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EDITORIAL COMMENT

Atrial Fibrillation Genomics

Time to Take the Next Step*

Dan M. Roden, MD

Nashville, Tennessee

A 63-year-old physician presents for genetic counseling. He has hypertension, well controlled with an angiotensin-converting enzyme inhibitor, and has taken a statin for 13 years. His mother has atrial fibrillation (AF), and recent genetic testing has identified AF risk alleles placing him at 4-fold increased risk for developing AF. He is concerned that waiting until the arrhythmia develops may expose him to thromboembolic risk and has read that antiarrhythmic drugs and ablation are less effective in individuals with his genotype. He therefore wishes to know whether anything can be done to prevent the development of the arrhythmia.

See page 1200

A traditional view of AF holds that the arrhythmia is a fellow traveler to other types of heart disease, and that it is relatively straightforward to manage. This image has been reinforced by trials such as AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) (1) that demonstrated the equivalence, or superiority, of a simple "rate control" strategy compared with attempts to restore sinus rhythm. The fundamental problem with this type of comparison is that strategies to restore and maintain sinus rhythm rely on drugs that do not target fundamental mechanisms, are not especially well tolerated, and have distinct, potentially lethal, adverse side effect liabilities. There is no doubt that there is a population of patients in whom rate control, along with appropriate anticoagulation, provides perfectly adequate symptom control and probably no effect on longevity. The emerging story around AF genomics and its implications for understanding fundamental mechanisms, and therefore predicting and perhaps even preventing the arrhythmia, provides one way forward in this issue.

"Lone" AF is a genetic disease. In the 1930s and 1940s, it was recognized that AF could occur in the absence of underlying heart disease or other risk factors we now recognize, such as advancing age, hypertension, diabetes, obesity, or metabolic syndrome, and in multiple family members (2,3). This subset then acquired the label of "lone" AF, a term that merely betrays our ignorance of underlying mechanisms. The last decade has seen the recognition that individuals with lone AF, who make up 10% to 30% of a tertiary care institution's referral population, have a strong family history of AF (4,5). Further, in the Framingham Heart Study, hypertension, diabetes, and a family history of AF were found to all independently add to risk of the arrhythmia in an individual (6). Thus, an emerging body of evidence over the last 10 years highlights a potential role for genetic variation as a risk factor for AF.

Studies in both families and in large populations have been used to identify DNA polymorphisms contributing to AF risk. Families with multiple affected members have been investigated by linkage analysis, candidate gene sequencing, or other methods to identify variants that segregate with the trait (7,8) and may therefore be causative. This approach has been modestly successful, identifying loci and seemingly logical variants in obvious candidate genes, such as those encoding ion channels. Difficulties with this approach are that many families are not large enough for conventional linkage analysis, and the phenotypes can be difficult to assign: some patients may carry a risk allele but not develop the arrhythmia (incomplete penetrance), and because AF is so common, some patients may develop the arrhythmia without necessarily having the risk allele in their family.

AF represents a triumph of the genome-wide association study. AF was one of the first complex traits successfully investigated using the genome-wide association study (GWAS) paradigm. In an initial GWAS reported in 2007 (9), a discovery set of only 550 Icelandic cases and 4,476 controls identified a very strong association with single nucleotide polymorphisms (SNPs) at chromosome 4q25, and this association was subsequently replicated in this report and others (10) in Caucasians and in a small number of Asians. Importantly, the cases were unselected for known risk factors such as hypertension or diabetes; the only exclusion was post-operative AF, and subsequent studies have identified 4q25 SNPs as risk factors in this setting as well (11). This result suggests that the 4q25 locus predisposes to AF in some fundamental fashion independent of other risk factors, and the identification of this novel association (and thus new pathway to the arrhythmia) represents a real triumph of the GWAS technique. Most recently, Ellinor and colleagues (12) performed a meta-analysis and replication using over 12,000 cases and identified a total of 9 risk loci. SNPs at the 4q25 locus conferred a relative risk of 1.64 ($p = 1.8 \times 10^{-74}$), whereas values at other loci were 1.13 to 1.24; SNPs at 2 loci were protective, with relative risks of 0.85 to 0.88.

The original 4q25 SNPs are located about 150,000 base pairs away from *PITX2*, which encodes a transcription factor

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From the Vanderbilt University School of Medicine, Nashville, Tennessee. The study was supported in part by a grant from the U.S. Public Health Service (U19 HL065962). Dr. Roden has reported that he has no relationships relevant to the contents of this paper to disclose.

first described as a modulator of pituitary development. Two months after the original 2007 GWAS reporting risk alleles at 4q25, a group of developmental biologists reported that deletion of *Pitx2c* (a cardiac-specific isoform implicated in early left-right differentiation in the heart) in mice resulted in failure of formation of the pulmonary vein myocardial sleeve, the site of origin of the abnormal automaticity that commonly drives AF (13). Mice in which a *Pitx2* allele has been deleted display increased susceptibility to AF by programmed stimulation and up-regulation of "pro-fibrillatory genes," including those in which rare variants have been associated with AF in families (14). Taken together, these data provide a strong argument that SNPs at the 4q25 locus confer AF risk by modulating *PITX2* function. However, studies relating 4q25 risk allele genotypes to *PITX2* expression in adult atrial samples have provided conflicting results, and the mechanism whereby 4q25 SNPs act to generate an AF-prone substrate in humans remains uncertain.

In this issue of the *Journal*, Lubitz et al. (15) add in several important ways to our understanding of the role of the 4q25 locus in mediating AF risk. First, they demonstrate that multiple SNPs within the locus actually confer risk independent of one another. One of these is remarkably close, 7,000 base pairs, to the actual *PITX2* gene, and thus adds to the indirect body of evidence that the 4q25 locus acts by modulating *PITX2* function. Second, they build on their own previous report (16) to show that combinations of independent SNPs at the 4q25 locus contribute in an additive fashion to AF risk. Thus, although the relative risk for any single allele identified by GWAS is <2, this value can rise to 4 to 5 in a small number of individuals with combinations of risk alleles. This resonates with the idea that combinations of risk alleles may be especially important in generating many human phenotypes; for example, our group has shown that 4q25 risk alleles are likely modulators of the penetrance of rare variants in families (17). Third, they report that the SNPs conferring AF risk in Caucasian populations are now replicated in a large Japanese cohort. This is not a surprise, given that the original 2007 report included a small number of individuals of Asian ancestry. Further, although it seems improbable that the fundamental pathways to AF (or most other diseases) will vary by ancestry, it is entirely possible that the specific risk variants will (18). Interestingly, individuals of African origin display an apparently reduced incidence of AF, despite an equivalent or greater burden of traditional risk factors such hypertension and diabetes (19). One report suggests that AF risk in African Americans is determined by the extent of global genetic admixture with Caucasian populations (20), and it remains an interesting and important unknown whether African-American subjects harbor protective alleles.

The next steps. The initial use of large-scale population approaches such as GWAS to study complex traits in an unbiased fashion was associated with hype suggesting that we would soon see genomic markers conferring very high risk. This expectation has not been met and is unrealistic for several reasons. First, complex traits are complex, so the expectation that a genetic test will definitively rule in or rule out a complex trait is unrealistic: genetics shades the odds for common disease. Second, GWAS attempts to identify associations between common genetic variants and disease, and the notion that common variants could confer high risk, at least for diseases that could occur at reproductive ages, runs counter to the concepts of conventional evolutionary pressure: such high-risk common alleles would not persist in the population. Interesting exceptions are in pharmacogenomics (where there has been no evolutionary pressure) (21,22) or in diseases presenting after reproduction, such as age-related macular degeneration (23). Indeed, one reason GWAS has been so successful in identifying robust signals for AF may be that the arrhythmia largely occurs in the post-reproductive period.

A failure to deliver on initial hype has created skeptics around the use of genomic information in clinical practice. GWAS for AF highlights the way in which these data will inform future practice in many diseases. No one would have guessed that variation in a developmental pathway would confer risk for AF. Although many details remain to be worked out, including whether, in fact, *PITX2* is the "culprit" gene, there is every reason to hope that understanding the mechanism whereby these alleles so consistently confer risk will then inform development of targeted and effective therapies for treatment and, more importantly, for prevention of the arrhythmia. Biomarkers based on this new understanding could be deployed to identify patients at very high risk of arrhythmia before development of the first episode. New drugs can and should be developed to treat and prevent the arrhythmia. A new biology, relating the risk alleles to other emerging factors, such as atrial fibrosis, should emerge. Thus, AF genomics has every potential to inform not only treatment of AF, but also its prevention. Focusing on using fundamental new knowledge to develop ways to prevent the onset of the arrhythmia in the 63-year-old physician does not seem completely unrealistic, and holds out the hope that AF will not become the epidemic that many have predicted as the population ages (19).

Reprint requests correspondence: Dr. Dan M. Roden, Vanderbilt University School of Medicine, Department of Clinical Pharmacology, 1285 MRB IV, Nashville, Tennessee 37232-0575. E-mail: dan.roden@vanderbilt.edu.

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