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SNP rs3737883 in *PPFIA4* Gene Associated with Atrial Fibrillation Risk: A Case–Control Study in a Chinese Population

Jiahui Zhuo [1], Pengyun Wang [2] and Chengqi Xu [1,*]

[1] Center for Human Genome Research, Key Laboratory of Molecular Biophysics of the Ministry of Education, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan 430074, China; u202213723@hust.edu.cn

[2] Department of Clinical Laboratory, Liyuan Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430077, China; wpy0110@mail.hust.edu.cn

* Correspondence: cqxu@mail.hust.edu.cn

Abstract

Atrial fibrillation (AF), the most prevalent cardiac arrhythmia, significantly elevates the risk of stroke and heart failure. The etiology of AF is complex and multifactorial, involving genetic predisposition, environmental risk factors, and their potential interactions. A previous genome-wide association study (GWAS) of AF in a Korean population has identified an association between the rs3737883 single-nucleotide polymorphism (SNP) in the *PPFIA4* gene and an increased risk of AF. However, the association needs to be replicated in other populations. In this paper, we conducted a case–control association study including 724 AF cases and 1475 controls, and successfully validated the association between SNP rs3737883 with the risk of AF in a Chinese population (OR = 1.33 with an adjusted p was 2.83×10^{-11}). Given that the *PPFIA4* variant has been reported to influence high-sensitivity cardiac troponin T (hs-cTnT) levels, we further investigated the relationship between rs3737883 and hs-cTnT in 48 AF patients. Notably, we observed that the risk allele was also associated with elevated hs-cTnT levels. Our findings provide further genetic substantiation for the association of rs3737883 with AF. These results suggest a potential association between the *PPFIA4* gene variant, hs-cTnT levels, and AF risk, although further studies are needed to clarify the underlying mechanisms.

Keywords: *PPFIA4*; rs3737883; GWAS; atrial fibrillation; genetics

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1. Introduction

Atrial fibrillation (AF) is the most prevalent clinically significant cardiac arrhythmia, characterized by rapid and irregular beating of the atria [1]. Epidemiological studies estimate its prevalence at 0.7–1.0% in the general population, escalating sharply to ~8% among individuals aged ≥ 80 years, underscoring its age-dependent burden [2]. Meanwhile, AF confers a 2-fold increase in all-cause mortality and it is a major contributor to stroke, congestive heart failure, and sudden cardiac death, collectively imposing substantial global health and economic costs [3].

The important role of genetic factors in the pathogenesis of AF has been demonstrated by the identification of some private, AF-causing mutations in ion channel genes such as *KCNQ1* and *SCN3B* [4,5], and non-ion channel genes such as *NUP155* [6]. Common genomic variants that contribute to the susceptibility of AF were also reported in several cohorts [7–10]. Disease-causing mutations for AF were identified in a small number of families with lone AF and contributed little to common complex AF [11]. Genome-wide

association studies (GWAS) have systematically interrogated the genetic architecture of AF without a priori functional hypotheses, identifying numerous risk loci—predominantly in European-ancestry cohorts, with subsequent replications in East Asian populations [12]. These efforts have revealed that common AF-associated variants frequently modulate cardiac developmental pathways (*e.g., *PITX2*, *ZFHX3*), implicating disturbed atrial structural remodeling as a convergent disease mechanism.

In 2017, Lee et al. performed a two-stage GWAS including 872 early-onset AF cases (≤60 years old) and 5512 controls in a Korean population, and identified five previously proven genetic loci (*1q24/PRRX1*, *4q25/PITX2*, *10q24/NEURL*, *12q24/TBX5*, and *16q22/ZFHX3*) and two novel genetic loci (*1q32.1/PPFIA4* and *4q34.1/HAND2*) associated with early-onset AF [13]. For the five previously proven AF genetic loci found in a Korean population, our group replicated six of them, and found that four loci, including variants in *4q25/PITX2*, *10q24/NEURL*, *12q24/TBX5*, and *16q22/ZFHX3*, were significantly associated with risk of AF in the Chinese population [8,14–16]. SNP was identified in *1q24/PRRX1* and *3p25/CAND2*; however, no significant association was observed in the Chinese Han population [15,17].

In the AF GWAS by Lee et al. in Korea, SNPs rs3737883 in the intron of the *PPFIA4* gene were found to be associated with AF; however, whether this variant is associated with AF in the Chinese population needs to be validated. To robustly validate the genetic association, we conducted a case–control association study comprising 724 AF cases and 1425 controls in a Chinese population. Our analysis confirmed the statistically significant association between SNP rs3737883 and AF risk, reinforcing previous findings and demonstrating population-specific relevance.

2. Materials and Methods

2.1. Study Subjects

All study subjects in the current case–control study were selected among the patients of Liyuan hospital and were self-described to be of Han ethnic origin. This study was approved by the ethics committee of Liyuan hospital, Tongji medical collage of Huazhong University of Science and Technology (No. [2023]IEC(SQ10)), and conformed to the guidelines set forth by the Declaration of Helsinki. Written informed consent was obtained from the participants. The study followed the Strengthening the Reporting of Genetic Association study (STREGA) statement checklist [18], which is an Extension of the STROBE Statement for reporting genetic association studies.

AF diagnosis was rigorously confirmed by at least two independent board-certified cardiologists, in accordance with the AHA/ACC/ESC guidelines [19]. The inclusion criteria were as follows: the diagnosis of AF patients was based on 12-lead electrocardiograms (ECG) and/or 24 h Holter monitoring, with strict adherence to standard electrophysiological criteria, including absence of discernible P waves, replaced by low-amplitude fibrillatory waves (f waves) exhibiting irregular morphology, amplitude, and temporal dispersion. Irregularly irregular ventricular response is characterized by variable RR intervals due to aberrant atrioventricular nodal conduction [20,21]. To ensure a homogeneous AF cohort, we excluded patients with the following: (1) concomitant arrhythmias (e.g., ventricular tachycardia, supraventricular tachycardias other than AF); (2) systemic confounders (e.g., hyperthyroidism, uncorrected thyroid dysfunction); (3) structural heart disease (e.g., congenital anomalies, hypertrophic/dilated cardiomyopathies, moderate-to-severe valvopathies) [22]. Lone AF was defined as AF patients with no CAD, congestive heart failure, hypertension, and diabetes. We limited the recruitment of AF patients to those under the age of 75 years.

Control subjects comprised individuals recruited from the same hospital during the same period, and without any evidence of AF or other types of arrhythmias based on data from ECG. Cases (AF patients) and controls were matched for geographical areas to minimize the confounding of geographical and ethnic factors.

Other data collected for the study subjects included demographic and clinical data on the age, gender, hypertension, and diabetes mellitus available from medical records. Hypertension was defined as ongoing medication of hypertension, systolic blood pressure of $\geq$140 mmHg or diastolic blood pressure of $\geq$90 mmHg. Diabetes mellitus was defined as ongoing diabetes therapy or a fasting plasma glucose level of $\geq$7.0 mmol/L.

2.2. SNP Genotyping

Genomic DNA of all subjects was extracted from blood samples using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) as described previously [23]. Genomic DNA aliquots were cryopreserved at -80 °C in ultralow-temperature freezers to ensure long-term macromolecular stability. Genotyping of rs3737883 was performed using the TaqMan allelic discrimination assay (Applied Biosystems, Foster City, CA, USA) using a QuantStudio 6 Flex (Thermo Fisher Scientific, Waltham, MA, USA) Realtime PCR system [24]. Genotype calling was performed using the automatic allele calling algorithm provided by QuantStudio Software v1.7.2, and all calls were manually reviewed by two independent researchers. Call rates were 100%, and 48 randomly selected samples were re-genotyped by Sanger sequencing with 100% concordance. Case and control status were blinded during experimental procedures.

2.3. hs-cTnT Test

The serum of 48 randomly selected AF patients was collected and hs-cTnT was determined in the serum using an Elecsys 2010 automated immunochemistry analyzer (Roche Diagnostics, Basel, Switzerland). The genotypes of these 48 randomly selected AF patients were analyzed as above. The difference in the mean values (ng/mL) between different genotype carriers was compared using Student's *t*-test.

2.4. In Silico eQTL Analysis

SNPs may associate with the expression levels of *PPFIA4* and act as expression quantitative trait locus (eQTL). We analyzed the data from GTEx (Genotype–Tissue Expression) database and evaluate whether SNP rs3737883 affects the gene expression levels of *PPFIA4*.

2.5. Statistical Analysis

Pearson's 2×2 or 2×3 contingency tables χ^2 tests were used to analyze the allelic or genotypic association between SNP and AF (PLINK, version 1.10,). Risk factors including age, hypertension, gender, and diabetes mellitus were used as potential confounders to adjust the association using a multivariate logistic regression model in SPSS (version 17.0). Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. Statistical power analysis was carried out by PS: Power and Simple Size Calculation software (software 3.1).

Missing data were minimal in the dataset. No missing values were observed for genotype or AF status. Missing covariates were as follows: hypertension (n = 12, 0.54%) and diabetes (n = 8, 0.36%). Age and sex were complete for all participants. Multivariable logistic regression was performed using complete case analysis. A sensitivity analysis using unadjusted models including all individuals yielded similar results.

3. Results

3.1. Study Populations

The case–control population in the current study included 724 AF cases and 1475 AF-free controls. The mean age of the cases was 57.41 ± 9.64 years and 59.63 ± 10.45 years in the controls, and 429 cases (59.2%) out of 724 were early onset with an age lower than 60 years at the first diagnosis (Table 1). A total of 310 out of 724 (65.1%) of AF patients were diagnosed with lone AF (Table 1).

Table 1. Demographic and clinical characteristics of study populations.

Characteristic	AF Cases (n = 724)	AF Controls (n = 1475)	*p*
Age (Years, Mean ± SD) [a]	57.41 ± 9.64	59.63 ± 10.45	1.65×10^{-6}
Gender, Female, n (%)	307 (42.4%)	685 (46.4%)	0.08
Diabetes, n (%)	147	326	0.33
Hypertension, n (%)	273	612	0.09
Lone AF n (%)	310	0	n.a.

[a] The ages of the cases were defined at the first diagnosis. The ages of the controls were defined at the time of enrollment. n.a.: no data.

The study population had enough statistical power (=100%) to detect an association between rs3737883 with AF, and with a type I error of 0.05 under the assumptions that the OR is greater than 1.48, and a risk allelic frequency of 0.61. Call rates were 100%, and 48 randomly selected samples were re-genotyped by Sanger sequencing with 100% concordance. The Hardy–Weinberg equilibrium (HWE) was tested in the control group using a chi-square goodness-of-fit test, and the SNP was in HWE ($p = 0.42$).

3.2. Allele A of rs3737883 Significantly Associated with Increasing AF Risk in a Chinese Population

After comparing the allele frequency of rs3737883 in AF cases and controls, we found a significant association between rs3737883 and AF risk. The frequency of the A allele of rs3737883, which is the risk allele in the previous report in a Korean population, was 0.70 in 724 AF cases and 0.60 in 1475 controls, and the A allele of rs3737883 conferred a significant increasing risk effect of AF in the Chinese population with an OR of 1.34 and an observed *p* value (*p-obs*) of 5.61×10^{-11}. After adjusting for potential confounders including age, hypertension, gender, and diabetes mellitus, the association remained significant (OR = 1.33 with an adjusted *p* or *p-adj* = 2.83×10^{-11}). Complete data for all covariates used in adjusted models were available for 2179 individuals (97.8% of the total sample). The individuals excluded due to missing covariates did not differ significantly in genotype or AF status.

3.3. The Effect of rs3737883 on AF Was Larger in Sub-Group with Hypertension than Sub-Group Without Hypertension

Considering that sex and the conditions of hypertension, diabetes, and lone AF may affect the association, the study population was divided into sub-groups based on gender, and whether individuals suffer from hypertension, type 2 diabetes, and lone AF. SNP rs3737883 showed significant association with AF in males (*p-obs* = 9.58×10^{-8}, *p-adj* = 1.24×10^{-7} with an OR of 1.37), females (*p-obs* = 8.73×10^{-5}, *p-adj* = 3.44×10^{-5} with an OR of 1.30), individuals with hypertension (*p-obs* = 1.24×10^{-8}, *p-adj* = 5.57×10^{-8} with an OR of 1.48), individuals without hypertension (*p-obs* = 2.05×10^{-4}, *p-adj* = 3.21×10^{-4} with an OR of 1.23), individuals with diabetes (*p-obs* = 1.57×10^{-5}, *p-adj* = 6.63×10^{-5} with an OR of 1.30), individuals without diabetes (*p-obs* = 2.27×10^{-7}, *p-adj* = 5.14×10^{-7} with

an OR of 1.55), and individuals with lone AF (*p-obs* = 3.45×10^{-6}, *p-adj* = 6.77×10^{-6} with an OR of 1.32).

A Breslow–Day test was used to compare the homogeneity of ORs between different sub-groups to analyze whether rs3737883 interacted with gender, hypertension or diabetes. The results showed that there were no significant differences between sub-groups divided by gender (observed OR was 1.38 with 95% CI from 1.21 to 1.54 in males and OR was 1.31, 95% CI from 1.14 to 1.51 in females, $p = 0.31$) or by diabetes (observed OR was 1.57 with 95% CI from 1.26 to 1.95 in diabetes and OR was 1.29 with 95% CI from 1.17 to 1.43 in non-diabetes, $p = 0.06$) (Table 2). However, we observed a significant difference in ORs between sub-groups with hypertension and no hypertension (observed OR = 1.49, 95% CI from 1.29 to 1.73 in the sub-group with hypertension and observed OR = 1.24, 95% CI from 1.10 to 1.39 in the sub-group without hypertension, $p = 1.21 \times 10^{-3}$) (Table 2). These results showed that the effect of rs3737883 on AF was larger in the sub-group with hypertension than the sub-group without hypertension.

Table 2. Analysis of allelic association of SNP rs3737883 with AF in the Chinese Han population.

Cohort (n, Case/Control)	Risk Allele	Risk Allele Frequency	Without Adjustment [a]		With Adjustment [b]	
			p-obs	OR (95% CI)	*p-adj*	OR (95% CI)
Total Cohort (724/1475)	A	0.70/0.60	5.61×10^{-11}	1.34 (1.22–1.47)	2.83×10^{-11}	1.33 (1.22–1.48)
Male (417/790)	A	0.69/0.59	9.58×10^{-8}	1.38 (1.21–1.54)	1.24×10^{-7}	1.37 (1.22–1.55)
Female (307/685)	A	0.71/0.61	8.73×10^{-5}	1.31 (1.14–1.51)	3.44×10^{-5}	1.30 (1.13–1.50)
Hypertension (273/612)	A	0.71/0.57	1.24×10^{-8}	1.49 (1.29–1.73)	5.57×10^{-8}	1.48 (1.27–1.71)
Without Hypertension 451/863	A	0.70/0.62	2.05×10^{-4}	1.24 (1.10–1.39)	3.21×10^{-4}	1.23 (1.10–1.38)
Diabetes (147/326)	A	0.74/0.60	1.57×10^{-5}	1.29 (1.17–1.43)	6.63×10^{-5}	1.30 (1.17–1.42)
Without Diabetes (577/1149)	A	0.70/0.60	2.27×10^{-7}	1.57 (1.26–1.95)	5.14×10^{-7}	1.55 (1.21–1.92)
Lone AF (310/1475)	A	0.70/0.60	3.45×10^{-6}	1.33 (1.17–1.51)	6.77×10^{-6}	1.32 (1.16–1.50)

p-obs: *p* value observed, *p-adj*: *p* value with adjustment, OR: odds ratio. [a] Uncorrected *p* value and odds ratio (OR) using Chi-square tests with Pearson's 2 × 2. [b] Adjusted *p* value by multivariate logistic regression analysis for potential confounders including age, gender, hypertension, and diabetes mellitus.

3.4. The Risk A Allele of rs3737883 Associated with a Higher Expression Level of PPFIA4 in Left Ventricle Tissue in the Human Heart

We performed an in silico eQTL analysis using the GTEx database, and the results showed that rs3737883 is associated with an expression level of *PPFIA4* in the left ventricle tissue of the human heart (n = 386). The carriers of the risk A allele of rs3737883 were found to have a higher *PPFIA4 mRNA* expression level in the left ventricle ($p = 1.77 \times 10^{-5}$) (Figure 1A). Rs3737883 located in the intron of the *PPFIA4* gene (Figure 1B), and whether it has a real biological function is unknown, or the real target gene needs to be further studied. We also investigated the predicted deleterious effects of rs3737883 using the Combined Annotation Dependent Depletion (CADD) score. Rs3737883 showed a significantly high CADD score (12.66) and demonstrated it is predicted to be deleterious.

3.5. The Risk A Allele of rs3737883 Is Associated with a Higher Serum hs-cTnT Level in AF Patients

Yang et al. conducted a transethnic GWAS on hs-cTnT and hs-cTnI levels in 24,617 and 14,336 participants free of coronary heart disease and heart failure from six population-based cohorts, and identified a novel locus rs3737882 in *PPFIA4* for hs-cTnT. The SNPs rs3737882 and rs3737883 reside within the same linkage disequilibrium (LD) block ($r^2 = 0.98$, and are separated by merely 49 bp on the genome), indicating their tight linkage. We further investigated the relationship between rs3737883 and hs-cTnT in the Chinese population. Notably, in 48 samples with AF, we observed that the risk allele A for AF was also associated with elevated hs-cTnT levels. The concentration was significantly

higher in 21 AA carriers (10.77 ± 3.31 ng/L) than in 27 patients with AG and GG genotype carriers (7.81 ± 2.42 ng/mL) ($p < 0.001$) (Figure 2).

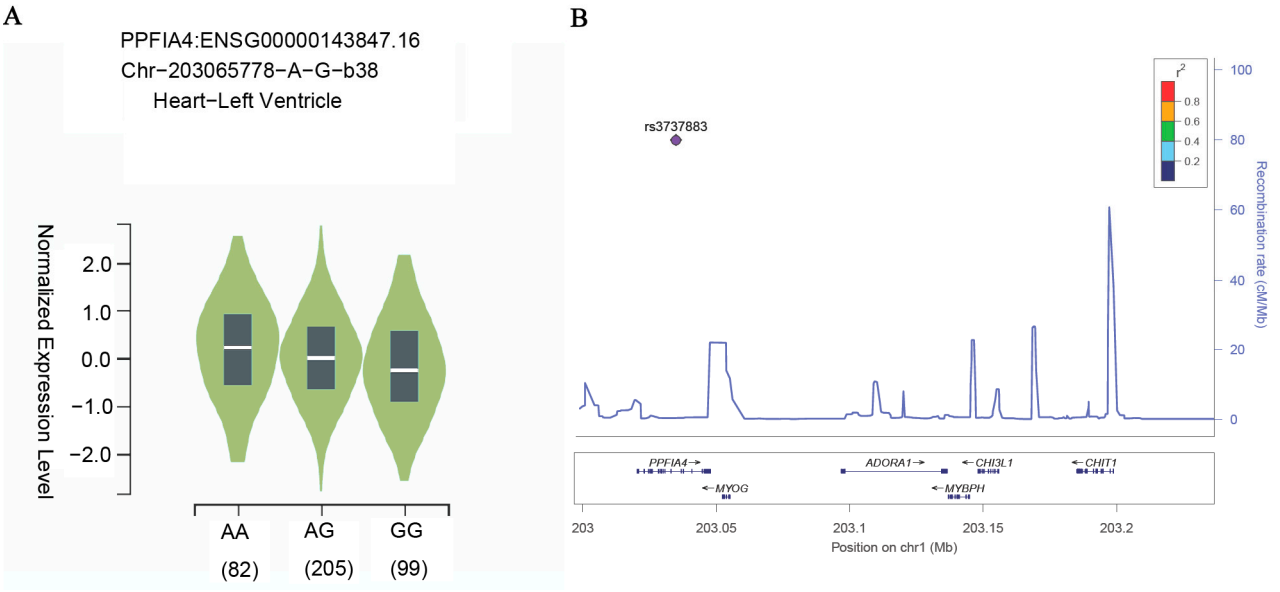


Figure 1. eQTL analysis showed that rs3737883 is associated with an expression level of *PPF1A4*. (**A**) in silico eQTL analysis using the GTEx database, and the carriers of the risk A allele of rs3737883 were found to have a higher *PPFIA4 mRNA* expression level in the left ventricle ($p = 1.77 \times 10^{-5}$). (**B**) rs3737883 located in the intron of the *PPFIA4* gene.

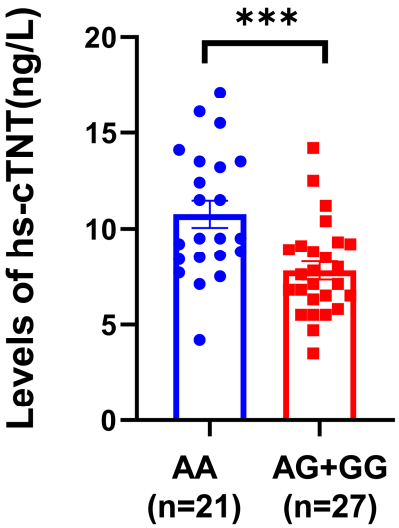


Figure 2. Risk A allele of rs3737883 is associated with higher serum hs-cTnT level in AF patients. Difference in serum hs-cTnT level between patients with different genotypes of rs3737883. hs-cTnT was determined in the serum using an automated immunochemistry analyzer. *** means $p < 0.001$.

4. Discussion

In this study, we assessed the association between rs3737883 in 1q32.1 with AF in a Chinese population. In the case–control population containing 724 AF cases and 1475 controls, rs3737883 was observed to be significantly associated with AF, and the A allele confers risk to AF. We also observed a larger effect of rs3737883 on AF in subjects with hypertension. What is more, we observed that the risk A allele of rs3737883 is associated with a higher expression level of *PPFIA4* in the left ventricle tissue in the human heart, and the risk A allele of rs3737883 is associated with a higher serum hs-cTnT level in AF patients.

GWAS were conducted between genomic variants and a disease trait at the whole genome level without prior assumptions of genomic locations or potential functions of candidate genes. In this case, most of the identified SNPs associated with disease were found to be located within intergenic or intronic genomic regions, and it has yet to be determined whether the positive SNPs have a real biological function or if the real target gene needs to be further studied [25–27]. Previous studies showed that 50–60% of the traits associated non-coding variants identified by GWAS were found located in DNase I hypersensitivity regions, and many of them act as cis-expression quantitative trait loci and are associated with the expression level of target genes [26,28]. In the study of Hsu et al., which combined the genome-wide gene expression data of left atrial appendages from 265 subjects and their SNP genotype data, twelve reported that AF genome-wide association loci displayed genome-wide significant cis-expression quantitative trait loci, at *PRRX1* (chromosome 1q24), *SNRNP27* (1q24), *CEP68* (2p14), *FKBP7* (2q31), *KCNN2* (5q22), *FAM13B* (5q31), *CAV1* (7q31), *ASAH1* (8p22), *MYOZ1* (10q22), *C11ORF45* (11q24), *TBX5* (12q24), and *SYNE2* (14q23) [29]. In the study of Hsu et al., they did not find any cis-eQTL effect for rs3777883 and other reported AF susceptibility SNPs in 1q32.1 in human left atrial appendages; these results were the same as in the GTEx database, which showed that rs3777883 significantly affects the gene expression level of *PPFIA4* in the left ventricle tissue (n = 386, $p = 5.9 \times 10^{-5}$), but not in the atrial appendages (n = 372, $p = 0.08$). These results suggested that rs3777883 may affect the risk of AF through regulating the expression level of *PPFIA4* in the left ventricle, but not in the atrial.

Both prior and current studies demonstrate that rs3777883 is significantly associated with elevated hs-cTnT levels, which are themselves prospectively linked to AF risk [30,31]. This aligns with the well-documented observation that AF patients exhibit higher troponin levels, even in the absence of acute coronary syndromes [18]. Furthermore, hs-cTnT independently predicts cardiovascular disease progression and mortality in AF populations, reinforcing its role as a prognostic biomarker [32]. We observed that rs3737883 is associated with both AF risk and elevated hs-cTnT levels. However, given the observational nature of this case–control study, we cannot infer causality or conclude that hs-cTnT mediates the association between the variant and AF. This dual association may point to shared biological pathways, but further functional and longitudinal studies are required to explore these relationships. Intriguingly, rs3777883 is also a cis-eQTL for *PPFIA4*, a gene highly expressed in cardiac, skeletal, and brain tissues. While *PPFIA4*'s role in AF remains underexplored, its tissue-specific expression pattern raises compelling questions about its potential involvement in electrical or structural atrial remodeling.

Several limitations must be acknowledged in interpreting our findings. First, the observational nature of this study constrains causal inference, and the potential for selection bias exists due to the hospital-based recruitment of participants, which may not fully represent the broader Chinese Han population. Second, time-varying confounding and unmeasured confounders which could potentially influence the observed association, including lifestyle factors, medication use, or subclinical cardiovascular conditions, could not be accounted for. Although we adjusted for major covariates, residual confounding cannot be ruled out. Third, pleiotropy represents a key limitation: while we previously discussed it as a supportive mechanism, the fact that rs3737883 is associated with both AF and hs-cTnT levels may reflect shared biological pathways or independent effects, complicating causal interpretation. Future studies should employ mediation analyses to clarify whether hs-cTnT lies on the causal pathway between the SNP and AF or whether these represent parallel outcomes. Fourth, misclassification of AF outcome is possible, particularly in the control group, where undiagnosed or subclinical AF may have gone undetected due to the absence of long-term cardiac monitoring. Fifth, despite adequate

statistical power for the main analysis, the sample size for hs-cTnT analysis (n = 48) was small, increasing the risk of type II error and limiting the generalizability of this secondary finding. Lastly, although we used a stringent significance threshold, the possibility of type I error due to multiple testing in sub-group analyses remains. These limitations underscore the need for larger, population-based cohorts with longitudinal follow-up, detailed phenotyping, and functional validation to confirm and extend our findings.

While this study reinforces the genetic association between *PPFIA4* variant rs3737883 and AF risk in a Chinese population, its clinical utility remains exploratory. The identified variant could potentially contribute to polygenic risk scores (PRS) for AF, particularly when combined with established clinical risk factors such as age, hypertension, and hs-cTnT levels. However, large-scale, prospective cohorts are needed to validate its predictive value before translation into routine clinical use.

5. Conclusions

To our knowledge, this is the first study to establish rs3737883 as a robust AF-susceptibility variant in a Chinese population. Our findings suggest that the association between this variant and AF may coincide with elevated hs-cTnT levels, but further studies are needed to determine whether this reflects a causal pathway or a parallel association.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the ethics committee of Liyuan hospital, Tongji medical collage of Huazhong University of Science and Technology (No. [2023]IEC(SQ10)). Approval date: 31 August 2023.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript:

AF	atrial fibrillation
hs-cTnT	high-sensitivity cardiac troponin T
GWAS	Genome-wide association studies
eQTL	expression quantitative trait loci
SNP	single nucleotide polymorphism
OR	odds ratio

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