Published in final edited form as:
J Electrocardiol. 2011 November ; 44(6): 641–644. doi:10.1016/j.jelectrocard.2011.07.027.

The 'Missing' Link in Atrial Fibrillation Heritability

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Abstract

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, represents a major health burden to individuals and health care system within the Western world. The lifetime risk for the development of AF at age 40 years has been estimated to be approximately 1 in 4. AF is associated with substantial morbidity and a two-fold increased risk of mortality. Given its increasing prevalence with age, coupled with the aging population, the number of Americans affected with AF is expected to increase from ~ 2.3 million in the year 2000 to nearly 16 million by 2050. This AF epidemic is further complicated by the lack of highly effective therapies. One reason for the lack of effective therapies for AF stems from incomplete understanding of the complex pathophysiology of the arrhythmia. AF has often been regarded as a condition that occurs in the context of atrial electrical and structural remodeling that can result from cardiac and systemic disorders. However, up to 30% of patients have no obvious cause and are said to have idiopathic or "lone" AF. Up until recently, AF was considered to be a sporadic, non-genetic disorder, but we and others have shown that lone AF has a substantial genetic basis. Mutations in genes encoding cardiac ion channels (*KCNQ1*, *KCNE1-5*, *KCNJ2*, *KCNA5* and *SCN5A*), gap junctions (*GJA5*), and signaling molecules (atrial natriuretic peptide [ANP], nucleoporins [*NUP155*]) have been reported in isolated cases and small kindreds. The advent of the human genome and HapMap projects and high-throughput genotyping has fundamentally accelerated our ability to discover the genetic contribution to common variation in human disease. In 2007, a genome-wide association study (GWAS) identified two genetic variants that associated with AF. More recently, two additional AF loci on chromosomes 16q22 and 1q21 have been identified. It is quite likely however, that the effects of alleles in many genes contribute to common complex diseases such as AF. The overall AF risk associated with common variants identified by the GWAS approach is small (odds ratios 1.1–2.5) and explains less than 10% of the heritability in lone AF. This raises the possibility that rare independent variants with large effects strong effects may account for a large fraction of the risk for lone AF.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and has become a disease of epidemic proportions, affecting 2–5 million Americans with increased morbidity, mortality and socioeconomic consequences of repeated hospital admissions, chronic disease management and disabilities.[1] The lifetime risk for the development of AF at age 40 years

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has been estimated to be approximately 1 in 4. [2, 3] It is projected that the number of persons in the U.S. with AF will exceed 16 million by the year 2050.[4]

Despite the overall advance in the treatment of patients with cardiac arrhythmias, therapeutic options in AF have remained largely unchanged. For most patients, the goal of therapy is to restore and maintain normal sinus rhythm, control heart rate and prevent systemic embolization. New developments in surgical and ablation techniques for AF are promising, but to date are still laborious, plagued by significant complications, and have limited applicability.

One reason for the lack of effective therapies for AF stems from incomplete understanding of the complex pathophysiology of this common arrhythmia. The familial aggregation and high heritability of AF in these studies are consistent with common genetic mechanisms for the arrhythmia. Evidence of a genetic contribution in the development of AF was first provided in 1943 by Wolff,[5] who documented transmission of AF in a family with an autosomal dominant pattern of inheritance. Since that time, large epidemiologic studies have documented evidence of heritability in AF. We and others have confirmed that a family history of AF is present in one-third of patients with lone AF indicating that familial AF is more common than previously recognized.[6–8] To date linkage analysis, candidate gene approach and association studies have been the preferred methods to study heritability of AF. However, less than 10% of inherited variance can be explained by all AF loci.

Linkage analysis

Several genes and loci have now been described for Mendelian forms of lone AF (Table 1). Although the first AF locus was reported in 1997, the gene responsible for the arrhythmia has still not yet been identified.[9] Four other AF loci have been subsequently been identified.[10–13] We recently identified a novel AF locus on chromosome 5p15 and established an abnormally prolonged P-wave determined as an ‘endophenotype’ for AF.[14] In 2003, the first gene (*KCNQ1*) responsible for an autosomal dominant form of AF was identified.[15] This work was followed by subsequent studies that implicated numerous other genes encoding ion channels in the pathogenesis of AF (Table 1). Although isolated families with Mendelian AF have been described, linkage analysis has facilitated the identification of individual mutations in several familial AF kindreds. We recently identified a novel heterozygous frameshift mutation in the natriuretic peptide precursor A (*NPPA*) gene that encodes atrial natriuretic peptide (ANP).[16] These diverse proteins are thought to predispose to AF through different electrical mechanisms, a notion that emphasizes the degree of heterogeneity that governs initiation and maintenance of AF.

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 (and ion) channels as potential candidate genes and screened for mutations in these genes in cohorts of subjects with AF. The genes that encode connexins, gap-junction proteins that mediate the spread of action potentials (APs) 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 connexin-40, exhibit atrial reentrant arrhythmias.[17] From this work, Gollob et al.[18] considered this gene as a potential candidate in individuals with lone 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 connexin-40 mutation 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 germ line rather than somatic mutation.

Association studies

Most patients with AF have one or more identifiable risk factors, but many patients with these same risk factors do not develop AF. Studies comparing cases of non-familial AF to age-related and gender-matched controls (association studies) have provided some insight into the genetic basis of acquired AF. 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 the renin-angiotensin-aldosterone system (RAAS), ion channels, neurohormonal and signaling pathways. Major limitations of such studies are relatively small sample sizes and a lack of replication in distinct populations, as well as phenotypic and genetic heterogeneity.

In recent years, genome-wide association (GWA) studies have been made possible by advances in genotyping technology that allow investigators to assay hundreds of thousands of SNPs spread over the entire human genome. Recently, a locus on the long arm of chromosome 4 (4q25) was identified in a GWA study to have a highly significant association with AF with a relative risk ranging from 1.39 to 1.72, depending on the population tested.[19] Although the mechanism for this observed association remains unknown, the locus is adjacent to the paired-like homeodomain transcription factor 2 (*PITX2*) gene which is critical for cardiac development.[20] More recently, the CHARGE-AF/AFGen Consortium[21] and Decode investigators[22] identified SNPs within the transcription factor *ZFXH3* that associated with AF. A novel locus associated with lone AF at 1q21 was identified in 2010.[23]

Challenges in AF genetics

It is now widely accepted that up to one-third of all lone AF patients have a genetic basis for their disease and that a large fraction of AF cases are multifactorial. However, the common variants identified by GWA studies and the AF genes discovered by linkage analysis and candidate gene approaches, explain only a small fraction of the genetic heritability of the arrhythmia. The ‘missing’ heritability of AF may be explained by low frequency variants with an intermediate penetrance (Figure 1). An important role for rare variants in inherited multifactorial susceptibility to AF was first suggested by the effects of rare missense variants in *SCN5A*, the α-subunit of the cardiac sodium channel.[24] This raises the possibility that rare independent variants with intermediate penetrance may account for a large fraction of the risk of developing AF.

A major focus in genetics recently has been identification of disease pathways, genes, and mutations in rare monogenic diseases. Discovery in these settings, in turn, provides the starting point for testing the role of pathway variants in commoner forms of disease. Ji et al.[25] resequenced the coding regions of *SLC12A3*, *SLC12A1*, and *KCNJ1* (each associated with a rare disease causing abnormal blood pressure via altered renal salt handling) in 2492 subjects from the Framingham Heart Study; they identified 92 non-synonymous variants and inferred a relationship between blood pressure and rare variant status. While most AF is secondary to other conditions, 10–30% of patients have lone AF. Although GWA studies have uncovered common genetic variants associated with AF, the overall risk for the arrhythmia with these variants is small (OR 1.1–2.5) and explains less than 10% of the heritability in lone AF (Figure 1).

Until recently, it has been difficult to systematically identify rare variants. However, recent advances in next generation sequencing, has now made it feasible to rapidly sequence whole

exomes or protein-coding regions of the genome. The combination of exome sequencing with bioinformatic selection now permits the systematic evaluation of rare variants associated with AF. Defining the genotype-phenotype relationships in AF kindreds carrying these rare genetic variants will add greatly to our understanding of the pathogenesis and genetic risk of AF.

Acknowledgments

This work was supported by U19 HL65962, HL075266, and an AHA Established Investigator Award (0940116N).

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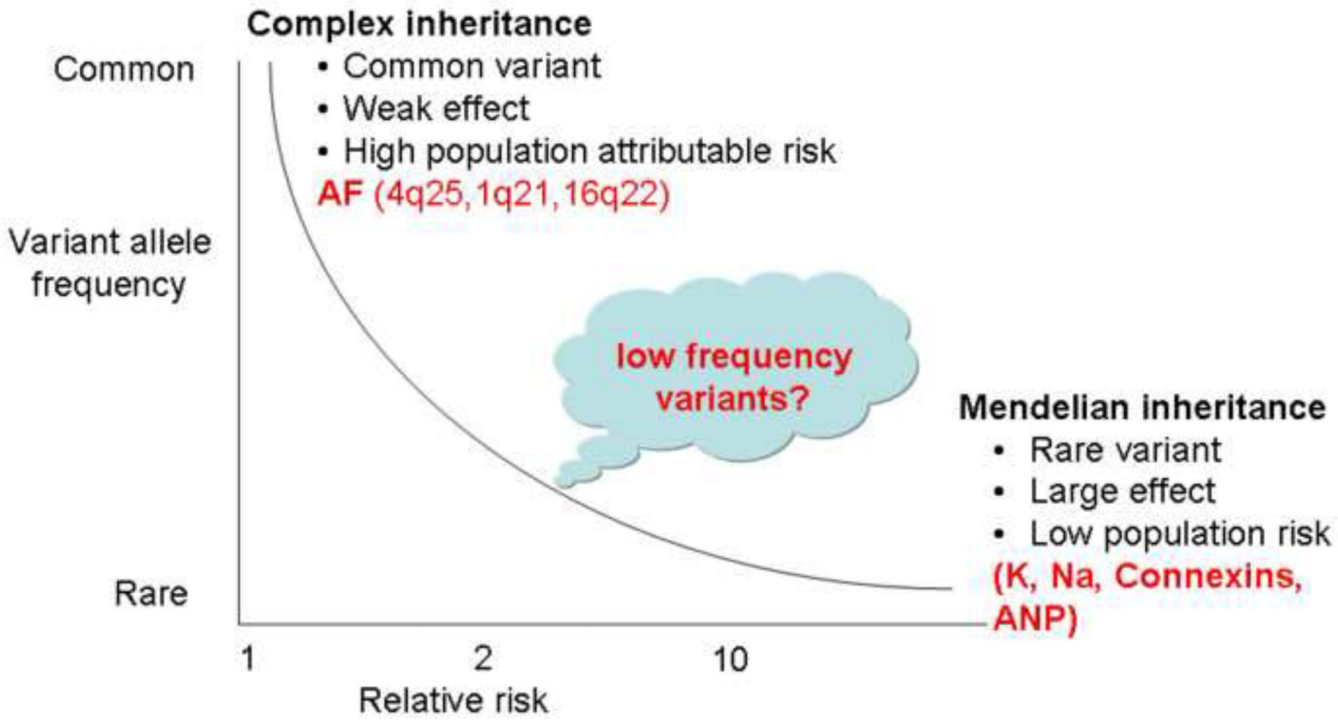

Figure 1. Missing link in atrial fibrillation (AF) heritability

Rare independent variants with intermediate effects may explain the missing heritability of AF.

Table 1

Genes and loci implicated in familial AF.

Chromosome	Culprit Gene	Functional Effect	Inheritance	Reference
11p15.5	*KCNQ1*	Enhanced slow component of the delayed rectifier potassium current (I_{ks})	AD	15
21q22.1	*KCNE2*	Enhanced *KCNQ1-KCNE2* potassium current	AD	26
17q23.1	*KCNJ2*	Enhanced inward rectifier current (I_{K1})	AD	27
12p13	*KCNA5*	Decreased ultrarapid component of the delayed rectifier potassium current (I_{Kur})	AD	28
3p22.2	*SCN5A*	Hyperpolarizing/depolarizing shift in $Na_v1.5$ inactivation	AD	24, 29, 30
1p35-p36	*NPPA*	Increased circulating levels of mutant atrial natriuretic peptide	AD	16
5p13	*NUP155*	Affects transport of hsp70	AR	31
1q21	*GJA5*	Decreased gap junction conductance	Somatic mutation	18
14q11	*MYH6*	Unknown	AD	32
Genetic loci				
10q22-24	Unknown	Unknown; overlaps with locus for dilated cardiomyopathy	AD	9
6q14-16	Unknown	Unknown; overlaps with locus for dilated cardiomyopathy	AD	10
10p11-q21	Unknown	Unknown	AD	13
5p15	Unknown	Unknown; associated with ↑ P-wave duration	AD	14

AD, autosomal dominant; AF, atrial fibrillation; AR, autosomal recessive; hsp70, heat hock protein.