Genes and Atrial Fibrillation
A New Look at an Old Problem

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Atrial fibrillation (AF) is an abnormality of the heart’s rhythm that is characterized by rapid and irregular activation of the atria. AF was first described in humans in 1906 and is now recognized to be the most common sustained cardiac arrhythmia and a major public health burden. The loss of coordinated atrial contraction results in a sustained cardiac arrhythmia and a major public health burden.2 These observations underscore the need for a better understanding of the pathophysiological basis of AF and for the development of new approaches to prevention and management.

AF is frequently observed as a complication of diverse cardiac and systemic disorders, including hypertension, coronary artery disease, valvular heart disease, and cardiomyopathies. Hence, AF has traditionally been regarded as a sporadic, nongenetic disorder. In approximately 10% to 20% of cases, an underlying cause cannot be identified, and AF is termed “idiopathic” or “lone.”7 One hundred years on, there is now accumulating evidence that genetic factors have a role in the pathogenesis of AF in a significant proportion of cases. The genes involved and the mechanisms by which defects in these genes alter atrial electrophysiological properties and promote arrhythmogenesis have recently begun to be explored and are summarized in this review.

Molecular Basis of Atrial Electrical Activity
Normal heart rhythm is generated by spontaneous firing of the pacemaker cells of the sinoatrial node. Cardiac impulses are propagated subsequently through the main body of the atrium to the atrophicventricular (AV) node and then via the bundle of His and Purkinje fibers to the ventricles. The passage of electrical signals across the cell membrane and from cell to cell is mediated by ion channels and electrogenic transporters.

Pacemaker Potentials
Pacemaker activity in the sinoatrial node is determined by the rate of diastolic depolarization, which is dependent on activation of a number of currents, including “funny” (I_f), T-type Ca2+ (I_CaT), L-type Ca2+ (I_CaL), and Na+/Ca2+ exchange (I_SCX) currents, as well as a reduction in repolarizing K+ (I_K) current. Cyclic Ca2+ release from the sarcoplasmic reticulum and activation of I_SCX is thought to be fundamental to pacemaker automaticity.8 The chronotropic state of pacemaker cells can be modified by changes in the relative balance of sympathetic and parasympathetic tone. Specifically, sympathetic stimulation increases heart rate by activation of I_f and I_CaL, thereby enhancing the rate of diastolic depolarization, whereas vagal stimulation reduces heart rate by inhibition of I_f and activation of a K+ current, I_KaCh, which reduces the rate of diastolic depolarization.9

Atrial Action Potential
The resting membrane potential of the human atrial cardiac myocyte is approximately −80 mV, close to the equilibrium potential for K+ ions, and is determined primarily by outward K+ current (I_K) and I_Kleak. The spreading signal initiated by the sinoatrial node causes a small depolarization of the atrial cell membrane potential that in turn triggers the activation of voltage-gated Na+ channels, I_Na, which results in rapid depolarization of the cell membrane potential to ≈40 mV (phase 0 of the action potential). Partial repolarization (phase 1) occurs due to an outward K+ current (I_K), followed by a plateau phase (phase 2) in which inward Ca2+ current (I_CaL and I_SCX) is approximately balanced by outward K+ current flow through 3 delayed-rectifier K+ currents (ultrarapid, I_Kur; rapid, I_Kr; and slow, I_Ks) and the small-conductance Ca2+-activated K+ current (I_KCaC). Inactivation of I_CaL and a gradual increase in the outward K+ currents terminate the plateau (phase 3), and finally, reopening of I_K channels restores the resting membrane potential (phase 4). The atrial action potential has a relatively shorter duration than the ventricular action poten-
tial (Figure 1) and may be less reliant on currents involved in the late phases of repolarization. A number of ion channels that have a modest effect or that are closed under baseline conditions show increased activation in response to physiologic stressors, such as metabolic stress (I\textsubscript{KATP}) and mechanical stretch (I\textsubscript{Kleak}, I\textsubscript{KAC}, and I\textsubscript{KL}). Changes in autonomic tone can further modify ion channel activation and atrial conduction. Acetylcholine release from parasympathetic nerves activates M-receptors and I\textsubscript{KAI}, which results in shortening of the atrial action potential duration (APD) and effective refractory period, as well as increased dispersion of refractoriness. Norepinephrine release from postganglionic fibers and circulating catecholamines activates \( \alpha \)- and \( \beta \)-adrenergic receptors, with subsequent shortening of the atrial APD and effective refractory period. A number of K\textsuperscript{+} currents, including I\textsubscript{Kur} and I\textsubscript{Cal} are highly responsive to adrenergic stimuli.

Molecular correlates for most of the ionic currents that contribute to the atrial action potential have been described (Table 1). Cardiac ion channels characteristically contain \( \alpha \)-subunits, which are membrane-spanning proteins that have a pore-forming domain that controls ion selectivity, as well as regulatory regions that control the open and closed conformation of the pore. The biophysical properties of \( \alpha \)-subunits may be modified by the binding of accessory \( \beta \)-subunits. A number of \( \beta \)-subunits have been identified that can bind specifically or promiscuously to 1 or more of the \( \alpha \)-subunits. Both \( \alpha \)- and \( \beta \)-subunits can interact with components of the actin cytoskeleton, intracellular scaffolding and signaling proteins, and the extracellular matrix. The formation of these macromolecular complexes is required for ion channel surface expression, localization, and function.

Characterization of expression patterns for individual ion channel subunits has been performed with heart tissue from various mammalian species. More recently, microarray analyses have facilitated systematic evaluation of chamber-specific ion channel subunit profiles in the human atrium and ventricle. It is now evident that there are multiple isoforms for many of the ion channel subunits. Some transcripts are expressed to a similar extent in the atria and ventricles, whereas others have restricted expression or differential levels of expression between these chambers (eg, I\textsubscript{Kur} is exclusively expressed in atrial tissue). Within the atrium, there is regional heterogeneity of ion channel subunit expression, with distinct patterns of transcripts in specialized conduction tissues, pulmonary veins, and the main body of “working” myocardium. For individual subunits, there may also be a transmural gradient of expression from epicardium to endocardium. Differences in gene expression and current density give rise to variations of the action potential morphology in different parts of the atrium and between the atrium and ventricle.

**Intercellular Conduction**

Atrial conduction is dependent not only on ionic fluxes but also on connections between cells and on structural properties of the atrial wall (Figure 2). Individual cardiomyocytes are linked end-to-end by intercalated disks to form a syncytium of elongated branching fibers. The intercalated disks are specialized areas of interdigitating cell membrane that are composed of adherens junctions, desmosomes, and gap junctions. The adherens junctions (containing N-cadherin, catenins, and vinculin) and desmosomes (containing desmin, desmoplakin, desmocollin, desmoglein, plakophilin, and plakoglobin) mediate cell-cell adhesion and anchor underlying cytoskeletal structures to the cell membrane, whereas the gap junctions (containing connexin proteins) are densely packed arrays of intercellular channels that permit transfer of ions and small molecules between cytoplasmic compartments of adjacent cells. The extracellular matrix, composed of collagen fibrils, elastin, fibroblasts, extracellular proteases, and various other macromolecules, provides a scaffolding that supports and maintains the alignment of cardiomyocytes, as well as being a determinant of force transmission, tensile strength, and overall geometry of the atrium. Changes in extracellular matrix composition and the development of interstitial fibrosis can impair the uniformity of conduction between cardiomyocytes.

**Electrophysiological Basis of AF**

Three classic models, focal activity, single-circuit reentry, and multiple-circuit reentry, have provided a conceptual framework for understanding the electrophysiological basis of fibrillatory conduction in the atrium for the past 50 years. Studies in various animal models, in conjunction with advances in optical mapping and computer modeling techniques, have more recently enabled these concepts to be further refined. Focal activity arises as a result of spontaneous rapid firing from 1 or more ectopic atrial sites due to an increased rate of depolarization or the generation of afterdepolarizations. After the seminal studies of Haissaguerre et al, the pulmonary vein cardiomyocyte sleeve has become recognized as a frequent source of ectopic impulse formation. The basis for enhanced pulmonary vein arrhythmicity is not fully understood but has been attributed to the combined effects of ion channel and tissue architectural characteristics, as well as...

![Figure 1. Atrial action potential. Compared with the ventricular action potential (dotted line), the atrial action potential (solid line) has a less negative resting potential, an abbreviated plateau phase, and slower terminal repolarization. These differences are predominantly due to increased \( h_o \) and \( h_{ squir } \) currents, as well as decreased \( k_i \) current. The phases (0 to 4) of the cardiac action potential are indicated.](http://circ.ahajournals.org/)

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TABLE 1. Major Ionic and Molecular Determinants of the Atrial Action Potential

<table>
<thead>
<tr>
<th>Current</th>
<th>Channel Components</th>
<th>α-Subunits*</th>
<th>β-Subunits†</th>
<th>Phase‡</th>
<th>Current Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline atrial action potential</td>
<td>Nav1.5, Nav1.3, Nav1.6</td>
<td>Navβ1, Navβ2</td>
<td></td>
<td>0</td>
<td>Voltage-gated Na⁺ current; responsible for cell depolarization and initial upstroke of action potential</td>
</tr>
<tr>
<td>hₚ</td>
<td>Kv4.3, Kv1.4, Kv1.7, Kv3.3, Kv3.4, Kv4.1</td>
<td>KChIP2, KCNE1-4, Navβ1-3, Navβ1</td>
<td></td>
<td>1, 2</td>
<td>Voltage-gated rapidly activating and inactivating (transient) outward K⁺ current; major determinant of early repolarization</td>
</tr>
<tr>
<td>bCAL</td>
<td>Cav1.2, Cav1.3</td>
<td>Cavβ2, Cavα₂δ</td>
<td></td>
<td>2, 3</td>
<td>Voltage-gated L-type Ca²⁺ current; contributes to plateau phase of repolarization and diastolic depolarization in pacemaker cells; current activity determined by feedback mechanisms linked to changes in intracellular [Ca²⁺]²</td>
</tr>
<tr>
<td>bCL</td>
<td>NCX1</td>
<td>None</td>
<td></td>
<td>2, 3</td>
<td>Na⁺/Ca²⁺ exchanger (3:1); net inward current during terminal repolarization and diastolic depolarization</td>
</tr>
<tr>
<td>k₁</td>
<td>Kv1.5, Kv1.2, Kv2.1, Kv2.1</td>
<td>Kvβ1, Kvβ2</td>
<td></td>
<td>1, 2</td>
<td>Rapidly activating delayed rectifier K⁺ current; contributes to repolarization</td>
</tr>
<tr>
<td>k₂</td>
<td>HERG</td>
<td>KCNE1, KCNE2</td>
<td></td>
<td>2, 3</td>
<td>Slowly activating delayed rectifier K⁺ current; contributes to repolarization in ventricle, but role in atrial action potential uncertain</td>
</tr>
<tr>
<td>k₃</td>
<td>KCNQ1</td>
<td>KCNE1-5</td>
<td></td>
<td>3</td>
<td>Ca²⁺-activated, small-conductance K⁺ channel, contributes to repolarization</td>
</tr>
<tr>
<td>k₄</td>
<td>SK2</td>
<td>None</td>
<td></td>
<td>3</td>
<td>Inward rectifier K⁺ current; major determinant of baseline resting potential</td>
</tr>
<tr>
<td>Contribute to pacemaker function</td>
<td>HCN4, HCN1, HCN2</td>
<td>KCNE2</td>
<td></td>
<td>4</td>
<td>Hyperpolarization-activated cyclic nucleotide-gated cation (&quot;funny&quot;) current; generates spontaneous activity in pacemaker cells</td>
</tr>
<tr>
<td>bATPase</td>
<td>Cav3.1, Cav3.2</td>
<td>Cavγ6</td>
<td></td>
<td>4</td>
<td>Inward T-type Ca²⁺ current; contributes to diastolic depolarization in pacemaker cells</td>
</tr>
<tr>
<td>bK₃</td>
<td>Kir3.1, Kir3.4</td>
<td>None</td>
<td></td>
<td>3, 4</td>
<td>Inward rectifier K⁺ current; minimally active under basal conditions, exerts negative chronotropic effect by slowing diastolic depolarization in response to vagal stimulation</td>
</tr>
</tbody>
</table>

PKA indicates protein kinase A; PKC, protein kinase C.

*α-Subunits identified at the RNA level in the human atrium; where multiple transcripts are present, those that are considered to have the major role in channel function are shown in bold.
†β-Subunits present in vivo that have been shown to interact with α-subunits in vitro.
‡Phases of action potential in which channel is active, with period of highest current shown in bold.

autonomic nervous system stimulation. Atrial ectopic activity may be sufficient to maintain AF or may trigger reentry.

Reentrant arrhythmia circuits arise due to differential impulse propagation within atrial tissue and require the presence of a localized region of conduction block, or wave break, which can be fixed or dynamic. Fixed defects may be structural or electrophysiological and include anatomic obstacles, myocardial fibrosis, and heterogeneity of ion chan-
channels or autonomic innervation, whereas dynamic or “functional” factors include membrane voltage and intracellular Ca\(^2+\) cycling properties that determine APD and conduction velocity. Functional reentrant circuits, or rotors, can generate wavelets that spread outward to activate neighboring tissue. AF can be maintained by continued rapid activity of a single “mother rotor” or by ongoing wave break in multiple propagating wavelets.

Once AF is established, a series of changes in the electrical and structural properties of the myocardium can ensue that provide a substrate for ongoing arrhythmogenesis. This phenomenon was elegantly summarized by Allessie and colleagues as “AF begets AF” and has been reviewed elsewhere.

In summary, atrial electrophysiology is a complex process, and coordinated interactions between multiple ionic and structural factors are critically required for normal impulse formation and propagation. It would not be surprising that defects in any of the molecular components that contribute to the tightly coordinated electrical activity of the atria (Figure 2; Table 1) could predispose to the development of AF.

**Familial Aggregation of AF**

The role of inherited gene defects in the pathogenesis of AF has only recently begun to be appreciated. The first case of a family with AF was reported in 1936. Since then, a number of small and large kindreds with AF have been described. Within the last few years, several studies have more systematically evaluated the prevalence of familial aggregation of AF. In 1 series of 914 patients with AF seen in a tertiary referral clinic, 50 individuals (5% of all AF patients, 15% of AF. In 1 series of 914 patients with AF seen in a tertiary referral clinic, 50 individuals (5% of all AF patients, 15% of AF patients) had a first- or second-degree relative with AF.

In 2004, the first epidemiological data for familial aggregation of AF were reported. In 2243 participants of the Framingham Heart Study, it was found that AF in 1 or more parent significantly increased the likelihood of offspring AF after adjustment for standard AF risk factors (odds ratio, 1.85; 95% CI, 1.12 to 3.06; \(P=0.02\)). Evidence of strong heritability of AF was also demonstrated in a study of 5269 patients from Iceland in which the relative risk of AF was 1.77 in first-degree relatives overall, but when only those affected individuals diagnosed before the age of 60 years were considered, the first-degree relatives of AF cases were 5 times more likely to have AF than the general population. Collectively, these data show that familial aggregation of AF is relatively common. Familial aggregation may result from inherited gene defects or from shared exposure to environmental or lifestyle factors. Current evidence in support of genetic factors having a primary role in AF pathogenesis is outlined below.

**Clinical Features of Familial AF**

Studies of families in which AF shows mendelian inheritance have been instrumental in identifying molecular defects that can promote AF development (see below). Family history is the most important clue to an underlying genetic cause of AF, and a diagnosis of familial AF should be considered in a kindred if (1) AF is a major clinical manifestation (phenotype) and (2) at least 2 first-degree family members are affected. Although familial AF is often presumed to be a disorder limited to young individuals with lone AF, reported families have shown a wide range of ages at AF diagnosis and varying clinical features (Table 2). Some families have AF only, whereas in others, AF is associated with conduction abnormalities (sinus bradycardia, AV conduction block), QT abnormalities, or changes in left atrial or left ventricular size and function. Left atrial size may be normal or increased at the time of diagnosis, with further increments due to chamber remodeling with chronicity of AF. Individuals with AF, particularly those with rapid ventricular rates, can present with congestive heart failure or may develop left ventricular dysfunction over time. Comorbid conditions, such as hypertension, that predispose to AF are common in the community and are often identified in 1 or more family members. Genotype-phenotype correlations for familial forms of AF have yet to be determined but ultimately should be useful for selection of genes for mutation screening and for ongoing patient management.

**Familial AF Disease Genes**

In 1997, Brugada and colleagues reported the first chromosomal locus, 1q22-q24, for familial AF. Although the disease-causing gene within this interval remains to be identified, this was a landmark study that established that AF could have a genetic basis. Molecular genetics studies have
now shown that familial AF is a genetically heterogeneous disorder. A number of chromosomal loci and disease genes have been associated with familial forms of adult-onset AF (Table 2). The majority of kindreds with adult-onset familial AF have an autosomal dominant mode of inheritance. One additional locus, 5p13, has been mapped in a family with neonatal-onset autosomal recessive familial AF.45

**KCNQ1 and KCNE Mutations**

The **KCNQ1** gene encodes the pore-forming α-subunit of the cardiac \( I_{Ks} \) channel (Table 1). **KCNQ1** was the first disease gene linked to adult-onset familial AF. Chen and colleagues55 mapped 1 large kindred to a locus on chromosome 11p15 and found a novel missense variant, S140G, in the **KCNQ1** gene in affected family members. No **KCNQ1** mutations were found in 6 additional small families or in 19 sporadic AF cases.35 Two subsequent studies have shown the prevalence of **KCNQ1** mutations in adult-onset familial AF to be low. In 1 series of 141 unrelated subjects with lone AF, no **KCNQ1** mutations were found,36 whereas our group identified 1 mutation in 50 probands with familial AF.36 **KCNQ1** mutations are a common cause of the long-QT syndrome, accounting for \( \approx 40\% \) of all genotype-positive individuals.47 **KCNQ1** mutations have also been identified in 2 cases of short-QT syndrome, 1 of which was a de novo mutation that was associated with AF and short QT intervals in utero.38,49

The discovery of **KCNQ1** mutations pointed to the **KCNQ1** genes, which are alternative \( I_{Ks} \) subunits of the cardiac \( I_{Ks} \) channel (Table 1), as promising candidate genes for familial AF. Yang and colleagues38,39 performed mutation screening of the **KCNE1**, **KCNE2**, **KCNE3**, **KCNE4**, and **KCNE5** genes in 30 probands of AF families and found 1 missense mutation, R27C, in the **KCNE2** gene in 2 families. The **KCNE** genes have also been evaluated in 2 series of 96 families50 and 50 families,36 respectively, with no further mutations identified. An R53H substitution in the **KCNE3** gene has been described in 1 family with AF.51 Although this variant was present in all affected family members and was absent from 288 control subjects, functional studies showed no change in the amplitude or kinetics of the cardiac \( I_{Ks} \) current. Although not definitive, these findings suggest that this sequence change represents a rare polymorphism rather than a disease-causing mutation.

**KCNJ2 Mutations**

The **KCNJ2** gene encodes the Kir2.1 protein that forms the \( I_{K1} \)-subunit of the cardiac **Kv1.5** channel (Table 1). Mutation screening of the **KCNJ2** gene in 30 probands with AF identified 1 missense mutation, V93I, in 1 family.38 No **KCNJ2** mutations were found in a series of 96 familial AF cases.50 **KCNJ2** mutations have been linked to Andersen syndrome, which is characterized by cardiac abnormalities, including long-QT syndrome and ventricular arrhythmias, as well as periodic paralysis and skeletal developmental anomalies. A **KCNJ2** mutation has been found in 1 family with short-QT syndrome.52

**KCNH2 Mutations**

The **KCNH2** gene encodes the human ether-a-go-go (HERG) protein that forms the \( I_{Kr} \)-subunit of the cardiac \( I_{Ks} \) channel (Table 1). **KCNH2** mutations are also a common cause of
long-QT syndrome, with a similar prevalence to KCNQ1 mutations. An N588K missense mutation in the KCNH2 gene has been identified in 3 unrelated families with short-QT syndrome. In 1 of these families, all affected individuals also experienced paroxysmal episodes of AF. No KCNH2 mutations were found in a series of 30 families with AF.

**SCN5A Mutations**

The SCN5A gene encodes the α-subunit of the cardiac sodium channel (Table 1). SCN5A mutations have been shown to cause a number of arrhythmic syndromes, including sick sinus syndrome, cardiac conduction defects, long-QT syndrome, Brugada syndrome, and sudden infant death syndrome. Five SCN5A mutations have been reported in families with dilated cardiomyopathy and conduction system disease, with AF an early manifestation of disease in many genotype-positive family members.

**LMNA Mutations**

The LMNA gene encodes the nuclear lamina proteins, lamin A and lamin C. LMNA mutations have been associated with a diverse range of human disorders, including familial dilated cardiomyopathy and conduction system disease. The cardiac phenotype in this disorder is characterized by a prodrift of progressive AV conduction abnormalities with or without AF, with the subsequent development of dilated cardiomyopathy. The prevalence of AF increases with age. In a subgroup of families, AF is the major presenting symptom.

**Functional Consequences of Familial AF Mutations**

The majority of mutations that have been associated with familial AF to date have been located in K+ ion channel genes. The S140G KCNQ1 and R27C KCNE2 variants increase $I_K$ channel activation, whereas the V93I KCNJ2 and N588K KCNH2 variants increase activation of the cardiac $I_K$ and $I_{Ks}$ currents, respectively. Each of these gain-of-function $K^+$ channel gene mutations results in shortening of the APD and hence, effective refractory period, thereby promoting AF by creating an electrical substrate for reentry. Functional studies of the E375X KCNA5 variant suggested an alternative AF mechanism, with the truncated protein found to have a dominant negative effect on $I_{Kur}$ activation with prolongation of the APD and an enhanced propensity for early afterdepolarizations that was exaggerated with sympaesthetic stimulation. These changes favor arrhythmia generation from an ectopic focus. The observation that both gain-of-function mutations (leading to shortening of APD) and loss-of-function mutations (leading to lengthening of APD) in $K^+$ channel genes can promote development of AF illustrates just how precisely atrial electrical activity is coordinated, ie, small deviations in either direction in terms of APD can predispose to AF.

Given the demonstrated low prevalence of mutations in these $K^+$ ion channel genes, it can be assumed that additional disease genes for familial AF remain to be discovered. Genes that encode other types of ion channels (Table 1) or structural proteins in the atria can also be considered as potential candidates for AF (Figure 2).

**Combined Atrial and Ventricular Phenotypes**

The majority of genes associated with familial forms of AF are expressed not only in the atria but also in the ventricles and hence might be expected to have an associated ventricular phenotype. For example, single gain-of-function molecular defects in the KCNQ1 and KCNH2 genes, respectively, have been proposed to account for both AF and short QT intervals in 2 kindreds, whereas loss-of-function SCN5A mutations can be manifest by AF together with dilated cardiomyopathy or Brugada syndrome. Concordance of atrial and ventricular phenotypes often does not occur, however. Although functional studies of AF-causing variants would suggest that short QT intervals might be present, affected family members with the S140G KCNQ1 mutation showed normal or long QT intervals, whereas those with the R27C KCNE2 and V93I KCNJ2 mutations all had normal QT intervals. Although genetic variants provide a molecular blueprint for disease, factors in addition to the presence of mutant protein are determinants of the clinical phenotype, and chamber-specific expression of ion channel binding partners, modifying genetic and environmental factors, or additional unrelated defects might be involved. Combined atrial and ventricular phenotypes due to a single gene defect may be difficult to differentiate clinically from AF with secondary left ventricular dysfunction or ventricular myopathies with secondary AF. The presence of ventricular involvement in inherited syndromes that include AF is important to recognize, because there are significant prognostic implications. For example, families in which AF occurs in association with short-QT syndrome have an increased risk of ventricular arrhythmias and sudden cardiac death and can be expected to have a worse prognosis than those with AF alone.

**Role of Atrial Stretch**

Consideration of a “2-hit” model in which inherited gene defects are unmasked by a second factor might help to explain mutations in genes that have atrial and ventricular expression but predominantly atrial phenotypes. We have recently identified a novel KCNQ1 mutation, R14C, in a family with a high prevalence of hypertension. AF was present only in older family members who were genotype positive and who had atrial dilatation. Patch-clamp studies and computer modeling showed no effect of mutant protein at baseline but a marked increase in $I_{Ks}$ activation and shortening of the atrial APD after exposure to hypotonic solution to induce cell stretch. Atrial dilatation is recognized as an independent risk factor for AF. Our data suggest that atrial stretch may be required to manifest inherited ion channel defects in some cases. Whether genetic factors identify subgroups at increased risk of AF within populations of individuals with hypertension or other conditions that can cause atrial dilatation remains to be determined.

**Single-Nucleotide Polymorphisms and AF**

The human genome contains DNA sequence variants that occur approximately every 1000 base pairs. Single-nucleotide
polymorphisms (SNPs) are the most common type of inherited genetic variation and consist of a change at a single base of a DNA molecule. SNPs may be benign or may alter protein function to a variable extent. A single SNP is generally not sufficient to cause disease but may act alone or in combination with other SNPs to increase susceptibility to disease or to precipitating factors and predisposing conditions. Inherited SNPs may account for a substantial proportion of familial clustering of AF in the general community. For some SNPs, a strong potential link with disease causation is based on in vitro experimental data. In many cases, however, deleterious effects have only been inferred on the basis of clinical data in patients who are SNP positive, or they have been predicted on the basis of the known function of a specific gene. An SNP that is linked to a disease locus may not itself have any pathogenic effects but may be a marker for a nearby SNP that does alter protein function. For example, SNPs in introns and untranslated regions, such as the ACE insertion/deletion and A1166C AGTR1, respectively, might be located in uncharacterized regulatory sequences but are more likely to be markers for pathogenic variants located in the vicinity.

SNPs in several cardiac ion channel genes, including components of the $I_{\text{Ks}}$ channel, have been linked with AF. Interestingly, familial AF-causing mutations in $I_{\text{Ks}}$ channel genes have all had gain-of-function effects, whereas the S38G variant in the KCNE1 gene reduces $I_{\text{Ks}}$ current density and prolongs atrial APD. AF has also been associated with SNPs in genes that alter regulation of ion channel function (eg, GNB3 and NOS3 genes), intracellular Ca$^{2+}$ handling, gap junction formation (eg, GJA5 gene), and activation of the renin-angiotensin system. Although these studies suggest that a variety of genetic defects that alter the electrical or structural milieu of the atrium can provide a substrate for arrhythmogenesis, they are far from being definitive. The majority of studies have evaluated commonly occurring SNPs but have not been replicated in independent populations or in different ethnic groups and have been substantially underpowered. Given the statistically significant but modest overall effects on disease risk found with the SNPs investigated to date, it is imperative that future studies be conducted in large patient cohorts, particularly when SNPs of relatively low allele frequency are being evaluated. The power for detecting significant associations with disease may be increased considerably by the use of haplotypes, which are groups of SNPs within 1 gene or on 1 chromosome that are inherited as a unit. In addition to AF susceptibility, SNPs may also prove to be useful for prediction of thromboembolic complications and responses to therapy.

**Somatic Mutations**

Genetic disorders are inherited in families by transmission of gene mutations in the germ cells. Mutations can also arise de novo in discrete cell lineages during embryonic development or postnatal life. Do novo mutations that occur in germ cells can be passed down to subsequent generations, whereas those that occur in somatic cells are not transmitted. Somatic mutations give rise to mixed populations of normal and mutant cells in specific tissues (mosaicism) that may have variable functional consequences. Clonal expansion of cells bearing somatic mutations that confer growth and survival advantages is thought to underlie many types of cancer. Somatic mutations have also been implicated in various neurologic, dermatologic, and hematologic disorders. Mitochondrial dysfunction due to accumulation of somatic mutations is thought to contribute to the normal aging process and to a number of age-related disorders, including heart failure and AF. A somatic mutation in the gene encoding the Go[s] protein that was localized to right ventricular outflow tract cells was found in 1 individual with adrenergically mediated ventricular tachycardia. In a recent study, somatic mutations in atrial cardiomyocytes were investigated as a cause of AF in 15 individuals with lone AF. Mutation screening of the GJA5 gene, which encodes the cardiac gap junction protein connexin40, was performed in genomic DNA isolated from peripheral blood lymphocytes and surgically resected atrial tissue. Three variants, P88S (in 2 subjects), M163V (in 1 subject), and G38D (in 1 subject), were present in atrial tissue DNA but not in lymphocyte DNA, whereas 1 variant, A96S (in 1 subject), was present in both atrial tissue and lymphocyte DNA. Functional studies showed that the P88S, G38D, and A96S variants reduced gap junction formation and/or coupling properties. These data suggest that connexin40 mosaicism in the atria could provide a substrate for reentrant arrhythmias and that genetic defects due to somatic mutations might underlie apparently “sporadic” AF in many cases. Although there was only 1 affected individual in the kindred with the A96S variant, the presence of this sequence change in lymphocyte and atrial DNA is consistent with germline transmission and the possibility of familial AF.

The cause of DNA variation in somatic cells is not well understood, but toxic effects of endogenous (eg, reactive oxygen species) or exogenous (eg, ionizing radiation, chemicals) factors may be involved. In addition to somatic mutations, genetic alterations could contribute to progressive cardiac dysfunction in a number of ways. Somatic DNA damage has been associated with stochastic deregulation of gene expression and cellular senescence in the murine heart. Recent studies have shown that small noncoding RNA molecules (microRNAs) are involved in cardiac development and are upregulated in pressure-induced hypertrophy and heart failure. Further studies of somatic mutations and epigenetic factors in the pathogenesis of AF and related cardiovascular disorders are warranted.

**Future Directions**

Over the past few decades, considerable progress has been made in understanding the molecular basis of atrial conduction and the electrophysiological perturbations that give rise to AF. There is now a growing body of evidence that AF can be a heritable disorder. Functional characterization of genetic variants identified in families and in sporadic cases of AF provides a reasonably compelling argument that inherited gene defects could have a direct role in AF development. The relative importance of genetic factors in the heritability of AF is still incompletely understood. Like many common diseases, familial forms of AF due to gene mutations with high penetrance are likely to account for a small proportion of all
TABLE 3. Association Studies of SNP in AF and Control Populations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant*</th>
<th>Association</th>
<th>Affected/Control Subjects; Population Studied</th>
<th>Functional Consequences†</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNQ1</td>
<td>P448R, R519H, G643S</td>
<td>NS</td>
<td>142/238; unselected AF</td>
<td>Reduced $\kappa_0$ density + prolonged APD; early afterdepolarizations (with reduced repolarization reserve only)</td>
<td>55–58</td>
</tr>
<tr>
<td>KCNE1</td>
<td>S38G</td>
<td>Significant</td>
<td>108/108; unselected AF</td>
<td>Reduced $\kappa_0$ density and $\kappa_{\text{CaL}}$</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significant</td>
<td>331/441; nonvalvular AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS</td>
<td>142/238; unselected AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D85N</td>
<td>NS</td>
<td>142/238; unselected AF</td>
<td>Unknown</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>KCNE4</td>
<td>E145D</td>
<td>Significant</td>
<td>142/238; unselected AF</td>
<td>Possible role in $\kappa_0$ activation</td>
<td>55</td>
</tr>
<tr>
<td>KCNE5</td>
<td>P33S</td>
<td>Significant</td>
<td>158/96; nonvalvular AF</td>
<td>Possible role in $\kappa_0$ activation</td>
<td>59</td>
</tr>
<tr>
<td>SCN5A</td>
<td>H558R</td>
<td>Significant</td>
<td>157/314; lone AF</td>
<td>Reduced $\kappa_0$ density</td>
<td>60</td>
</tr>
<tr>
<td>GNB3</td>
<td>825C→T (splice site, exon 9)</td>
<td>Significant</td>
<td>291/292; nonvalvular AF</td>
<td>Short G-protein $\beta_2$-subunit isofrom due to alternate splicing; increased $\kappa_i$, decreased $\kappa_{\text{CaL}}$</td>
<td>61</td>
</tr>
<tr>
<td>NOS3</td>
<td>−786T→C (promoter)</td>
<td>Significant</td>
<td>331/441; nonvalvular AF</td>
<td>Reduced eNOS promoter activity and nitric oxide levels; predicted increased $\kappa_{\text{CaL}}$ + decreased vagal activity and $\kappa_{\text{CaL}}$</td>
<td>57,62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS</td>
<td>51/289; CCF + AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E298D</td>
<td>Significant</td>
<td>51/289; CCF + AF</td>
<td>Reduced basal nitric oxide production; predicted effects as for T-786C</td>
<td>57,62</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>331/441; nonvalvular AF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a,4b (tandem repeat, intron 4)</td>
<td>NS</td>
<td>331/441; nonvalvular AF</td>
<td>Unknown</td>
<td>57,62</td>
<td></td>
</tr>
<tr>
<td>SLN</td>
<td>−65G→C (5′UTR)</td>
<td>Significant</td>
<td>147/92; nonvalvular AF</td>
<td>Possible effect on sarcolipin function, SERCA2 regulation and intracellular $\left[Ca^{2+}\right]$</td>
<td>63</td>
</tr>
<tr>
<td>GJA5</td>
<td>−44G→A (promoter)</td>
<td>Significant</td>
<td>14/16; lone AF</td>
<td>Reduced CX40 promoter activity; predicted impairment of gap junction formation</td>
<td>64,65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significant</td>
<td>173/232; unselected AF</td>
<td></td>
<td></td>
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<tr>
<td>ACE</td>
<td>I/D (intron 16)</td>
<td>Significant</td>
<td>51/289; CHF + AF</td>
<td>Increased levels of circulating ACE in I/D; DD genotypes; predicted to promote cardiomyocyte hypertrophy and fibroblast proliferation</td>
<td>62, 66–68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS</td>
<td>510/520; nonvalvular AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>77/83; lone AF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>250/250; nonvalvular AF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGT</td>
<td>−217G→A, −6G→A (promoter)</td>
<td>Significant</td>
<td>250/250; nonvalvular AF</td>
<td>Increased angiotensinogen promoter activity; predicted effects as for ACE I/D variant</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS</td>
<td>250/250; nonvalvular AF</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>−152G→A, −20A→C (promoter)</td>
<td>NS</td>
<td>250/250; nonvalvular AF</td>
<td></td>
</tr>
<tr>
<td>M235T</td>
<td>Significant</td>
<td>250/250; nonvalvular AF</td>
<td>Increased angiotensinogen levels (linkage disequilibrium with T174M); predicted effects as for ACE I/D variant</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>T174M</td>
<td>NS</td>
<td>250/250; nonvalvular AF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGTR1</td>
<td>1166A→C (3′UTR)</td>
<td>NS</td>
<td>250/250; nonvalvular AF</td>
<td>Unknown</td>
<td>67</td>
</tr>
</tbody>
</table>

Ref indicates reference number; CCF, congestive cardiac failure; NS, not significant; eNOS, endothelial nitric oxide synthase; SERCA2, sarcoplasmic/endoplasmic reticulum $\text{Ca}^{2+}$ ATPase; CX40, connexin40; and I/D, insertion/deletion.

*Amino acid substitutions and other genomic alterations that result from DNA sequence variants are indicated.
†Data from in vitro studies of specific SNPs and laboratory assays in SNP-positive patients, or predicted consequences based on known gene function.

It is anticipated that studies of single-gene mutations in families will point to key molecules in which DNA sequence variants that predispose to more common forms of AF may be found. Genetic studies in families have primarily evaluated cardiac ion channel defects; however, perturbation of diverse cellular pathways that affect impulse propagation in the atria could provide a substrate for AF. The ongoing challenge for researchers is to elucidate not only the genetic and environmental components that contribute to AF but also the relative importance of each of these factors and interactions between them. For example, environmental factors may enhance the effects of gene defects, and genetic factors may increase susceptibility to environmental changes. Further studies of the role of SNPs in the heritability of AF will require adequately powered associa-
Figure 3. The AF pyramid. Genetic and environmental (E) factors are thought to contribute to AF pathogenesis, although the relative importance of these factors has yet to be determined. Single-gene mutations that cause AF in families represent a minority of cases but may be relatively more common in young individuals with AF. The increasing prevalence of AF with age is likely to result from the effects of 1 or more predisposing SNPs, together with increases in “environmental” factors. The latter is loosely used to refer to the atrial context, i.e., altered atrial structure or function due to other disease states or exogenous factors.

Disease association studies are only the first step, however, and prospective evaluation of predictive models that incorporate clinical and genomic variables will subsequently be required. Characterization of genetic variants that are causative or that increase susceptibility to AF holds promise for in vitro rectifier potassium channel transcripts in human atrium versus ventricle. Circulation. 1998;98:2422–2428.

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Disclosures

None.

References


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Diane Fatkin, Robyn Otway and Jamie I. Vandenberg

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