Update of Diagnosis and Management of Inherited Cardiac Arrhythmias

Wataru Shimizu, MD, PhD

Over the past 2 decades, a number of inherited cardiac arrhythmias, including congenital long QT syndrome (LQTS) and Brugada syndrome (BrS), have been shown to have a link to mutations in genes encoding for ion channels or other membrane components. The recent HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited arrhythmia syndromes has updated the clinical diagnosis of congenital LQTS and BrS. Genetic studies have identified 13 forms of congenital LQTS in 50–80% of clinically affected patients. Genotype-phenotype correlations have been investigated in the 3 major genotypes, LQT1, LQT2 and LQT3 syndromes, resulting in genotype-specific management and therapy. More detailed analyses of each genotype have suggested mutation location-, type-, or function-specific differences in clinical phenotype among the LQT1, LQT2, and possibly LQT3 genotypes. In BrS, only one-third of affected patients can be genotyped, mainly in the sodium channel gene, SCN5A; therefore, clinical studies of genotype-phenotype relationships have been limited. More recently, a genome-wide association study using a gene array explored the role of common genetic variants (polymorphisms) as the susceptible or modifier gene in both congenital LQTS and BrS. (Circ J 2013; 77: 2867–2872)

Key Words: Brugada syndrome; Genetic study; Long QT syndrome; Sudden death; Ventricular fibrillation

Since the late 1990s, molecular genetic studies have identified a link between mutations in genes encoding for cardiac ion channels or other membrane components and several inherited cardiac arrhythmias, including congenital and acquired long QT syndrome (LQTS), Brugada syndrome (BrS), progressive cardiac conduction defect (Lenegre disease), catecholaminergic polymorphic ventricular tachycardia (CPVT), short QT syndrome, familial atrial fibrillation, and familial bradycardia syndrome. Among such inherited cardiac arrhythmias, congenital LQTS is a Rosetta stone for investigating the genotype-phenotype correlations, because multiple genes encoding the different ion channels or membrane adaptors have been identified by genetic screening in approximately 50–80% of subjects with clinically diagnosed congenital LQTS. Mutations in the cardiac RyR2 gene or calsequestrin gene can be found in approximately 60% of typical CPVT patients with associated bidirectional and/or multifocal ventricular tachycardia (VT). Therefore, genotype-phenotype correlations have been rigorously investigated, especially in patients with congenital LQTS, and genetic testing has now become the gold standard for the diagnosis or LQTS, which enables us to stratify the risk of cardiac events and to manage LQTS patients theoretically and appropriately. However, the responsible mutations have been identified in only a small number of patients with other inherited cardiac arrhythmias. In BrS, the first mutation was identified in an α subunit of the sodium channel gene, SCN5A, in 1998, but a world-wide cohort study has reported that mutations in the major player, SCN5A, can be identified in only 11–28% of clinically diagnosed BrS patients. Moreover, most of the mutations identified in inherited arrhythmias other than congenital LQTS have been found in a single family or a small number of families. Therefore, genotype-phenotype correlations have been much less examined other than for congenital LQTS. Furthermore, 2 international expert consensus statements have been recently published on (1) the indications of genetic testing, and (2) the diagnosis and management in patients affected by inherited cardiac arrhythmias and their family members. These statements are the collaborative efforts of 2 or 3 medical societies representing electrophysiology in North America, Europe and Asian-Pacific area: the Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA) and the Asia Pacific Heart Rhythm Society (APHRS). In this review article, the updated diagnosis and management of inherited cardiac arrhythmias, in particular congenital LQTS and BrS, will be introduced.

Congenital LQTS

Congenital LQTS is a hereditary disorder characterized by prolongation of the QT interval on standard 12-lead ECG and a polymorphic VT known as torsade de pointes (TdP).

Update of Clinical Diagnosis of Congenital LQTS

The clinical diagnosis of congenital LQTS is mainly based on
the rate-corrected QT (QTc) interval at rest, cardiac events such as syncope, aborted cardiac arrest and sudden cardiac death, and a family history of apparent LQTS. For the measurement of QT interval to diagnose congenital LQTS, it is of particular importance to exclude secondary causes of QTc prolongation, which can occur with QT prolonging drugs and/or cardiac conditions, such as electrolyte imbalance and bradycardia. The Schwartz score has long been used to diagnose congenital LQTS, especially those with LQT1, has long been expected, Therefore, novel tools to unveil latent mutation carriers of LQTS, especially those with LQT1, has long been expected, because identification of patients with latent LQTS may afford the opportunity to initiate potentially life-saving pharmacotherapy and health style modifications. Exercise or catecholamine infusion, such as epinephrine, an α+β adrenergic agonist, or isoproterenol, a β-adrenergic agonist, has long been used for more than 2 decades as provocation testing to unmask latent forms of congenital LQTS. Recently, epinephrine provocation testing has become a standard test as a catecholamine infusion.

### Genetic Diagnosis of Congenital LQTS

Genetic studies have identified 13 autosomal dominant forms of Romano-Ward-type congenital LQTS caused by mutations in genes of the potassium, sodium and calcium channels or the membrane adapter located on chromosomes 3, 4, 7, 11, 12, 17, 20 and 21 (Table 1). KCNQ1 and KCNE1, α and β subunits of the potassium channel gene, are responsible for LQT1 and LQT5, and mutations in KCNQ1 or KCNE1 result in decrease (loss of function) in the slowly activating component of the delayed rectifier potassium current (I_Ks). Similarly, mutations in KCNH2 and KCNE2, α and β subunits of the potassium channel gene, cause defects in the rapidly activating component of the delayed rectifier potassium current (I_Kr), which are responsible for LQT2 and LQT6 forms. Mutations in SCN5A, the gene encoding the α subunit of the sodium channel, are responsible for LQT3 by increasing (gain of function) the late sodium current (I_Na). Mutations in KCNJ2 encoding the inward rectifier potassium current (I_Ks) prolong the QT interval associated with the periodic paralysis and dysmorphic features underlying Andersen’s syndrome (LQT7). A mutation in Ankyrin-B, a member of a family of versatile membrane adapters, underlies LQT4 syndrome, with intracellular calcium overload. Mutation in CACNA1C results in an increase of the L-type calcium current (I_Ca,L), producing dysfunction in multiple organ systems, including congenital heart disease, syndactyly, immune deficiency, and autism, as well as the pronounced QT prolongation responsible for LQT8. CAV3 encoding caveolin-3 and SCN4B encoding Nav1.4, an auxiliary subunit of the cardiac sodium channel, are responsible for LQT9 and LQT10, respectively. Mutations in both genes result in a gain of function of late I_Na, causing long QT interval like that in LQT3. A mutation in AKAP-9, whose product, Yotia, assembles with KCNQ1, is responsible for LQT11. Mutations in syntrophin-α1 (SNTA1), a cytoskeletal protein, interact with the cardiac sodium channel, and are attributable to LQT12 with an LQT3-

### Table 1. Defect of Ion Channel or Membrane Adaptor Responsible for Congenital Long QT Syndrome

<table>
<thead>
<tr>
<th>Loci</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Ion channel</th>
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<tbody>
<tr>
<td><strong>Romano-Ward syndrome</strong></td>
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<tr>
<td>LQT1</td>
<td>11 (1p15.5)</td>
<td>KCNQ1 (homozygous)</td>
<td>I_Ks(a)</td>
</tr>
<tr>
<td>LQT2</td>
<td>7 (7q35–q36)</td>
<td>KCNH2</td>
<td>I_Kr(b)</td>
</tr>
<tr>
<td>LQT3</td>
<td>3 (3p21)</td>
<td>SCN5A</td>
<td>I_Na</td>
</tr>
<tr>
<td>LQT4</td>
<td>4 (4q25–q27)</td>
<td>ANK2</td>
<td>Na-K ATPase, I_Na-Ca</td>
</tr>
<tr>
<td>LQT5</td>
<td>21 (21q22.12)</td>
<td>KCNE1</td>
<td>I_Ks(b)</td>
</tr>
<tr>
<td>LQT6</td>
<td>21 (21q22.12)</td>
<td>KCNE2</td>
<td>I_Ks(b)</td>
</tr>
<tr>
<td>LQT7</td>
<td>17 (17q23.1–q24.2)</td>
<td>KCNJ2</td>
<td>I_Kr(b)</td>
</tr>
<tr>
<td>LQT8</td>
<td>12 (12p13.3)</td>
<td>CACNA1C</td>
<td>I_Ca,L</td>
</tr>
<tr>
<td>LQT9</td>
<td>3 (3p25)</td>
<td>CAV3</td>
<td>I_Ks(b)</td>
</tr>
<tr>
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<td>11 (11q23.3)</td>
<td>SCN4B</td>
<td>I_Kr(b)</td>
</tr>
<tr>
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<td>7 (7q21–q22)</td>
<td>AKAP-9</td>
<td>I_Kr(b)</td>
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<tr>
<td>LQT12</td>
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<td>SNTA1</td>
<td>I_Ks(b)</td>
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<td>11 (11q23.3–24.3)</td>
<td>KCNJ5</td>
<td>I_Ks(b)</td>
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<tr>
<td><strong>Jervell &amp; Lange-Nielsen syndrome</strong></td>
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</tr>
<tr>
<td>JLN1</td>
<td>11 (11p15.5)</td>
<td>KCNQ1 (homozygous)</td>
<td>I_Ks(a)</td>
</tr>
<tr>
<td>JLN2</td>
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</table>
like phenotype. Most recently, a mutation in KCNJ5 encoding the α-subunit of the acetylcholine-sensitive potassium current (I_{K,ACh}) channel, is responsible for LQT3. Among the 13 genotypes, the 3 major genotypes, LQT1, LQT2 and LQT3, constitute more than 80% of genotyped patients with LQTS. However, the precise prevalence of the LQTS genotype is still unknown, because all of the 13 responsible genes are not screened in clinical practice. In all 13 genotypes, decreases in outward potassium currents (I_{Ks}, I_{K1}, I_{K,Ca}) or increases in the inward sodium or calcium current (late I_{Na}, I_{Ca-L}) prolong the action potential (AP) duration and the QT interval, a common phenotype in LQTS. The prolongation of the AP plateau phase allows recovery from inactivation and reactivation of L-type calcium channels, producing early afterdepolarization (EAD), EAD-induced ventricular premature contractions (VPCs) capture the vulnerable window created by increased transmural and spatial dispersion of ventricular repolarization, thus resulting in TdP. In LQT1, loss of function in KCNQ1, which is active during the terminal phase of the AP, prolongs the terminal repolarization phase and produces delayed afterdepolarization (DAD), triggering typical multifocal or bidirectional VT.

Autosomal recessive forms of Jervell & Lange-Nielsen syndrome are associated with neurosensorial deafness and more severe phenotype (marked QT prolongation and lethal ventricular arrhythmias) compared with Romano-Ward syndrome. Two genotypes, JLN1 and JLN2 are responsible for homozygous or compound heterozygous mutations in KCNQ1 and KCNE1, both of which are responsible for a decrease in the I_{K1}. Genotype-phenotype correlations have been rigorously investigated for the past 2 decades as will be presented next. Therefore, genetic testing for patients with congenital LQTS has been reimbursed by national insurance since 2008 in Japan. In the major centers in Japan, LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is available. However, the HRS/EHRA expert consensus statement has proposed the state and/or indication of genetic testing for inherited cardiac arrhythmias. As a class 1 indication, comprehensive or LQT1-3 targeted LQTS genetic testing is recommended: (1) for any patient for whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient’s clinical history, family history, and expressed ECG, and/or (2) for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (eg, electrolyte abnormalities, hypertrophy, bundle branch block, etc., ie, otherwise idiopathic) on serial 12-lead ECGs defined as QTc >480 ms (prepuberty) or >500 ms (adults); (3) mutation-specific LQTS genetic testing is recommended for family members and other appropriate relatives subsequent to identification of the LQTS-causative mutation in an index case. On the other hand, comprehensive or LQT1-3 targeted LQTS genetic testing may be considered as a class IIb indication for any asymptomatic patient with normal or borderline QTc values ≤460 ms (prepuberty) or ≤480 ms (adults).

**Genotype-Phenotype Correlations in Congenital LQTS**

Genotype-specific clinical phenotype, management and therapy have been reported, and genotyping especially for the LQT1, LQT2, and LQT3 syndromes has enabled us to stratify risk, and manage or treat LQTS patients appropriately. Genotype-phenotype correlations in congenital LQTS have been well reviewed in the literature, so will be only briefly discussed for the LQT1, LQT2, and LQT3 syndromes.

Cardiac events in LQT1 patients are well known to occur most frequently during exercise (62%), and swimming is a common trigger. Most of their first cardiac events occur before the age of 15 years, particularly in males. Therefore, strict exercise restriction, in particular restriction of swimming, diving or competitive sports, is needed for LQT1 patients, especially males. β-blockers are most effective in preventing episodes of syncope and sudden cardiac death in LQT1. Moss et al reported in the international cohort of 600 LQTS patients that time-dependent β-blocker use was associated with a significant 74% reduction in the risk of first cardiac events. An implantable cardioverter-defibrillator (ICD) is a class I indication for LQTS patients who are survivors of a cardiac arrest, and as a class IIa indication for those who experience recurrent syncopal events while on β-blocker therapy.

Cardiac events are less likely to occur during exercise (13%) and more likely during rest/sleep (29%) in LQT2 patients. Being startled by an auditory stimulus (telephone, alarm clock, ambulance siren, etc) is a specific trigger. In addition to exercise restriction, avoiding specific acoustic triggers is required and effective in the management of LQT2. β-blockers are also effective in LQT2 patients, although their efficacy is somewhat less than in LQT1 patients. Shimizu et al demonstrated in an international cohort of 858 LQT2 patients that time-dependent β-blocker use significantly reduced the risk of first cardiac events by 63%, confirming the efficacy of β-blockers as first-line therapy in LQT2. Maintaining the extracellular potassium concentration by long-term oral potassium supplementation is effective in shortening the QT interval in LQT2 patients. The indication of ICD is similar to that in LQT1 syndrome.

LQT3 patients are more likely to have cardiac events during rest/sleep (39%). In these patients, β-blockers are less effective than in LQT1 or LQT2 patients. The class IB sodium channel blocker, mexiletine, is more effective in shortening the QT interval in LQT3 than in LQT1 or LQT2 syndrome, and can be useful, as add-on therapy, for LQT3 patients with QTc >500 ms who show shortening of their QTc by >40 ms following an acute oral drug test (class IIa indication).

Regardless of genotype, the HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with congenital LQTS recommends β-blocker use. β-blockers are recommended for patients with a diagnosis of LQTS who are: (1) asymptomatic with QTc >470 ms, and/or (2) symptomatic for syncope or documented VT/VF as a class I indication. β-blockers can be useful in patients with a diagnosis of LQTS who are asymptomatic with QTc <470 ms as a class IIa indication.

A recent international cohort from the USA, Europe and Japan consisting of 1,206 LQTS patients with 95 different mutations located in the LQT1–3 genes suggested that mutations with a wider variation in QTc interval are associated with increased risk of cardiac events. These findings appear to be genotype-specific, with a pronounced effect in patients with
LQT1 syndrome but no effect in patients with LQT2 syndrome.\textsuperscript{23}

**Mutation Location-, Type-, or Function-Specific Risk Stratification of Congenital LQTS**

More than several hundred mutations have been reported in the 3 major genotypes (LQT1–3), and each mutation in each gene shows a respective location, type or function. This indicates a variety of clinical phenotypes or responses to therapy depending on the location, type or function of the mutation even in the same genotype. For the LQT1 syndrome, in 2004 Shimizu et al\textsuperscript{24} compared the arrhythmic risk and sensitivity to sympathetic stimulation with treadmill exercise testing between Japanese LQT1 patients with transmembrane mutations and those with C-terminal mutations in KCNQ1. A longer QTc interval and more frequent cardiac events were observed in the LQT1 patients with transmembrane mutations compared with those with C-terminal mutations. The QTc interval was more remarkably prolonged with exercise in the LQT1 patients with transmembrane mutations. Thereafter, a larger international cohort from the USA, Europe and Japan consisting of 600 LQT1 patients confirmed the more severe phenotype in LQT1 patients with transmembrane mutations.\textsuperscript{25} The international cohort also suggested that LQT1 patients with mutations having dominant-negative (>50%) ion-channel effects showed a greater risk for cardiac events than those having haplo-insufficiency (<50%) ion-channel effects. For LQT2 syndrome, Moss et al reported in 2002 that LQT2 patients with mutations in the pore region of KCNH2 had a greater arrhythmic risk than those with non-pore mutations.\textsuperscript{26} This was also confirmed by a larger international cohort, which investigated the clinical aspects of 858 LQT2 patients with KCNH2 mutations categorized by the distinct location, coding type, and topology of the channel mutations.\textsuperscript{27} The LQT2 patients with KCNH2 missense mutations located in the transmembrane S5-loop-S6 region are reported to be at greatest risk. No data about the arrhythmic risk according to mutation location or type have been so far reported in patients with LQT3 or other LQTS genotype. These data suggest the possibility of mutation location-, type-, or function-specific management or treatment in patients with LQT1 or LQT2 syndrome.

**Polymorphism as a Modifier for Arrhythmic Risk in Congenital LQTS**

Heterogeneity of clinical manifestations within family members who carry the same mutation is one of the unresolved features of congenital LQTS.\textsuperscript{1,13,28} Such intrafamilial variability in clinical phenotype indicates the significant role of modifying and triggering factors.\textsuperscript{29} Common genetic variants (polymorphisms) have long been postulated to act as modifiers of clinical phenotype. To address this issue, Duchatelet et al\textsuperscript{22} recently investigated a cohort from France, Italy and Japan including 112 duos (1 with cardiac events and 1 asymptomatic and untreated) of patients with known heterozygous LQT1 or LQT2 mutations. They genotyped 25 polymorphisms described and untreated) in patients with known heterozygous LQT1 or LQT2 mutations. They genotyped 25 polymorphisms described in all 12 genotypes, either decreases in the inward sodium or increases in the outward potassium currents (transient outward potassium current [Ito], adenosine-sensitive potassium current [I\textsubscript{ATP}]) are responsible for the Brugada phenotype.\textsuperscript{36,37} Among the 12 genotypes, over 300 mutations have been identified in the major player, SCN5A, the sodium channel gene, but they account for only 11–28% of clinically diagnosed BrS patients.\textsuperscript{3} Mutations in calcium channel genes, including CACNA1C (Cav1.2, BrS3), CACNB2b (Cavβ2b, BrS4) and CACNA2D1 (Cavα2δ1, BrS9) are found to be in approximately 12–13% of Brugada probands.\textsuperscript{38} Mutations in glycerol-3-phosphate dehydrogenase 1-like enzyme (GPD1L, BrS2), SCN1B (β1-subunit of Na channel, BrS5), KCNE3 (Kir2.6, BrS6), SCN3B (β3-subunit of Na channel, BrS7), KCNJ8 (BrS8), KCND3 (BrS10), MOG1 (BrS11), and KCNE5 (BrS12) are rare.\textsuperscript{39} Overall, approximately two-thirds of clinically diagnosed BrS patients have not yet been genotyped. The HRS/EHRA consensus statement proposed the indication of genetic testing for BrS.\textsuperscript{4}

**Brugada Syndrome**

BrS is characterized by a coved-type or type-1 ST-segment elevation in the right precordial ECG leads and associated with a high risk of sudden cardiac death from ventricular fibrillation (VF) without structural heart diseases.\textsuperscript{1,29–32}

**Update of Clinical Diagnosis of BrS**

The clinical diagnosis of BrS has long been based on the Brugada Consensus Report, published in 2002, in which 3 ST-segment elevation patterns were proposed.\textsuperscript{30} Type 1 ST-segment elevation is characterized by a J point elevation >2 mm (0.2 mV) followed by a negative or isoelectric T-wave. Type 2 ST-segment elevation has a saddleback appearance with a J point elevation >2 mm followed by a trough displaying >1 mm ST elevation with either a positive or biphasic T-wave. Type 3 ST-segment elevation also has a saddleback appearance with a J point elevation <1 mm. The type 1 Brugada ECG is more frequently recognized just before and after episodes of VF, and is considered to be linked to a higher incidence of VF and sudden cardiac death.\textsuperscript{31} The second Brugada Consensus Report in 2005 proposed that type 1 ST-segment elevation in at least 2 right precordial leads (V1–3) is required for definite diagnosis of BrS.\textsuperscript{32} However, several reports thereafter have indicated that a type 1 ECG recorded in at least 1 right precordial lead was enough to diagnose BrS.\textsuperscript{33} The recently published HRS/EHRA/APHRS expert consensus statement on diagnosis and management has proposed that BrS is definitively diagnosed when a type 1 ST-segment elevation is observed either spontaneously or after intravenous administration of a sodium channel blocking agent (ajmaline, flecainide, pilsicainide, or procainamide) in at least ONE right precordial lead (V1 and V2), which are placed in a standard or superior position (up to the 2nd intercostal space).\textsuperscript{34} Although it has long been suggested that 1 of (1) documented VF, (2) polymorphic VT, (3) a family history of sudden cardiac death (<45 years old) or coved-type Brugada ECG in family members, (4) inducibility of VF with programmed electrical stimulation, (5) syncope or (6) nocturnal agonal respiration is required to diagnose BrS, documentation of VF/VT is NOT essential to diagnose BrS in the new HRS/EHRA/APHRS expert consensus statement.\textsuperscript{5}

**Genetic Diagnosis of BrS**

Genetic studies in BrS so far have identified 12 responsible genes on chromosomes 1, 3, 7, 10, 11, 12, 17 and 19 (Table 2).\textsuperscript{1} In all 12 genotypes, either decreases in the inward sodium or calcium currents (fast INa, ICa-L) or increases in the outward potassium currents (fast INa, ICa-L) or increases in the outward potassium currents (fast INa, ICa-L) are responsible for the Brugada phenotype.\textsuperscript{36,37} The clinical diagnosis of BrS has long been based on the Brugada Consensus Report, published in 2002, in which 3 ST-segment elevation patterns were proposed.\textsuperscript{30} Type 1 ST-segment elevation is characterized by a J point elevation >2 mm (0.2 mV) followed by a negative or isoelectric T-wave. Type 2 ST-segment elevation has a saddleback appearance with a J point elevation >2 mm followed by a trough displaying >1 mm ST elevation with either a positive or biphasic T-wave. Type 3 ST-segment elevation also has a saddleback appearance with a J point elevation <1 mm. The type 1 Brugada ECG is more frequently recognized just before and after episodes of VF, and is considered to be linked to a higher incidence of VF and sudden cardiac death.\textsuperscript{31} The second Brugada Consensus Report in 2005 proposed that type 1 ST-segment elevation in at least 2 right precordial leads (V1–3) is required for definite diagnosis of BrS.\textsuperscript{32} However, several reports thereafter have indicated that a type 1 ECG recorded in at least 1 right precordial lead was enough to diagnose BrS.\textsuperscript{33} The recently published HRS/EHRA/APHRS expert consensus statement on diagnosis and management has proposed that BrS is definitively diagnosed when a type 1 ST-segment elevation is observed either spontaneously or after intravenous administration of a sodium channel blocking agent (ajmaline, flecainide, pilsicainide, or procainamide) in at least ONE right precordial lead (V1 and V2), which are placed in a standard or superior position (up to the 2nd intercostal space).\textsuperscript{34} Although it has long been suggested that 1 of (1) documented VF, (2) polymorphic VT, (3) a family history of sudden cardiac death (<45 years old) or coved-type Brugada ECG in family members, (4) inducibility of VF with programmed electrical stimulation, (5) syncope or (6) nocturnal agonal respiration is required to diagnose BrS, documentation of VF/VT is NOT essential to diagnose BrS in the new HRS/EHRA/APHRS expert consensus statement.\textsuperscript{5}

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Genotype-Phenotype Correlations in BrS

Genotype-phenotype correlations have been less investigated compared with congenital LQTS, and are limited to BrS1 caused by sodium channel gene (SCN5A) mutation. Mild conduction abnormalities have been described in BrS patients with SCN5A mutations. Smits et al reported longer PQ and HV intervals at baseline and a larger increase in PQ and QRS intervals in BrS patients with SCN5A mutations than in those without.\(^{30}\) Moreover, the PQ interval and QRS duration were more significantly prolonged with aging in BrS patients with SCN5A mutations during the follow-up period.\(^{41}\)

An unresolved matter in BrS is the higher prevalence of BrS in Asian countries.\(^{1,31,32,36}\) Bezzina et al identified a haplotype B consisting of 6 individual DNA polymorphisms within the proximal promoter region of SCN5A in Asians only (allele frequency of 22%), not in either Caucasians or African-Americans.\(^{42}\) Luciferase reporter activity of the haplotype B is reduced by 62% in cardiomyocytes compared with the wild type. Haplotype A,\(^{42}\) PR and QRS durations, the indices of conduction velocity, were significantly longer in haplotype B individuals, with a gene-dose effect in both 71 Japanese BrS patients without SCN5A mutations and 102 Japanese controls.\(^{42}\) Moreover, sodium channel blockers increased both PR and QRS duration genotype-dependently with a gene-dose effect.\(^{42}\) These data demonstrated that the SCN5A promoter haplotype B might contribute to the higher incidence of BrS in Asian populations.

New Insight From Gene Array Studies

Causative mutations, mainly in SCN5A, can be identified in approximately one-third of clinically diagnosed patients with BrS. In many cases, symptoms are sporadic, and genetic studies in Brugada families harbouring mutations in SCN5A have demonstrated low disease penetration.\(^{43}\) These findings indicate a more complex inheritance model involving multiple variants of different genes. However, genetic testing using the conventional candidate gene approach has largely failed to discover new disease-responsible genes. Bezzina and international collaborators have recently conducted GWAS to explore the role of common genetic variants in susceptibility to BrS in 383 individuals with BrS and 1,115 ancestry-matched controls.\(^{44}\) Two genomic regions displayed a significant association: SCN10A at 3p22.2 (rs10428132) and a genomic interval including HEY2 at 6q22.32 (rs9388451). A replication study in 2 independent case–control sets from Europe and Japan confirmed both associations and revealed an additional association signal in SCN5A at 3p21 (rs11708996). The association signals at SCN5A-SCN10A suggest that genetic polymorphisms modulating cardiac conduction can influence susceptibility to BrS. The association signal near HEY2, together with new functional evidence that Hey2 regulates cardiac electrical activity, suggests that BrS may originate from altered transcriptional programming during cardiac development.\(^{45}\) These findings provide new insights into the pathogenesis of BrS and suggested that common genetic variation can influence predisposition to a rare disease.\(^{46}\)

Acknowledgments

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