Promoting Arrhythmia Susceptibility

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In general, gain-of-function mutations confer susceptibility to type 3 LQTS (LQT3), which accounts for an estimated 5% to 10% of LQTS, whereas loss-of-function mutations give rise to type 1 BrS (BrS1), which accounts for ≈15% to 30% of BrS.3 On the basis of on an estimated incidence of 1 in 5000 for either LQTS or BrS, 1 in 50 000 individuals should host a rare SCN5A mutation that is pathogenic for LQTS/BrS.

More recently, a globally broader role for SCN5A has been under investigation. Rather than being merely a gene associated with rare, autosomal dominant Mendelian disorders, genetic variation in SCN5A may confer increased arrhythmia susceptibility to the population at large. Initially, amino acid substitutions in the sodium channel were considered infrequent sightings, and when present, pathogenesis was inferred. We recently discovered 39 missense “mutations” (28 rare and novel) that clustered predominantly in nontransmembrane-spanning regions of the channel.18 However, these mutations were not found in a cohort of either LQTS or BrS but were scattered among >800 healthy subjects from 4 distinct ethnicities. Thus, an estimated 3% to 5% of healthy subjects may in fact host a rare SCN5A missense variant of uncertain functional clinical significance. This low rate of “background noise” must be considered carefully in the interpretation of clinical genetic testing for LQTS/BrS.

In addition, 8 of these variants are common polymorphisms defined as an allelic frequency >0.5%, and all 8 have been characterized functionally.16,17 A brief consideration of two of the most common polymorphisms and their role in pharmacogenetic susceptibility is worth mentioning. S1103Y, also annotated as Y1102, is the third most common polymorphism in blacks (behind H558R and R34C) and is relatively specific to the black population, with an allelic frequency of ≈6% to 7%.16 S1103Y confers increased population-based susceptibility for ventricular arrhythmias and sudden cardiac death among blacks in the setting of QT-prolonging drugs and disease.10,11

H558R is the most common sodium channel cSNP in all ethnic groups examined, with an estimated minor allele frequency of 29% (blacks), 23% (Hispanics), 20% (whites), and 9% (Asians).16 Functional studies have shown that the R558-encoding minor allele can dramatically alter the phenotype of true disease-causing SCN5A mutations.18 Additionally, in the context of the less common 2016–amino acid–encoding, alternatively spliced transcript that contains a glutamine at residue 1077 (Q1077), current expression associated with R558-containing channels was profoundly reduced.12 Bench-to-bedside extrapolations would suggest that the estimated 5% to 10% of whites, Hispanics, and blacks homozygous for the minor R558-encoding allele would have an estimated 30% “reduced depolarization capacity.”12,17

For more clinically advanced than the H558R story, Bezzina and colleagues13 have now discovered a novel

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Now, because of this international all-star cast of channelologists, the proverbial street lamp is shining on a new location in the SCN5A gene and has illuminated an excitingly novel genetic mechanism that may promote arrhythmia susceptibility. In this issue of Circulation, Bezzina and colleagues13 reveal their discovery of a novel ethnic-specific promoter variant (HapB) that may genetically reduce the “antifibrillatory reserve” of a host. To appreciate the magnitude of these investigators’ sleuthing, one must consider where the street lamp has been shining for the past decade.

Since the sentinel discovery of SCN5A as a disease gene for LQTS in 1995,1 SCN5A genetic testing has focused on the 27 translated exons that encode the 2015 or 2016 amino acids of the channel (depending on which alternatively spliced SCN5A transcript is generated). To date, ≈56 LQT3-associated mutations (mostly missense) and 77 BrS1-associated mutations (mostly missense) have been reported.2,3,14,15 This compendium of rare LQT3/BrS1-associated SCN5A mutations can be viewed at the web-based Inherited Arrhythmias Database (http://pc4.fsm.it:81/cardmoc).

The SCN5A-encoded voltage-gated cardiac sodium channel α-subunit (hNaV1.5) is one of the critical ion channels necessary to orchestrate both the cardiac action potential and excitation-contraction coupling of the ventricular myocyte.1 Rare mutations in SCN5A have been implicated in a cadre of the cardiac channelopathies, including congenital long-QT syndrome (LQTS), Brugada syndrome (BrS), progressive cardiac conduction disease, idioventricular fibrillation, autosomal recessive sick sinus syndrome, sudden infant death syndrome, and even a cardiacopathy characterized by dilated cardiomyopathy, conduction disease, and atrial fibrillation.1–9 In addition, some common nonsynonymous single nucleotide polymorphisms (cSNPs or coding polymorphisms) may increase the risk of drug-induced torsade de pointes and sudden cardiac death, particularly among blacks, whereas other cSNPs may result in a “reduced depolarization capacity.”10–12

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ethnic-specific genetic variant that promotes slowing of cardiac conduction and may promote pharmacogenetic susceptibility during exposure to sodium channel blockers. Unlike the aforementioned genetic variants, however, this finding resulted from moving the street lamp to a very different corner in \( SCN5A \) where they illuminated the promoter of the channel. Their search began some 18,555 bp upstream of the first translated “ATG.” These investigators resequenced 2.8 kb of the \( SCN5A \) promoter (from position −2190 to 613 of \( SCN5A \) numbered relative to the major transcription initiation site of the \( SCN5A \) promoter). Fortuitously, this resequencing was performed on a single individual of Asian origin who would be found to be a homozygote for 6 different polymorphisms occurring along this stretch: −1418T>C, −1062T>C, −847T>G, −835insGC, −354G>C, and 287C>T.

Beyond this individual, the story quickly becomes very intriguing and potentially relevant to the global subpopulation of Asians. The investigators found that although >1700 nucleotides separated the first and last polymorphisms, the more common variant at each position almost always resided on the same allele, whereas the lesser common variants almost always traveled together as well. Thus, these polymorphisms were in near-total linkage disequilibrium and defined 2 distinct \( SCN5A \) promoter haplotypes: haplotype A (HapA), constituting an allele containing the common variants at each of the 6 positions, and haplotype B (HapB), defining the promoter sequence containing the less common variant at each position. Moreover, HapB is specific to the Asian population (absent in whites and blacks) with a minor allele frequency of 21% to 24%, indicating that ∼30% to 35% of Asians are heterozygous for HapA/HapB and 4% to 5% are homozygous for HapB/HapB.

In theory, a genetic variant that compromised the transcriptional efficiency of the promoter and resulted in decreased expression of \( SCN5A \) transcripts could potentially mimic the effect of a loss-of-function mutation occurring within the open reading frame of \( SCN5A \). Accordingly, one might expect that a functionally significant promoter variant would promote a phenotype of conduction slowing or even BrS. Once again, in an elegant demonstration of translational research, Bezzina and colleagues have partially fulfilled this theory.

Taking advantage of the firefly-derived luciferase assay, the investigators demonstrated that the HapA \( SCN5A \) promoter construct was much brighter than HapB. HapB-\( SCN5A \) promoter was 62% dimmer. Consistent with this in vitro demonstration of a pronounced reduction in \( SCN5A \) transcript when driven by the HapB promoter, Asian subjects, whether BrS1-negative Japanese or Japanese control subjects, showed a promoter allele–dependent effect on cardiac conduction. The presence of ≥1 HapB promoter allele(s) was strongly associated with longer PR and QRS intervals both at baseline and during pharmacological challenge. The PR and QRS intervals were ∼20 to 30 ms longer in HapB/HapB subjects compared with those homozygous for the wild-type promoter (HapA). In fact, more than one fourth of the variability in the PR interval and nearly one half of the QRS variability were attributed to the patient’s promoter haplotype. Moreover, the investigators demonstrated that HapB may confer pharmacogenetic susceptibility. During drug challenge with a sodium channel blocker, there was a significant promoter-dependent effect on the QRS interval: ∆QRS = 18 ms in HapA/HapA subjects compared with HapA/HapB (24 ms) and HapB/HapB (30 ms).

As testimony to great science, what the investigators did not observe is as intriguing as the identified relationship between promoter haplotype and cardiac conduction. Specifically, the authors did not find HapB to be a novel pathogenic mechanism for BrS itself. Several BrS1-associated missense mutations confer a state of haploinsufficiency whereby the only sodium current generated arises from the normal allele producing 50% of the normal hNaV1.5 current density. Extrapolating from their luciferase assay results, one would predict that individuals homozygous for HapB might have a nearly two-thirds reduction in hNaV1.5; consequently, these individuals would display a BrS-like ECG pattern. Reflecting that the line from firefly to human is not particularly straight, the authors found no such link to BrS. The allelic frequencies for HapA and HapB were no different between Japanese control subjects or the 71 Japanese patients with \( SCN5A \)-negative BrS (BrS1 negative). Specifically, HapB was not overrepresented in BrS. Moreover, the promoter haplotype allele frequencies were in Hardy-Weinberg equilibrium, suggesting that neither survival benefit nor detriment among Asians can be linked directly to \( SCN5A \) promoter status.

Nonetheless, these wonderful discoveries now stimulate new questions. Does \( SCN5A \) promoter haplotype status modify the phenotype of Asians with BrS? Specifically, do Asians with HapB/HapB-BrS1 have a more severe phenotype than those with HapA/HapA-BrS1? Does HapB confer increased susceptibility for the uncommon and unwanted side effect of sudden cardiac death during exposure to class I antiarrhythmics like flecainide? Reduction of sodium current is a risk factor for sudden cardiac death. The Cardiac Arrhythmia Suppression Trial (CAST) demonstrated that such sodium channel blockers increased the incidence of sudden cardiac death.19 Given that CAST was conducted predominantly in whites and that HapB is an Asian-specific \( SCN5A \) promoter haplotype, HapB could not have mediated pharmacogenetic susceptibility for sudden cardiac death in the CAST population. However, could HapB decrease the “antifibrillatory reserve” of an Asian host? Will HapB become a clinical biomarker for Asians as a pharmacogenetic risk factor? With the Japanese Antiarrhythmics Long-Term Study 2 reporting a relative increase in the use of class I antiarrhythmic medications for atrial fibrillation in Japan, the discovery of this functional promoter variant is timely and may perhaps even save lives.20

With these sentinel observations, it is quite likely that the street lamp will continue to expose the consequences of dysfunctional cardiac channel promoters. The role of genetic variation in channel promoters in arrhythmogenesis will undoubtedly be the subject of intense investigation. Now, it likely remains only a matter of time before a third street lamp is lit and the effect of genetic variation occurring within the darkest region of the cardiac channel genes, the introns, is illuminated.
Disclosures

Dr Ackerman and Mayo Medical Ventures provided intellectual property and consultation to Genaissance Pharmaceuticals for the FAMILION genetic test for cardiac channel mutations. Dr Bunch reports no conflicts.

References


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