Review Article

The role of transcription factors in atrial fibrillation

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Abstract: Atrial fibrillation (AF) is a complex disease that results from genetic and environmental factors and their interactions. In recent years, genome-wide association studies (GWAS) and family-based linkage analysis have found amounts of genetic variants associated with AF. Some of them lie in coding sequences and thus mediate the encoded proteins, some in non-coding regions and influence the expression of adjacent genes. These variants exert influence on the development of cardiovascular system and normal cardiac electrical activity in different levels, and eventually contribute to the occurrence of AF. Among these affected genes, as a crucial means of transcriptional regulation, several transcription factors play important roles in the pathogenesis of AF. In this review, we will focus on the potential role of *PITX2*, *PRRX1*, *ZHFX3*, *TBX5*, and *NKX2.5* in AF.

Keywords: Atrial fibrillation (AF); transcription factors; *PITX2*; *PRRX1*; *ZFHX3*; *TBX5*; *NKX2.5*

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Atrial fibrillation (AF), the most common cardiac arrhythmia, is characterized by absence of P waves and irregular R-R intervals (1). AF has an estimated prevalence rate of 0.4% to 1.0% in the general population, and there are approximately 10 million AF patients in China and the number of AF patients is estimated to reach 15.9 million in the United States by 2050 (2-5). AF is a complex disease that results from genetic and environmental factors and their interactions (6,7). Framingham Heart Study has revealed that familiar historys plays an important role in AF [OR =1.40, 95% confidence interval (CI): 1.13-1.74, with P value =0.02] and suggested that genetic variations may play important roles in the pathogenesis of AF (8).

Using linkage analysis and positional cloning approach, several genetic loci, such as *KCNQ1*, *KCNE2*, *KCNJ2*, *KCNA5*, *KCNH2*, *SCN5A*,*SCN3B*,*NPPA* and *NUP155*, have been found for familiar or monogenic AF and casual genes, including *KCNQ1*, *KCNE2*, *KCNJ2*, *KCNA5*, *KCNH2*, *SCN5A*, *SCN3B*, *NPPA* and *NUP155* have been identified. In recent years, using genome-wide association study (GWAS), deep sequencing and cis-eQTL mapping, more genetic loci have been revealed for non-familiar or common AF, including 1q24, 4q25, 7q31, 9q22, 10q22, 14q23, 15q24, 16q22, and 10p11-q21 (9-11). Notably, variants of five transcription factors mentioned above may play important roles in the pathogenesis of AF. In this review, we will focus on the potential role of transcription factors those indentified by GWAS in AF.

Paired-like homeodomain 2 (*PITX2*)

The association between variants (rs2200733 and rsl0033464) on 4q25 and AF was first identified by GWAS enrolled three populations of European descent and a Chinese at 2007 (12). Later, the association was verified in Italian population, Polish population and Chinese (13-15). Clinical studies showed that rs10033464 affected the response to antiarrhythmic drug (AAD) in AF patients, while rs2200733 were supposed to be an independent predictor of AF recurrence after direct current cardioversion

(DCCV). Furthermore, those AF risk variations on 4q25 were associated with increased risk of both early and late AF recurrence after catheter ablation (16-19). Though the expression of paired-like homeodomain 2 *(PITX2)* in human adult left atrial appendages has been reported not associated with the AF risk SNPs on chromosome 4q25 (20), *PITX2* may participate in the mechanism of AF, regarding that *PITX2* is the nearest gene which lies approximately 150,000 base pairs downstream the AF associated variants on 4q25 (21).

PITX2, a member of the paired-like homeodomain transcription factor family, encodes three protein isoforms: *PITX2a*, *b*, *c*. Studies showed that *Pitx2* mediated asymmetric left-right signaling in vertebrate situs-specific morphogenesis, especially L/R atrial identity and asymmetrical ventricular remodeling (22-25). *PITX2c* expresses not only in the left atrium and pulmonary vein of embryonic and postnatal mice, but also in rare left atrial myocardial cells in left atrium of 1-year-old mice (24). And in heart of adult human or mouse, the expression level of *PITX2c* in left atrium is about 100-fold higher than in right atrium or in ventricles (26). Specific *Pitx2* knockout mice survived with obvious congenital malformations, conduction system abnormalities, and pulmonary myocardial defects (25). Although the cardiac function and morphology were normal, the action potential was shortened and ectopic automaticity was promoted in the left atrium cardiomyocytes of heterozygous *Pitx2c*-deficient ($Pitx2c^{+/-}$) mouse (26).

Whole-genome expression array observed that amounts of genes that were affected by the expression of *PITX2c* might explain the molecular mechanism for abnormal electrical activity and susceptibility to AF in $PITX2c^{+/-}$ mouse (26). Sinoatrial node (SAN) specific genes *Shox2*, *Tbx3* and *Hcn4*, were up-regulated in the *PITX2* null-mutant embryos (27). *PITX2c* can bind and inhibit the expression of *Shox2*, which plays an essential role in sinoatrial and pacemaking development. *Shox2*, a homeodomain transcription factor, regulates the SAN genetic program through the repression of *Nkx2.5* and *Tbx3* (27-29). *Tbx3*, a member of T-box transcription factors, can influence the specification and formation of the SAN, and the development of left atria as well (28,30,31). Hyperpolarization-activated, cyclic nucleotide-gated 4 (*Hcn4*), a pacemaker channel gene, maintains a stable cardiac rhythm by preventing sinus pauses and has no contribution to the heart rate acceleration (27,32,33). Furthermore, studies showed that *PITX2c* also down-regulated the expression of *Nppa* and *Kcnq1*. *NPPA* encodes the atrial natriuretic peptide hormone that regulates intravascular volume, and *KCNQ1* encodes potassium channel. Variants in both *NPPA* and *KCNQ1* can cause I(Ks) "gain-of-function" and atrial AP shortening, and result in calcium current change, which known as a common pathogenesis of familial AF (27,34-37). Other target genes of Pitx2, include channel and calcium handling genes, and genes that stabilize the intercalated disc in postnatal atrium (38). And a latest integrated genomic analysis discovered that two microRNAs, miR-17-92 and miR-106b-25, were up-regulated by Pitx2. The transcription of these microRNAs can repress Shox2 and Tbx3, and play roles in the abnormal electrical activity (39).

Paired-related homeobox gene 1 (*PRRX1*)

The association between rs3903239 in paired-related homeobox gene 1 (*PRRX1*) on 1q24 and AF was reported in a GWAS study which contained a large number of Europeans and Japanese (40). A latest rare variant joint analysis also found that damaging variants within the *PRRX1* region remained significantly associated with AF (P value =0.01) after Bonferroni correction (41). Both studies highlighted that *PRRX1* may affect the susceptibility to AF.

PRRX1 encodes a homeodomain transcription factor, which localized in the nucleus and highly expressed in the developing heart (especially the conducting system). It's first observed in the developing chick cardiovascular system, including epicardium, valve, endocardial cushion and the wall of the large arteries and veins (42). Instead of directly interacting with deoxyribonucleic acid (DNA) in its homeodomain, *Prrx1* plays its function by binding the muscle creatine kinase enhancer (43,44). The interaction between *Prrx1* and MADS-domain transcription factors was suggested to influence smooth muscle structural proteins and pulmonary vasculature dysgenesis was observed in the *Prrx1* knockout fetal mouse (43-48). According to highly expression of *PRRX* genes in the developing vascular system, PRRX1 and PRRX2 may play important roles in the differentiation of vascular smooth muscle cells (49). Abnormalities of great vessel were observed in double mutants' knockout mouse too (50). A normal heartbeat is initiated in the SAN or pacemaker region, while abnormal electrical activity originated in pulmonary veins can serve to trigger and maintain AF in many pathological conditions (51). These abnormal developments of pulmonary vasculature may offer pulmonary veins the morphological substrate involved in AF. A case-control study has revealed that

an anatomic PV variant, left common ostium (LCO) is associated with the development of AF with OR of 2.1 (P value =0.004) (52). The re-entrant PV tachycardia is also suggested to be a mechanism underlying the initiation of paroxysmal AF (53). Additionally, the distribution and structure of myocardium in the pulmonary veins can also influence the radiofrequency ablation of AF (54).

Zinc finger homeobox 3 (*ZFHX3*)

The variation rs7193343 in *ZFHX3* on chromosome 16q22 was first reported to be associated significantly with AF in GWAS [OR of 1.21 ($P=1.4\times10^{-10}$)] (55). And this association was replicated in the Polish population (14). Two SNPs (rs2106261 and rs6499600) in *ZFHX3* are strongly associated with AF risk, while another one (rs16971436) is borderline significant in a Chinese Han populations (56). And significant association of SNP rs2106261 with AF was identified in another Chinese Han population (57). Moreover, the polymorphism in *ZFHX3* magnifies the AF risk in HF patients (58).

ZFHX3 encodes a cardiac transcription factor containing multiple homeodomains and zinc finger motifs. Two missense mutations in *ZFHX3* exon were identified and in silico analysis showed that these mutations resulted in damage of the ZFHX3 protein structure (59). ZFHX3 interacts with the terminal end of protein inhibitor of activated STAT 3 (*PIAS3*), which is a specific inhibitor of signal transducer and activator of transcription 3 (STAT3) through binding to activated tyrosine-phosphorylated STAT3 dimers and subsequently preventing DNA binding to the complex (60,61). STATs were proved to mediate the inflammatory process as the major downstream mediators of many different inflammatory signaling pathways in a pacing-induced AF porcine model. Small GTPase Rac1, a molecular target of statin, mediating the activation of STAT3 by angiotensin II, and JAK/STAT pathways, was activated in this animal model (62). As an independent risk of AF, inflammation play roles in the pathophysiological mechanisms of the initiation and maintenance of AF (63). So this activated angiotensin II/Rac1/STAT signaling was suggested to contribute to electrical and structural remodeling and inflammatory changes in pacing-induced AF model (62). In tachypaced HL-1 cells, the expression of ZFHX3 and PIAS3 decreased, while activated STAT3 up-regulated. Knockdown of ZFHX3 together with PIAS3 activated pacing-induced STAT3 signaling more effectively than knockdown ZFHX3 alone. On the contrary, overexpression of ZFHX3 reversed the above effect (64). These data indicated that inhibition of ZFHX3 and activation of STAT3 might contribute to AF. Nuclear localization and SUMOylation are important to ZFHX3, and ZFHX3 is observed cooperating with PML NBs to regulate protein SUMOylation in different biological processes in endothelial cells. Cause SUMOylation serves as a third quality control of misfolded and damaged proteins, which contribute to the pathogenesis of many forms of cardiac disease and heart failure, ZFHX3 may also play roles in AF through mediating the SUMOylation of related proteins (65,66).

T-box 5 (*TBX5*)

A large scale of GWAS study with 4,304 cases and 46,508 controls from Iceland of European origin revealed the association between T-box 5 (*TBX5*) on 12q24.1 and AF. SNP rs3825214 variant in *TBX5* is strikingly associated with PR interval, QRS duration and AF (67). Another genetic study replicated the association between *TBX5* and AF in Europeans and Japanese, using multiple approaches containing large-scale genotyping, cis-eQTL mapping and functional validation (68). We also demonstrated that rs3825214 in *TBX5* was associated with lone AF in Chinese Han population (69). Furthermore, *TBX5* indwells in the gene modules associated with AF identified by weighted gene co-expression network analysis of human left atrial tissue (70).

TBX5 belongs to the evolutionarily conserved T-box family of transcription factors, and may play a role in heart development and specification of limb identity (71). In humans, mutations in *TBX5* can cause Holt-Oram syndrome, which includes congenital heart defects, conduction system abnormalities, and upper limb deformities (72,73). In an atypical Holt-Oram syndrome family, affected patients have mild skeletal deformations and almost none has congenital heart disease, and paroxysmal AF. A novel mutation in *TBX5*, c.373 G>A, is co-segregated with the disease and leads to p.G125R, a gain-of-function protein that can interact with NKX2.5. The mutated TBX5 enhances the DNA-binding properties of the recombinant and activates *Nppa* and *Cx40* promoters. This activation accelerats the AF related genes expression such as *Nppa*, *Cx40*, *Kcnj2*, and *Tbx3* (74). *Tbx5*$^{-/-}$ mice can't survive before birth because of failure of heart tube looping and an under-developed caudal part. The expression of *Nppa* and *Cx40* reduced in heterozygous *Tbx5* knockout mice, while up-regulated and resulted in spontaneous beating phenotype

when *Tbx5* was overexpressed in P19C16 embryonic carcinoma cells (75-77). Furthermore, TBX5 can also interact with TBX3, which controls the SAN gene program, induces pacemaker activity and changes ectopic automaticity in atrial myocardium (30,74).

NK2 homeobox 5 (*NKX2.5*)

In a three-generation family with inherited cardiac anomalies, the mutation c.768T>A in NK2 homeobox 5 (*NKX2.5*) on 5q34 was identified associated with atrial septal defect and AF (78). Another *NKX2.5* loss-of-function mutation, p.F145S, was identified in AF family, whose inheritance pattern was autosomal dominant with complete penetrance (79). More mutations, such as p.E21Q, p.T180A, p.N19D and p.F186S were indentified and expand the spectrum of NKX2.5 mutations linked to AF (80,81).

NKX2.5, a homeobox-containing transcription factor, continuously expresses in heart from development to maturity, and plays its function in the formation and development of heart. Mutations in *NKX2.5* cause a variety of heart malformation diseases: atrioventricular (AV) conduction abnormalities, atrial septal defects, high degree AV block and tetralogy of Fallot (82,83). Functional analysis associated the mutant proteins with significantly reduced transcriptional activity of NKX2.5 by directly inhibiting its transcription or affecting its nuclear distribution or DNA-binding ability (84). A meta-analysis of GWAS revealed the association between the genetic variations in *NKX2.5* and PR interval (85). Another study enrolled 7,575 individuals (mean age 46 years, 54% women) who underwent routine 12-lead electrocardiography found that variations of *NKX2.5* were associated with the PR interval in the general population. PR interval reflects atrial and AV nodal conduction and individuals with prolonged PR interval have a higher risk of future AF and cardiac sudden death, so *NKX2.5* may affect the disturbances of PR interval and contribute to AF (86).

In transgenic mice that carry a loss of function allele (I183P) for NKX2.5, PR prolongation was observed as early as 2 weeks and quickly developed into complete AV block at 4 weeks. Meanwhile, the expression of two gap junctional proteins: *Cx50* and *Cx43* dramatic decreased. These *Nkx2.5* mutated mice all got congenital structurally normal hearts, yet displayed progressive AV conduction defects and HF (87). Other studies showed that *Nkx2.5* might reduce the genes which were potentially sufficient to provide automaticity in the pulmonary myocardium. And *Cx40*-negative, *Hcn4*-positive phenotype in the pulmonary myocardium caused by variation of *Nkx2.5* could be an important trigger of AF (88). Furthermore, *NKX2.5* controls *PITX2* expression in inchoate cardiac lateral plate mesoderm instead of pulmonary myocardium, via direct binding to the consensus DNA-binding site within the asymmetry enhancer element of *PITX2*. Considering the role of *PITX2* mentioned before, they may work together to influence the cardiac development and susceptibility substrate of AF (89).

In summary, genetic variations may influence the function of transcription factors and affect the ion channels, development of cardiac conduct system or myocardium fibrosis, and play important roles in the pathogenesis of AF. Identification of the exact targets which are regulated by AF-related transcription factors may lead to potential new treatments to AF.

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