Genetics of Atrial Fibrillation

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KEYWORDS

• Atrial fibrillation • Arrhythmia
• Mutation • Gene • Genetics

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and is increasing in both incidence and prevalence.[1,2] More than 2 million Americans currently have AF, and estimates project that between 5 and 12 million will be affected by 2050.[1,2] AF is associated with substantial morbidity, including one third of all strokes in patients older than 65[3] and a twofold increased risk of mortality.[4,5] The costs attributable to the care of individuals with AF are in excess of $6.4 billion per year.[3]

AF is often associated with hypertension and structural heart disease, and traditionally has not been considered a genetic condition. However, a number of recent studies have demonstrated that AF and in particular, lone AF, have a substantial genetic basis.[6–9] Mutations in several ion channels have been identified in individuals with familial AF,[10–17] although they appear to be rare causes of the arrhythmia.[18,19] Recently, a genome-wide association study has led to the identification of genetic variants associated with common forms of AF. In the course of this review we will discuss the heritability of AF, the methods used to identify causal variants underlying AF, and our current understanding of genetic variation implicated in AF.

ATRIAL FIBRILLATION IS A HERITABLE CONDITION

While familial forms of AF have long been reported,[20] a genetic predisposition for more common forms of AF has only recently been recognized. In 2003, Fox and coworkers[8] studied more than 5000 individuals whose parents were enrolled in the original Framingham Heart Study. Over a 19-year follow-up period, they found that the development of AF in the offspring was independently associated with parental AF, particularly if the offspring cohort was restricted to those younger than 75 and without antecedent heart disease. Having a parent with AF approximately doubled the 4-year risk of developing AF, even after adjustment for risk factors such as hypertension, diabetes mellitus, and myocardial infarction.

Arnar and colleagues[6] similarly described a genetic predisposition to AF in a study of more than 5000 Icelanders in 2006. After assessing relatedness from a nationwide genealogical database, 80% of those with AF were related to another individual with AF. The relative risk of AF for first-degree relatives of a family member with AF was 1.77, when compared with individuals in the general population. The relative risk for AF increased to 4.67 when the sample was restricted to individuals less than 60 years old.

A version of this article originally appeared in *Medical Clinics of North America*, volume 92, issue 1.
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Cardiol Clin 27 (2009) 25–33
doi:10.1016/j.ccl.2008.09.007

Further evidence of the heritability of AF was demonstrated in a chart review of more than 2000 patients with AF referred for evaluation at the Mayo Clinic.[9] Five percent of subjects had a family history of AF, and the number was as high as 15% among those with lone AF. In 2005, we found that nearly 40% of individuals with lone AF referred to the Arrhythmia Service at Massachusetts General Hospital had at least one relative with the arrhythmia, and a substantial number reported having multiple affected relatives.[7] In over 90% of cases, AF in the relatives could be verified. To obtain a crude index of heritability, we determined the prevalence of AF among each class of relative compared with that among age- and sex-matched subjects. The relative risk of AF was increased among family members, and ranged from twofold in fathers to nearly 70 fold in male siblings.

GENETIC STUDIES IN ATRIAL FIBRILLATION

Once a condition is found to be heritable, there are several techniques that are commonly used to identify the genetic basis of a disease. These include linkage analysis, candidate gene resequencing, and association studies. We will discuss each of these methods in the context of their application to AF.

Linkage Analysis

The genes that underlie simple monogenic disorders with a Mendelian pattern of inheritance can be identified using linkage analysis. When passed from generation to generation, genetic markers that lie close together on the same chromosome are likely to be transmitted en bloc in proportion to their proximity to each other. A genome-wide search for groups of markers that co-segregate with the disease as it travels through a family tree is performed to identify the approximate location of a genetic disease locus. Linkage studies report a logarithm of the odds, or LOD score, that reflects the likelihood of two markers or a marker and disease co-segregating when compared to chance alone. A LOD score of 3 or more (or odds of greater than 1000:1) is considered statistically significant. Traditionally, restriction enzyme sites and microsatellite repeats have been used as genetic markers, but more recently, it has become possible to use single nucleotide polymorphisms, or SNPs.[21] The ease of use in genotyping has made SNPs the most widely used genetic markers today.

Linkage analysis can be used to narrow the search for a causative gene to a chromosomal locus, or relatively small region of the human genome associated with disease. However, this limited region may still contain hundreds of genes spread over millions of base pairs. Once a genetic locus is identified, online data from human genome databases developed as a result of the Human Genome Project are used to identify candidate genes within the locus. These genes are then sequenced in affected individuals in an attempt to identify the sequence variants that correlate with the disease.

Once a base pair change is identified, it is important to differentiate between a mutation and a genetic polymorphism, or common variant in the genome. For a sequence alteration to be considered a mutation it must segregate with the disease, have a plausible mechanism, and not be found in healthy controls. Ultimately, the mutation should be sufficient to cause the phenotype, either in a human kindred or in a genetic model organism.

Although several genetic loci have been reported in kindreds with Mendelian AF in which specific genetic mutations have yet to be identified (**Table 1**),[22–25] linkage analysis has facilitated the identification of individual mutations in several cases of familial AF.[10,26]

In one such family of Chinese descent, Chen and coworkers[10] identified a mutation in *KCNQ1*, which encodes a potassium channel that underlies the slowly repolarizing current in cardiomyocytes known as I_{Ks} (**Fig. 1**). The investigators were able to map the disease locus to a 12-megabase region on the short arm of chromosome 11, in a four-generation family with AF. The *KCNQ1* gene was located within this region, and sequencing revealed a serine to glycine missense mutation at position 140 (S140G) in affected family members. The S140G mutation is located in the first transmembrane-spanning segment[27] at the outer edges of the voltage-sensing domain and far from the pore-forming region of the potassium channel structure. The S140G mutation results in a gain of channel function, in contrast to mutations in *KCNQ1* associated with the long QT syndrome that typically result in a loss of channel function. In cultured cells, expression of the S140G mutant channel resulted in dramatically enhanced potassium channel currents and markedly altered potassium channel gating kinetics, which would be predicted to increase I_{Ks}. Such an increase would be expected to lead to a shortening of the action potential duration and thus predispose atrial myocytes to reentry and subsequent AF (see **Fig. 1**).

While the identification of this mutation provided an initial inroad into the pathogenesis of AF, this family also illustrates our limited understanding of the role of the KCNQ1 channel in atrial versus ventricular repolarization. Specifically, it remains unclear why a mutation that results in an in vitro gain of function in KCNQ1 is associated with delayed ventricular repolarization, as manifested by

Table 1
Genes and loci implicated in familial atrial fibrillation

Genes				
11p15.5	*KCNQ1/KvLQT1*	Increases I_{Ks}, Expected to shorten APD	AD	10,14
21q22.1	*KCNE2/MiRP1*	Increases I_{Ks}	AD	11
17q23.1-24.2	*KCNJ2*	Increases I_{K1}; Expected to shorten APD	AD	12
12p13	*KCNA5*	Loss of I_{Kur} ; prolongs APD	AD	13
3p21	*SCN5A*	Hyperpolarizing shift of resting membrane potential; Expected to prolong APD	AD	15–17
1p36-p35	*NPPA*	Results in mutant atrial natriuretic peptide; associated with shortened APD	AD	26
Genetic Loci				
Chr	Gene	Comments	Inheritance	Reference
5p13	Unknown	Associated with sudden death	AR	24
6q14-q16	Unknown	Overlaps with locus for DCM	AD	23
10q22-q24	Unknown	Overlaps with locus for DCM	AD	22
10p11-q21	Unknown		AD	25

Abbreviations: Chr, Chromosome; AD, autosomal dominant; AR, autosomal recessive; DCM, dilated cardiomyopathy.

a prolonged QT interval, in more than half of the individuals with the S140G mutation.

Other gain of function mutations in *KCNQ1* have been associated with the short QT syndrome.[28] Hong and colleagues[29] reported an unusual case of AF detected in utero and confirmed on electrocardiogram upon delivery of the newborn. The infant's electrocardiogram also displayed a short QT interval. Based on this association, they sequenced the *KCNQ1* gene and found a valine to methionine mutation in position 141 (adjacent to the mutated position found by Chen and colleagues). Like the S140G mutation, in vitro expression of V141M mutant channels displayed markedly enhanced current density and altered gating kinetics.

More recently, Hodgson-Zingman and colleagues[26] identified a frameshift mutation in *NPPA* in a family with AF. The mutation in *NPPA*, which encodes atrial natriuretic peptide, resulted in increased levels of a circulating mutant peptide. Electrophysiological assessment in a rat heart model revealed decreased action potential

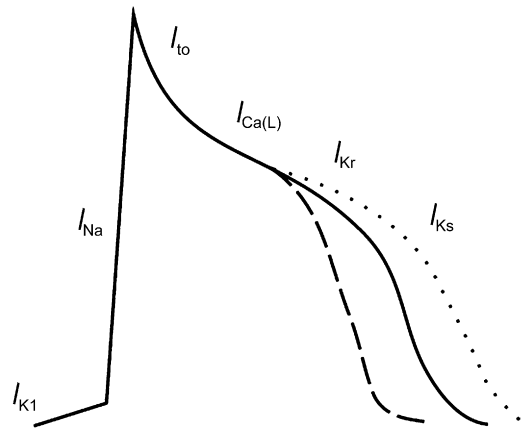

Fig. 1. Both gain of function and loss of function mutations in I_{Ks} have been associated with AF. Mutations in *KCNQ1* and *KCNE2* increase the current I_{Ks}, which is predicted to shorten the action potential (*dashed line*) in cardiac myocytes and render atrial myocytes susceptible to reentrant arrhythmias. Mutations in *KCNA5* (encodes Kv1.5) that are predicted to prolong the action potential duration (*dotted line*) have also been associated with AF.

duration, consistent with known mechanisms of reentrant mediated AF.[30]

Candidate Gene Studies

A candidate gene can be any gene that is hypothesized to cause a disease. Based on the work relating *KCNQ1* to AF, investigators have considered other potassium channels as potential candidate genes for AF and screened for mutations in these genes in cohorts of subjects with AF.

Otway and colleagues[14] examined 50 kindreds with AF and amplified the genes for *KCNQ1* and *KCNE1-3*, which encode accessory subunits of KCNQ1. They found a single mutation in *KCNQ1* in only one family—an arginine to cysteine change at amino acid position 14 (R14C) in *KCNQ1*. Unlike the S140G mutation discovered by Chen and colleagues,[10] R14C had no significant effect on KCNQ1/KCNE1 current amplitudes in cultured cells at baseline. However, upon exposure to hypotonic solution, mutant channels exhibited a marked increase in currents compared with wild type channels. Interestingly, of those who carried the R14C mutation, only those with left atrial dilatation had AF, leading the authors to propose a ''two-hit'' hypothesis for AF. They also identified a mutation in *KCNE2* in two of the kindreds. Like the S140G mutation in *KCNQ1* the mutation in *KCNE2* (R27C) dramatically increased the amplitude of I_{Ks}.[11]

Finally, other work has suggested that the relationship between potassium channels and AF extends beyond I_{Ks}. The work of Xia and colleagues[12] may also implicate *KCNJ2* which encodes, an inward rectifier potassium channel that underlies the I_{K1} current, in AF. In their work, a V93I mutation was found in all affected members in one kindred with familial AF. The V93I also leads to gain of function KCNJ2 channels, which increase potassium current amplitudes. However, there is still an incomplete understanding of how an increase in the background current I_{K1} might lead to atrial arrhythmias.

We have screened our cohort with lone AF for mutations in *KCNQ1*, *KCNJ2* and *KCNE1-5* and were unable to find any mutations in these genes.[18] These findings suggest that potassium channels are an uncommon cause of AF and there is much more to be learned about the diversity of molecular pathways that lead to this arrhythmia.

The genes encoding connexins, gap-junction proteins that mediate the spread of action potentials between cardiac myocytes, have also been examined as potential candidates for AF. Prior work has shown that mice with null alleles of *GJA5*, the gene for connexin40, exhibit atrial reentrant arrhythmias.[31] From this work, Gollob and coworkers[32] considered this gene as a potential candidate in individuals with idiopathic AF who underwent pulmonary vein isolation surgery. An analysis of DNA isolated from their cardiac tissue showed that 4 of the 15 subjects had mutations in *GJA5* that markedly interfered with the electrical coupling between cells. In three of the patients, DNA isolated from their lymphocytes lacked the same mutation in *GJA5* indicating that the connexin40 mutations had been acquired after fertilization or was a somatic mutation. One of the four individuals carried the mutation in both cardiac tissue and lymphocytes consistent with a germline rather than somatic mutation. However, more information about the transmission of AF in relatives of these individuals was not available.

Association Studies

Although traditional methods such as linkage analysis can be applied to families where the phenotype and pattern of inheritance are consistent with a monogenic disorder, the mode of transmission for AF is less clear. Association studies have been used in an attempt to identify the genetic basis of AF and other apparently complex traits. In an association study the frequency of a genetic marker, such as a SNP, is compared between individuals with an outcome (cases) and those without an outcome (controls). Over the past 10 years, many case-control and cohort studies have been performed in subjects with AF, leading to the identification of variants associated with disease. These studies have typically tested a small number of variants and have been directed at candidate genes previously believed to be involved in AF. Examples include genes encoding products involved in regulation of the renin-angiotensin-aldosterone axis[33–40] and calcium handling,[41] as well as neurohormonal[39] and lipoprotein[42] pathways. Additionally, genes encoding gap junction proteins,[43,44] ion channels,[15,45–49] interleukins,[50,51] signaling molecules,[34,45,52] and mediators of other molecular pathways[53] have been examined (summarized in **Table 2**). Unfortunately, these studies have been limited by a low prior probability of any polymorphism truly being associated with AF. Further complicating these analyses are the small sample sizes and a lack of replication in distinct populations, as well as phenotypic and genetic heterogeneity.

In recent years, genome-wide association studies (GWAS) have been made possible by advancements in genotyping technology that allow investigators to assay hundreds of thousands of SNPs spread over the entire human genome. The studies are typically executed using a case-control

Table 2
Polymorphisms associated with atrial fibrillation

Gene	Variant	Cases	Controls	OR	*P* Value	Replicated?	Comments	Reference
–	rs2200733	3913	22,092	1.72	3.3×10^{-41}	Yes	Identified in GWAS	62
–	rs10033464	3913	22,092	1.39	6.9×10^{-11}	Yes	Identified in GWAS	62
ACE	D/D	51	289	1.5	.016	Yes	In patients with CHF	34
ACE	D/D	404	520	1.89	<.001	Yes		36
CYP11B2	T-344C	63	133	2.65	.03	No	In patients with CHF	40
AGT	M235T	250	250	2.5	<.001	No		33
AGT	G-6A	250	250	3.3	.005	No		33
AGT	G-217A	250	250	2.0	.002	No		33
AGT	T174M	968	8267	1.2	.05	No		37
AGT	20 C/C	968	8267	1.5	.01	No		37
CETP	Taq1B	97	97	0.35	.05	No		42
GJA5	−44A	14	16	5.3	.0019	Yes		44
GJA5	−44A, +71G	173	232	1.514	< .006	Yes (for -44A only)		43
EDN2	A985G	26	84	5.89	.018	No	In patients with HCM	39
NOS3	894T/T	51	289	3.2	.001	No	In patients with CHF	34
NOS3	T-786C	331	441	1.4	.05	No		45
GNB3	C825T	291	292	0.46	.02	No		52
hsp70	Met439Thr	48	194	2.43	.016	No	In postoperative CABG patients	53
IL6	G-174C	26	84	3.25	.006	No	In postoperative CABG patients	50
IL10	A-592C	196	873	0.32	3.70×10^{-03}	No	Lone AF	51
KCNE4	E145D	142	238	1.66	.044	No		49
KCNE5	97T	158	96	0.52	.007	No		48
KCNH2	K897T	1207	2475	1.25	.00033	No		46
MinK/KCNE1	38G	108	108	1.8	.024	Yes		47
MinK/KCNE1	38G	331	441	1.73	<.005	Yes		45
MMP2	C1306T	196	873	8.1	1.26×10^{-02}	No	Lone AF	51
SLN	G-65C	147	92	1.98	.011	No		41

Abbreviations: ACE, Angiotensin I converting enzyme; AF, atrial fibrillation; AGT, Angiotensinogen; CABG, coronary artery bypass graft; CETP, cholesteryl ester transfer protein; CHF, congestive heart failure; CYP11B2, Aldosterone synthase; EDN2, endothelin 2; GJA5, connexin 40; GNB3, guanine nucleotide binding protein; GWAS, genome-wide association study; HCM, hypertrophic cardiomyopathy; hsp70, heat shock protein 70; IL6, interleukin 6; IL10, interleukin 10; NOS3, nitric oxide synthase 3;S LN, sarcolipin gene.

study design.[54] GWAS attempt to identify novel genetic polymorphisms that are significantly more or less common in a group with a disease as compared with a control group. Since the markers are spread over the entire genome, these experiments give no weight to existing candidate genes. Such studies have been used successfully in the past several years to identify potential novel pathways for diabetes,[55] obesity,[56] coronary heart disease,[57,58] macular degeneration,[59] and repolarization.[60]

Although GWAS have the potential to identify new pathways for disease, they also have a number of limitations. In particular, with hundreds of thousands of individual associations being tested, these studies have a high likelihood of producing false-positive associations. There is still discussion within the field of what the threshold level should be for genome-wide significance.[61] False-positive results can also emerge from population stratification or the failure to properly control for ethnicity, thus resulting in over- or underrepresentation of spurious ethnic-specific markers. Although variations in study design have been proposed in an effort to eliminate false associations, ultimately replication of the associations in other populations is the best method of validation.[54]

The biological significance of the identified variants is another concern. Most variants found in genetic association studies have been associated with relatively weak effects, with typical odds ratios ranging from approximately 1.3 to 1.5. Although such variants may generate new ideas about disease pathogenesis, understanding the biological mechanisms by which the majority of variants confer disease susceptibility remains challenging.

Recently, a team led by the researchers at deCODE genetics have reported the results of a GWAS for AF. Gudbjartsson and colleagues[62] examined over 300,000 SNPs and identified two polymorphisms on the long arm of chromosome 4 (4q25) that were highly associated (rs2200733 and rs10033464, $P = 3.3 \times 10^{-41}$ and 6.9×10^{-11}, respectively) with AF or atrial flutter in a group of Icelanders. To improve both the validity and generalizability of the findings, the study was replicated in other populations in Iceland, Sweden, the United States, and Hong Kong. Neither variant was correlated with obesity, hypertension, or myocardial infarction suggesting that the genetic variants are not associated with AF by affecting those risk factors.

How do the variants on chromosome 4 lead to AF? At present, the mechanism of action of these variants is unclear. Interestingly, these SNPs lie upstream from a gene that could plausibly play a role in the pathogenesis of AF, the paired-like homeodomain transcription factor 2, *PITX2*. This gene is known to be critical in the development of the left atrium,[63–66] pulmonary myocardium,[67] and in the suppression of left atrial pacemakers cells in early development.[68] One can speculate that these variants may alter the function of PITX2 either in early development or in adulthood and thus predispose to AF. However, currently there is no direct link between the *PITX2* gene and these noncoding variants more than 50,000 base pairs away. Future work examining the correlation between these variants and PITX2 RNA levels, protein levels, or tissue specificity will hopefully clarify the mechanism underlying the association of these SNPs with AF.

REFINING GENETIC STUDIES OF ATRIAL FIBRILLATION

To continue to improve upon the utility of genetic studies for AF we will need to overcome a number of obstacles. A critical step in any genetic study is the ability to correctly assign the diagnosis. AF represents a particular challenge because many individuals are asymptomatic, some have paroxysmal disease, and yet others develop AF late in life. Genotypic and phenotypic heterogeneity further complicate the classification of AF. Rather than a single entity, AF may represent the final common pathway for a number of distinct pathogenic insults such as heart failure, hypertension, or thyroid abnormalities.

To address these challenges, we will have to continue to improve upon the characterization and classification of AF. The identification of endophenotypes, or subtle, heritable traits that co-segregate with AF, may help to refine ongoing genetic studies. For AF, endophenotypes such as specific P-wave morphologies, pulmonary venous anatomy as assessed by CT or MRI, or biomarkers that are heritable and easily detectable may be helpful.

SUMMARY

Recent studies of AF have identified mutations in a series of ion channels; however, these mutations appear to be relatively rare causes of AF. A genome-wide association study has identified novel variants on chromosome 4 associated with AF, although the mechanisms of action for these variants remain unknown. Ultimately, a greater understanding of the genetics of AF should yield insights into novel pathways, therapeutic targets, and diagnostic testing for this common arrhythmia.

ACKNOWLEDGMENTS

This work was supported by a grant from the Disque Deane Foundation to Dr. Ellinor and a National Institutes of Health training grant (5T32HL007575) to Dr. Lubitz.

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