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Genetics of Atrial Fibrillation

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***Background*—**Atrial fibrillation (AF) is a common arrhythmia seen in clinical practice. Occasionally, no common risk factors are present in patients with this arrhythmia. This suggests the potential underlying role of genetic factors associated with predisposition to developing AF.

***Methods and Results*—**We conducted a comprehensive review of the literature through large online libraries, including PubMed. Many different potassium and sodium channel mutations have been discussed in their relation to AF. There have also been non–ion channel mutations that have been linked to AF. Genome-wide association studies have helped in identifying potential links between single-nucleotide polymorphisms and AF. Ancestry studies have also highlighted a role of genetics in AF. Blacks with a higher percentage of European ancestry are at higher risk of developing AF. The emerging field of ablatogenomics involves the use of genetic profiles in their relation to recurrence of AF after catheter ablation.

***Conclusions*—**The evidence for the underlying role of genetics in AF continues to expand. Ultimately, the role of genetics in risk stratification of AF and its recurrence is of significant interest. No established risk scores that are useful in clinical practice are present to date. **(*J Am Heart Assoc*. 2018;7:e009884. DOI: 10.1161/JAHA.118.009884.)**

Key Words: ablatogenomics • ancestry studies • atrial fibrillation • genetics • genome-wide association studies

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is characterized by rapid and disorganized electrical activation of the atria, leading to uncoordinated contraction. The loss of synchronized contraction leads to stasis of blood in the atria and subsequent predisposition to the development of stroke secondary to formation of atrial thrombi.[1] AF is commonly associated with coronary artery disease, valvular heart disease, cardiomyopathies, hypertension, hyperthyroidism, obesity, and sleep-apnea syndrome. Alcohol, caffeinated beverages, and energy drinks have also been linked to AF.[2] In some instances, no risk factor can be identified. This has suggested possible underlying genetic predispositions to developing AF. Furthermore, AF has also been shown to occur in families.[3] AF is linked to atrial size and the extent of atrial fibrosis, which are affected by autonomic tone, inflammation, atrial pressure, and genetic factors.[4]

In this review, we will discuss genetic alterations implicated in AF and explore their electrophysiological consequences. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. This work has been exempted from institutional review board approval.

Basis of the Heart's Electrical Conduction System

Electrical signals that initiate normal heart rhythm are generated by spontaneous depolarization of the pacemaker cells of the SA node located in the wall of the right atrium at the junction where the superior vena cava enters it. These signals are then propagated to the AV node located in the posteroinferior region of the interatrial septum. The AV node delays the propagation of the electrical signal to the ventricles, allowing optimization of ventricular filling. The signal subsequently propagates through the left and right bundles of His, followed by the Purkinje fibers of the left and

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Clinical Perspective

What Is New?

- Atrial fibrillation (AF) is the most common sustained arrhythmia and is reaching epidemic proportions in the aging population, with significant morbidity and mortality.
- A substantial proportion of AF in the population is not explained by traditional risk factors.
- Both common and rare genetic variants increase susceptibility to AF in an individual in the presence of ethnic-specific risk factors.
- Studies in lone forms of AF suggested a traditional monogenic syndrome with reduced penetrance.
- Several mendelian loci for typical forms of AF have been identified, but the genes have not yet been cloned.
- Rare forms of familial AF are caused by mutations in potassium channel genes, and there are single families with mutations in a nuclear pore and a natriuretic peptide gene.
- Candidate gene association studies have identified many genes associated with AF.
- Common loci/variants with small effects have been identified in genome-wide association studies, including a locus on chromosome 4q25.

What Are the Clinical Implications?

- The translation of AF genetic variants into disease pathways and novel therapeutic modalities is ongoing.
- The combination of common genetic variants in the AF genetic risk score could risk stratify patients with AF.
- The genetic data might help in AF management by predicting cardioversion success, antiarrhythmic drug response, AF recurrence after ablation, stroke, and sudden cardiac death and by guiding the ablation strategy for AF (ablatogenomics).

right ventricles. These signals are then conducted across cardiac myocyte membranes.

The cardiac action potential is largely influenced by the shift of sodium, calcium, and potassium ions. Every phase in the action potential results from a major ionic current. Intercalated disks between myocytes provide cell-to-cell adhesion and anchor the cytoskeletal structures to the cell membrane via adherens junctions and desmosomes. In addition, they organize other proteins responsible for the transport of ions and small molecules between cells.[5] This transfer of ions plays an important role in the propagation of the action potential.

Potassium Channel Mutations

The several types of potassium channels expressed on cardiac cells are responsible for maintaining resting membrane potential in addition to playing a role in the different phases of repolarization. Potassium channels are composed of pore-forming subunits with multiple other partner proteins, including accessory β-subunits. The α-subunits include 2 to 6 transmembrane domains organized in dimers and tetramers that make the full channel. One of the first ion channel mutations that has been studied involves the delayed-rectifier potassium current, I_{Ks}. Mechanistically, gain-of-function mutations in both subunits lead to increased potassium repolarizing currents. This results in shortening of the action potential duration (APD) and effective refractory period in cardiomyocytes, thus creating profibrillatory substrate in the atria.

Mutations Involving I_{Ks}

The first variant described to be associated with AF is an S140G mutation in the voltage-gated channel potassium subfamily Q member 1 (*KCNQ1*) gene.[6] The *KCNQ1* gene encodes the pore-forming α-subunit of the cardiac potassium channel Kv7.1, which is required for the slowly activating slow rectifier potassium current (I_{Ks}). Analysis of the S140G mutation revealed a gain-of-function missense mutation increasing I_{Ks} and reducing the APD and effective refractory period in atrial myocytes. Other similar gain-of-function mutations in *KCNQ1* were later discovered.[7–16] Recently, a loss-of-function mutation in *KCNQ1* was identified to be associated with early-onset lone AF.[17]

The regulatory β-subunits of the channels producing the I_{Ks} current are encoded by 5 potassium voltage-gated channel subfamily E (*KCNE*) genes: *KCNE1*,[18] *KCNE2*,[19,20] *KCNE3*,[21] *KCNE4*,[22] and *KCNE5*[23]; gain-of-function mutations in all 5 genes have been associated with AF.

Mutations Involving the Rapidly Repolarizing Potassium Current

The α-subunit of the voltage-gated potassium channel Kv11.1, which generates the rapidly repolarizing potassium current, is encoded by the potassium voltage-gated channel subfamily H member 2 (*KCNH2*) gene. Mutations in the *KCNH2* gene are linked to a higher incidence of AF.[24] A mutation in the *KCNH2* gene, resulting in a gain of function of the rapidly repolarizing potassium current, was also found in a family with short QT syndrome and AF.[25] This gain-of-function mutation leads to a shortening of the APD. A loss-of-function mutation in the *KCNH2* gene has also been linked to AF.[22]

Mutations Involving the Transient Outward Potassium Current

The potassium voltage-gated channel subfamily D member 3 (*KCND3*) gene encodes the α-subunit of voltage-gated potassium channel Kv4.3, which contributes to transient outward

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potassium current. A gain-of-function mutation in this gene is suggested to be associated with early-onset lone AF.[26] The association is unclear because Mann et al reported *KCND3* mutations that had "no change" on cardiac cellular electrophysiological characteristics.[22] It remains unclear if the differences in functional effects of variants have implications for these genes being involved in AF.

Mutations Involving the Inward Rectifier Current

The potassium voltage-gated channel subfamily J member 2 (*KCNJ2*) gene encodes the α-subunit of inwardly rectifying potassium channel Kir2.1, which facilitates the inward rectifier current. Xia et al evaluated 30 Chinese kindreds with AF and identified a missense mutation in *KCNJ2* leading to a gain of function of the inward rectifier current.[27] This impairment of inward rectification via the inward rectifier current results in a shortening of the QT interval.[28]

Mutations Involving the Acetylcholine-Induced Inwardly Rectifying Current

Kir3.4 potassium channel subunits mediate the acetylcholine-induced inwardly rectifying current in the heart and are encoded by the potassium voltage-gated channel subfamily J member 5 (*KCNJ5*) gene. Calloe et al identified a loss-of-function mutation in *KCNJ5* that resulted in a decreased acetylcholine-induced inwardly rectifying current in a patient with AF.[29]

Mutations Involving K_{ATP}

The potassium voltage-gated channel subfamily J member 8 (*KCNJ8*) gene encodes the cardiac K_{ATP} channel Kir6.1. The Kir6.1 channel is inhibited by ATP and activated by ADP in conditions of metabolic stress, leading to a decreased APD during metabolic stress. A mutation in the *KCNJ8* has been associated with a gain of function of the K_{ATP} channel,[30] leading to an increase in AF susceptibility.[31]

The ATP-binding cassette subfamily C member 9 (*ABCC9*) gene encodes the sulfonylurea receptor 2A subunit of the K_{ATP} channel subunit involved in maintaining electrical stability under stress. Olson et al identified loss of function attributable to a missense mutation in the *ABCC9* gene in a 53-year-old woman with a 10-year history of paroxysmal AF originating from the vein of Marshall.[32]

Mutations Involving the Rapidly Repolarizing Potassium Current

The potassium voltage-gated channel subfamily A member 5 (*KCNA5*) gene encodes the α-subunit of the voltage-gated potassium channel Kv1.5, responsible for the rapidly repolarizing potassium current. A loss-of-function nonsense mutation, resulting in an increased APD and early after depolarization, was identified by Olson et al.[33] The *KCNA5* nonsense mutation disrupted the atrial-specific Kv1.5 channel, leading to electrical instability and susceptibility to AF. Other investigators have reported similar loss-of-function mutations leading to AF.[34,35] However, Christophersen et al[35] further showed that mutations in the *KCNA5* gene can additionally lead to gain of function for the rapidly repolarizing potassium current in vitro. The gain of function of the rapidly repolarizing potassium current possibly leads to lone AF by decreasing the atrial APD and increasing excitability in atrial tissue.[35] The potential for either a gain-of-function or loss-of-function mutation to lead to lone AF was also shown by Nielsen et al, who reported that either an increase or a decrease in the heart rate–corrected QT increases the risk of AF.[36]

Mutations Involving the Funny Current

Macri et al[37] identified a novel trafficking-defective mutation in the amino-terminus of the hyperpolarization activated cyclic nucleotide-gated potassium channel 4 (*HCN4*), which plays a role in the funny current. The funny current is an inward current responsible for spontaneous pacemaker ability of the SA node during the diastolic depolarization phase. This loss-of-function mutation in the *HCN4* channel gene was suggested to be a possible mechanism in early-onset AF.[37]

Mutations Involving Calcium-Dependent Potassium Current

Recently, Tsai et al identified one missense exon mutation in the potassium voltage-gated channel subfamily N member 3 (*KCNN3*) gene that encodes the intermediate/small conductance calcium-activated potassium channel, KCa2.3, responsible for the slow calcium-activated potassium current in patients with AF.[38] The different potassium channel mutations that have been associated with AF are summarized in Table 1.

Sodium Channel Mutations

Action potential activation and propagation are a result of voltage-gated sodium channels. These channels are activated fast and are also rapid to inactivate. A few of the channels remain active later than the fast channels and are responsible for late sodium current. The most prevalent sodium channel in the heart is composed of an α-subunit, $Na_V1.5$, in association with accessory β-subunits (Navβ1-4). The opening of the

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Table 1. Potassium Channel Mutations Linked to AF

Gene	Locus	Product	Function	Type	Mechanism	References
KCNQ1	11p15.5-p15.4	α-Subunit of voltage-gated potassium channel Kv7.1	I_{Ks}	GOF	Increased I_{Ks}	6–17
KCNE1	21q22.12	β-Subunit of voltage-gated potassium channel Kv7.1	I_{Ks} modulation	GOF	Increased I_{Ks}	18
KCNE2	21q22.11	β-Subunit of voltage-gated potassium channel Kv7.2	I_{Ks} modulation	GOF	Increased I_{Ks}	19 and 20
KCNE3	11q13.4	β-Subunit of voltage-gated potassium channel Kv7.3	I_{Ks} modulation	GOF	Increased I_{Ks}	21
KCNE4	2q36.1	β-Subunit of voltage-gated potassium channel Kv7.4	I_{Ks} modulation	GOF	Increased I_{Ks}	22
KCNE5	Xq23	β-Subunit of voltage-gated potassium channel Kv7.5	I_{Ks} modulation	GOF	Increased I_{Ks}	23
KCNH2	7q36.1	HERG human ether-a-go-go (α-subunit of voltage-gated potassium channel Kv11.1)	I_{Kr} modulation	GOF, LOF		22, 24, and 25
KCND3	1p13.2	α-Subunit of voltage-gated potassium channel Kv4.3	I_{to}	GOF		22 and 26
KCNJ2	17q24.3	α-Subunit of inwardly rectifying potassium channel Kir2.1	I_{K1}	GOF	Increased I_{K1}	27 and 28
KCNJ5	11q24.3	α-Subunit of inwardly rectifying potassium channel Kir3.4	I_{KACh}	LOF		29
KNCJ8	12p12.1	α-Subunit of inwardly rectifying potassium channel Kir6.1	IK_{ATP}	GOF		30 and 31
ABCC9	12P12.1	SUR2A subunit of the K_{ATP} channel	IK_{ATP}	LOF		32
KCNA5	12p13.32	α-Subunit of voltage-gated potassium channel Kv1.5	I_{Kur}	GOF, LOF	LOF with reduced I_{Kur}	33–35
HCN4	15q24.1	Hyperpolarization activated cyclic nucleotide-gated potassium channel 4	I_f	LOF		37
KCNN3	1q21.3	Intermediate/small conductance calcium-activated potassium channel, KCa2.3	I_{KCa}			38

AF indicates atrial fibrillation; GOF, gain of function; HERG, human ether-a-go-go; I_f, funny current; I_{K1}, inward rectifier current; I_{KACh}, acetylcholine-induced inwardly rectifying current; IK_{ATP}, ATP-sensitive potassium channel; I_{KCa}, calcium-dependent potassium current; I_{Kr}, rapidly repolarizing potassium current; I_{Ks}, delayed-rectifier potassium current; I_{Kur}, rapidly repolarizing potassium current; I_{to}, transient outward potassium current; LOF, loss of function; SUR2A, sulfonylurea receptor 2A.

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voltage-gated sodium channels causes the inward sodium current, which results in rapid depolarization of the cell membrane potential from the resting membrane potential. There is no clear genotype-to-phenotype association between sodium channel mutations and AF. Loss-of-function mutations are thought to induce AF by decreasing atrial conduction velocity, and gain-of-function mutations do so by increasing atrial APD and excitability.[39]

Mutations Involving the Inward Sodium Current

The sodium voltage-gated channel α subunit 5 (*SCNA5*) gene encodes the α-subunit of Nav1.5. Mutations in this gene are associated with Brugada syndrome, long-QT syndrome type 3, and other cardiac conduction disorders.[40] Olesen et al[41] reported an association with early-onset lone AF when 8 mutations and 2 rare variants were identified in a cohort of 192 patients. The *SCNA5* gene is associated with both a gain and a loss of function.[41–46] These mutations exhibited compromised peak sodium current and an increased sustained sodium current.

The β-subunits of the sodium channel Nav1.5 ($Na_v\beta1$, $Na_v\beta2$, $Na_v\beta3$, and $Na_v\beta4$) are encoded by sodium voltage-gated channel β subunit genes: *SCN1B*, *SCN2B*, *SCN3B*, and *SCN4B*, respectively. In a cohort of 480 patients with AF, Watanabe et al[47] identified 2 nonsynonymous variants in *SCN1B* and 2 variants in *SCN2B*. Both mutations were classified as loss of function.[47] In another cohort of patients with AF, a loss-of-function mutation was linked to the *SCN3B* gene by Wang et al.[48] Later, Olesen et al[49] found 3 loss-of-function *SCN3B* mutations in 192 unrelated lone patients with AF. This mutation reduced sodium channel current, which is thought to increase AF susceptibility.[49] The first study to determine an association between AF and the *SCN4B* gene was done by Li et al, who found 2 novel heterozygous loss-of-function *SCNB4* mutations in 2 unrelated families.[50]

In addition, the *SCN1Bb* gene encodes a second β1 transcript, named Navβ1B. In 2 patients with lone AF and 1 with Brugada syndrome, Olesen et al identified a nonsynonymous *SCN1Bb* gene mutation.[51] This same mutation has been previously found to be associated with Brugada syndrome.[52] Hu et al had discovered that the *SCN1Bb* gene mutation resulted in a 57% decrease in the peak sodium current and a 71% increase in the Kv4.3 current, suggesting a loss of function of the inward sodium current and a gain of function of Kv4.3 current (transient outward potassium current).[52] Once again, uncertainty exists with regard to the underlying mechanism; and in almost every instance, there are only rare kindreds described.

Mutations Involving the Late Sodium Current

The *SCN10A* gene encodes the voltage-gated sodium channel Nav1.8, which is responsible for the late sodium current in cardiomyocytes. Nav1.8 is also expressed in sensory neurons within dorsal root ganglia.[53] The *SCN10A* gene has been linked to both a gain-of-function and a loss-of-function mutation by Savio-Galimberti et al in 274 patients with early-onset AF[54] and by Jabbari et al in 225 patients with AF.[55] In addition, the gene has been shown to have an effect on the modulation of cardiac SCN5A expression, suggesting a possible link between *SCN10A*, cardiac physiological characteristics, and the predisposition to arrhythmias.[56] It is uncertain if *SCN10A* has an effect independent from *SCN5A*. The different sodium channel mutations associated with AF are summarized in Table 2.

Table 2. Sodium Channel Mutations Linked to AF

Gene	Locus	Product	Function	Type	Mechanism	References
SCN5A	3p22.2	α-Subunit of Nav1.5	I_{Na}	GOF, LOF	LOF: reduced sodium current density, hyperpolarizing shift in channel steady-state activation GOF: depolarized shift of voltage dependence of steady-state inactivation	41–46
SCN1B	19q13.11	β-Subunit of Nav1.5 (Navb1)	I_{Na} modulation	LOF	Reduced sodium current and altered channel gating	47
SCN2B	11q23.3	β-Subunit of Nav1.5 (Navb2)	I_{Na} modulation	LOF	Reduced sodium current and altered channel gating	47
SCN3B	11q24.1	β-Subunit of Nav1.5 (Navb3)	I_{Na} modulation	LOF		48 and 49
SCN4B	11q23.3	β-Subunit of Nav1.5 (Navb4)	I_{Na} modulation	LOF		50
SCN1Bb	19q13.1	β-Subunit of Nav1.5 (Navβ1B)	I_{Na} modulation	LOF		51 and 52
SCN10A	3p22.2	α-Subunit of Nav1.8	I_{Na-L} modulation	GOF, LOF		54 and 55

AF indicates atrial fibrillation; GOF, gain of function; I_{Na}, inward sodium current; I_{Na-L}, late sodium current; LOF, loss of function.

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Non–Ion Channel Mutations

Mutations in the Nuclear Pore Complex

The *NUP155* gene encodes nucleoporin 155, an essential component of the nuclear pore complex. The nuclear pore complex spans the nuclear envelope and is involved in the nucleocytoplasmic exchange of mRNA and protein. Oberti et al located, on chromosome 5q13, a locus linked to AF, inherited in an autosomal recessive pattern in a single large family with AF.[57] Zhang et al[58] then went on to discover that the specific gene related to the association found by Oberti et al[57] was, in fact, *NUP155*. This was determined as a loss-of-function mutation that is thought to affect mRNA export of important atrial genes from the nucleus to the cytoplasm.[58]

Mutations in Nuclear Lamins

The *LMNA* gene encodes the lamin A and lamin C proteins, which are intermediate-filament proteins associated with maintaining nucleus structural integrity, chromatin organization, cell cycle regulation, DNA replication, RNA transcription, and apoptosis. Mutation in the *LMNA* gene has been associated with dilated cardiomyopathy and muscular dystrophy.[59] Beckmann et al determined a heterozygous missense mutation in *LMNA* in 9 mutation carriers in a family with a history of AF, supraventricular tachycardia, ventricular fibrillation, muscle weakness, and sudden cardiac death.[60] However, in a study of 103 patients with nonvalvular AF, Saj et al showed that *LMNA* mutations are not a frequent cause of AF.[61]

Mutations in Connexins

The association between connexins and AF remains weak, but several studies have been done to uncover a potential association. The gap junction α-1 protein (*GJA1*) and *GJA5* genes encode connexins, which are gap-junction channel proteins that conduct action potentials from cell to cell in atrial myocytes. *GJA1* specifically encodes connexin43. Thibodeau et al[62] noted a *GJA1* loss-of-function mutation in atrial tissue in 1 of 10 unrelated patients with nonfamilial, lone AF. The mutation led to intracellular retention of the protein, a reduction in gap junction conduction, and a failure of electric coupling between atrial cells.[62] *GJA5* encodes connexin40. Four novel somatic heterozygous missense mutations were identified in 4 of the 15 patients with idiopathic AF studied by Gollob et al.[63] The *GJA5* loss-of-function mutation resulted in impairment of connexin transport and gap-junction assembly at the cell surface with failure of electric coupling between cells. This, in turn, was associated with AF by decreasing conduction velocity and increasing the risk of reentrant circuits.[63] Sun et al went on to confirm the intracellular retention of connexin40 in the endoplasmic reticulum because of the *GJA5* mutation.[64] Moreover, other studies have described germline mutations in *GJA5*,[65–67] with Yang et al linking *GJA5* to an autosomal dominant inheritance pattern.[66]

Mutations in Atrial Natriuretic Peptide

Atrial natriuretic peptide is a circulating hormone produced in the atria and is involved in regulating blood pressure through natriuresis, diuresis, and vasodilatation. Atrial natriuretic peptide is encoded by the *NPPA* gene, a mutation that has been linked to familial AF.[68] A heterozygous frame shift mutation in *NPPA* leads to a shortened atrial APD and effective refractory period and an increase in the levels of mutant atrial natriuretic peptide. In addition, other rare variants in *NPPA* have been identified, but it is still difficult to determine if the differences in functional effects of variants have implications in these variants being involved in AF.[69] Abraham et al found a link between the mutations in *KCNQ1* and *NPPA* genes, which led to I_{Ks} gain of function, atrial APD shortening, and subsequent altered calcium current associated with familial AF.[11] However, Roberts et al found no relation between *NPPA* and the risk of AF development while examining nonsynonymous genetic variants in *NPPA* in patients with early-onset AF.[70]

Mutations in Genes Involved in Cardiogenesis

The *GATA4*, *GATA5*, and *GATA6* genes encode cardiac transcription factors that play a key role in regulation of target gene expression in cardiogenesis. Yang et al found 2 novel heterozygous *GATA4* loss-of-function mutations in 2 unrelated families with AF, inherited in an autosomal dominant pattern.[71] In addition, *GATA4* mutations were found in patients with AF by Wang et al.[72] Yang et al found 3 novel heterozygous *GATA5* loss-of-function mutations in 3 of 130 unrelated probands with familial AF, inherited in an autosomal dominant pattern.[73] Wang et al also found a *GATA5* variant and determined that it was linked to significantly decreased transcriptional activity.[74] In 1 of 138 patients, Yang et al found a novel heterozygous *GATA6* loss-of-function mutation that was linked to an autosomal dominant trait transmission with complete penetrance.[75] A similar link between *GATA6* and familial AF was found by Li et al.[76] Yang et al then found 2 additional novel heterozygous *GATA6* mutations in 2 of 110 unrelated probands with familial AF,[77] exhibiting similar inheritance to those seen in prior studies and associated with decreased transcriptional activity. *GATA4*, *GATA5*, and *GATA6* mutations could perhaps predispose to AF because of an abnormality in pulmonary vein myocardial sleeve

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development, leading to irregularities in intrinsic pacemaker activity and reentry circuits.[78,79]

The *NKX2-5* and *NKX2-6* are genes responsible for the NK2 homeobox protein, which has a role in the regulation of target gene expression in cardiogenesis. The *GATA4*, *GATA5*, and *GATA6* genes function in coordination with *NKX2-5.* Huang et al[80] determined a novel heterozygous *NKX2-5* loss-of-function mutation showing autosomal dominant inheritance in a family with AF. The *NKX2-5* mutation was associated with significantly decreased transcriptional activity.[80–82] The *NKX2-5* mutation predisposition to AF may be attributable to a pulmonary vein myocardial sleeve developmental abnormality.[83] The first association of *NKX2-6* gene with AF was made by Wang et al,[84] who found a novel heterozygous *NKX2-6* mutation in 1 of 150 unrelated patients with lone AF. The *NKX2-6* mutation showed an autosomal dominant inheritance pattern.[84] The expression profile and functional roles of *NKX2-6* partially overlap with those of *NKX2-5* during cardiovascular development,[85] suggesting a link to AF.

The *GREM2* gene encodes gremlin-2, a bone morphogenetic protein antagonist. *GREM2* is a crucial regulator of the cardiac rhythm gene system acting upstream of *PITX2* (codes for a cardiogenesis transcription factor associated with AF development[86]). Müller et al[87] identified a *GREM2* gain-of-function mutation in 2 lone cohorts with AF, and by modeling zebrafish, they determined that *GREM2* was required for cardiac laterality and atrial differentiation during embryonic development. Increased gremlin-2 levels led to increased atrial differentiation but decreased cardiac contraction rates and slower contraction velocity in atrial cardiomyocytes.[87]

Mutations in Genes Involved in Calcium Homeostasis

Mutations in genes involved in calcium homeostasis, such as the junctophilin-2 (*JPH2*) gene[88] and the ryanodine receptor 2 (*RYR2*) gene,[89] cause destabilization of the cardiomyocytes inducing arrhythmias because of an increase in calcium triggering–delayed after depolarizations.

Candidate Gene Association Studies

Links have been made between polymorphisms in the angiotensinogen (*AGT*) gene and the angiotensin-converting enzyme (*ACE*) gene in the renin-angiotensin system and susceptibility to AF.[90] It is thought that ultimately increased angiotensin II in the atria increases atrial pressure, resulting in atrial fibrosis.

Early identification of genetic associations with AF was done through candidate-gene association studies. These studies are based on the prior knowledge of function of specific genes and comparing the frequency of genetic variants in AF cohorts with individuals without disease.[91] Several common genetic variants have been found to be more prevalent in patients with AF compared with disease-free populations. The limitation in candidate-gene association studies is poor pretest probability of the selected genetic variants to actually be involved in the pathogenesis of AF. They have been underpowered and not replicated. Nonetheless, candidate gene association studies have identified genetic variants in guanine nucleotide binding protein β polypeptide 3 (*GNB3*),[92] interleukin-6 (*IL6*),[93] interleukin-10 (*IL10*),[94] metalloproteinase-2 (*MMP2*),[94] and sarcolipin (*SLN*).[95]

The *eNOS* gene has been linked to nonvalvular AF. The endothelial NO synthase protein regulates the L-type calcium channel needed for cardiomyocyte contractility.[96] The cholesteryl ester transfer protein *TaqIB* polymorphism has been linked to AF in the presence of albuminuria, increased C-reactive protein, and ischemic heart disease.[97] Mutations in the nesprin-2 (*SYNE2*) and zinc finger homeobox 3 (*ZFHX3*) genes have also been linked to AF.[38] The different non–ion channel mutations associated with AF are summarized in Table 3.

Genome-Wide Association Studies Identifying AF Variants

Genome-wide association studies (GWASs) have been used to identify common single-nucleotide polymorphisms (SNPs) that may play a role in the development of AF. The first identified SNPs associated with AF were the SNPs *rs2200733* and *rs10033464*, residing close to the pituitary homeobox 2 (*PITX2*) gene located 150 000 base pairs upstream of chromosome locus 4q25. The SNP *rs2200733* was most significantly associated with AF in European and Chinese populations.[98] Since then, additional GWASs have identified other SNPs associated with AF. Genes closest to GWAS loci are not necessarily target genes, and further studies to define functional effects of these loci are needed.

PITX2 is a homeodomain transcription factor that plays a vital role in the embryologic development of the heart. It takes part in the right-left asymmetrical development of the heart, the suppression of sinus node formation in the left atrium,[99] and the formation of the pulmonary vein myocardial sleeves.[83] AF has been associated with irregular ectopic signals being generated from the pulmonary vein myocardial sleeves, with the mainstay of AF treatment being the ablation of ectopic foci mostly at the pulmonary vein location. Several studies have shown a relationship between PITX2 and its predisposition to AF.[100–104]

Ellinor et al conducted a meta-analysis of SNPs and their association with the development of AF.[105] Although

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Table 3. Non–Ion Channel Mutations Linked to AF

Gene	Locus	Product	Function/Mechanism	Type	References
NUP155	5p13.2	Nucleoporin 155	Nuclear pore complex/reduction in nuclear membrane permeability	LOF	57 and 58
LMNA	1q22	Lamin A/C	Nuclear envelope structure	. . .	60 and 61
GJA1	6q22.31	Connexin43	Gap-junction protein/impaired intracellular transport and intercellular electrical coupling	LOF	62
GJA5	1q21.2	Connexin40	Gap-junction protein/impaired intracellular transport and intercellular electrical coupling	LOF	63–67
NPPA	1p36.22	Natriuretic peptide precursor	Blood pressure regulation/elevated levels of mutant ANP	GOF	11 and 68–70
GATA4	8p23.1	Cardiac transcription factor	Cardiogenesis	LOF	71 and 72
GATA5	20q13.33	Cardiac transcription factor	Cardiogenesis	LOF	73 and 74
GATA6	18q11.2	Cardiac transcription factor	Cardiogenesis	LOF	75–77
NKX2-5	5q35.1	Homeobox protein Nkx-2.5	Cardiogenesis	LOF	80–82
NKX2-6	8p21.2	Homeobox protein Nkx-2.6	Cardiogenesis	. . .	84
PITX2	4q25	Pituitary homeobox 2	Cardiogenesis	LOF	86
GREM2	1q43	Gremlin-2	Bone morphogenetic protein antagonist	GOF	87
JPH2	20q13.12	Juctophilin-2	Calcium homeostasis	LOF	88
RYR2	1q43	Ryanodine receptor 2	Calcium homeostasis	GOF	89
AGT	1q42.2	Angiotensinogen	Renin-angiotensin system	. . .	90
ACE	17q23.3	Angiotensinogen converting enzyme	Renin-angiotensin system	. . .	90
GNB3	12p13.31	β3-Subunit of heterotrimeric G protein	Signal integration	. . .	92
IL6	7p15.3	Interleukin-6	Cytokine	. . .	93
IL10	1q32.1	Interleukin-10	Cytokine	. . .	94
MMP2	16q12.2	Matrix metalloproteinase-2	Zinc-dependent enzyme	. . .	94
SLN	11q22.3	Sarcolipin	Sarcoplasmic reticulum calcium-ATPase	. . .	95
eNOS	7q36.1	Endothelial NO synthase	Regulates L-type calcium channel	. . .	96
CETP	16q13	Cholesteryl ester transfer protein	Transfer between lipoproteins	. . .	97
SYNE2	14q23.2	Nesprin-2	Cytoskeleton LINC complex	. . .	38
ZFHX3	16q22.2 to 2q22.3	Zinc finger homeobox 3	Transcription factor	. . .	38

AF indicates atrial fibrillation; ANP, atrial natriuretic peptide; GOF, gain of function; LINC, linker of the nucleoskeleton and cytoskeleton complex; LOF, loss of function.

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associations can be logically made, nearby genes may actually be functionally irrelevant in general. SNPs associated with AF include the SNP *rs6666258* located on chromosome 1q21 in an intron of the gene *KCNN3*, which plays a role in encoding a calcium-activated potassium channel involved in atrial repolarization. The SNP *rs3903239* is located on chromosome 1q24, 46 000 base pairs upstream from the closest gene *PRRX1*, which encodes a homeodomain transcription factor for development of great vessels and lung vascularization.[106] The SNP *rs2040862* is located on chromosome 5q31, in an intron of the gene *WNT8A*, which is a gene of unknown function with relation to the heart. The SNP *rs3807989* is located on chromosome 7q31 in an intron of the gene *CAV1*, which encodes caveolin-1, critical for definition of microdomains of the plasma membrane involved in electric signal transduction. In addition, defects in *CAV1* have been linked to cardiac hypertrophy,[107] dilated cardiomyopathy, and pulmonary hypertension.[108] The SNP *rs10821415* is located on chromosome 9q22, in an intron of the gene *C9orf3* that encodes aminopeptidase O, a protease that cleaves angiotensin III to angiotensin IV. The cleavage of angiotensin III is required to downregulate the renin-angiotensin system.[109] The SNP *rs10824026* is located on chromosome 10q22, 5000 base pairs upstream of *SYNPO2L* (later *CHAP*), which encodes a cytoskeletal heart-enriched actin-associated protein that plays a role in skeletal and cardiac muscle development.[110] The SNP *rs1152591* is located on chromosome 14q23, in an intron of the gene *SYNE2*, which encodes nesprin 2, part of the linker of the nucleoskeleton and cytoskeleton complex. These proteins are involved in maintaining cellular architecture, cytoskeletal organization, biomechanical signaling, and nuclear integrity.[111] The SNP *rs7164883* is located on chromosome 15q24 in an intron of the gene *HCN4*, which encodes the cardiac pacemaker channel responsible for the funny current. The funny current is an inward current responsible for spontaneous pacemaker ability of the SA node during the diastolic depolarization phase. A mutation in the *HCN4* channel gene leads to diminished action potential firing frequency, leading to an increased susceptibility of AF.[37] The SNP *rs2106261* is located on the chromosome locus 16q22 near zinc finger homeobox 3 (*ZFHX3*), which produces a transcription factor involved in myogenic differentiation. Polymorphisms of this gene have been linked to AF.[105]

Sinner et al further conducted another meta-analysis to identify additional SNPs associated with the development of AF.[112] The SNP *rs4642101* is located on chromosome 3p25, in an intron of the gene *CAND2*, which encodes a TATA-binding protein-interacting protein 120b involved in myogenesis.[113] Sinner et al observed a link between knockdown of *CAND2* and prolongation of APD in zebrafish.[112] The SNP *rs13216675* is located on chromosome 6p22, intergenic of the gene *GJA1*, which encodes connexin 43, a gap-junction channel protein in atrial myocytes. A *GJA1* loss-of-function mutation in atrial tissue in 1 of 10 unrelated patients was associated with predisposition to AF.[62] The SNPs *rs12415501* and *rs6584555* are located on chromosome 10q24, in an intron of the gene *NEURL*. The *NEURL* gene encodes E3 ubiquitin ligase, which interacts with many types of transcription factors, particularly *PITX2*. Sinner et al speculate that the *NEURL* mutation may increase predisposition to AF by ubiquitin-mediated alteration of PITX2 activity.[112] The SNP *rs10507248* is located on chromosome 12q24, in an intron of the gene *TBX5*, which encodes T-box-5, a transcription factor involved in cardiac conduction system development.[55] The SNP *rs6490029* is located on chromosome 12q24, in an intron of the gene *CUX2*, which encodes cutlike homeobox 2, a transcription factor involved in cell cycle progression related to spinal cord neurogenesis.[114] Christophersen et al[115] performed genome-wide association analyses and exome-wide association analyses on a large cohort of patients with AF and identified 12 new loci associated with AF. In a meta-analysis of GWASs in 31 studies, 10 new genetic loci were found. In a meta-analysis of exome-wide association studies, 2 additional novel loci were discovered (in addition to 1 also seen in the GWAS meta-analysis, *SLC35F1/PLN*).[115] The different SNPs associated with AF are summarized in Table 4.

Ancestry Studies

Blacks are more likely to have risk factors for AF (hypertension, heart failure, diabetes mellitus, and higher body mass index), but paradoxically are at lower risk for AF than whites.[116] Marcus et al[116] sought to determine if European ancestry in black individuals was an independent risk factor for AF. Blacks are genetically heterogeneous, with both African and European ancestral genomes. Biogeographical ancestry analysis (admixture analysis) can determine the percentage of European or African ancestry in an individual by using ancestry informative markers. Ancestry informative markers are genetic markers that are known to have major allele frequency differences between ancestral populations. The analysis can be used to study if there is an association between complex phenotypes and genetic ancestral background in admixed populations. Marcus et al[116] used the fact that blacks have mixed ancestral genomes to determine if higher percentage of European ancestry was associated with increased risk of AF. Patients were recruited from the CHS (Cardiovascular Health Study) (4543 whites and 822 blacks) and the ARIC (Atherosclerosis Risk in Communities) study (10 902 whites and 3517 blacks). From the Illumina custom ITMAT-Broad-CARe array, 1747 ancestry informative markers were used; results showed that for every 10% increase in European ancestry, there was a 13% increased risk of AF

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Table 4. SNPs Associated With AF From GWASs

SNP	Locus	Gene	Location Relative to Closest Gene	References
rs6666258	1q21	*KCNN3-PMVK*	Intronic	105
rs6817105	4q25	*PITX2*	150 kb Upstream	105
rs3903239	1q24	*PRRX1*	46 kb Upstream	106
rs2040862	5q31	*WNT8A*	Intronic	105
rs3807989	7q31	*CAV1*	Intronic	107, 108
rs10821415	9q22	*C9orf3*	Intronic	109
rs10824026	10q22	*SYNPO2L*	5 kb Upstream	110
rs1152591	14q23	*SYNE2*	Intronic	111
rs7164883	15q24	*HCN4*	Intronic	37
rs2106261	16q22	*ZFHX3*	Intronic	105
rs4642101	3p25	*CAND2*	Intronic	112
rs13216675	6p22	*GJA1*	Intergenic	62
rs12415501	10q24	*NEURL*	Intronic	112
rs6584555	10q24	*NEURL*	Intronic	112
rs10507248	12q24	*TBX5*	Intronic	55
rs6490029	12q24	*CUX2*	Intronic	114
rs72700118	1q24	*METTL11B/KIFAP3*	Intergenic	115
rs3771537	2p13	*ANXA4/GMCL1*	Intronic	115
rs2540949	2p14	*CEP68*	Intronic	115
rs2288327	2q31	*TTN/TTN-AS1*	Intronic	115
rs337711	5q22	*KCNN2*	Intronic	115
rs2967791	5q31	*KLHL3/WNT8A/FAM13B*	Intronic	115
rs4946333	6q22	*SLC35F1/PLN*	Intronic	115
rs7508	8p22	*ASAH1/PCM1*	3′UTR	115
rs35176054	10q24	*SH3PXD2A*	Intronic	115
rs75190942	11q24	*KCNJ5*	Intronic	115
rs6800541	3p22	*SCN10A* (EWAS)	Intronic	115
rs89107	6q22	*SLC35F1/PLN* (EWAS)	Intronic	115
rs11047543	12p12	*SOX5* (EWAS)	Intergenic	115

AF indicates atrial fibrillation; EWAS, exome-wide association study; GWAS, genome-wide association study; SNP, single-nucleotide polymorphism; UTR, untranslated region.

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(hazard ratio, 1.13; 95% confidence interval, 1.03–1.23; P=0.007). European ancestry still predicted incident AF after adjusting for confounders. Similar results were shown using 3192 ancestry informative markers from a genome-wide Affymetrix 6.0 array in ARIC study blacks. Marcus et al[116] concluded that European ancestry predicted risk of incident AF and that blacks with a higher percentage of European ancestry were at higher risk.

Ablatogenomics

Because of the increasing data highlighting the important role of genetics in AF, there is potential for genetic status to guide therapeutic strategies in the treatment of AF. Catheter ablation is a widely used technique to control rhythm in AF. For a significant number of patients, it does not prove beneficial because of AF recurrence. Because it is an intervention with multiple health risks, it would be beneficial to predict which patients are more likely to benefit from the procedure. Although still premature, genetic risk scores with other additional factors may eventually guide a physician's decision on whether to perform catheter ablation on patients, and this is part of the emerging field of ablatogenomics.[117] Polymorphisms in the chromosome locus 4q25, which contains 2 SNPs (*rs2200733*, shown to be most strongly related to AF; and *rs10033464*, near *PITX2*), have been

shown to modulate risk for AF recurrence after catheter ablation.[117,118] Shoemaker et al further compared polymorphisms in 4q25, 1q21 (*rs13376333* in *KCNN3*), and 16q22 (*rs7193343* in *ZFHX3*) and noted the strongest association with AF being polymorphisms in chromosome 4q25.[119,120] Nonpulmonary vein triggers and left atrial scars perpetuate AF, limiting the success rate of ablation. Mohanty et al[121] found that certain polymorphisms actually increase the risk of scar and nonpulmonary vein triggers in patients with AF, making pulmonary vein antrum isolation inadequate in controlling the arrhythmia. Patients carrying variants with high risk of having nonpulmonary vein triggers would strengthen the need for operators to try to identify these foci.[121]

There are established risk factors of AF recurrence after catheter ablation, and these include hypertension, obesity, disorders in sleep breathing, metabolic syndrome, and dilation of the left atria. Persistent AF is also a risk factor for AF recurrence after ablation.[122,123] Several factors guide decision making to pursue ablation, and these include type of AF, left atrial size, severity of symptoms, presence of systolic dysfunction, and estimated risk of complications of the procedure itself.[124] Although GWASs have reflected statistical associations between cohorts, in reality, there is limitation to the usefulness of just 1 SNP polymorphism to be used as a predictor of recurrence, but there may be usefulness in adding it to our already established risk factors to help in further risk stratifying patients before performing procedures. The ablatogenomics approach for AF is still in its early stages, and there are no clear data that show improved AF recurrence risk stratification when adding genetic profiles to already established risks for AF recurrence.

Because no other SNP polymorphism has been strongly linked to AF recurrence after ablation, there are no data on an "incremental" genetic risk score for this. A large-scale study that explores the cost-effectiveness of adding these SNP polymorphisms to established risk factors would be helpful, especially now that genomic sequencing costs are rapidly becoming cheaper.

Lubitz et al[125] developed a genetic risk prediction of AF by concluding that comprehensive AF genetic risk scores (based on summing dosage of each AF risk allele) were associated with incident AF. These scores exceeded clinical risk factor associations with AF in European ancestry.[125] At this point, the vast number of genetic mutations linked to AF makes it difficult to translate genetic risk stratification into clinical practice. In addition, predictive value of genetic profiling is limited by the heritability of a disease and its prevalence. Even if predictive value is useful enough that it would be applicable to health care, personalizing medical interventions on a larger scale to revolutionize health care is hard to imagine given there are so many genetic links to AF.[126]

Conclusion

The available data relating genetics to AF have been rapidly increasing over the past years. GWASs are still ongoing to better understand the association between various genes and AF with attempts to identify mechanistic links. By further investigating already discovered genes and discovering new genes, we can better understand the inheritance patterns and genetic basis underlying the development of AF. Ultimately, our aim is to somehow integrate the knowledge of genetic risk factors into clinical practice. To make this feasible, continued research in the field is needed to identify stronger associations of genes to AF, and a better understanding of pathophysiological characteristics is needed to determine causality. There is promise in genetic testing in the future, but at this point, no unifying genetic risk stratification method has been established that can be useful in clinical practice.

Disclosures

None.

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