Cardiac Sodium Channel (SCN5A) Variants Associated with Atrial Fibrillation

Dawood Darbar, MD; Prince J. Kannankeril, MD; Brian S. Donahue, MD, PhD; Gayle Kucera, RN; Tanya Stubblefield, RN; Jonathan L. Haines, PhD; Alfred L. George, Jr, MD; Dan M. Roden, MD

Background—Genetic studies have identified ion channel gene variants in families segregating atrial fibrillation (AF), the most common arrhythmia in clinical practice. Here, we tested the hypothesis that vulnerability to AF is associated with variation in SCN5A, the gene encoding the cardiac sodium channel.

Methods and Results—We resequenced the entire SCN5A coding region in 375 subjects with either lone AF (n=118) or AF associated with heart disease (n=257). Controls (n=360) from the same population were then genotyped for the presence of mutations or rare variants identified in the AF cases. In 10 probands (2.7%), 8 novel variants not found in the control population (0%; P=0.001) were identified. All variants affect highly conserved residues in the SCN5A protein. In 6 families with >1 affected member, the novel variant cosegregated with AF. We also identified 11 rare missense variants in 12 probands (3.2%) that have previously been associated with inherited arrhythmia syndromes (eg, congenital long-QT syndrome and Brugada syndrome).

Conclusions—Mutations or rare variants in SCN5A may predispose patients with or without underlying heart disease to AF. The findings of the present study expand the clinical spectrum of disorders of the cardiac sodium channel to include AF and represent important progress toward molecular phenotyping and directed rather than empirical therapy for this common arrhythmia. (Circulation. 2008;117:1927-1935.)

Key Words: atrial fibrillation ■ SCN5A protein, human ■ cardiac sodium channel Na(v)1.5, human ■ genetics

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice. In the United States, >2 million adults have AF with the prevalence increasing with age.1 This condition is a major cause of morbidity and mortality because of long-term medication use, stroke, and congestive heart failure.2,3 Risk factors for AF include advanced age, hypertension, structural heart disease, and congestive heart failure.4 However, AF can develop in younger subjects (generally defined as <65 years) in the absence of known risk factors, a condition classified as “lone” AF.

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Studies of kindreds with AF suggest a genetic basis for the condition, especially in younger subjects.5–10 Loci on chromosomes 10q22,6 6q14–16,7 and 5p15,11 as well as mutations in several cardiac potassium channel genes, have been linked to familial AF. Specific mutations in the KCNQ1 gene have been observed in families with AF and the long-QT syndrome (LQTS).8 Similarly, occasional kindreds with mutations in other potassium channel genes, including KCNE2,9 KCNJ2,10 and KCNA5,12 have been reported. Whereas these potassium channel subunit gene mutations have been important in establishing the role of single-gene disorders in AF, such isolated or “private” sequence variations are often in residues of unknown function, effects on channel conductance are inconsistent, and in most instances it may be difficult to discriminate rare polymorphisms of no functional significance from true mutations. The role of potassium channel subunit gene mutations in AF thus remains unclear at present, but screening of large patient cohorts suggests that such mutations are not a major cause of AF.13

The human cardiac sodium channel is responsible for the fast depolarization upstroke of the cardiac action potential and is a molecular target for antiarrhythmic drugs, some of which can be effective in treating atrial arrhythmias. Mutations in the human cardiac sodium channel gene (SCN5A) have been associated with inherited susceptibility to ventricular arrhythmias (LQTS, Brugada syndrome [BS], or idiopathic ventricular fibrillation),14 sudden infant death syndrome (SIDS),15–17 impaired cardiac conduction,18,19 and more complex overlapping phenotypes.20,21 Subclinical expression of SCN5A mutations may also manifest as drug-induced arrhythmias22 and other forms of arrhythmia susceptibility.23 Although variants in SCN5A have been reported to occur in disorders that are sometimes associated with AF,24–27 no studies have appeared that have systematically evaluated
the prevalence of SCN5A variants in a cohort of patients with AF in the presence or absence of structural heart disease.

Here, we evaluated the prevalence and spectrum of SCN5A sequence variants in 375 AF patients, including a large subgroup with lone AF. We observed novel as well as rare sequence variants in 375 AF patients, including a large gene.

Methods

Study Subjects

Between November 2002 and October 2005, subjects with AF were prospectively enrolled in the Vanderbilt AF Registry, which comprises clinical and genetic databases.28 At enrollment, a detailed medical and drug history was obtained in all patients. Patients were recruited from the Vanderbilt Cardiology and Arrhythmia Clinics, the emergency department, and inpatient services. Individuals >18 years of age with a diagnosis of AF confirmed by ECG, who presented with symptoms, or who were diagnosed during a routine physical examination were included in the AF Registry. Subjects were excluded if AF was diagnosed in the setting of recent cardiac surgery. The study protocol was approved by the Vanderbilt University Institutional Review Board and participants were enrolled after informed written consent was obtained.

Probands and their relatives were clinically classified by a family classification system, a two-generation sibship, or a single generation.27 The relationship between the clinical phenotype (AF) and the genotype was determined for probands, together with their relatives, and validated by resequencing an independent polymerase chain reaction–generated amplicon from the subject (work performed by the Vanderbilt DNA Sequencing Facility). All variants were validated by sequencing an independent polymerase chain reaction–generated amplicon from the subject (work performed by the Vanderbilt DNA Sequencing Facility). All variants were validated by resequencing an independent polymerase chain reaction–generated amplicon from the subject (work performed by the Vanderbilt DNA Sequencing Facility). All variants were validated by resequencing an independent polymerase chain reaction–generated amplicon from the subject (work performed by the Vanderbilt DNA Sequencing Facility).

Genotype–Phenotype Relations

The relationship between the clinical phenotype (AF) and the SCN5A genotype was determined for probands, together with their relatives, in whom an SCN5A variant was identified.

Statistical Analysis

Means for baseline risk factors were calculated for cases and controls. The significance of associations was tested with the χ² test for categorical variables and with the Student t test for continuous variables. The Fisher exact test was used to analyze
differences in the allele frequencies of variants between cases and controls.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Study Cohort**

During the 3-year enrollment period, 396 patients with AF were approached and 375 (95%) agreed to participate in the study. The study cohort included 118 patients (31%) with lone AF (Table 1). The majority of subjects (94%) were white, and 5% were black. AF was diagnosed at a mean age of 50±14 years. One-hundred-sixty-five patients (44%) had a history of hypertension, 79 (21%) had coronary artery disease, 60 (16%) had diabetes mellitus, and 53 (14%) had a history of cardiomyopathy with left ventricular ejection fraction <40%. The mean left ventricular ejection fraction was 51±14%, the mean left ventricular end-diastolic diameter was 52±9 mm, the mean left ventricular end-systolic diameter was 35±11 mm, and the mean left atrial diameter was 44±9 mm. A family history of AF was present in 99 patients (26%), consistent with previous reports.6,32

**Prevalence of SCN5A Variants in AF Patients**

Resequencing identified 8 novel variants in 10 probands (2.7%) that were not found in the population-based controls (0%; P=0.001). In addition, 11 previously reported rare nonsynonymous coding region variants were identified in 12 probands (Table 2). All variants affect highly conserved residues in the SCN5A protein with 16/19 substitutions leading to the addition, removal, or reversal of side chain charge. All probands were heterozygous. Known common nonsynonymous SCN5A polymorphisms were also identified in the AF cohort: H558R (minor allele frequency 25%), S1103Y (0.7%) and R34C (0.5%).

**Novel SCN5A Variants**

Figure 1 illustrates the locations on the channel protein structure of the 8 novel SCN5A variants that were discovered in AF subjects. None of these 8 variants have been previously published or deposited in publicly-accessible databases, and none were detected in the control subjects that we genotyped (n=720 alleles). Six of these 8 probands reported an affected family member, and analysis of the families revealed evidence of cosegregation of the gene variant with the phenotype in 6/6 kindreds (Figure 2). Clinical characteristics of variant-positive probands are summarized in Table 3.

<p>| Table 2. Cardiac Sodium Channel (SCN5A) Variants in Patients With Atrial Fibrillation |
|-----------------------------------------------|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Amino Acid Change</th>
<th>Previously Reported</th>
<th>All AF</th>
<th>Lone AF</th>
<th>Typical AF</th>
<th>Controls (Minor Allele Frequency)</th>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>M138I</td>
<td>Novel</td>
<td>1/752</td>
<td>0/236</td>
<td>1/516</td>
<td>0/720</td>
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<td>1/752</td>
<td>1/236</td>
<td>0/516</td>
<td>0/720</td>
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<td>1/234</td>
<td>1/514</td>
<td>0/720</td>
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<tr>
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<td>1/742</td>
<td>1/230</td>
<td>0/512</td>
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<tr>
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<td>0/236</td>
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<td>0/720</td>
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<tr>
<td>R1826C</td>
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<td>0/234</td>
<td>1/516</td>
<td>0/720</td>
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<tr>
<td>V1951M</td>
<td>Novel</td>
<td>1/748</td>
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<td>1/516</td>
<td>0/720</td>
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<td>Previously reported rare SCN5A variants</td>
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<td>2/516</td>
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<td>0/236</td>
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<td>7/720</td>
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<td>F2004L</td>
<td>Rare variant, SIDS</td>
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<td>0/236</td>
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<td>2/720</td>
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<tr>
<td>Previously reported common SCN5A variants</td>
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<td></td>
<td></td>
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<td>3/514</td>
<td>30/720</td>
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<td>H558R</td>
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<td>189/752</td>
<td>59/236</td>
<td>130/516</td>
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<tr>
<td>S1103Y</td>
<td>Common</td>
<td>5/750</td>
<td>1/236</td>
<td>4/514</td>
<td>15/720</td>
</tr>
</tbody>
</table>

The denominator refers to the No. of chromosomes that were successfully screened and is therefore twice the No. of patients.
Four of the 8 novel variants were identified in probands (AF 119, 240, 482 and 527) with early onset lone AF (age 36±14 years); 1 (AF 119) had undergone atrioventricular node ablation and pacemaker implantation for treatment of drug-refractory AF. In all 4 kindreds of these probands, AF cosegregated with the \( \text{SCN5A} \) variant, and the affected family members all had lone AF (age at diagnosis 38±16 years).

In the 4 other subjects with novel \( \text{SCN5A} \) variants (AF 100, 271, 406, and 529) AF was associated with underlying structural heart disease (dilated or hypertrophic cardiomyopathy, hypertension, or ischemic heart disease). In 1 kindred (AF 406), the proband had paroxysmal AF and nonobstructive hypertrophic cardiomyopathy, and the novel \( \text{SCN5A} \) mutation (V1951M) cosegregated with AF in his father, paternal grandmother, and 2 siblings. In another kindred, the proband developed late-onset persistent AF in the setting of dilated cardiomyopathy; in this subject, the baseline ECG showed a prolonged QTc (500 ms). The proband has a daughter with highly symptomatic paroxysmal AF. Although AF is clearly documented in the mother of proband 271, with no DNA available it is uncertain if she carries the R1826C variant. For AF kindred 529, no other affected family members have been identified.

Rare \( \text{SCN5A} \) Variants

Eleven previously reported rare \( \text{SCN5A} \) variants were also identified (Figure 3). Seven have been previously identified in subjects with congenital LQTS, BS, either LQTS or BS, or SIDS. The other rare variants that we identified have been observed at low minor allele frequencies (<0.5%) in populations of assumed healthy individuals. Six (46%) of the 13 probands with rare \( \text{SCN5A} \) variants reported an affected family member (≥2 affected individuals) and, as with the novel variants, analysis of the families revealed evidence of cosegregation of the gene variant with the phenotype in all 6 kindreds. This suggests that AF may also cosegregate with rare sodium channel variants.

Discussion

AF is the most common cardiac arrhythmia, affecting ~2% of the US population, and results in substantial morbidity and mortality. Evidence for the heritability of AF susceptibility has come from several sources including analysis of AF kindreds who exhibit the arrhythmia as a primary electrical disease, analysis of AF presenting in the setting of another familial disease, and analysis of genetic backgrounds that may predispose to AF.
Monogenic familial AF was first reported in 1943,\textsuperscript{42} and although it may be uncommon, no attempt has been made to determine the overall prevalence of familial AF. Analysis of Framingham data suggests a genetic susceptibility to AF based on the observation that parental AF increased the risk of AF in offspring.\textsuperscript{43} Other studies indicate that 5% of patients with AF and up to 15% of individuals with lone AF may have a familial form of the disease.\textsuperscript{6,32} Although a gene locus for AF was first reported in 1997,\textsuperscript{5} the gene responsible for AF in these kindreds has not yet been identified. A second locus for AF on the proximal long arm of chromosome 6 was reported in 2003.\textsuperscript{7} A third locus for AF has been identified on the distal short arm of chromosome 5 and is associated with conduction disease.\textsuperscript{11}

The voltage-gated cardiac sodium channel SCN5A conducts the inward sodium current ($I_{Na}$) that initiates the cardiac action potential. The SCN5A-mediated late sodium current also influences repolarization and refractoriness. Several diseases associated with ventricular conduction abnormalities have been associated with mutations in SCN5A, including LQTS and BS. In addition, recent studies have provided a link between SCN5A mutations and a syndrome of dilated cardiomyopathy and AF.\textsuperscript{25,26} In 1 study, a missense mutation was discovered in a large family with a variably expressed phenotype of dilated cardiomyopathy, AF, sinus node dysfunction, and conduction system disease. Additional SCN5A mutations were identified in 4 smaller dilated cardiomyopathy families, 3 of which also had AF. Among the 37 SCN5A mutation–carriers within these 5 families, 43% had documented AF. Each of the identified mutations was predicted to cause loss of cardiac sodium channel function. Although the mechanisms whereby some mutations produce AF and others generate ventricular phenotypes remains to be determined, a possible explanation for the phenotypic variability in sodium channel–linked disease may be related to chamber- or disease-specific interactions between the channel and its partners. The latter may be well-described proteins, such as sodium channel β-subunits, or entirely novel proteins.

We identified 8 novel SCN5A variants in the AF cohort. Because these 8 variants affect highly conserved residues, they are predicted to perturb cardiac sodium channel function. Our segregation analysis supports 6 of the novel SCN5A variants as being causative for AF. For the remaining 2 variants (T1131I, R1826C), the association is less conclusive because only the probands have so far been
shown to have AF. However, the absence of these variants in a large appropriately matched control population excludes the possibility that these mutations are common polymorphisms, a finding that is consistent with disease-associated mutations.

In contrast to our results reported here, a recent study failed to identify any SCN5A mutations in a cohort of 157 lone AF patients.27 Because AF is a genetically heterogeneous disorder, a possible explanation is that a larger sample size may be required to determine if SCN5A mutations can cause lone AF. It is also possible that the heteroduplex analysis used to identify mutations may have missed some SCN5A variants that were identified by direct resequencing, the approach we used. Finally, certain mutations in SCN5A may only cause syndromic AF (ie, in association with cardiomyopathies or other structural heart disease). Support for the latter explanation is provided by the results of our study, where half of the novel SCN5A variants were identified in patients with associated cardiac disease.

We also identified 11 previously reported rare SCN5A variants in the AF cohort. Interestingly, 5 of these variants have been previously identified in subjects with congenital LQTS (L618F and A572D),33–35 BS (R376H and E1053K),36,37,44 either LQTS or BS (R1193Q), 38–40 or SIDS (S216L, A997S, and F2004L).15,17 Although the remaining variants have been observed at low minor allele frequencies in populations of presumed healthy individuals, 3 alleles (S216L, F2004L) have recently been characterized after they were discovered in Norwegian SIDS victims.16 Importantly, however, 7 of these variants have been previously demonstrated to exhibit abnormal functional properties in heterologous expression experiments (S216L, R376H, L618F, A997S, E1053K, R1193Q, and F2004L).15,17

One conceptual model proposed for AF pathogenesis describes reduced atrial refractory period as a substrate for re-entrant arrhythmias.45 This model is supported by reports of gain-of-function mutations in genes that encode subunits of cardiac channels responsible for generating $I_{Ks}$ (KCNQ1/11

<table>
<thead>
<tr>
<th>Kindred ID</th>
<th>Phenotype</th>
<th>Genotype</th>
<th>Ethnicity</th>
<th>Age of Onset, y</th>
<th>Associated Conditions</th>
<th>ECG</th>
<th>LA and LV Size</th>
<th>EF (%)</th>
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<tr>
<td>AF100</td>
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<td>M138I</td>
<td>Black</td>
<td>64</td>
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<td>E428K</td>
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<td>LAE</td>
<td>58</td>
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<td>H445D</td>
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<td>Paroxysmal AF</td>
<td>R1826C</td>
<td>White</td>
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<td>CAD, Hypertension</td>
<td>Normal</td>
<td>LAE, LVH</td>
<td>60</td>
</tr>
<tr>
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<td>Paroxysmal AF</td>
<td>V1951M</td>
<td>White</td>
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<td>70</td>
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<tr>
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<td>Black</td>
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<td>SB</td>
<td>LAE, LVE</td>
<td>50</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; DCM, dilated cardiomyopathy; LAE, left atrial enlargement; LVE, left ventricular enlargement; LVH, left ventricular hypertrophy; and SB, sinus bradycardia.

Figure 3. Rare and disease-associated SCN5A variants in AF probands indicated by position within the sodium channel protein topology.
of disorders of the cardiac sodium channel to include AF and represent an important step in progress toward molecular phenotyping and thus directed rather than empirical therapy for this common and morbid condition.

Acknowledgments
We are grateful to Dr Dana Crawford for assistance with the statistical analyses. Data from this study have been deposited at the Pharmacogenetics Knowledge Base (www.pharmGKB.org).

Sources of Funding
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Disclosures
None.

References

Limitations
Several limitations of the present study warrant consideration. First, the AF kindreds are small and thereby segregation analysis was limited. Second, cost prevented us from comprehensively resequencing the population-based controls. Although it’s possible that additional novel SCN5A variants may have been identified, determining whether these rare genetic variants found in affected subjects are pathogenic remains a challenge. In familial arrhythmia syndromes, the absence of a nonsynonymous variant in an appropriately matched control population is often considered adequate evidence to label the variant a disease-causing mutation. The third limitation of this study relates to the paroxysmal nature and variable symptoms in AF, as well as the older age of onset in many individuals, all of which can make assignment of the clinical phenotype challenging.

In summary, we report that nearly 6% of AF probands carry heterozygous mutations or rare variants in the cardiac sodium channel. The variants affected highly conserved residues and were not present in a large control population. Furthermore, the variants cosegregated within the families with AF, providing strong support for the variants being functional and disease-associated. The findings of the present study expand the clinical spectrum of disorders of the cardiac sodium channel to include AF and represent an important step in progress toward molecular phenotyping and thus directed rather than empirical therapy for this common and morbid condition.

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References


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**CLINICAL PERSPECTIVE**

The human cardiac sodium channel is responsible for the fast depolarization upstroke of the cardiac action potential and is a molecular target for antiarrhythmic drugs, some of which are effective in treating atrial arrhythmias. Mutations in the human cardiac sodium channel gene (*SCN5A*) have been associated with inherited susceptibility to ventricular arrhythmias (eg, long-QT syndrome, Brugada syndrome, and sudden infant death syndrome), progressive cardiac conduction disorders, and more complex overlapping phenotypes. Although variants in *SCN5A* have been reported to occur in disorders that are sometimes associated with atrial fibrillation (AF), no studies have appeared that have systematically evaluated the prevalence of *SCN5A* variants in a cohort of patients with AF. To address this question, we resequenced the entire *SCN5A* coding region in 375 subjects with either lone AF (n = 118) or AF associated with heart disease (n = 257). Controls (n = 360) from the same population were then genotyped for the presence of mutations or rare variants identified in the AF cases. In 10 probands (2.7%), 8 novel variants not found in the control population (0%; *P* = 0.001) were identified. All variants affect highly conserved residues in the SCN5A protein. In 6 families with >1 affected member, the novel variant cosegregated with AF. These data suggest that mutations in *SCN5A* may predispose patients with or without underlying heart disease to AF, expand the clinical spectrum of disorders of the cardiac sodium channel to include AF, and represent important progress toward molecular phenotyping and directed rather than empirical therapy for this common arrhythmia.
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Circulation. 2008;117:1927-1935; originally published online March 31, 2008; doi: 10.1161/CIRCULATIONAHA.107.757955

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