current (I_{to}) has been thought to be central to the pathogenesis of BrS, and Di Diego and coworkers demonstrated that there was a higher intensity of I_{to} in males than in females in right ventricle epicardial cells, which may partly explain why BrS is more prevalent in males than in females (Di Diego et al., 2002). In addition, the hormonal influence may also play an important role in the genesis of BrS; for example, testosterone may influence expression of the cardiac L-type Ca^{2+} channel and modulate sodium current dispersion (Scragg et al., 2004; Barajas-Martinez et al., 2009).

The type I ECG pattern may spontaneously manifest or be unmasked by class IC sodium channel blockers such as flecainide, pilsicainide, and propafenone. Provocative pharmacological testing via intravenous application of such drugs is often used for screening family members of BrS patients (Antzelevitch et al., 2005). Acetylcholine may accentuate the ECG abnormalities in affected individuals, which correlates well with the fact that arrhythmic events are most common at rest or during sleep, concurrent with sympathetic withdrawal (Matsuo et al., 1999). Other external factors such as "fever" may trigger the manifestation of the BrS phenotype. Temperature simulating fever may result in shift of activation and reduction in the slope factor, and eventually reduces sodium current amplitudes, generating changes in the BrS ECG patterns (Antzelevitch and Brugada, 2002).

2.3 Cardiac structural abnormalities

BrS was initially proposed as a primary "pure electric heart disease" with structurally normal hearts, but recent evidence has emerged to suggest that histological alterations could occur in cardiac tissues from BrS patients. The right ventricular outflow tract has also been shown to be severely affected by intramyocardial fibrosis in explanted BrS hearts (Papavassiliu et al., 2004; Frustaci et al., 2005). It is proposed that the ECG abnormalities such as ST-segment elevation may be a common electrical manifestation of subtle structural abnormalities in the right ventricle in patients with BrS (Rossenbacker and Priori, 2007).

2.4 Arrhythmogenicity

The clinical symptoms of BrS include syncope, sudden cardiac arrest, and sudden death due to ventricular arrhythmias. The molecular and cellular mechanisms by which ST segment elevation leads to ventricular arrhythmias in patients with BrS have not been fully elucidated. It is believed that prolongation of the epicardial action potential beyond the endocardial action potential leads to the coved-type ST segment elevation "dome", resulting in heterogeneity of repolarization. A heterogeneous loss of the action potential dome causes a marked epicardial and transmural dispersion of repolarization in the right ventricular myocardium, which predisposes to phase 2 reentry and triggers polymorphic tachycardia and ventricular flutter or fibrillation (Antzelevitch, 2001).

2.5 Treatment

Implantation of implantable cardioverter defibrillators (ICDs) is the most effective approach to therapy for

BrS, but it cannot prevent the occurrence of VF, which makes investigations of alternative pharmacological treatments for BrS necessary. It has been reported that I_{to} blockers such as quinidione can normalize the ST segment and prevent VF induction in patients with BrS. Other potential pharmacologic approaches to therapy include reduction of vagal tone, an increase of sodium or calcium currents, and blocking of potassium currents designed to prolong the action potential duration (Sacher et al., 2006; Antzelevitch and Nof, 2008).

3 Genetics of the Brugada syndrome

In 1998, Wang and colleagues reported the identification of the first gene for BrS (Chen et al., 1998). The finding for the first time demonstrated that BrS was a distinct syndrome on the molecular level and that genetic factors were critical causes of BrS. BrS is now known to be inherited in an autosomal dominant mode, although the disease can be sporadic in a significant proportion of patients. To date, BrS has been associated with mutations in eight different genes including *SCN5A* (Nav1.5, BrS1), *GPD1L* (BrS2), *CACNA1C* (Cav1.2, BrS3), *CACNB2* (Cavβ2, BrS4), *SCN1B* (Navβ1, BrS5), *KCNE3* (MiRP2, BrS6), *SCN3B* (Navβ3, BrS7), and *HCN4* (BrS8) (Table 1). The particular molecular mechanisms of BrS associated with each gene are given below.

3.1 BrS1, cardiac sodium channel alpha subunit gene (*SCN5A*)

The *SCN5A* gene is located on chromosome 3p21–24. The full size of *SCN5A* consists of 28 exons spanning approximately 80 kb of genomic DNA. It encodes a protein of 2016 amino acids with a putative structure that consists of four homologous domains (DI–DIV), each of which contains six membrane-spanning segments (S1–S6). The *SCN5A* gene encodes the α subunit of the main cardiac sodium channel Nav1.5 responsible for generating the rapid upstroke of the cardiac action potential and plays a key role in cardiac impulse initiation, conduction and propagation.

Using a candidate gene approach, we found that mutations in *SCN5A* caused BrS (Chen et al., 1998). Chen et al. identified a missense mutation, a splice-donor mutation, and a frameshift mutation in several families with BrS. Mutant sodium channels with the missense mutation recovered from inactivation more rapidly than wild type channels, while the frameshift mutation caused a premature stop codon and generated a non-functional sodium channel (Chen et al., 1998). Since then, nearly 300 mutations in *SCN5A* have been identified in BrS patients, accounting for 18%–30% cases, which makes *SCN5A* the most common gene for BrS (Schulze-Bahr et al., 2003; Kapplinger et al., 2010).

Four main categories of *SCN5A* mutations have been reported in BrS: missense, nonsense, splice-donor, and frameshift mutations, all of which are scattered throughout the coding region of *SCN5A*. Functional studies performed with mammalian cell lines and mouse models have demonstrated that BrS is caused by loss of function mutations in *SCN5A*, which lead to reduced I_{Na} current density during the early phase of the cardiac action potential. Dysfunction of I_{Na} may be achieved through different mechanisms: (1) decreased expression of the sodium channel or decreased trafficking of the channel to the cell membrane, (2) a shift in voltage and time dependence of channel currents, (3) accelerated inactivation of sodium channel, and (4) entry of the channel into an intermediate state of inactivation (Antzelevitch et al., 2005).

Modulatory effects of compound mutations can account for phenotypic expression of BrS. One group reported additive effects of two heterozygous *SCN5A* missense mutations (P336L and I1660V) in one BrS family. In the family, only the proband carried both mutations and displayed the BrS phenotype, whereas neither mutation alone produced the clinical phenotype (Cordeiro et al., 2006).

Variants or single nucleotide polymorphisms (SNPs) are associated with arrhythmias such as BrS. *SCN5A* SNPs can serve as a modifier of BrS. Recently, Bezzina et al.

Table 1 Disease genes for Brugada syndrome (BrS)

disease	location	gene	OMIM	ion channel	effect of mutation	incidence/%	reference
BrS1	3p21	*SCN5A*	600163	I_{Na} α-subunit	loss of function (I_{Na}↓)	18%–30%	Chen et al., 1998
BrS2	3p22.3	*GPD1L*	611778	associated with I_{Na} α-subunit	loss of function (I_{Na}↓)	11%–12%	London et al., 2007
BrS3	12p13.3	*CACNA1C*	114205	I_{Ca} α-subunit	loss of function (I_{Ca}↓)	rare	Antzelevitch et al., 2007
BrS4	10p12	*CACNB2*	600003	I_{Ca} β-subunit	loss of function (I_{Ca}↓)	rare	Antzelevitch et al., 2007
BrS5	19q13.1	*SCN1B*	600235	I_{Na} β-subunit	loss of function (I_{Na}↓)	rare	Watanabe et al., 2008
BrS6	11q13–q14	*KCNE3*	604433	I_{ks}/I_{ko} β-subunit	gain of function (I_{ko}↑)	rare	Delpón et al., 2008
BrS7	11q23.3	*SCN3B*	608214	I_{Na} β-subunit	loss of function (I_{Na}↓)	rare	Hu et al., 2009
BrS8	15q24–q25	*HCN4*	605206	I_f	unknown	unknown	Ueda et al., 2009

sequenced the *SCN5A* promoter and identified an SNP haplotype consisting of 6 polymorphisms in an Asian population, which may contribute to the high prevalence of BrS in the Asian population (Bezzina et al., 2006). The functional effect of another *SCN5A* SNP H558R was previously reported. It was shown to modulate the function of a BrS mutation R282H. In heterologous cells, coexpression of the 588R allele with R282H mutation may rescue defective cell surface expression of a mutant SCN5A protein and produce a significantly greater sodium current (Poelzing et al., 2006).

BrS patients with or without *SCN5A* mutations can be clinically differentiated on ECG features. Yokokawa et al. compared the ECG pattern between the BrS patients with or without *SCN5A* mutations, and found that the P-wave duration in patients carrying the *SCN5A* mutations was much longer, which suggests that the reduced sodium current and the intraatrial conduction velocity may account for the mixed clinical manifestation (Yokokawa et al., 2007).

3.2 BrS2, glycerol-3-phosphate dehydrogenase 1-like gene (*GPD1L*)

The *GPDL1* gene is located on chromosome 3p22.3 and is composed of 8 exons distributed over at least 60 kb of genomic DNA. It encodes the glycerol-3-phosphate dehydrogenase 1-like protein with homology to glycerol phosphate dehydrogenase (GPD1). The 352 amino acid protein contains a NAD^+-binding site and a dehydrogenase catalytic site.

In 2005, Weiss et al. reported a large family with both BrS and progressive conduction disturbance, and linkage analysis identified a new locus on chromosome 3p22–p24 for BrS that was not related to *SCN5A* (Weiss et al., 2002). Further studies identified a missense mutation A280V in *GPD1L* in this family with low penetrance (37%). HEK293 cells co-transfected with A280V mutant *GPD1L* and WT *SCN5A* showed nearly 50% I_{Na} current amplitude compared with WT *GPD1L* and WT *SCN5A*. Immunostaining demonstrated a marked decrease in cell membrane expression of Nav1.5, which suggested that the mechanism of *GPD1L*-caused BrS2 was related to BrS1 (London et al., 2007). In a different study, Valdivia et al. further investigated the biophysical characteristics of the *GDP1L* mutation. They showed that the mutation resulted in glycerol-3-phosphate PKC-dependent phosphorylation of SCN5A at serine 1503 (S1503) through a GPD1L-dependent pathway, and markedly reduced I_{Na} current density, which suggested a mechanism linking mutations in *GPD1L* to cardiac arrhythmia (Valdivia et al., 2009). In 2007, Van Norstrand et al. further reported *GPD1L* mutations in a small subset of sudden infant death syndrome (Van Norstrand et al., 2007), but one recent report showed that the contribution of *GPD1L* mutations to BrS is probably small. Makiyama et al. screened the *GDP1L* mutation in 220 Japanese BrS patients; however, no disease-causing mutation was detected (Makiyama et al., 2008).

3.3 BrS3, L type voltage-dependent calcium channel alpha 1C subunit gene (*CACNA1C*)

The *CACNA1C* gene at chromosome 12p13.33 spans approximately 640 kb of genomic DNA and contains 50 exons (44 invariant and 6 alternative exons). It encodes the pore-forming α_1-subunit of L-type voltage gated Ca^{2+} channel (Cav1.2), the predominant cardiac form with 2138 amino acids. The Cav1.2 channel is activated upon cell membrane depolarization by creating a rapid increase in intracellular free Ca^{2+} concentration, and the resulting Ca^{2+} current inactivates slowly and plays an important role in maintaining the plateau phase of the cardiac action potential duration (Bodi et al., 2005).

Antzelevitch et al. performed molecular genetic studies and identified several novel *CACNA1C* mutations in a cohort of 82 patients with BrS. Interestingly, two of these mutations (A39V and G490R) were identified in patients with both BrS and short QT syndrome, and created a novel BrS3/SQT clinical entity. Biophysical experiments demonstrated that *CACNA1C* mutations may attenuate the calcium currents. CHO cells transfected with G490R or A39V with other Cav1.2 subunits resulted in a marked reduction in $I_{L,Ca}$ current. Furthermore, the mutant A39V Cav1.2 channel was trafficking-defective, while the G490R Cav1.2 showed normal trafficking (Antzelevitch et al., 2007; Schimpf et al., 2008).

3.4 BrS4, voltage-dependent calcium channel beta 2 subunit gene (*CACNB2*)

The cardiac L-type calcium channel is comprised of a pore forming α_{1c}-subunit and ancillary $\alpha_2\beta$ and $\beta 2$ subunits, which are important modulators of the electrophysiological properties of calcium channels. These peripheral subunits are encoded by different genes. The *CACNB2* gene consists of 14 exons covering 421 kb of genomic DNA on chromosome 10p12, and codes for the 660 amino acid $\beta 2$-subunit (Cav$\beta 2$) of Cav1.2 (Bodi et al., 2005).

Antzelevitch et al. reported one loss of function *CACNB2* mutation (S481L) in a cohort of 82 BrS probands. When the mutation was expressed in CHO cells together with other components of the Cav1.2 channel, the $I_{L,Ca}$ channel current was markedly reduced although this mutant was not trafficking-defective (Antzelevitch et al., 2007). In another recent study, Cordeiro et al. described a novel BrS-associated *CACNB2b* mutation (T11I). The T11I missense mutation resulted in accelerated inactivation of the L-type calcium channel without significantly affecting peak current, which suggested that the faster current decay may result in predisposition to BrS phenotype (Cordeiro et al., 2009).

3.5 BrS5, voltage-gated sodium channel beta I subunit gene (*SCN1B*)

The cardiac sodium channel is a protein complex composed of a pore forming α-subunit and other subunits including several single transmembrane regulatory β-subunits. It has been shown that β-subunits are multi-functional molecules that modulate channel gating and expression. *SCN1B* encodes subunit β1, a member of the gene family *SCN1B–4B*, spans 9.8 kb of genomic DNA on chromosome 19q13.1, and is composed of six exons (Makielski and Farley, 2006).

Recently, Watanabe et al. identified novel *SCN1B* mutations (E87Q and W179X) in families with conduction disease and BrS. Coexpression of mutant beta 1 protein with WT subunits reduced the peak sodium current (Watanabe et al., 2008). Polymorphisms in *SCN1B* showed a potential risk of BrS and may modify phenotypic expression of the disease. In 30 Japanese BrS patients, Ogawa et al. performed genetic screening and revealed that one SNP (IVS3 + 2996(TTA)8) of *SCN1B* was significantly associated with the development of BrS-like ECG pattern, and might render male, middle-aged Japanese individuals more susceptible to BrS (Ogawa et al., 2010).

3.6 BrS6, Isk-related voltage-gated potassium channel subunit 3 gene (*KCNE3*)

KCNE3 is the member of the *KCNE* gene family encoding single transmembrane domain proteins, so called MinK related peptides (MiRPs), which act as ancillary subunits of Kv channels. *KCNE3* consists of three exons distributed over 13 kb of genomic DNA on chromosome 11q13–14, and encodes a 103 amino acid ancillary β-subunit (MiRP2). The cytoplasmic domain of MiRP2 has been suggested to be involved in controlling gating, and a previous study provided definitive evidence for a functional role of *KCNE3* in the modulation of I_{to} in the human heart (Abbott and Goldstein, 2001). During genetic screening of 105 BrS probands, Delpón et al. identified one novel mutation R99H in *KCNE3*, which was shown to cause a gain of function in I_{to}. Co-transfection of *KCNE3* R99H mutation with *KCND3* (KV4.3) resulted in a significant increase in the I_{to} intensity compared to WT *KCNE3* + *KCND3* (Delpón et al., 2008).

3.7 BrS7, voltage-gated sodium channel beta III subunit gene (*SCN3B*)

Six β-subunits for voltage-gated sodium (Na^+) channels have been identified and are encoded by 4 different genes: *SCN1B–SCN4B*. Spanning 25.6 kb of genomic DNA on chromosome 11q23, *SCN3B* is composed of six exons, and encodes the β3-subunit of the cardiac sodium channel with 215 amino acid residues (Makielski and Farley, 2006). Recently, the defect of *SCN3B* has been reported to be linked to BrS. The missense *SCN3B* mutation (L10P) led to reduced expression of the Nav1.5 protein and a smaller sodium channel current (Hu et al., 2009).

3.8 BrS8, hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 gene (*HCN4*)

Potassium channel gene *HCN4* consists of eight exons on chromosome 15q24–q25, and encodes a protein of 1203 amino acids, which contains 6 putative transmembrane segments, a pore region, and a cyclic nucleotide-binding domain. As the main hyperpolarization-activated cyclic nucleotide isoform contributing to native funny channels (I_f) of the sinoatrial node, *HCN4* is essential for the proper function of the developing cardiac conduction system and is involved in the generation of cardiac rhythmic activity (Stieber et al., 2003).

Studies have suggested that *HCN4* defects contributed to the pathology of sick sinus syndrome (SSS). Recently, a mutation in this gene was found to be associated with BrS in a 41-year-old man. Ueda et al. identified a 4-bp insertion at the splice site (IVS2DS) in the *HCN4* gene, which would cause a frameshift and addition of 44 C-terminal residues and premature truncation. However, the hypothesis that *HCN4* mutations cause BrS needs to be further tested, and an electrophysiological study of the effects of the mutation will provide insights into the mechanism underlying the pathogenesis of BrS (Ueda et al., 2009).

4 Genetic testing and personalized medicine

Genetic testing includes several applications: diagnostic testing, presymptomatic testing, and pharmacogenetic testing. Diagnostic testing is performed on a patient with the presence of clinical symptoms and signs to establish a definitive diagnosis. Presymptomatic testing is used for suspected individuals who have a family history of the disease to assess the risk of disease. Pharmacogenetics is the study of how genetic differences affect efficacy in response to medication, and pharmacogenetic tests are used for prediction of treatment response and supporting therapeutic decisions. The potential goal of genetic testing is not only to establish the most accurate diagnosis even before the onset of symptoms, but also to provide prognostic and therapeutic tools to help treatments tailored to individual patients, so called personalized medicine (Ginsburg and Willard, 2009; Pereira and Weinshilboum, 2009).

Identification of genes for long QT syndrome (LQTS) has resulted in commercial genetic testing for patients and families with LQTS and a history of sudden cardiac death, which is the first commercial genetic testing in the field of cardiovascular medicine (Tan et al., 2006; Ruan et al., 2008; Fowler et al., 2010). Individuals with the clinical

diagnosis of LQTS are recommended to have genetic testing performed, which may guide genotype-specific therapies. Among LQTS patients with genetically identifiable mutations, 99% of them carry mutations in three major genes, KCNQ1 (type 1 LQTS), KCNH2 (type 2 LQTS), and SCN5A (type 3 LQTS). Type 1 LQTS is treated primarily with beta blockers, and stricter exercise restriction. Type 2 LQTS is also treated with beta blockers, and patients are discouraged from competitive sports. Type 3 LQTS is treated with sodium channel blockers such as mexiletene and flecanimide. Beta blockers are of limited use for type 3 LQTS. Implantation of an implantable cardioverter defibrillator is recommended for LQT3 patients with bradycardia.

Identification of *SCN5A* as the BrS gene has resulted in commercial testing for patients with suspected BrS. Although *SCN5A* mutations account for only about 20% to 30% of clinically affected patients with type 1 BrS ECG, it is particularly valuable for identifying borderline cases and asymptomatic carriers in at-risk family members (Robin et al., 2007). Interestingly, data from a recent study showed that if the genetic screening was preformed in patients with type 1 BrS ECG and atrioventricular block (AVB), the yield of positive genotyping increased substantially from 13% to 23% (Bai et al., 2009). For BrS patients with positive SCN5A mutations and severe symptoms, implantation of an implantable cardioverter defibrillator is recommended.

5 Conclusions

Since the identification of the first disease-causing gene for BrS by Wang and colleagues in 1998, BrS has gained recognition as a major cause of sudden death throughout the world. BrS provides a model for understanding the pathogenesis of inherited arrhythmias. Significant advances have been made to understand the clinical, genetic, cellular, ionic, and molecular mechanisms of this disease; however, much remains to be learned. Genetic analysis is still limited by the fact that less than 50% of patients can be genotyped. Genetic studies will continue to provide important insights into the pathophysiological mechanisms of BrS, which may have far-reaching effect on the diagnosis, treatment and prevention of BrS.

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