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Bone morphogenetic protein 10 and atrial fibrillation

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ABSTRACT

Background: The association between bone morphogenetic protein 10 (BMP10) and atrial fibrillation (AF) has been widely investigated by observational studies, but their causal relationships remain inconclusive. Here, we aimed to evaluate the causal effect of BMP10 on the risk of AF through single-nucleotide polymorphisms.
Methods: A Mendelian randomization (MR) analytic framework was applied to data from two BMP10-specific genome-wide association studies comprising a total of 11,036,163 single-nucleotide polymorphisms of European ancestry. Instrument genetic variants associated with BMP10 were selected. A total of 12 AF-specific genome-wide association studies comprising a total of 5,095,117 European participants were included. Summary statistic-based methods of inverse variance weighted, MR Egger, weighted median, simple mode, and weighted mode methods were used. Pleiotropy and sensitivity were assessed.
Results: Specific to AF-specific genome-wide association studies, we found that BMP10 was not associated with AF among different methods (all $P > 0.05$). We further identified no significant horizontal pleiotropy (all $P > 0.05$) and no fundamental impact among various data.
Conclusions: This large-scale population study upon data from BMP10- and AF-specific genome-wide association studies and a longitudinal biobank cohort indicates plausible non-causal associations between BMP10 and AF in the European populations. Further studies regarding ancestral diversity are warranted to validate such causal associations.

1. Introduction

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia [1]. It occurs when a diffuse and chaotic pattern of electrical activity in the atria suppresses or replaces the normal sinus mechanism. AF is accountable for extensive population morbidity, mortality, and health care expenditure [2]. In the United States, approximately 2.3 million people are presently diagnosed with AF and this number is expected to increase to 5.6 million by 2050 [3]. The typical pathological change in patients with AF is atrial arrhythmogenic remodeling, which is defined as any change in atrial structure or function that promotes atrial arrhythmias [4]. Atrial remodeling can be due to underlying cardiac conditions and systemic processes and conditions such as aging, or AF itself. However, the underlying molecular biological mechanisms are not yet fully understood, let alone causal relationships.

Bone morphogenetic protein 10 (BMP10) is a member of the transforming growth factor β (TGF-β) superfamily and is an atrial-specific biomarker released to blood during atrial development and structural changes [5,6]. BMP10 acts directly on vascular smooth muscle cells for induction and maintenance of their contractile state [7]. In addition to age, sex, body mass index, and other biomarkers, BMP10 identified patients with prevalent AF with an AUC of 0.743 [8]. Two studies indicated that elevated BMP10 outperformed 11 other cardiovascular biomarkers in predicting recurrent AF after catheter ablation [9,10]. BMP10 and AF are closely related, but the causal relationship between them is not yet clear.

Mendelian randomization is a complementary approach to epidemiologic observations that uses genetic variation as an instrumental

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variable and assesses its association with clinical outcomes [11]. Due to the nature of genetic randomization, Mendelian randomization could explore the causal association. Here, we used the summary-level data of BMP10 as the exposure and the summary-level data of AF as the outcome to investigate the causal relationship between BMP10 and AF.

2. Methods

We conducted a 2-sample Mendelian randomization analysis of BMP10 on AF using summary-level data from publicly available genome-wide association studies from similar populations of predominantly European ancestry of each of BMP10 and AF. All studies comprising the genome-wide association studies have existing ethical permissions from their respective institutional review boards and include participant-informed consent and rigorous quality control. However, as this study was derived from summary-level data, ethics approval was not required for the present study.

2.1. Data source

Our primary genetic instruments for BMP10 were derived from the largest, predominantly white European ancestry, publicly available summary association data (ID prot-a-254) with 3,301 participants and 10,534,735 single-nucleotide polymorphisms [12]. We used another summary data (ID prot-c-3587_53_1) with 501,428 single-nucleotide polymorphisms [13] as validation (Table S1).

The outcome data were from three platforms, namely European Molecular Biology Laboratory-European Bioinformatics Institute, FinnGen, and United Kingdom Biobank. We used summary data of ebi-a-GCST006414 with 1,030,836 participants (60,620 cases and 970,216 controls) and 33,519,037 single-nucleotide polymorphisms [14], ebi-a-GCST006061 with 537,409 participants (55,114 cases and 482,295 controls) and 12,095,506 single-nucleotide polymorphisms [15], ebi-a-GCST90013902 with 407,746 participants and 11,039,196 single-nucleotide polymorphisms [16], and ebi-a-GCST90013952 with 407,746 participants and 11,037,947 single-nucleotide polymorphisms [16] from European Molecular Biology Laboratory-European Bioinformatics Institute, finn-b-I9_AF with 138,994 participants (22,068 cases and 116,926 controls) and 16,379,794 single-nucleotide polymorphisms, finn-b-I9_AF_EXNONE with 218,792 participants (22,068 cases and 196,724 controls) and 16,380,466 single-nucleotide polymorphisms, and finn-b-I9_AF_REIMB with 127,442 participants (10,516 cases and 116,926 controls) and 16,379,586 single-nucleotide polymorphisms from FinnGen and ukb-a-536 with 337,199 participants (3,818 cases and 333,381 controls) and 10,894,596 single-nucleotide polymorphisms, ukb-b-11550 with 462,933 participants (3,518 cases and 459,415 controls) and 9,851,867 single-nucleotide polymorphisms, ukb-b-6217 with 463,010 participants (6,900 cases and 456,110 controls) and 9,851,867 single-nucleotide polymorphisms, and ukb-b-964 with 463,010 participants (5,669 cases and 457,341 controls) and 9,851,867 single-nucleotide polymorphisms from United Kingdom Biobank. We also included FinnGen_AF from FinnGen, a large public–private partnership aiming to collect and analyze genome and health data from 500,000 Finnish biobank participants (Table S1).

2.2. Instrument genetic variants selection

We included all single-nucleotide polymorphisms associated with BMP10 ($P < 1 \times 10^{-5}$) as the instrument genetic variants and pruned all single-nucleotide polymorphisms with the stringent pairwise linkage disequilibrium (based on a distance window of 10,000 kB and an R^2 of 0.001) to ensure statistical independence. Besides, we checked the F statistics for the selected single-nucleotide polymorphisms to avoid weak instrument bias [11] (single-nucleotide polymorphisms with F statistic values >10 were considered to be independently associated with BMP10).

2.3. Assumptions of Mendelian randomization

All selected instrument genetic variants met the following hypotheses: (1) The selected variants are significantly associated with BMP10, (2) The selected variants are not associated with any other known confounders, (3) The variants have an effect on AF only through BMP10.

2.4. Mendelian analysis

We applied 2-sample Mendelian randomization using association estimates derived from the abovementioned data. We extracted the instrument genetic variant–specific association estimates with AF and harmonized the direction of estimates by effect alleles. Then we computed Mendelian randomization estimates for each instrument with the Wald estimator. We calculated standard errors with the Delta method. For Mendelian randomization analysis, we used inverse variance weighted along with the complementary MR Egger, weighted median, simple mode, and weighted mode methods to assess the evidence of the causal effects of each of BMP10 on AF as consistency of results across methods strengthens an inference of causality [17]. We used the inverse variance weighted method to evaluate the heterogeneity in instrument effects. If there was heterogeneity (Cochran Q statistic < 0.05), inverse variance weighted with a random effects model was conducted, otherwise, inverse variance weighted with a fixed effects model was conducted.

2.5. Pleiotropy assessment

Mendelian randomization estimates derived from the inverse variance weighted approach could be biased in the presence of directional horizontal pleiotropy. The MR-Egger regression allows for the estimation of an intercept term that can be used as an indicator of unbalanced directional pleiotropy. MR-Egger provides less precise estimates and relies on the assumption that the strengths of potential pleiotropic instruments are independent of their direct associations with the outcome. The intercept obtained from MR-Egger regression was used as a measure of unbalanced pleiotropy (Pegger < 0.05 indicated significance).

2.6. Sensitivity analysis

MR-PRESSO regresses the instrument genetic variant-AF estimates against the instrument genetic variant-BMP10 estimates to test for outlier instrument genetic variants. Outliers are detected by sequentially removing all variants from the analyses and comparing the residual sum of squares as a global measure of heterogeneity ($P < 0.05$ for detecting outliers); outliers are then removed and outlier-corrected estimates are provided. MR-PRESSO still relies on the assumption that at least half of the variants are valid instruments.

2.7. Statistical analysis

All analysis was conducted with the *TwoSampleMR* package (version 0.5.6) [17] in the R environment (version 3.6.3).

3. Results

3.1. Instrument genetic variants selection

After clumping, we included 18 and 2 single-nucleotide polymorphisms as instrument genetic variants in prot-a-254 and prot-c-3587_53_1, respectively (Table S2). Since the limited instrument genetic variants in prot-c-3587_53_1, only prot-a-254 was used as exposure data in the subsequent analysis. The F statistics of all included variants were more than 10 (Table S2).

3.2. Mendelian analysis

In Mendelian randomization analysis, we found that there was heterogeneity in ebi-a-GCST006061 and ebi-a-GCST006414 (all Q < 0.05) and there was no heterogeneity in ebi-a-GCST90013902 and ebi-a-GCST90013952 (Q = 0.157 and 0.159, respectively), so inverse variance weighted with a fixed effects model was conducted in the ebi-a-GCST006061 and ebi-a-GCST006414 whereas inverse variance weighted with a random effects model was conducted the ebi-a-GCST006061 and ebi-a-GCST006414. From the inverse variance weighted method, BMP10 did not associate with AF (OR = 1.03 (0.96–1.11), $P = 0.399$, and OR = 1.01 (0.96–1.06), $P = 0.636$, OR = 1.06 (0.95–1.18), $P = 0.293$, and OR = 1.06 (0.95–1.18), $P = 0.297$ in ebi-a-GCST006061, ebi-a-GCST006414, a-GCST90013902, and ebi-a-GCST90013952, respectively) (Fig. 1, Figure S1&S2). MR Egger, weighted median, simple mode, and weighted mode methods obtained consistent results (Fig. 1).

In FinnGen outcome data, we found no heterogeneity in finn-b-I9_AF, finn-b-I9_AF_EXNONE, finn-b-I9_AF_REIMB, and FinnGen_AF (Q = 0.922, 0.376, 0.694, and 0.558, respectively), so inverse variance weighted with a fixed effects model was conducted. From the inverse variance weighted method, BMP10 did not associate with AF (OR = 1.01 (0.95–1.08), $P = 0.790$, and OR = 1.01 (0.96–1.07), $P = 0.621$, OR = 1.01 (0.93–1.10), $P = 0.884$, and OR = 1.02 (0.97–1.06), $P = 0.520$ in finn-b-I9_AF, finn-b-I9_AF_EXNONE, finn-b-I9_AF_REIMB, and FinnGen_AF, respectively) (Fig. 2, Figure S3&S4). Other methods obtained consistent results (Fig. 2).

We found heterogeneity in ukb-a-536, ukb-b-11550, ukb-b-6217, and ukb-b-964 (Q = 0.002, 0.008, 0.011, and 0.000, respectively) in United Kingdom Biobank, so inverse variance weighted with a random effects model was conducted. From the inverse variance weighted method, BMP10 did not associate with AF (OR = 1.00 (1.00–1.00), $P = 0.678$, and OR = 1.00 (1.00–1.00), $P = 0.691$, OR = 1.00 (1.00–1.00), $P = 0.674$, and OR = 1.00 (1.00–1.00), $P = 0.802$ in ukb-a-536, ukb-b-11550, ukb-b-6217, and ukb-b-964, respectively) (Fig. 3, Figure S5&S6). Other methods obtained consistent results (Fig. 3).

3.3. Pleiotropy assessment

The MR-Egger intercept test identified no significant horizontal pleiotropy ($P = 0.285$, 0.197, 0.714, and 0.705 in ebi-a-GCST006061, ebi-a-GCST006414, a-GCST90013902, and ebi-a-GCST90013952, $P = 0.56$, 0.05, 0.86, and 0.49 in finn-b-I9_AF, finn-b-I9_AF_EXNONE, finn-b-I9_AF_REIMB, and FinnGen_AF, and $P = 0.701$, 0.491, 0.531, and 0.069 in ukb-a-536, ukb-b-11550, ukb-b-6217, and ukb-b-964, respectively) among various data (Figs. 1–3).

3.4. Sensitivity analysis

The leave-one-out analysis identified no fundamental impact (Figure S7), which indicated the results were robust.

4. Discussion

Our two-sample Mendelian randomization design allowed us to estimate the impact of genetically predicted BMP10 on AF and we found no causal relationship between BMP10 and AF. Previous large-scale clinical trials investigated the role of BMP10 in AF. The baseline BMP10 plasma concentrations in 1,112 AF patients who underwent a first elective catheter ablation were measured in the prospective Swiss-AF-PVI cohort study. After a 12-month follow-up, patients with increased BMP10 plasma concentrations had a 2.28-fold probability of AF recurrence in an unadjusted Cox proportional hazard model and a 1.98-fold probability after multivariable adjustment [10]. Another study also demonstrated elevated plasma concentrations of BMP10 outperformed 11 other cardiovascular biomarkers in predicting recurrent AF after catheter ablation [9]. In addition to increasing the recurrence rate of AF after catheter ablation, elevated BMP10 is also associated with ischaemic stroke in patients with AF. Plasma BMP10 was measured in patients with AF without oral anticoagulation in the ACTIVE A and AVERROES trials (2,974 patients), and with oral anticoagulation in the ARISTOTLE trial (13,079 patients). The novel atrial biomarker BMP10 was independently associated with ischaemic stroke in patients with AF irrespective of oral anticoagulation treatment and seems to be more specifically related to the risk of ischaemic stroke in AF [18]. This study also found that BMP10 was not independently associated with bleeding or death in patients with AF [18]. However, Swiss-AF which included 2,219 patients concluded for every 1 ng/mL increase in BMP10, all-cause death increased 1.60-fold and major adverse cardiovascular events increased 1.54-fold [19]. Although BMP10 is associated with some outcome indicators in patients with AF, the causal relationship between BMP10 and AF is first proposed here through single-nucleotide polymorphisms.

Our study has several strengths. We systemically explored the causal relationship between BMP10 and AF at the genetic level leveraging AF-specific genome-wide association study data of 2,383,737 AF cases and controls from European Molecular Biology Laboratory-European Bioinformatics Institute, 985,228 AF cases and controls from FinnGen, and 1,726,152 AF cases and controls from United Kingdom Biobank for the first time. Additionally, we only chose single-nucleotide polymorphisms

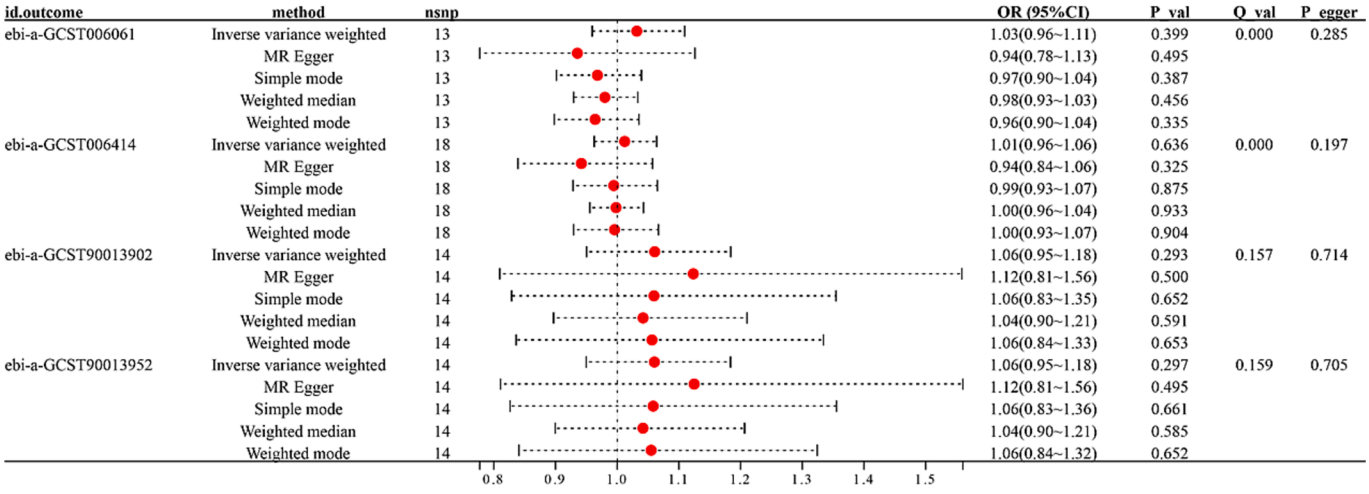

Fig. 1. Associations of BMP10 with AF in European Molecular Biology Laboratory-European Bioinformatics Institute.

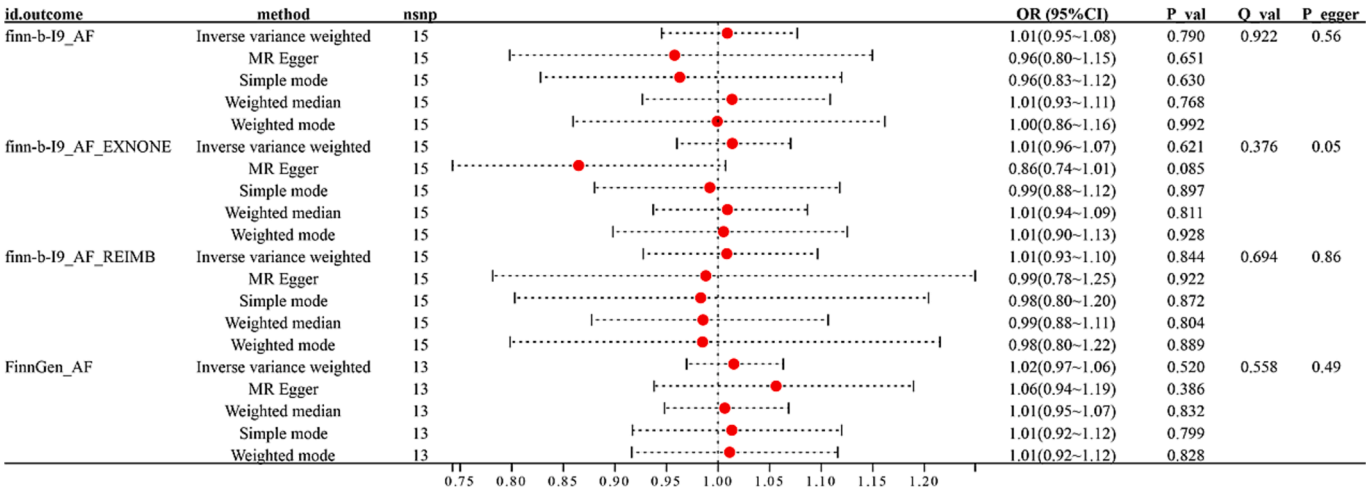

Fig. 2. Associations of BMP10 with AF in FinnGen.

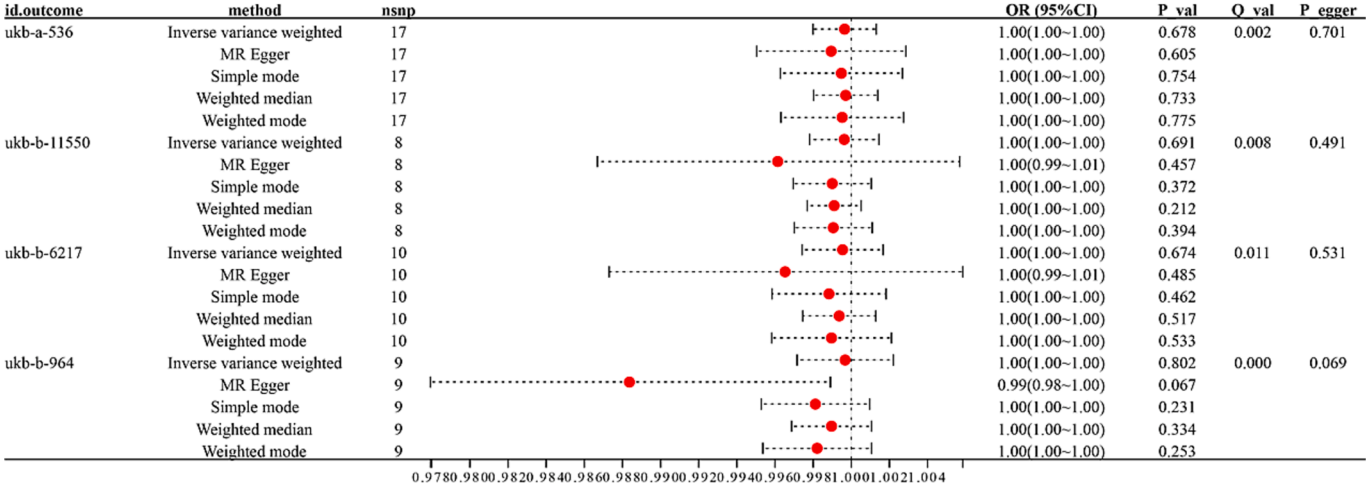

Fig. 3. Associations of BMP10 with AF in United Kingdom Biobank.

with conventional genome-wide significance for the instruments to strengthen causal inference. Finally, we used multiple Mendelian randomization methods based on individuals of European descent, providing confidence in result robustness and largely reducing population stratification.

There are still some limitations that need to be acknowledged. Due to the limited genome-wide association study data related to BMP10, we can only choose a more relaxed threshold for screening instrument genetic variants, but this threshold has been validated in previously published articles [20–22]. Similarly, because we do not have the authority to obtain specific BMP10 levels, we cannot conduct linear and nonlinear Mendelian randomization studies. Fortunately, there is no direct causal relationship between BMP10 and AF, and these analyses may not be of much significance at the moment. Finally, it is necessary to identify more variables related to circulating BMP10 and data from multiple races to further validate our results.

In conclusion, we first discussed the causal relationship between BMP10 and AF through the Mendelian randomization analysis. The non-causal relationship we get is more accurate because these estimates are less affected by socio-economic, environmental, and behavioral factors. In conclusion, there is no causal relationship between BMP10 and AF.

Ethics approval and consent to participate

Review and/or approval by an ethics committee was not needed for this study because our research is based on public databases.

Availability of data and material

All the data generated or analyzed during this study are included in this published article and its supplementary information files.

CRediT authorship contribution statement

Liang Liu: Data curation, Formal analysis, Writing – original draft. **Yi Liang:** Funding acquisition, Methodology, Resources, Writing – original draft. **Qi-Gang Lan:** Investigation, Resources, Supervision. **Jun-Zhang Chen:** Methodology, Software, Validation. **Rui Wang:** Investigation, Resources, Visualization. **Jing-Hong Zhao:** Formal analysis, Project administration, Software, Writing – review & editing. **Bo Liang:** Formal analysis, Methodology, Software, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101376.

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