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A CONTEMPORARY REVIEW ON THE GENETIC BASIS OF ATRIAL FIBRILLATION

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Abstract

Atrial fibrillation is the most common sustained cardiac arrhythmia, and affected individuals suffer from increased rates of heart failure, stroke, and death. Despite the enormous clinical burden that it exerts on patients and health care systems, contemporary treatment strategies have only modest efficacy that likely stems from our limited understanding of its underlying pathophysiology. Epidemiological studies have provided unequivocal evidence that the arrhythmia has a substantial heritable component. Subsequent investigations into the genetics underlying atrial fibrillation have suggested that there is considerable interindividual variability in the pathophysiology characterizing the arrhythmia. This heterogeneity may partly account for the poor treatment efficacy of current therapies. Subdividing atrial fibrillation into mechanistic subtypes on the basis of genotype illustrates the heterogeneous nature of the arrhythmia and may ultimately help guide treatment strategies. A pharmacogenetic approach to the management of atrial fibrillation may lead to dramatic improvements in treatment efficacy and improved patient outcomes

Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is associated with a reduced quality of life and increased risk of stroke and death.[1-3] Annual U.S. health care costs associated with treating the condition have been estimated at $6.65 billion.[4] The considerable health care burden will accelerate as the prevalence of AF has been projected to nearly triple by the year 2050.[5] Unfortunately, present treatment strategies suffer from limited efficacy and risks of adverse events[6, 7] stemming from our limited understanding of the mechanisms of AF, a notion that is reflected by persistent disagreement regarding its underlying pathophysiology and approach to catheter ablation.[8]

Recognition that AF has a heritable component has led to an intensive search for the genetic culprits responsible for the disorder. Identification of genes that predispose to the arrhythmia has begun to provide further insight into the factors that govern its initiation and maintenance.[9] Based on the diverse genetic culprits identified thus far, it has become increasingly clear that AF is a heterogeneous disorder that will likely necessitate a personalized therapeutic approach to optimize treatment outcomes.[9]

AF as a Genetic Disease

A variety of clinical features including advanced age, structural heart disease, and hypertension have been identified as risk factors for AF.[10] Although the majority of AF subjects develop the arrhythmia in the context of pre-existing forms of cardiovascular disease, approximately 15% of cases occur in otherwise healthy individuals.[11] The development of AF in the absence of traditional risk factors, referred to as lone AF, suggested a potential role for genetics as a mediator of disease. Indeed, a family with lone AF transmitted with an autosomal dominant pattern of inheritance was first documented by Wolff in 1943.[12] Epidemiological studies have found that individuals who have a first-degree relative with lone AF carry a 7- to 8-fold increased risk.[13] Even more dramatic, the presence of an affected sibling was associated with a 70- and 34-fold increased risk in males and females, respectively.[14]

Although more pronounced in the context of lone AF, the form of the arrhythmia associated with structural heart disease has also been shown to have a heritable component. A prospective cohort analysis from the Framingham Heart Study involving 2,243 subjects found that parental AF conferred a 1.85-fold increased risk in offspring.[15] A similar study from Iceland involving 5,269 patients corroborated the latter result, identifying a 1.77-fold increased risk of developing AF in first-degree relatives.[16] This greater vulnerability is not attenuated by adjustment for traditional risk factors linked to the arrhythmia, suggesting that the heightened risk is secondary to an underlying genetic etiology.[17] Collectively, these findings provide convincing epidemiological evidence to suggest that genetics play a critical role in the development of both lone and structural AF.

Mechanistic Subtype of AF 1: Gain-of-Function Potassium Channels and Enhanced Atrial Action Potential Repolarization

The first causative gene responsible for familial AF was found in 2003. The culprit locus on this occasion was mapped to the short arm of chromosome 11 (11p15.5) in a four-generation Chinese family with an autosomal dominant pattern of inheritance for lone AF.[18] Chromosome 11p15.5 was noted to contain the *KCNQ1* gene, which encodes the pore-forming α subunit of the slow component of the delayed rectifier potassium current (I_{Ks}). Loss-of-function mutations within *KCNQ1* had previously been recognized as

the cause for long QT syndrome type 1, a cardiac channelopathy associated with malignant ventricular arrhythmias and sudden cardiac death.[19] Given its biological plausibility based on its established link with a cardiac arrhythmic disorder, *KCNQ1* was considered an ideal candidate gene. Sequencing of *KCNQ1* identified a Ser140Gly mutation that segregated with AF cases within the family.

Following identification of the putative culprit mutation, in vitro functional studies using COS-7 cells found that coexpression of mutant Ser140Gly *KCNQ1* with *KCNE1*, the β subunit of I_{Ks}, resulted in markedly increased current density relative to the wild-type gene. These findings suggested that the Ser140Gly mutation resulted in a gain of function leading to increased I_{Ks}. Given that I_{Ks} is responsible for repolarization of cardiomyocytes, a gain-of-function mutation would be hypothesized to result in more rapid repolarization of cells, leading to a shortened effective refractory period (ERP)—the length of time a cell requires following depolarization before it can be re-excited. The presence of a shortened ERP within atrial cardiomyocytes is felt to contribute to the development of a substrate capable of supporting multiple-circuit reentry that may predispose to a form of AF reflective of the multiple wavelet hypothesis.[20]

The importance of *KCNQ1* in the pathogenesis of AF has been further strengthened by additional linkage analyses and reports that have identified *KCNQ1* mutations in familial AF cases.[21-23] It should be noted that 9 of the 16 individuals from the original family possessing the *KCNQ1* Ser140Gly had prolonged QT-intervals on 12-lead electrocardiography that is inconsistent with a gain-of-function effect, since an increased I_{Ks} would be predicted to result in a shortened QT-interval. The explanation for this discrepancy remains unclear but may be reflective of different electrical properties in the atria and ventricles or may be secondary to an inability to accurately recapitulate the electrical milieu of the heart with in vitro functional models.

Since the original landmark discovery, candidate gene approaches that screened AF cases for mutations within multiple potassium channel genes has led to further insight into the role of three additional potassium channel genes in AF pathogenesis secondary to gain-of-function mutations, namely *KCNE2*, *KCNJ2*, and *KCNE5*.[24-26]

An identical mutation within *KCNE2*, which encodes the β subunit of the rapid component of the delayed rectifier potassium current (I_{Kr}), was discovered in 2 of 28 unrelated Chinese kindreds with familial AF.[24] The probands within both families were found to carry an Arg27Cys mutation that appeared to segregate with affected members from both kindreds and was absent from 462 healthy controls. It should be noted that there were multiple unaffected members in each family who carried the *KCNE2* Arg27Cys mutation. This apparent discrepancy may be reflective of low penetrance or may potentially reflect the possibility that *KCNE2* Arg27Cys is a disease-contributing as opposed to a disease-causing variant. Ensuing functional work on the mutant form of *KCNE2* was suggestive of a gain of function that would result in acceleration of cardiomyocyte repolarization due to enhanced I_{Ks}.

A *KCNJ2* gene mutation was identified in a single AF proband following screening of 30 Chinese AF kindreds for mutations within 10 ion channel or channel-binding related genes (*KCNQ1*, *KCNH2*, *SCN5A*, *ANK-B*, *KCNJ2*, *KCNE1-5*).[25] *KCNJ2* encodes Kir2.1, which is responsible for the cardiac inward rectifier potassium current IK_1. This channel mediates a potassium current that contributes to the resting membrane potential of the cell and influences cardiac excitability and repolarization. It is also the causative gene for congenital long QT syndrome type 7, also referred to as Andersen-Tawil Syndrome. The proband and the other four affected family members were all found to carry a Val93Ile mutation within *KCNJ2*, a mutation that was absent from 420 healthy individuals. While there were two healthy family members that carried the mutation, their unaffected status may have been secondary to incomplete penetrance or their relatively young ages (33 and 42 years old). Functional analysis of the mutant protein revealed increased current density consistent with a gain-of-function effect. The putative predisposing mechanism of Val93Ile *KCNJ2* for AF involves enhanced repolarization and a reduction in refractory period, as hypothesized with *KCNQ1* and *KCNE2*.

The final potassium channel gene implicated in the pathogenesis of AF through an acceleration of cardiomyocyte repolarization is *KCNE5*.[26] Investigators screened 158 AF cases for mutations within the coding region of *KCNE5* and identified a Leu65Phe mutation in a 66-year-old female with a persistent form of the arrhythmia. She had no family history of AF, unlike the familial forms of AF observed with the previous potassium channel genes, and had risk factors including hypertension and ischemic heart disease. Although the possibility of a de novo mutation cannot be excluded given that other family members were not screened, the sporadic nature of this case, coupled with the presence of pre-existing risk factors, suggest that *KCNE5* Leu65Phe may actually reflect a disease-contributing genetic variant as opposed to a disease-causing mutation for AF.

The finding that gain-of-function potassium channel mutations predispose to AF has led to an understanding that enhanced atrial repolarization accounts for a mechanistic subtype of the arrhythmia (Table 1). This observation leads to reduced atrial tissue refractoriness, providing a substrate capable of supporting multiple self-perpetuating micro-reentrant circuits.

Mechanistic Subtype of AF 2: Loss-of-Function Potassium and Sodium Channels and Delayed Atrial Action Potential Repolarization

Loss-of-Function Potassium Channel Mutations

The initial potassium channel gene mutations implicated in the development of AF had been shown to result in gain-of-function effects based on in vitro functional analysis. An alternative form of AF driven by opposing pathophysiology had been suggested by previous work, which noted the development of a polymorphic atrial tachycardia that subsequently degenerated into AF after injection of cesium chloride, a potassium channel blocker, into the sinus node artery of dogs.[27] These findings led the investigators to coin the term "atrial torsade" and suggested that loss-of-function potassium channel gene mutations may also predispose to AF. Subsequent screening for potassium channel mutations in AF identified a novel nonsense mutation (E375X) within the *KCNA5* gene.[28] *KCNA5* encodes an atrial-specific voltage-gated potassium channel, $K_V1.5$, which is responsible for the ultra-rapid component of the delayed rectifier potassium current (I_{Kur}). The *KCNA5* E375X nonsense mutation resulted in a truncated protein lacking the S4-S6 voltage sensor, the pore region, and the C-terminus.

Functional studies revealed that this truncated form of *KCNA5* was unable to conduct current, which is consistent with a loss-of-function effect.[28] In vitro studies using human atrial myocytes and in vivo studies with a murine model found that administration

AF Subclassification	Culprit Gene(s)	Functional Effect
Enhanced atrial action potential repolarization	KCNQ1 KCNE2 KCNJ2 KCNE5	Enhanced slow component of the delayed rectifier potassium current (I_{Ks}) Enhanced KCNQ1-KCNE2 potassium current Enhanced inward rectifier current (I_{K1}) Enhanced I_{Ks}
Delayed atrial action potential repolarization	KCNA5 SCN5A	Decreased ultra-rapid component of the delayed rectifier potassium current (I_{kur}) Hyperpolarizing shift in Nav1.5 inactivation
Conduction velocity heterogeneity	GJA5 GJA1	Heterogeneous reduction in gap junction conduction
Cellular hyperexcitability	SCN5A	Depolarizing shift in Nav1.5 inactivation
Hormonal modulation of atrial electrophysiology	*NPPA*	Increased circulating levels of mutant ANP
Cholinergic	Unknown	Enhanced cholinergic sensitivity

Table 1. Mechanistic subclassification of lone atrial fibrillation and putative pharmacogenetic strategy (modified from reference 9).

of 4-aminopyridine, a known blocker of *IKur*, dramatically increased the incidence of early afterdepolarizations. The authors hypothesized that increased early afterdepolarizations associated with a prolonged atrial action potential duration could trigger AF akin to that seen in torsade de pointes within the ventricles, which occurs with loss-of-function potassium channels in long QT syndrome. The importance of loss-of-function *KCNA5* mutations in the pathogenesis of AF has been reaffirmed by subsequent reports.[29, 30]

Loss-of-Function Sodium Channel Mutations

The *SCN5A* gene had been implicated in numerous arrhythmic disorders including the Brugada syndrome, congenital long QT syndrome type 3, and sick sinus syndrome.[31-33] A study involving 375 patients with a mixture of lone (118) and structural AF (257) identified 8 novel mutations in 10 different subjects that were absent from 360 healthy controls.[34] The variants involved highly conserved residues within *SCN5A* and segregated with disease in all six of the familial cases. This report provided strong evidence that mutations within *SCN5A* represented an important cause of AF in patients with and without heart disease.

The first *SCN5A* mutation associated with AF that was functionally characterized was found after screening 57 patients with lone AF or AF with hypertension and a confirmed family history of AF.[35] A single novel mutation was found, Asn1986Lys, which was absent from 300 ethnically matched controls. The affected father of the proband also carried the mutation; however, further genetic profiling of the family was not possible due to lack of consent. Expression of the mutant gene within *Xenopus laevis* oocytes suggested a loss-of-function effect as evidenced by a significant hyperpolarizing shift in the midpoint of steady-state inactivation. This alteration was predicted to prolong the atrial action potential duration, and therefore the *SCN5A* Asn1986Lys was hypothesized to predispose to AF through a manner akin to the aforementioned atrial torsade.

Mechanistic Subtype of AF 3: Gap Junction Impairment and Conduction Velocity Heterogeneity

Connexins

Connexin proteins form specialized channels, termed gap junctions, at the intercellular junction between adjacent cells that permit the flow of charged ions between the cytoplasmic compartments of neighbouring cells.[36] The resultant intercellular communication facilitates coordinated propagation of cardiac action potentials that enables the myocardium to depolarize in an organized manner. Connexin proteins oligomerize into hexameric structures known as connexons or hemichannels, which form functional gap junctions by interacting with hemichannels from adjacent cells.[37] The two most highly expressed connexin isoforms within the heart are connexin 40 and 43. Notably, connexin 40 is exclusively expressed within atrial myocytes and is absent from ventricular cells.[37] The importance of connexins to AF has been suggested by animal studies, which revealed that connexin 40 knockout mice exhibited an increased vulnerability to atrial tachyarrhythmias.[38]

Given the apparent importance of connexin 40 in atrial electrophysiology, our group screened 15 patients with sporadic, lone AF for somatic mutations within connexin 40.[39] We hypothesized that somatic (atrial tissue-specific) mutations, as opposed to heritable germ-line mutations, may account for the development of AF in healthy individuals with no family history of the arrhythmia. DNA was obtained from both peripheral blood lymphocytes and resected atrial tissue of patients who had undergone an open-heart pulmonary vein isolation procedure. In 4 of the 15 patients, genetic mutations within the connexin 40 gene (*GJA5*) were identified. Findings consistent with a tissue-specific or somatic basis of the mutations were found in 3 of the 4 patients, as evidenced by the presence of the mutation within the resected atrial tissue and not in peripheral blood lymphocytes. This observation supported the concept that tissue-specific mutations, analogous to the genetic basis of most cancers, may lead to the development of common cardiac arrhythmic disorders. Since myocardial cells do not divide, a somatic mutation must have occurred in an early myocardial progenitor cell during embryogenesis, leading to genetic mosaicism within the atrial tissue.

Functional studies of the mutant connexin proteins were performed in a gap junction-deficient cell line, N2A cells. Cells expressing mutant connexins showed a significant loss of function in the ability to electrically couple paired cells. The identified

mutant connexins demonstrated a dominant negative effect on wild-type Cx40 as well as a transdominant negative effect on wild-type Cx43.[40] This latter finding provides strong support for the concept of heteromeric interaction of Cx40 and Cx43 in hemichannel formation.

Following this initial report, we subsequently identified a novel somatic frameshift mutation within connexin 43 in a sporadic case of lone AF.[40] The frameshift mutation (c.932delC) was identified in an otherwise healthy female who was diagnosed with AF at 48 years of age following a longstanding history of palpitations. The single base pair deletion resulted in a truncated C-terminal domain of connexin 43 containing 36 aberrant amino acids. Subcloning of polymerase chain reaction products from left atrial tissue was consistent with genetic mosaicism, while protein trafficking studies revealed intracellular retention of the mutant protein. As observed with connexin 40 mutants, the aberrant form of connexin 43 abolished gap junction formation in the presence of both wild-type connexin 40 and 43, consistent with dominant- and transdominant negative loss-of-function effects, respectively.

Collectively, these findings provide compelling evidence that somatic or atrial-specific genetic defects within both connexin 40 and 43 predispose to the development of sporadic, lone AF. The presence of genetic mosaicism in the context of these loss-of-function connexin mutations is likely critical for their role in promoting arrhythmogenesis within atrial tissue. A predisposition to the chaotic electrical reentry circuits characterizing AF will likely be greater in the presence of an arrhythmogenic substrate that exhibits substantial regional variability in conduction velocity. Furthermore, the general notion that regional variability of cardiac electrical properties is proarrhythmic provides support for a potential broader role of genetic mosaicism in the pathogenesis of AF. It should be noted, however, that genetic mosaicism does not appear to be a prerequisite for the development of AF in the presence of connexin mutations. Since our original findings, multiple reports have emerged in the literature implicating connexin 40 mutations in cases of familial AF.[41, 42]

Mechanistic Subtype of AF 4: Cellular Hyperexcitability

Initial studies had implicated loss-of-function *SCN5A* mutations in the development of AF, but the arrhythmogenic potential of gain-of-function *SCN5A* mutations had also been well documented in long QT syndrome type 3.[43] Long QT syndrome type 3 develops secondary to an *SCN5A* gain-of-function effect that prolongs cardiac repolarization through an increased late sodium current.[44] The importance of *SCN5A* gain-of-function mutations in AF pathogenesis was confirmed after investigations involving a four-generation Japanese family with an autosomal dominant form of AF that carried a novel *SCN5A* Met1875Thr mutation.[45] The novel variant exhibited perfect genotype-phenotype segregation within the family, consistent with its being fully penetrant, and was also absent from 210 ethnically matched controls. The proband was noted to have increased right atrial excitability during radiofrequency catheter ablation for AF. Functional analysis of Met1875Thr revealed a pronounced depolarizing shift in the midpoint of steady-state inactivation consistent with a gain-of-function effect. No increased late sodium current was observed, accounting for the presence of normal QT intervals within affected individuals.

A second study from our group involving a mother and son with lone AF identified a Lys1493Arg mutation involving a highly conserved residue within the DIII-IV linker located 6 amino acids downstream from the fast inactivation motif of sodium channels.[46] Biophysical studies demonstrated a significant positive shift in the voltage dependence of inactivation and a large ramp current near resting membrane potential, consistent with a gain of function. When expressed in HL-1 atrial cardiomyocytes, enhanced cellular excitability was observed in the form of spontaneous action potential depolarizations and a lower threshold for action potential firing as compared to wild-type cells. Collectively, these studies suggest that gain-of-function mutations within *SCN5A* are associated with AF.

The existing evidence suggests that *SCN5A* gain-of-function mutations predispose to AF by enhancing cellular hyperexcitability. The depolarizing shift in steady-state inactivation increases the probability that the channel will be in the open conformation and capable of conducting current.[46] This alteration in the gating of the $Na_v1.5$-mediated current will presumably result in a predisposition for cells to reach threshold potential and fire, consistent with enhanced automaticity. This increase in focal discharges has the potential to serve as the trigger for AF. In addition, $Na_v1.5$ channels have recently been identified in the autonomic ganglia that surround the pulmonary veins.[47] Mutations within *SCN5A* may therefore result in neuronal hyperexcitability that may trigger AF through a parasympathetic pathway and contribute to the rapidly firing ectopic foci observed in the region of the pulmonary veins in some patients with the arrhythmia.

Mechanistic Subclass of AF 5: ANP Modulation of Atrial Electrophysiology

The most recent gene to be associated with AF does not implicate an ion channel but instead involves a circulating hormone, the atrial natriuretic peptide (ANP). Although known to be important in cardiac physiology, ANP had been largely viewed as cardioprotective in the setting of heart failure.[48] It was known, however, to be capable of modulating the electrical activities of the heart, and there were reports of its effects on specific ion channels.[49, 50] However, little work had been done on ANP in the context of AF, and previous studies examining ANP levels as a biomarker in AF had been negative.[51]

Linkage analysis of a Caucasian family of northern European ancestry with autosomal dominant AF mapped the causative locus to the small arm of chromosome 1 (1p36-35).[52] Review of the genes within this region revealed the presence of *NPPA*, the gene encoding ANP, and subsequent sequencing revealed a two base-pair deletion in exon 3 that resulted in a frameshift associated with loss of the stop codon. Extension of the reading frame results in an elongated peptide that is 40 amino acids in length relative to the wild-type 28 amino acid length. The deletion was present in all of the affected family members but absent in unaffected family members and 560 control patients. Functional studies involving an isolated rat whole-heart model suggested that the mutant ANP resulted in shortened action potential duration and reduced effective refractory period, although the mechanism was not entirely clear.

ANP mediates its effects on cells by binding to natriuretic peptide receptors that possess intracellular guanylate cyclase activity.[53] Previous work has suggested that ANP molecules with an elongated C-terminus may be more resistant to degradation and therefore may circulate at higher levels.[54] Therefore the authors hypothesized that increased circulating ANP may result in elevated intracellular levels of cGMP that may in turn, through an unknown

mechanism, reduce the effective refractory period.

Triggered by the insight that ANP may influence vulnerability for AF, our group screened for a potential association between common genetic variants within *NPPA* and AF. Notably, two common genetic variants that create nonsynonymous amino acid changes within *NPPA*, rs5063, and rs5065 had previously been implicated in conditions associated with AF.[55, 56] A small Chinese study had suggested that the presence of rs5063 resulted in an increased risk of AF.[57] However, our study involving 620 AF cases and 2,446 controls found no association between either single nucleotide polymorphism (SNP) and the risk of AF.[58]

Mechanistic Subclass of AF 6: Cholinergic (Vagal) AF

The autonomic nervous system has been recognized as a critical component of arrhythmogenesis. In the setting of lone AF, the sentinel observations of the eminent electrophysiologist Phillipe Coumel have implicated the parasympathetic nervous system as a major culprit.[59] Common triggers for the paroxysmal onset of AF in young individuals with structurally normal hearts include states associated with high vagal tone, such as sleep and the postprandial period. The mechanism through which the parasympathetic nervous system mediates lone AF appears to be in part dependent upon I_{KAch}.[60] Activation of I_{KAch} triggers an efflux of potassium ions that leads to shortening of the atrial action potential duration and the corresponding refractory period. The heterogeneous vagal innervation of the atria has the potential to result in regional variation of refractory periods.61 The resultant dispersion in cellular refractoriness throughout the atria has the potential to serve as an ideal substrate for reentry and arrhythmogenesis. To date, there have been no genetic culprits identified within vagal pathways that predispose to AF. Given its obvious importance in the pathogenesis of the arrhythmia, we anticipate that genetic culprits within this mechanistic subclass will emerge in the coming years.

Genome-Wide Association Studies

The previous discussion has focused on rare genetic variants as being causative for AF; however, genome-wide association studies have also provided evidence implicating common genetic variants in the pathogenesis of the arrhythmia. To date, three common genetic variants, or SNPs, have been found to associate with an increased risk of AF development.

4q25

The first genome-wide association study performed for AF involved 550 patients with AF or flutter and 4,476 control patients from Iceland.[62] Investigators discovered an association with SNPs on chromosome 4q25, the most significant being rs2200733 with an odds ratio of 1.84 (95% CI, 1.54-2.21). Replication studies using additional samples from Iceland (2,251 cases and 13,238 controls), Sweden (143 cases and 738 controls), the United States (636 cases and 804 controls), and China (333 cases and 2,836 controls) further reinforced the association with rs2200733. The odds ratio for the combined European population was 1.72 while that for the Chinese cohort was 1.42. The haplotype block corresponding to the associated SNPs does not contain a known gene, therefore the mechanism for this association is currently unknown. The primary genetic suspect has been *PITX2*, the nearest known gene in the region, which encodes a transcription factor involved in cardiac development. Following identification of this possible association, investigations using animal models have suggested that reduced expression of *PITX2* may predispose to an increased vulnerability to AF although the underlying mechanisms remain unclear.[63, 64]

16q22

Following identification of the 4q25 locus, two subsequent genome-wide association studies concurrently identified separate SNPs, rs7193343 and rs2106261, that both localized to an intronic region within the *ZFHX3* gene on chromosome 16q22.[65, 66] *ZFHX3* encodes a transcription factor whose function in the heart is currently unclear. The *ZFHX3* gene has recently been implicated in a vasculitis involving the coronary arteries (Kawasaki disease).[67] The association of 16q22 with AF was weaker than 4q25 in subjects of European ancestry and did not originally replicate in a Chinese population.[65] As with the 4q25 locus, further work is necessary to better appreciate the apparent relationship between these SNPs within16q22 and AF.

1q21

The initial two common genetic variants linked with AF were identified predominantly in the context of AF associated with structural heart disease. A third GWAS was performed that focused exclusively on lone AF.[68] The study involved 1,335 lone AF cases and 12,844 unaffected controls and identified a third common genetic variant that associated with the arrhythmia (adjusted odds ratio of 1.56), which was subsequently replicated in two independent lone AF cohorts. The genetic variant, rs13376333, localizes to chromosome 1q21 and is intronic to *KCNN3*, a calcium-activated potassium channel that is felt to influence atrial repolarization.

Summary

AF is the most common cardiac arrhythmia and is associated with increased rates of heart failure, stroke, and death. Despite its clinical impact, current treatment strategies have relatively modest efficacy that is likely driven by our limited understanding of its underlying pathophysiology. Clinical and epidemiological findings have provided unequivocal evidence that the arrhythmia has a substantial heritable component. Subsequent investigations into the genetics underlying AF have suggested that there is considerable interindividual variability in the pathophysiology that results in AF development. This heterogeneity may partly account for the poor treatment efficacy of many contemporary therapies. Subdividing AF into mechanistic subtypes on the basis of genotype serves to illustrate the heterogeneous nature of the arrhythmia and may ultimately help guide treatment strategies. We anticipate that a pharmacogenetic approach to the management of AF will lead to dramatic improvements in treatment efficacy and result in better patient outcomes and a reduction in the burden that this arrhythmia is currently exerting on health care systems.

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