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REVIEW

Genetics of Atrial Fibrillation: State of the Art in 2017

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Genetic variation is an important determinant of atrial fibrillation (AF) susceptibility. Numerous rare variants in protein-coding sequences of genes have been associated with AF in families and in early-onset cases, and chromosomal loci harbouring common risk variants have been mapped in AF cohorts. Many of these loci are in non-coding regions of the human genome and are thought to contain regulatory sequences that modulate gene expression. Disease genes implicated to date have predominantly encoded cardiac ion channels, with predicted mutation effects on the atrial action potential duration. More recent studies have expanded the spectrum of disease-associated genes to include myocardial structural components and have highlighted an unsuspected role for cardiac transcription factors. These paradigm-shifting discoveries suggest that abnormalities of atrial specification arising during cardiac development might provide a template for AF in later adult life. With the escalating pace of variant discovery, there is an increasing need for mechanistic studies not only to evaluate single variants, but also to determine the collective effects of each person's burden of rare and common genetic variants, co-morbidities and lifestyle factors on the atrial substrate for arrhythmogenesis. Elucidation of an individual's genetic predisposition and modifiable environmental risk factors will facilitate personalised approaches to AF treatment.

Keywords Genetics • Atrial fibrillation • Genomic risk score • Ion channels • Transcription factors

Introduction

Atrial fibrillation (AF) is a heritable disorder and substantial progress has been made over the past decade in elucidating its genetic underpinnings. Numerous rare variants that putatively cause AF have been identified in families and in sporadic cases, and chromosomal loci have been mapped for common variants that affect AF susceptibility in the general population. These studies have established a key role for ion channel defects in generating a substrate for AF with both gain-of-function and loss-of-function mechanisms demonstrated. More recent data have expanded our perspectives on how ion channel variants promote AF, with evidence for epistatic effects of combinations of variants and gene-environment interactions. Genetic variants in a broad range of non-ion channel genes can also affect AF risk. In particular, the finding of variants within and in the vicinity of genes encoding cardiac transcription factors has opened a new avenue of investigation into how cardiac developmental abnormalities might predispose to AF in later life. Despite these advances, genetic testing of patients with AF has been limited. Current knowledge about the molecular basis of AF and strategies to incorporate genetic information into clinical management will be summarised in this review.

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Variant Discovery

Rare Variants

Much of what we know about genetic causes of AF has been obtained from studies of cohorts of individuals with early-onset (<66 years) lone AF or families in which AF segregates as a Mendelian trait. These patient groups have a high *a priori* likelihood of a genetic aetiology of AF, and there is an expectation that this is primarily due to single rare variants of large effect size. The first gene mutation associated with AF was found in a three-generation kindred using linkage analysis and candidate gene screening [1]. A novel missense variant in the *KCNQ1* gene that encodes a voltage-gated potassium (K^+) channel was identified. This discovery launched a cascade of candidate gene screening studies and numerous variants in other ion channel components of the atrial action potential have been reported (Table 1; reviewed in [2]). Recently, studies in zebrafish have provided new insights into the types of K^+ channels that are active in the heart, demonstrating atrial-specific roles of the two-pore domain K^+ channels, TASK-1 and TWIK-1 [3,4]. Mutation screening of the genes encoding these channels in two cohorts of patients with early-onset and familial AF identified TASK-1 loss-of-function variants in two cases [3]. Rare variants in a broad range of non-ion channel genes have now been associated with AF, many of these encoding cardiac transcription factors (Table 1).

Although the list of putative AF ''disease genes'' continues to grow, it is unclear whether variants in all of these genes are truly causative of AF. Robust genetic evidence for disease association is lacking in all but a handful of these genes, with most variants seen in single cases or in small families that are underpowered for linkage analysis. Moreover, only a few variants in each gene have been described [5,6]. The criteria used to define pathogenicity have evolved over time and many variants previously deemed to be disease-causing mutations would be re-classified using contemporary guidelines [7].

Historically, variant annotation relied on factors such as novelty (as assessed by absence from 100+ healthy control subjects), and disruption of conserved amino acid residues. Interrogation of population sequence databases, such as generated by the Exome Aggregation Consortium (>60,000 subjects), has now revealed that a number of reported cardiomyopathy-associated variants thought to be novel can also be seen in apparently healthy individuals in the general population [8,9]. Functional evaluation of variants has often been limited to bioinformatics predictions that take factors such as sequence conservation into account or *in vitro* analyses, with few examples of animal models that recapitulate human AF. It is now recognised that loss-of-function variants are commonly present in the human genome [10] and not all of these will be disease-causing. It can be expected that at least some function-altering variants identified in AF patients will be tolerated or have effects that are not directly applicable to AF. The impact of these variants is likely to depend to a large extent on the gene involved and its relative importance to atrial biology. Taken together, these considerations query the extent to which reported variants are *sufficient* alone to cause AF and prompt critical review of the ''disease gene'' list.

Common Variants

In most individuals, AF is a complex trait that results from the combined effects of age, and genetic and acquired risk factors. Common variants that modify susceptibility to AF can be identified by genome-wide association studies (GWAS) undertaken in large cohorts of unrelated cases and control subjects. The first major GWAS in AF was reported in 2007, with a significant locus identified in an intergenic non-coding region on chromosome 4q25 [11]. The international AFGen Consortium has been instrumental in advancing this field and subsequent studies undertaken in tens of thousands of subjects identified a further 13 genetic loci [12,13]. Very recently. Christophersen et al. [14] performed a meta-analysis of common and rare variant association studies that included >240,000 cases and >220,000 reference samples. Twelve novel genetic loci were identified, all in non-coding sequences, with suspected target genes encoding ion channels, sarcomeric proteins and transcription factors. In an accompanying manuscript, Low and colleagues from Japan [15] described a GWAS in >8,000 AF cases and identified six loci, many of which were specific to individuals of Asian ancestry.

In total, there are now over 30 AF-associated GWAS loci (Table 1, Figure 1). The majority of these loci occur in intergenic regions or in introns and are presumed to contain regulatory sequences that influence gene expression. The GWAS ''hits'' identify sentinel variants (single nucleotide polymorphisms [SNPs]) that are markers for suites of SNPs that are co-inherited. Further evaluation of each locus is required to identify and characterise potential enhancer or repressor elements and to define function-altering ''business'' SNPs. The target genes controlled by these regulatory elements may be in close proximity, or located more distally on the same chromosome (*cis*) or on another chromosome (*trans*). Some progress has been made in identifying enhancer elements in the chromosome 4q25 locus (see Transcription Factors below) but most GWAS loci have yet to be fully explored.

New Approaches to Variant Discovery

Several new strategies have been used to look for both rare and common variants in AF. In contrast to sequencing of single candidate genes, whole-exome sequencing (WES) enables every gene to be assessed. This wealth of additional information magnifies the issue of variant interpretation, especially for genes that have uncharacterised roles in cardiac function. Although WES has been used to identify variants in known disease genes in families with AF [16,17], there have been surprisingly few success stories in ''unsolved'' cases. Weeke et al. [18] performed WES in six

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