Editorial Commentary

The puzzle of genetics in Brugada syndrome: a disease with a high risk of sudden cardiac death in young people

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Brugada syndrome (BrS) is an arrhythmia syndrome that carries a high risk of death for sufferers. First reported by Brugada *et al.* in 1992, BrS is as an inherited cardiac disorder characterized by a distinct electrocardiogram (ECG) pattern. BrS mainly affects young people, with the average age at diagnosis being 40±22 years, and males (1-3), although some old and female BrS patients have also been reported (4-6).

Since 1st diagnostic criteria of BrS was published in 2002, the diagnostic criteria for BrS have changed over time (7-11). BrS is currently diagnosed when ST-segment elevation showing type 1 morphology ≥2 mm in ≥1 lead among the leads V1 or V2 positioned in the 2nd, 3rd, or 4th intercostal space in 12-lead electrocardiogram, appears spontaneously or after a provocative drug test with administration of class I antiarrhythmic drugs and an assessment of the patient's clinical presentations and genetic mutations (10).

Many clinical conditions, including neuromuscular diseases, electrolyte imbalance or alcohol intoxication, may elicit the ECG patterns of BrS; such cases are referred to as acquired BrS or Brugada phenocopy (12-14). Provocative pharmacological testing with class I sodium channel blockers can be used to differentiate congenital BrS from acquired BrS. Because genetic testing is recommended only for congenital BrS, acquired BrS must be ruled out before a diagnosis of true congenital BrS is made.

Although some studies have reported that BrS is an inherited disorder that is mostly autosomal dominant and displays incomplete penetrance, many sporadic BrS cases have been recorded. Priori *et al.* reported that the overall disease penetrance in 4 small BrS families with mutations in the *SCN5A* gene was 16%(range, 12.5% to 50%) (15). The gene *SCN5A* encodes α subunits of the human major cardiac sodium channel (Nav1.5), and it was reported as the first BrS-causal gene in 1998. Defects in the genes encoding for calcium channels and potassium channels have also been linked with BrS phenotype. After two decades, variants in several susceptibility genes have been identified in Sodium Voltage-Gated Channel Alpha Subunit 5 (*SCN5A*), calcium voltage-gated channel subunit alpha1 C (*CACNA1C*), calcium channel, voltage-dependent, beta 2 (*CACNB2*), calcium voltage-gated channel auxiliary subunit alpha2delta 1(*CACNA2D1*), glycerol-3-phosphate dehydrogenase 1 like (*GPD1L*), sodium channel beta-1 subunit (*SCN1B*), sodium voltage-gated channel beta subunit 2 (*SCN2B*), sodium voltage-gated channel beta subunit 3 (*SCN3B*), potassium voltage-gated channel subfamily D member 3 (*KCND3*), potassium voltage-gated channel subfamily E member 3 (*KCNE3*), potassium voltage-gated channel subfamily D member 5 (*KCNE5*), potassium voltage-gated channel subfamily J member 8 (*KCNJ8*), Sodium Voltage-Gated Channel Alpha Subunit 10 (*SCN10A*), RAN Guanine Nucleotide Release Factor (*RANGRF*), plakophilin-2 (*PKP2*), potassium voltage-gated channel subfamily B member 2 (*KCNB2*), and Hairy/enhancer-of-split related with YRPW motif protein 2 (*HEY2*), accounting for less than 30% of BrS cases (3,16,17). However, in approximately 70% of BrS patients, the genes that caused their disease are unknown.

Large geographic differences have been reported, not

only in the prevalence of BrS in the community-based or hospital-based populations, but also in the prevalence of ECG abnormalities and genetic mutations among BrS patients. BrS is generally believed to occur more frequently in Southeast Asia (estimated prevalence: 12:10,000) than in Western countries (estimated prevalence: 1–5:10,000) (3,18). A pooled analysis of the community- and hospital-based population studies on BrS worldwide showed that the prevalence of Brugada type 1 ECG pattern is higher in Asia than in Europe or the United States; similarly, the prevalence of Brugada type 2/3 ECG pattern is also higher in Asia than in Europe or the United States (19). Furthermore, geographic differences in genetic susceptibility to mutations in SCN5A have also been described: 20–25% of BrS cases presented with *SCN5A* mutations in Caucasian populations (20,21), compared with 11–14% in Japanese populations, and <10% in the Han Chinese population in Taiwan (22). The prevalence of certain *SCN5A* promoter polymorphisms in a haplotype variant was fairly higher in Asians. This variants could reduce transcriptional activity *in vitro*, and modulate variability in cardiac conduction as assessed by PR and QRS durations (23). A recent report suggested that some single-nucleotide polymorphisms (SNPs) associated with BrS or electrocardiogram traits exist across various populations. The cumulative risk of BrS-related SNPs in Han Chinese BrS patients is similar to that in Caucasian BrS patients; however, the risk appears to be correlated with the absence of *SCN5A* mutations (24,25). This finding suggested that the disposition of disease-causal genes among BrS patients in the Asian populations might partly differ from that in the Caucasian population.

As disease penetrance for BrS is incomplete and age-related, genetic testing may be used for diagnosis and for the screening of at-risk family members. In 2013, the Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/Asia-Pacific Heart Rhythm Society (APHRS) expert consensus stated that comprehensive or BrS1 (*SCN5A*)-targeted genetic testing could be useful for patients for whom a cardiologist has established a clinical index of suspicion for BrS based on the patient's clinical history, family history, and the resting surface 12-lead ECGs and/or provocative drug challenge testing) (9). To date, over 20 genes have been reported to be associated with BrS and are routinely tested as single-gene causes for this condition on a variety of clinical genetic testing panels worldwide. Hosseini *et al.*'s evidence-based review of genes reported to cause BrS and routinely clinically tested in patients indicated that 20 of 21 genes lacked sufficient genetic evidence to support their causality for BrS (26). Furthermore, ancestral differences also impact the interpretation of classification of pathogenicity of variants identified from BrS patients (27). The causality of BrS-associated genes is much disputed; many of these genes demand further research but may be clinically validated in the future.

Although controversies still exist, more than two decades of extensive research in BrS has helped physicians and researchers to gain a better understanding of the overall spectrum of the condition, including its molecular pathophysiology, genetic background, and disease management. Sanger sequencing, which was considered as the gold standard technology for DNA sequencing, was applied for the mutation screening of BrS (28). However, recent years have seen the development of new technologies that provide high-throughput screening, such as microarrays, whole-exome sequencing, and whole-genome sequencing, which are able to identify a variant at a single nucleotide resolution in relatively medium- to large-sized genomic regions. These technological genomic advancements enable the detection of genetic variations in patients, with high accuracy and reduced cost (24,29-32). Therefore, it is only a matter of time before the puzzle of genetics in BrS is solved.

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Footnote

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