

## Review Article

# Genetics of Atrial Fibrillation and Possible Implications for Ischemic Stroke

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Atrial fibrillation is the most common cardiac arrhythmia mainly caused by valvular, ischemic, hypertensive, and myopathic heart disease. Atrial fibrillation can occur in families suggesting a genetic background especially in younger subjects. Additionally recent studies have identified common genetic variants to be associated with atrial fibrillation in the general population. This cardiac arrhythmia has important public health implications because of its main complications: congestive heart failure and ischemic stroke. Since atrial fibrillation can result in ischemic stroke, one might assume that genetic determinants of this cardiac arrhythmia are also implicated in cerebrovascular disease. Ischemic stroke is a multifactorial, complex disease where multiple environmental and genetic factors interact. Whether genetic variants associated with a risk factor for ischemic stroke also increase the risk of a particular vascular endpoint still needs to be confirmed in many cases. Here we review the current knowledge on the genetic background of atrial fibrillation and the consequences for cerebrovascular disease.

## 1. Introduction

Of all cardiac arrhythmias, atrial fibrillation (AF) is the most common, affecting approximately 1-2% of the population [1]. The prevalence is higher in men compared to women and increases with age, which is reflected by the finding that 25% of the population aged over 40 will develop AF [2]. Patients with AF frequently have other cardiovascular and noncardiovascular comorbidities, the most important condition being hypertension [3], which is an important risk factor for the development of AF [4]. AF is not a benign disease as it is associated with increased rates of death, stroke, ischemic heart disease, heart failure, and peripheral thrombo-embolic events. In patients with AF, various independent factors raise the risk of stroke such as the presence of hypertension, advancing age and diabetes and the previous occurrence of a stroke or transient ischemic attack (TIA) [5, 6]. Epidemiological studies have identified various risk factors for AF which include age, male sex, hypertension

and the presence of structural heart abnormalities. However, it was suspected that the totality of the risk could not be explained exclusively by these factors, and a genetic risk component was suspected [7]. Although the vast majority of AF is sporadic and nonfamilial, familial (hereditary) forms of AF have been identified (Table 1). Also, the genetic background of AF in the general population has been studied through association studies (Table 1). Since stroke is a major complication of AF, genetic variants associated with this arrhythmia may be implicated in ischemic cerebrovascular disease. We present an overview of the current knowledge in the monogenic forms and complex genetics of AF and discuss the consequences for ischemic stroke.

## 2. Pathophysiology

Various structural cardiac abnormalities can result in a process of remodeling in the ventricles and atria. This remodeling is characterized by the proliferation of myofibroblasts

TABLE 1: Genetics of atrial fibrillation.

	Gene/Locus	Mechanism of action	Study design/Inheritance
Sodium channels	SCNA5 [8–17]	Cellular hyperexcitability (gain-of-function) as well as prolongation of the atrial action potential duration (loss-of-function)	Candidate gene/Familial and sporadic
	SCN1B/SCN2B [18]	Decreased peak sodium current amplitude	Candidate gene/Sporadic
Potassium channels	KCNQ1 [19–22]	Enhanced atrial action potential repolarization	Linkage/Familial
	KCNE2 [23]	Enhanced atrial action potential repolarization	Candidate gene/Familial
	KCNJ2 [24]	Enhanced atrial action potential repolarization	Candidate gene/Familial
	KCNE5 [25]	Enhanced atrial action potential repolarization	Candidate gene/Familial and sporadic
Other	KCNA5 [26–28]	Delayed atrial action potential repolarization	Candidate gene/Familial and sporadic
	NPPA [29]	Shortening of the atrial action potential duration	Linkage/Familial
	GJA5 [30–32]	Dispersion of conduction velocity	Candidate gene/Sporadic
	10q22 [33]	Unknown	Linkage/Familial
	6q14–16 [34]	Unknown	Linkage/Familial
	5p15 [35]	Unknown	Linkage/Familial
	4q25 (PITX2) [36, 37]	Unknown	Genome wide association/Sporadic
	16q22 (ZFHX3) [38]	Unknown	Genome wide association/Sporadic
	1q21 (KCNN3) [39]	Unknown	Genome wide association/Sporadic

and the development of fibrosis. Interstitial fibrosis leads to electrical uncoupling and conduction slowing, which promotes AF. If atrial fibrillation persists for several days, electrical and structural remodeling occurs promoting further maintenance of AF [40, 41]. Electrophysiologically several mechanisms have been identified which trigger and maintain the arrhythmia.

The mechanisms by which AF becomes thrombogenic are complex and have not been completely elucidated. It has become clear that the mere presence of blood stasis is not a sufficient explanation for thrombus formation. Various alterations related to AF and associated comorbidities as abnormal changes in flow, vessel wall, and blood components, probably drive a hypercoagulable state [42].

Considering the pathophysiology and taking into account the suspected genetic background in the disease it could be assumed that mutations or variants in genes of ion channels, which are of importance in atrial electrophysiology, are implicated in AF. This has been confirmed by linkage, candidate, and genome-wide genetic association studies.

### 3. Monogenetic Forms of AF

**3.1. Familial AF.** Studies aimed to identify the pathogenesis of AF have focused on the familial forms of the disease. In these rare familial forms different loci, as well as mutations in a range of genes have been linked to AF. Various mutations in genes encoding sodium channels (SCN5A, SCN1B, and SCN2B), potassium channels (KCNQ1, KCNE2, KCNJ2,

KCNE5, and KCNA5), natriuretic peptide (ANP) and Connexin 40 have been identified. Additionally, the culprit genes at loci on chromosome 10q22 [33], 6q14-16 [34], and 5p15 [35] have yet to be found.

**3.1.1. Sodium Channel Mutations.** The human cardiac sodium channel (SCN5A) is responsible for fast depolarization of cardiomyocytes and has been a therapeutic target for antiarrhythmic drugs. Initially mutations in SCN5A were identified in families with long QT syndrome [8]. Over the years, more than 200 mutations have been reported in SCN5A which are associated with variable cardiac diseases like Brugada syndrome, progressive conduction defect, sick sinus node syndrome, dilated cardiomyopathy and AF [9]. Genotype-phenotype correlations revealed that most mutations are linked to specific clinical spectrums, but that clinical overlaps exist for the same genetic defects [10]. Both Brugada syndrome and long QT syndrome can be complicated with supraventricular arrhythmias which often include AF [11]. More evidence for the role of mutations in SCN5A in the pathophysiology of AF was provided by the identification of a family with a dilated cardiomyopathy and AF carrying a mutation in SCN5A [12]. Additionally, novel mutations in the same gene were reported in familial forms of AF with and without structural cardiac disease [13–16]. It was determined that rare variants in SCN5A are present in nearly 6% of AF probands [14]. In two studies, functional analysis of the mutation showed a depolarizing shift in steady-state inactivation resulting in cellular hyperexcitability (gain of

function) [15, 16]. A loss of function was suggested by the study of another variant which revealed a hyperpolarizing shift in steady-state inactivation resulting in prolongation of the atrial action potential duration [13]. This delayed atrial repolarization could induce atrial torsades resulting in AF. Different mechanisms, both loss of function as well as gain of function, have been suggested in various syndromes. Furthermore, there is a wide spectrum of mutations which are associated with overlapping syndromes, suggesting environmental or other genetic factors to be of importance in determining the phenotype.

Interestingly, nonsynonymous variants were identified in other sodium channel subunits, two in SCN1B and two in SCN2B, in patients with AF which were absent in controls [18].

**3.1.2. Mutations in Potassium Channel Genes.** The voltage-gated potassium current has a prominent role in the repolarization of the atrial action potential. Other potassium channels are of importance for the inward rectifier currents and the control of the resting potential. Multiple gain-of-function as well as loss-of-function mutations within potassium channel genes have been identified. A mutation in KCNQ1, a gene encoding the pore-forming  $\alpha$  subunit of a cardiac voltage-gated potassium channel, was originally documented as the causative gene for long QT syndrome [19]. A mutation in the same gene was the first identified genetic defect linked to lone AF [20]. It was hypothesized that the pathogenic mechanism consisted of a gain of function by increasing the repolarizing current and shortening of the atrial action potential duration [20]. Various other gain of function mutations have subsequently been identified in isolated families in KCNQ1 [21, 22] as well as in other potassium channel genes, including KCNE2 [23], KCNJ2 [24], and KCNE5 [25]. Additionally, in another potassium channel gene, KCNA5, loss-of-function mutations were identified in a small number of families [26–28]. Functional analysis of this mutation revealed delayed action potential repolarization and prolongation of the atrial action potential duration (a mechanism similar as reported for a SCN5A mutation [13]).

**3.1.3. Atrial Natriuretic Peptide (ANP).** In a linkage study of a family with autosomal dominant AF, a mutation in the natriuretic peptide precursor gene (NPPA) was identified [29]. The mutation produced the loss of a stop codon resulting in the expression of a longer peptide. The concentration of the mutant peptide was 5 to 10 times increased in the plasma compared to the wild type suggesting a longer half-life potentially due to resistance to degradation. In an isolated whole-heart model, the mutant peptide caused shortening of the atrial action potential duration (analogous to what is reported for most of the potassium channel mutations).

Another possible pathophysiological mechanism of the mutation might involve structural changes resulting in atrial fibrosis due to exposure to high concentrations of (mutant) ANP [29].

**3.1.4. Connexin 40.** The initially discovered genes found in familial AF were a rare cause of lone AF [43, 44]. Therefore,

additional research focused at other pathogenic pathways. Attractive genes included the connexins, which are proteins that form gap junctions and provide low-resistance electrical coupling between cells. Especially the gene GJA5, coding for connexin 40, gained interest since it is expressed at high levels in atria. Furthermore, conduction disturbances have been identified in GJA5-knockout mice resulting in atrial vulnerability and possibly arrhythmogenesis [45]. Sequencing of genomic DNA from cardiac tissue of 15 patients with idiopathic AF indeed identified four missense mutations, of which three were thought to be of somatic origin. The mutated protein was heterogeneously distributed in atrial tissue and a loss-of-function was hypothesized [30], resulting in exaggerated dispersion of conduction velocity predisposing to and sustaining AF. Moreover, a similar genetic mosaicism in atrial tissue linked to AF was recently reported in one patient with lone AF for the GJA1 gene, coding for the connexin 43 protein [46].

**3.2. AF in Other Inherited Disorders.** In several genetic cardiac syndromes, both with and without structural abnormalities, AF has been described as part of the clinical spectrum. Short and long QT and Brugada are associated with supraventricular arrhythmias, which often comprise AF. Various other inherited cardiac disorders are characterized by the occurrence of AF as hypertrophic cardiomyopathy, ventricular preexcitation and abnormal left ventricle hypertrophy linked to mutations in the PRKAG gene [11].

## 4. Complex Genetics of AF

Whereas genetic studies in familial forms of AF have implicated various genes in a limited number of cases, epidemiologic studies in the general population have documented a genetic component to AF in sporadic AF. Parental AF was shown to increase the risk for future AF, an association which was stronger at younger age and for lone AF [47–49]. Candidate gene studies in sporadic AF investigating common variants in the genome suggested a role for polymorphisms in regions implicated in familial AF [17, 31, 32, 50–54] as well as others [55–63]. An association for a common polymorphism in SCN5A with paroxysmal AF was reported, although replication of this finding is lacking [17]. Common variants in GJA5 have also been shown to associate with atrial fibrillation in sporadic AF [31, 32]. The sample sizes in most of these studies were relatively small and large replication studies were lacking. Meta-analyses of studies determining the role of polymorphisms in the renin-angiotensin system-related gene with AF suggested a possible association between angiotensin converting enzyme (ACE) insertion/deletion and AF risk [64, 65]. However a large replication study recently failed to replicate any of the reported associated polymorphisms at this locus or any other locus [66].

Since most of the candidate gene studies have not been successful, results of genome-wide studies were anxiously awaited as for many complex diseases [67]. Two sequence variants on chromosome 4q25 were identified in the first reported genome-wide association study in AF [36]. These

variants have been replicated extensively. Two additional variants in this region were found, and the possibility of multiple susceptibility signals at this locus was hypothesized [37]. The reported variants were adjacent to the PITX2 gene, a transcriptional factor critical for determining left-right asymmetry and for the differentiation of the left atrium [68]. Increasing the initial sample size revealed an additional sequence variant in the ZFHX3 gene in chromosome 16q22 as a risk factor for AF [38]. A third locus was identified on chromosome 1q21 in KCNN3, a gene which encodes a potassium channel protein involved in atrial repolarization [39]. The variant rs2200733 on 4q25 remained the variant with the largest effect size, with an estimated odds ratio in the range of 1.80 (95% CI 1.50–2.15) [37]/1.90 (95% CI 1.60–2.26) [69]. Increasing sample sizes in genetic association studies will potentially reveal yet unknown loci implicated in AF.

## 5. Implications for Ischemic Stroke

Ischemic stroke can be categorized into several etiological subgroups: cardioembolic stroke, large-artery atherosclerosis, small-vessel disease, undetermined (cryptogenic, multiple causes, or incomplete evaluation), or other causes [70]. Approximately 20% of ischemic strokes are due to cardiac embolism mainly caused by atrial fibrillation (AF), which can be either paroxysmal or persistent with both variants resulting in a similar stroke risk [71]. It is thought that some strokes of undetermined origin are actually due to undiagnosed paroxysmal AF [72]. Since stroke can be a clinical complication of sporadic AF, the risk of stroke is also increased in familial cases of AF. Other inherited cardiac disorders characterized by AF can also present with stroke. In hypertrophic cardiomyopathies, for instance, the stroke risk is increased and this is directly linked to the occurrence of AF [73].

Stroke is considered a complex disease where a genetic component in the etiology is suspected. Candidate gene studies in stroke have resulted in largely disappointing findings [74]. Findings of a large genome wide association study in stroke could not be replicated [75, 76]. An association was reported in a genome-wide association study in stroke for the initially reported risk variant rs2200733 on 4q25 with AF, OR 1.26 (95% CI 1.17–1.35) [77]. This association was most pronounced in the cardioembolic subgroup of stroke. We replicated these findings and identified this variant exclusively in cardioembolic stroke, suggesting that this variant is indirectly linked to stroke through AF [78]. The effect size of this genetic variant in cardioembolic stroke is somewhat smaller than what has been reported for AF, OR: 1.52 (95% CI 1.35–1.71) [77] and 1.47 (95% CI 1.28–1.71) [78]. This could be due the fact that in most selected controls, stroke-free status was ensured while AF-free status was not determined. Additionally, not all patients with cardioembolic stroke are diagnosed with AF (in our replication study this percentage was 61%). Similar findings were obtained for the variant on 16q22 which also confers risk for primarily cardioembolic stroke [38].

### 5.1. Influence of Cryptogenic Stroke?

The initial report on the association of the 4q25 locus with stroke stated that in subgroup analysis, the association of the 4q25 locus with stroke remained after all patients who suffered from cardioembolic stroke were excluded [77]. This study included five study populations totaling 29474 controls and 6222 patients. Our replication study was performed in six different populations with 3750 controls and 4199 patients. All studies included hospital-based populations (apart from the controls in one cohort in the discovery study). Phenotyping was performed according to similar protocols. Potentially the lack of replication after excluding stroke of cardioembolic embolism could be due to the somewhat smaller sample size. Additionally the findings of the initial report after excluding cardioembolic stroke might be caused by phenotypic misclassification or ascertainment bias: patients classified as having a stroke of undetermined etiology could in reality have a stroke of (unidentified) cardioembolic etiology because AF was not detected during the hospital stay or because the investigation into cardioembolic sources was not extensively performed. In our replication study, the variants on 4q25 lacked association with true cryptogenic stroke, arguing against a large percentage of these patients suffering from unrevealed cardioembolic stroke. This analysis was not performed in the initial report. Additionally in our replication study, we identified an interaction between cardioembolic stroke and the risk variant on 4q25 supporting the hypothesis that the relation is mainly caused by this subtype of stroke.

Since the genotyping of these variants has become commercially available, it might be tempting to offer patients with stroke of cryptogenic etiology genetic testing for AF inducing variants. Patients carrying the risk variant (of which the allele frequency is estimated to be 10% in the general population) could, for example, be more extensively studied for paroxysmal AF. Our results do not provide evidence for performing such individually based genotyping since no association was identified in cryptogenic stroke patients.

*5.2. Stroke as a Phenotype or Stroke as a Conglomerate of Phenotypes.* The findings from these genetic association studies underline that genetic risk factors may predispose to a particular subgroup of stroke. The fact that a variant on chromosome 9 associated with myocardial infarction and coronary artery disease also is associated with stroke due to large-vessel atherosclerotic disease emphasizes this assumption [79, 80]. Stroke is a heterogeneous disorder, and this heterogeneity might be the reason for the disappointing results in genetic association studies in the stroke field so far. It can be assumed that genetic risk factors are implicated only in subgroups of stroke, and, therefore, analyzing each subgroup is of importance. In order to obtain convincing results from GWAS, accurate stroke phenotyping and large sample sizes for each stroke subtype will be required.

*5.3. Stroke as a Vascular Endpoint.* Stroke can be regarded as the clinical outcome of other underlying diseases; this seems

applicable not only to AF and cardioembolic stroke but also for stroke due to large-vessel disease and atherosclerosis. One could argue that data of various disease traits that share underlying pathogenic mechanisms could be combined in meta-analyses of genome-wide association studies to increase power. Moreover, it could be considered to analyze cases of underlying diseases together with cases of the associated clinical outcome. For instance, data obtained in genome-wide association studies in AF can be merged with the data of all cardioembolic stroke cases. Similarly, coronary artery disease, peripheral artery disease and stroke due to large-vessel disease could be jointly examined. This does not entirely exclude the possibility that genetic variants will be identified for ischemic stroke in general. However, the other approaches (combining vascular diseases or merging risk factors and their outcomes) could increase power and could eventually lead to the identification of genetic polymorphisms conferring risk for (subtypes of) stroke. Although typically this will lead to findings of small effect size, this does not imply that the biological relevance cannot be greater than the genetic effect.

In complex diseases (as stroke), it is assumed that various environmental factors together with genetic variants can result in a certain disease phenotype. Interfering with several (but not necessarily all) of these factors might already result in reducing risk and, therefore, less clinical outcomes in the general population. Identifying the pathophysiological meaning of a genetic variant associated with AF could potentially lead to new therapeutic targets in AF and indirectly lead to a reduction in cardioembolic stroke.

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