

REVIEW ARTICLE

# Genetic basis of atrial fibrillation



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**Abstract** Atrial fibrillation is the most common sustained arrhythmia and remains as one of main challenges in current clinical practice. The disease may be induced secondary to other diseases such as hypertension, valvular heart disease, and heart failure, conferring an increased risk of stroke and sudden death. Epidemiological studies have provided evidence that genetic factors play an important role and up to 30% of clinically diagnosed patients may have a family history of atrial fibrillation. To date, several rare variants have been identified in a wide range of genes associated with ionic channels, calcium handling protein, fibrosis, conduction and inflammation. Important advances in clinical, genetic and molecular basis have been performed over the last decade, improving diagnosis and treatment. However, the genetics of atrial fibrillation is complex and pathophysiological data remains still unraveling. A better understanding of the genetic basis will induce accurate risk stratification and personalized clinical treatment. In this review, we have focused on current genetics basis of atrial fibrillation.

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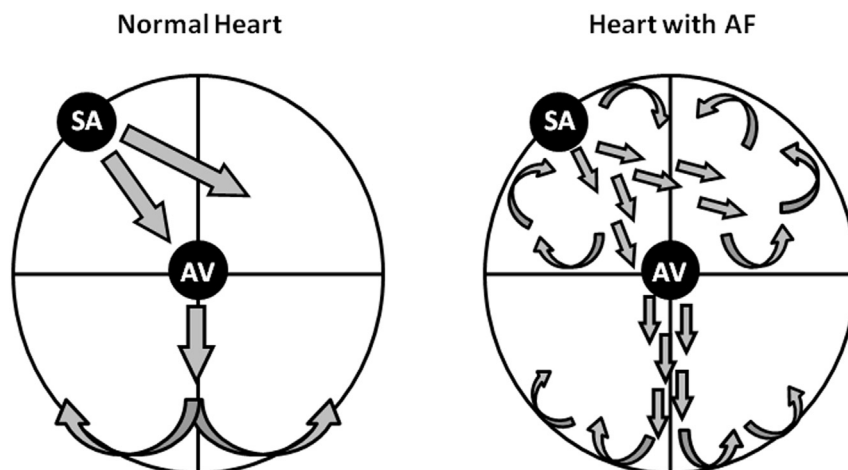
## Introduction

Atrial fibrillation (AF) is the most common sustained abnormal heart rhythm (arrhythmia) encountered in current clinical practice. It is an erratic and unpredictable activation of the atria, causing an irregular ventricular response characterized by irregular waves in the electrocardiogram (ECG) which manifests clinically as fibrillation pulse (Fig. 1).<sup>1</sup> AF has a prevalence of 1% in the general population, which increases with age to about 6% in people

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**Fig. 1** Diagram showing electrical activity of a normal heart (left) and a heart with atrial fibrillation (right). In a normal heart, sino-atrial (SA) node starts electric signals whose induces contraction of auricles. Then, these electrical signals pass to ventricles through atrio-ventricular (AV) node, inducing contraction of ventricles. In atrial fibrillation (AF) conditions, the normal beat in the two auricles is irregular due to a chaotic electrical signal. It induces an irregular and fast heart beat which supposes that the blood doesn't flow correctly from the atria to ventricles.

over the age of 65 and approximately 10% of individuals by 80 years of age.<sup>2–4</sup> Epidemiological studies suggest that AF affects nearly 3 million people in the United States, 8.8 million Europeans, and 30 million individuals worldwide.<sup>5,6</sup> With the accelerating aging population process and the improved survival of patients with other cardiovascular disorders, AF is estimated to increase 5-fold in prevalence by 2050.<sup>7,8</sup> Individuals with AF have nearly twice the risk of death compared with the general population and it is responsible for over 1/3 of all cardioembolic episodes.<sup>9</sup>

Recent guidelines suggested that AF be classified on the basis of the temporal pattern of the arrhythmia.<sup>1,10</sup> Therefore, AF may be paroxysmal (transient) or persistent. Paroxysmal AF accounts for 35–40% of all cases seen by physicians and is not a benign entity, especially in individuals with underlying cardiac pathology. The disease carries a high mortality and despite being a self-terminating arrhythmia, there is a 30–50% chance of converting to a chronic state depending on the underlying pathology.<sup>11</sup> AF is generally known as a common complication in various cardiac and systemic disorders including valvular heart disease, hypertension, atherosclerotic disease and hyperthyroidism. In some cases, AF can also exist in the absence of the previously mentioned predisposing factors, defined as lone AF, and it accounts for 2–16% of all cases.<sup>12</sup> Despite the natural history of lone AF has not been well-studied, current data suggest that it is associated with a low risk of progression to permanent AF, mortality, congestive heart failure, and stroke/transient ischemic attack.<sup>13,14</sup>

Taken all these data together, genetics play a key role both as cause as well as modifier of the disease. According to the patterns of heredity, AF could be familial following a Mendelian hereditary pattern or non-familial AF, which typically occurs in association with underlying cardiovascular disease. Therefore, genetic factors, interacting with non-genetic or environmental factors, contribute to the risk of non-familial AF. Indeed, in 1936 the first report of familial AF was published in three young brothers diagnosed with AF.<sup>15</sup>

Seven years after, in 1943, Wolff et al published a family with lone AF transmitted with an autosomal dominant pattern of inheritance.<sup>16</sup> Epidemiological studies have found that individuals who have a first-degree relative with lone AF carry up to 8-fold increased risk.<sup>17</sup> Even more remarkable, the presence of a clinically affected sibling is associated with a 70-fold increased risk in males and 34 in females.<sup>18</sup> The Framingham Heart Study, which involved 2243 subjects, identified that parental AF conferred a 1.85-fold increased risk in offspring.<sup>19,20</sup> A similar study from Iceland performed in a cohort of 5269 patients corroborated the result, identifying a 1.77-fold increased risk of AF in first-degree relatives.<sup>21</sup> Finally, in a study of Danish twins, over 60% of the variance of AF was estimated to be explained by genetics.<sup>22</sup> Taking into account all these results, genetics play a critical role in the development of lone AF. Finally, complications of familial AF can occur at any age, although some people suffering of AF never experience any health problems associated with the arrhythmia.

## Genetics

Recent advances in genetics have given new insights into the development of AF. Current efforts are focused on two areas: genetic alterations and gene expression regulation in ion channels. The gene expression studies are usually performed in animal models. These experiments are principally providing information on the molecular changes triggered by the disease and the mechanisms by which the AF becomes chronic.<sup>23–25</sup> Research in the identification of genetic defects provides a direct link into the etiology for AF. Genetic basis of AF can be currently studied from different perspectives: 1) AF as a monogenic disease—different members of a family have the arrhythmia as a primary electrical disease—, 2) arrhythmia presenting in the setting of another familial disease, and 3) genetic background that may predispose to the disease without

family segregation. The first two analyses are familial forms of AF and require the segregation analysis of relatives, with or without pathology. These familial forms are due to rare variants in the population. The third case, research in non-familial AF, is characterized by being multifactorial, the result of the interaction of environment and genetic factors, which play a smaller role in the disease, albeit an important one. It is due to common variants in the population and the analysis is performed as an association study, aimed at identifying differences in segregation of genetic backgrounds which may explain the development of and susceptibility to AF.<sup>26</sup>

### Rare variants

In recent years, several rare genetic variants in genes encoding ion channels or associated proteins have been associated with AF.<sup>27</sup> They could alter the depolarization/repolarization of ion channels, leading to AF. To date, there are published nearly 80 rare genetic variants in 39 genes encoding different proteins like (Table 1): sodium ion channels (*SCN5A*, *SCN1B*, *SCN2B*, *SCN3B*, *SCN4B* and *SCN10A*), potassium (*ABCC9*, *HCN4*, *KCNQ1*, *KCNA5*, *KCNJ2*, *KCNJ5*, *KCNJ8*, *KCNE1*, *KCNE2*, *KCNE3*, *KCNE4*, *KCNE5*, *KCNE3*, *KCNH2* and *KCND3*) and calcium (*RyR2*, *CACNB2* and *CACNA2D4*). In some of these cases carrying a pathogenic variant in ion channels, AF has been described concomitant with other monogenic diseases like Long QT syndrome (LQTS)—Early-onset AF (<50 years) is observed in 2% of LQTS patients—,<sup>28–30</sup> Brugada syndrome (BrS)—AF is the most common atrial arrhythmia in Brugada syndrome (BS), with an incidence reported between 6 and 53% by different series—,<sup>31,32</sup> Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)—Atrial arrhythmias are frequently observed in CPVT patients with an incidence of 10%—,<sup>33–35</sup> and Short QT syndrome (SQTS).<sup>36</sup> Concretely, high incidence of atrial arrhythmias in patients with SQTS has been reported with nearly 20%–25% of cases.<sup>37–41</sup>

In addition, rare variants in non-ion channels genes have been also associated with AF such as in genes encoding gap junctions (*GJA1* and *GJA5*) as well as the *NPPA* gene, encoding atrial natriuretic peptide (ANP),<sup>42</sup> albeit with precise molecular pathways yet to be established. Moreover, rare variants in *LMNA*, *NUP155*, *JPH2*, *SYNE2* and *GREM2* (genes encoding structural proteins of nucleus and involved in muscle function) have been identified in AF cohorts, demonstrating abnormalities in cardiac excitation. Finally, genes related to cardiac transcription factors have also been identified as being associated with AF. Specifically, genetic variation in *ZFH3*, *NKX2.5*, *NKX2.6*, *PITX2*, *GATA4*, *GATA5*, and *GATA6* has been identified, although the mechanisms whereby these lead to disease have remained unclear.<sup>43–49</sup>

### Common variants

In 2005, the genome-wide association study (GWAS) technique was utilized to identify genetic loci associated with disease.<sup>50</sup> Until this year, linkage and candidate gene sequencing methods were the predominant approaches used to identify AF genes. The first description of an

**Table 1** Rare genetic variants associated with AF.

Gene	Gene name
<i>ABCC9</i>	ATP-binding cassette, subfamily C, member 9
<i>CACNB2</i>	Calcium channel, voltage-dependent, beta 2 subunit
<i>CACNA2D4</i>	Calcium channel, voltage-dependent, alpha 2/delta subunit 4
<i>GATA4</i>	Transcription factor GATA-4
<i>GATA5</i>	Transcription factor GATA-5
<i>GATA6</i>	Transcription factor GATA-6
<i>GJA1</i>	Connexin 43
<i>GJA5</i>	Connexin 40
<i>GREM2</i>	Gremlin-2
<i>HCN4</i>	Hyperpolarization activated cyclic nucleotide-gated potassium channel 4
<i>JPH2</i>	Junctophilin-2
<i>KCNA5</i>	Potassium voltage-gated channel, shaker-related subfamily, member 5
<i>KCND3</i>	Potassium voltage-gated channel, Shal related subfamily, member 3
<i>KCNE1</i>	Potassium voltage-gated channel, Isk related family, member 1
<i>KCNE2</i>	Potassium voltage-gated channel, Isk related family, member 2
<i>KCNE3</i>	Potassium voltage-gated channel, Isk related family, member 3
<i>KCNE5</i>	KCNE1-like
<i>KCNH2</i>	Potassium voltage-gated channel, subfamily H (eag-related), member 2
<i>KCNJ2</i>	Potassium inwardly-rectifying channel, subfamily J, member 2
<i>KCNJ5</i>	Potassium inwardly-rectifying channel, subfamily J, member 5
<i>KCNJ8</i>	Potassium inwardly-rectifying channel, subfamily J, member 8
<i>KCNN3</i>	Potassium channel, calcium activated intermediate/small conductance subfamily N alpha, member 3
<i>KCNQ1</i>	Potassium voltage-gated channel, KQT like subfamily, member 1
<i>LMNA</i>	Lamin A/B
<i>NKX2.5</i>	Homeobox protein Nkx2.5
<i>NKX2.6</i>	Homeobox protein Nkx2.6
<i>NPPA</i>	Natriuretic peptide precursor A
<i>NUP155</i>	Nucleoporin 155
<i>PITX2c</i>	Paired-like homeodomain 2c
<i>RYR2</i>	Ryanodine receptor 2
<i>SCN1B</i>	Sodium channel, voltage-gated, type I, beta subunit
<i>SCN2B</i>	Sodium channel, voltage-gated, type II, beta subunit
<i>SCN3B</i>	Sodium channel, voltage-gated, type III, beta subunit
<i>SCN4B</i>	Sodium channel, voltage-gated, type IV, beta subunit
<i>SCN5A</i>	Sodium channel, voltage-gated, type V, alpha subunit
<i>SCN10A</i>	Sodium channel, voltage-gated, type X, alpha subunit
<i>SYNE2</i>	Nesprin-2
<i>ZFH3</i>	Zinc finger homeobox-3, transcription factor

association between common single nucleotide polymorphisms (SNPs) and AF (chromosome 4q25, rs2200733), using GWAS was performed in 2007.<sup>51</sup> To date, several common genetic polymorphisms have been associated with the risk of AF development and risk of stroke, and predispose to recurrences of AF on antiarrhythmic drugs or ablation success.<sup>52</sup> Hence, nearly 1/3 of all AF patients carry common variants that predispose to AF.<sup>53,54</sup> In general, every single nucleotide polymorphism (SNP) only carries a small relative risk, but they can be combined to generate more precise information.<sup>55</sup> A general contention is that SNPs presumably act as promoters or enhancers of proximate genes. Currently, it has been published 18 SNPs being the 15 closest gene: *PITX2*, *ZFHX3*, *KCNN3*, *CAV1*, *PRRX1*, *C9ORF3*, *HCN4*, *SYNPO2L/MYOZ1*, *CAND2*, *GJA1*, *NEURL*, *CUX2*, *TBX5*, *SYNE2*, and *WNT8A* (Table 2).

## Future of genetics

Concerning rare variants already associated with AF, the discovery of pathophysiology of ion channels may help unravel the concise role played by the genetic variant in arrhythmogenicity. However, most rare variants remain as potentially pathogenic or of unknown significance and translation into clinical practice should be done with caution. It is necessary to clarify the role of interactions between rare and common genetic variants in the predisposition to AF.<sup>56</sup> Thus, these variants, by mechanisms yet to be understood, can interact to modify their respective electrophysiological phenotypes.<sup>57</sup> Some of the causative variants in the identified AF loci remain unknown and some of the discovered variants in these loci have yet to be proven to be causative. This is a main challenge as several SNP identified by GWAS are rarely the causative variants, but a genetic marker in linkage disequilibrium with the causative variation, which could remain still undetected due to the fact that it is a non-coding insertion or deletion,

a genetic rearrangement, a variation in copy number, or an epigenetic modification,<sup>27</sup> variants that still remain highly unexplored.

The rare and common variants identified so far do not seem to fully account for the considerable heritability of AF observed in epidemiologic studies. There is a range of possible explanations for this missing heritability, including unidentified rare or common genetic variants, gene–gene interactions, gene–environment interactions or variations in copy number (CNV). Current genetic technologies allow performing a wide variety of analyses in families suffering from AF in order to identify the single cause of AF or genetic variants predisposing to the disease. Hence, comprehensive large-scale exome and genome sequencing for AF as well as GWAS studies will identify both rare and common genetic variants associated with AF. In addition, animal models and bioinformatic simulations may help to clarify the cellular mechanism involved in pathophysiology of AF.<sup>58</sup>

## Conclusions

Currently, AF is the most common cardiac arrhythmia and is associated with increased rates of heart failure, stroke, and sudden death. Despite recent advances, current diagnosis, treatment strategies and preventive measures have a limited efficacy. It is mainly due to the complicated pathophysiology of the disease as well as to complicated inheritance mechanisms of the genes, which induce a substantial interindividual variability leading to a varied AF development. Furthermore, with regard to genetic variants associated with AF, it is important to have a better understanding of molecular signaling events or mechanisms that ultimately lead to the disruption of normal electrical excitation. In the following years further genetic studies will identify new genetic alterations associated with AF. Molecular studies should definite corroborate theses genotype–phenotype associations in order to clarify the pathophysiological pathways leading to atrial arrhythmias.

## Conflicts of interest

The authors declare that they have no conflict of interests.

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**Table 2** Common genetic variants associated with AF.

Locus	SNP	Nearest gene
4q25	rs6817105	<i>PITX2</i>
4q25	rs2200733	<i>PITX2</i>
16q22	rs2106261	<i>ZFHX3</i>
1q21	rs6666258	<i>KCNN3</i>
1q21	rs13376333	<i>KCNN3</i>
1q24	rs3903239	<i>PRRX1</i>
7q31	rs3807989	<i>CAV1</i>
14q23	rs1152591	<i>SYNE2</i>
9q22	rs10821415	<i>C9ORF3</i>
15q24	rs7164883	<i>HCN4</i>
10q22	rs10824026	<i>SYNPO2L/MYOZ1</i>
5q31	rs2040862	<i>WNT8A</i>
3q25	rs4642101	<i>CAND2</i>
6q22	rs13216675	<i>GJA1</i>
10q24	rs12415501	<i>NEURL</i>
10q24	rs6584555	<i>NEURL</i>
12q24	rs10507248	<i>TBX5</i>
12q24	rs6490029	<i>CUX2</i>

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