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The Role of Pharmacogenetics in Atrial Fibrillation Therapeutics – Is Personalized Therapy in Sight?

Dawood Darbar, MD

Divisions of Cardiovascular Medicine and Clinical Pharmacology, Vanderbilt University, Nashville, TN

Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide requiring therapy. Despite recent advances in catheter-based and surgical therapy, antiarrhythmic drugs (AAD) remain the mainstay of treatment for symptomatic AF. However, response in individual patients is highly variable with over half the patients treated with rhythm control therapy experiencing recurrence of AF within a year. Contemporary AADs used to suppress AF are incompletely and unpredictably effective and associated with significant risks of proarrhythmia and non-cardiac toxicities. Furthermore, this ‘one-size’ fits all strategy for selecting antiarrhythmics is based largely on minimizing risk of adverse effects rather than on the likelihood of suppressing AF. The limited success of rhythm-control therapy is in part due to heterogeneity of the underlying substrate, interindividual differences in disease mechanisms, and our inability to predict response to AADs in individual patients. Genetic studies of AF over the last decade have revealed that susceptibility to and response to therapy for AF is modulated by the underlying genetic substrate. However, the bedside application of these new discoveries to the management of AF patients has thus far been disappointing. This may in part be related to our limited understanding about genetic predictors of drug response in general, the challenges associated with determining efficacy of response to AADs and lack of randomized genotype-directed clinical trials. Nonetheless, recent studies have shown that common AF susceptibility risk alleles at the chromosome 4q25 locus modulated response to AADs, electrical cardioversion and ablation therapy. This monograph discusses how genetic approaches to AF have not only provided important insights into underlying mechanisms but also identified AF sub-types that can be better targeted with more mechanism-based ‘personalized’ therapy.

Keywords

atrial fibrillation; genetics; antiarrhythmics drugs; response; genomics; mechanisms

WHY IS THERE A NEED TO 'PERSONALIZE' THERAPY FOR ATRIAL FIBRILLATION?

Atrial fibrillation (AF) has become a disease of global epidemic proportions due to the burgeoning population of elderly individuals. The global burden of AF was recently estimated at ~33.5 million with progressive increases in incidence, prevalence and AF-related mortality having major implications for healthcare costs and public health policy.¹ The number of persons in the U.S. with AF by the year 2050 is projected to exceed 16 million.² The socioeconomic impacts of AF are substantial, as are the consequences of frequent visits to the emergency room and hospitalizations, chronic disease management and loss of productivity.³⁻⁵

While most patients with symptomatic AF are initially treated with rhythm control therapy, failure to suppress AF with antiarrhythmic drugs (AADs) leads to consideration of catheter-based ablation in selected patients. Currently, the pharmacologic management of AF in clinical practice varies considerably due to ineffective therapies for maintaining sinus rhythm, the toxicities associated with AADs,⁶ and evidence that, on average, rate and rhythm control approaches are equivalent.⁷⁻⁹ However, a rhythm control strategy is often needed in patients with intolerable symptoms during AF, and may be appropriate for broader use since patients in the AFFIRM trial had better outcomes if sinus rhythm was achieved and maintained.¹⁰ Without the ability to match an individual patient with the treatment option most likely to suppress AF, the current 'one-size' fits all approach for selecting an AAD focuses primarily on minimizing side-effects and not on efficacy. The 2014 ACC/AHA/HRS guidelines recommend a rate-control strategy for all asymptomatic patients.¹¹ The failure of AADs to show superiority over rate control in large populations of AF patients may reflect the underlying heterogeneity of AF, and our inability to select individuals most likely to respond to rhythm control therapy. Given that the current success rate for maintaining sinus rhythm with AADs is ~50% over 6-12 months, continued research aimed at refining AAD therapy is urgently needed.¹²

DEFINING THE GENETIC ARCHITECTURE OF ATRIAL FIBRILLATION

A major reason for why AADs do not suppress AF relates to poor understanding of the underlying pathophysiology of the condition. Over the last decade, diverse genetic approaches to AF (Figure 1) have not only better defined underlying mechanisms but also provided important insights into variability in response to AF therapy.

Heritability of AF

Familial AF was first reported in 1943 when Wolff identified three brothers with early onset AF.¹³ More recently, many epidemiologic studies have supported the idea of heritability in AF, especially AF that occurs in patients without recognized heart or systemic disease, previously called "lone" but now better termed as early onset AF.¹⁴⁻¹⁸

Linkage studies

Several genes and loci have been identified for rare Mendelian forms of early onset AF (Table 1).¹⁹⁻²³ We identified a novel AF locus on chromosome (chr) 5p15 and established an abnormally prolonged P-wave as an ‘endophenotype’ in a family with early onset AF.²⁴ Linkage analysis has facilitated the identification of individual mutations in several familial AF kindreds. In 2003, the first gene *KCNQ1*, which encodes a cardiac potassium channel responsible for a rare autosomal dominant form of AF was identified.²⁵ This discovery was followed by studies that implicated genes encoding other cardiac ion channels and associated proteins in the pathogenesis of familial AF. For example, Mayo Clinic investigators identified a novel heterozygous frameshift mutation in the natriuretic peptide precursor A (*NPPA*) gene that encodes atrial natriuretic peptide (ANP).²⁶

More recently, we performed whole exome sequencing on 18 individuals in six familial AF kindreds in which candidate gene variants were absent.²⁷ After filtering rare variants by multiple metrics, we identified at least two or more rare variants in 5/6 of the kindreds and no plausible variant contributing to familial AF was identified in the remaining kindred. However, very high priority candidate genes not previously implicated in AF, were identified in four AF families (Table 1).

Candidate gene approach

Based on the work linking *KCNQ1* to familial AF, investigators screened other cardiac potassium and ion channels as potential candidate genes in probands and families with early onset AF with several rare variants identified (Table 1). Otway and colleagues examined 50 kindreds with early onset AF and identified a *KCNQ1* mutation (R14C) in one family.²⁸ At baseline the R14C mutation did not affect the *KCNQ1/KCNE1* current amplitudes when expressed in a heterologous expression system. However, upon exposure to hypotonic solution, mutant channels exhibited a marked increase in currents when compared with wild-type channels. Surprisingly, only those patients with left atrial dilatation had AF. These findings and Vanderbilt data showing that penetrance of rare AF-associated variants is modulated by common AF risk alleles at the chr4q25 locus support the concept of a “two-hit” genetic model for the development of AF.²⁸⁻³⁰

Mutations in genes encoding connexins, proteins important in transmitting electrical activity between cardiac myocytes, have also been associated with early onset AF. This stems from early work in mice with null alleles for *GJA5*, encoding connexin-40, showing increased susceptibility to reentrant atrial arrhythmias.³¹ This led Gollob and colleagues to screen *GJA5* in probands with early onset AF undergoing the surgical maze procedure.³² Isolation of DNA from atrial tissue identified *GJA5* mutations in 4 of the 15 subjects. These mutations disrupted electrical coupling between cardiac cells. Furthermore, in 3 of the patients, somatic mutations acquired after fertilization were identified. The remaining AF proband carried a germ-line mutation in *GJA5*. However, a new study from the same group showed convincingly that somatic mosaicism does not play a major role in the pathogenesis of AF.³³

Genetic association studies

While AF is common especially in the elderly, the familial forms of the condition are rare. While many patients with AF have one or more identifiable risk factors such as hypertension, the majority of patients with these same risk factors never develop AF. One hypothesis that has been proposed is that genetic determinants increase AF susceptibility in some individuals with identifiable risk factors – a basis for the “two-hit” genetic model.³⁰ Initially, association studies comparing AF cases to controls typically tested a small number of variants in candidate genes previously believed to be involved in AF pathogenesis. However, recent advances in genotyping technology have allowed us to assay hundreds of thousands of single nucleotide polymorphisms (SNP) that span the entire human genome and thus made genome-wide association studies (GWAS) possible. In 2007, a locus on chr4q25 was identified in a GWAS as having a highly significant association with AF with a relative risk ranging from 1.39 to 1.72 per copy.³⁴ Although the mechanism for this observed association continues to be unclear, the locus is ~150 kb upstream from the paired-like homeodomain transcription factor 2 (*PITX2*) gene which is critical for cardiac development. This association was replicated in four large populations³⁵ and also holds in post-cardiac surgery AF.³⁶ Eight additional AF susceptibility loci were identified and replicated when a meta-analysis of AF GWAS was performed in 2012 (Table 2).³⁷ More recently, five additional novel AF genes were uncovered by a large consortium of investigators.³⁸ The identified loci and genes not only implicate transcription factors related to cardiopulmonary development and cardiac-expressed ion channels, but also cell signaling proteins.

As there is a high prevalence of AF in patients with the Brugada syndrome, it is perhaps not surprising that there is significant overlap in genes associated with the two diseases.³⁹ Both rare mutations and common polymorphisms encoding cardiac sodium and potassium channels have been identified in patients with both AF and Brugada syndrome.⁴⁰⁻⁴³ Furthermore, a recent study showed that the prevalence of three risk loci associated with Brugada syndrome was lower in AF patients than in patients without the arrhythmia, suggesting that these risk alleles may protect against the development of AF.⁴⁴

IMPACT OF GENETIC STUDIES OF ATRIAL FIBRILLATION

Traditional linkage analysis and candidate gene approaches have identified rare mutations encoding cardiac ion channels, gap junction proteins and signaling molecules linked with early onset AF. In contrast, GWAS have identified many common AF susceptibility loci. Collectively these approaches have not only provided important insights into underlying mechanisms of AF and uncovered novel therapeutic targets but also identified genetic subtypes of AF.

Improved understanding of underlying mechanisms

Modulation of atrial action potential duration—A major mechanism by which genes linked with familial AF increase susceptibility to the arrhythmia is by modulation of the atrial action potential duration (APD). The first cardiac ion channel linked with familial AF was associated with a gain-of-function mutation in *KCNQ1*, encoding the delayed rectifier

potassium current I_{Ks} .²⁵ Subsequently both gain- and loss-of-function mutations in cardiac potassium, sodium, and calcium channels have been linked with familial AF (Table 1). Interestingly, these same genes have also been linked with diverse phenotypes including long QT syndrome, Brugada syndrome and cardiac conduction disease.⁴⁵ However, it remains unclear how mutations in cardiac ion channels can give rise to divergent phenotypes in the atrium and ventricle. The first non-ion channel gene linked with familial AF was identified in 2008. A frameshift mutation in *NPPA* encoded a mutant ANP that, when infused in a rat whole-heart Langendorff preparation, shortened the monophasic APD and effective refractory period.²⁶ While the precise mechanism(s) by which circulating mutant ANP increases susceptibility to AF have not been determined, a transgenic mouse model overexpressing the humanized *NPPA* may provide novel insights.⁴⁶

Modulation of gap junction proteins—Both germ-line and somatic mutations and common SNPs in *GJA5*, encoding connexin-40, have been associated with early-onset AF.^{31, 32, 47, 48} Genetic variants encoding gap-junction proteins likely mediate increased risk for AF not only by reducing expression of the protein but also impairing electrical communication between cells and creating heterogeneity of atrial conduction.

Regulation of cardiac developmental genes—Genetic association studies have also provided important insights into underlying mechanisms of AF. Although the strongest signal consistently associated with AF in GWAS is located at the chr4q25 locus, the precise mechanism(s) by which these SNPs increase susceptibility to AF has not been fully worked out. Due to the distance between the chr4q25 AF risk locus and *PITX2* (~150 kb upstream), it is unlikely to simply tag a causative polymorphism within *PITX2* or its promoter. As this region is evolutionary highly conserved, the chr4q25 locus is much more likely to code for a regulatory RNA element that modulates transcription of nearby genes.⁴⁹⁻⁵¹ Following identification of the chr4q25 AF risk locus, there has been increasing interest in *PITX2* and its role in the development of AF. *PITX2* codes for a homeobox transcription factor (Pitx2c) involved in development of the pulmonary vein myocardium and signaling pathways that regulate the electrophysiologic substrate responsible for atrial arrhythmias.^{52, 53} Pitx2c expression was 100-fold higher in the left than right atrium in humans.⁵⁴ One potential explanation for left atrial selectivity in Pitx2c expression is suppression of genes such as *SHOX2* and *TBX3* which signal development of increased cellular “automaticity”- a property that enables spontaneous electrical depolarization in the right atrial cells that form the sinus node, but are AF triggers when present in the left atrium and the pulmonary veins.^{52, 55} Furthermore, heterozygous *Pitx2*^{+/-} mice demonstrate shortened atrial refractoriness and APD, and increased inducibility of AF.^{53, 54} Collectively, these studies strongly support the idea that AF risk alleles inhibit transcription of *PITX2* which allows up-regulation of *SHOX2* and *TBX3* in the left atrium promoting an electrical substrate for AF.

The emergence of *PITX2* as an important modulator in development of the pulmonary vein myocardium led to the screening of other cardiac developmental genes. Recently our group resequenced *GREMLIN2*, a cardiac developmental gene in 193 probands with early onset AF, and identified a rare Q76E variant within the coding sequence.⁵⁶ Loss- and gain-of-function experiments in zebrafish revealed that, through bone morphogenetic protein (BMP)

signalling *GREMLIN2* is required for cardiac laterality and atrial differentiation during development. *GREMLIN2* overactivity resulted in slower cardiac contraction rates in zebrafish, and modulation of previously identified AF candidate genes including *Gja5*, *Sarcolipin*, *Cacna1c*, *Kcne2* and *Nppa* in differentiated mouse embryonic stem cells. Moreover, by imaging live zebrafish overexpressing *GREMLIN2*, we found a regular cardiac rhythm but abnormal conduction propagation specifically in atrial cardiomyocytes. This is the first study to implicate regulators of BMP signalling in human AF and not only provides important insights into AF mechanisms but also potentially a new therapeutic target.

Role of atrial fibrosis and inflammation—The important role of inflammation and atrial fibrosis in the pathogenesis of AF was first suggested in the 1990's when studies showed that patients with early-onset AF had histological evidence of myocarditis.⁵⁷ This was further supported by the high incidence and prevalence of AF after cardiac surgery and its suppression with anti-inflammatory drugs.⁵⁸ In animal studies, induction of atrial fibrosis has been associated with increased risk for atrial arrhythmias and in humans the extent of atrial fibrosis has correlated with success of ablation therapy.⁵⁹ While the role of many common AF risk alleles has not been fully elucidated, there is now increasing evidence that atrial fibrosis may be a key mediator for increased risk of developing AF.

Besides its role in the development of the pulmonary vein myocardium, *PITX2* may also play a role in structural and electrical remodeling of the atria. *PITX2*^{-/-} knock-out mice develop 4-chamber cardiac enlargement, histological evidence of atrial fibrosis and up-regulation of collagen precursor genes.⁵² In contrast, *PITX2*^{+/-} heterozygous mice have no evidence of cardiac enlargement but have increased expression of genes regulating Wnt signaling, a key fibrosis pathway.⁵⁴ Common SNPs at the 7q31 AF locus encode caveolin-1 which internalizes transforming growth factor (TGF)- β receptors leading to suppression of this signaling pathway and prevention of atrial fibrosis. Variants in *CAVI* have not only been associated with myocardial fibrosis but also pulmonary hypertension (Table 2).

The zinc finger homeobox 3 transcription factor, encoded by *ZFHX3*, plays an important role when responding to TGF- β signaling.^{60, 61} *SYNP02L* and *SYNE2* encode cytoskeletal and nucleo-proteins that link the nucleo-skeleton to the nuclear membrane structures and may play an important role in cardiac development.⁶² *SYNE2* and *emerin* interact with α -catenin regulating the Wnt signaling pathway. *PRRX1* is a transcription factor that is thought to be important for normal lung development and has been associated with pulmonary fibrosis. Scleroderma fibroblasts stimulated with TGF- β show increased expression of *C90RF3*. Another possible mechanism by which *NPPA* variants may mediate increased risk for AF is by causing both electrical and structural remodeling of the atria with the development of atrial fibrosis. While overexpression of the humanized *NPPA* variant in mice does not appear to cause atrial enlargement,⁴⁶ a different *NPPA* mutation identified in four Italian families was associated with an atrial myopathy, massive biatrial enlargement and atrial standstill.⁶³

Identification of novel therapeutic targets

We previously identified the tyrosine signaling pathway as a novel therapeutic target for the treatment of AF when a rare variant in *KCNA5*, encoding the Kv1.5 cardiac potassium channel, was linked with AF.⁶⁴ More recently rare variants in *SCN10A*, encoding the Nav1.8 sodium channel, have not only been associated with AF but also shown to modulate both the peak and late sodium current (I_{Na-L}) (Table 1).^{65, 66} Vanderbilt investigators showed that early afterdepolarizations could be blocked by a specific Nav1.8 blocker supporting I_{Na-L} block as a novel therapeutic target for the treatment of AF.⁶⁷

The identification of signaling pathways important in cardiac protein expression, function and turnover of cardiomyocytes, a process termed “proteostasis”, has uncovered novel AAD targets for AF.⁶⁸ We recently identified a novel variant in heat shock factor (*HSF*)-1 that cosegregated with early-onset AF in a large family with familial AF using a whole exome sequencing approach.²⁷ Since heat shock proteins (HSP) play an important role in proteostasis, targeting this pathway with drugs such as geranylgeranylacetone that enhance HSP expression may protect against AF and represents a novel mechanism-based target for the treatment of AF.⁶⁹ Importantly, an autosomal recessive mutation in *NUP155* linked with early-onset AF regulates transport of *Hsp70* mRNA and protein in and out of the nuclear membrane.⁷⁰ While the precise mechanism by which *NUP155* increases risk of AF is not clear, up-regulation of genes important in the pathogenesis of AF is one potential mechanism. The histone acetyl deacetylases (HDAC) also play an important role in proteostasis. Studies have shown that suppression of HDAC6 with tubastatin A prevented the progression of AF in a tachycardia-induced dog model suggesting that targeting this pathway may be another novel approach for the treatment of AF.^{71, 72}

Identification of genetic subtypes with differential response to therapy

Genetic studies have not only uncovered common and rare genetic variation associated with AF but also identified genetic sub-types of AF with differential response to therapy. One of the earliest pharmacogenetic studies of AF asked the question if response to AADs was modulated by the angiotensin-converting enzyme (*ACE*) *I/D* polymorphism in patients with symptomatic AF.⁷³ The only significant predictors of failure of AAD therapy were early-onset AF and *ACE DD/ID* genotypes. Furthermore, a graded response was observed with patients with the *II* genotype experiencing the greatest suppression of symptomatic AF and those with the *DD* genotype responding the least well to AADs. This was the first study to support stratification of therapeutic approaches by *ACE* genotype.

In 2012, we assessed whether the common AF risk loci on chr4q25 (near *PITX2*), 16q22 (in *ZFHX3*), and 1q21 (in *KCNN3*) modulated symptomatic response to AADs in patients with symptomatic AF.⁷⁴ The discovery (n=478) and validation cohorts (n=198) were age and gender matched Caucasian patients enrolled in the Vanderbilt AF Registry. Response was defined as successful rhythm control if the patient remained on the same AAD for a minimum of 6 months with ≥75% reduction in AF symptoms. Multiple clinical variables (including age, hypertension, early-onset AF) failed to predict response to AAD therapy. However, a SNP at the 4q25 locus (rs10033464) was significantly associated with successful symptom control (odds ratio [OR] 2.97, 95% confidence interval [CI] 1.42-6.21, P=0.003).

Furthermore, individuals who carried the 4q25 SNP responded better to class I vs. class III AADs in both the discovery and validation cohorts. More recently, our group showed that the same chr4q25 AF locus predicted a 24% shorter recurrence-free time from AF than did the presence of the wild-type SNP after AF ablation,⁷⁵ confirming an earlier study.⁷⁶ These variants were also independent predictors of AF recurrence after restoration of sinus rhythm after electrical cardioversion.⁷⁷ Collectively, this data supports the concept of selecting AF therapies based on genotype. These results not only support the role of the chr4q25 locus in modulating response to AADs, cardioversion and AF ablation but also point to potential subtyping of AF by genotype.

TRANSLATION OF GENETIC DISCOVERIES INTO CLINICAL PRACTICE

While genetic approaches to AF have revealed that susceptibility to and response to therapy for AF is modulated in part by the underlying genetic substrate, the translation of these discoveries to the bedside management of AF patients has thus far been limited.³⁰ This relates in part to poor understanding of the underlying mechanisms of AF in individual patients, challenges associated with determining efficacy of response to AAD therapy and lack of genotype-directed prospective clinical trials.

Poor understanding of underlying mechanisms

Despite recent advances in our understanding of the underlying mechanisms of AF, selecting patients for a trial of AAD therapy based on clinical variables is still associated with ~50% failure rate. An improved understanding of the underlying pathophysiology of AF in individual patients would not only ‘personalize’ selection of AADs based on genotype with increased efficacy of suppression of AF but also reduce the likelihood of adverse effects. Recently, a proof-of-concept study (discussed below) that takes advantage of the mechanistic insights gained from *PitX2* mice models of AF provides the first direct example of translating genetic discoveries to select therapy that is directed at the underlying mechanism of paroxysmal AF.⁷⁸

Challenges of assessing efficacy of antiarrhythmic drugs

A major obstacle in translating genetic discoveries to the bedside care of patients with AF relates to the challenges associated with measuring efficacy of AADs. While the traditional endpoint used to assess efficacy has been “time to first symptomatic AF episode,” poor correlation with frequency of symptomatic episodes and failure to measure asymptomatic episodes makes this a poor endpoint.^{79, 80} AF burden has not been used to assess efficacy of AADs because of historical limitations in non-invasive ambulatory monitoring technology and lack of reliable algorithms to identify and provide quantitative summaries for AF. However, recent technological advances that allow continuous monitoring of cardiac rhythm have now made it possible to rigorously define AF burden (which includes both symptomatic and asymptomatic episodes) and use it as a surrogate endpoint to assess AF therapy.^{81, 82} As AF burden is less prone to investigator bias, excludes sampling error associated with episodic monitoring, and is not reliant on patient symptoms, it may be a more robust endpoint to assess efficacy of AF therapy.⁸³ Furthermore, it is favored to become the metric of choice to assess not only response to AADs but also monitoring after

AF ablation therapy.⁸⁴ Recent advances in continuous electrocardiographic monitoring, especially the advent of the insertable cardiac monitors has now made it possible to measure AF burden accurately and use it as an endpoint for assessing efficacy of therapy for AF.^{85, 86}

Lack of genotype-directed clinical trials

The failure to replicate associations between common genetic variants and response to therapy for AF, the small effect sizes associated with AF susceptibility SNPs and a dearth of randomized control trials that are genotype-directed has also impeded our ability to translate the genetic discoveries to the bedside care of patients with AF.³⁰ The failure to replicate is largely because there are very few well-characterized AF treatment response cohorts with the exception of the Vanderbilt AF Registry.⁷³ In the future, a sub-study of CABANA called CABANAgene will provide another large cohort in whom replication studies can be performed.³⁰ While the ORs for susceptibility to AF have not been large (1.1-1.7), it is important to note that when Vanderbilt investigators evaluated whether AF risk SNPs modulated response to therapy, the ORs were markedly greater than those seen in prediction of AF itself. Currently an open label, randomized sequential cross-over pilot study to determine whether differential response to flecainide (class IC) vs. sotalol (class III) AADs is modulated by chr4q25 AF risk alleles is underway and will provide important data on whether a genotype-based approach to selection of AADs is not only feasible but also more efficacious (Figure 2).

IMPLICATIONS FOR ATRIAL FIBRILLATION THERAPY

It is apparent that determining whether a rare disease-causing variant encoding a cardiac ion channel, gap junction protein or signaling molecule leads to a gain or loss-of-function has obvious therapeutic implications. However, the applicability of such an approach to patients with the more common forms of AF is limited. One major challenge relates to distinguishing pathogenic mutations from rare polymorphisms. Numerous approaches have been proposed to distinguish benign SNPs from pathogenic mutations including examining the variant type and location, segregation of the variant with the phenotype in affected family members, and analyzing the degree of conservation of the encoded amino acid across species.^{87, 88} Furthermore, multiple “heuristic” prediction algorithms have been developed to determine the likelihood of a rare variant being pathogenic.⁸⁹ Identification of variants in the same gene in other kindreds and uncovering de novo variants in sporadic cases have also been proposed.⁹⁰ The final criterion used to determine pathogenicity is by functionally characterizing rare variants in vitro. While these assays may not always recapitulate the phenotype, we and others have extensively used this approach to confirm pathogenicity of rare variants.⁹¹ The second major challenge relates to developing an assay whereby pathogenic variants can be rapidly functionally characterized as almost all the AF-causing mutations are rare or ‘private’ within a particular kindred. Nonetheless, insights into the genetic mechanisms of AF have resulted in proof-of-concept studies that provide some optimism for the translation of these discoveries to the bedside care of patients with AF.

Genotype-specific therapy

A recent study illustrates the proof-of-principal for genotype-directed treatment of familial AF. In collaboration with Dr. George's laboratory, we investigated whether WT-*KCNQ1* or the *KCNQ1*-S140G familial AF mutation possess distinct pharmacological properties that may enable targeted inhibition of the I_{Ks} -selective blocker HMR-1556.⁹² While a low concentration of the blocker had little effect on WT- I_{Ks} , it was capable of inhibiting the mutant channel. In cultured adult rabbit left atrial myocytes, expression of S140G- I_{Ks} shortened APD but cells expressing WT- I_{Ks} did not. The familial *KCNQ1*-S140G gain-of-function mutation demonstrated increased sensitivity for the I_{Ks} blocker pointing to the possibility of selective therapeutic targeting.

Mechanism-based therapy

Patients with mutations in the ryanodine receptor (RyR2) and in the sarcoplasmic reticulum Ca binding protein calsequestrin (Casq2) display increased risk for AF. Investigators at Vanderbilt examined the underlying mechanisms of AF associated with loss of Casq2 and tested a mechanism-based drug therapy for AF.⁷⁸ Atrial burst pacing was used to quantify AF susceptibility in isolated hearts from Casq2^{-/-} and Casq2^{+/+} mice. AF was induced in 11/12 Casq2^{-/-} mice hearts but not in Casq2^{+/+} hearts. Atrial optical mapping revealed multiple independent activation sites arising from the pulmonary vein region. The dual RyR2 and sodium channel blocker R-propafenone significantly reduced frequency and amplitude of sub-threshold diastolic calcium elevations (SCaE) and delayed afterdepolarizations in atrial myocytes and intact atria and prevented induction of AF. In contrast, S-propafenone, an equipotent sodium channel blocker but much weaker RyR2 inhibitor, only partially reduced SCaE and delayed afterdepolarizations and failed to prevent AF. These findings strongly suggest that targeting AF with R-propafenone may be a more mechanism-based approach to treating AF. A prospective study in humans using such a mechanism-based approach for the treatment of paroxysmal AF is planned in the near future.

CONCLUSIONS

Over the last decade, there have been tremendous advances in defining the genetic architecture of AF. Both traditional and contemporary genetic approaches have identified rare mutations linked with AF and common genetic variation. Collectively, these studies have provided important insights into underlying mechanisms of AF, identified novel therapeutic targets, and defined genetic sub-types of AF. Although the clinical application of these discoveries to the bedside management of patients with symptomatic AF has thus far been limited, recent proof-of-concept studies and planned randomized genotype-directed trials provide optimism that within 5 years, a 'personalized' more mechanism-based approach to the treatment of this common condition can be achieved.

Review criteria

The following combination of key terms were searched in the PubMed database in January 2015: "atrial fibrillation"; "familial"; "inherited"; "family", "ion channel variants", "mutations", "pharmacogenomics/genetics", and; "rare variants". While I restricted the

search to full-length manuscripts and contemporary reviews published in English, recently published abstracts in *Circulation* were also reviewed. The reference lists of selected articles were searched for further leads.

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Strategies for genetic analysis

FIGURE 1. Genetic approaches to defining the genetic architecture of AF

Traditional linkage analysis and next generation sequencing have identified rare mutations in single genes in moderate to large-sized familial kindreds. These mutations are associated with a small population attributable risk. In contrast, genetic association studies have identified common genetic variants associated with AF in multiple genes that are associated with a large population attributable risk. (Filled in symbols indicate individuals with AF).

FIGURE 2.

Conceptual model of an open label, randomized sequential cross-over pilot study to determine whether response to flecainide vs. sotalol is modulated chr4q25 risk variants. AAD: antiarrhythmic drug; AF: atrial fibrillation; AFEQT: AF-specific quality of life questionnaire.

Linkage analysis, positional cloning and candidate gene approaches have identified rare genetic variants linked with AF and provided novel insights into underlying mechanisms.

TABLE 1

Gene	Mode of inheritance	Effect on function	Physiologic effect	Associated phenotypes	Reference
<i>KCNQ1</i>	AD	Gain-of-function Loss-of-function	↓ Atrial APD	Prolonged QT	25, 28, 93-100
<i>KCNE1</i>	AD	Loss-of-function	↓ Atrial APD	Frequent PACs	101, 102
<i>KCNE2</i>	AD	Gain-of-function Loss-of-function	↓ Atrial APD		103-106
<i>KCNE5</i>	AD	Gain-of-function	↓ Atrial APD		103, 104
<i>KCND3</i>	AD	Gain-of-function	↓ Atrial APD		107
<i>KCNJ2</i>	AD	Loss-of-function Gain-of-function	↓ Atrial APD		108-110
<i>GJA5</i>	Somatic mutations Isolated early-onset AF cases	↓Electrical cell-to-cell coupling	Regions of heterogeneous conduction		32, 48, 111, 112
<i>KCNK5</i>	AD	Loss-of-function Gain-of-function	↑ Atrial APD, EADs and TA		64, 113-115
<i>SCN5A</i>	AD	Gain-of-function	↑↓ Atrial APD	HCM, DCM	40, 116-119
<i>SCN1B/2B/3B</i>	AD	Loss-of-function	EADs, TA		43, 120-123
<i>SCN10A</i>	AD	Gain-of-function Loss-of-function	↑APD, EADs, TA	Slow ventricular rates	65, 66
<i>CACNA1C</i>	AD	Gain-of-function	↑APD, EADs, TA		124
<i>CACNB2</i>	AD	Loss-of-function	↑APD, EADs, TA		27, 125
<i>NPPA</i>	AD	Loss-of-function	↓ Atrial APD	Atrial myopathy	26, 29, 93, 126, 127
<i>NUP155</i>	AR	Nuclear protein transport (hsp70)		Sudden cardiac death	70
<i>HSP-1</i>	AD	Modulation of heat shock protein			27
<i>EVC2</i>	AD	Associated with long QT syndrome, Brugada			27
<i>SCNN1D</i>	AD	Sodium channel gene expressed in the heart			27
<i>CACNA2D4</i>	AD	Linked with cardiac conduction disease, Long QT and Brugada syndromes			27

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AD, autosomal dominant; APD, action potential duration; EADs, early after-depolarizations; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; hsp, heat shock protein; PACs, premature atrial contractions; TA, triggered activity.

TABLE 2

Thirteen AF susceptibility loci were identified by a genome-wide association study meta-analysis.^{37,38}

SNP	Locus	Closest gene	Functional Effect	Minor/major allele	MAF (%)	RR (95% CI)	Meta P-value
rs6817105	4q25	<i>PITX2</i>	development of pulmonary vein myocardial sleeve	C/T	13.1	1.64 (1.54-2.21)	1.8×10^{-74}
rs2106261	16q22	<i>ZFHX3</i>	unknown	T/C	17.6	1.24 (1.17-1.30)	3.2×10^{-16}
rs6666258	1q21	<i>KCNN3</i>	calcium activated potassium channel	C/G	29.9	1.18 (1.13-1.23)	2.0×10^{-14}
rs3903239	1q24	<i>PRRX1</i>	development of great vessels	G/A	44.7	1.14 (1.10-1.18)	9.1×10^{-11}
rs3807989	7q31	<i>CAV1</i>	atrial signal transduction protein	A/G	40.4	0.88 (0.84-0.91)	9.6×10^{-11}
rs10821415	9q22	<i>C9orf3</i>	unknown	A/C	42.4	1.13 (1.08-1.18)	7.9×10^{-9}
rs10824026	10q22	<i>SYNPO2L</i>	cardiac protein that localizes to Z-disc	G/A	15.8	0.85 (0.81-0.9)	1.7×10^{-8}
rs1152591	14q23	<i>SYNE2</i>	structural protein of cardiac sarcomere	A/G	47.6	1.13 (1.09-1.18)	6.2×10^{-10}
rs7164883	15q24	<i>HCN4</i>	ion channel (I_h) involved in cardiac pacemaking	G/A	16.0	1.16 (1.10-1.22)	1.3×10^{-8}
rs12415501	10q24	<i>NEURL</i>	modulates atrial APD	T/C	16.0	1.18 (1.13-1.23)	6.5×10^{-16}
rs10507248	12q24	<i>TBX5</i>	development of conduction system	T/C	73.0	1.12 (1.08-1.16)	5.7×10^{-11}
rs4642101	3p25	<i>CAND2</i>	modulates atrial APD	G/A	65.0	1.10 (1.06-1.14)	9.8×10^{-9}
rs13216675	6p22	<i>GJA1</i>	coordinates electrical activity between adjacent myocytes	T/C	69.0	1.10 (1.06-1.14)	2.2×10^{-8}

APD, action potential duration; GWAS, genome-wide association study; MAF, minor allele frequency; RR, relative risk;