Sodium Current Disorders
Geneticist's View

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KEYWORDS

• Genetics • Sodium • Ion channel

KEY POINTS

- Cardiac sodium channel function may be affected by mutations in several genes that cooperate to determine its function (multiple genes for the same phenotype).
- Cardiac sodium channel gene (*SCN5A*) is the most common cause of cardiac sodium channel dysfunction and is associated with multiple clinical phenotypes (multiple phenotypes for the same gene).
- Genetic testing for sodium channel–related disease has important diagnostic implications but, with the exception of long QT syndrome type 3 (LQT3), genotype-phenotype correlation and genotype-based clinical management are poorly defined.
- Distinguishing the true disease-causing mutations from rare variants is challenging and requires the use of multiple tools and specific training to maximize the interpretative skills and clinical applicability of the results of genetic testing.

INTRODUCTION

In the past 20 years impressive advancements have occurred in the understanding of molecular genetics of cardiac rhythm disorders. With the discovery of the causative genes for major inherited diseases, diagnostic genotyping is introduced in the clinical practice. Genetic tests are performed not only for diagnostic purposes but also for risk stratification, assessment of drug treatment, and therapy strategy selection. In the field of inherited arrhythmogenic diseases, the identification of the genes responsible for cardiomyopathies and ion channel diseases has opened the molecular era in the understanding of the pathophysiology of inherited arrhythmogenic diseases and improved ability in prognosis and treatment. Although genetic tests are progressively entering the clinical practice, specific skills are needed to use the test results in a correct way to not lose potential benefits and to not stretch their indications. Performing genetic analyses without clear clinical indications and endpoints may bring about more problems than solutions.[1–3] This article summarizes the phenotypes associated with cardiac sodium channel mutations and related genes and outlines the possibilities and limitations of genetic testing.

PHENOTYPES ASSOCIATED WITH SCN5A AND RELATED GENES

Since the first cardiac sodium channel mutation identified in long QT families, mutations of genes encoding alpha subunit of the human cardiac sodium channel $Na_v1.5$ have been associated with

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a spectrum of inherited arrhythmia syndromes, including LQT3, Brugada syndrome (BrS), cardiac conduction disease, dilated cardiomyopathy (DCM), sick sinus syndrome (SSS), and atrial fibrillation (AF).[4] From a genetic standpoint, several investigators have shown that cardiac sodium channel should be considered a macromolecular complex with several functionally related proteins that cooperate to control the opening and closing of the Na^+ conducting pore protein ($Na_v1.5$). This concept is well illustrated by the identification of $Na_v1.5$ regulatory gene mutations that affect cardiac sodium current in the absence of a mutation in the ion conducting channel ($Na_v1.5$) and cause clinical phenotypes almost undistinguishable from those described previously. The following paragraphs briefly summarize the phenotypes and their genetic determinants to highlight the genetic heterogeneity of sodium channel disorders. The second part of the article focuses on the clinical impact of such heterogeneity.

Long QT Syndrome Type 3

LQT3 was the first phenotype associated with mutations in *SCN5A* encoding for $Na_v1.5$.[5] LQT3 accounts for 5% to 10% of long QT syndrome (LQTS) patients with identified mutations and its clinical presentation is described by Ruan and colleagues elsewhere in this issue.

The available data suggest high penetrance (80%) with heart rate corrected QT interval (QTc), often above 500 ms; a severe outcome; and reduced response to β-blockers.[6–8] It is important, however, to highlight that this typical LQT3 phenotype was outlined in cohorts with definite gain-of-function and pathogenetic mutations. The recent mounting drive to expanded indications for genetic testing toward subjects with borderline QT interval is having an impact on the average LQT3 patient profile. Subjects with borderline QTc and presumably low risk of events are being identified and current risk stratification schemes may not apply in these cases.

To generate an LQTS phenotype due to an abnormality of sodium current, a gain-of-function effect with a net increase of inward sodium current (I_{Na}) current has to be present. This can be obtained not only by genetic variants directly affecting the channel protein $Na_v1.5$, but also three other genes may cause LQTS through a gain-of-function effect on the cardiac sodium channel: LQTS type 9 (LQT9) caused by caveolin (*CAV3*) mutations, LQTS type 10 (LQT10) caused by sodium channel beta four subunit (*SCN4B*) mutations, and LQTS type 12 (LQT12) caused by syntrophin gene (*SNTA1*) mutations (**Table 1**). When mutated, these genes cause an increase in depolarizing I_{Na} but this effect is reached through a variety of possible mechanisms. This evidence highlights the complexity of the pathophysiological mechanism that can lead to a genetic dysfunction of cardiac sodium current but it also has direct clinical implications. Cardiologists who want to approach genetic testing for suspected LQT3 (or related) patients need to have quantitative information on the sensitivity and clinical implications of the test.

The most relevant piece of information is the prevalence of these variants. An expert consensus document on genetic testing in inherited arrhythmogenic diseases[9] provided a systematic evaluation of the available evidence and produced lists of key genes, which are worth screening for clinical purposes. As for LQTS, the consensus is that the only relevant sodium-related gene is *SCN5A*, whereas all the others are considered too rare to justify systematic testing in the clinical setting.

Brugada Syndrome

BrS is an arrhythmogenic disease characterized by ST segment elevation in right precordial leads and an increased risk of sudden cardiac death due to ventricular fibrillation. The clinical features are described by Ruan and colleagues elsewhere in this issue. As in the case of LQT3, BrS was initially linked to sodium channel mutations[10] but in this case the net functional consequence is that of a loss of function. Because I_{Na} controls both action potential duration and conduction velocity, BrS patients show not only typical ST elevation but also conduction delay and a tendency to short action potential duration. This translates into a borderline short QT interval on the electrocardiogram. ST elevation seems due to a combination of delayed conduction in the right ventricular outflow tract and a transmural (epicardium vs endocardium) unbalance of inward and outward currents.[11]

With the progressive accumulation of knowledge, it has become clear that additional genes that alter the inward/outward current balance in the myocardium can cause BrS. The list of genes associated with BrS is continuously expanding. The cardiac sodium current remains, however, the most relevant culprit.[12] As in the case of LQT3, sodium current can be affected through a variety of mechanisms and genes involved in the sodium channel macromolecular complex (see **Table 1**). Reduced sodium current and a BrS phenotype can also be due to mutations in *SCN5A*-regulating genes: *GPD-1L*, *SCN1B*, *SCN2B*, *SCN3B*, and *MOG1*.

No study has systematically carried out parallel screening of all known BrS genes in a large cohort of clinically affected subjects, so precise estimate