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Genetic basis of Brugada syndrome

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The Brugada syndrome (BrS) is an inherited channelopathy characterized by an elevated ST segment or J wave appearing in the right precordial leads (V1–V3), often followed by a negative T wave. First described in 1992, the syndrome is associated with a high incidence of sudden cardiac death secondary to a rapid polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF).¹ The electrocardiogram characteristics of the BrS are dynamic and often concealed but can be unmasked by potent sodium channel blockers such as ajmaline, flecainide, procainamide, disopyramide, propafenone, and pilsicainide.^{2–4}

The past decade has witnessed steady progress in our ability to understand the genetic basis for this syndrome (Table 1). *SCN5A* the gene that encodes the α -subunit of the cardiac sodium channel, was the first gene linked to BrS.⁵ BrS has been associated with mutations in *SCN5A* in approximately 15% of probands.^{6–8} Over 100 mutations in *SCN5A* have been linked to the syndrome in recent years (see reference⁹; also see <http://www.fsm.it/cardmoc>). Some of these mutations have been studied in expression systems and shown to result in loss of function due to (1) failure of the sodium channel to express; (2) a shift in the voltage and time dependence of sodium channel current (I_{Na}) activation, inactivation, or reactivation; (3) entry of the sodium channel into an intermediate state of inactivation from which it recovers more slowly; or (4) accelerated inactivation of the sodium channel. Mutations in the *SCN5A* gene account for approximately 15% of BrS probands. A higher incidence of *SCN5A* mutations has been reported in familial than in sporadic cases.⁷ Of note, negative *SCN5A* results generally do not rule out causal gene mutations, since the promoter region, cryptic splicing mutations, or presence of gross rearrangements are generally not part of routine investigation. A recent report by Hong et al¹⁰ provided the first case of a dysfunctional sodium channel created by an intronic mutation giving rise to cryptic splice site activation in *SCN5A* in a family with BrS. The deletion of fragments of segments 2 and 3 of domain IV of *SCN5A* caused a complete loss of function. Bezzina and coworkers¹¹ recently provided interesting evidence in support of the hypothesis that an *SCN5A* promoter polymorphism common in Asians modulates variability in cardiac conduction and may contribute to the high prevalence of BrS in the Asian population. Sequencing of the *SCN5A* promoter identified a haplotype variant consisting of six polymorphisms in nearcomplete linkage disequilibrium that occurred at an allele frequency of 22% in Asian subjects and was absent in whites and blacks. The results of the study demonstrate that sodium channel transcription in the human heart may vary considerably among individuals and races and may be associated with variable conduction velocity and arrhythmia susceptibility.

A second locus on chromosome 3, close to but distinct from *SCN5A*, has recently been linked to the syndrome¹² in a large pedigree in which the syndrome is associated with progressive conduction disease, a low sensitivity to procainamide, and a relatively good prognosis. The gene was recently identified as the glycerol-3-phosphate dehydrogenase 1-like gene (*GPD1L*). A mutation in *GPD1L* has been shown to result in a reduction of I_{Na} .¹³

The third and fourth genes associated with the BrS were reported earlier this year and shown to encode the $\alpha 1$ -(*CACNA1C*) and β - (*CACNB2b*) subunits of the L-type cardiac calcium channel. Mutations in the α - and β -subunits of the calcium channel can also lead to a shorter than normal QT interval, creating a new clinical entity consisting of a combined Brugada/short QT syndrome.⁸

In this issue of *Heart Rhythm*, Koopman and coworkers¹⁴ present the results of an interesting study designed to evaluate *SCN5A* exon copy numbers in mutation-negative BrS probands to assess whether multiple copies of gene exons may underlie the phenotypic expression of the syndrome in a Dutch cohort of 38 BrS patients. In addition, the study probed the extent to which *GPDIL* mutations contribute to BrS in this cohort and explored a contribution of other candidate genes including those encoding sodium channel β -subunits (*SCN1B*, *SCN2B*, *SCN3B*, *SCN4B*), caveolin 3 (*CAV3*), the Iroquois family of transcriptional factors 3–6 (*Irx-3*, *Irx-4*, *Irx-5*, *Irx-6*), and the adherens junction proteins plakophilin-2 (*PKP2*) and plakoglobin (*PKGB*).

The Iroquois family of transcriptional factor are of special interest because *Irx-3* and *Irx-5*, in particular, are believed to contribute to the transmural gradient of the transient outward current (I_{to}),^{15,16} which is at the heart of the arrhythmogenic mechanism responsible for sudden death in BrS.¹⁷ *Irx-4* and *Irx-5* have been shown to interact with the cardiac transcriptional corepressor mBop^{15,18} and thus to repress expression of *Kcnd2*, which encodes the α -subunit of the I_{to} channel. *Irx-6* was also considered a candidate gene in this study because its expression pattern is similar to that of *Irx-5*.¹⁹ Failure to thus far identify genes associated with I_{to} may be due to the fact that mutations in these genes may be fatal early on because of the prominence of this current in heart and nervous system tissues.

The results of this extensive and well-designed study were negative, suggesting that multiple copies of *SCN5A* gene exons, mutations in *GPDIL*, or mutations in these other candidate genes did not play a major role in the manifestation of BrS in this small Dutch cohort. It should be emphasized that because of the size of the study population and its geographic localization, these negative results do not exclude the participation of any of these factors or genes as a cause of BrS; they merely suggest that they are not a major cause in this ethnic group. As the authors are quick to point out, these results do not “exclude the possibility of mutations in these genes in other cohorts.”

The study by the Amsterdam group also identified a number of polymorphisms in the various genes studied, which may be of great value to future studies examining the association between common genetic variations and modulation of arrhythmia susceptibility. The precise prevalence of these polymorphisms in this and other ethnic groups understandably must await studies with much larger samples.

Understanding the predisposition to arrhythmogenesis and sudden cardiac death at the genetic and genomic level is a responsibility that we must acknowledge and meet with studies such as this one that are designed to identify the genetic basis for ion channelopathies that take the lives of infants, children, and young adults. We have devoted substantial resources to prevention of sudden cardiac death in elderly patients with structural heart disease and must not forget our responsibility to younger members of our society who are at a risk for sudden cardiac death because of inherited disease. They too deserve highly informed appropriate treatment that will allow them full lives without the threat of sudden arrhythmic death. The argument for genetic testing is especially compelling in the case of BrS because the clinical manifestations of BrS generally appear later in life, in some cases resulting in sudden death without any warning. Risk stratification of younger family members is best achieved by genetic screening. Identification of mutation carriers among family members of symptomatic probands

alerts the physician to closely follow these individuals and to proceed with the implantation of an implantable cardiac defibrillator or other therapy if and when appropriate.

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Table 1

Genetic basis for the Brugada syndrome

	Locus	Ion channel	Gene
BrS1	3p21	I _{Na}	<i>SCN5A</i> , <i>Na_v1.5</i>
BrS2	3p24	I _{Na}	<i>GPD1L</i>
BrS3	12p13.3	I _{Ca}	<i>CACNA1C</i> , <i>Ca_v1.2</i>
BrS4	10p12.33	I _{Ca}	<i>CACNB2b</i> , <i>Cavβ2b</i>