Transcription factors and atrial fibrillation

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Atrial fibrillation (AF) is a prevalent cardiac arrhythmia with a significant genetic component. In recent years, familial and population-based genetic studies in AF have led to the emergence of transcription factors as potentially important contributors to arrhythmia susceptibility. Further evidence to implicate transcription factors in AF has come from studies in animal models, which demonstrate that these proteins play critical roles during AF-related atrial remodelling. Transcription factors have the potential to create a pro-arrhythmogenic substrate in the pulmonary veins and the atrium. However, further research is necessary to fully characterize the mechanistic links between these proteins and AF pathogenesis. In the future, such studies could potentially lead to the development of novel therapies for the arrhythmia. This review focuses on the association between transcription factors and AF.

Keywords
Transcription factors arrhythmias • Atrial fibrillation

1. Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and represents a major burden to healthcare systems. The prevalence of AF increases markedly with advancing age.1,2 AF is associated with multiple complications including dementia, heart failure, and stroke.3–8 AF is also associated with a significant increase in mortality.9 Over the past decade, we have come to appreciate that AF is a heritable disease. A report from the Framingham Heart Study in 2003 demonstrated that one-third of AF patients have a first-degree relative with the arrhythmia.10 Ellinor et al.11 reported that 38% of subjects with lone AF have at least one relative with the arrhythmia. A subsequent study from Iceland also demonstrated similar findings.12 Finally, in a recent large Danish study, Øyen et al.13 provided further corroborating evidence regarding familial aggregation of lone AF.

The identification of the genetic substrate underlying AF is likely to provide valuable insights into the molecular basis of the arrhythmia. The genetic variants underlying AF reported to date fall into two ends of a spectrum. At one extreme, rare and highly penetrant mutations have been identified in familial forms of AF, while at the other, common variants with small effect sizes have been identified in population-based genetic studies. Monogenic mutations in AF families have been discovered using conventional methods of gene discovery, such as linkage analysis and candidate-gene screening.14 On the other hand, common genetic variants underlying AF in the general population have been discovered using genome-wide association studies (GWASs).15–18 Transcription factors are emerging as important contributors to AF susceptibility, both in familial forms of AF and AF in the general population.

Transcription factors bind to specific DNA sequences in the promoter regions of genes and regulate gene expression.19,20 The human genome encodes more than 500 transcription factors, some of which are ubiquitous while others are tissue-specific.21 Cardiac-specific transcription factors are involved in the regulation of cardiac development and morphogenesis. These proteins play critical roles in regulating the expression of genes involved in cardiac septation, chamber formation, valvulogenesis, and development of the cardiac conduction system.22

Over the past decade, a number of transcription factor mutations have been reported to underlie congenital heart diseases.22 Examples include mutations in Nkx2-5, Tbx5, Tbx1, Gata4, Gata6, Zic3, Fap2B, and Fog2.22 The majority of these mutations are associated with structural cardiac defects such as atrial septal defects, ventricular septal defects, valvular abnormalities, outflow tract abnormalities, and abnormal chamber development. Not uncommonly, transcription factor mutations result in complex overlapping phenotypes with extracardiac manifestations.22

The results of genetic studies in AF suggest that, in addition to their role in structural congenital heart defects, transcription factors play an important role in the pathogenesis of AF. Further evidence to support the role of transcription factors in AF has come from studies in animal models with pacing-induced AF and transgenic animal models.23,24 These studies have demonstrated that transcription factors are important modulators of atrial remodelling. The role of genetic variants in the pathogenesis of AF has been reviewed comprehensively in a number of previous articles.25,26 In this review, we focus on the evidence linking transcription factors with AF and also discuss the potential mechanistic links between these proteins and arrhythmia susceptibility.
2. Transcription factors and familial forms of AF

Transcription factor mutations in AF pedigrees have been identified using linkage analysis and candidate-gene screening. To date, transcription factor mutations have been reported in five core cardiac transcription factor genes; TBX5, GATA-4, -5, -6, and NKX2.5 (summarized in Table 1). The studies linking transcription factor mutations to familial forms of AF are discussed in more detail below.

2.1 TBX5 mutations and AF

The T-box (TBX) transcription factors recognize a palindromic sequence of 20–24 nucleotides referred to as a T-site or half of the sequence, called the T(2) site.40 Multiple subtypes of the TBX family of transcription factors are recognized (TBX1, TBX2, TBX3, TBX5, TBX18, and TBX20).41

TBX5 was the first transcription factor gene to be reported in congenital heart disease. Mutations in TBX5 cause Holt–Oram syndrome, a condition that commonly presents with atrial septal defects, ventricular septal defects, cardiaconduction abnormalities, and upper limb abnormalities.42,43 Holt–Oram syndrome is predominantly inherited as an autosomal dominant condition. The majority of TBX5 mutations underlying this condition lead to a premature stop codon, which is predicted to result in haploinsufficiency.27 The clinical presentation of Holt–Oram syndrome is highly variable—patients may present with isolated cardiac abnormalities or complex overlapping phenotypes.44

The association between Holt–Oram syndrome and AF has only recently been recognized. In 2008, Postma et al.27 identified a pedigree with an atypical form of Holt–Oram syndrome, where the majority of affected individuals had musculoskeletal defects and a premature onset of AF. Of note, only a small minority of family members had structural cardiac defects. The causative mutation (G125R) was associated with a gain-of-function effect and caused markedly increased activation of three downstream target genes; NPPA, Cx40, and KCNJ2. Interestingly, all the three of these genes have previously been implicated in the pathogenesis of AF.14

2.2 GATA mutations and AF

GATA transcription factors preferentially bind to the consensus DNA-binding sequence (A/T)GATA(A/G) through two zinc fingers (CysX2-CysX17-CysX2-Cys).45 The GATA family consists of six transcription factors. GATA-1, -2, and -3 are expressed in haematopoietic cells, whereas GATA-4, -5, and -6 are expressed in the heart.46

Multiple GATA mutations have been reported to underlie congenital heart disease. GATA-4 mutations have been identified in patients with atrial and ventricular septal defects, pulmonary stenosis, hypoplastic right ventricle, endocardial cushion defects, and Tetralogy of Fallot.47,48 GATA-5 mutations have also been identified in patients with Tetralogy of Fallot.35 GATA-6 mutations have been reported in patients with persistent truncus arteriosus, Tetralogy of Fallot, and atrial septal defects.49–51

More recently, a number of candidate-gene studies have implicated GATA gene variants in AF. To date, four studies have focused on the potential role of GATA-4 variants in AF. Yang et al.30 screened a Chinese cohort of 130 AF patients and identified two novel mutations (S70T and S160T). Wang et al.30 screened 150 Chinese AF patients and identified two further GATA-4 mutations (Y38D and P103A). Similarly, Jiang et al.31 screened 160 Chinese patients with AF and identified two GATA-4 mutations (G16C and H28D). All six of the aforementioned mutations were associated with a loss-of-function effect. Finally, Posch et al. screened 96 AF patients of European descent and identified a single GATA-4 mutation (M247T) in a pedigree with AF. However, the mutation was not characterized functionally.31

Three previous candidate-gene studies have investigated the potential role of GATA-5 variants in AF. Wang et al.33 sequenced 118 Chinese lone AF patients and identified a single novel GATA-5 mutation (W200G). Gu et al. screened 110 unrelated Chinese AF families and identified two novel mutations (Y138F and C210G). The W200G, Y138F, and C210G mutations were associated with loss-of-function type modulation.32 Yang et al.34 screened a cohort of 130 AF patients of Chinese descent and identified three potential causal GATA-5 variants (G184V, K218T, and A266P). They did not, however, perform functional analysis of the variants.

The prevalence of GATA-6 variants in AF has been investigated in three candidate-gene studies. Li et al.25 sequenced 140 AF patients of Chinese descent and identified a single novel variant (G469V). Functional analysis revealed that the G469V variant results in a loss-of-function effect. Yang et al. have performed two studies investigating the prevalence of GATA-6 variants in Chinese AF patients. In the first study, two novel heterozygous variants (Q206P and Y265X) were identified after screening a cohort of 110 patients.27 The variants segregated with AF, however, were not functionally characterized. In a more recent study, they screened a cohort of 138 AF patients and identified a further novel

Table 1 Transcription factor mutations underlying AF

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Functional effect</th>
<th>Comment</th>
<th>Ref.</th>
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<tr>
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<td>G125R</td>
<td>Gain-of-function</td>
<td>Associated with atypical Holt–Oram syndrome</td>
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<td>GATA-4</td>
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<td></td>
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</tr>
<tr>
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<td>S160T</td>
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<td>NKX2.5</td>
<td>T768A</td>
<td>Impaired dimmerization</td>
<td>Associated with ASD, conduction abnormalities, and syncope</td>
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<td>NKX2.5</td>
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VSD, ventricular septal defect; ASD, atrial septal defect; TOF, Tetralogy of Fallot.
GATA-6 variant (Y235S). Functional analysis revealed that the Y235S variant results in a loss-of-function effect. Overall, therefore, candidate-gene studies in AF cohorts suggest that loss-of-function mutations in GATA transcription factors increase susceptibility to AF. However, the prevalence of GATA variants in the general population is low (estimated at 0.01–0.02%).

### 2.3 NKX2-5 mutations and AF

NKX2-5 is a member of the NK2 family of transcription factors and binds to DNA through a conserved homodomain. NKX2-5 mutations are associated with structural heart defects, such as atrial septal defects, ventricular septal defects, Tetralogy of Fallot, double outlet right ventricle, Ebstein’s abnormality, aortic stenosis, abnormalities of the aorta, and cardiac conduction abnormalities.

- The evidence linking NKX2-5 mutations to AF is relatively limited. Gutierrez-Roelens et al. identified an NKX2-5 mutation (T768A) in a pedigree with a complex overlapping phenotype of AF, atrial septal defects, cardiac conduction abnormalities, and recurrent episodes of syncope. Functional analysis of the mutation revealed a decreased ability of the transcription factor proteins to form dimers. However, the ability of the mutant NKX2-5 protein to transactivate the downstream target gene NPPA was not affected. In subsequent candidate-gene studies, Ritchie et al. identified a single NKX2-5 mutation (F145S) in a cohort of 160 AF patients, whereas Boldt et al. did not identify any NKX2-5 mutations in a cohort of 96 AF patients. Functional analysis of the F145S variant was not performed. Consistent with the findings from candidate-gene studies relating to GATA transcription factors, NKX2-5 mutations appear to be rare causes of AF.

### 3. Transcription factors and AF in the general population

While familial forms of AF are caused by rare and highly penetrant mutations, AF in the general population is predicted to be caused by more common variants with smaller effect sizes. GWASs are powerful tools to investigate how common genetic variants influence risk in common disease phenotypes. The basic approach in the GWAS involves assaying up to a million single nucleotide polymorphisms (SNPs) distributed across the entire genome and testing for association with disease in large cohorts of unrelated patients.

In addition to the reports of transcription factor mutations in monogenic AF, GWASs indicate that transcription factors are potentially important contributors to AF in the general population. The risk SNPs at three of the GWAS loci for AF are located in the vicinity of transcription factor genes; PITX2, ZFHX3, and PRRX1. The evidence linking these transcription factors to AF is discussed in more detail here.

### 3.1 PITX2 as a candidate gene for AF

The first GWAS for AF, which was reported in 2007, identified a susceptibility locus for AF on chromosome 4q25. Multiple association studies have since replicated this finding. The association signal at the 4q25 locus lies within a genomic region that has not been reported to encode any genes or transcripts. However, the closest gene, which is located 150 000 bases away, is PITX2. PITX2 is a paired-like homeodomain transcription factor. PITX2 has been reported to be involved in the determination of right-left asymmetry and suppresses the default formation of a sinoatrial node in the left atrium. PITX2 also plays a major role in establishing atrial identity, which is a major determinant of normal development and connection of the pulmonary venous myocardium.

Since the results from the aforementioned GWAS were reported, a number of functional studies have provided further evidence to support the role of PITX2 in AF. Studies in murine models have demonstrated that knockout of PITX2 increases susceptibility to atrial arrhythmias and is associated with pro-arrhythmogenic alterations in the action potential. The expression of the PITX2 gene is also down-regulated in atrial tissue from AF patients.

Previous candidate-gene studies have screened for PITX2 mutations in AF patients. Boldt et al. screened a cohort of 96 AF patients and failed to identify any causative mutations. While the study was limited by a small sample size, these results indicate that PITX2 mutations are not a common cause of AF.

### 3.2 ZFHX3 as a candidate gene for AF

Following the identification of the PITX2 locus for AF, two different cohorts independently identified a susceptibility signal for AF on chromosome 16q22. The risk SNP at the 16q22 locus was located within one of the introns of the ZFHX3 gene. Since the original discovery, the risk SNPs at ZFHX3 have also been associated with AF among Chinese patients.

ZFHX3 encodes the homeodomain zinc finger transcription factor protein. ZFHX3 has previously been demonstrated to mediate neural and myogenic differentiation. Furthermore, in a number of neoplastic diseases, ZFHX3 has been demonstrated to function as a tumour suppressor gene. The potential role of this gene in cardiac development or function has yet to be determined.

### 3.3 PRRX1 as a candidate gene for AF

The latest GWAS meta-analysis for AF was reported in 2011. The strongest observed novel association in the study was on chromosome 1q24 at the PRRX1 gene. PRRX1 encodes a homobox transcription factor, which displays high levels of expression during myocardial development. Furthermore, PRRX1 demonstrates high expression levels in the walls of the great arteries, veins, and the pulmonary vasculature. PRRX1 plays a critical role in the development of the pulmonary vasculature. In a murine model, ablation of PRRX1 expression results in abnormal development of the pulmonary vasculature with associated severe lung defects and cyanosis. At a cellular level, PRRX1 promotes differentiation of endothelial precursor cells to promote the formation of vascular networks. Abnormalities of great vessel formation have also been reported in PRRX1/PRRX2 double-mutant mice. Specifically, these mice display abnormal architecture of the aortic arch, an anomalous retro-oesophageal right subclavian artery, and an elongated ductus arteriosus.

### 3.4 Potential mechanistic links between GWAS SNPs and transcription factor genes

It is important to note that while a number of compelling candidate genes have been identified at the GWAS loci for AF, the mechanistic link between the GWAS SNPs and the candidate genes has yet to be elucidated. The characterization of the mechanistic link is particularly challenging for candidate genes such as PITX2, which is located at a significant distance (~150 kb) from the risk SNPs at the 4q25 locus. It has been proposed that SNPs that confer a low risk of disease for complex traits like AF influence disease risk by altering the quantity of target gene expression.
4. Transcription factors and atrial remodelling

Atrial remodelling refers to a persistent change in the structure and function of the atrium. Atrial remodelling can result in alterations in the cellular/extracellular matrix, referred to as structural remodelling, and/or ion channel expression, referred to as electrophysiological remodelling. Interstitial fibrosis is a central feature of structural remodelling. Other changes include hypertrophy, dedifferentiation, and apoptosis of atrial myocytes. The most prominent changes associated with electrophysiological remodelling are transcriptional down-regulation of L-type calcium channels and up-regulation of potassium channel subunits underlying the \( I_{K1} \) and \( I_{K(A2)C} \) currents.

In recent years, studies involving animal models with pacing-induced AF, transgenic animal models of AF, and tissue samples from human subjects have characterized multiple signal transduction pathways involved in pro-arrhythmogenic atrial remodelling. While these investigations are far from complete, emerging evidence suggests that transcription factors play central roles in a number of major signalling pathways involved in both structural and electrical remodelling. Examples include the angiotensin II (Ang II) pathway, the redox signalling pathway, and the c-fos proto-oncogene (OS). The redox signalling pathway, and the c-fos proto-oncogene (OS).

In addition to the transcription factors identified in the major signal transduction pathways involved in atrial remodelling, expression profiling studies have demonstrated altered expression of transcription factors such as transforming growth factor TSC-22, transcription elongation factor B (TFIIB), early growth response factor 1 (EGR1), general transcription factor IIH polypeptide 2 (GTF2H2), and cardiac specific transcription factor NFAT.

5. Mechanistic insights

The current paradigm of AF posits that the arrhythmia arises due to a complex interplay between focal triggers and a susceptible atrial substrate. Transcription factors are likely to play an important role in the generation of ectopic pulmonary vein triggers and also the formation of a substrate for atrial re-entry. Of note, the transcription factors identified in genetic studies of AF have been demonstrated to regulate the expression of a range of genes that may play a role in maintaining electrical stability in the atrium (Figure 1).

5.1 Transcription factors and focal triggers

The most frequent site of origin of the focal triggers that initiate and potentially drive AF is the pulmonary veins. Interestingly, two of the transcription factors that have been implicated in genetic studies of AF, PITX2 and NKX2-5, have also emerged as important regulators of pulmonary vein development. Both transcription factors are highly...
expressed in the pulmonary venous myocardium and regulate the differentiation of mesenchymal cells into pulmonary vein myocardium. Therefore, variants in these transcription factors could potentially alter the electrophysiological properties of the pulmonary veins and also result in defective morphogenesis. A number of studies have demonstrated that patients with AF have anatomical differences in the pulmonary veins including longer muscle sleeves, thicker pulmonary vein myocardial tissue, and dilatation of superior pulmonary veins. Furthermore, previous studies have demonstrated that conduction delays in pulmonary veins may be attributable to altered myocyte fibre direction. NKX2-5 plays an important role in limiting pacemaker activity to the sinoatrial and atrioventricular nodes by maintaining the atrial gene programme. NKX2-5 represses expression of genes such as HCN4 in the atria and the atrial layer of the venous valves. PITX2 plays an important role in suppression of formation of a sinoatrial node in the left atrium by suppressing the signature nodal gene programme. Based on these observations, it is plausible that genetic variation in PITX2 and NKX2-5 results in a failure to suppress the sinoatrial node lineage gene programme resulting in ectopic expression of pacemaker genes in the pulmonary veins and/or the atrium.

5.2 Transcription factors and a susceptible atrial substrate

A susceptible atrial substrate is typically characterized by altered conduction velocity and refractory period, which promotes the stabilization of atrial re-entry circuits. The transcription factor variants identified in genetic studies may play an important role in regulating the expression of genes that influence atrial conduction velocity and/or refractory periods. Further evidence to support this notion has emerged from studies in patients with Holt–Oram syndrome and AF. As discussed previously, Posch et al. identified a gain-of-function mutation in TBX5, which resulted in an up-regulation of expression of NPPA, Cx40, and KCNJ2. Altered expression of these genes has been reported to promote re-entry. Furthermore, mutations in NPPA, Cx40, and KCNJ2 have been identified in familial forms of AF. Xia et al. identified a missense mutation in KCNJ2, which resulted in a gain-of-function effect. Gollob et al. reported four novel mutations in the Cx40 gene in AF patients. Functional analysis revealed a reduction in electrical coupling between cells. In a more recent study, Yang et al. performed candidate-gene screening of the Cx40 gene and identified three further mutations that segregated with disease. Hodgson-Zingman et al. reported a gain-of-function mutation in NPPA in an AF pedigree. Functional analysis revealed that the mutation resulted in pathologically high levels of mutant atrial natriuretic peptide (ANP), which in turn resulted in a shortening of the atrial action potential duration.

Transcription factors also play central roles in atrial remodelling, which as discussed previously is a major contributor to the development of a susceptible atrial substrate. For instance, NFAT, which forms part of the Ca²⁺/calmodulin/calcineurin/NFAT pathway, mediates down-regulation of Cav1.2 channel α-subunit expression. The result is an attenuated I_Ca,L current and a shortening of the atrial refractory
expression of the Nav1.5 channel, which underlies the $I_{Na}$ current. $I_{Na}$ is the main determinant of the conduction velocity, and an attenuated $I_{Na}$ current is predicted to slow atrial conduction. As discussed above, shortening of the atrial refractory period and slowed conduction are predicted to stabilize atrial re-entry circuits. In addition to electrophysiological remodelling, transcription factors also contribute to structural remodelling in the atrium. Structural remodelling increases susceptibility to atrial re-entry by enhancing conduction heterogeneity. The transcription factors involved in atrial fibrosis are summarized in Table 2.

5.3 Transcription factor mutations and variable clinical phenotypes

Mutations within a single transcription factor gene can result in diverse phenotypes, ranging from severe developmental abnormalities to relatively subtle disorders, such as AF. The pathophysiological mechanisms underlying these disparate clinical manifestations are presently unclear.

Transcription factors form part of complex regulatory networks designed to precisely control gene expression during cardiac development. These regulatory pathways are sensitive to transcription factor dosages. Therefore, haploinsufficiency or increased dosage of specific transcription factors is predicted to disturb the stoichiometric balance of the regulatory networks. For instance, altered transcription factor dosage may alter the balance between transcription activators and repressors, or it may alter the balance between subunits that form a transcription complex. Multiple studies in murine models have demonstrated the importance of proper transcription factor dosage during cardiac development. On the basis of these observations, it is plausible that mutations that cause subtle reductions in transcription factor activity correlate with subtle phenotypes such as AF, while more profound dosage effects, e.g. due to null mutations, may result in severe developmental defects.

The precise mechanistic effect of a transcription factor mutation may also be influenced by its location on the protein. Transcription factors are modular proteins that contain a number of different functional domains, including DNA-binding domains, transactivation domains, dimerization domains, and nuclear localization signals. Mutations in different domains may disrupt interaction with DNA, alter protein–protein interactions, or lead to defective localization of the protein. Therefore, the location of the mutation may have a significant impact on the clinical phenotype. A number of previous studies have demonstrated that variations in the location of transcription factor mutations can result in clinically distinct phenotypes.

6. Future perspectives

The majority of the traditional pharmacological agents used for the treatment of AF target ion channels. However, these drugs exhibit only moderate efficacy and are associated with significant side effects which may limit their use. Therefore, there exists a need for novel therapeutic agents for AF.

Transcription factors represent promising therapeutic targets for the treatment of AF. Numerous molecules that have the potential to modulate transcription factor function have been developed in recent years. Examples include molecules that block transcription factor DNA binding, molecules that block transcription factor dimerization, decoy oligonucleotides, and molecules that alter nuclear localization and histone modification.

To date, the therapeutic potential of transcription factor modulators has been investigated most extensively in the context of malignancies. A number of important transcription factors, including NF-κB, STAT1, STAT3, and AP-1, demonstrate increased activation in malignancies. Multiple previous studies have demonstrated that drugs that inhibit progression of malignancies exert their effect through altered function of these transcription factors. Interestingly, the same transcription factors have also previously been implicated in AF-related atrial remodelling. On the basis of these observations, it is plausible that drugs aimed at transcription factors could also protect the atrium against adverse remodelling.

Transcriptional regulation of atrial genes is a highly complex process, which is currently not completely understood. Before drugs that modulate cardiac transcription factors can be developed, it is necessary to develop an in-depth understanding of the role of transcription factors in signalling pathways involved both in AF-related remodelling and in inherited forms of AF. A potential future area of research to elucidate the mechanistic link between transcription factors and AF susceptibility is to investigate the effects of variable expression of these proteins in animal models. Studies in animal models may involve characterization of the cardiac electrophysiological phenotype and performing gene expression profiling in order to identify downstream target genes. As discussed previously, for some transcription factors, such as PITX2, studies in murine models have already begun to elucidate the mechanistic link between altered transcription factor function and AF.

Induced pluripotent stem (iPS) cells have recently emerged as potentially powerful tools for the investigation of mechanisms of cardiac arrhythmogenesis. In recent studies, iPS technology has been used to generate functional cardiomyocytes from patients with inherited arrhythmia syndromes, such as long QT syndrome. These cells have faithfully recapitulated the electrophysiological features of the condition in vitro. IPS cells may be well suited to assess the role of transcription factors in arrhythmia susceptibility. An intriguing future possibility is to use iPS technology to generate cardiomyocytes from patients with monogenic transcription factor mutations and assessing the phenotype using cellular electrophysiology.

In recent years, the emergence of novel genotyping technologies such as exome sequencing and whole genome sequencing has fundamentally accelerated our ability to uncover the genetic substrate underlying both familial diseases and more complex traits. These techniques have the potential to identify multiple additional genes and non-coding regulatory elements that influence susceptibility to AF. The identification of these genes and regulatory elements will provide valuable insights into the complex biological pathways underlying AF and may define the role of transcription factors in AF more clearly. Ultimately, these discoveries may inform drug development.

In addition to drug development, discoveries from genetic studies in AF have the potential to enhance risk stratification and prognostication for AF. The potential utility of GWAS SNPs for individualized risk prediction of complex traits like AF has recently received much attention. As discussed previously, multiple SNPs that confer an increased risk of AF have been identified by GWAS. However, thus far, attempts to use these GWAS SNPs to predict the risk of complex diseases have been associated with significant limitations. The major current limitation relates to the small effect sizes of the SNPs. In the future, as additional variants are identified by genetic studies for AF, genotype-based risk prediction may become a reality.
7. Conclusions

The regulation of gene expression is a highly complex process that involves combinatorial interactions between multiple different components. Central players in these regulatory processes are transcription factors. In recent years, research into the genetic basis of AF has led to the emergence of transcription factors as potentially important contributors to arrhythmia susceptibility. Multiple transcription factors have been implicated in both monogenic forms of AF and the more complex form of AF encountered in the general population. Further research is currently needed to elucidate the mechanistic link between these transcription factors and arrhythmia susceptibility. Ultimately, these could potentially lead to the development of novel, more effective therapeutic interventions for this common and morbidd arrhythmia.

Conflict of interests: none declared.

References


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