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CEP68/FLRT2: The Potential Druggable Genes For Atrial Fibrillation Identified By Systematic Druggable Genome-Wide Mendelian Randomization

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Abstract

Background

Atrial Fibrillation (AF), a globally prevalent arrhythmia with escalating incidence, still lacks effective treatments focusing on its substrate. Mendelian Randomization (MR) has been widely used to discover potential druggable targets. Thus, we aim to explore novel druggable targets for AF through MR analyses.

Methods

We conducted traditional and summary MR analysis integrating obtained druggable genes and AF genome-wide association data to examine the causal effect of cardiac (atrial/ventricular) and blood Expression Quantitative Trait Loci (eQTLs) and blood protein QTLs (pQTLs) on AF. A Phenome-Wide Association Study (PheWAS) was performed to find potential side effects.

Results

Twenty-one druggable genes were identified as potentially associated with AF (ALB, BAZ2A, CASQ2, CEP68, F10, FLRT2, GYPC, HABP4, JAM2, KCNJ5, KDM1B, PMVK, PRKD3, PROZ, PSMC5, PXN, SF3B1, THRB, TNNT3, TPMT, WDR1), two of which (CEP68 and FLRT2) were significant in both cardiac and blood tissue. Further, PheWAS showed that CEP68 was highly correlated with atrial fibrillation/flutter.

Conclusion

This study identified 21 potential druggable target genes for AF utilizing MR and SMR analyses, with 2 of them (CEP68 and FLRT2) showing significant associations in both cardiac tissue and blood. Our findings provide genetic evidence for these targets, which will be useful for AF drug development.

1. Introduction

Atrial Fibrillation (AF) is a supraventricular tachyarrhythmia with uncoordinated atrial activation, resulting in ineffective atrial contraction [1]. Based on data from Global Health Data Exchange, the global incidence of AF in 2017 has been estimated at 3.046 million new cases (403 new cases per million inhabitants) [2]. Projections indicate that, by 2050, the prevalence of AF in the United

States may rise to between 6 and 12 million individuals [3]. A particularly compelling aspect of AF is its genetic predisposition. Empirical studies indicate that individuals diagnosed with AF prior to the age of 60 demonstrate an almost fivefold increased likelihood of having a direct relative with the same condition [4], underscoring the significance of familial medical history in risk assessment.

Over the years, treatments for AF have been widely explored. Currently, most medications predominantly target ventricular rate control [1]. Antiarrhythmic agents like amiodarone, which focus on rhythm control, are associated with more hospitalizations and adverse effects, such as bradycardia and extracardiac toxicities [1, 5, 6]. Despite catheter ablation has been applied to maintain sinus rhythm, it is an invasive procedure associated with complications ranging from cardiac tamponade to stroke [1]. Contemporary management strategies predominantly focus on symptomatic relief rather than addressing the underlying substrate of AF. Furthermore, preventative measures aimed at averting the onset of AF are inadequately defined within current paradigms, and upstream treatment strategies for AF are not well understood [7]. Nevertheless, the development of genomics has broadened the prospects for developing new targeted drugs for modifying the AF substrate. Selecting genetically supported targets can double the success rate of clinical drug development [8]. Over the past few years, the emergence of genome-wide association studies (GWAS) has identified many Single-Nucleotide Polymorphisms (SNPs) associated with AF [9]. At the same time, the global heterogeneity in genetic background makes it challenging to perform downstream analyses using the GWAS approach [10].

To expand on this, Mendelian randomization (MR) offers a methodological framework for assessing the causal relationships between modifiable risk factors and clinical outcomes [11]. By integrating DNA data, including gene expression Quantitative Trait Locus (eQTL) or protein Quantitative Trait Locus (pQTL) with GWAS results, investigators can isolate target genes from risk variants through causal inference methodologies [12]. Thus, we performed a systematic druggable genome-wide MR study to explore the drug targets for the treatment of AF.

2. Materials and Methods

This study did not require ethical approval or participant consent, as it utilized publicly available summary-level GWAS data, with the original studies having already met these ethical requirements. First, we identified potentially druggable genes and filtered the cardiac eQTLs, blood eQTLs, and blood pQTLs data. This data was then subjected to MR and Summary-data-based Mendelian randomization (SMR) analyses using AF GWAS data to pinpoint genes significantly associated with AF. Second, we conducted colocalization analyses and utilized Heterogeneity In Dependent Instruments (HEIDI) tests to determine if the observed associations were mediated by the same causal variant. Finally, we performed a Phenome-Wide Association Study (PheWAS) to explore the relationships between the potentially druggable targets and various characteristics. The diagram of experimental design is presented in (Figure 1).

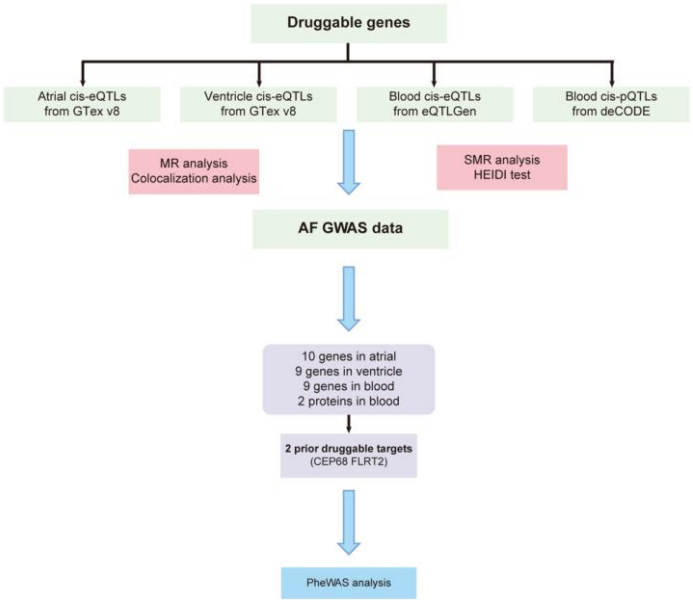

Figure 1: Overview of the study design. AF, atrial fibrillation; MR, Mendelian randomization; SMR, summary Mendelian randomization; HEIDI, heterogeneity in dependent instruments; eQTL, expression quantitative trait loci; pQTL, protein quantitative trait loci; GWAS, genome-wide association studies; PheWAS, Phenome-wide association study.

2.1. Druggable Genes

Our list of druggable genes were sourced from the Drug–Gene Interaction Database [13] and a review conducted by Finan [14], both of which have been referenced by a previous study [15]. The DGIdb is a web-based resource that provides comprehensive information on drug-gene interactions and druggable genes sourced from various publications, databases, and online platforms [13]. We obtained the category data from DGIdb, which was released in February 2022.

2.2. eQTL and pQTL Datasets

The blood eQTL dataset was sourced from eQTLGen, which includes cis-eQTLs for 16,987 genes based on 31,684 blood samples from healthy individuals of European descent [16]. We retrieved significant cis-eQTL results (FDR <0.05) and allele frequency information. Cardiac (atrial/ventricular) eQTL data were sourced from the GTEx project, which encompasses cis-eQTL data from 49 tissues derived from 15,201 samples contributed by 838 donors [17]. Additionally, we acquired blood pQTL data from the deCODE study, which analyzed the associations between 27.2 million sequence variants and 373 diseases and other traits relative to the levels of 4,907 plasma proteins measured in 35,559 Icelanders [18].

2.3. AF Datasets

The summary statistics regarding AF were extracted from the GWAS conducted by Nielsen et al. [9]. This study analyzed a total of 60,620 cases and 970,216 controls of European ancestry from six contributing sources: The Nord-Trøndelag Health Study (HUNT), deCODE, the Michigan Genomics Initiative (MGI), DiscovEHR, UK Biobank, and the AFGen Consortium [9]. A comprehensive overview of all the data sources mentioned can be found in (Table 1).

Table 1: The details of the data source used in this study. AF, atrial fibrillation; eQTL, expression quantitative trait loci; pQTL, protein quantitative trait loci; QTL, quantitative trait loci.

Dataset	Data subtype	Sample size	Population	Study
Druggable genes	DGIdb	/	/	Freshour.SL, et al. 2020 [14]
	Prior druggable gene	/	/	Finan.C, et al 2017 [14]
QTL datasets	Blood cis-eQTL	31,684	European	eQTLGen consortium [14]
	Atrial cis-eQTL	372	European	GTEx consortium [14]
	Ventricle cis-eQTL	386	European	GTEx consortium [14]
	Blood cis-eQTL	35,559	European	deCODE consortium [14]
GWAS	AF GWAS	Cases: 60,620	European	Nielsen.JB, et al. 2018 [14]
		Controls: 970,216		

2.4. AF Datasets

The two-sample MR analyses were performed using the R package TwosampleMR (Version 0.5.9) [19]. We used the eQTLs of the drug genome as our exposure data. SNPs with an FDR below 0.05 and located within 1 MB of each gene's transcriptional start site (TSS) were selected for analysis. Using European samples from the 1000 Genomes Project [20], SNPs were clumped with an r^2 threshold < 0.001. The two-sample MR approach is based on three assumptions: (i) the genetic variants designated as an instrumental variable (IV) are associated with the target exposure, i.e. gene expression levels; (ii) there are no unmeasured confounders influencing the associations between the genetic variants and the outcome; and (iii) the genetic variants affect the outcome solely through their impact on the exposure, indicating no pleiotropy [21]. MR analyses were performed to estimate the effect of the eQTLs of the drug genome on AF. Prior to the MR analysis, we employed MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) [22] to eliminate outlying IVs influenced by pleiotropy. When only one SNP was available for analysis, Wald's ratio method was applied to compute the causal effect. In cases where multiple SNPs were available, Inverse-Variance Weighting

(IVW) was applied [23]. Cochran's Q method was used to estimate heterogeneity [24]. MR-Egger's intercept method was used to evaluate horizontal pleiotropy [25]. The strength of the genetic instruments was indicated by F statistics, with values below 10 suggesting weak instruments [26]. Statistical power was calculated by using the mRnd method [27]. FDR-adjusted P-values were computed to filter the significant SNPs, with a significant threshold set at 0.05.

2.5. Colocalization Analysis

We performed the colocalization analysis using the R package coloc (V.5.2.3.) [28]. This colocalization analysis aims to identify whether the eQTLs and AF are affected by the same genetic variants. We set the prior probability of the SNP being a significant eQTL (p1) at 1 × 10-4; the probability of a SNP being associated with AF (p2) at 1 × 10-4 and migraine (p12) at 1 × 10-5. Colocalization assesses the posterior probability for 5 hypotheses (ppH0–ppH4) [28] and we restricted our analysis to genes reaching the ppH4 value of ≥0.75 [29].

2.6. SMR Analysis and HEIDI Test

Employing the SMR software (V.1.3.1) [30], we conducted the SMR analysis as a supplementary method to confirm the causal effect between AF and eQTLs/pQTLs of the drug genome. This method allows for the exploration of associations between GWAS data and eQTL studies and can also be applied to integrate additional omics information [30, 31]. Additionally, we performed the HEIDI test to validate whether the gene expression and AF share the same causal variant [30]. For the SMR analysis, FDR-adjusted P-values were calculated to address multiple testing concerns. Genes exhibiting pSMR < 0.05 and pHEIDI > 0.05 were deemed significant.

2.7. Phenome Wide Association Analysis

We conducted a PheWAS to identify potential side effects associated with our druggable genes. This method enables the association of a single genetic variant with various phenotypes throughout the phenome [32]. The exposure consisted of the significant druggable genes identified in the previous steps, while the outcomes were obtained from the phenotype statistics of the UK Biobank cohort [33]. This data has been processed by the Scalable and Accurate Implementation of Generalized Mixed Model (SAIGE), which accounts for unbalanced case-control ratios and sample size.

3. Results

3.1. Druggable genome

A total of 3,953 druggable genes were retrieved from the DGIdb (Table S1). Additionally, we sourced another 4,463 druggable genes from a review [14] (Table S2). By merging these datasets, we identified 5,883 distinct druggable genes, which have been officially designated by the Human Genome Organization Gene Nomenclature Committee for further analysis (Table S3).

3.2. MR Analysis and Colocalization Analysis

We intersected previously identified druggable genes with eQTLs derived from atrial, ventricular and blood tissue. The atrial eQTLs comprised 1,093 gene symbols, the ventricular eQTLs contained 1,011 gene symbols, and the blood eQTLs accounted for 7,609 gene symbols. The results of MR analyses are detailed in (Table S4-S6). Our analysis identified 40 significant genes associated with AF in atrial tissue, 38 in ventricular tissue, and 59 in blood tissue. All of these genes exhibited F statistics exceeding 10, indicating no evidence of weak instrument bias. Notably, five genes (ALOX15, CEP68, PNMT, PROZ, WNT3) were found to be significant across all three tissue types, and their MR results are illustrated in (Figure 2).

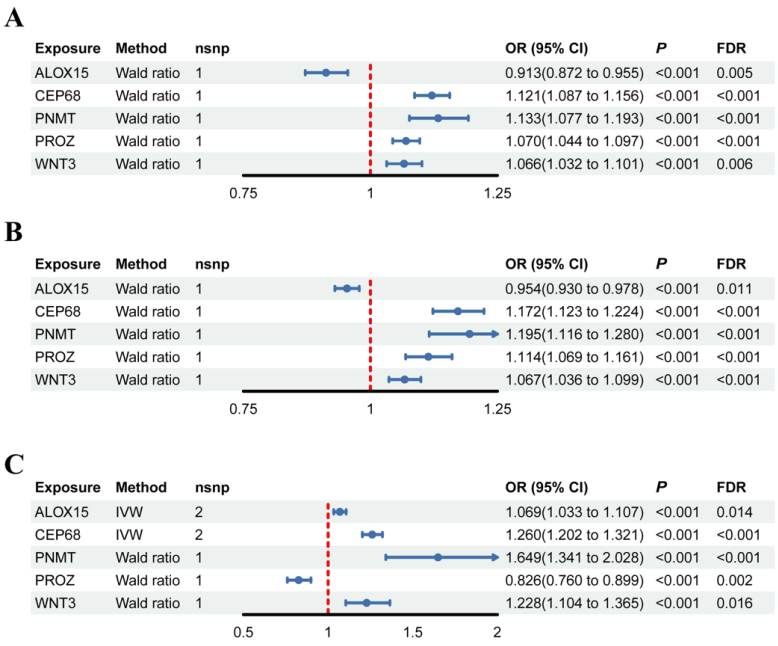

Figure 2: MR results of genes which are significant in all the three tissues. (A) Forest plot for MR results between atrial eQTLs and AF. (B) Forest plot for MR results between ventricle eQTLs and AF. (C) Forest plot for MR results between blood eQTLs and AF. AF, atrial fibrillation; eQTL, expression quantitative trait locus; FDR, false discovery rate; IVW, inverse-variance weighted; MR, Mendelian randomization.

Subsequently, we selected a range of commonly used medications for the treatment of AF, including Amiodarone, Flecainide, Propafenone, Sotalol, Dofetilide, Dronedarone, Disopyramide, Quinidine, Atenolol, Diltiazem, and Digoxin [6]. We obtained their target genes from the Drugbank [34] as a control in our study. Detailed information regarding these drugs and their corresponding target genes is presented in (Table S7), while the results of MR analyses can be found in (Table S8). Notably, only one gene, CACNA1D, showed significant levels in blood tissue; however, this significance was lost after FDR correction (CACNA1D: OR = 0.83, P = 0.032, FDR-P = 0.443).

The significant druggable genes identified were subjected to colocalization analysis. A total of 23 genes exhibited a ppH4 greater than 0.75 (Table S9). Among the five previously mentioned genes, two (PNMT, WNT3) did not yield significant colocalization results. ALOX15 showed significant results in atrial tissue, while CEP68 demonstrated significant findings in both atrial and blood tissue. Additionally, PROZ produced significant results in both atrial and ventricular tissues.

3.3. SMR Analysis and HEIDI Test

To further validate our results, we performed the SMR analysis and HEIDI test (Table S10-S11). In the analysis using eQTLs as the exposure, we compared the MR and colocalization results with those from SMR analysis and HEIDI test, selecting the genes significant in both. This resulted in the identification of 10 genes in atrial tissue (CASQ2, CEP68, FLRT2, GYPC, KCNJ5, KDM1B, PROZ, THRB, TNNT3, TPMT), 9 genes in ventricle tissue (CASQ2, F10, GYPC, KDM1B, PROZ, PXN, THRB, TNNT3, TPMT) and 9 genes in blood tissue (ALB, BAZ2A, CEP68, HABP4, JAM2, PRKD3, PSMC5, SF3B1, WDR1). In the analysis with pQTLs as the exposure, two proteins (PMVK, FLRT2) reached statistical significance in SMR analysis (PMVK: P < 0.001, FDR-P < 0.001; FLRT2: P < 0.001, FDR-P = 0.04), with PMVK also passing the HEIDI-test. Additionally, FLRT2 demonstrated significant results in MR analysis and colocalization in atrial tissue. The MR and SMR analyses result of CEP68 and FLRT2 are summarized in (Table 2).

Table 2: Results of MR and SMR analysis of CEP68 and FLRT2. CI, confidence interval; FDR, false discovery rate; HEIDI, heterogeneity in dependent instruments; MR, mendelian randomization; OR, odds ratio; ppH, Posterior Probability of Hypothesis; SMR, summary-data-based Mendelian randomization.

	SMR analysis					MR analysis					Colocalization	
		b_SMR	se_SMR	p_SMR	p_HEIDI	FDR	OR	95%CI	Q	Pleiotropy	ppH3	ppH4
CEP68	Atrial	0.114	0.017	<0.001	0.795	<0.001	1.121	1.087 to 1.156	NA	NA	0.109	0.891
	Blood	0.226	0.032	<0.001	0.217	<0.001	1.26	1.202 to 1.321	0.728	NA	0.014	0.986
FLRT2	Atrial	-0.122	0.036	0.001	0.71	0.006	0.885	0.831 to 0.942	NA	NA	0.077	0.781
	Blood	-0.106	0.028	<0.001	0.008	/	/	/	/	/	/	/

3.4. Phenome Wide Association Analysis

We conducted PheWAS analyses on the genes CEP68 and FLRT2, both of which yielded significant results in blood and cardiac tissues. Given that most drugs target interactions in the blood, we evaluated whether the target genes in this context correlate with other phenotypes. Our findings indicated a strong correlation between CEP68 and AF and atrial flutter, which aligns with our previous analyses. The PheWAS results for CEP68 are illustrated in (Figure 3). In contrast, FLRT2 showed no significant associations with the phenotypes examined. Detailed results can be found in (Table S12-S13).

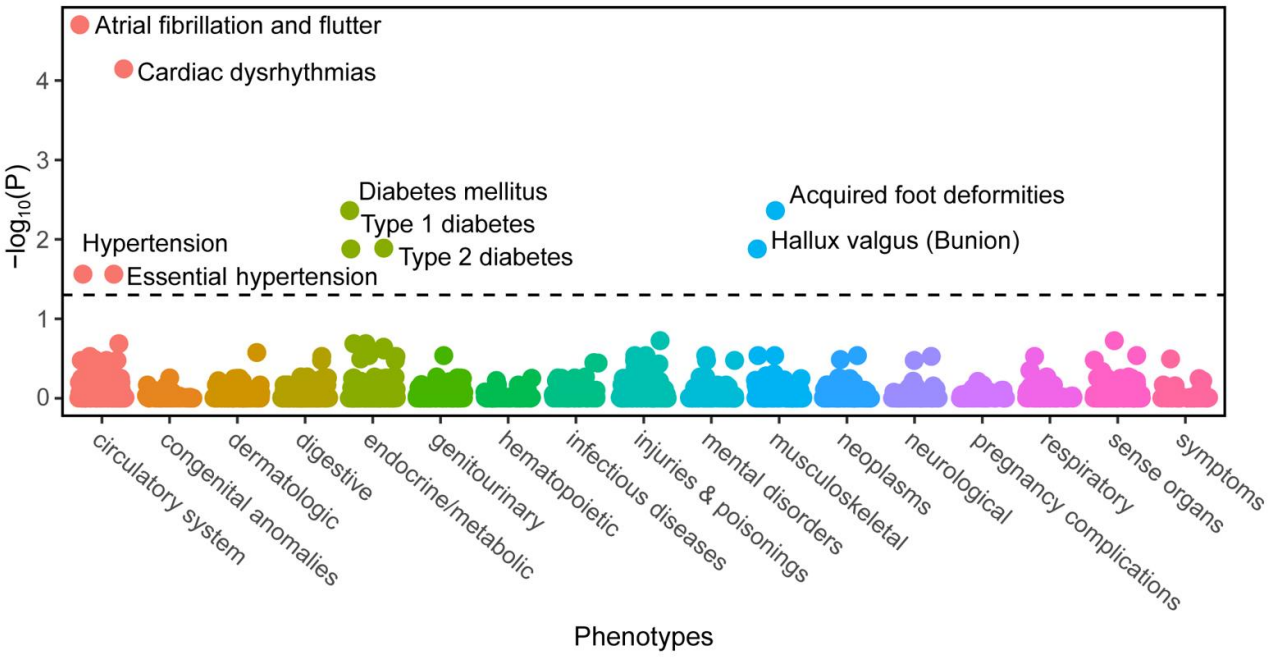

Figure 3: Manhattan plot for phenome-wide MR results of blood CEP68.

3. Discussion

Through MR and SMR analyses, this study has identified 21 potential druggable genes associated with AF: ALB, BAZ2A, CASQ2, CEP68, F10, FLRT2, GYPC, HABP4, JAM2, KCNJ5, KDM1B, PMVK, PRKD3, PROZ, PSMC5, PXN, SF3B1, THRB, TNNT3, TPMT, and WDR1. We subsequently conducted PheWAS on these genes to validate additional phenotypes. Developing medications for AF presents significant challenges; while current drugs primarily focus on symptom control, there are no existing treatments that target the underlying substrate of AF. Our MR analysis of genes associated with commonly used drugs showed no significant associations with AF.

CEP68 and FLRT2 showed significant results in both cardiac and blood tissues. The CEP68 gene, located on chromosome 2p14, plays a crucial role in centrosome cohesion, a process essential for maintaining the structural integrity of the centrosome during the

cell cycle [35]. Notably, differential expression of CEP68 has been linked to environmental smoking [36], which is recognized one of risk factors for AF [37]. A previous study identified CEP68 as a target for tyrosine phosphorylation in Epidermal Growth Factor (EGF) signaling [38], which has been shown to offer the potential cardioprotective effect in the heart [39]. Our MR analysis revealed a positive correlation between CEP68 expression and AF; however, whether EGF exerts cardioprotective effects through CEP68 remains to be confirmed. Additionally, our PheWAS analysis affirmed a strong association between CEP68 and AF. Nevertheless, the biological functions of the CEP68 gene are not yet fully understood. This study provides new insights into the function of CEP68, suggesting its association with AF and its potential as a therapeutic target for treatment.

FLRT2, a member of the fibronectin leucine rich transmembrane protein family, acts as a chemorepellent for Unc5-positive neurons, influencing their migration within the developing cerebral cortex [40]. The clear relationship between FLRT2 and AF remains to be fully elucidated. This protein is widely expressed across various human tissues, including the heart, brain, skeletal muscle, and ovaries [40]. A GWAS study has identified FLRT2 as one of the loci associated with resting heart rate and AF [41], suggesting its potential as a therapeutic target for AF, despite not passing the HEIDI test in blood pQTLs. Research indicates that silencing FLRT2 can accelerate vascular aging, while its overexpression may counteract this effect [42].

Furthermore, FLRT2 plays a crucial role in heart development, particularly in the morphogenesis of the epicardium [43]. Since both vascular aging and epicardial morphogenesis are linked to the pathophysiology of AF [37], drugs targeting FLRT2 could represent a promising avenue for the upstream therapy in AF management. Additionally, a GWAS has highlighted FLRT2's association with resting heart rate and AF [41], reinforcing its relevance. Notably, the expression of FLRT2 in peripheral blood mononuclear cells is diminished in patients with Obstructive Sleep Apnea (OSA) [44], modifiable risk factor of AF [37]. Therefore, therapies targeting FLRT2 may reduce the risk of AF in patients with OSA. In recent years, FLRT2 has emerged as playing a significant role in the development of cancer. Jiang et al. found that FLRT2 suppresses the progression of bladder cancer by inducing ferroptosis, a form of cell death characterized by lipid peroxidation [45]. In breast cancer, FLRT2 is often downregulated due to hypermethylation, leading to increased cell proliferation and migration [46]. Moreover, FLRT2 has been shown to interact with FGFR2, potentially inhibiting the progression of prostate cancer [47]. Recent studies have also reported associations between AF and cancer, revealing several potential mechanisms linking the two conditions [48, 49]. Currently there are no drugs that explicitly target FLRT2. Further basic experiments are needed to investigate the potential role of FLRT2 in the interplay between cancer and AF.

The pathological changes of the atrial substrate, such as atrial fibrosis, structure remodeling and electrophysiological remodeling, are encompassed in the concept of Atrial Cardiomyopathy (ACM) [50], which can progress to stroke and heart failure [50, 51]. Growing evidence identifies AF and sick Sinus Node Dysfunction (SND) as 2 phenotypes of ACM [52–54]. Ischemic stroke (IS) can precede or follow AF diagnosis [55], potentially triggered by AF-induced oxidative stress and endocardial remodeling in atrial cardiomyocytes, processes driving electrical and structural instability [50, 56, 57]. Furthermore, patients with isolated SND also exhibit a substantially elevated risk of IS, indicating the role of the underlying atrial myopathy independent of AF [52, 53, 58–60]. Consequently, developing druggable targets aimed at modifying the atrial substrate may also contribute to preventing AF, SND, and even ACM-related ischemic stroke. Further basic and clinical studies are needed to improve our understanding.

This study has several notable strengths. Firstly, the integration of diverse omics datasets including eQTLs and pQTLs provided a comprehensive and multi-faceted approach to identifying potential druggable targets for AF. Secondly, the incorporation of colocalization analyses and HEIDI test added a valuable layer of causal inference to our findings. These methods contributed to establishing more robust associations between the identified genes and AF, thereby minimizing the likelihood of false negatives and false positives. Furthermore, the comprehensive nature of our druggable gene list ensured that a wide range of potential targets was taken into account. Lastly, PheWAS analysis verified the safety of the druggable targets and informed the drug development strategies.

This study acknowledges several limitations. First, the number of Instrumental Variables (IVs) utilized in MR for eQTL is limited, and with most analyses involving no more than three SNPs. This constraint influences the credibility of the MR findings, suggesting that future research should consider more SNPs. Future research should incorporate a larger number of SNPs for more

comprehensive analyses. Second, the absence of comprehensive pQTL data of cardiac tissue in public databases has hindered our ability to conduct a thorough analysis of pQTLs related to this tissue. The future availability of comprehensive pQTL data for cardiac tissue will deepen our understanding in this domain. Third, the data used in this study were primarily derived from populations of European ancestry, which may not fully represent other ethnic groups. This may constrain the applicability of our results to more diverse populations, thus, genome-wide association studies should be replicated for other population groups. Fourth, the validation of the identified genes was confined to in silico analyses. While MR analyses provided valuable insights, they cannot substitute for essential basic and clinical research. Therefore, more clinical studies are necessary to verify our conclusions in the future.

4. Conclusion

This study identified 21 potential drug target genes for AF using MR and SMR analyses. Among these, two genes, CEP68 and FLRT2, exhibited significant associations in both cardiac tissue and blood. Our findings provide genetic evidence supporting these targets. Although the roles of CEP68 and FLRT2 in AF are not yet fully understood, this study paves the way for future investigations into the pathophysiology of AF and the development of novel therapies. Further clinical studies evaluating the safety and efficacy of drugs targeting these genes are essential for confirming their potential therapeutic benefits.

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