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AF Genetics: Is There a Practical Clinical Value Now or In The Future?

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Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia and has significant clinical impact. Over the last decade, our understanding of the genetics of AF has expanded dramatically. After a heritable predisposition for AF was identified, many investigators have in turn identified both common and rare variants associated with AF. Ongoing work is focused on translating these variants into disease pathways and novel therapeutic modalities. In this review, we focus on our understanding of the current concepts behind the genetics of AF and outline a vision for the incorporation of genetic data into clinical practice.

The prevalence of atrial fibrillation (AF) increases with age, affecting approximately 10% of individuals by 80 years of age.[1] AF results in increased risk of congestive heart failure, stroke, dementia, and mortality. Although we have a deep understanding of the epidemiology and the many clinical risk factors for AF,[2] current treatment options remain limited and are largely focused on controlling the adverse outcomes attributable to the arrhythmia. In recent years, we and others have used genetics in an attempt to further define the molecular pathways underlying AF and to improve patient specific AF risk prediction.[3] This review is based on a systematic literature search using PubMed to identify all studies investigating the genetic basis of AF (emphasizing recent publications), with the goal to present the current landscape of AF genetics and its potential clinical applications.

Atrial Fibrillation: A Disease with a Genetic Basis

A genetic basis for AF was initially suggested in the 1940s with the report of three brothers with the arrhythmia.[4] While large families with AF remain rare, in the last decade the heritability of AF in the general population has been well described. Investigators from the

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Framingham Heart Study found that one in three participants with AF had at least one parent who was also affected with AF.[5] Individuals with a first-degree relative with AF had about a 40% increased risk even after accounting for established clinical risk factors for AF.[6] Similarly, investigators in Iceland demonstrated that risk of AF decreased with increasing genetic distance between relatives.[7] For example, if an individual had a brother with AF, their risk was higher than if they had a cousin with AF. Further support of the heritability of AF has arisen from studies of twins,[8] chart reviews in cardiology clinics[9] and studies of early-onset AF.[10, 11]

The Role of Rare Genetic Variants in AF

In a seminal study, Yi-Han Chen and colleagues identified a gain of function mutation in *KCNQ1* in a large Chinese kindred with AF.[12] *KCNQ1* encodes the potassium channel α-subunit underlying the slowly repolarizing current, I_{Ks}. The association between mutations in *KCNQ1* and AF in turn led to the screening of ion channels and wide range of other genes in many subsequent candidate gene studies. In sum, these efforts have identified rare mutations in a variety of genes generally involved in cardiac depolarization and repolarization, such as potassium channels, the cardiac sodium channel, and gap junction proteins.[13–15] In addition, mutations in several transcription factors involved in atrial development have also been identified in patients with lone AF.[16–18] Yet the influence of these variants is complex: for instance in one example, two different alleles of the same SNP are associated with increased AF risk.[19, 20] Supplemental Table S1 provides a comprehensive list of AF associated rare variants or mutations that have been reported to date. Although the importance of these discoveries to our understanding of AF pathogenesis should not be diminished,[21] the clinical implications may be limited since individually the discovered mutations appear to account for a small proportion of patients with AF.

Genome Wide Association Studies: Identification of Common Disease Variants

Large families with monogenic AF are rare in the general population, limiting the utility of classical genetic mapping techniques in the study of AF genetics. However in the last decade, technological advances have enabled efficient genome-wide genotyping of hundreds of thousands of single nucleotide polymorphisms (SNPs), allowing genome-wide association studies (GWAS) to be performed which have identified genetic regions associated with a variety of traits and conditions including AF. The first application of GWAS to AF led to the identification of the chromosome 4q25 AF susceptibility locus in an Icelandic population, a finding replicated in two additional cohorts of European and Asian ancestry.[22] Since this initial report, chromosome 4q25 has been the most comprehensively studied of the AF risk loci. A full list of GWAS loci associated with AF is provided in Supplemental Table S2.

The AF-associated SNPs at the 4q25 locus are located in an extensive genomic desert that lies about 150 kilobases (kb) from the paired-like homeodomain transcription factor-2 (*PITX2*), a transcription factor that plays a critical role in cardiac and gastrointestinal rotation during embryogenesis.[23] Moreover, Pitx2c has been associated with suppression of sinus node formation in the developing left atrium,[24] and Pitx2 knock-out mice were found

to have an increased susceptibility to inducible atrial arrhythmias with programmed stimulation.[25] A recent report demonstrated that three independent alleles at the 4q25 locus increase AF risk when occurring simultaneously.[26] Interestingly, a separate study of common SNPs at the 4q25 locus demonstrated that expression of common SNPs can modify expression of ion channel genes and influence whether carriers of rare polymorphisms at other loci will develop AF.[27] Therefore this locus seems to have wide ranging effects on AF susceptibility, and recent investigations suggest another mechanism may involve microRNA regulation of other transcription factors.[28]

AF-related genetic variants have also been found at chromosome 1q21 intronic to the *KCNN3* gene.[29] Also known as SK3 or KCa2.3, this gene encodes a calcium-activated, small conductance potassium channel that is highly expressed in electrically excitable cells in the cardiac and neural tissues.[30–32] In rabbit models, inhibition of this channel results in inhibition of pacing-induced shortening of pulmonary venous atrial action potential duration,[33] and blockade of SK_{Ca} in canines resulted in increased atrial action potential duration (APD) heterogeneity and facilitated the development of reentrant arrhythmias.[34] These findings make *KCNN3* a potential drug target for AF therapy.

In 2012, a GWAS from 16 studies consisting of over 6,000 individuals with AF and more than 50,000 individuals without AF led to the identification of six additional AF-related genetic loci.[35] Three of the AF associated genetic variants were located near transcription factors presumably regulating atrial size, structure or development (*PITX2*, *ZFHX3*, *PRRX1*). Another three variants were near ion channels or related proteins that potentially regulate the atrial action potential (*KCNN3*, *HCN4*, *CAV1/2*). In an effort to identify more target loci in AF, Sinner, et al combined genotyping from two ethnic groups with expression quantitative trait loci (eQTL) mapping to identify another 5 loci associated with AF.[36] This study also provided functional characterization of the genes implicated at 2 loci, demonstrating an effect on APD in zebrafish knockdown experiments of the genes *NEURL* and *CAND2*. With many AF loci now identified, current studies are focusing on the mechanism of action of these gene products and how these genes are ultimately involved in AF pathogenesis.

Clinical Screening for AF Mutations and AF-associated SNPs

Unlike Long QT syndrome in which 3 genes account for more than 60% of the disease, over 30 genes have been implicated in AF through candidate gene studies, and 14 loci through GWAS. This genetic heterogeneity and the low prevalence of mutations in any single gene precludes the clinical utility of genetic testing despite the commercial availability of genetic panels. [37] However it is now possible to rapidly and cost efficiently sequence the exome (protein-coding region of the genome) or even the entire genome. In upcoming years these more comprehensive techniques will likely shift us away from our current focus on a small number of genes or gene panels. Using such an approach we may find that individuals with AF have an increased burden of rare or novel variants throughout the genome that lead to the arrhythmia,[21] or that combinations of genotypes place patients at increased risk.[26] Such a finding could in turn lead to a reconsideration of the utility of mutation screening in AF.

Applying Genetics to AF Risk Prediction

Risk prediction models for AF have been derived using a variety of clinical variables, able to correctly assign higher predicted risks to those that develop AF about 60–70% of the time.[38–40] In 2010, we found that adding the top 3 AF SNPs at *PITX2*, *ZFHX3* and *KCNN3* offered little improvement to our predictive ability for AF beyond typical clinical risk factors.[6] However a separate study demonstrated that the relative risk of developing AF was predicted by the number of risk alleles that a patient harbored (Figure).[26, 41] More recently, Everett et al. devised an AF risk prediction algorithm in the Women's Genome Health Study, which consists of 20,822 women without cardiovascular disease at baseline. Inclusion of a more comprehensive genetic risk score based on 9 SNPs resulted in slight improvements in predictive accuracy beyond established AF risk factors though it did not improve the ability to classify participants into prespecified risk categories.[3]

AF SNPs and Clinical Outcomes: From PVI outcomes to drug response

As noted, the AF risk locus at *PITX2*/4q25 is by far the most well studied of the risk loci identified to date. Since approximately 20% of individuals of European ancestry carry at least one copy of the top *PITX2*/4q25 AF risk allele, many recent studies have examined the relation between AF risk SNPs and a variety of clinical outcomes (summarized in Table 1). For instance, recent studies by investigators at Vanderbilt have found that a 4q25 SNP is associated with the response to antiarrhythmic agents and is an independent predictor of AF recurrence after cardioversion.[42–44] Body et al and Virani et al have independently demonstrated associations between risk variants on 4q25 and post-operative AF,[45, 46] implying a genetic susceptibility to the arrhythmia even in the context of what appears to be a secondary trigger. In addition, multiple reports have found that common AF risk alleles on 4q25 conferred an increased risk of AF recurrence after pulmonary vein isolation procedures.[42, 47, 48] However, a separate study in individuals of Asian ancestry found that the presence of the top 4 SNPs associated with AF at the *PITX2* and *ZFHX3* loci did not predict clinical AF recurrence after ablation, suggesting that earlier positive predictive results may have been either due to a small sample size or genetic differences amongst disparate ethnic groups.[49] Therefore defining the clinical niche where the presence of specific genotypes translate into clinical outcome prediction is still a work in progress.

Stroke Risk and AF

Perhaps the best studied of AF outcomes is stroke, and the relation between AF and stroke offers a unique opportunity for the incorporation of genetics in clinical practice. Clinically, current AF related stroke risk is estimated using risk prediction scores such as CHADS2 and CHA_2DS_2VASc, [50] yet these prediction tools are obviously imperfect. Prior observations suggest a heritable component underlying ischemic stroke, with an estimated 37.9% heritability associated with all ischemic strokes and 32.6% for cardioembolic strokes.[51] In line with these observations, AF-associated genetic variants on chromosomes 4q25 and 16q22 have been associated with cardioembolic strokes.[51–53] Assessment of multiple independent genetic markers for AF appears to identify individuals at high and low risks of stroke.[3, 26] Recently, an AF genetic risk score has been shown to predict a cohort of patients

at highest risk for incident AF and stroke, which may become a useful clinical tool to target therapy to patients at highest risk (Figure).[54] It is exciting to think that patients at highest risk for stroke may be able to be identified *a priori* through intensive surveillance of those at highest risk, or perhaps with implantation of long term monitoring devices to identify these patients before a stroke occurs. Future work will need to delineate if AF-associated genetic markers associate with stroke independent of known AF, and if knowing a patient's genotype will improve risk stratification beyond the CHA_2DS_2VASc score.

Future studies relating AF variants to clinical outcomes

Current published studies examining the relation between AF-risk variants and clinical outcomes have been limited, typically testing a few SNPs and looking at one or two clinical outcomes of interest. Often these studies have used a limited number of individuals with each outcome (Table 1). With a limited number of individuals with each endpoint and genotype, it is quite possible that the published results illustrate a positive publication bias rather than a true association. Thus, it is not surprising that in most studies the clinical impact of the known AF risk variants has been minimal.

There are now more than a dozen loci that have been found to be associated with AF through GWAS. Additionally, multiple susceptibility signals at a single locus can identify individuals at a marked increased risk for the arrhythmia.[26] Therefore it is clear that the next iteration of studies examining AF related outcomes will require testing with a more comprehensive panel of SNPs with a larger number of patients to ensure adequate statistical power. This effort will likely require multi-center collaboration with thousands of individuals to ensure appropriate power. The recent study by Tada, et al can serve as a model for this approach, where testing 12 SNPs in over 27,000 led to the identification of patients at elevated risk for incident AF and stroke.[54] Similar methods be used to investigate clinical outcomes that have been tested in smaller patient samples (for instance outcomes after ablation, cardioversion success, or response to antiarrhythmic therapy) to more rigorously test the hypothesis that genotypes may predict clinical outcomes. Such an approach will not only enhance our knowledge of the pathophysiology of AF, but will eventually pave the way for the next frontier of personalized medicine with therapy tailored to improved estimates of a patient's individual risk.

Conclusions

Unraveling the complex genetics of AF may ultimately allow identification of discrete clinical subtypes and mechanisms for the arrhythmia.[55, 56] With our rapidly expanding understanding of the genetic risk factors associated with AF, we hopefully will be able to identify new pathways involved in its pathogenesis, new pharmacologic targets, and patients at risk for specific clinical outcomes. In particular, the intersection of AF with stroke and genetics is particularly promising as it offers the possibility of identifying patients at greatest risk for incident AF and possibly an opportunity to intervene before adverse outcomes occur. We anticipate that within the next few years, much of the data that has been accrued regarding the genetic underpinnings of atrial fibrillation will now be applied to improve clinical risk prediction and used to guide therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary

Atrial fibrillation (AF) is heritable and in recent years many genetic loci have been associated with the arrhythmia. Current efforts are directed at determining if AF genetic data can be used to refine clinical risk prediction, predict response to medical or procedural treatments, or help to determine the sequelea of AF such as heart failure and stroke.

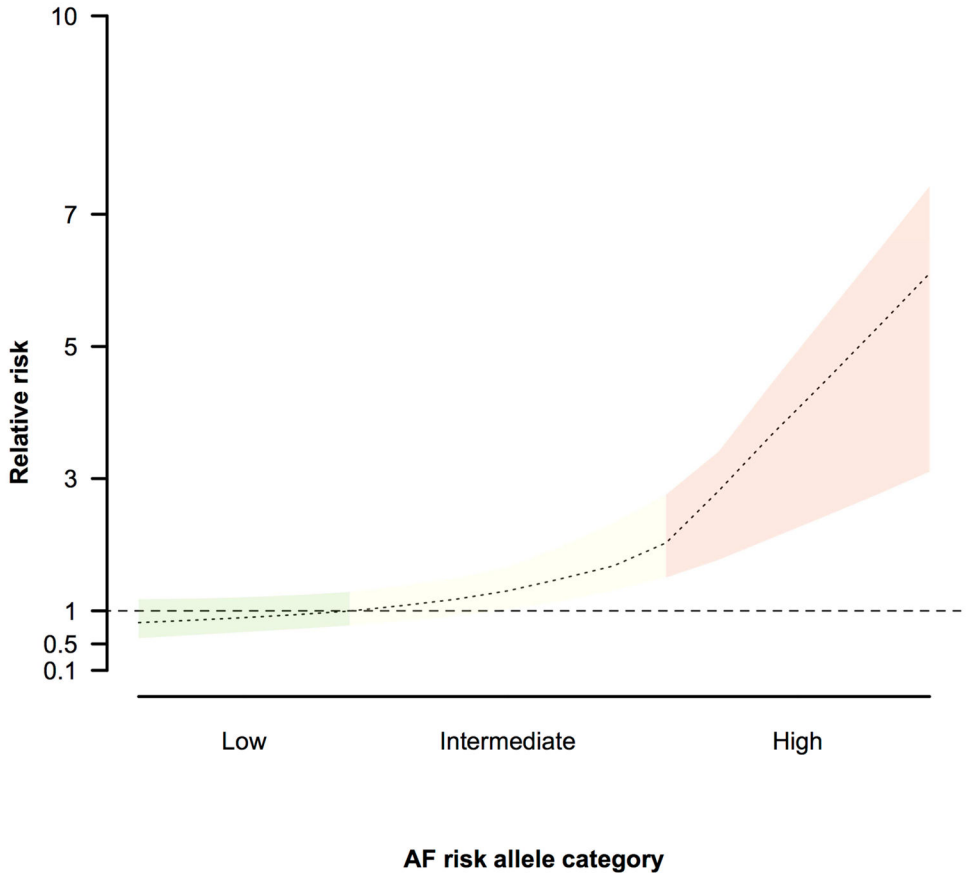

Figure.

All common genetic variants can be combined in a genetic risk score for AF. The risk score can then be applied to stratify patients into various categories of risk. One could imagine that patients in the highest risk group would be appropriate for more intensive monitoring for the development of AF.

Table 1

Clinical implications of genetic variation at the 4q25 locus for AF

Condition	SNPs	Study size	OR	CI	P value	References
Cardioversion success	rs2200733 rs10033464	184	2.1	1.2–3.3	8×10^{-3}	44
AF recurrence post ablation	rs220073 rs10033464	200	0.76	0.6–1.0	0.016	42
	rs2200733 rs10033464	195	2.0	1.0–3.8	0.039	47
Antiarrhythmic drug response	rs10033464	399	4.7	1.8–12	1.3×10^{-3}	43
Stroke	rs2200733	6,222	1.3	1.2–1.4	2.18×10^{-12}	51
	rs1906591	4,199	1.6	1.4–1.9	9.2×10^{-12}	57
Sudden cardiac death	rs2200733	27,629	1.3	1.1–1.5	7.9×10^{-4}	58