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Review article

Improved understanding of the pathophysiology of atrial fibrillation through the lens of discrete pathological pathways

Muhammad A. Balouch, Matthew J. Kolek, Dawood Darbar*

Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

*Email: dawood.darbar@vanderbilt.edu

ABSTRACT

Atrial fibrillation (AF) is a common disorder with a complex and incompletely understood pathophysiology. Genetic approaches to understanding the pathophysiology of AF have led to the identification of several biological pathways important in the pathogenesis of the arrhythmia. These include pathways important for cardiac development, generation and propagation of atrial electrical impulses, and atrial remodeling and fibrosis. While common and rare genetic variants in these pathways are associated with increased susceptibility to AF, they differ substantially among patients with lone versus typical AF. Furthermore, how these pathways converge to a final common clinical phenotype of AF is unclear and might also vary among different patient populations. Here, we review the contemporary knowledge of AF pathogenesis and discuss how derangement in cardiac development, ion channel dysfunction, and promotion of atrial fibrosis may contribute to this common and important clinical disorder.

Keywords: Atrial fibrillation, pathophysiology, genetics, inflammation, fibrosis

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INTRODUCTION

Atrial fibrillation (AF), the most common sustained heart rhythm disorder in adults, is becoming increasingly prevalent.[1,2] It is projected that 12–16 million people in the US will have AF by 2050.[3,4] The lifetime risk of developing AF for Americans reaching 80 years of age is approximately one in four.[5] The risk of stroke in patients with AF increases five-fold with resultant adverse functional outcome and ~2-fold increase in mortality.[6] More recently AF has been associated with increased risk for incident myocardial infarction.[7] Because of the global health burden of AF, identification of those at increased risk may improve diagnoses and management. Traditional risk factors for AF include male gender, advanced age, Caucasian race, hypertension, diabetes mellitus type II, valvular heart disease, and other forms of underlying heart disease. Recently, some newer risk factors for AF have been identified including the metabolic syndrome, obstructive sleep apnea, and obesity.[8,9,10,11] In addition, multiple studies support the contribution of genetic factors to AF susceptibility. Lone AF, which is AF in the absence of underlying hypertension, valvular, ischemic or underlying structural heart disease, is present in 10–30% of all AF patients.[12] Given its clinical and genetic heterogeneity,[13] AF is likely to represent a final common phenotype with the convergence of multiple pathways.

Some of the dominant theories on AF pathogenesis include electrical and structural remodeling and inflammation. In addition, common and rare genetic variants modulating cardiac development, altering ion channel function and promoting atrial fibrosis are considered to play an important role in both acquired and lone AF.[14] An improved understanding of the pathophysiology of AF is critical as it is a complex and highly heterogeneous disease. While our current armamentarium of treatments for this disorder has recently expanded, it is still limited by a lack of efficacy, concerns about adverse effects, and, by a rudimentary process for selecting specific strategies for individual patients. The overarching goal of studying AF should be to improve treatment. Improving our understanding of AF by examining different pathophysiological pathways that contribute to the final phenotype holds the promise of a mechanism-based, individualized approach to treatment. Here, we review the substrate, development, and progression of AF, based on different pathophysiological pathways, explore how these pathways converge to promote AF, and highlight how these data can be used to optimize treatment strategies.

CARDIAC DEVELOPMENTAL PATHWAYS

Normal cardiac development during embryogenesis plays an essential role in the development of AF later in life. Recent positional cloning, candidate gene, and genome-wide association studies have identified common and rare variants in genes important in cardiac development. Here, we will discuss these in some detail.

Genome-wide association studies

In 2007, a genome-wide association study (GWAS) identified and replicated two common AF susceptibility SNPs on chromosome 4q25 in Caucasians of European descent.[15] While these SNPs are intragenic, the closest gene is the paired-like homeodomain transcription factor 2 (*PITX2*) that is critical not only for cardiac formation but also for pulmonary vein development. *PITX2* is involved in left-right signaling during embryogenesis; loss of function of *PITX2* results in severe cardiac malformations including right cardiac isomerism, double-outlet right ventricle, malformation of the great vessels and paired sino-atrial node formation.[16] In electrically-stimulated adult mice with structurally normal hearts, *PITX2* haploinsufficiency has demonstrated predisposition to AF.[17] In atrial biopsy studies, *PITX2* expression is severely diminished in AF patients compared to those with no history of AF.[18] *PITX2c* isoform deficiency in mice can result in right atrial isomerization, loss of suppression of a sinus node development default pathway in the left atrium and loss of the pulmonary myocardium, predisposing to AF.[17,19,20]

A recent meta-analysis of AF GWAS identified a novel locus on chromosome *1q24* that associated with AF.[21] The closest gene to this locus, *PRRX1*, encodes paired-related homeobox gene 1, a transcription factor that is important for normal cardiac development. Defects in *PRRX1* and *PRRX2* cause abnormal development of the great vessels and pulmonary vasculature.[22,23] Since the pulmonary vein myocardial sleeve is a target during AF ablation,[17,24] modulation of AF pulmonary myocardial development may increase AF risk.

Positional cloning and linkage analysis

In 2004 an autosomal recessive inheritance of AF was reported in a large family from Uruguay.[25] The disease was severe with AF occurring at the fetal stage or during infancy with associated sudden cardiac death and ventricular arrhythmias. Linkage analysis mapped the locus to chromosome *5p13*(*arAF1*)[25] and a homozygous mutation (*R391H*) was identified subsequently in a nucleoporin gene (*NUP155*).[26] *NUP155* is a major component of the nuclear pore complex (NPC) within the nuclear envelope that facilitates the transport of DNA and mRNA from the nucleus to the cytoplasm.[27] Heterozygous deletions in *NUP155* in mice leads to spontaneous AF.[26] In vitro analysis showed that this mutation impaired nuclear permeability to *NUP155* gene products.[26] Recently, *NUP155* was shown to interact with histone deacetylase 4 (*HDAC4*) and the possibility that the phenotype may also be related to altered transcriptional activity should be considered.[28] However, the mechanistic link between the *NUP155* mutation and AF remains unclear. One postulated mechanism relates to a reduction in nucleocytoplasmic transport due to *NUP155* deficiency altering the expression of atrial genes and likely influencing maturation of cardiac ion channel proteins, which may modulate action potential duration (APD) and cause AF.[29] Further studies are required in order to define the underlying mechanisms by which *NUP155* mutations cause AF.

Mayo clinic investigators identified a novel mutation in the natriuretic peptide precursor-A (*NPPA*) gene on chromosome *1p36-p35*, which encodes atrial natriuretic peptide (ANP), in a large kindred with early-onset AF and atrial conduction disease in an autosomal dominant pattern of inheritance.[30] Furthermore a Chinese study has reported an association between lone AF and a common *NPPA* variant.[31] These findings however could not be replicated in Americans of European descent.[32] ANP plays a central physiological role in regulating vascular tone and blood volume and induces diuresis, natriuresis, and vasodilation by activating the intracellular second messenger cGMP.[33] In addition cardiac ion channels (sodium, potassium and calcium) are regulated by ANP through cGMP signaling.[34,35,36] ANP can promote AF either by shortening of the atrial action potential duration (APD) and effective refractory period (ERP),[37] or by autonomically-mediated shortening of the atrial monophasic action potential (MAP) duration and the ERP in dogs.[38] Therefore, it is hypothesized that *NPPA* mutation can lead to AF. However, the precise mechanism(s) by which NPPA mutations cause AF has not yet been fully delineated and studies in transgenic mouse models will provide further insights.

ION CHANNEL MODULATION PATHWAYS

Cardiac ion channels play an important role in cardiac function. Cardiac disease can alter ion channel trafficking, with adverse consequence to both the electrical and mechanical function of the heart.[39] Studies have identified various mutations in cardiac ion channel genes which may increase susceptibility to AF.

Linkage and candidate-gene studies

In 2003 a mutation in *KCNQ1* was identified in a Chinese kindred and linked to familial AF.[40] *KCNQ1* encodes for cardiac ion channel subunits involved in conduction of the delayed rectifier potassium current (I_{ks}) responsible for the terminal phase of the action potential plateau.[41,42] Gain-of-function mutation in *KCNQ1* likely results in prolongation of atrial APD and resultant refractoriness causing increased susceptibility to AF.[40] Similar effect is postulated with mutations in *KCNE2* which encodes for subunits of I_{ks} conducting ion channel and *KCNJ2* which encodes the strong inward rectifier K+ channel protein Kir2.1.[43,44] A gain-of-function mutation (*E299V*) in *KCNJ2* is responsible for increased susceptibility to atrial reentry and AF.[44]

A *KCNE5* mutation has been linked with non-familial or acquired forms of AF. *KCNE5* is expressed in both atria and ventricles.[45,46] Its gene product expressed in heterologous systems causes suppression of I_{ks} and is hypothesized to compete with the *KCNE1* β subunit for the *KCNQ1* α subunit resulting in its down regulation[47]; thus making *KCNE5* a possible AF candidate gene. Ravn et al. in 2008 reported AF association with *L65F* which involves substitution of phenylalanine for leucine at position 65 in the *KCNE5*.[48]

KCNA5 encodes for Kv1.5, a voltage gated potassium channel conducting ultra-rapid delayed rectifier potassium current I_{kur}, which is an atrial-specific repolarizing current that may play a role in AF pathogenesis.[29] Loss-of-function mutations in *KCNA5* have been identified in AF families,[49,50] which prolong the APD and trigger premature after depolarization in human atria, predisposing to

stress-provoked triggered activity and AF.[29] Our group discovered a rare *KCNA5* variant in an AF family with AF occurring at a young age. This variant is predicted to disturb a tyrosine kinase proline-rich motif important in regulating I_{Kur}. This mutation causes the channel to be resistant to kinase with reduction in the wild type current. Thereby, these changes might cause AP shortening for the development of AF.[51]

Another potassium channel gene important for atrial and ventricular repolarization is *KCNH2* which encodes for the rapid delayed rectifier current I_{kr}. Mutations in the *KCNH2* are associated with a higher incidence of AF.[52]

Rare non-synonymous variants in the β-subunits of cardiac sodium channels (SCN1B and SCN2B) have been found in AF patients.[53] These mutations occur in the extracellular domain, which regulate the sodium channel gating and cell surface expression.[54] Reduced sodium current resulting from mutations in *SCN1B* and *SCN2B* can generate AF –prone substrate through multiple mechanisms such as shortening of refractoriness and slowing of conduction.[53] Furthermore, loss-of-function mutations in the β-subunits can cause a Brugada-type AF.[53]

Cardiac L-type calcium channel mutations involving the α1- and β 2b-subunits have been linked to the Brugada syndrome and other inherited cardiac channelopathies.[55] *CACNA1C* gene on chromosome 12p13.3 forms the α1c subunit of the L-type calcium channel (Cav1.2) which is the binding site for all currently available calcium channel blockers[56,57] whereas *CACNB2* gene encodes the β-subunit Cav β2. Abnormal intracellular calcium handling may play a crucial role in AF initiation and continuation.[58,59] A higher rate of spontaneous sarcoplasmic reticulum calcium release is found in atrial myocytes of patients with chronic or paroxysmal AF, which is considered pro-arrhythmogenic.[60,61] About 20% to 30% cases of Brugada syndrome and short-QT syndrome are known to have associated AF.[62,63]

Genome-wide association studies

Multiple AF related loci affecting ion channels have been identified in recent GWASs. Some of the important associations include *PITX2*, *PRRX1*, *SCN5A*, *SCN10A*, *KCNN3* and *CAV-1*.[21] Both *PITX2* and *PRRX1* play a key role in pulmonary myocardial development.[19,23] Although the precise mechanism(s) by which these AF loci increase AF susceptibility is unclear, an up-regulation of *KCNQ1* results from PITX2 suppression in transgenic mice, in addition to differential expression and distribution of the inward-rectifier potassium I_{k1} current.[18,64,65,102] GWAS in individuals of European descent have identified a genomic region related to AF on chromosome 1q21 (*KCNN3*).[66] *KCNN3* gene encodes for small conductance voltage-independent calcium-activated potassium channels that are expressed in various excitable tissues including the brain[67] and the heart.[68,69] *KCNN3* channels are distributed in the atria and the ventricles and have a prominent role during the late phase of cardiac action potential.[68,69] Other members of the family expressed predominantly in the atria are *KCNN1* and *KCNN2*. Li et al. observed APD prolongation and an increased number of early after depolarization in the atrial myocytes of $KCNN2^{-/-}$ knockout mice. Atrial arrhythmias, mainly pacing-induced AF, were more frequent in both heterozygous and homozygous *KCNN2* mice.[70] Variation in either *KCNN2* or *KCNN3* may modulate ion-channel function, as in vitro both subunits exhibit co-assembly in channel complexes.[71]

Caveolin-1 gene (*CAV1*) on chromosome *7q31* encodes a signal transduction cell-membrane protein expressed selectively in the atria.[72] The *CAV1* protein by co-localizing, negatively regulates the activity of *KCNH2* protein, a potassium channel involved in cardiac repolarization that has been linked to AF.[52] Dilated cardiomyopathy has been reported in *CAV1* knockout mice.[73] Mutations in *HCN4*, on chromosome *15q24*, have shown association with dysfunction of the sinus node. *HCN4* encodes the potassium-sodium hyperpolarization-activated cyclic nucleotide-gated channel which constitutes the predominant sino-atrial node pacemaker channel.[74,75]

SCN5A and *SCN10A* cardiac sodium channel related genes are associated with AF. The voltage-gated sodium channel Nav1.5, involved in conduction of the inward sodium current I_{Na} responsible for initiating cardiac AP, is encoded for by *SCN5A*.[76,77] Screening for *SCN5A* variants in a large AF cohort found mutations in 5.9% of those with AF.[78] AF has been associated with loss-of-function mutations in *SCN5A*, in addition to dilated cardiomyopathy, sinus node dysfunction, and/or conduction disorder.[76] The H558R polymorphism in *SCN5A* has also been linked to incidence of AF.[79]

SCN10A encodes the Nav1.8 channel and has been associated with PR and QRS duration variability, atrioventricular and intraventricular conduction velocity.[80,81] The Nav1.8 channel is known to be expressed in the dorsal root ganglia[82,83] and the retina.[79] The functional characterization of Nav1.8 current in heterologous expression experiments indicate that the current activates much more slowly

than does Nav1.5 current, and this difference may in turn contribute to variable cell-to-cell charge transfer that underlies fast conduction in heart.[84]

INFLAMMATION AND ATRIAL FIBROSIS PATHWAYS

In 1997, Frustaci et al. reported myocarditis like histological changes in the atria of lone AF patients, supporting involvement of inflammation in the pathogenesis of AF.[85] The high incidence of AF after cardiac surgery and the role of anti-inflammatory drugs in preventing AF support the association of inflammation with AF.[86,87] Higher baseline levels of C-reactive protein (CRP), an acute-phase protein, have been linked to future development of AF, and patients with AF have been shown to have elevated levels of CRP.[88,89] It has also been postulated that an elevated CRP level may be an outcome of the underlying cardiac pathology rather than a marker of AF itself.[90] In conditions such as oxidative stress and ischemia, which promote apoptosis and energy depletion, CRP may initiate AF by disrupting the normal structure of cell membrane.[91]

Atrial fibrosis may play an important role in both initiation and maintenance of AF.[92,93] Induced atrial fibrosis in animal studies has shown a greater tendency for developing AF.[94,95,96] Atrial tissue specimens from patients with AF have been shown to have increased fibrosis.[97,98] Fibrosis may induce AF by premature or burst atrial pacing that in a normal heart will not lead to AF.[95,99] Severity of left atrial (LA) fibrosis correlates with favorable treatment outcomes in AF patients.[100,101]

There is substantial evidence suggesting the potential of multiple common AF-susceptibility variants to modulate atrial fibrosis. In addition, all these variants are likely to mediate their effect not only by regulating atrial conduction slowing, but also by modulating electrical remodeling that promote AF, such as shortening of the ERP.

Genome-wide association studies

PITX2 encodes a transcription factor critical for left-right patterning in the atria, suppression of sino-atrial node formation on the left, and development of the pulmonary myocardium during embryogenesis. Given its critical role in cardiac development, its dysfunction may be predicted to cause atrial structural remodeling. In addition, it has been shown that *PITX2* is expressed in adult human hearts, especially in the left atrium, suggesting that this transcription factor plays a physiological role beyond cardiac development.[102] Chinchilla et al. found that *PITX2c*$^{-/-}$ mutant mice had enlarged cardiac chambers, increased fibrosis seen on histological staining of the ventricles, and increased expression of collagen precursor genes in the atria.[18] In a separate study, *PITX2c*$^{+/-}$ mice were found to have structurally normal hearts, however differential expression of genes involved in Wnt signaling (a key fibrosis signaling pathway) was demonstrated in microarray analysis.[102]

Another locus associated with AF in a recent meta-analysis of AF GWAS was at 7q31 in *CAV1*. This gene encodes a cellular membrane protein caveolin-1, which is expressed in the atria. *CAV1* is associated with myocardial fibrosis, and its variants have been associated with pulmonary hypertension.[103] *CAV1* knockout mice display dilated cardiomyopathy.[73] Caveolin-1 associated lipid rafts internalize TGF-β receptors resulting in inhibition of TGF-β signaling.[104]

While the role of several other variants associated with AF in GWAS is unknown, a growing body of evidence implicates atrial fibrosis as a plausible link between these genes and AF. The transcription factor zinc finger homeobox 3 (encoded by *ZFHX3*) is a tumor-suppressor gene that by associating with runt-related transcription factor 3 (*RUNX3*) translocates in response to an important fibrosis mediator, TGF-β.[105,106] *SYNPO2L* knock-down in zebra fish resulted in abnormal skeletal and cardiac muscle development and function. The gene encodes an actin-binding protein which is a component of the cytoskeleton and is expressed in the heart.[107] Nesprin-2, encoded by *SYNE2*, in combination with nesprin-1, creates a network that links the actin cytoskeleton and nuclear membrane structures to the nucleoskeleton in muscle. Alpha-catenin's interaction with emerin and nesprin-2 regulates the Wnt signaling-dependent transcription, which is a fibrosis related pathway in the heart, lung and kidney.[108,109] The homeodomain transcription factor encoded by *PRRX1* is expressed in the developing heart, especially the connective tissue. It is involved in normal pulmonary development and is linked to fibrosis in the lungs and liver.[110,111] A higher expression of C9ORF3 is shown in TGF-β stimulated normal and scleroderma fibroblasts.[112]

Linkage analyses

A possible pathophysiological mechanism of *NPPA* variants in AF may involve exposure to higher levels of mutant ANP causing structural changes promoting atrial fibrosis.[30] In fact, a missense mutation in *NPPA* was recently identified in four families in Northeast Italy with the clinical phenotype of atrial myopathy, massive biatrial enlargement, and atrial standstill.[113]

INTERTWINING OF PATHWAYS

Emerging evidence suggests that development of AF might be predicated on the interaction between clinical and genetic factors. In this proposed 'two hit' or 'multiple hit' paradigm [Figure 1], deleterious changes in confluent pathways might predispose patients to develop this complex clinical disorder. We previously studied 11 AF families in which we found 42 mutations in AF candidate genes. When affected individuals were also genotyped for *4q25* SNPs, a striking interaction between candidate gene mutations and *4q25* variants emerged. Zero out of 13 patients who had the wild-type *4q25* allele developed AF prior to the age of 50, whereas 21 of 29 who had *4q25* variant alleles developed AF before age 50 ($P = 1.12 \times 10^{-5}$).[114]

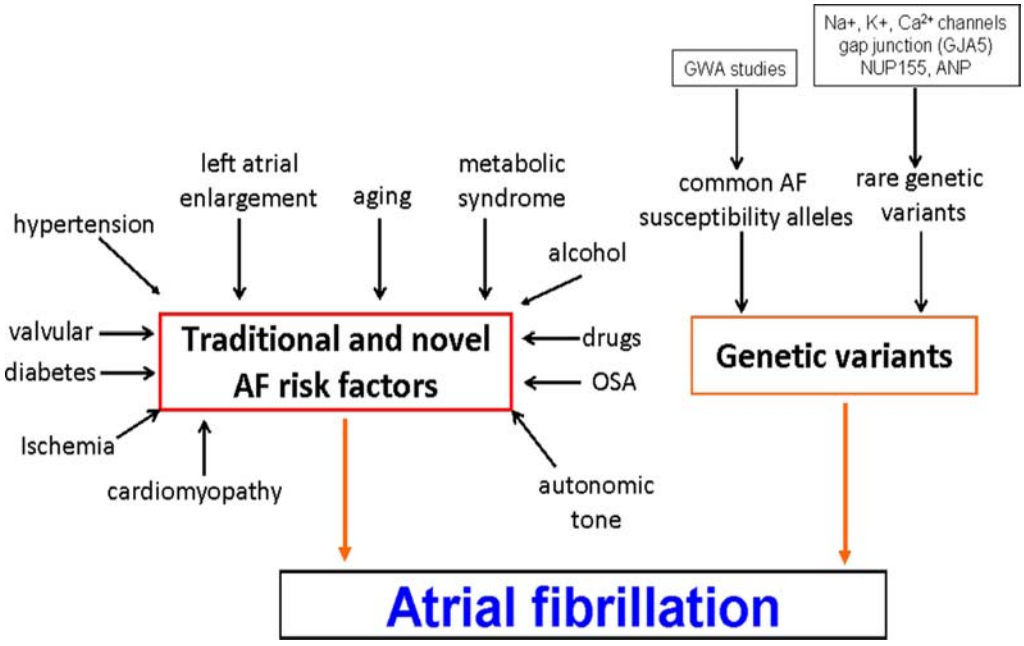

Figure 1. 'Double hit' hypothesis proposes that a combination of genetic and acquired risk factors predispose to the development of atrial fibrillation.

A frameshift mutation in *NPPA* was previously linked to familial AF. Functional characterization revealed that the mutant ANP was associated with shortened APD and ERP, suggesting that ion channel modulation was the pathophysiological link with AF. In addition, several studies have implicated *NPPA* mutations in cardiac structural changes. *NPPA* knock-out mice were found to develop left ventricular hypertrophy (LVH), even when fed a normal diet.[115] A separate mouse study found that *NPPA* knock-out mice developed LVH and had a several-fold increase in heart interstitial collagen volume compared with wild-type littermates.[116] In humans, as discussed above, a missense mutation in *NPPA* was linked to a familial syndrome of atrial standstill and extreme biatrial enlargement, a striking example of an atrial myopathy with relative sparing of the ventricles.[113] Thus, genetic variants in *NPPA* may affect all three pathways that can potentially lead to the clinical phenotype of AF: ion channel modulation as evidenced by changes in APD and ERP, cardiac development as *NPPA* is part of the signaling pathway for PITX2 and atrial fibrosis [Figure 2a].

Variants in *CAV1* were associated with AF in GWAS. The gene encodes a membrane protein thought to play a role in cardiac structural changes and fibrosis. A frameshift mutation in *CAV1* was found in affected members of a large family with primary pulmonary hypertension.[103] Furthermore, *CAV1*

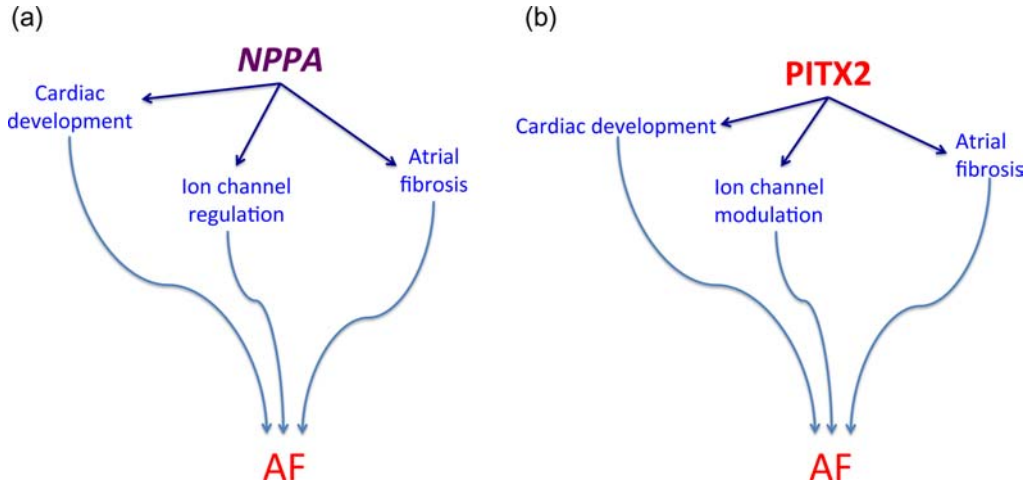

Figure 2. (a) Variants in *NPPA* are postulated to modulate ion channel function, cardiac development and atrial fibrosis supporting the idea that the convergence of multiple pathways is important in the pathogenesis of the AF. (b) Cardiac development, electrical remodeling and atrial fibrosis are important contributors to AF development that are mediated by PITX2. This further supports the heterogeneity of AF pathogenesis.

knockout mice display dilated cardiomyopathy.[73] However, *CAV1* is also thought to play a role in cardiac electrophysiology. *CAV1* SNPs have been associated with longer PR interval (a known AF risk factor) in GWAS. Interestingly, *CAV1* was shown to co-localize with *KCNH2*, the channel encoded by *HERG* (also called *KCNH2)* which is responsible for the I_{kr} current. A *CAV1* knock-down model resulted in decreased I_{kr} current, whereas overexpression of *CAV1* resulted in increased current.[117] *KCNH2* is itself a gene associated with AF in GWAS.[21] Therefore, *CAV1* seems to play a dual role in the pathophysiology of AF, by modulating cardiac fibrosis and ion channel function.

PITX2, a homeobox transcription factor, has been associated with AF[15] and has a complex role in cardiac development most importantly left-right signaling during embryogenesis.[16] Experiments in mice models with *PITX2c* deletions have revealed atrial enlargement, increased atrial expression of collagen precursor genes and increased fibrosis.[18,102] Electrophysiological findings in similar mice models with *PITX2c* deletions included complete AV block, AF, a more depolarized atrial resting membrane potential, and a lower amplitude atrial action potential. In addition decreased atrial expression of *SCN5A*, *SCN1B*, *KCNJ2*, *KCNJ4*, and *KCNJ12*, was observed as compared to control mice.[102] Thus, *PITX2* seemingly plays a vital role in AF pathophysiology with contributions to cardiac development, electrical remodeling, and atrial fibrosis [Figure 2b].

IMPLICATIONS FOR TREATMENT OF AF

Recent advances in catheter ablation, hybrid surgical and catheter ablation, and new oral anticoagulants have improved treatment options for patients with AF. However, there is much room for improvement especially in selecting individualized treatment strategies for patients that will maximize efficacy and minimize risks. For example, an evidence-based strategy to select patients for treatment with rate control therapy, AADs, and invasive treatment does not exist and is sorely needed. Improved understanding of the genetic mechanisms that underlie AF in individual patients should lead to personalized strategies to maximize efficacy and minimize adverse events. The I_{kr} blockers sotalol and dofetilide maintain sinus rhythm by prolonging repolarization and increasing refractoriness, thus abolishing the excitable gap necessary for arrhythmia propagation. These agents may be particularly effective in maintaining sinus rhythm in AF patients who harbor potassium channel gene variants. Conversely, sodium channel-blockers such as flecainide and sotalol, which abolish reentry by slowing conduction, might cause ventricular pro-arrhythmias in AF patients with loss-of-function sodium channel variants. These important considerations have not been tested in human pharmacogenomic studies.

Many patients with AF are treated with AV nodal blockers to prevent tachycardia and its associated complications. Mounting recent evidence from pharmacogenomic studies suggests that these agents, particularly beta-blockers, are less effective in patients with variants in the beta-adrenergic signaling

pathway. Several studies have shown that common SNPs in the beta-adrenergic receptor genes *ADRB1* and *ADRA2C* modulate the response to beta-blocker therapy in HTN[118,119,120] and HF.[120,121,122] We tested whether the polymorphisms in the *ADRB1* gene are associated with response to rate control therapy in 543 patients in the Vanderbilt AF registry. The *Arg389Gly* variant showed association with adequate rate control (adjusted OR 1.42) as defined by the AFFIRM criteria.[123]

Several recent studies highlight the challenges of pharmacological and catheter-based rhythm control strategies in AF patients with *4q25* (*PITX2*) variants. Our group showed that AF patients with the wild-type allele at the *4q25* SNP rs10033464 were significantly more likely to respond to Class I and III AADs as compared with carriers of the variant allele (OR 4.7, $P = 0.001$).[123] Husser et al. demonstrated that carriage of *4q25* variants was associated with post-catheter ablation recurrence of AF.[124] In the Vanderbilt AF registry, *4q25* variants were associated with unfavorable outcomes after catheter ablation, with shorter time to recurrence of atrial arrhythmias (survival time ratio 0.76) that was especially evident for patients with left atrial diameter >5 cm.[125] A similar outcome was shown after patients underwent DC-cardioversion.[126] Collectively, these findings highlight the importance of the *4q25* variants in creating an atrial pro-arrhythmic substrate due to deleterious electrical and structural remodeling, with subsequently difficult-to-treat sub-type of AF.

CONCLUSIONS

Data from linkage analyses in AF families, candidate gene and GWA approaches and animal models, have provided important insights into the underlying pathophysiology of this complex and heterogeneous disorder. Despite these advances however, AF persists as a common and the most challenging arrhythmia to treat in clinical practice. Here, we proposed viewing AF through the lens of biological pathways important in the pathogenesis of the arrhythmia. This perspective will not only improve our understanding of disease onset and progression, but inform us on how to best individualize therapy to maximize efficacy and minimize adverse effects.

COMPETING INTEREST

None of the authors have any competing interests to declare.

AUTHOR'S CONTRIBUTION

Muhammad A.Balouch, M.D.
Mathew J. Kolek, M.D.
Dawood Darbar, M.D.

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