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CLINICAL REVIEW

Genome and atrial fibrillation

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Abstract

Atrial fibrillation (AF), the most common type of arrhythmia, can cause several adverse effects, such as stroke, heart failure, and cognitive dysfunction, also in addition to reducing quality of life and increasing mortality. Evidence suggests that AF is caused by a combination of genetic and clinical predispositions. In line with this, genetic studies on AF have progressed significantly through linkage studies, genome-wide association studies, use of polygenic risk scores, and studies on rare coding variations, gradually elucidating the relationship between genes and the pathogenesis and prognosis of AF. This article will review current trends in genetic analysis concerning AF.

KEYWORDS
atrial fibrillation, genome, GWAS, polygenic risk factor

1 | INTRODUCTION

Atrial fibrillation (AF), the most common type of cardiac arrhythmia, has been associated with reduced quality of life, decreased healthy life expectancy, and increased mortality. The incidence of AF has continued to increase with the aging of society.[1] Although aging has been considered the most important risk factor for AF, several clinical risk factors do exist, including hypertension, diabetes, alcohol consumption, obesity, and inactivity or excessive exercise.[2] Racial differences in the incidence of AF have also been described, with rates known to be higher in Caucasians than in Asians and Hispanics, suggesting the involvement of genetic factors.[3] AF increases the risk of stroke, heart failure, and cognition impairment, which significantly reduce quality of life and increase mortality.[1] Therefore, early detection of AF and prompt therapeutic interventions for the same are especially important. In recent years, the advent of various devices, such as portable ECGs, Apple Watch, long-time ECGs, and implantable electrocardiograms, has allowed for the early detection of AF; nonetheless, there are still quite a few cases of asymptomatic AF, making early detection difficult.[4,5]

Apart from anticoagulation, rate control, and rhythm control with antiarrhythmic drugs as treatment approaches for AF, rhythm control with ablation therapy has dramatically improved. As such, there has been a paradigm shift toward early rhythm control for patients with recently diagnosed AF.[6] The detection of AF-related genes, the association between AF-associated genes and the development of AF, the association between genes and AF phenotypes and comorbidities, and the association between AF-associated genes and therapeutic efficacy and prognosis are particularly important and deserve further attention and clarification. In this review, we briefly summarize genomic studies concerning AF published to date.

2 | HISTORY OF GENETIC ANALYSIS OF AF

2.1 | Linkage analysis of familial AF

Individual family members with hereditary AF have been tremendously helpful in unraveling the molecular biology of diseases. To begin with, linkage analysis has been performed on several affected individuals and families with a clear genetic pattern. The first mutation associated with familial AF was a gain-of-function mutation (S140G) in the ion channel *KCNQ1*, which is a gene that encodes the alpha subunit of the I_{Ks} channel. The S140G mutation is likely to initiate and maintain AF by reducing the action potential duration and effective refractory period of atrial myocytes.[7]

The frameshift mutation in the natriuretic peptide precursor A gene (*NPPA*), which encodes atrial natriuretic peptide (ANP), was reported in another AF family.[8] In subjects with the mutation, elevated levels of circulating ANP were detected.[8] After measuring the action potential duration and effective refractory period using isolated rat hearts perfused with normal or the mutant form of ANP, the authors showed that perfusion with the mutant ANP shortened the atrial action potential duration and effective refractory period, thereby creating a substrate for AF.[8] Gain-of-function mutations in the transcription factor *TBX5* have been reported to be associated with familial AF.[9] These mutations were reported to enhance DNA binding and activation of both Nppa and Cx40 promoter and augment expression of Nppa, Cx40, Kcnj2, and Tbx3, thereby leading to the development of AF.[9]

The autosomal recessive gene for *MYL4* was identified in patients with early-onset AF.[10] In zebrafish, mutant *MYL4* leads to a disruption in the sarcomere structure, atrial enlargement, and electrical abnormalities, which are associated with human AF.[10] A loss-of-function (LOF) variant in the *KCN5A* gene encoding the ultrarapid component of the atrial-specific delayed potassium current (Ikur) has been reported in familial AF. The E375X mutation, which is a functional deletion due to the appearance of an early stop codon, may cause AF by promoting action potential prolongation and early after-depolarization.[11] Thus, despite having identified the genes responsible for AF, the mutations identified so far have been limited, and their impact on the overall extent of AF has been mediocre.

2.2 | Genome-wide association study of AF

In contrast to familial studies, genome-wide association studies (GWASs) allow for the analysis of the entire population by comparing individuals with and without AF on a large scale. The first GWAS on AF in 2007 found a strong association between AF and two sequence variants near the *PITX2* gene on chromosome 4q25, subsequently highlighting *PITX2* as an AF-related gene.[12] Various studies have suggested an association between *PITX2* and the mechanism of AF onset. The pulmonary vein is connected to the left atrium by the myocardial sleeve and engages in the development of AF. One report showed that *Pitx2*c-deficient mice did not form the initial pulmonary myocardial cells and failed to develop a pulmonary myocardial sleeve.[13] Another study by Wang et al. reported that *Pitx2* directly inhibits the sinoatrial node-specific genetic program in the left atrium and contributes to the prevention of atrial arrhythmias.[14] Evidence suggests a dose-dependent relationship between *Pitx2* expression and the expression of AF susceptibility genes, calcium handling, and microRNAs, which in turn has a significant impact on the susceptibility to AF development.[15] Chinchilla et al. reported that PITX2 expression was significantly decreased in human patients with sustained AF. They also reported that the loss of *Pitx2* in the atrial myocardium decreased sodium and potassium channel expression via altered miRNA expression. These cellular and molecular changes induced atrial electrical and structural remodeling and ultimately arrhythmogenesis.[16] Our group also reported that the minor allele frequency of *PITX2* single-nucleotide variant (SNV) rs6817105 (T > C) in chromosome 4q25 was significantly higher in the 574 patients with AF than in the 1554 non-AF controls and that rs6817105 minor allele variants caused sinus node dysfunction and left atrial enlargement.[17] Although numerous studies have investigated the involvement of *PITX2* in AF, the involved mechanisms have yet to be fully elucidated. Nonetheless, Mun et al. generated a *PITX2* knockout human induced pluripotent stem cell (iPSC) line using the CRISPR/Cas9 gene, which may be useful for elucidating the aforementioned mechanism in vitro.[18] Unlike cells expressing only specific mutant channels, iPSCs allow us to understand action potentials in the entire myocardial cells. In addition, such cells are useful for understanding stimulus propagation throughout the myocardial cell, including the membrane potential waveform, and for elucidating cellular heterogeneity in a three-dimensional structure, allowing for the investigation of the possible mechanisms of AF.

After the first GWAS on AF, several other GWASs, which primarily targeted Europeans, had emerged.[19–21] Moreover, a number of meta-analyses reported that *KCNN3* and *ZFHX3* were associated with AF.[22–24] The AFGen Consortium, which combined large-scale genotyping with cis-eQTL (expression quantitative trait loci) mapping, found four new loci (*NEURL*, *GJA1*, *TBX5*, and *CAND2*) in European participants, as well as novel loci near *NEURL* and *CUX2* in Japanese participants.[19] A meta-analysis of GWAS in 2012 reported that the three loci most significantly associated with AF were previously identified as AF susceptibility loci in chromosomes 4q25 near *PITX2* (rs6817105), 16q22 in *ZFHX3* (rs2106261), and 1q21 in *KCNN3* (rs6666258). Seven new genomic loci-associated with AF (*PRRX1*, *WNT8A*, *CAV1*, *C9orf3*, *SYNPO2L*, *SYNE2*, and *HCN4*) were also reported.[20]

Two additional major GWASs had been published in 2018. Accordingly, a large meta-analysis of GWASs by Roselli et al. in 2018, which included 65 446 AF cases, identified 97 loci significantly associated with AF.[25] In 2018, Nielsen et al. determined the association between 34 740 186 genetic variants and AF, comparing a total of 60 620 cases and 970 216 controls of European ancestry from six contributing studies (The Nord-Trøndelag Health Study, deCODE, the Michigan Genomics Initiative, DiscovEHR, UK Biobank, and the AFGen Consortium), and identified 142 independent risk variants at 111 loci.[26] The aforementioned study also highlighted genes deemed important for myocardial ion channel (*HCN4*, *KCND3*, *KCNH2*, *KCNJ5*, *KCNN2*, *KCNN3*, *SCN10A*, *SCN5A*, and *SLC9B1*) and calcium signaling function (*CALU*, *CAMK2D*, *CASQ2*, and *PLN*), which may also affect myocardial electrical properties, and myocardial transcription factors (*ARNT2*, *EPHA3*, *FGF5*, *GATA4*, *GTF2I*, *HAND2*, *LRRC10*, *NAV2*, *NKX2-5*, *PITX2*, *SLIT3*, *SOX15*, and *TBX5*). In addition, several candidate genes for AF function that may be involved in myocardial and skeletal muscle structure and function (*AKAP6*, *CFL2*, *MYH6*, *MYH7*, *MYO18B*, *MYO1C*, *MYOCD*, *MYOT*, *MYOZ1*, *MYPN*, *PKP2*, *RBM20*, *SGCA*, *SSPN*, *SYNPO2L*, *TTN*, *TTN-AS*, and *WIPF1*) were also reported.[26]

Although several AF-related genes were detected, *PITX2* is still the most strongly associated with AF. Additionally, several other genes whose mechanisms have been under investigation were identified. The *ZFHX3* protein is a regulatory factor for STAT3-mediated signal transduction, and its interaction with the protein inhibitor activates STAT3, an important mediator of the inflammatory process.[27] Our group found that the *ZFHX3* SNV rs2106261 minor allele was associated with decreased AF recurrence rates after pulmonary vein isolation due to low baseline inflammation.[28] Kao. et al. reported that *ZFHX3* knockdown in atrial myocytes dysregulated calcium homeostasis increased the conduction velocity, shortened the action potential duration (APD), and increased atrial arrhythmogenesis, all of which may contribute to the occurrence of AF.[29] Furthermore, small-conductance, calcium-activated K^+ (SK, *KCNN*) channels contribute to cardiac action potential repolarization and are implicated in AF susceptibility.[30] *CAV-1*, which encodes the fibroblast structural protein caveolin-1, is an important inhibitor of the TGF-β1 pathway and is downregulated in AF.[31] Sinner et al., who analyzed optical mapping data, reported that the knockdown of the *CAND1* or *NEURL* gene in zebrafish prolonged atrial APD_{80}. In addition, another study showed that *NEURL* and *PITX2* interacted with each other.[32]

The genetic variants identified in GWAS studies are mainly located in noncoding regions of the genome. However, these variants are meaningful and are presumed to alter the activity of transcriptional regulatory elements, such as enhancers and repressors, and the transcription of nearby genes. In fact, most GWAS variants have no direct pathway from GWAS associations to the gene and disease mechanism. Hence, combining GWAS with expression quantitative trait loci (eQTL) data,[33] multi-omics data,[34] and STARR-seq[35] will continue to be necessary. Notably, while most GWASs have targeted people of European ancestry, some have examined Asians, with results showing that AF-related genes seemed to vary according to race.[21,32]

2.3 | AF prediction using polygenic risk scores

AF has been identified as a major cause of stroke, heart failure, cognitive dysfunction, shortened healthy life expectancy, and increased mortality. Early detection and therapeutic interventions are essential for preventing AF. As such, polygenic risk scores (PRSs) are now being used to assess AF risk due to the high number of AF-related genes detected in previous GWASs. In 2014, Lubitz et al. reported on the utility of a genetic risk score using AF-related genes in 64 683 and 11 309 individuals of European and Japanese ancestry, respectively. They reported the presence of four AF susceptibility signals on chromosome 4q25 and similar polygenic AF susceptibility between European and Japanese individuals.[36] A 2016 study by the same authors also reported that the AF genetic risk scores were associated with cardioembolic stroke and incident AF beyond clinical AF risk factors.[37]

Another paper also reported that the AF genetic risk score can identify 20% of individuals who are at a two-fold increased risk for incident AF and at 23% increased risk for ischemic stroke.[38] A 2018 study by Khera et al. that used polygenic predictors confirmed that 6.1% of the UK Biobank population had a three-fold or greater risk for AF and that the top 1% had a 4.63-fold risk of AF.[39] In the same year, Weng et al. reported that among patients who had not developed AF at age 55, those in the low-and high-polygenic and clinical risk tertiles had a 22.3% and 48.2% lifetime risk for AF, respectively. After adjustment for genetic predispositions, the same study showed that lower clinical risk factor burden was associated with later-onset AF.[40]

Recently, Mars et al. reported that the risk of AF increased from 24.4% in patients with a mean PRS to 61.1% among those with a PRS in the top 2.5%.[41] After comparing the late-onset (age > 60) and early-onset groups, the authors found that the PRS contributed more toward detecting the early-onset group were as the clinical factors calculated from the CHARGE-AF calculator contributed more toward the late-onset group (Figure 1).[41,42]

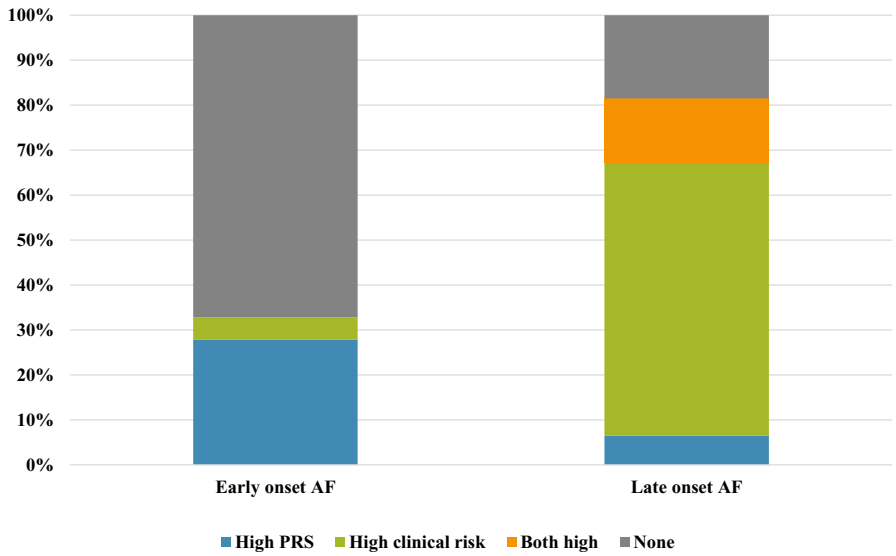


FIGURE 1 Differential contribution of polygenic risk scores and clinical factors to AF. A comparison between the late-onset (age > 60) and early-onset groups (age ≤ 60) showed that PRS contributed more toward detecting the early-onset group, whereas clinical factors calculated from the CHARGE-AF calculator contributed more toward detecting the late-onset group. PRS, polygenic risk scores.

Our group identified five AF-associated SNVs (in *PRRX1*, *ZFHX3*, *PITX2*, *HAND2*, and *NEURL1*) showed a 4.92-fold difference in AF risk between those with the highest and lowest weighted genetic risk score (WGRS)[43] (Figure 2A). Receiver operating characteristic analysis of the WGRSs yielded an area under the curve (AUC) of 0.73 and 0.72 for the screening and validation cohort, respectively. Muse et al., who calculated the WGRS for 12 AF-related loci, found a three-fold difference between the highest and lowest quintiles after adjusting for other clinical risk factors (age, gender, BMI, hypertension, and diabetes).[44] Another study has also reported that health behavior-induced modification of genetic predisposition can lead to the development of AF.[45] Moreover, in our study, we showed that our AF predictive logistic model, which combined WGRS and AF clinical risk factors (age, body mass index, gender, and hypertension), demonstrated better discrimination of AF than did WGRS alone (AUC, 0.84; sensitivity, 75.4%; specificity, 80.2%)[43] (Figure 2B).

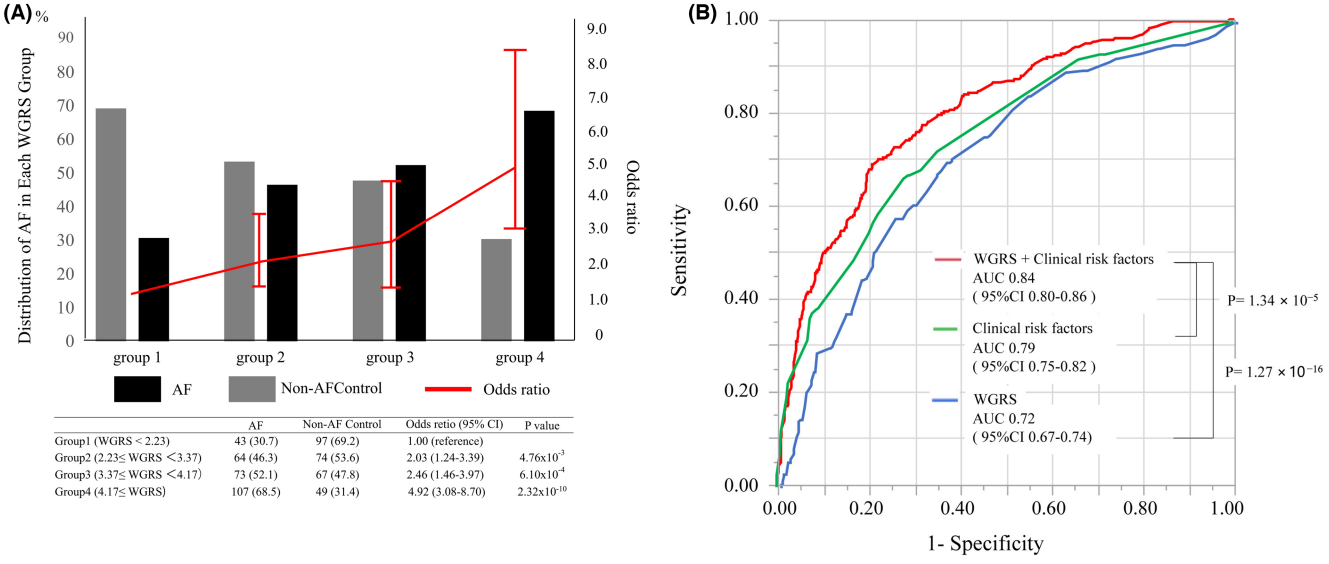
Most recently, Marston et al., who analyzed a total of 36662 subjects without prior AF from four TIMI trials, reported that AF PRS is a strong independent predictor of incident AF and provides complementary predictive value when added to a validated clinical risk score and NT-proBNP.[46] While various studies have been conducted on the ability of the PRS to predict AF and stroke, PRS alone cannot sufficiently predict AF. However, the optimal number of SNVs to incorporate has not yet been established and will require further study.

2.4 | Clinical features and AF-associated SNVs

Rate control is an acceptable treatment strategy to prevent heart failure in patients with AF. Evidence shows that carriers of the common Arg389Gly SNV in *ADRB1*, a β1-adrenergic receptor gene, required lower doses of rate control medications to achieve target heart rates in AF.[47] Arg389Gly is a loss-of-functional SNV that reduces adenylyl cyclase levels and attenuates the β-adrenergic cascade in response to the same adrenergic stimulation. This consequently causes slow conduction and prolongs the effective refractory period of the atrioventricular node, promoting low heart rates during AF. Our group showed that the *GJA1* SNP rs1015451 (T > C) minor allele, which encodes the connexin-43, was significantly associated with higher AF heart rate.[48] However, this SNV is not consistent with AF-related SNVs and is one of the heart rate-related SNVs during sinus rhythm.[49]

Zeemering et al., who performed RNA sequencing in the right and left atrial appendage tissue of AF patients, detected genes associated with persistent but could not find a gene associated with heart failure.[50] Ahlberg et al. reported that *CILP*, which encodes cartilage intermediate layer protein 1, was a genetic marker for atrial and ventricular fibrosis and can promote heart failure.[51] Our group reported that the *HCN4* SNV rs7164883, which encodes the cardiac hyperpolarization-activated cyclic nucleotide-gated I_f channel, was a genetic marker of tachycardia-induced cardiomyopathy in patients with AF.[52] *HCN4* is highly expressed in the conduction system and is involved in heart rate control. In addition, *HCN4* mediates protein kinase A-dependent phosphorylation of sarcoplasmic reticular, mitochondrial, and ion channel proteins and regulates Ca^{2+} cycling.[53]

Regarding the effects of rhythm control treatment in AF, the SNV in rs10033464 at 4q25 was identified as an independent predictor of successful rhythm control in patients with AF using the same antiarrhythmic drugs.[54] Another common SNV in chromosome 4q25 (rs2200733) was reported to be an independent predictor of AF recurrence after cardioversion.[55]



	AF	Non-AF Control	Odds retio (95% CI)	P value
Group1 (WGRS < 2.23)	43 (30.7)	97 (69.2)	1.00 (reference)	
Group2 (2.23≤ WGRS <3.37)	64 (46.3)	74 (53.6)	2.03 (1.24-3.39)	4.76×10^{-3}
Group3 (3.37≤ WGRS <4.17)	73 (52.1)	67 (47.8)	2.46 (1.46-3.97)	6.10×10^{-4}
Group4 (4.17≤ WGRS)	107 (68.5)	49 (31.4)	4.92 (3.08-8.70)	2.32×10^{-10}

FIGURE 2 AF prediction using genetic risk score and clinical factors. (A) There was a 4.92-fold difference in AF risk between the highest and lowest weighted genetic risk score (WGRS) using five AF-associated SNVs (in *PRRX1*, *ZFHX3*, *PITX2*, *HAND2*, and *NEURL1*). WGRS, weighted genetic risk score. (B) Receiver operating characteristic analysis of WGRS yielded an area under the curve (AUC) of 0.73 in the screening cohort. The AF predictive logistic model constructed using a combination of WGRS and AF clinical risk factors (age, body mass index, gender, and hypertension) demonstrated better discrimination of AF than did WGRS alone (AUC, 0.84; sensitivity, 75.4%; specificity, 80.2%).

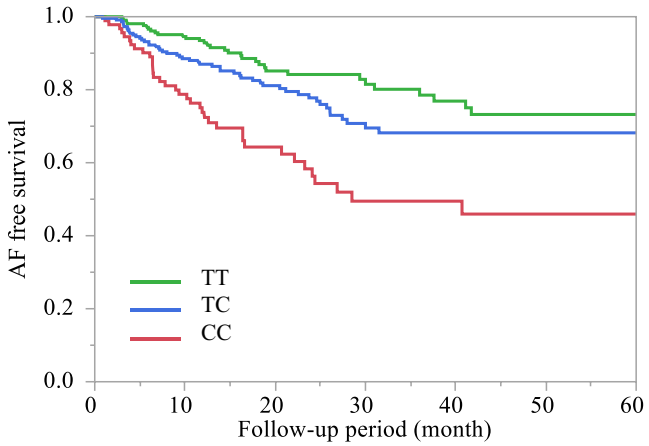


FIGURE 3 Kaplan–Meier analysis of AF recurrence with the *GJA-1* SNP rs1015451 (T > C) in each genotype group. The Kaplan–Meier analysis showed that AF patients with the *GJA1* SNV rs1015451 minor C allele were prone to AF recurrence.

The recurrence of AF after ablation and genetics has also been studied. Reyat et al. reported that patients with decreased left atrial myocyte *PITX2* and increased plasma concentrations of BMP10, an atrial secretory protein suppressed by *PITX2*, were at risk for recurrent AF after ablation.[56] There are conflicting reports regarding whether the SNVs in the *PITX2* gene, which is most implicated in the development of AF, are involved in the recurrence of AF after ablation, with no clear conclusions having yet been reached.[57,58] One report showed that the PRS of AF-associated genes could predict recurrence after AF ablation; however, recent reports have ruled out its involvement.[59,60] Our group reported that AF patients with *GJA1* SNV rs1015451 minor allele are prone to AF recurrence, suggesting its potential as a novel genetic marker for AF recurrence after AF ablation[61] (Figure 3). Thus, it is possible that genes other than those associated with AF participate in the recurrence of AF after ablation, a matter requiring further investigation.

2.5 | Association between AF and genetic cardiomyopathy

Genes associated with AF overlap with those associated with cardiomyopathy and channelopathy. The *SCN5A* gene may provoke an AF phenotype, common in patients who also manifest Brugada syndrome and/or conduction system disease.[62]

Arrhythmia may be the first manifestation of hereditary cardiomyopathy.[63] Yoneda et al. reported that genetic testing identified a disease-associated variant in 10.1% of patients (16.8% in participants with AF diagnosed before the age of 30 years and 7.1% after the age of 60 years). Disease-associated variants (*TTN*, *MYH7*, *MYH6*, etc.) were more often associated with inherited cardiomyopathy syndromes than with inherited arrhythmias.[64] They also reported that the rare variants in cardiomyopathy and arrhythmia genes might be associated with an increased risk of mortality among patients with early-onset AF, especially those diagnosed at a younger age.[65] The most prevalent genes with disease-associated variants were *TTN*, *MYH7*, and *LMNA*, which were found in 26, 33%, and 22% of the patients, respectively.[65] A case–control study also showed an association between an LOF variant in the *TTN* gene and early-onset AF.[65] The frequency of individuals with at least one rare LOF variant in *TTN* was higher in the participants with early-onset AF than in the control participants (2.1% vs. 1.1%).[66] Of individuals with AF onset prior to age 30 years, 6.5% carried a *TTN* LOF variant. *TTN* encodes a sarcomere protein, titin, and the *TTN* variants in early-onset AF partially overlapped with the variants associated with dilated cardiomyopathy.[66] Recently, Bourfiss et al. published an unusual report in which they indicate that although pathogenic and possibly pathogenic SNVs of DCM, HCM, and ARVC are rare, carriers of SNVs with unclear function also raise mortality and morbidity.[67] However, they also stated that clinical symptoms and family history should be considered.[67] Should AF and the cardiomyopathy genes be identified, the next step would be to evaluate other source of evidence for a cardiomyopathy phenotype, such as magnetic resonance imaging, cardiac echocardiography, cardiac biopsy.[63]

3 | SUMMARY

The genetic analysis of AF has significantly evolved from single gene analyses of familial AF subjects to GWASs. However, GWASs do not necessarily cover all aspects of genetic analysis; hence, there are still several genes whose mechanisms of involvement in the disease remain unknown. With the increased prevalence of GWAS, the risk of developing AF is now being examined using PRS. However, the contribution of clinical factors to the risk of AF also appears to be significant, suggesting that prediction models using PRS alone are insufficient. Therefore, the evaluation of such models using various early detection devices is also needed. It may be necessary to construct a model for predicting the onset of AF that integrates not only genes but also biomarkers, Omics, *artificial intelligence*, etc. Genes that predict the onset of AF do not necessarily predict the recurrence of AF after ablation, indicating the need for a GWAS on recurrence alone after AF ablation. Regardless of whether the onset of AF can be accurately predicted, deciding on which intervention is best for the patients is more important. Future studies should therefore focus on effective interventions.

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CONFLICT OF INTEREST STATEMENT

None.

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