

Gene regulatory networks in atrial fibrillation

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Abstract

Atrial fibrillation (AF) is the most frequent arrhythmogenic syndrome in humans. With an estimate incidence of 1%-2% in the general population, AF raises up to almost

10%-12% in 80+ years. Thus, AF represents nowadays a highly prevalent medical problem generating a large economic burden. At the electrophysiological level, distinct mechanisms have been elucidated. Yet, despite its prevalence, the genetic and molecular culprits of this pandemic cardiac electrophysiological abnormality have remained largely obscure. Molecular genetics of AF familial cases have demonstrated that single nucleotide mutations in distinct genes encoding for ion channels underlie the onset of AF, albeit such alterations only explain a minor subset of patients with AF. In recent years, analyses by means of genome-wide association studies have unraveled a more complex picture of the etiology of AF, pointing out to distinct cardiac-enriched transcription factors, as well as to other regulatory genes. Furthermore a new layer of regulatory mechanisms have emerged, *i.e.*, post-transcriptional regulation mediated by non-coding RNA, which have been demonstrated to exert pivotal roles in cardiac electrophysiology. In this manuscript, we aim to provide a comprehensive review of the genetic regulatory networks that if impaired exert electrophysiological abnormalities that contribute to the onset, and subsequently, on self-perpetuation of AF.

Key words: Atrial fibrillation; Genetics; MicroRNAs; Genome-wide association studies; PITX2

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Core tip: Atrial fibrillation (AF) is the most prevalent arrhythmogenic defect in the human population. Genetic factors such as mutations in distinct ion channel encoding genes have been described, yet representing less than 10% of all AF cases. Genome wide association studies have widened the genetic culprits contributing to AF. We provide herein a state-of-the art review on the genetic components underlying AF. Experimental evidences demonstrated that PITX2 plays a pivotal role regulating cellular, molecular and electrophysiological characteristics of the developing and adult heart that, if impaired, predispose to AF, leading to complex regulatory networks with transcriptional and post-transcriptional (microRNA)

regulatory mechanisms.

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BACKGROUND

Atrial fibrillation (AF) is the most frequent arrhythmogenic syndrome in humans. With an estimate incidence of 1%-2% in the general population, AF raises up to almost 10%-12% in 80+ years^[1-5]. Cardiovascular risk factors such diabetes, obesity, hypertension and hyperthyroidism promote AF^[6-9]. In addition, the occurrence of AF can be also triggered by preceding cardiovascular diseases such as hypertrophic cardiomyopathy and valvular heart diseases^[10,11] as well as it can be boosted by cardiac surgery, obstructive sleep apnea and inflammatory processes^[12-15]. Importantly, besides the global risk factors for AF, it is well-established that the debut of an AF episode triggers subsequent and more severe AF episodes, leading to electrical and structural remodeling of the diseased heart, a condition quoted as "AF begets AF"^[16,17]. Thus AF *per se* is a progressive disease. Electrical remodeling involves progressive changes in the cardiac electrical properties, possibly triggered by oxidative stress imbalance, leading to EADs, DADs and/or changes in the ADP configuration^[18,19], culminating thus in rotor formation^[20] (Figure 1). Structural remodeling involves atrial dilation, fibrosis and/or inflammation^[21,22] which then indirectly promotes the generation of rotors and thus electrical re-entry circuitries^[20] (Figure 1). Moreover, suffering from AF predisposes to additional health problems, ranging from bleeding and stroke^[23-25], cognitive decline and dementia^[26,27], ventricular dysfunction^[28,29] and even sudden death^[30] (Figure 1). Thus, these data support the notion that AF is an epidemic disease with large socio-economic burden worldwide.

While large epidemiological data support the previously mentioned predictive risk factors for AF, there are also unquestionable evidences that in a subset of AF patients no concurrent previous risk factors are diagnosed and thus AF occurs in an isolated manner, a condition dubbed lone AF^[31-34]. These observations, in addition to seminal observations supporting that AF can also be familial^[35], strengthen the notion of a genetic component on the onset of AF. In this context, two waves of genetic information have been gained over the last decades. Seminal studies on familial AF cases followed by genetic linkage analyses, and subsequently by genetic screening of candidate genes identified a large number of point mutations in distinct genes encoding for proteins involved in cardiac electrophysiology^[36-38]. These data, along with meticulous electrophysiological mapping analyses and *in silico* data modeling, provided an important cornerstone to understand AF pathophysiology^[39-43].

However, genetic identification of candidate AF genes can only explained around 10%-15% of all AF patients. Thus, new approaches to untangle the genetic bases of AF were envisioned. Genome-wide association analyses (GWAS) lightened the discovery of new genes associated to AF. Seminal worked by Gubbjartsson *et al.*^[44] firstly identify common risk variants highly associated to the onset of lone AF in distinct large European and Chinese patient cohorts. Subsequent GWAS studies and meta-GWAS have further identified new candidate genes for AF pathophysiology^[45-49], yet the functional link between these variants and the AF pathophysiology is a rather unexplored. A tortuous route to dissect their functional roles is envisioned, given that most of these risk variants are located rather apart from gene coding sequences. Thus, a first proposal based on these findings is that risk variants might affect gene regulatory networks within the vicinity and thus underscore AF onset. In addition, a novel layer of complexity in gene regulatory networks has emerged with the discovery of non-coding RNAs that can mediate post-transcriptional regulation. In this review, we aim to elaborate on the current state-of-the-art of the gene regulatory networks involved in AF pathophysiology.

CONTRIBUTION OF THE IMPAIRED CARDIAC ACTION POTENTIAL TO THE AF PATHOPHYSIOLOGY

The cardiac action potential is driven by inward and outward flow of distinct ion currents along the cardiomyocyte membrane. In atrial and ventricular cardiomyocytes, the configuration of the action potential is initiated by the upstroke depolarization of the sodium current, followed by a repolarization mediated by distinct potassium currents until the resting membrane potential is restored. A conduction-contraction coupling is modulated within each action potential by a complex regulatory network of calcium handling^[50]. Interestingly, nodal conductive cells display a distinct upstroke configuration which is modulated by cation selective currents, yet repolarization is rather similar to working cardiomyocytes. A large number of mutations in the *SCN5A* gene, coding for the pore-forming subunits of the I_{Na} current, have been associated to AF, alone^[51-56] or in combination to other concurrent cardiac pathologies^[57-62]. Similarly, mutations in *SCN1B*, *SCN2B*, *SCN3B* and *SCN4B* ancillary subunits, respectively, have also been linked to AF^[63-67]. At present, the functional interpretation of these findings suggest that impaired I_{Na} current can promote AF onset, yet electrophysiological evidences are only available for a subset of these mutations. Importantly, mutations in *SCN5A* are also linked to other cardiac arrhythmias such as long QT and Brugada^[68-70] demonstrating a pivotal role for *SCN5A* on cardiac electrophysiology and illustrating that distinct phenotype might be acquired depending on subtles differences on the mutation location as well as on plausible modulatory accompanying proteins. In addition, mutations in the *HCN4* cation channel, responsible for the cardiac

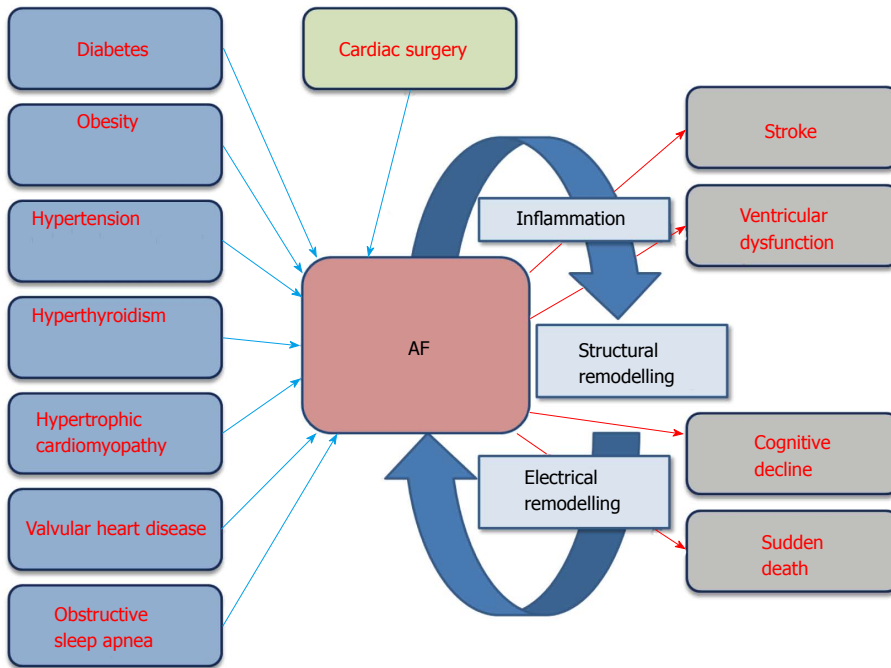


Figure 1 Schematic representation of the clinically relevant risk factors influencing the onset of atrial fibrillation. Atrial fibrillation (AF) leads thereafter to distinct cellular and molecular remodeling events, including structural and electrical remodeling, in part as caused by inflammatory process. In addition, progression of AF is highly associated with the onset of additional cardiac pathophysiologies.

action potential upstroke of conductive cells, have also been reported in AF^[71].

Mutations in genes encoding for proteins controlling the repolarization phase of the cardiac action potential have also been associated to AF. In particular, *KCNQ1*^[36,72-79], *KCNAS*^[80] and *KCNE2*^[38,81] mutations have been identified. In this setting, point mutations seem to shorten the repolarization phase providing an electrophysiological substrate for AF onset. Similarly, alteration of the resting membrane potential have been related to trigger AF onset and a large number of mutations in the gene coding for *KCNJ2* have been reported^[37,38,82,83]. Similarly as for the sodium channels, mutation in potassium channels have been associated to AF and concomitantly with other arrhythmogenic syndromes such as long^[72] and short^[84] QT, respectively.

Multiple lines of evidences have demonstrated the essential role of impaired calcium homeostasis as a triggering factor of AF^[2,85-90]. In this context, mutations in *RYR2* are associated to AF^[91] and in conjunction with other cardiac pathophysiological conditions such as catecholaminergic polymorphic ventricular tachycardia^[92,93]. Curiously, *RYR2* mutations can also affect sodium channel expression^[94]. Importantly, murine model of *RYR2* mutation leads to AF, reinforcing the genetic evidences of impaired calcium homeostasis as a trigger of AF^[95].

In addition, mutations in gap junction proteins such as *GJA1* (connexin43)^[96,97] and *GJA5* (connexin40)^[98-104], which are critical for the coordinated transmission of the electrical impulse among cardiomyocytes, have also been identified in association to AF. Seminal work described that mutation in connexin proteins were occurring in somatic cells (*i.e.*, cardiomyocytes)^[98], whereas more recently germline mutations have also been identified^[98-104] and the concept of somatic cell mutation challenged^[105]. In this setting, electrophysiological analyses of connexin

mutations in the AF context demonstrated that cardiomyocyte electrical transmission is impaired^[106-111] and thus can result in cardiac re-entry circuitries and then on AF.

Furthermore, mutations in several other genes, besides those directly contributing to the electrophysiological properties of the heart, have also been identified in the AF setting. In particular, mutations in the transcription factors *TBX5*^[112], *NKX2.5*^[113-117] and *NKX2.6*^[118] as well as in the nuclear pore component *NUP155*^[119] and the atrial natriuretic factor (*ANP*)^[120]. A summary of gene mutations associated to AF is provided on Figure 2. It is important to highlight in this context that mutation in *NUP155* was found in patients with AF and early sudden death^[118], while *TBX5* and *NKX2.5* are developmental transcription factors that play determinant roles during cardiogenesis and mutations in these genes have also been reported in distinct congenital heart diseases as well as GWAS candidate genes in other cardiac electrophysiological defects^[121-128].

NOVEL GENES LINKED TO AF

As previously said, classical genetic approaches provided an entry site to discover discrete genes involved in AF pathophysiology, but felt short to explain most of the diagnosed AF cases. Genome-wide association studies (GWAS) introduced a revolutionary genetic approach to understand AF, and cardiac arrhythmias at large^[129,130]. Seminal work by Gudbjartsson *et al.*^[44] identified risk variant at 4q25 highly associated to lone AF. Soon thereafter these observations were corroborated in distinct studies worldwide^[131-136], yet with some controversial findings^[137,138]. Surprisingly, 4q25 risk variants are located in a gene desert, being the closest annotated gene a homeobox transcription factor, *PITX2*, around 150 kb downstream. Soon thereafter, experimental observations provided

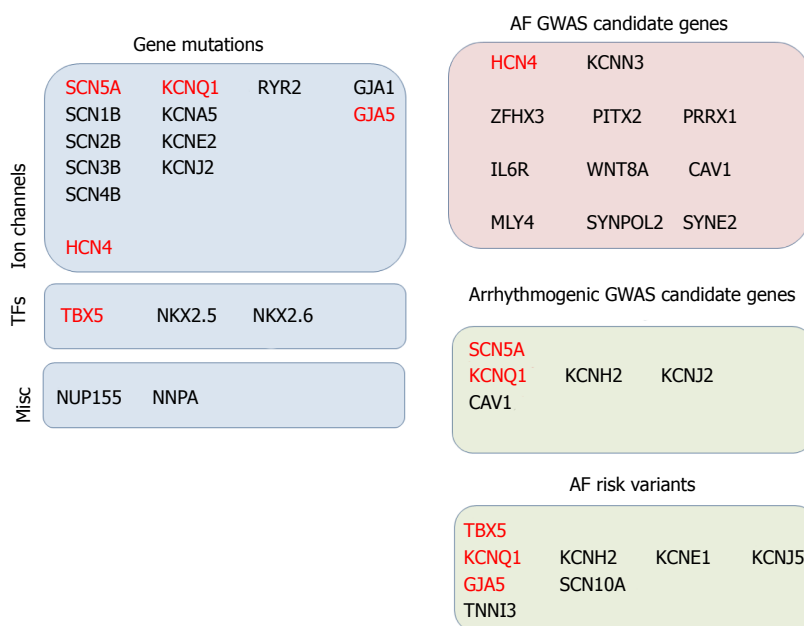


Figure 2 Schematic representation genes associated to atrial fibrillation. On the one hand, gene mutations associated to atrial fibrillation (AF) are illustrated. On the other hand, genes associated to AF by means of GWAS are also illustrated. In the latter, three subset of genes are provided: (1) those directly linked to AF GWAS analyses; (2) those related to AF, but identified in arrhythmogenic syndromes GWAS analyses; and (3) risk variants association studies in small AF cohorts by a candidate approach strategy. Genes highlighted in bold represent those genes identified in AF by multiple approaches. GWAS: Genome-wide association analyses.

evidences that impaired *Pitx2* function in animal models triggered increase atrial arrhythmias susceptibility^[139,140]. However, how risk variants can influence *PITX2* expression and/or function have only been partially revealed^[141], since regulatory elements containing the risk variants can molecularly interact with *PITX2* but also *ENPEP* promoter elements in a tissue- and developmental-specific manner^[141]. Importantly, controversial findings in humans have been reported. Chinchilla *et al.*^[136] firstly described decreased *PITX2* expression in AF patients, yet these claims were challenged since no correlation between risk variants and *PITX2C* expression was observed^[142]. However, more recently a correlation with *PITX2A* expression has been reported, limiting their functional significance since data were obtained from right atrial biopsies^[143]. Thus, further investigations are required to clarify these controversial findings.

Besides *PITX2*, additional GWAS have enlightened the putative role of other novel genes in AF pathophysiology, such as *KCNN3*^[47], *ZFH3*^[45,48], *IL6R*^[49] and *MLY4*^[144]. In most cases, these findings have been corroborated in independent studies with distinct ethnicity cohorts as for *ZFH3*^[145,146], and *IL6R*^[147], but to date no additional reports are available for *KCNN3* and *MYL4*.

While arguments for the plausible involvement in AF have been provided in all cases, experimental evidences remain largely missing. *KCNN3* loss-of-function mutant mice display no overt cardiac electrophysiological defects, yet overexpression leads to sudden death^[148]. Similarly *ZFH3* function role in the heart is scarce, yet recent findings suggests that atrial arrhythmias^[149] and pacing^[150] leads to significant impaired *ZFH3* expression. Importantly, risk variants associated to *KCNN3*, *ZFH3* and *IL6R* lie within intronic regions, respectively, and thus have no predictive functional consequences. Therefore, as in the cases of 4q25 risk variants (*PITX2*), a functional role on plausible regulatory elements is hypothesized,

but functional evidences are yet missing.

In addition to these GWAS studies, at least two meta-GWAS studies have digged for additional risk variants associated to AF^[46,151]. In this context, six new loci have been uncovered using such approach; *CAV1*, *HCN4*, *SYNE2*, *SYNPOL2*, *PRRX1* and *WTN8A*. Replication analyses of the risk variants have been confirmed for *SYNE2*^[152] and *PRRX1*^[149], are controversial for *CAV1*^[53,153,154] or have not been reported to date for *HCN4* and *SYNPOL2*. Importantly, a 12-SNPs risk score have been developed that can individually identify the risk of AF and stroke^[155].

While this approach broadens the plausible genetic bases of AF, it is also true that their contribution to explain AF pathophysiology would be directed linked to the statistical significance associated with those findings. It is important to say in this context that risk variants associated to *PITX2* display highest significance values, *KCNN3*, *ZFH3* and *IL6R* are moderately significant and those revealed by meta-GWAS display the lowest, yet statistical significant, values. In a simplistic way, this could be transferred as *PITX2* being contributing to larger spectrum of AF pathophysiology and thus being in the upper level of a hierarchical signaling pathway while *CAV1*, *HCN4*, *SYNE2*, *SYNPOL2*, *PRRX1* and *WTN8A* will be rather discretely contributing to AF pathophysiology in a rather discrete, small subset of AF patients, and therefore being at the bottom of such hierarchy. We have recently provided experimental evidences supporting this notion, as detailed below.

GWAS studies have also been reported in other electrophysiological parameters such as PR interval^[129,156-158], heart rate^[157], QRS interval^[157] as well as physiopathological conditions such as Brugada syndrome^[159] and long QT^[160-162]. Several of these cardiac arrhythmogenic conditions are sometimes directly associated to AF, such as for example impaired PR interval or Brugada syndrome. Importantly,

such GWAS studies have identified multiple genes, some of which are shared with AF, such as *CAV1* (PR interval^[129,156-158]) while other have been previously involved in AF pathophysiology, such as *KCNQ1*, *KCNH2*, *SCN5A*, *KCNJ2* (long QT GWAS analyses^[160-162]). In addition to GWAS studies, risk variants have been associated to AF using more discrete/small AF patient cohorts. Among them it is important to highlight risk variants at the following loci; *KCNQ1*^[163-165], *KCNH2*^[163], *KCNE1*^[163], *KCNJ5*^[166], *GJA5*^[167] and *TBX5*^[168]. In addition to these GWAS studies, several independent AF cohort studies have reported risk variants associated to AF in other loci, such as *TNNI3*^[169] and *SCN10A*^[170,171], yet the functional relevance of these findings remains unsolved. These data suggest that complex and intricate gene networks are likely to be operative between these regulatory genes resulting in AF (Figure 3) as well as other electrophysiological associated disorders.

A NOVEL AND EMERGING LAYER OF GENE REGULATORY CONTROL

Gene regulatory networks have been classically associated as hierarchical interactions between master genes, such as transcription factors, and structural genes, such as actin and myosin genes forming the sarcomere or genes encoding ion channels configuring therefore the cardiac action potential. In this setting, transcriptional regulation has been considered the master regulatory point, deciding whether to go or not to go, whereas translation and post-translational modifications are considered as minor regulatory nodes. Over the last decade, we have witnessed the discovery that large part of the so called "rubbish DNA" in fact codes for a large variety of non-coding RNAs species with highly relevant functional properties. In broad sense, non-coding RNAs can be sub-classified into long non-coding (lncRNAs) and small non-coding RNAs, exerting a distinct and variable functional roles^[172]. Among small non-coding RNAs, microRNAs have emerged as the larger group, playing a pivotal role on post-transcriptional regulation of mRNA transcript expression^[173]. MicroRNAs are 22-24 nt non-coding RNAs which can block translation or trigger transcript degradation by binding to complementary seed sequence in the 3'untranslated region (3'UTR) of nascent mRNA transcripts^[173]. At present the hallmark of microRNA transcriptomics has been uncovered in the developing and adult heart in both normal and pathological conditions^[174,175]. In the context of AF the microRNA fingerprint has been profiled in different settings^[176-178], providing highly valuable biomarkers^[179-183] as well as opening new avenues to dissect the functional role of these differentially expressed microRNAs in AF pathology. In addition distinct sets of microRNAs have also been reported to selectively modulate expression of distinct gene encoding for ion channels, opening thus new pathways to dissect their genetic contribution to AF.

AN INTEGRATIVE GENE REGULATORY NETWORK LINKED TO AF

As stated above, evidence on the functional role of multiple genes have been provided by the identification and experimental testing of AF patient gene mutations. In this setting, a causative link can, in most cases, be established. However, GWAS analyses provide circumstantial evidences whereas functional linkage between the risk variants and coding genes, whether protective or deleterious, is not directly established. To date, an example of successful linkage have been reported^[184] in the cardiovascular context, however in most cases, this is not yet established. Therefore, dissecting the functional role of GWAS candidate genes represents the first step for the analyses of their causative link.

Large set of evidences suggest that multiple genetic pathways can contribute to the onset of AF. Over the last years we have carefully dissected the role of the homeobox transcription factor *PITX2* in this context and we have made efforts to dissect the regulatory interaction of *PITX2* with those genes previously reported to play a role in AF pathophysiology. Several studies have demonstrated that *PITX2* can influence expression of distinct ion channels in the developing and adult hearts. Wang *et al.*^[138] firstly demonstrate that *PITX2* haploinsufficiency is sufficient to increase AF susceptibility. These authors demonstrated that *PITX2* haploinsufficiency led to developmental impaired expression of key transcription factors (*SHOX2*, *TBX3*) directing sinoatrial morphogenesis and thus impacting on the normal onset of the cardiac pacemaker structures. However, in this context, no basal AF occurs and no ECG defects were observed. In this line of thinking soon thereafter Kirchoff *et al.*^[139] demonstrate similar findings and furthermore reported that expression of multiple ion channels were impaired as well as cell-cell interacting proteins (Figure 3). However, none of these genes were reported to play a pivotal role on cardiac action potential and thus, molecular and electrophysiological links were still on its infancy. Using a distinct experimental approach, *i.e.*, an atrial-specific *PITX2* conditional transgenic mouse line, Chinchilla *et al.*^[135] revealed that ECG defects were observed at rest (no triggering needed), electrophysiological measurements were impaired, *i.e.*, increased resting membrane potential and prolonged action potential duration, and furthermore using a candidate approach analyses, distinct ion channels were also impaired, particularly *SCN5A* (I_{Na}), *KCNJ2* (I_{K1}) and *KCNH2* (I_{Kr}). Thus, these data demonstrate for the first time that functional impairment of *PITX2* leads to molecular defects which provoke electrophysiological alterations and thus increase rate of atrial arrhythmias. In line with these findings, Tao *et al.*^[185] using a *PITX2* deletion conditional approach in the adult heart also demonstrated that basal ECG defects were observed, similar to those already reported by Chinchilla *et al.*^[135], and moreover they

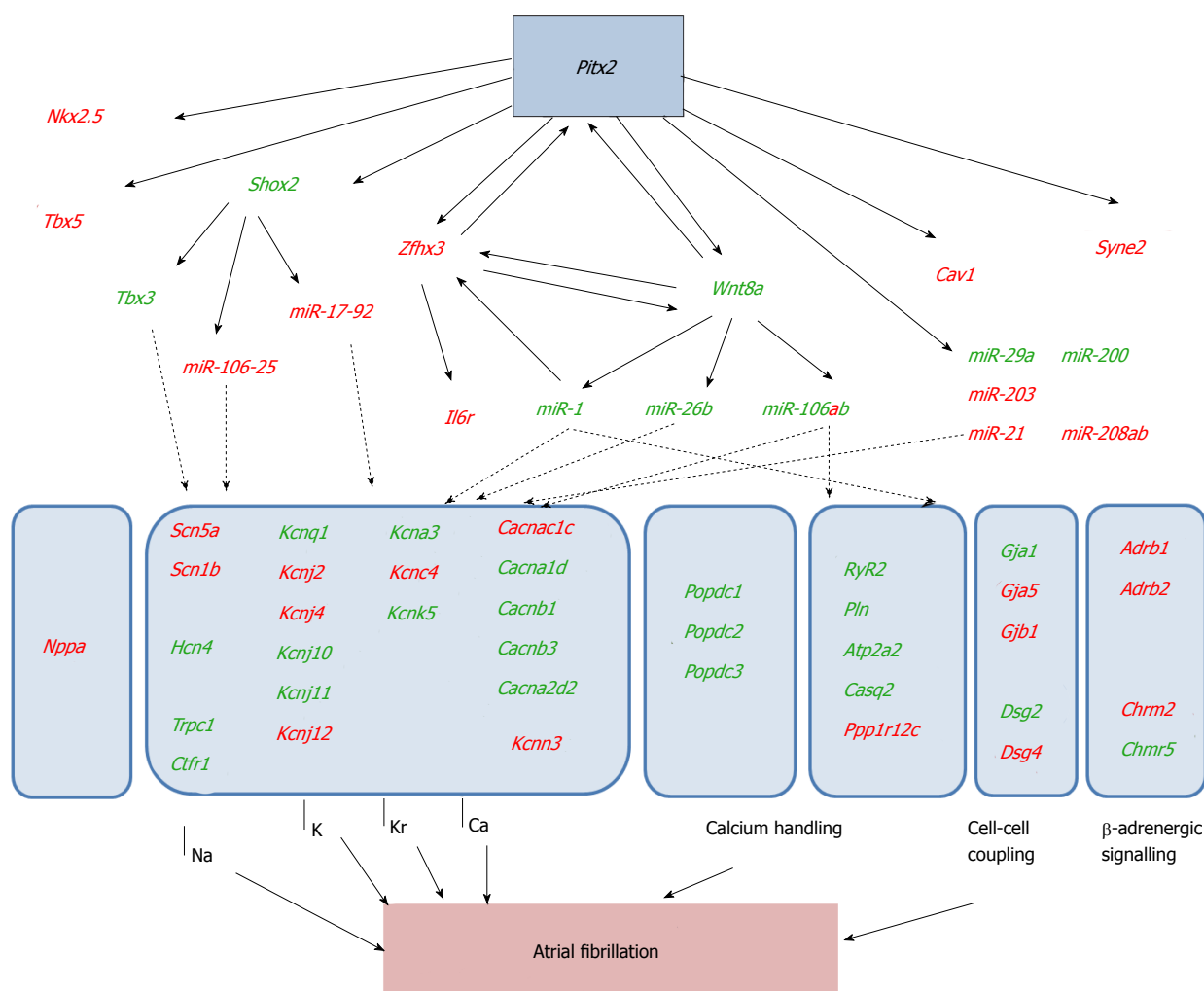


Figure 3 Schematic representation of the *Pitx2* downstream pathways involved in pro-arrhythmic events leading to atrial fibrillation. Multiple lines of evidences demonstrate that *PITX2* exerts a pivotal role regulating expression of distinct ion channels, cell-cell coupling, blood pressure controllers and beta-adrenergic stimulation. Most of these pathways are modulated by microRNAs which are under control of *PITX2* action. Red denotes down-regulation and green up-regulation.

demonstrated that key determinants of the cardiac action potential were impaired, such as *KCNQ1* (I_{Ks}), *KCNH2* (I_{Kr}), *CACNA1C* (I_{Ca}), among others. Overall these data demonstrated that *Pitx2* insufficiency can both promote and trigger molecular and electrophysiological alterations, namely affecting the depolarization, repolarization and resting membrane potential characteristics of the cardiac action potential. They also illustrate that alteration of a single transcription factor can influence the functional role of multiple ion channels previously reported to be associated to AF. Therefore it can be inferred that *PITX2* is upstream of this hierarchical signaling pathway and its impairment would explain a large fraction of AF patients.

In addition to *PITX2*, other GWAS studies have provided evidence on the plausible role of distinct gene in AF pathophysiology, yet as previously said, their functional implication has been poorly documented. We investigated whether these genes would be under control of *PITX2*. Using a series of gain and loss-of-function approaches, Lozano-Velasco *et al.*^[149] demonstrated that *PITX2* can modulate expression of *ZFH3*, *KCNN3* and *IL6R*. The

role of *ZFH3* in atrial arrhythmias is basically unexplored. However, given its transcriptional capacity it might be plausible that it can modulate multiple genes previously related to AF. The role of *KCNN3* in atrial arrhythmias is under debate, its plausible contribution to the configuration of the cardiac action potential, if any, seems to be residual. On the other hand, the involvement of *IL6R* could be related to inflammatory processes that, if impaired, are associated to AF as previously mentioned. We have noticed that *IL6R* expression in the atrial chambers is impaired in *PITX2* deficient mice yet plasma levels of soluble *IL6* and *TFN α* ligands are not altered. While these data support a tissue-specific involvement of *IL6R*, its links to AF remain to be elucidated.

We also investigated if *PITX2* can influence the role of those genes related to AF by meta-GWAS analyses. Among them, previous evidences support that *PITX2* can modulate expression of *Hcn4*^[138]. More recently, Lozano-Velasco *et al.*^[151] demonstrated that also *CAV1*, *SYNE2* and *WNT8A* are modulated by *PITX2*. It is important nonetheless to highlight that risk variants associated

to *CAV1* and *SYNE2* have also been reported in other cardiac electrophysiological disorders yet their functional role remains poorly characterized. Importantly, WNT signaling has been largely documented to play pivotal role during cardiac development and homeostasis^[186,187], however WNT8 has not been reported to play fundamental roles therein^[188].

Given the potential signaling properties of WNT8A and those transcriptional capacity exerted by *ZFH3* we explored in any of those pathways might be involved on the regulation of distinct ion channels previously reported to be modulated by *PITX2* and related to AF. Gain- and loss-of-function approaches demonstrated that *WNT8A* but not *ZFH3* can modulate expression of calcium handling proteins^[151]. Importantly, impaired expression of *WNT8A* is observed in *PITX2* insufficiency models with basal ECG alterations but not in those with normal ECG recordings^[151], supporting the notion that WNT signaling plays a fundamental role conferring susceptibility vs triggering capacity to the atrial chambers during AF onset.

In addition to gene regulatory mechanisms driven by *PITX2*, several lines of evidence support that *PITX2*-regulated microRNAs also contribute to AF pathophysiology. Chinchilla *et al.*^[135] already demonstrated that impaired miR-1 expression in *PITX2* deficient mice underlie abnormal resting membrane potential configuration (by modulating *KCNJ2* and *KCNJ12* post-transcriptional regulation). Huang *et al.*^[153] has confirmed that *PITX2* inhibits miR-1 expression, which negatively regulates *ZFH3*. Wang *et al.*^[189] demonstrated that two distinct genomic microRNA clusters, namely *miR-17-92* and *miR-106b-25*, as well as *miR-335* and *miR-423*, are under control of *PITX2*. Genetic deletion of *miR-17-92* and *miR-106b-25* microRNA clusters, respectively display normal baseline electrophysiological parameters but were susceptible to pacing-induced AF. Cardiac-specific deletion (Nkx2.5Cre) of *miR-17-92* cluster resulted in prolonged PR interval. Compound double mutant mice using conditional Nkx2.5Cre mediated deletion resulted in sinus node dysfunction, a condition reminiscent of sick sinus syndrome in humans. Molecular analyses revealed that *SHOX2* and *TBX3* expression were impaired. Furthermore, RYR2-mediated calcium-leak was reported in *miR-106b-25* deficient mice^[190] since several members of this cluster, namely miR-106b, miR-93 and miR-25 directly target the 3' UTR of Ryr2. More recently, Lozano-Velasco *et al.*^[149] demonstrate that a large number of microRNAs, previously reported to be associated to AF in patients, are also modulated by *PITX2*. In particular, *miR-1*, *miR-26b*, *miR-29a*, *miR-30e*, *miR-106b*, *miR-133* and *miR-200* were up-regulated in absence of *PITX2* whereas *miR-21*, *miR-106a*, *miR-203*, *miR-208a* and *miR-208b* were down-regulated. Several of these microRNAs, such as *miR-1*, *miR-133*, *miR-21*, *miR-106b* and *miR-26* have been previously reported to regulate calcium (*CACNA1C*^[191]; *RYR2*^[190]), sodium (*SCN5A*^[192]), potassium (*KCNJ2*^[193], *KCNE1*^[194], *KCNB2*^[194]), cation (*HCN4*^[195]) channel subunits, respectively. Overall, these

data demonstrate a highly complex gene regulatory networks leading to AF as summarized in Figure 3.

CONCLUSION

In this review we have highlighted the complexity of risk factors influencing the onset of AF, both clinically and genetically. Several lines of evidences demonstrated that *PITX2* exerts a pivotal role on the genetic determinants of AF^[136,139,140,149,185]. While it has been robustly demonstrated that *PITX2* insufficiency predisposes to atrial arrhythmia genesis in experimental mouse models^[136,139,140,149,185], discrepancies remain as whether *PITX2* is impaired in AF risk variants human patient carriers^[136,142,143]. Importantly some discrepancies also exist as whether predisposes or triggers AF^[136,139]. Our recent findings suggest the notion that *PITX2* insufficiency in the embryo predisposes whereas *PITX2* insufficiency in the adult atrial chamber triggers AF. In this context, we have provided evidences that such switching mechanisms seems to be regulated by WNT signaling and the downstream activation/repression of key microRNAs^[149,165], yet future experiments are needed to provide additional evidences on this front. In the last decade, our understanding of the downstream pathways controlled by *PITX2* has advanced at a quick pace. Several studies have demonstrated that *PITX2* controls signaling pathways regulation sinus node formation^[189,196], including therein the pivotal role of a microRNA cluster^[189,190]. These data shed light thus on the concurrence of AF with other cardiac physiopathological conditions such as sick sinus syndrome^[190]. Similarly we and others have demonstrated the key role exerted by *PITX2* regulating microRNAs impacting on calcium handling and thus on profibrillatory risk factors^[136,153,189]. It remains nonetheless to be established if *PITX2* also leads to impaired regulation of inflammatory processes and/or redox signaling which might impact on structural remodeling of the atrial chambers. To date, no evidences of atrial fibrosis have been reported in any of the *PITX2* deficient mouse models^[136,139,140,149,185], while some incipient evidences have been reported on the inflammatory link^[149] but not on redox signaling. Thus, future lines of research should be envisioned to clarify this point.

In addition, whereas our understanding of the *PITX2* downstream signaling pathways in the context of AF have progressively increased, scarce insights are currently available on the impact of AF clinically related risk factors on *PITX2*. A link between 4q25 risk variant carriers and increase left atrial volume has been recently reported^[197] in AF patients, however it remains to be established this is modulated by *PITX2*, as suggested by previous evidence in *PITX2* deficient mice in which atrial volume is already increased at fetal developmental stages^[136]. A recent study reported that aging and hypertension, two well-established risk factors for AF, severely decreased *PITX2* expression in a rat experimental model when both risk factors were combined^[198]. We recently reported that *Pitx2* is severely impaired in dilated cardiomyopathy patients as well as in an experimental heart failure pig model, shedding light

into a possible connection between ventricular dysfunction and AF^[199,200]. Yet, it remains to be established if other clinically relevant AF risk factors, such as diabetes, obesity, hyperthyroidism, valvular heart disease and/or obstructive sleep apnea are also impairing *PITX2* function and thus predisposing to AF. Overall these data demonstrate the pivotal role of *PITX2* regulating multiple aspect that if impaired are pro-arrhythmic and they also open new pathways to explore therapeutical approaches that could eventually lead to minimize the burden of AF in the human population.

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