EDITORIAL COMMENT

Genomic Medicine and Atrial Fibrillation*

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Recent developments and improved understanding in genomics (the interactions and functions of genes) have profoundly changed the perspective of researchers and medical practitioners toward diseases that had previously been associated with environmental factors alone (1). It is now widely recognized that many common disorders, such as heart disease, cancer, infections, Parkinson’s disease, and Alzheimer’s disease, are rooted in environmental factors as well as in genetic variation. Recent research strongly supports the concept that defective genes and/or gene variation plays a much larger role in the development of certain disorders than was previously suspected.

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Epidemiology and clinical implications of atrial fibrillation. Atrial fibrillation (AF) is a common disorder that is proving to be an excellent example of the interaction between environmental and genetic factors. Atrial fibrillation is one of the primary causes of mortality, morbidity, and socioeconomic consequences from hospitalizations. Atrial fibrillation is characterized by a rapid and irregular activation of the atrial myocardium at a rate of approximately 400 to 600 pulses/min. The uncontrolled rapid ventricular response rate may eventually cause ventricular dysfunction and heart failure. Additionally, the loss of effective atrial contraction may also cause blood stasis and promote the occurrence of thromboemboli and stroke. As a result, AF requires long-term anticoagulant and rate-control therapy, and sometimes more sophisticated treatments, such as ablation and implantable devices.

Atrial fibrillation and atrial flutter account for approximately 9,000 deaths and 400,000 hospitalizations annually, and they are the cause of stroke in about 15% of patients (2). The prevalence of AF is estimated to be between 0.5 and 1% in the general population, and the condition affects approximately 2.2 million individuals in the U.S. alone (3). The incidence and prevalence of AF increases with age: approximately 70% of those diagnosed with AF are between 65 and 85 years old (3). Braunwald (4) has recently described AF as a growing “epidemic” as the population of elderly continues to increase. Still, the real frequency of AF is probably underestimated (5) because of the high rate (30% to 45%) of asymptomatic arrhythmia, which frequently goes undetected.

In spite of AF’s clinical relevance, the origin and the mechanisms underlying this common arrhythmia have, until recently, been obscure. Atrial fibrillation has been recognized since the early 1900s and typically has been associated with conditions that increase atrial pressure or cause atrial dilation (Table 1). Atrial fibrillation is also associated with cardiomyopathies (6–10), diseases of the cardiac muscle which are known to be genetically determined in a large proportion of patients. Finally, AF may also occur in patients without any other evidence of heart or systemic disease, a condition known as lone AF. Lone AF accounts for 2% to 31% of the AF patient population (5) and usually affects young and middle-aged adults.

Although very little was known about the molecular determinants of AF until a few years ago, recent advances have significantly improved our understanding of this condition. These include new insights into the genetic basis of the disease and the discovery of gene expression changes that produce electrical and structural remodeling of the atria during AF.

Genetic epidemiology of AF. The familial occurrence of AF has been known for many decades yet traditionally has been considered a rare event (5,11). However, the study of the familial forms of AF caused by a gene defect was considered key to the discovery of factors that constitute initiation of AF.

The first important advance in this direction has been the identification of a genetic locus for familial AF on chromosome 10q22-q24, by Brugada et al. (12). Three families from Catalonia, Spain, were studied and showed an autosomal dominant pattern of transmission and early onset of the arrhythmia (age 1 to 45 years). Positional cloning and analysis of candidate genes to identify the disease gene are currently ongoing. Since the beginning of their studies, Brugada et al. (11) have collected probands from more than 100 families with familial AF. Their findings revealed that not all families were affected by the chromosome 10q22-q24 locus, suggesting that familial AF is a genetically heterogeneous disorder caused by more than one gene. Their findings also supported the notion that familial AF may be more common than previously suspected.

In this issue of the Journal, Darbar et al. (13) report the results of a large survey performed in the arrhythmia clinic at the Mayo Clinic in Rochester, Minnesota. Out of 914 patients with AF, 36% had lone AF, and of that patient population, 15% had a familial history of the disorder (5% of the overall population). These findings discount the old idea that familial AF is a rare condition. The age of onset in the 50 probands with familial AF ranged from 25 to 55 years. The investigators were able to identify four multigenera-

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mutations (long QT syndrome, Brugada syndrome, or cases of ventricular arrhythmia due to sodium channel myocardium may suggest an ion channel disease, such as response and without primary involvement of the nuclear lamina, such as emerin and lamin (Table 1) (6,14).

On the other hand, the phenotype with AF rapid ventricular response suggests an underlying more diffuse myocardial disease. Indeed, the coexistence of atrial arrhythmia (includ-
ing AF) and conduction defects are found in cardiomyopathy, which is improved after sinus rhythm restoration or rate-control. These families had also experienced a significant incidence of stroke. On the other hand, affected members of the fourth family frequently had asymptomatic AF, with slow ventricular response, atrial myopathy, progression to conduction delay, and “ventricular” cardiomyopathy.

The two different phenotypes described in the study of Darbar et al. (13) may indicate two distinct mechanisms underlying these conditions. Indeed, the coexistence of atrial arrhythmia (including AF) and conduction defects are found in cardiomyopathies caused by mutations of cytoskeletal genes of the nuclear lamina, such as emerin and lamin (Table 1) (6,14). On the other hand, the phenotype with AF rapid ventricular response and without primary involvement of the “working” myocardium may suggest an ion channel disease, such as cases of ventricular arrhythmia due to sodium channel mutations (long QT syndrome, Brugada syndrome, or idiopathic ventricular tachycardia) (14). Most recent advances in the molecular genetics of AF support this hypothesis and are discussed later.

The attempt to define the epidemiology of familial AF by Darbar et al. (13) has several limitations. These include the possibility of a referral bias overestimating the frequency of lone AF, an underestimate due to clinically silent forms, or survey results based on family history rather than clinical evaluation of relatives. Further, the relative frequency of the rapid- and slow-ventricular rate AF in the overall population is unknown. However, the relevant messages emerging from this study are that the familial occurrence of AF is not rare, that the condition is probably due to several different genes and molecular mechanisms, that it may be associated with young age and complications such as stroke and cardiomyopathy, and that patients with this disorder should undergo adequate screening, therapy, and counseling.

Role of gene mutations in the origin of AF. The hypothesis that ion channels could have a major role in causing AF has been recently confirmed by two studies. The first study tested the hypothesis of an association between AF and a genetic variation (polymorphism) in the minK gene (KCNE1), encoding the beta subunit of the potassium channel (KvLQT1/minK) (15). The KvLQT1 potassium channel, formed by the alpha (KvLQT1) and beta (minK) subunits, determines the “slow” component of the K+ current, causing cellular depolarization in atrial myocardium. In a Chinese population with risk factors for AF (including valvular heart disease, hypertension, and left ventricular dysfunction), patients with the 38G allele were more likely to develop AF than patients with the 38S allele. Unfortunately, the func-

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*Polymorphism.

AF = atrial fibrillation; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; JB = junctional rhythm; SB = sinus bradycardia; SSS = sick sinus syndrome; WPW = Wolf-Parkinson-White pre-excitation syndrome.

Table 1. Genotype/Phenotype Correlations in Atrial Fibrillation
tional significance and the electrophysiologic consequences of the genetic variation are currently unknown. However, these findings may provide new insights into the pathophysiology and potential treatment of the disease.

The second recent study reports the discovery of the first gene causing lone AF in a Chinese family with autosomal dominant transmission (16). Not surprisingly, the disease-gene ( KCNQ1 or KvLQT1) encodes the alpha subunit of the cardiac IKs potassium channel, as well as the KCNQ1/KCN2 and KCNQ1/KCN3 potassium channels, and is again involved in atrial remodeling. The disease-causing mutation (S140G) causes a gain-of-function of the KCNQ1/KCN1E and KCNQ1/KCN2E channels, reducing the action potential duration and the effective refractory period, therefore inducing a mechanism able to initiate and maintain AF. Interestingly, different mutations in the same gene were found to cause loss-of-function and lead to long QT syndrome (17). The phenotypic heterogeneity of KCNQ1 is not surprising, as it is also observed in other ion channel diseases. For example, as mentioned before, different mutations in SCN5A may cause long QT, conduction defects, and Brugada syndrome (14). The finding of major involvement of K+ channels in the etiology of AF offers the opportunity to develop novel therapeutic strategies, such as IKs blockers.

Role of the changes in gene expression (electrical remodeling) in maintaining AF. A well-known principle in human genetics states that every phenotype is determined by the interaction of three factors: major genes with a strong effect; several weak genes with a modifier effect, leading to susceptibility or protection; and the environment. In the case of AF phenotype, recent studies have shown that changes in gene expression (the molecular environment) are critical in maintaining the arrhythmia and transforming paroxysmal episodes in a chronic irreversible condition. Once initiated, AF induces an alteration of the electrophysiological properties that favors induction and maintenance of the arrhythmia—a process called “electrical remodeling” (18). The rapid atrial rate causes a progressive intracellular Ca2+ loading, which threatens cell viability and induces a final common pathway of defensive responses in the cell. These include transcriptional down-regulation of the Ca2+ channel (ICa), decrease of the Ca2+ current, alteration in both the inward and outward K+ currents, and decrease of the action potential and of the refractory period that eventually promotes and maintains AF by multiple-circuit re-entry. Furthermore, the Ca2+ overload and the decreased Ca2+ exchange induce cellular myolysis and activation of the fetal gene program leading to structural remodeling, and reduce atrial contraction (atrial stunning) contributing to blood stasis and thromboembolism. Overall, the atrial ionic remodeling follows pathways very similar to those in ventricular remodeling in heart failure, suggesting a common underlying mechanism (19).

The advances in understanding the remodeling process may have important clinical implications in terms of prevention (such as early cardioversion, implantable atrial defibrillator, and preventive atrial pacing methods) and therapies to drive reverse remodeling (5). This new understanding will clearly influence future investigations of genes involved in the remodeling pathways that may cause or modulate AF.

Conclusions. The new insights on genes and genotype/phenotype correlations involved in AF have impressively increased our understanding of the pathophysiological mechanisms leading to arrhythmia. The new knowledge supports investigations about novel disease genes, their interactions with remodeling mechanisms, and potential therapies to treat AF at the ion channel and cellular levels. In this process, unraveling the clinical and molecular genetics of AF has a central role that may provide new insights into the structural and electrical phenotypes resulting from genetic mutations. Eventually genomic information in AF patients will impact the optimal approach to care, from prevention and diagnosis to therapy and counseling. At that point systematic genetic screening will become standard in the management of familial AF in clinical practice.

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REFERENCES