Polymorphisms and atrial fibrillation: sorting the wheat from the chaff

Patrick T. Ellinor* and David J. Milan

Cardiovascular Research Center and Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston, MA 02114, USA

Online publish-ahead-of-print 28 February 2008

This editorial refers to ‘The non-synonymous coding Iκr-channel variant KCNH2-K897T is associated with atrial fibrillation: results from a systematic candidate gene-based analysis of KCNH2 (HERG)’ by M.F. Sinner et al., on page 907

In the last 5 years, we have gained an increasing appreciation for the genetic contribution to atrial fibrillation (AF). While Mendelian families with AF have been reported, they have typically been considered rare. Studies from Framingham and Iceland have demonstrated a genetic basis for AF in the general population. Family members of those with AF have an odds ratio of ~1.8 for developing the arrhythmia. This risk is considerably greater for younger patients and those with lone AF.

One approach to identify common genetic determinants of a disease in a population is to perform an association study between a single nucleotide polymorphism (SNP) and the condition of interest. Such a study can be performed using one to many hundreds of thousands of SNPs across the genome. In the case of AF, numerous prior associations have been reported between AF and variants in the cardiac sodium and potassium channels, gap junction proteins, and inflammatory markers, among others. However, the studies to date have generally been underpowered, have not been replicated, and have a low pre-test probability of the SNP actually causing AF.

Sinner et al. have described the relationship between the K897T SNP in KCNH2/HERG and AF in >1200 affected individuals and 2400 controls. Based on the well-known relationship between variation in KCNH2/HERG and ventricular repolarization, the authors hypothesized that this gene may also be associated with alterations in atrial repolarization, and thus AF. Starting with 40 SNPs across the KCNH2 gene, they determined the frequency of each SNP in 671 cases and 694 controls and found five associated with AF. These five SNPs were then analysed in an additional 531 cases with AF and 1781 control subjects, and one, the well-known K897T polymorphism, emerged. This SNP had an odds ratio of 1.25 (95% confidence interval (CI) 1.11–1.41, P = 3.3 x 10⁻⁴) with the 897K allele being associated with an increased risk of AF, while the 897T allele had a reduced risk. This association remained after correction for the age and sex of the subjects.

With such a large, well-powered cohort, these investigators have raised the standard for future association studies on AF. However, this study was subject to some limitations. It would have been interesting to know the relationship between AF and ventricular repolarization in this population; unfortunately electrocardiograms were unavailable from the control subjects. This study is also limited by the lack of information on other covariates associated with AF, such as congestive heart failure and hypertension. Further, all of the subjects in the study were of European descent so the results may not be applicable to other races and ethnicities. Finally, with an odds ratio of 1.25, this variant in KCNH2 has a relatively modest overall effect in the population, implying that additional genetic variants for AF remain to be identified.

What do we know of the K897T polymorphism? This SNP has a minor allele frequency of ~23% in Caucasians and is therefore common in the general population. As summarized in Table 1, it has been extensively studied for its role in ventricular repolarization. In 2002, Pietila and colleagues described the association between the QT interval and K897T in 413 individuals. They found that the minor allele, 897T, was associated with QT prolongation but only in the subset of 187 women. The following year, Bezzina et al. reported the opposite, that 897T was associated with QT shortening in 1382 subjects and was more predictive in females. This result was replicated by investigators from the KORA study who found that 897T is associated with a 1.9 ms reduction in the QT interval per allele and with a greater decrease in women than men. Recently, a similar result was noted in the Framingham Heart Study, with a reduction in the corrected QT interval by 1.6 ms per 897T allele. Thus, while there is some inconsistency, on the whole the preponderance of epidemiological data supports the association between the QT shortening effect and the 897T allele.
The results from these association studies create an apparent paradox. It has been well described in humans and in animal models of AF that electrical remodelling leads to shortening of the atrial action potential duration and that AF begets AF. There are also several reports of AF associated with short QT syndrome. Therefore, we would anticipate that AF would be associated with the 897T allele; however, it is the more common 897K allele that is associated with AF in the current study.

How then do we reconcile the current findings with the expectation that AF is usually associated with shortening of atrial refractory periods? Unfortunately, a clear answer does not emerge from functional studies of this polymorphism. Characterization of the 897T and K alleles in cell lines has been inconsistent, with multiple functional studies of this polymorphism. Characterization of the functional studies might be due to subtle differences in experimental conditions, or the inherent limitations in heterologous expression systems.

It is interesting to note that there are a small number of cases where AF has been associated with prolonged repolarization. Two distinct gain-of-function mutations in KCNQ1 have been reported in a family and an individual with AF. While such an alteration would be expected to result in a prolongation of the action potential duration and QT interval. The observed differences between the clinical findings of a shortening of the QT interval and the expression studies might be due to subtle differences in experimental conditions, or the inherent limitations in heterologous expression systems.

In sum, these disparate clinical, electrophysiological, and genetic findings highlight our limited understanding of the determinants of atrial repolarization. The study of Sinner et al. provides a foundation for further investigation of the relationship between KCNH2 and AF, and will ultimately require replication at other centres. It also emphasizes that large cohorts with adequate power are necessary when examining genetic associations, a particularly important point given the emergence of genome-wide studies for AF and other cardiovascular traits.

**Conflict of interest:** none declared.

**References**


Prenatal echographic recognition of hypertrophic cardiomyopathy leading to heart transplantation in the newborn

Daniela Prandstraller1, Ornella Leone2, Elena Biagini3, Fernando M. Picchio1, and Claudio Rapezzi2*

1Pediatric and Congenital Adult Cardiology Unit, University of Bologna and S. Orsola-Malpighi Hospital, Bologna, Italy; 2Department of Pathology, University of Bologna and S. Orsola-Malpighi Hospital, Bologna, Italy; 3Institute of Cardiology, University of Bologna and S. Orsola-Malpighi Hospital, via Massarenti 9, 40138 Bologna, Italy

*Corresponding author. Tel: +39 051349858, Fax: +39 051344859, Email: claudio.rapezzi@unibo.it

A healthy, non-diabetic 27-year-old woman attended a routine foetal echography during the 32nd week of an uneventful first pregnancy. Growth of the (female) foetus was normal for the gestational phase and no general malformation was observed. However, the echocardiographic evaluation (Panel A) showed massive left ventricular (LV) hypertrophy (end-diastolic thickness 19 mm; right-ventricular free wall, 12 mm) and cardiac muscle cell disorganization (myocyte disarray). These findings were confirmed at birth (Panel B) by echocardiographic demonstration of massive cardiac hypertrophy, with a 20 mm maximal LV wall thickness uncorrected for body surface area. A systolic gradient >30 mmHg was detected in both ventricular outflow tracts. LV ejection fraction was 80%. ECG (not shown) was diagnostic for biventricular hypertrophy, with deep inferior and anterolateral Q-waves. The PR interval was normal. Metabolic diseases were excluded based on the results of comprehensive blood and urine analyses. Screening for the beta-myosin heavy chain, cardiac myosin binding protein C, and cardiac troponin I gene mutations was negative. Both parents had normal physical examinations, ECG, and echocardiography. No family history of heart disease could be traced. From the first hours after birth, the baby girl presented severe congestive heart failure, which was unresponsive to aggressive pharmacological treatment. Heart transplantation was therefore performed at the age of 2 months, and 20 months later the girl is currently in good health. The transplantation was therefore performed at the age of 2 months, and 20 months later the girl is currently in good health. Heart transplantation was therefore performed at the age of 2 months, and 20 months later the girl is currently in good health.

Hypertrophic cardiomyopathy (not secondary to metabolic disorders) can occasionally be congenital. In utero recognition of this disease allows timely planning of clinical management, including possible need for heart transplantation.

Panel A. Foetal echography at 32 weeks shows massive cardiac hypertrophy involving the right-ventricular free wall, interventricular septum, and LV posterior wall.

Panel B. Postnatal echography shows cardiac morphology similar to that in foetal echocardiography.

Panel C. and D. Gross and histopathologic features from the explanted heart show right and left ventricular hypertrophy (interventricular septum, 19 mm; LV postero-lateral wall, 20 mm; right-ventricular free wall, 12 mm) and cardiac muscle cell disorganization (myocyte disarray). AO, aorta; Liv, liver; LL, left lung; LV, left ventricle; RV, right ventricle; RL, right lung; S, spine.

Funding to pay the Open Access publication charges for this article was provided by the University of Bologna (RFO 2006).