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Atrial Fibrillation Genetic Considerations: The Basic Scientist's Perspective

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Abstract: Common atrial fibrillation (AF) is a complex disease, and its pathogenesis involves multiple genetic factors, environmental factors, and interactions among these factors. Genetic factors clearly contribute to the risk of common AF. Parental AF increases by more than threefold the risk of AF under age of 75 years in offspring, and first-degree relatives have almost fivefold more risk of developing AF before the age of 60 years. Candidate gene case–control studies investigated the roles of several genes in common AF and thromboembolism in AF, including *KCNE1, KCNE4, KCNE5, GNB3, AGT, CETP, coagulation factor II, α-fibrinogen, factor XIII*, and *IL6*. Genomewide single nucleotide polymorphism association studies is the state-of-the art study design for dissecting the common complex AF trait and have successfully identified two SNPs on chromosome 4q25 that are associated with risk of atrial fibrillation. Rare families with AF have been reported, and studies of these families identified mutations in several genes for AF, including *KCNQ1, KCNE2, KCNE3*, and *KCNJ2*. Two autosomal dominant AF genes were mapped to chromosome 10q and 6q, and one autosomal recessive gene for AF was mapped to 5p, but these genes have not yet been identified. Also, AF can occur in patients with dilated cardiomyopathy with *SCN5A* and *LMNA* mutations, long QT syndrome patients with an *ankyrin-B* mutation, and short QT syndrome patients with a *KCNH2* mutation. Genetic studies of AF will continue to provide insight into molecular mechanisms for the pathogenesis of AF and will facilitate realization of genetic testing and genotype-based therapies (personalized medicine) for AF patients.

Keywords: Atrial fibrillation; Case-control association study; Genetics; Linkage analysis; Mutation.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia associated with increased mortality and substantial morbidity. Genetic studies of other types of cardiac arrhythmias, mainly long QT syndrome (LQTS) and Brugada

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syndrome (BrS), have driven the realization of personalized medicine, known as the right drug/therapy for the right patients, in this specific medical field. To date, disease-causing genes have been identified for an estimated 50% to 75% of LQTS and 25% of BrS cases. The genes identified for LQTS include potassium channel genes *KCNQ1* (LQT1),[1] *KCNH2* (LQT2),[2] *KCNE1* (LQT5),[3,4] and *KCNE2* (LQT6)[5] and the cardiac sodium channel gene *SCN5A* (LQT3).[6,7] Mutations were also identified in LQTS patients and were associated with other diseases in genes, including a structural ankyrin gene *ANK2* (LQT4, sick sinus syndrome with bradycardia); a potassium channel gene *KCNJ2* (LQT7, Anderson syndrome); a calcium channel gene *CACNA1C* (LQT8, Timothy syndrome); and a potassium channel gene *HCN4* (LQT9, sick sinus syndrome).[8] The LQTS mutations in *SCN5A* are gain-of-function mutations, whereas loss-of-function mutations in *SCN5A* cause BrS.[9] More than 90% of genotyped LQTS patients belong to LQT1, LQT2, and LQT3 types, and genotype–phenotype correlation was well defined in these three types of LQTS.

Commercial genetic testing called Familion is now available for LQTS and BrS patients (http://www.familion.com/). The testing results have a direct impact on treatment options for individual patients. The LQT1 patients respond to β-blockade, LQT2 patients respond to β-blockade and elevated serum potassium levels, and LQT3 patients respond to sodium channel blockers.[10] Symptomatic LQTS and BrS patients (*SCN5A* positive) may be managed with implantation of ICDs (implantable cardioverter-defibrillators).[10,11]

Genetic studies of AF have made some progress, but much remains to be done. This chapter reviews recent advances and discusses future perspectives in the field of AF genetics. We are optimistic that, in the future, personalized medicine will be a reality for AF patients as it is for LQTS and BrS patients.

Genetic Component of Atrial Fibrillation

Studies have clearly demonstrated that genetic factors contribute to the development of AF. Familial forms of AF were reported but were very rare. The AF in these large families is inherited in a Mendelian fashion. Two forms of inherited AF have been reported, autosomal dominant and autosomal recessive forms. Large families with autosomal dominant AF have been reported,[12,13] but autosomal recessive AF has been reported in only one family to date.[14] Simplex cases of AF are common in clinical practice. Some simplex cases may represent autosomal recessive AF, but most of them may simply be sporadic AF. No X-linked AF has been reported.

The common form of AF is most likely to be a complex disease, which is believed to be caused by multiple genetic factors, environmental factors, and interactions among these factors. Indeed, many risk factors have been identified for AF, including advanced age, male gender, valvular heart disease, coronary artery disease, hypertension, heart failure, left ventricular dysfunction, hyperthyroidism, and diabetes.[14] Studies showed that there was a genetic component in the common form of AF. Fox et al. reported the first population-based study to estimate heritability of AF and found the odds ratios (ORs) for the parent–offspring pair based on a prospective cohort of 2,234 offspring involved in the Framingham Heart Study.[15] Seventy of the offspring developed AF during follow-up.[15] Atrial fibrillation in at least one parent significantly increased the risk of AF in offspring, with an OR

of 1.85, which increased to 3.23 with study participants younger than 75 years or to 3.17 when offspring with overt heart disease were excluded.[15] Interestingly, maternal AF was a stronger risk factor than paternal AF. These results demonstrate that there is a genetic predisposition to AF, and parental AF increases the risk of AF in offspring.

The second population study to examine the heritability of AF was carried out in Iceland by Arnar et al.[16] The risk ratios (RRs) of AF were estimated based on studies of 5,269 AF patients and 10,000 controls (RR is defined as the risk of AF in the relatives divided by the risk in the general population). Familial aggregation was demonstrated. The RRs for the first-degree through fifth-degree relatives were 1.77, 1.36, 1.18, 1.10, and 1.05, respectively. Although these RRs are statistically significant values, the risk of AF is very small for the third-degree to fifth-degree relative (RR < 1.18). Interestingly, the RR for first-degree relatives increased to 4.67 in study subjects under the age of 60 years, indicating that the first-degree relatives of AF patients have an almost fivefold higher risk to have AF than the general population. The RRs for second-degree through fifth-degree relatives in subjects under 60 years were 2.13, 1.34, 1.35, and 1.02, respectively. The risk of AF disappeared for the fifth-degree relatives.

Ellinor et al. studied 110 patients with lone AF (AF without structural heart disease). The RRs were very high, 8.1 for sons, 9.5 for daughters, 70 for brothers, 34 for sisters, 4 for mothers, and 2 for fathers.[17] Because the population used for this study was an ascertained population for genetic studies (not random), selection bias may have augmented the RRs, and precaution should be taken to extrapolate the findings from this study to the general population of AF.

In summary, the studies discussed demonstrated that AF has substantial familial aggregation and strong heritability, indicating that there are genetic variants that predispose to the risk of common AF.

Classification of Atrial Fibrillation Genes: Disease-Causing Genes, Susceptibility Genes, and Disease-Linked Genes

We can classify the genes that are associated with AF into three major categories: disease causing, susceptibility, and disease linked. Disease-causing genes are referred to as the genes with mutations that are directly responsible for the pathogenesis of disease, most often single-gene disorders.[18] In this case, the mutations are clearly defined as the primary cause of the disease. For example, *KCNQ1* mutations cause LQTS,[2,7] and *SCN5A* mutations cause BrS.[9] Disease-causing genes for AF are discussed in detail in a separate section.

Susceptibility genes are more often related to common complex disease traits (e.g., the common form of AF). Variants or single-nucleotide polymorphisms (SNPs) in these genes increase the risk for development of disease and may or may not cause the disease in the context of other genetic and environmental factors.[18] The susceptibility genes are commonly identified by a case–control association study showing significantly different allelic or genotypic frequencies of SNPs between control and patient populations. Susceptibility genes for AF are discussed in a separate section.

Disease-linked genes are referred to as the genes with expression or function that is linked to the disease by molecular biology studies or microarray or proteomic analyses.[18] Northern blot, Western blot, reverse tran-

scriptase polymerase chain reaction (RT-PCR), and other molecular biological techniques can be used to identify candidate genes with expression that differs between AF patients and controls. Examples include genes encoding heat shock proteins *HSP10, HSP60*, and *HSP70*[19] and *sarcolipin* (a homologue of phospholamban). At least five studies reported oligonucleotide microarray analysis for profiling expression of thousands of genes from AF tissues and non-AF tissues,[20–24] and two complementary DNA (cDNA) microarray studies were also reported for studying AF.[25,26] Each study identified many genes with expression that is associated with AF; however, the relationship of these genes to the disease as a cause or a consequence was not established. Furthermore, each study identified a different set of genes associated with AF. The main problem may be related to the small number of samples used in each study. Future studies with an expanded sample size (e.g., hundreds of patients and controls) may eventually identify a common set of genes with expression that is truly associated with AF (signature pattern). Some of these genes may serve as excellent biomarkers for the disease.

Disease-Causing Genes for Atrial Fibrillation

Disease-causing genes are discussed in detail in Chapter 6. In brief, a gain-of-function mutation (S140G) in *KCNQ1* was associated with autosomal dominant AF in a Chinese family.[27] More than 50% of the affected members (9/16) in the family are also affected with LQTS, which is caused by loss-of-function or dominant-negative mutations in the *KCNQ1* gene.[1] Another gain-of-function *KCNQ1* mutation, V141M, was identified in a patient with both AF and short QT syndrome.[28] A heterozygous mutation R27C of *KCNE2* was identified in two AF patients.[29] Mutation R27C did not affect KCNH2–KCNE2 I_{Kr} (rapid delayed rectifier potassium current) current, but it had a gain-of-function effect on the KCNQ1–KCNE2 potassium current. The mutation did not alter the functions of the hyperpolarization-activated cyclic nucleotide-gated (HCN) potassium channel family either.

Mutation R53H in *KCNE3* was identified in three patients in a very small Chinese family with AF (note that a 40-year-old normal family member also carried the mutations).[30] A mutation in *KCNJ2*, V93I, was identified in three patients carrying the mutation, as well as two other normal family members aged 42 and 33 years, in one Chinese family.[31] Although the V93I mutation increased inward potassium current at –90 to –80 mV and outward potassium current at –60 to –40 mV, the hypothesis that *KCNJ2* mutations cause AF needs to be further tested considering the minor change from a valine to isoleucine and the finding that two normal family members also carried the V93I mutation.

These studies suggest that mutations in ion channels can cause AF. Interestingly, some mutations in non-ion channel genes are also associated with AF in the context of other diseases. Mutations in the lamin A/C gene (*LMNA*) were identified in families with both dilated cardiomyopahty and AF.[32] A mutation in the *ankyrin-B* gene was identified in a family with LQT4, sick sinus syndrome with bradycardia, and AF.[33] Mutations in *SCN5A* were identified in families with both dilated cardiomyopathy and AF.[34] A mutation in *KCNH2*, N588K, was identified in a small family with both short QT syndrome and AF.[35]

Two genetic loci for autosomal dominant AF have been mapped to chromosome 10q22–24,[12] and 6q14–16[13]; however, the specific genes have not been identified yet.

Atrial fibrillation can also inherit as an autosomal recessive trait.[14] The first autosomal recessive AF gene has been mapped to 5p13,[14] but the specific gene remains to be identified.

Susceptibility Genes for Atrial Fibrillation

The most frequently used method for identifying the susceptibility genes for a common complex disease is the candidate gene case–control association studies. In this study design, a candidate gene is selected based on its potential involvement in the disease.[18,36] Single-nucleotide polymorphisms (SNPs) are identified in the candidate gene by searching the HapMap database (www.hapmap.org) and literature or by direct DNA sequence analysis of a panel of patients. The SNPs are genotyped in a group of patients (cases) and matched controls, and the frequencies of SNP alleles or genotypes are then analyzed by a χ^2 test or a Fisher exact test. An allele or genotype is associated with the disease if its occurrence in the cases is significantly different from that in the controls. Several case–control studies were reported for AF, and are summarized next.

Ion Channel Genes

In a Chinese population in Taiwan, Lai et al. showed a significant association between the *KCNE1* SNP G38S and AF.[37] The 38G allele increased the risk of AF, with an OR of 2.16 in heterozygotes and 3.58 in homozygotes. The functional effect of this SNP was reported.[38] The 38G allele reduced the I_{Ks} (slow delayed rectifier potassium current) potassium current, which is consistent with a finding that *KCNE1* null mice developed AF.[39] However, this result contradicts the finding that the gain-of-function mutations in *KCNQ1* were associated with AF in the familial form of AF.[27] Further studies are needed to clarify the discrepancy. Of note is that *KCNE1* SNP G38S was not associated with AF in a different Chinese population from mainland China.[40]

Other members of the *KCNE* potassium channel subunit genes were also investigated for their association with AF. The SNP E145D in the *KCNE4* gene was associated with AF in a Chinese population (OR = 1.66, $p = 0.044$).[40] The SNP T97C in *KCNE5* was associated with AF in a population from Denmark.[41] The 97T allele was associated with a reduced risk of AF, with an OR of 0.52.

G-Protein Gene

Schreieck et al. showed that the C825T SNP in the G-protein β3 subunit gene (*GNB3*) was significantly associated with AF in a German population.[42] The TT genotype plays a protective role in AF, with an OR of 0.46 ($p = 0.02$).

Genes in the Renin–Angiotensin System

In a Chinese population in Taiwan, Tsai et al. reported that three SNPs (M235T, G-6A, and G-217A) in the angiotensinogen (*AGT*) gene were associated with risk of AF, with ORs ranging from 2.0 to 3.3, but the insertion/deletion polymorphism in the angiotensin I-converting enzyme (*ACE*) gene and the A1166C polymorphism of the angiotensin II type I receptor gene (AT_1R) were not associated with risk of AF.[43] The study implicates involvement of the renin–angiotensin system in the pathogenesis of AF. In a different study

in Japanese patients with hypertrophic cardiomyopathy, the insertion/insertion (I/I) genotype of the (*ACE*) gene was a significant risk factor for AF.[44,45] The earlier study was supported by a report showing that the expression of *ACE* was threefold increased during chronic persistent AF.[46] Furthermore, in a population from the Netherlands, the *ACE* insertion/deletion polymorphism did not show any significant risk of AF.[47]

Gene in Lipid Metabolism

The *CETP* gene encodes the cholesteryl ester transfer protein that enables the transfer of cholesteryl esters from high-density lipoprotein (HDL) to low-density lipoprotein (LDL), which lowers HDL cholesterol. The TaqIB SNP in *CETP* was associated with AF in a cohort from the Netherlands (OR = 0.35, $p = 0.008$).[47]

Genes Involved in Thrombosis and Hemostasis

Because AF is associated with increased risk of stroke and thromboembolic events in AF, several candidate genes involved in thrombosis were analyzed for their association with AF. Factor V Leiden is a SNP in the coagulation factor V gene, R506Q, that produces a resistance to degradation by activated protein C and increases the risk of venous thrombosis. Factor V Leiden was not associated with the risk of AF or with the risk of left atrial thrombus formation in a Japanese population.[48] In a large U.S. population with 13,559 adult patients with nonvalvular AF, factor V Leiden was not significantly associated with risk of stroke in AF.[49] In a study with 1,531 participants involved in the Stroke Prevention in Atrial Fibrillation III Study (SPAFIII), the factor V Leiden SNP and levels of prothrombin fragment F1.2 (F1.2), β-thromboglobulin (BTG), and fibrinogen were not associated with thromboembolism in AF.[50] This finding was confirmed in two independent Italian populations.[51,52]

Factor II is another coagulation factor and a leading risk factor for venous thrombosis. Pengo et al. showed that SNP G20210A in the *factor II* gene was associated with systemic thromboembolism (OR = 3.0, $p < 0.05$).[51] Poli et al. showed that the same SNP was associated with AF (OR = 2.4, $p < 0.05$) but not with cerebral or peripheral embolic events in AF.[52] Hatzinikolaou-Kotsakou et al.[53] showed that both factor II SNP G20210A and factor V Leiden were associated with AF, with ORs of 4.9 and 4.6, respectively, but the study population was small (55 patients and 17 controls).

The T312A SNP in the *α-fibrinogen* gene was associated with poststroke mortality in a U.K. AF population.[54] In patients with AF, individuals with the A allele showed decreased survival, whereas in the normal population, it did not affect the survival. SNP T312A is close to the FXIIIa crosslinking site at A328. A common SNP in *factor XIII*, V34L, was associated with rapid FXIII activation but was not associated with AF.[55] However, patients with allele 34L showed higher plasma levels of *IL6*, which may induce a prothrombotic state in AF patients.[55] Patients with AF had higher blood levels of IL6 and fibrinogen after surgery, and the –174G/C SNP in the promoter of *IL6* was associated with postoperative AF (GG genotype, OR = 3.25, $p = 0.006$).[56]

It is important to note that the results from the case–control association studies should be interpreted with caution as many of these studies are compounded by the selection bias of cases and controls, population admixture, imperfect matching of cases with controls, phenotyping errors, and small sample sizes.

Genomewide Single Nucleotide Polymorphism Association Studies

To date, case–control association studies for AF have been limited to candidate genes. Recent technological advances in high-throughput genotyping of SNPs have driven down the costs to perform genomewide case–control association studies and make genomewide SNP association studies practical reality. The genomewide association study has the advantage of identifying novel genes associated with AF. More than 50,000 SNPs are required to provide the genome coverage, and a p value less than 5×10^{-7} was proposed to be the cutoff value for achieving significance (80% power).[57]

On average, sequence variants occur every 1,000 bp in the human genome,[58] and approximately 90% of sequence variants are SNPs.[59] Over 5 million SNPs have already been reported[60] and can be identified at the National Center for Biotechnology Information (NCBI) database and the HapMap database (http://www.hapmap.org/). High-throughput genotyping technologies have been developed for genomewide SNP genotyping, and an example is Affymetrix microarrays, with 500,000 SNPs. Successful genomewide SNP association studies were reported for age-related macular degeneration (the complement factor H gene),[61] type 1 diabetes (the innate immunity viral RNA receptor gene region),[62] and the QT interval trait (the NOS1 regulator *NOS1AP*).[63] In July, 2007, Gudbjartsson et al. reported the results from a genome-wide SNP association study for 550 patients with atrial fibrillation and 4,476 controls from Iceland.[64] Genotyping was carried out using the Illumina Hap300 Beadchip with 316, 515 SNPs. A strong association was identified between two SNPs on chromosome 4q25 and atrial fibrillation.[64] The result was replicated in three other European populations and a Chinese population from Hong Kong.[64] However, the SNPs were not located in any know or putative gene, thus, the specific gene at the locus was not identified.

Future Perspectives

In the next 5 to 10 years, the field of genetics of AF will witness advances in the following research areas:

1. Genetic studies of rare large families will continue to provide important insights into the pathophysiological mechanisms of AF. In particular, identification of novel non-ion channel genes will be critical to pinpoint other signaling pathways involved in AF.
2. Genomewide SNP association studies will be a new innovative tool to identify many susceptibility genes for AF.
3. Candidate gene case–control association studies will continue to identify some susceptibility genes for AF.
4. Molecular characterization of disease-causing genes, susceptibility genes, and disease-linked genes for AF using a variety of technologies, including transgenic/knockout/knockin mouse models, will provide insight regarding the pathogenesis of AF.
5. Genotype–phenotype correlation studies will lead to genotype-specific therapy (personalized medicine) in AF and move the basic scientific findings to the clinic.

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