Published in final edited form as:

Heart Rhythm. 2008 October ; 5(10): 1441–1443. doi:10.1016/j.hrthm.2008.08.008.

Cardiac Sodium Channel Variants: Action Players with Many Faces

Dawood Darbar, M.D.

Divisions of Cardiovascular Medicine and Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville, TN

The Cardiac Sodium Channel

The cardiac voltage-dependent sodium channel, *SCN5A*, conducts the inward sodium current (I_{Na}) that initiates the cardiac action potential and is a molecular target for antiarrhythmic drugs, many of which are effective in treating atrial fibrillation (AF). Mutations in *SCN5A*, which encode the α -subunit of human cardiac Na^+ channels, have been associated with inherited susceptibility to ventricular arrhythmias (long QT syndrome [LQTS], Brugada syndrome or idiopathic ventricular fibrillation),^{1–3} impaired cardiac conduction disease,^{4–6} and more complex overlapping phenotypes.^{7,8} Furthermore, subclinical expression of *SCN5A* mutations may also manifest as drug-induced arrhythmias^{9,10} and other forms of arrhythmia susceptibility in certain populations.^{11,12} Apart from these discoveries, there has been tremendous progress in defining the functional consequences of *SCN5A* mutations and relating specific biophysical defects to abnormal cardiac excitability. Much of this work has exploited heterologous expression of recombinant human cardiac sodium channels and cellular electrophysiological approaches. These revelations have greatly enhanced our understanding of the molecular genetics and pathophysiology of inherited and acquired cardiac arrhythmia syndromes. Although there have been extraordinary advances in this field, there remain new frontiers for exploring the role of *SCN5A* mutations in rare and more common forms of heart disease such as AF.

AF Genetics

Most AF is considered secondary to other conditions; however, up to 30% of patients have no obvious cause and are said to have idiopathic or “lone” AF. Clinical and basic investigation suggests that the mechanisms underlying AF are heterogeneous, with multiple factors contributing to the initiation or to the maintenance of the arrhythmia. There is increasing support for a prominent familial component to AF, and a number of loci that confer increased vulnerability to AF have been described.^{13–15} In addition, mutations in genes encoding cardiac potassium channels (*KCNQ1*, *KCNE2*, *KCNJ2* and *KCNA5*) have been reported in isolated cases and small kindreds.¹⁶ Thus far, familial AF has been linked to mutations in potassium channels that are predicted to either shorten or lengthen the duration of the cardiac action potential.¹⁷ However, a recent report has identified a novel molecular genetic basis for AF with the identification of a novel mutation in the natriuretic peptide precursor A gene (*NPPA*), which encodes atrial natriuretic peptide (ANP).¹⁸ This mutation segregated with

Correspondence/Reprints: Dawood Darbar, M.D., Vanderbilt University School of Medicine, 2215B Garland Avenue, Room 1285A, MRB IV, Nashville, TN 37232, Tel: 615-322-0067, Fax: 615-343-4522, E-mail: dawood.darbar@vanderbilt.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

familial AF, thereby uncovering an unexpected association between a defect in a circulating hormone and susceptibility to AF.

SCN5A as a Candidate Gene for AF

Recent studies have suggested a link between a syndrome of dilated cardiomyopathy (DCM) and AF.^{19, 20} A missense mutation was discovered in a large, multigenerational family with a variably expressed phenotype of DCM, AF, sinus node dysfunction, and conduction system disease. Additional *SCN5A* mutations were identified in four smaller DCM families, three of which also had AF. Among the 37 *SCN5A* mutation-carriers within these five families, 43% had documented AF. Each of the identified mutations was predicted to cause loss of cardiac sodium channel function. One frameshift mutation and two previously characterized alleles (T220I, D1275N) were predicted to cause loss of cardiac sodium channel function. Importantly, patients with Brugada syndrome caused by *SCN5A* loss-of-function mutations have also been shown to have an increased incidence of AF, ranging from 20% to 39%.^{21, 22} Consistent with a loss of sodium channel function, these patients had slower atrioventricular (AV) conduction, longer atrio-His and His-Ventricular intervals and longer refractory period of the AV node compared to normal controls.²¹ Thus, it is possible that certain *SCN5A* mutations may give rise to AF in the atrium and a cardiomyopathy phenotype in the ventricle, supporting the notion that ventricular and atrial tachyarrhythmias associated with *SCN5A* mutations may be allelic disorders.^{23, 24} Taken together, these studies provide a compelling rationale for *SCN5A* as a candidate gene for AF.

SCN5A Mutations and Familial AF

We recently resequenced the entire *SCN5A* coding region in 375 subjects with either lone AF or AF associated with heart disease and identified heterozygous mutations or rare variants in nearly 6% of AF probands.²⁵ The variants identified affected highly conserved residues and were not present in a large control population. Additional compelling data supporting the association of *SCN5A* variants with AF were cosegregation of the variants within the families with AF. Further support for the role of the sodium channel in the pathophysiology of AF comes from a recent study by Ellinor et al.²⁶ who identified a novel *SCN5A* mutation (N1986K) associated with the arrhythmia in an AF kindred. Functional characterization of the mutant channels revealed a hyperpolarizing shift in channel steady-state inactivation, indicating a loss-of-function type modulation. One of the affected family members underwent implantation of pacemaker due to sick sinus syndrome, suggesting the underlying conduction disturbance may be related to loss-of-function of cardiac sodium channels.

In this issue of *Heart Rhythm*, Benito et al.²⁷ identified a 3-generation family with manifest long QT intervals due to a gain-of-function mutation (Y1795C) in *SCN5A*. Interestingly, three of the adults in this family also displayed early onset paroxysmal lone AF. A flecainide challenge in two of the affected family members demonstrated not only shortening of the QT interval but also termination of AF. Although atrial arrhythmias are rare in patients with LQTS, except for LQTS4,²⁸ a recent report has shown that early-onset AF was observed in almost 2% of patients with genetically proven LQTS.²⁹ Thus, the presence of AF in LQTS may not be unexpected but Benito et al show for the first time that a gain-of-function mutation in *SCN5A* can give rise to a mixed phenotype of LQTS and AF. Furthermore, an understanding of the molecular mechanism of the underlying genetic lesion gives rise to the possibility of molecular phenotyping and directed rather than empiric therapy for AF. Thus, Benito et al have added lone AF due to *SCN5A* gain-of-function mutations to the expanding clinical spectrum of sodium channel related cardiac phenotypes.

Even though the fundamental mechanism of each disorder may differ considerably, considerable phenotypic overlap exists, including kindreds with both the LQTS and Brugada

syndrome, those with both Brugada syndrome and conduction system disease and now LQTS and AF. One 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. Indeed, our group has recently shown that mutations in the sodium channel β -subunits are also associated with AF.³⁰

AF reported by Benito et al may well arise from increased action potential duration and early afterdepolarizations (EADs) in atrial cells, a mechanism that has been previously postulated.³¹ We must, however, keep an open mind with respect to potential mechanisms. For example, recent work implicates ion channels as participants in macromolecular signaling complexes that regulate myocyte differentiation through coupling with downstream intracellular partners or even through direct transcriptional effects.³²

Conclusions

Recent studies have provided evidence of a genetic contribution to AF. Mutations in genes that encode for cardiac ion channels have been associated with familial AF. In addition, a number of loci that confer increased vulnerability to AF have been described. The prevailing conceptual model proposed for AF pathogenesis describes reduced atrial refractory period as a substrate for re-entrant arrhythmias. This is supported by reports of gain-of-function mutations in genes encoding subunits of cardiac potassium channels responsible for generating I_{Ks} (*KCNQ1/KCNE2*) and I_{K1} (*KCNJ2*) and these are predicted to decrease action potential duration. Such understanding provides a therapeutic rationale for prolonging the atrial refractory period. In contrast, Benito et al describe a *SCN5A* gain-of-function mutation in family with a mixed phenotype of LQTS3 and familial lone AF. As this mutation translates into action potential prolongation, a sodium channel blocker would be an appropriate mechanism-based therapy for AF in this family. Although a unifying effect of the AF-associated potassium and sodium channel variants on membrane conductance is unlikely, an improved understanding of the pathogenesis of AF is a critical step in a path to targeted rather than empiric therapy for this common and morbid condition.

Acknowledgements

This work was supported in part by NIH grants HL75266 and U01 HL65962.

References

1. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 1998;392:293–296. [PubMed: 9521325]
2. Wang Q, Shen J, Li Z, et al. Cardiac sodium channel mutations in patients with long QT syndrome, an inherited cardiac arrhythmia. *Hum Mol Genet* 1995;4:1603–1607. [PubMed: 8541846]
3. Wang Q, Shen J, Splawski I, et al. *SCN5A* mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* 1995;80:805–811. [PubMed: 7889574]
4. Schott JJ, Alshinawi C, Kyndt F, et al. Cardiac conduction defects associate with mutations in *SCN5A*. *Nat Genet* 1999;23:20–21. [PubMed: 10471492]
5. Tan HL, Bink-Boelkens MT, Bezzina CR, et al. A sodium-channel mutation causes isolated cardiac conduction disease. *Nature* 2001;409:1043–1047. [PubMed: 11234013]
6. Wang DW, Viswanathan PC, Balser JR, et al. Clinical, genetic, and biophysical characterization of *SCN5A* mutations associated with atrioventricular conduction block. *Circulation* 2002;105:341–346. [PubMed: 11804990]
7. Bezzina C, Veldkamp MW, van Den Berg MP, et al. A single Na(+) channel mutation causing both long-QT and Brugada syndromes. *Circ Res* 1999;85:1206–1213. [PubMed: 10590249]

8. Grant AO, Carboni MP, Neplioueva V, et al. Long QT syndrome, Brugada syndrome, and conduction system disease are linked to a single sodium channel mutation. *J Clin Invest* 2002;110:1201–1209. [PubMed: 12393856]
9. Makita N, Horie M, Nakamura T, et al. Drug-induced long-QT syndrome associated with a subclinical SCN5A mutation. *Circulation* 2002;106:1269–1274. [PubMed: 12208804]
10. Liu K, Yang T, Viswanathan PC, et al. New mechanism contributing to drug-induced arrhythmia: rescue of a misprocessed LQT3 mutant. *Circulation* 2005;112:3239–3246. [PubMed: 16301357]
11. Splawski I, Timothy KW, Tateyama M, et al. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. *Science* 2002;297:1333–1336. [PubMed: 12193783]
12. Plant LD, Bowers PN, Liu Q, et al. A common cardiac sodium channel variant associated with sudden infant death in African Americans, SCN5A S1103Y. *J Clin Invest* 2006;116:430–435. [PubMed: 16453024]
13. Brugada R, Tapscott T, Czernuszewicz GZ, et al. Identification of a genetic locus for familial atrial fibrillation. *N Engl J Med* 1997;336:905–911. [PubMed: 9070470]
14. Ellinor PT, Shin JT, Moore RK, et al. Locus for atrial fibrillation maps to chromosome 6q14–16. *Circulation* 2003;107:2880–2883. [PubMed: 12782570]
15. Darbar D, Hardy A, Haines JL, et al. Prolonged signal-averaged P-wave duration as an intermediate phenotype for familial atrial fibrillation. *J Am Coll Cardiol* 2008;51:1083–1089. [PubMed: 18342226]
16. Darbar D. Genetics of atrial fibrillation: Rare mutations, common polymorphisms, and clinical relevance. *Heart Rhythm* 2008;5:483–486. [PubMed: 18313611]
17. Fatkin D, Otway R, Vandenberg JL. Genes and atrial fibrillation: a new look at an old problem. *Circulation* 2007;116:782–792. [PubMed: 17698744]
18. Hodgson-Zingman DM, Karst ML, Zingman LV, et al. Atrial natriuretic peptide frameshift mutation in familial atrial fibrillation. *N Engl J Med* 2008;359:158–165. [PubMed: 18614783]
19. McNair WP, Ku L, Taylor MR, et al. SCN5A mutation associated with dilated cardiomyopathy, conduction disorder, and arrhythmia. *Circulation* 2004;110:2163–2167. [PubMed: 15466643]
20. Olson TM, Michels VV, Ballew JD, et al. Sodium channel mutations and susceptibility to heart failure and atrial fibrillation. *JAMA* 2005;293:447–454. [PubMed: 15671429]
21. Morita H, Kusano-Fukushima K, Nagase S, et al. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. *J Am Coll Cardiol* 2002;40:1437–1444. [PubMed: 12392834]
22. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada Syndrome. Report of the Second Consensus Conference. Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005;117:17.
23. Chen YH, Xu SJ, Bendahhou S, et al. KCNQ1 gain-of-function mutation in familial atrial fibrillation. *Science* 2003;299:251–254. [PubMed: 12522251]
24. Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nat Genet* 1996;12:17–23. [PubMed: 8528244]
25. Darbar D, Kannankeril PJ, Donahue BS, et al. Cardiac sodium channel (SCN5A) variants associated with atrial fibrillation. *Circulation* 2008;117:1927–1935. [PubMed: 18378609]
26. Ellinor PT, Nam EG, Shea MA, et al. Cardiac sodium channel mutation in atrial fibrillation. *Heart Rhythm* 2008;5:99–105. [PubMed: 18088563]
27. Benito B, Brugada R, Perich RM, et al. A mutation in the sodium channel is responsible for the association of long QT syndrome and familial atrial fibrillation. *Heart Rhythm*. In press
28. Mohler PJ, Schott JJ, Gramolini AO, et al. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. *Nature* 2003;421:634–639. [PubMed: 12571597]
29. Johnson JN, Tester DJ, Perry J, et al. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. *Heart Rhythm* 2008;5:704–709. [PubMed: 18452873]
30. Watanabe H, Darbar D, Ingram CR, et al. Loss of function mutations in sodium channel beta subunits associated with atrial fibrillation and ST-segment elevation. *Circulation* 2007;116(16):S11-54.abstract
31. Satoh T, Zipes DP. Cesium-induced atrial tachycardia degenerating into atrial fibrillation in dogs: atrial torsades de pointes? *J Cardiovasc Electrophysiol* 1998;9:970–975. [PubMed: 9786077]

32. Gomez-Ospina N, Tsuruta F, Barreto-Chang O, et al. The C terminus of the L-type voltage-gated calcium channel Ca_v1.2 encodes a transcription factor. *Cell* 2006;127:591–606. [PubMed: 17081980]