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Original Article

A novel gain-of-function mutation *SCN5A*-N470K associated with African American familial atrial fibrillation

Xinyu Cao[1,2], Faisal A Darbar[1], Xin Wu[1], Lu Zhang[1], Dawood Darbar[1,2,3,4], Liang Hong[1,2,3]

[1]Division of Cardiology, Department of Medicine, University of Illinois Chicago, Chicago, IL 60612, USA; [2]Department of Biomedical Engineering, University of Illinois Chicago, Chicago, IL 60612, USA; [3]Department of Physiology and Biophysics, University of Illinois Chicago, Chicago, IL 60612, USA; [4]Jesse Brown Veterans Administration, Chicago, IL 60612, USA

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Abstract: Objectives: The cardiac sodium channel Nav1.5, encoded by the *SCN5A* gene, is crucial for the generation and propagation of cardiac action potential. While SCN5A mutations have been linked to familial atrial fibrillation (AF), the functional impact of certain mutations remains unclear. This study aims to identify new *SCN5A* mutation associated with AF and investigate the mechanism of the mutation dysregulation of SCN5A channel function underlying AF. Methods: We identified a three-generation African American family with a history of familial AF. Functional characterization of an SCN5A mutation was performed using whole-cell patch-clamp recordings in HEK cells expressing the recombinant mutant channels. Results: The proband, along with his mother and maternal grandmother, all presented with early-onset symptomatic paroxysmal AF, which co-segregated with the *SCN5A*-N470K mutation. The N470K mutation exhibited different electrophysiological properties when compared to the wild-type channel. Functional evaluation of the *SCN5A*-N470K variant revealed an increased peak sodium current, a hyperpolarizing shift in the voltage-dependence of steady-state activation, and a depolarizing shift in voltage-dependent inactivation. Additionally, N470K mutation did not produce significantly larger persistent current. Conclusion: The *SCN5A*-N470K mutation represents a gain-of-function alteration characterized by increased peak sodium current, and enhanced window current defined by the overlap of voltage-dependent inactivation and activation curves. These changes may alter myocardial excitability or conduction, providing a plausible mechanism by which the *SCN5A*-N470K mutation increases susceptibility to AF in this African American family.

Keywords: Nav1.5, *SCN5A*, atrial fibrillation, gain-of-function, mutant

Introduction

Atrial fibrillation (AF) is the most prevalent clinically significant cardiac arrhythmia [1-3], presenting a substantial public health challenge worldwide [4]. It is associated with increased risks of cardiovascular mortality, all-cause mortality, stroke, heart failure, and dementia. The pathophysiology of AF is complex, often stemming from the heterogeneity of underlying molecular mechanisms and disruptions in cardiac ion channel function caused by genetic mutations [5].

The voltage-gated sodium channel Nav1.5, encoded by the *SCN5A* gene, plays a key role in the rapid depolarization phase of cardiac action potential duration (APD) in cardiomyocytes [6]. *SCN5A* mutations have been associated with inherited ventricular arrhythmia syndromes such as long QT syndrome, Brugada syndrome, and ventricular fibrillation, as well as impaired cardiac conduction disease and AF, highlighting the crucial role of the Nav1.5 channel in maintaining normal cardiac electrical activity. Dysfunction of the atrial Nav1.5, driven by genetic mutations, has been shown to alter the atrial APD in AF. *SCN5A* mutations associated with cardiac arrhythmias can be categorized into two types: gain-of-function mutations, which increase sodium influx by altering sodium channel gating, and loss-of-function mutations, which reduce *SCN5A* expression or lead to the production of defective channel proteins. Both mutations have been implicated in familial (early-onset) AF [7].

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There is growing evidence that some *SCN5A* mutations associated with early-onset AF are ethnic-specific. For instance, the R34C mutation in *SCN5A* is observed predominantly in African Americans, with over 80% of cases occurring within this population. Similarly, the S1103Y mutation in *SCN5A* has been detected exclusively in African American individuals (100% prevalence in African Americans). We previously identified the *SCN5A* variant N470K, which co-segregated with AF in an African American family [8]. Although genetic studies have provided significant insights into *SCN5A* mutations, the specific impact of certain race-specific mutations on AF remains unclear.

To understand the role of the *SCN5A*-N470K mutation in AF, we investigated its effects on Nav1.5 channel function. Our results revealed that the N470K mutation disrupted the sodium channel gating process and exhibited an enhanced window current. These findings indicate that *SCN5A*-N470K is a gain-of-function mutation associated with early-onset AF in African American patients.

Material and methods

Clinical evaluation of the familial AF kindred

We identified a three-generation African American family with a history of familial AF enrolled in a clinical-DNA biorepository. At enrollment, all participants underwent a detailed medical history and completed an atrial fibrillation symptom questionnaire after providing written informed consent under protocols approved by the Institutional Review Boards of Vanderbilt University Medical Center and the University of Illinois Chicago. The research was approved by the University of Illinois Chicago Institutional Review Boards (No. STUDY2018-1299). We also perform comprehensive phenotyping of first-degree relatives of the proband or index cases as previously described. Utilizing the Resequencing and Genotyping Service supported by the National Heart, Lung, and Blood Institute (NHLBI), direct sequencing was performed on polymerase chain reaction (PCR)-amplified exons, with identified variants validated by resequencing an independently generated PCR amplicon from the participant.

Cell culture and transfection

The wild-type (WT) voltage-gated sodium channel Nav1.5 and the N470K mutant were expressed in HEK-293 cell lines (Sigma-Aldrich, St. Louis, USA). HEK cells were reseeded onto coverslips in six-well plates containing Dulbecco's modified Eagle's medium (Invitrogen), supplemented with 10% fetal bovine serum (FBS, Invitrogen), 100 U/mL penicillin, and 100 μg/mL streptomycin, and incubated at 37°C in a 5% CO_2 environment. The N470K single-point mutation in the pRc/CMV-hNav1.5 plasmid was introduced using standard PCR techniques. The PCR protocol involved an initial denaturation at 98°C for 1.5 minutes, followed by 25 cycles of amplification (98°C for 20 seconds, 60°C for 30 seconds, and 72°C for 5 minutes), with a final extension at 72°C for 15 minutes, and a subsequent hold at 4°C for 30 minutes. The template plasmid was digested with DpnI (NEB, R0176S), and the PCR product was used to transform Stbl2 competent cells (Invitrogen, 10268019). Plasmids were then isolated using the QIAprep Spin Miniprep Kit (Qiagen, 27106). After confirming the mutation by DNA sequencing, the plasmids containing cDNA encoding human Nav1.5 channels (pRc/CMV-hNav1.5) and green fluorescent protein (pIRES-GFP) were co-transfected into HEK-293 cells using Lipofectamine 3000, following the manufacturer's protocol. Patch-clamp experiments were performed 24-48 hours post-transfection, with transfected cells identified by the GFP fluorescence signal, which were used for electrophysiological measurements [9, 10].

Electrophysiologic measurements and analysis

Whole-cell patch-clamp recordings were performed using an Axopatch 200B amplifier and pClamp10 software, connected to an Axon Digidata 1440A system (all from Molecular Devices, USA). The extracellular solution comprised: 1 mM $MgCl_2$, 2 mM $CaCl_2$, 5 mM KCl, 10 mM HEPES, and 130 mM NaCl, with the pH adjusted to 7.4 using NaOH. The intracellular solution included: 2 mM EGTA, 5 mM HEPES, 15 mM CsCl, 20 mM NaCl, and 120 mM CsF, with the pH adjusted to 7.2 using CsOH. Electrophysiological recordings were conducted at 21 ± 3°C, using pipettes with a resistance of 4-5 MΩ. The steady-state activation (*G-V*) curve was fitted using the *Boltzmann* equation [11, 12]: $G/G_{max}=1/(1+exp(V-V_{1/2})/k)$, where $V_{1/2}$ is the potential of half activation, k is the *Boltzmann* coefficient, V is the test pulse, and G/G_{max} is the relative conductance normalized by the maximal conductance. Steady-state

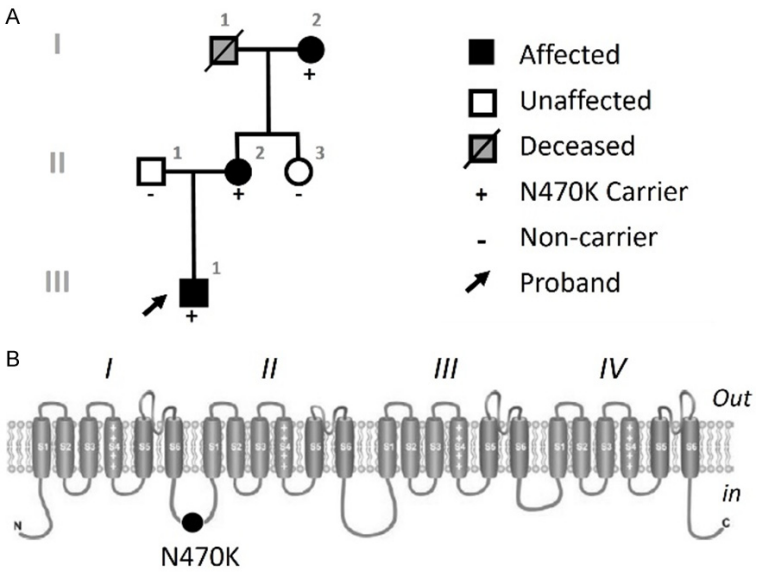

Figure 1. *SCN5A*-N470K Mutation Associated with AF in an African American Family. A. Pedigree of the family carrying the *SCN5A*-N470K mutation. Solid symbols represent individuals with AF, while open symbols indicate unaffected members. The presence (+) and absence (-) of the *SCN5A*-N470K mutation are noted for each family member. Squares represent males, and circles represent females. The black arrow points to the proband. B. Schematic representation of location of the *SCN5A*-N470K mutation in the cardiac $Na_v1.5$ sodium channel. The mutation is depicted as a black sphere.

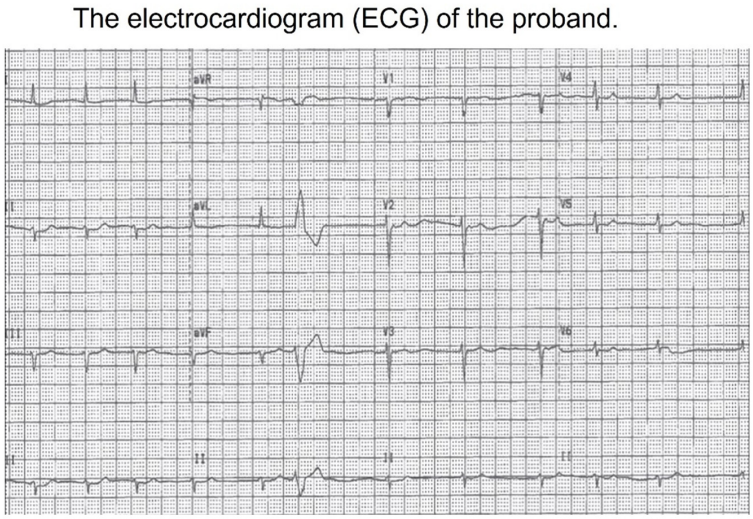

Figure 2. The electrocardiogram (ECG) recording from the proband. The ECG recording from the proband shows atrial fibrillation with controlled ventricular rates, despite the absence of atrioventricular (AV) nodal blockers, indicating the presence of a conduction disorder. The heart rate (HR) of the proband is 75 bpm, QRS duration is 88 ms, QTc interval is 420 ms.

inactivation was fitted by the *Boltzmann* equation: $I/I_{max}=1/(1+exp(V-V_{1/2})/k)$, where $V_{1/2}$ is half-maximal inactivation, k is the *Boltzmann* coefficient, V is the test pulse, and I/I_{max} is the relative conductance normalized by the maximal conductance.

Data and statistical analysis

All data are presented as the mean ± standard error of the mean (SEM). The "n" value represents the number of independent experiments performed. Statistical significance between groups was assessed using a two-tailed Student's t-test, with a *p*-value of less than 0.05 considered statistically significant.

Results

Clinical phenotype of the family and mutation detection

The proband (**Figure 1**, III:1) of African descent, harboring the *SCN5A*-N470K mutation, presented with symptomatic paroxysmal AF at 17 years of age. The initial presenting electrocardiogram (ECG) revealed AF with controlled ventricular rates in the absence of atrioventricular (AV) nodal blockers, suggesting an associated cardiac conduction disorder (**Figure 2**). He was started on low-dose AV nodal blockers until he underwent successful pulmonary vein isolation (PVI). The proband's mother (**Figure 1**, II:2) experienced symptomatic early-onset paroxysmal AF at 47 years of age and was initially treated with sotalol. However, she continued to experience symptomatic recurrences of AF and subsequently underwent a successful PVI. The maternal grandmother (**Figure 1**, I:2) presented with minimally symptomatic AF at 52 years of age. Due to severe left atrial enlargement, a rate-control strategy was chosen for management. The clinical characteristics of the African American familial AF kindred are summarized in

Table 1. Clinical characteristics of a familial atrial fibrillation (AF) kindred

Member	AF Phenotype	Age of onset	AF treatment	LA and LV size	EF (%)
III:1	Paroxysmal	17	Successful PVI	normal	60
II:2	Paroxysmal	47	Successful PVI	normal	60
I:2	Permanent	52	Rate control therapy; digoxin	LAE	55

PVI, pulmonary vein isolation; LA, left atria; LV, left ventricular; LAE, left atrial enlargement; EF, ejection fraction.

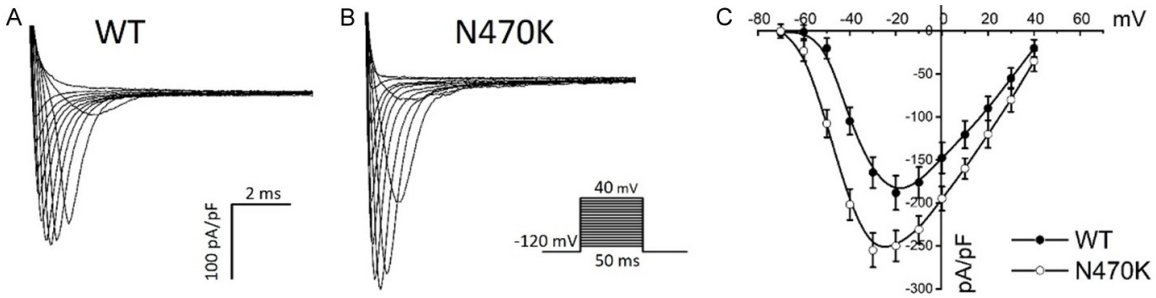

Figure 3. Currents of Nav1.5 Wild-Type (WT) and N470K Mutation Expressed in HEK293 Cells. (A, B) Representative current traces for WT (A) and N470K (B) channels; the experimental protocol is shown in the inset. Currents were recorded from a holding potential of -120 mV, with test potentials ranging from -100 to +40 mV in 10 mV increments. (C) Average current-voltage (I-V) relationships for WT and N470K channels. Filled circles represent WT, and open circles represent N470K mutation (n = 12 for WT, n = 10 for N470K). Data are presented as mean ± SEM.

Table 2. Biophysical properties of wild-type (WT) and *SCN5A*-N470K mutation channels

	WT	N470K
Steady-state Activation	(*n* = 12)	(*n* = 10)
$V_{1/2}$ (mV)	-39.1 ± 1.1	-43.5 ± 1.7*
Steady-state Inactivation	(*n* = 11)	(*n* = 11)
$V_{1/2}$ (mV)	-84.5 ± 2.3	-78.1 ± 1.3*
Current density (pA/pF)	(*n* =1 2)	(*n* = 10)
at -20 mV	-188.5 ± 19.9	-250.3 ± 18.4*

$V_{1/2}$, voltage of half-maximal (in)activation; *n* = number of tested cells; data are presented as the mean ± SEM. *$P < 0.05$.

Table 1. Resequencing of *SCN5A* revealed that the proband harbored a heterozygous 1410C>G variant, which co-segregated with AF in the family. The *SCN5A*-N470K variant results in the substitution of a highly conserved asparagine (N) with lysine (K) at position 470 in the *SCN5A* gene, located in the intracellular linker between domains I and II (**Figure 1**). The *SCN5A*-N470K variant was absent in unaffected family members.

Effects of N470K on sodium current amplitude

The biophysical properties of the *SCN5A*-N470K mutant channel were investigated using voltage-clamp recordings following the transient transfection of HEK cells with either wild-type (WT) or N470K channels. Whole-cell patch-clamp configuration was employed to measure sodium currents. Currents were recorded by holding the cells at a membrane potential of -120 mV and applying 50 ms test pulses at potentials ranging from -100 to +40 mV in 10 mV increments. The current-voltage (I-V) relationships were analyzed for WT and N470K channels. The N470K mutation exhibited a significantly higher sodium current density compared to WT channels, with the peak sodium current density of -250.3 ± 18.4 pA/pF for N470K and -188.5 ± 19.9 pA/pF for WT (**Figure 3**; **Table 2**). This increase in peak sodium current density suggests that the N470K mutation enhances Nav1.5 sodium channel function.

Effects of N470K on sodium channel gating process

We then investigated the impact of the N470K mutation on the gating properties of the Nav1.5 sodium channel. The N470K mutation disrupted the voltage dependence of both activation and steady-state inactivation of the channel. The $V_{1/2}$ of the voltage dependence of activa-

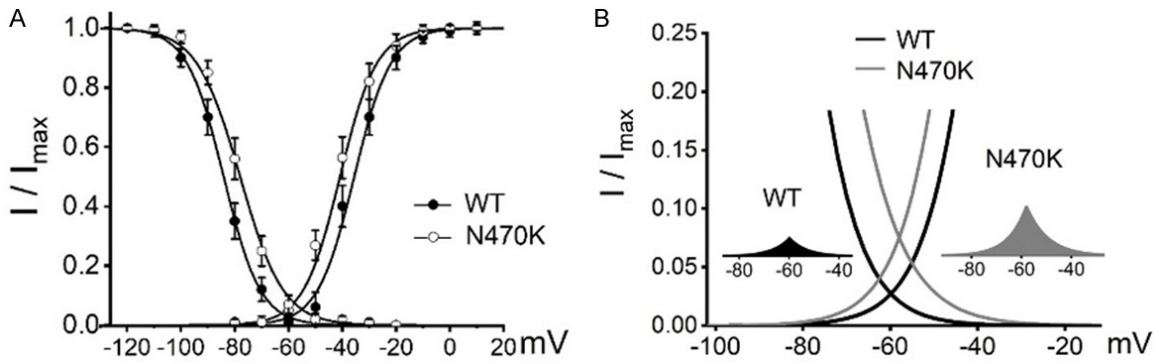

Figure 4. Effects of N470K mutation on Nav1.5 channel gating process. (A) Voltage dependence of activation and steady-state inactivation for WT and N470K channels. Inactivation currents were elicited by stepping to -20 mV following prepulses from -120 to -20 mV in 10 mV increments for 500 ms. Activation currents were recorded from a holding potential of -120 mV with test potentials ranging from -100 to +40 mV in 10 mV steps. The curves represent Boltzmann fits of the data points. (B) An expanded view of the overlapping area between activation and steady-state inactivation from (A). The left inset shows the sodium window current for the WT Nav1.5 channel (black), while the right inset shows the sodium window current for the N470K mutation (gray).

tion is -43.5 ± 1.7 mV in N470K, compared to -39.1 ± 1.1 mV in the WT channel, indicating that N470K caused a leftward (hyperpolarization) shift in the voltage dependence of activation. Additionally, the $V_{1/2}$ of the steady-state inactivation is -78.1 ± 1.3 mV in N470K, compared to -84.5 ± 2.3 mV in the WT channel, indicating that N470K caused a rightward (depolarization) shift in the steady-state inactivation. These results suggest that the N470K mutation causes a hyperpolarizing shift in activation and a depolarizing shift in inactivation of the SCN5A channel (**Figure 4**). This combination of a leftward shift in activation and a rightward shift in steady-state inactivation creates an overlap between the activation and inactivation curves, resulting in an enhanced "window current" compared to the WT channel (**Figure 4**). This alteration suggests a "gain-of-function" effect, with increased channel availability in the N470K mutant. The increased channel availability might either prolong atrial APD, inducing early afterdepolarizations, or increase sodium ion entry during atrial diastole, promoting delayed afterdepolarizations trigger AF.

Effects of N470K on sodium channel late sodium current

The "gain-of-function" effect observed in the N470K mutation is not only attributed to increased window current and peak sodium current but may also involve persistent late sodium current. To investigate whether the N470K variant enhances late sodium current, we recorded sodium currents by depolarizing the membrane to -20 mV in both N470K and WT channels from a holding potential of -120 mV. The results showed that the N470K mutant did not produce a significantly larger persistent current compared to the WT channel (**Figure 5**), indicating that the N470K mutation does not enhance the late sodium current in the Nav1.5 channel.

Discussion

We have identified and characterized a novel gain-of-function mutation in the SCN5A sodium channel, N470K, which is associated with familial AF in an African American family. The N470K mutation induced a significant shift in the voltage-dependence of steady-state inactivation towards positive potentials and voltage-dependent activation towards negative potentials. This shift resulted in an increased window current determined by the overlap of the inactivation and activation curves. We postulate that the enhanced window current may alter excitability or conduction in myocardial tissue, providing a plausible mechanism by which the *SCN5A*-N470K mutation increases susceptibility to AF in the African American kindred.

The voltage-gated sodium channel family consists of nine members, designated as Nav1.1 through Nav1.9. Among these, Nav1.5 is the cardiac-specific isoform, commonly known as the cardiac sodium channel. Sodium channel dysfunction has been linked with diseases [13-

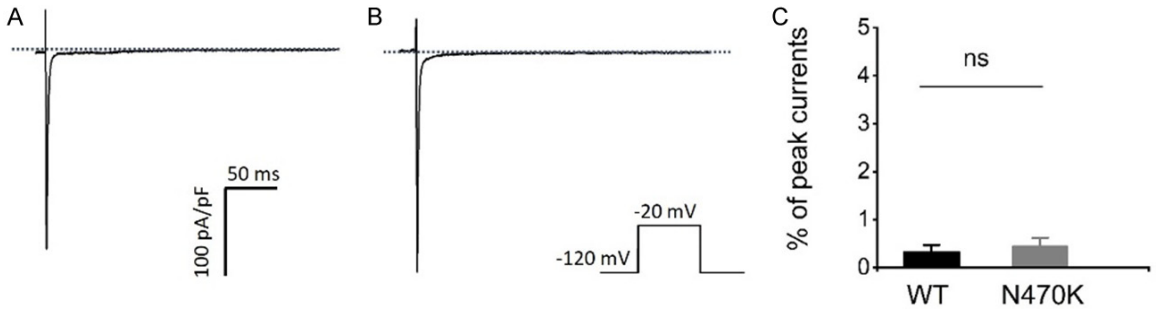

Figure 5. The N470K mutation does not exhibit substantial late sodium currents. (A, B) Representative sodium current traces recorded in WT (A) and N470K (B) channels. Currents were activated by depolarizing to -20 mV from a holding potential of -120 mV. The dashed line indicates 0 pA. (C) N470K mutation channels show no evidence of persistent inward sodium currents. Data are presented as mean ± SEM. "ns" denotes non-significant.

16]. The primary function of Nav1.5 is to facilitate the influx of sodium ions into myocytes from the extracellular side, generating an inward sodium current (known as I_{Na}). This current is essential for the depolarization of atrial, ventricular, and Purkinje myocytes, playing a critical role in the maintenance and rapid propagation of electrical impulses in cardiomyocytes [17]. Structurally, the Nav1.5 channel consists of an intracellular N-terminus, an intracellular C-terminus, and four homologous domains (DI to DIV). Each domain contains six transmembrane segments (S1 to S6) connected by extracellular and intracellular loops. The four functional domains collectively form an ion-conducting pore, with extracellular loops between segments S5 and S6 lining the pore, which is crucial for ion selectivity and permeation.

During the depolarization phase of the action potential (phase 0) in cardiomyocytes, electrical impulses trigger the outward movement of the positively charged S4 segments, leading to fast activation of the sodium channel and allowing a rapid influx of sodium ions into the cell. This is followed by channel inactivation, which occurs in two distinct states: fast and slow inactivation. Fast inactivation occurs when the intracellular pore is blocked by an "inactivation gate" formed by the cytoplasmic linker between domains III and IV (DIII-IV linker). Key regions involved in fast inactivation within Nav1.5 include isoleucine, phenylalanine, and methionine in the intracellular DIII-IV linker. In contrast, slow inactivation is linked to conformational changes in the channel's selectivity filter, lined by residues in the extracellular loops (P-loops) between segments S5 and S6 of the DI, DII, DIII, and DIV domains [18].

The Nav1.5 sodium channel is encoded by the *SCN5A* gene, which consists of 28 exons. Mutations in *SCN5A* can impair the expression or function of the Nav1.5 channel, leading to a range of clinical conditions. These genetic variations, known as pathogenic or disease-causing mutations, are linked to several disorders, including AF, long QT syndrome (LQTS), Brugada syndrome (BrS), sick sinus syndrome, dilated cardiomyopathy, and idiopathic ventricular fibrillation. Since the *SCN5A* gene was cloned in 1992, extensive research has provided valuable insights into the role of *SCN5A* mutations in cardiac arrhythmia.

AF is the most common cardiac arrhythmia in clinical practice, affecting over 30 million people worldwide. It significantly increases the risk of heart failure, stroke, and death [4]. Our group and others have demonstrated that genetic susceptibility to AF varies across racial and ethnic groups [19-21]. Recent clinical studies have highlighted the importance of race-ethnicity-associated genetic backgrounds in these populations [22-24]. For instance, the *SCN5A* mutations R34C and S1103Y have been predominantly observed in African American patients [25, 26], the V1951L mutation is more common in Hispanics, and the R1193Q and P1090L mutations are found exclusively in Asian populations [27]. We have identified rare variants linked with AF, including N470K, as African American ethnic-specific mutation [8].

Although genetic and epidemiological research has provided significant insights into *SCN5A*

variants and their association with AF across racial and ethnic groups, the roles of some race-specific polymorphisms in AF remains unclear. Mutations in *SCN5A* are linked to inherited arrhythmias, and both gain-of-function and loss-of-function mechanisms have been proposed to explain how these mutations contribute to cardiac arrhythmias [7]. For example, gain-of-function mutations in *SCN5A* have been reported to cause LQT3 [28], while loss-of-function mutations are associated with BrS [29]. AF can also manifest as a familial condition, particularly in younger individuals, with both loss-of-function and gain-of-function mutations in *SCN5A* being linked to hereditary AF [30, 31].

Loss-of-function mutations in *SCN5A* are postulated to increase the risk of AF by slowing intra-atrial conduction, a hypothesis supported by the high incidence of AF. The reduction in channel function may result from decreased peak Na^+ current, altered gating properties, disruptions in channel trafficking to the cell membrane, or the formation of nonfunctional channels at the membrane. Boddum et al. reported a loss-of-function *SCN5A*-I1343V mutation in a patient with persistent AF [32]. *In vitro* electrophysiological studies demonstrated that the I1343V mutation caused a reduced peak Na^+ current without altering inactivation kinetics compared to the WT, confirming a loss-of-function in the channel. The diminished Na^+ inward current could delay the upstroke of the action potential, potentially slowing conduction and contributing to the development of AF [32].

Gain-of-function mutations in *SCN5A* are believed to promote AF by increasing atrial myocyte excitability. This can occur through two primary mechanisms: 1) prolongation of the APD, which may lead to early afterdepolarizations; 2) enhanced Na^+ entry into atrial cardiomyocytes during diastole, which can cause delayed afterdepolarizations. These mechanisms may also account for the increased risk of AF observed in individuals with LQT3. Makiyama et al. reported that the *SCN5A*-M1875T gain-of-function mutation in AF patients exhibited a depolarized shift in the voltage dependence of steady-state inactivation [30]. Similar biophysical defects were observed in another gain-of-function mutation, *SCN5A*-K1493R [33].

In the present study, we characterized the *SCN5A*-N470K variant as a gain-of-function mutation linked with familial AF. The N470K mutation caused a depolarized shift in the voltage dependence of steady-state inactivation, similar to the effects observed with the *SCN5A*-M1875T and *SCN5A*-K1493R mutations, and also induced a hyperpolarized shift in voltage-dependent activation. This combination of shifts in activation and inactivation resulted in an overlap of the activation and inactivation curves, leading to an enhanced "window current" and increased sodium channel availability. The depolarized shift in steady-state inactivation disrupted the channel's transition to the inactive state, increasing the availability of sodium channels for opening. Additionally, the hyperpolarized shift in voltage-dependent activation facilitated channel opening, significantly increasing the open probability of the channel. These changes enhanced the overall function of the channel. The increased peak sodium currents observed in the N470K variant could lead to greater Na^+ influx into cardiomyocytes. Although the N470K mutation did not produce persistent sodium currents, it demonstrated a typical gain-of-function effect on the cardiac Nav1.5 channel. This included an increase in peak Na^+ current density, a significant depolarizing shift in steady-state inactivation, and a hyperpolarizing shift in voltage-dependent activation, all of which enhanced window currents and increased channel availability. The elevated peak Na^+ currents in the N470K mutant may result in repolarization failure or early afterdepolarizations, potentially triggering abnormal electrical activity. Furthermore, the increased channel availability could enhance conduction velocity and support the propagation of fibrillation waves.

Moreover, HEK cells are heterologous expression system to study the function of ion channels. Although heterologous expression approaches have provided insights into the pathophysiology of AF, their direct clinical impact has been limited. This is partly because these *in vitro* methods for characterizing ion channel mutation cannot fully capture the broad spectrum of changes associated with AF mutations. There is growing interest in developing patient-specific cellular disease models using human induced pluripotent stem cells (hiPSCs). This approach enables the generation of patient-derived hiPSC lines, their differentiation into specific cardiac cell types, and the replication

of the electrophysiological characteristics of functional human cardiomyocytes (CMs). The human iPSC-derived atrial cardiomyocytes (atrial iPSC-CMs) provides unique advantages by overcoming limitations of heterologous *in vitro* currently available to assess the genetic causes of AF. Future studies are required to use this model to identify underlying AF mechanisms of the N470K mutation.

Conclusions

We have identified a novel gain-of-function mutation in *SCN5A* in an African American family with familial AF. Our findings provide important insights into the mechanisms by which *SCN5A* mutations cause arrhythmias and highlight the significance of *SCN5A* variants across ethnic and racial differences in AF.

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Disclosure of conflict of interest

None.

Address correspondence to: Dawood Darbar and Liang Hong, Division of Cardiology, Department of Medicine, University of Illinois at Chicago, Chicago, IL 60612, USA. E-mail: darbar@uic.edu (DD); hong2004@uic.edu (LH)

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