# Your Father and Grandfather's Atrial Fibrillation: A Review of the Genetics of the Most Common Pathologic Cardiac Dysrhythmia

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**Abstract:** Atrial fibrillation (AF) remains the most common pathologic dysrhythmia in humans with a prevalence of 1-2% of the total population and as high as 10% of the elderly. AF is an independent risk marker for cardiovascular mortality and morbidity, and given the increasing age of the population, represents an increasing burden of disease. Although age and hypertension are known risk factors for development of AF, the study of families with early onset AF revealed mutations in genes coding for ion channels and other proteins involved in electrotonic coupling as likely culprits for the pathology in select cases. Recent investigations using Genome-Wide Association Studies have revealed several single nucleotide polymorphisms (SNPs) that appear to be associated with AF and have highlighted new genes in the proximity of the SNPs that may potentially contribute to the development of the dysrhythmia. Here we review the genetics of AF and discuss how application of GWAS and next generation sequencing have advanced our knowledge of AF and further investigations may yield novel therapeutic targets for the disease.

## INTRODUCTION

Despite significant gains over the past few decades, heart disease remains the most common cause of death in the United States. Large scale epidemiology studies have led to advances in our understanding of modifiable risk factors such as tobacco use, diabetes, hypertension, obesity and diet as playing an extensive role in the pathophysiology of cardiovascular diseases (CVD). However, in addition to the aforementioned modifiable risk factors, genetics have been shown to play a role in the risk of developing CVD. These conclusions initially stemmed from population studies (such as the Framingham Heart Study), where researchers observed that a first-degree relative with a history of ischemic cardiac disease predisposes an individual to myocardial infarction [1]. The genetic investigations of such familial cases have lead to a better understanding of the pathogenesis of myocardial infarction: for example the identification of premature cardiac disease in a family with a possibly causative LDL mutation that was highly correlated with cardiovascular events [2]. Subsequently, genome wide association studies (GWAS) have led to further discovery of alleles that predisposed to CAD [3]. While the connection between these polymorphisms (or mutations) and disease pathogenesis remains largely elusive, recent work by Kathiresan and colleagues has identified some novel mechanistic pathways [4].

The study of the genetics of atrial fibrillation (AF), the most common pathologic dysrhythmia in humans, has

followed along a similar pathway. Initially, AF was recognized as a sequela of heart failure and valvular disease, and was thought to be secondary to acquired heart diseases. Epidemiological studies subsequently noted the correlation of age and hypertension with the risk of development of AF [5]. Early observations raised the possibility of the heritability of AF. In 1957, Gould reported 5 generations of a family with 22 members who developed AF in the absence of other cardiac disease [6]. This early report of familial lone AF described the dysrhythmia as "well tolerated", however, Gould's observations was reported long before it was recognized that AF carried with it a five-fold increase in the risk of thromboembolic stroke.

Today, the prevalence of AF in the general population is 1-2% [7], and while the majority of cases are attributed to the underlying cardiac disease, up to 20% of cases have no secondary factors that are thought to predispose to AF [8]. It is this population of patients with so called "lone AF" or AF without clear preexisting cardiac disease, that typically has a family history of the disease, and has opened the door for genetic studies to identify possible causal candidate genes.

## PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

Despite the high frequency of disease, the precise molecular mechanisms responsible for AF are poorly understood. Seminal work by Haissaguerre [9] and colleagues revealed the presence of electrical activity in the muscular sleeve of the pulmonary veins that may serve as triggers for AF. The classic teaching revolves around hemodynamic stress to the left atrium from volume overload, ischemia, valvular disease, or surgical intervention, which leads to left atrial stretch and disruption in the vicinity of the pulmonary

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veins allowing for opportunities for both propagation of pulmonary vein electrical activity and re entry in the atrium. Why certain patients are more prone to develop AF when subjected to similar stressors remains unclear. Over the last few years, there has been an explosion of interest in the molecular and electrotonic forces that drive this arrhythmia, which are only now beginning to be uncovered through the use of genome-wide association studies (GWAS). In this review we will discuss results that have established a genetic basis of AF and how future studies in this area may lead to a greater understanding of this arrhythmia and advance treatment.

## GENETIC HITS FOR ATRIAL FIBRILLATION

After early reports of familial AF in the 1940s and 50s, it was clear there was a hereditary component, but medical science was not advanced enough to characterize this further. Modern genetic techniques were not applied until 1997 when Brugada reported a genetic locus for AF in a series of family members afflicted with the disease at an early age [10]. The genetic renaissance in AF did not begin until after 2003 with the identification of voltage-gated potassium channel (KCNQ1) mutations in a family with AF [11]. Since that time, at least 7 additional reports of mutations in this channel alone have been published [12-18]. One of the difficulties of these classic linkage studies is the unreliability of the phenotype: the unpredictable age of onset of AF (and sometimes the insidious presence of AF in asymptomatic individuals), makes it challenging to link the genotype to the phenotype in the relatives of the proband.

It is not surprising that mutations in ion channels contribute to AF risk given our understanding of the pathology of the disease. Specifically, altering conduction in the atrial myocardium in general would be expected to increase one's risk of AF, and mutations that subtly decrease the conduction reserve may only develop a fibrillation phenotype if they undergo an additional first epigenetic "hit" such as an environmental factor, myocardial infarction, trauma or valvulopathy for instance. Other mutations that more substantially influence conduction would be expected to lead to the phenotype in the absence of such a primary "hit". The genetics of the former group is much more diverse since their phenotype is derived from multiple factors, which makes the genetic studies difficult to interpret. Polymorphisms of patients with lone AF (especially at a young age) have been much more informative as these subjects have a greater genetic dependence on their phenotype.

With this mechanism in mind, it is no wonder that mutations in genes coding for potassium channels, sodium channels, and gap junctions dominate the familial cases of AF (Table **1**).

### The Sodium Channel

The primary sodium channel responsible for action potential initiation and propagation through the atria, conduction system and ventricles is NaV1.5. The α domain of this channel, which comprises the transmembrane pore, is a product of the gene SCN5A. Multiple mutations in the coding region of this gene have been found in patients with early onset lone AF [19]. Mutations in the genes coding for the β

subunits, which are involved in modulating the voltage responsiveness of the pore via noncovalent and disulfide bridging interactions, have also been reported in patients with the Brugada syndrome and lone AF [20]. It is notable that localization of NaV1.5 is vastly different in mouse compared to human cardiomyocytes and these differences may contribute to the differences in heart rate observed in the species. In the mouse, it remains localized at the intercalated disk at the ends of myocytes, while in humans it localizes predominately at the Z-lines [21]. This difference may allow for the rapid heart rate of the mouse up to 600 beats per minute. without dysynchrony and loss of contraction. Interestingly, apart from regulating voltage sensitivity, the β subunits are involved in expression and localization of the pore [22] and multiple mutations in the β subunits have been identified in patients with AF and this may reflect differences in either voltage regulation or localization of the Na channel on the subcellular level [20, 23, 24].

In addition to NaV1.5, other sodium channel mutations have been identified in AF populations. The sodium channel NaV1.8, was first recognized in nociceptive neurons, but has been demonstrated in cardiomyocytes and is expressed to a greater degree in atrial tissue. NaV1.8 is coded by the gene SCN10A that has been linked to a shortened PR interval with recent reports implicating this gene to the genesis of AF [25]. Other sodium channel proteins are scarcely expressed in cardiomyocytes and have not been associated with the development of AF at this time.

### The Potassium Channel and Short QT Syndromes

Potassium channels were implicated early in heritable dysrhythmia syndromes with the identification of the human-ether a-go-go related gene (HERG) among the first identified and mechanistically related to the long QT syndrome and ventricular dysrhythmias [26]. Among families with heritable AF, mutations in potassium channels are among the most genetically diverse with many distinct cases reported (Table **1**). These mutations are quite rare in the AF population in general and they exhibit variable effects on ventricular repolarization. For example, in addition to the long QT syndromes observed with the loss of function mutations of potassium channel, families with short QT intervals have been described [27] which in some cases also predispose to sudden death [28]. The three genes implicated in the short QT syndrome are KCNH2 (formerly known as HERG), KCNQ1 and KCNF2. Interestingly, KCNH2 mutations have been detected in familial AF in the setting of a short QT interval [29]. Mutations in KCNQ1 resulting in AF exhibited short [30], prolonged [11] or normal QT intervals [13]. It however remains unclear why these mutations have variable effects on ventricular repolarization.

### The Gap Junction

Gap junctions couple cardiomyocytes and allow for the propagation of the action potential and transmission of small molecules (less than 1000 Da) between cells. The dominant gap junction protein in the atrial myocardium is connexin 40, and 4 mutations in the gene coding for connexin 40 (GJA5) have been reported in early onset lone AF [31]. The identified mutations are functionally distinct with one preventing

**Table 1.     Genes associated with atrial fibrillation that were identified from patient with early onset AF and from GWAS.**

| Genes Identified in Cases of AF | | | | |
|---|---|---|---|---|
| **Gene** | **Gene Product** | **Locus** | **Exon** | **Reference** |
| KCNQ1 | K channel | 11p15 | YES | [13] |
| KCNE1 | K channel | 21q22 | YES | [47, 48] |
| KCNE2 | K channel | 21q22 | YES | [49] |
| KCNE3 | K channel | 11q13 | YES | [50] |
| KCNE4 | K channel | 2q36 | YES | [51] |
| KCNE5 | K channel | Xq22 | YES | [52] |
| KCND3 | K channel | 1p13 | YES | [53] |
| KCNH2 | K channel | 7q36 | YES | [29] |
| KCNA5 | K channel | 12p13 | YES | [54, 55] |
| KCNJ2 | K channel | 17q24 | YES | [56] |
| ABCC9 | K channel | 12p12 | YES | [57] |
| SCN5A | Na Channel | 3p21 | YES | [19] |
| SCN10a | Na Channel | 3p22 | YES | [25] |
| SCN1B | Na Channel | 19q13 | YES | [20] |
| SCN2B | Na Channel | 11q23 | YES | [23] |
| SCN3B | Na Channel | 11q23 | YES | [58] |
| NUP155 | Nucleoporin | 5p13 | YES | [59] |
| GJA1 | Gap junction | 6q22 | YES | [34, 60] |
| GJA5 | Gap junction | 1q21 | YES | [61] |
| NPPA | ANP | 1p36 | YES | [62] |
| GATA 4 | TRANSCRIPTION FACTOR | 8p23 | YES | [63] |
| GATA6 | TRANSCRIPTION FACTOR | 18q11 | YES | [64] |
| LMNA | LAMIN A/C | 1q22 | YES | [65, 66] |
| NKX2.5 | TRANSCRIPTION FACTOR | 5q34 | YES | [67] |
| GREM2 | BMP antagonist | 1q43 | YES | [68] |
| Genes identified from GWAS | | | | |
| KCNN3-PMVK | K channel | 1q21 | YES | [43] |
| PRRX1 | homeobox | 1q24 | NO | [69] |
| PITX2 | TRANSCRIPTION FACTOR | 4q25 | NO | [38, 69] |
| ZFHX3 | TRANSCRIPTION FACTOR | 16q22 | YES | [70] |
| CAV1 | scaffolding protein | 7q31 | NO | [46, 69] |
| SYNE2 | Nuclear membrane protein | 14q23 | YES | [69, 46] |

**(Table 1) contd….**

| Genes identified from GWAS | | | | |
|---|---|---|---|---|
| C9orf3 | zinc-aminopeptidase | 9q22 | YES | [69, 46] |
| HCN4 | Neucleotid-gated K channel | 15q24 | NO | [69, 46] |
| MYOZ1 | Calcineurin tethering protein | 10q22 | NO | [69] |

connexin trafficking to the membrane, while another results in appropriate membrane localization but fails to form functional junctions. It was proposed that the resulting heterogeneous loss of gap junction coupling contributes to the arrhythmia potential by increasing the sink/source mismatch. This is further supported by an additional report of a GJA5 mutation resulting in no defect in membrane formation of gap junctions with wild-type connexin 40, but reduced the gap junction coupling when coexpressed with wild-type connexin 43 [32]. Interestingly, a single deletion mutation resulting in truncation of the c-terminus of connexin 43 (a domain known to mediate multiple protein interactions [33]) prevents gap junction formation between atrial myocytes and was identified in patients with lone AF [34]. Of note, the voltage gated sodium channel (NaV1.5) has been shown to interact with connexin 43 [35] and disruption of such gap junction-ion channel interactions may also contribute to the propensity of arrhythmias. Like ion channels, mutations in gap junctions are convenient to identify in patients with early onset or lone AF, however their prevalence in the idiopathic AF population remains rare.

**GENOME-WIDE ASSOCIATION STUDIES**

The realization that Mendelian inheritance of AF may be relatively rare, coupled with the explosion of GWAS studies in other fields, led to genome wide investigations to discover polymorphisms more common in patients with AF. While the GWAS have the advantage of not being biased by preconceived notions of gene functions, they are also limited in their ability to determine causal relationships especially for detection of SNPs from intronic DNA. For a comprehensive review of GWAS studies to date, see Tucker and Ellinor [36].

GWAS of AF were first published in the mid 2000s and initially identified a gene-sparse region of chromosome 4q25 that is associated with AF [37]. Subsequent studies revealed a 6-fold risk of AF in patients with 6 risk alleles that were identified in this region [38]. The causal relationship for the 4q25 region and AF has been attributed to the proximity of the PITX2 gene which is located ~150 Kb downstream from the 4q25 locus. PITX2 (Pitx2c cardiac isoform) codes for a transcription factor expressed in the left atrium (among other places) during cardiogenesis [39] and is involved in the formation of the atrial septum, outflow tract and pulmonary vein myocardial sleeves [40]. Knock-out of PITX2 in mice slows atrial conduction and increases susceptibility to AF after burst pacing [41].

Much attention has been paid to the PITX2 variants as they have the strongest association with AF in multiple ethnic populations from the 9 variants identified by GWAS to date [42]. Other candidate gene variants identified by GWAS include KCNN3, PRRX1, WNT84, CAV1, SYNE2, HCN4, and ZFHX3. Many of these variants are far from the coding regions of their linked genes, and though the causal relationship of PITX2 to AF is somewhat convincing from knockout studies, the causal relationship of the remaining variants to disease remains unclear.

The gene KCNN3 codes for a small conductance calcium activated potassium channel SK3, and it is curious that of all the potassium channel mutations detected in the aforementioned familial linkage studies, no mutation in the KCNN3 gene itself had been found to relate to AF [43]. Overexpression of the SK3 channel in a mouse model caused an increased risk of sudden death associated with bradyarrhythmias and heart block, possibly due to atrioventricular nodal dysfunction [44].

It remains a challenge to determine the functional role, if any of the SNPs, particularly those in the non-coding regions. Recently, elegant work by Tsai and others has examined the 9 target genes detected by GWAS using next-generation sequencing in patients with extreme AF phenotypes. In this study, patients with high frequency rates of AF were examined with the assumption that subjects with extreme phenotypes are more likely to have loss of functional alleles with more deleterious effects [45]. By a-priori targeting the genes previously detected by GWAS, novel de novo mutations in patients of the 9 GWAS candidate genes [46] were identified. Importantly, this study reported mutations in the 5' UTR and the exons, which would result in predictable changes in gene expression and/or amino acid composition.

**CONCLUSION**

Our understanding of AF in the past 20 years has advanced from the observation that AF has a familial component to identification of more than 30 specific mutations that predict the disease (Table **1**). The decreasing cost of next-generation sequencing will likely result in increased testing and identification of these mutations in patients with AF. While routine genetic testing for AF is not currently performed, it is possible that in the future, genotyping may help guide prognosis, risk of future events such as cerebrovascular accidents, or even therapy (such as pulmonary vein ablation or response to medical therapies). For instance, it is unknown whether patients with specific mutations would benefit more from adrenergic receptor blockade over calcium channel blockade or whether certain patients may garner more benefit from a rhythm control strategy based on the genetic cause for the disease. It is important to stress that these studies are still in their infancy, and given the modest effect size of SNPs identified to date on the development of

AF, it remains unclear how much additional prognostic information is added to traditional risk factors. As further SNPs are identified, and multimarker models are developed using multiple SNPs for disease prediction, genetic testing may play a role in the future. More importantly, as we better understand the role of these SNPs in disease pathogenesis, we may develop novel therapeutic targets for the treatment of AF.

Here, we have reviewed the genetic studies that have advanced our understanding of this dysrhythmia. Future work will be to determine how to use knowledge of specific mutations to guide therapy and hopefully reduce the morbidity and mortality of AF.

## LIST OF ABBREVIATIONS

AF          =    Atrial Fibrillation

CVD         =    Cardiovascular Diseases

GWAS        =    Genome-wide Association Studies

LDL         =    Low Density Lipoproteins

SNPs        =    Single Nucleotide Polymorphisims

UTR         =    Untranslated Region

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

## ACKNOWLEDGEMENTS

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