The cardiac sodium channel mediates the rapid upstroke of the cardiac action potential and thereby constitutes a critical determinant of cardiac excitability and conduction. Mutations in the SCN5A gene encoding the α-subunit of this channel have been linked to a broad clinical spectrum of arrhythmia disorders, including long QT syndrome, Brugada syndrome, sick sinus syndrome, conduction disease, and most recently, atrial fibrillation. These primary arrhythmia syndromes were originally considered pure electrical entities occurring in the absence of structural heart disease, and the presence of myocardial abnormalities in these disorders was originally actually excluded by definition. Evidence is now accumulating, however, that sodium channelopathy can also be associated with the development of cardiac fibrosis, dilatation, and hypertrophy. Such structural changes within the myocardium may in turn further predispose to the development of ventricular arrhythmias. These findings have led to reevaluation of the initial view that mutations in a cardiac ion channel would only lead to pure electrical dysfunction and raised the intriguing possibility that the structural alterations could be a direct consequence of sodium channel dysfunction rather than a consequence of long-standing arrhythmia. The mechanism by which a dysfunctional sodium channel leads to structural changes in myocardial tissue, however, remains unclear.

In this issue of Circulation: Arrhythmia and Electrophysiology, Ge et al report on a novel SCN5A mutation (A1180V) linked to dilated cardiomyopathy (DCM), expanding the repertoire of SCN5A mutations associated with DCM. Previously, the D1275N mutation was discovered independently by McNair et al and Olson et al in the same large family with the syndrome of DCM, atrial arrhythmias, sinus node dysfunction, and conduction disease. This family had been originally described by Greenlee et al in 1986. The D1275N mutation has also been associated with mild ventricular structural alterations in a Finnish family with conduction defects and atrial arrhythmias and was linked by our group to the phenotype of atrial standstill without ventricular dilatation. Besides D1275N, Olson et al reported another 3 mutations (T220I, D1595H, 2550–2551insTG) segregating in very small families and 1 mutation (R814W) arising de novo that they identified through systematic analysis of a cohort of 156 unrelated probands with DCM. Other mutations have been linked to DCM in sporadic cases. These include R814Q occurring homozygously and the compound heterozygous occurrence of the W156X and R225W mutations.

Clinically, conduction disease seems to be a common feature of DCM-related SCN5A mutations. The initial clinical manifestation of the A1180V mutation carriers appears to be late-onset and progressive atrioventricular block. In the multigenerational family with the D1275N mutation, chamber enlargement was typically preceded by sinus node dysfunction and conduction disease. Similarly, sinus bradycardia and/or conduction disease was a feature in carriers of T220I, 2550–2551insTG, D1595H, R814Q, and W156X/R225W. Atrial tachyarrhythmias, also found in carriers with the A1180V mutation, appear to be another prevailing feature. Among the 37 carriers of the different SCN5A mutations from the study of Olson et al, 43% had documented atrial fibrillation, with a mean age at diagnosis of 27.8 years. Atrial arrhythmias have also been reported in relatively young carriers of the D1275N mutation in other studies. Although an increasing number of SCN5A mutations have now been associated with the development of DCM, the causal relationship between them remains unclear. Some patients with SCN5A-related DCM had a substantially long clinical history of conduction disorder and/or atrial fibrillation (>10 years), raising the distinct possibility that the observed structural abnormalities are in fact representative of tachycardia-induced cardiomyopathy secondary to chronic arrhythmia. Indeed, the DCM phenotype in carriers of SCN5A mutations in general displays age-dependent penetrance, suggesting that sufficient time is required for the structural abnormalities to develop. Although Olson et al provide some evidence (Holter monitoring and serial ECGs) that the DCM in D1275N carriers was not a consequence of long-standing atrial tachyarrhythmias with rapid ventricular rates, this possibility cannot be completely excluded. In the 1-year-old girl with compound heterozygosity for W156X/R225W studied by our group, we considered tachycardiomypathy unlikely because arrhythmia episodes before death were of short duration. Large-scale long-term follow-up studies will be required to determine whether DCM is a...
primary consequence of SCN5A mutations or a secondary effect of chronic arrhythmia. Furthermore, although in some families evidence for causality can be derived from the cosegregation of the mutation with the DCM phenotype in a number of individuals, this is not the case for all mutations, raising the possibility that DCM in some of the sporadic cases may in fact be related to other (genetic) causes. Because causality of SCN5A mutations in DCM may still be regarded as questionable, particularly in the absence of cosegregation in a large number of family members, it is still pertinent to exclude known DCM-related genes.

At present, all known DCM-related SCN5A mutations except for 2550–2551insTG have been characterized in heterologous expression systems. In agreement with the observed conduction disease, biophysical properties consistent with loss of sodium channel function have often been observed for these mutations. The R225W mutation caused a drastic reduction in peak current density, whereas W156X abolished sodium current completely. T220I led to a relatively mild reduction in peak current density, in conjunction with a small negative shift in voltage dependence of inactivation and a slower recovery from inactivation. In contrast, cells expressing A1180V exhibited unchanged peak current densities compared with wild type, and similar observations have been made for D1275N, R814W, R814Q, and D1595H. These latter mutations, however, display diverse kinetic defects, not all necessarily leading to reduced sodium channel function. Similar to R814W, the A1180V mutation is associated with reduced sodium current at high frequencies, although the underlying causative kinetic changes are different between the 2 mutations. R814W displayed increased window current and enhanced slow inactivation, whereas A1180V caused a hyperpolarized shift in steady-state inactivation in addition to slow recovery from inactivation. D1595H channels primarily exhibit impaired fast inactivation, whereas the main feature of D1275N consists of a small depolarizing shift in activation. Finally, R814Q has been shown to cause a hyperpolarizing shift in steady-state inactivation. Thus, few commonalities exist between these DCM-related mutations. This lack of electrophysiological similarities further hampers our understanding of the mechanisms involved in SCN5A-related DCM. However, one must acknowledge that comparison across studies may be hindered by the different experimental conditions and cellular expression systems used. Interestingly, the presence of a late sodium current has been reported for A1180V but not for any of the others. Minor differences in QT-interval duration were observed during exercise between nonaffected carriers of A1180V and noncarriers. However, all QT intervals were within the normal range, and therefore, the association between the observed late sodium current and clinical ECG phenotype remains unclear.

One possible mechanism proposed for cardiac dilatation as a consequence of sodium channel dysfunction draws on insight into mechanisms in other genetic forms of DCM. To date, gene defects leading to DCM have been reported in >20 genes. One group of genes encodes components of the cytoskeleton (among which are dystropin, δ-sarcoglycan, and desmin), which are believed to cause DCM by a mechanism of impaired force transmission. The cardiac sodium channel has been shown to interact with cytoskeletal components such as the dystrophin protein complex, and it has been proposed that sodium channel mutations causing cardiomyopathy cause loss or weakening of such interactions. Two scenarios can be envisaged, both of which could weaken the interaction of the sodium channel with the cytoskeleton: (1) The mutation decreases the density of sodium channels on the sarcolemma, or (2) the mutation directly or indirectly affects the binding site of a structural protein to the sodium channel. However, the unchanged current densities observed in most of the mutations involved (including A1180V) imply unaltered surface density, thus making the first option less plausible. With regard to the second possibility, none of the DCM-associated mutations described so far are located within known (putative) binding sites for structural proteins. Thus, a mechanism for SCN5A-related DCM involving cytoskeletal interactions is not readily explained by current knowledge.

Many have speculated on a role for altered calcium homeostasis as a consequence of alterations in intracellular sodium concentrations ([Na\(^+\)]). Ge et al refer to a potential role for reduced sodium channel activity in this process. In this regard, it must be realized that the action potential amplitude may not change significantly in the face of reduced sodium channel function. Similar amplitude of the upstroke, albeit slow, requires an equal amount of sodium entry. Therefore, reduction of sodium current will not necessarily change [Na\(^+\)]. In contrast, a persistent sodium current, an increase of the late sodium current, or a window current, as shown for A1180V and R814W, results in a higher influx of sodium and could lead to an increased [Na\(^+\)], and secondarily to increased intracellular calcium. Increased intracellular calcium due to increased [Na\(^+\)], is associated with cellular remodeling and development of hypertrophy and heart failure. However, a persistent sodium current during the action potential plateau is a feature of most of the long QT syndrome (LQT3)-associated SCN5A mutations but LQT3 patients do not develop cardiac dysfunction. Notwithstanding, a role for altered calcium homeostasis remains purely speculative and awaits intracellular sodium and calcium measurements in myocytes from transgenic mouse models carrying such mutations.

Most SCN5A mutations do not lead to DCM, although one might argue that mild dilatation may not have been clinically relevant or actively screened for in these cases. Because the incidence of DCM is low among SCN5A mutation carriers, analysis of large cohorts of patients does not seem feasible. Another complicating factor relates to variable and age-dependent disease penetrance and severity. Environmental factors and genetic modifiers may determine disease expressivity by potentially influencing the incidence and/or progression of DCM among these patients. To overcome these complexities, future studies on transgenic mice carrying SCN5A mutations associated with DCM in humans may provide more insight into disease characteristics, progression, and prognosis, as well as underlying mechanisms in SCN5A-related DCM. These insights may ultimately provide clinically relevant diagnostic, prognostic, and therapeutic tools. At present, however, the limited available information on this
issue precludes any definite answers to the many questions still unanswered.

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None.

**References**


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