A mutation in the sodium channel is responsible for the association of long QT syndrome and familial atrial fibrillation

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BACKGROUND Type 3 long-QT syndrome (LQT-3) is caused by gain-of-function mutations in the SCN5A encoding the cardiac sodium channel. Familial atrial fibrillation (AF), previously considered a potassium channelopathy, has recently been related to sodium genetic variants, both in isolated forms and in patients with underlying heart disease.

OBJECTIVE The purpose of this study was to describe the first family associating LQT-3 and AF due to a gain-of-function mutation in SCN5A and assess the usefulness of the sodium blocker flecainide in individuals with both phenotypes.

METHODS Complete family screening was performed after identifying a proband showing paroxysmal AF and a long QT interval suggestive of LQT-3. Secondary causes of AF were ruled out in all individuals. Flecainide was used in two patients for LQT-3 diagnosis and therapeutic treatment of AF. Genetic screening was performed by direct sequencing of the exons and exon-intron boundaries of SCN5A.

RESULTS We identified a three-generation family (eight members), all of them showing long QT intervals. Paroxysmal AF initiated between 20 and 35 years of age in all three adults. The flecainide test led to shortening of the QTc interval. Flecainide was also effective in acutely restoring sinus rhythm. A Y1795C mutation was identified in all members.

CONCLUSION This is the first report showing an association of familial AF and LQT-3 due to a mutation in SCN5A. This finding provides further evidence of the role of SCN5A in AF. We also confirm the usefulness of flecainide in this particular complex phenotype, both as a diagnostic tool for LQT-3 and as an acute treatment for AF.

KEYWORDS Long-QT syndrome; Atrial fibrillation; Genetics; Sodium channel; Channelopathies

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Introduction

Congenital long-QT syndrome (LQTS) is a disorder characterized by prolonged QT interval on the electrocardiogram (ECG) and susceptibility to develop torsades de pointes ventricular tachycardia, which can lead to syncope or sudden death.[1] Among the different forms of LQTS, types 1, 2, and 3 (LQT-1, LQT-2, and LQT-3) are the most common in clinical practice, accounting for 85%–95% of cases.[2,3] Unlike LQT-1 and LQT-2, both loss-of-function potassium channelopathies, LQT-3 is caused by gain-of-function mutations in SCN5A, the cardiac sodium-channel gene.[4] By one mechanism or another, the consequence in all cases is the prolongation of the action potential duration, which favors the occurrence of early afterdepolarizations, a trigger for torsades de pointes.[1]

Familial atrial fibrillation (AF) has been classically related to mutations leading either to a gain of function (genes KCNQ1,[5,6] KCNE2,[7] KCNJ2,[8] KCNH2[9]) or to a loss of function (gene KCNA5[10]) of potassium channels. In the former case, AF has been reported in association with the short-QT syndrome, given that both disorders would be a consequence of the same potassium defect at the atrial and ventricular levels.[6,9] However, in recent years, increasing evidence has pointed toward a role of the sodium channel in the pathophysiology of AF. First, the association of AF with known sodium channelopathies was described, both in patients with Brugada syndrome and in those with progressive cardiac conduction defect, in whom there is a higher prevalence of the atrial arrhythmia.[11–13] Likewise, a family with

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dilated cardiomyopathy and AF carrying a mutation in SCN5A was recently reported, suggesting that mutations in the sodium channel may also lead to AF in association with structural heart disease.[14] Finally, two very recent publications have demonstrated that SCN5A mutations are associated with AF, both in isolated forms[15,16] and in patients with underlying heart disease.[15]

In this report we describe what is, to the best of our knowledge, the first family that associates LQT-3 and AF. The causative mutation was Y1795C identified on the SCN5A gene encoding the cardiac sodium channel. Thus, we provide further evidence of the role of SCN5A in AF. We also describe the usefulness of the sodium blocker flecainide in this family, both as a diagnostic tool for the LQT-3 and as an acute treatment for AF.

Methods

Clinical evaluation

A proband presenting with paroxysmal AF and showing a long QT interval on the surface ECG was first identified. The patient was studied with complete clinical history, physical examination, 12-lead ECG, transthoracic echocardiogram, and 24-hour Holter monitoring. QT and corrected QT (QTc) intervals according to Bazett's formula were measured in lead II from the baseline 12-lead ECG, as described elsewhere.[2] Mean values of three consecutive beats were obtained. A prolonged QTc was defined as a QTc longer than 440 ms for men and 460 ms for women.

All available relatives were evaluated by a detailed clinical history, physical examination, ECG, and echocardiogram. In addition, four members older than 5 years underwent a stress test (conventional Bruce protocol) to evaluate QT adaptation to exercise-induced tachycardia. A 24-hour Holter monitoring was performed to assess changes in QTc during daytime and nighttime. For the stress test, measurements of QT and QTc were calculated from the average values of three cycles in lead II at baseline, first stage, second stage, maximum effort, and recovery, while in the Holter monitoring, QT and QTc were calculated from the mean of seven cycles during daytime (6 A.M.–10 P.M.) and nighttime (10 P.M.–6 A.M.). In members suffering from AF, known possible causes for secondary AF were ruled out. Finally, two of the adults underwent an electrophysiological (EP) study to evaluate inducibility of both atrial and ventricular arrhythmias.

Since LQT-3 was suspected on the basis of ECG morphology, two members (the proband and her son) underwent a flecainide test before genetic confirmation. The flecainide test was performed according to the standard regimen described to unmask Brugada syndrome, that is, a 10-bolus infusion of 15 mg each, administered at 1 minute intervals up to a maximum dose of 2 mg/kg of body weight.[17] Twelve-lead ECG recordings with measurements of QT and QTc intervals were obtained at baseline and at the end of the drug infusion.

Genetic analysis

The study was approved by the local Institutional Review Board. After providing informed written consent, all family members underwent blood extraction for genetic analysis. Genomic DNA was isolated from peripheral blood leuko-

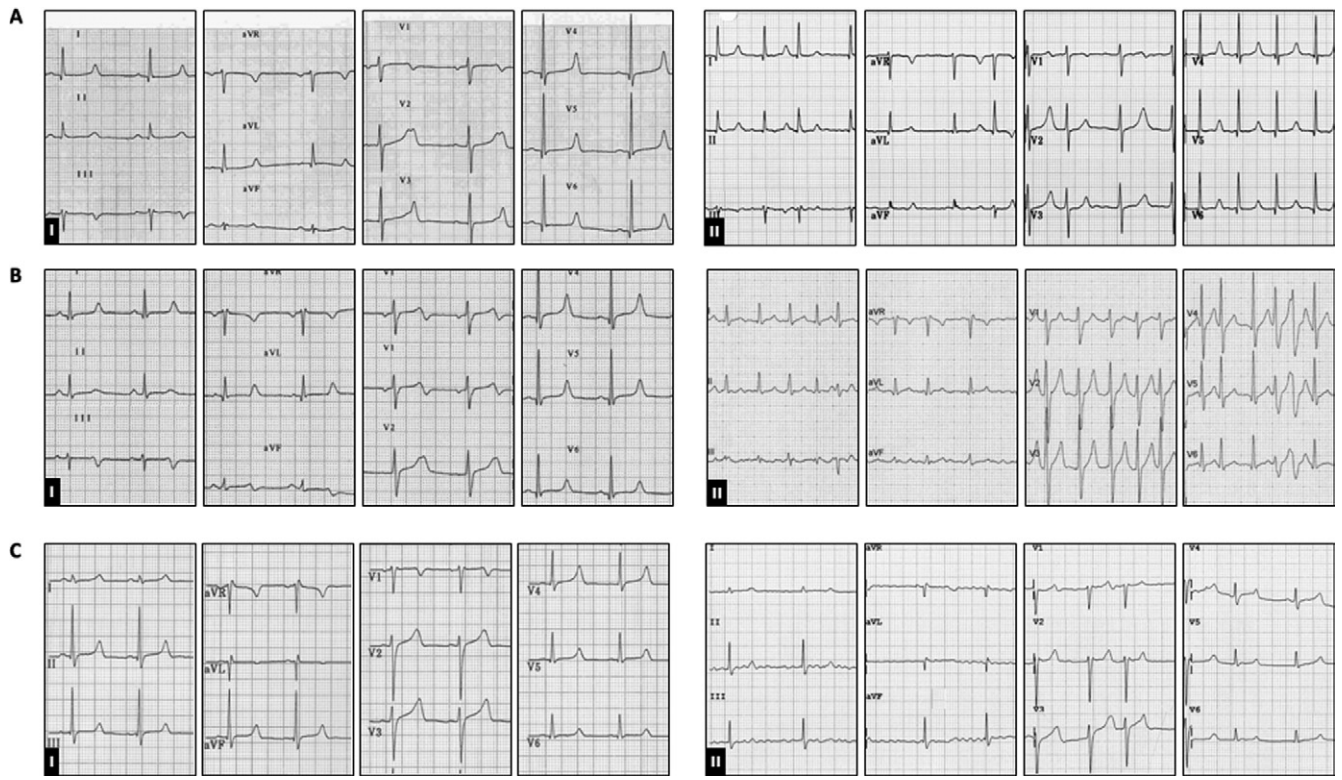

Figure 1 Surface ECGs of the three adult family members affected with LQTS and AF. Twelve-lead ECGs in sinus rhythm (I) and in AF (II) are shown.