


RESEARCH LETTER

Genetic Polymorphisms for Estimating Risk of Atrial Fibrillation in the General Population: A Prospective Study

Atrial fibrillation (AF) is a common cardiac disease and major risk factor for stroke, heart failure, and death. Tools for prediction of AF have been developed to identify individuals who might benefit from preventive therapies, incorporating conventional cardiovascular risk factors, and the effects of such risk factors have been evaluated across several cohorts. Recently, a heritable component to AF has been reported, and polymorphisms in 3 genetic regions have been reproducibly associated with AF: chromosome 4q25, located 150 kb from the closest gene—a transcription factor (PITX2) involved in cardiac development; chromosome 16q22, intrinsic to another transcription factor of unknown function, expressed in cardiac tissue (ZFHX3); and an amino acid–altering variant in KCN2, one of the major cardiac voltage-gated potassium channels. Rare genetic variants segregating with AF are typically exclusive to individual families and unlikely to contribute to AF prediction at the population level, but genetic polymorphisms could provide important predictive information.

Methods. The single nucleotide polymorphism (SNP) with the strongest association at each of the 3 genetic regions reproducibly associated with AF in genome-wide or candidate gene studies was genotyped in a large population-based cohort of middle-aged participants from southern Sweden (Malmö Diet and Cancer study). Data collection and clinical definitions have been described previously. Briefly, 30,447 randomly selected individuals (born 1923-1950) attended a baseline examination between 1991 and 1996 with (1) sampling of venous blood, (2) measurement of blood pressure and anthropometric measures, and (3) completion of a questionnaire. Cardiac disease end points were ascertained from national registers (Swedish Cause of Death Register and Swedish Hospital Discharge Register). Follow-up for AF extended through January 1, 2009.

DNA extracted from peripheral blood cells was assigned to batches without regard to AF status or personal identity. The batches were genotyped with the same set of reagents using real-time polymerase chain reaction with 2.5 ng of DNA as the polymerase chain reaction template for allelic discrimination (ABI 7900HT; Life Technologies). Genotype calls were obtained using SDS version 2.3 software (Life Technologies) and fluorescence intensity plots curated manually.

Association of genotype with AF was studied using both cross-sectional and prospective study designs. In cross-sectional analyses, the association of SNPs with AF diagnosed before baseline was examined using logistic regression analysis. In prospective analyses, the association of SNPs with incident AF during follow-up was examined in individuals free of AF at baseline using Cox proportional hazards models with censoring at death, emigration, or end of follow-up. Kaplan-Meier estimates of absolute AF risk per genotype were calculated. The proportionality of hazards assumption was confirmed using a Schoenfeld global test.

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Polymorphisms associated with AF were assessed for predictive discrimination using the Harrell concordance (C) statistic, a generalization of the area under the receiver operating characteristic curve, with confidence interval estimates using a jackknife resampling method in the Stata package Somers D (Stata Corp). Model calibration was evaluated using the Gronnesby-Borgan test implemented in the Stata package stcoxgof (Stata Corp). All analyses were performed using SAS version 9.2 (SAS Institute) or Stata version 11.1 (Stata Corp).

Informed consent was obtained from all participants, and the study was approved by the ethics committee of Lund University, Lund, Sweden. The study protocol is consistent with the principles of the Declaration of Helsinki.

Results. Baseline characteristics for the Malmö Diet and Cancer study cohort have been published previously. Clinical data were available for 28,473 individuals, 26,946 of whom had DNA available. The mean (SD) age was 58.1 (7.6) years, and the majority were women (60.6%). At baseline, 287 individuals had been diagnosed as having AF (prevalence, 1.0%). During a follow-up period of up to 17.8 years (median follow-up, 14.1 years; interquartile range, 12.9-15.7 years), 2,050 individuals developed AF. The Kaplan-Meier estimate of cumulative AF incidence was 11.9% (95% CI, 10.7%-13.3%).

The call rate was higher than 95% for all 3 SNPs. Minor allele frequencies (MAFs) were similar to those in previous studies and the European panel of the HapMap project (4q25: T allele, MAF 10.1%; 16q22: A allele, MAF 30.4%)}.
Table. Prediction of Atrial Fibrillation With Genetic Polymorphisms and Conventional Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cross-sectional Results</th>
<th>Prospective Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age</td>
<td>2.12 (1.75-2.57)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.94 (1.48-2.54)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI</td>
<td>1.21 (1.03-1.42)</td>
<td>.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.91 (1.89-4.49)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>1.80 (1.13-2.87)</td>
<td>.02</td>
</tr>
<tr>
<td>History of MI</td>
<td>1.59 (0.95-2.67)</td>
<td>.04</td>
</tr>
<tr>
<td>History of HF</td>
<td>1.855 (0.86-34.91)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>4q25 (rs2200733)</td>
<td>2.15 (1.69-2.74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>16q22 (rs2106261)</td>
<td>1.28 (1.02-1.61)</td>
<td>.03</td>
</tr>
<tr>
<td>KCNH2 (rs1805123)</td>
<td>0.86 (0.68-1.09)</td>
<td>.22</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio.

The upper part of the table presents effect estimates with 95% CIs per risk factor from multivariable models, including conventional risk factors and genetic polymorphisms. Cross-sectional results refer to logistic regression models of prevalent cases at baseline, and prospective results refer to Cox proportional hazards models of incident cases during follow-up. Effect estimates for genetic polymorphisms are shown per risk allele for age per 10 years and for BMI (calculated as weight in kilograms divided by height in meters squared) per 5 U. P values refer to Wald χ² tests. The lower part of the table presents C statistics with 95% CIs and calibration statistics with corresponding P values for each model. Calibration refers to Hosmer-Lemeshow tests for cross-sectional analyses and Groenneby-Borgan likelihood ratio tests for prospective analyses.

Comment. In this large, prospective study, 2 genetic polymorphisms with high prevalence in the population predicted AF independently of and with similar risk magnitude to single clinical risk factors. However, genetic polymorphisms did not significantly improve predictive accuracy when added to clinical risk factors. The findings do not support the utility of clinical genotyping for AF risk prediction with these SNPs, which are currently being marketed by commercial companies for direct-to-consumer genetic testing with provision of absolute genetic risk estimates.

The association with the K897T missense variant in KCNH2 was not replicated and also recently failed to replicate in a large case-control sample. These results do not support the large effect described in the initial report but cannot rule out a small effect.
Additional, independent SNPs on 4q25 have been associated with AF, and a polymorphism on chromosome 1q21 was recently associated with lone AF. Although these polymorphisms with smaller effects are unlikely to improve predictive accuracy, future studies will be needed to evaluate the predictive information content of genome-wide SNP data. Furthermore, recent studies have demonstrated that asymptomatic episodes of AF may not be uncommon and may confer increased stroke risk. Characterization of populations for such episodes might reveal that genotypic risks based on clinical AF are underestimates.

J. Gustav Smith, MD
Christopher Newton-Cheh, MD, MPH
Peter Almgren, MSc
Olle Melander, MD, PhD
Pyotr G. Platonov, MD, PhD

Author Affiliations: Department of Cardiology, Lund University, Lund, Sweden (Drs Smith and Platonov); Department of Clinical Sciences, Lund University, Malmö, Sweden (Drs Smith and Melander and Mr Almgren); Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge (Drs Smith and Newton-Cheh); and Center for Human Genetic Research and Cardiovascular Research Center, Harvard Medical School and Massachusetts General Hospital, Boston (Dr Newton-Cheh).

Correspondence: Dr Smith, Department of Cardiology, Faculty of Medicine, Lund University, Skåne University Hospital, SE-221 85, Lund, Sweden (gustav.smith@med.lu.se).

Author Contributions: Dr Smith had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Smith, Newton-Cheh, Melander, and Platonov. Acquisition of data: Smith and Melander. Analysis and interpretation of data: Smith, Newton-Cheh, Almgren, Melander, and Platonov. Drafting of the manuscript: Smith and Melander. Critical revision of the manuscript for important intellectual content: Smith, Newton-Cheh, Almgren, Melander, and Platonov. Statistical analysis: Smith, Almgren, and Melander. Obtained funding: Smith, Melander, and Platonov. Administrative, technical, and material support: Melander and Platonov. Study supervision: Newton-Cheh, Melander, and Platonov.

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INVITED COMMENTARY

Genetic Prediction for Common Diseases: Will Personal Genomics Ever Work?

A major promise of human genetics has been the use of genetic information to predict the risk of common diseases in order to prevent and treat these conditions more effectively. Most common diseases have a complex etiology, and genes are expected to explain much of their risk. However, even though PubMed already retrieves more than 2 million articles with “gene OR genetic” (n=2,015,109 as of February 10, 2011) and half (n=1,040,434) are tagged as “Human,” there are formidable difficulties in materializing this promise.1

Genome-wide association studies have now successfully identified thousands of common genetic variants that influence the risk of complex diseases. Large-scale evidence, agnostic testing with stringent statistical criteria, and rigorous replication standards guarantee that this literature has high credibility. Nevertheless, the discovered gene variants do not markedly expand our predictive ability compared with what can be achieved by using only information from long-known traditional risk factors. In this issue of the Archives, Smith et al2 add another example for...