Original Article

The genetic architecture of blood pressure variability: A genome-wide association study of 9370 participants from UK Biobank

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Abstract
Long-term blood pressure variability (BPV) is a risk factor for cardiovascular diseases, dementia, and stroke. However, its genetic architecture is not fully understood. This study aims to explore its genetic factors and provide more evidence on the mechanisms and further pathological study of BPV. The genome-wide association study (GWAS) is based on the UK Biobank cohort. There were four data collection rounds from 2006 to 2020, and 9370 participants with more than three blood pressure measurements were included. They had a median age of 55 and a male percentage of 50.1%. The phenotypes (BPV) were calculated by four methods and the genetic data contains 6,884,260 single nucleotide polymorphisms (SNPs) after imputation and quality control. A linear regression model was performed with adjustments for sex, age, genotype array, and a significant principal component. Subgroup analysis was performed on hypertension-free participants. The significant and suggestive significant P thresholds were set as $5 \times 10^{-8}$ and $1 \times 10^{-6}$. Six genetic loci (BAD, CCDC88B, GPR137, PLCB3, RPS6KA4 for systolic BPV, and WWC2 for diastolic BPV) were identified by coding region SNPs at the suggestive significant P threshold ($1 \times 10^{-6}$). Among them, gene CCDC88B and RPS6KA4 reached the significant P threshold ($5 \times 10^{-8}$), with the strongest signal of SNP rs1229536170 ($P = 6.36 \times 10^{-8}$, $\beta = -0.29$). The annotation results indicate that genes CCDC88B, GPR137, RPS6KA4, and BAD are associated with long-term SBPV. Their functions of inflammation, epithelial dysfunction, and apoptosis are related to artery stiffness, which was reported as potential mechanisms of BPV.

KEYWORDS
blood pressure, genetic variation, genome-wide association study, polymorphism, single nucleotide
1 | INTRODUCTION

Blood pressure variability (BPV) means the variation between different blood pressure measurements during a period, such as hours, days, months, or years. Accumulating evidence demonstrated that BPV might contribute to end-organ damage (EOD) independent of blood pressure levels, increasing the risk of cardiovascular disease, cerebrovascular disease, and dementia. In clinical settings, the necessity of hypertension treatment was widely accepted for preventing EOD and avoiding consequent lethal complications associated with hypertension, while BPV is seldom considered. However, observational studies suggested that hypertensive persons with high BPV had a higher risk of EOD, and some animal studies indicated that BPV might play a more critical role than blood pressure level in EOD.

Both genetic and environmental factors can influence BPV, while exploration of the genetic factors of BPV is challenging due to the complex requirement of obtaining longitudinal blood pressure readings and genetic sequences on the same population. To the best of our knowledge, several GWAS studies focused on the time-age changing of blood pressure, and only one GWAS study has explored the genetic factor of BPV. It was performed in 2013 based on the Anglo-Scandinavian Cardiac Outcome Trial study, with a sample size of 3802 and a phenotype of Variation Independent of Mean (VIM, calculated by fitting a model for SD of blood pressure and mean blood pressure for individuals), identifying 17 correlated single nucleotide polymorphisms (SNPs) within gene NLGN1 on chromosome 11.

The UK Biobank is a prospective cohort study conducted in the United Kingdom with four rounds of data collection between 2006 and 2020. Blood pressure readings and genotyping data were included in the UK Biobank cohort. This GWAS was conducted based on UK Biobank data to identify the significant genetic variants and related genes that determine blood pressure variation. To better target the causal SNPs, downstream fine-mapping methods were also performed. Functional annotation and expression quantitative trait loci (eQTLs) analysis were included in this study to understand better the role of genetic variants in the biological mechanisms of BPV. This study aims to explore the genetic factors of BPV and provide insight into further pathological and therapeutic studies of BPV.

2 | METHOD

2.1 | Data source and study setting

The analysis relied on the UK Biobank datasets (approved application number: 65563). The UK Biobank is a prospective cohort study conducted in the United Kingdom. More than 500,000 people aged from 40 to 69 years old were recruited from England, Scotland, and Wales between 2006 and 2010 and underwent a range of surveys, physical measurements, and chemical tests. Blood, urine, and saliva were also collected. There were four rounds of data collection, and the median dates of four visits were January 2009, January 2013, May 2018, and February 2020. Genotyping was performed on the UK BiLEVE array (50,000 participants) and the UK Biobank Axiom array (450,000 participants).

During each visit, the resting blood pressure was measured by Omron 705 IT electronic blood pressure monitor. The participant was asked to sit with their feet parallel, toes pointing forward, and the soles of their feet flat on the floor. The right arm was only used if the left was not practical. During each data collection round, the mean value of blood pressure readings would be calculated if there were more than one measurement in UK Biobank data collection within a few minutes. Before calculation, abnormal blood pressure (more than 200 or less than 20 mmHg) values were removed. Electronic blood pressure monitor values were preferred, and manual readings would be used if there were no electronic blood pressure readings. Hypertension diagnosis was derived from baseline self-report, including hypertension diagnosis and medication. BMI was calculated from height and weight measured during the initial Assessment Centre visit. If either height or weight readings were omitted, BMI would be estimated by impendence measurement.

2.2 | Inclusion criteria

The cohort used for this GWAS study consisted of UK Biobank participants with "white British" ancestry, which is derived from both principal component (PC) analysis and self-declared ethnicity. Genetic ethnic grouping showed that 409,585 participants had white British ancestry, and all of them were self-reported as "white British" in the baseline survey. Only those who had at least three blood pressure measurements were included in the genome-wide analysis study among white British ancestry participants (Figure 1).

Totally 501,136, 20,332, 43,047, and 3859 participants had BP measurements during different data collection rounds. Eventually, 10,891 participants had more than three BP measurements, and 9413 were white British. Participants who withdrew from UK Biobank were also excluded.

2.3 | Phenotype

The interested phenotypes were systolic and diastolic BPV, which were calculated using different blood pressure readings measured in different follow-up visits. We applied different methods in this study: (1) Standard Deviation (SD); (2) Coefficient of Variation (CV), defined as SD/mean; (3) Average Real Variability (ARV), calculated as the average absolute difference between consecutive measurements; (4) Successive Variation (SV), defined as the square root of the average squared difference between successive blood pressure measurements.

2.4 | Genotyping

2.4.1 | Pre-individual quality control

Removed individuals that meet any of the following conditions: (1) missing SNPs more than 2%; (2) had sex discrepancy between health.
records and genotype data; (3) heterozygosity rate that deviated more than 3 SD from the mean; (4) detected highly related individual pairs (pi-hat more than .2) and removed individuals with a lower call rate.

2.4.2 Pre-marker quality control

Removed SNPs that meet any of the following conditions: (1) missing rate more than 2%; (2) the minor allele frequency less than .01; (3) Hardy-Weinberg equilibrium p-value less than $1 \times 10^{-6}$.

2.4.3 Imputation and post-quality control

Genotyping and imputation were performed based on 1000 Genomes Project Phase 3 Reference Panel on Michigan Imputation Server. Then, SNPs with MAF < .05 or missing rate > 2% were excluded from the analytical genetic data.

2.5 GWAS

The linear regression model was performed on those genetic data and different phenotypes, with adjustments for sex, age, genotype array (BiLEVE and Axiom array), and significant principal component (PC). Principal component analysis (PCA) was conducted on EIGENSOFT 6.1.4, the most widely used implementation of PCA. Then the significant PCAs was included as covariates instead of using first 10 or 20 PCAs empirically. GWAS on SD, CV, ARV, and SV were conducted for SBP and DBP. If a SNP in any of the four results was significant, then it would be included as a significant SNP. Each GWAS result was summarized by Manhattan plots. Quantile-quantile (Q-Q) plots were used to detect the systematic differences between actual p-values and expected p-values. The significant p-value was set as $5 \times 10^{-8}$, and the suggestive significant p-value was $1 \times 10^{-6}$. GWAS was conducted on PLINK 1.9. Manhattan plots and Q-Q plots were plotted by R 4.0.5.

2.6 Downstream analysis

2.6.1 Heuristic fine-mapping

Heuristic fine-mapping and Bayesian fine-mapping were used in this study. Heuristic fine-mapping method was conducted by examining the correlation ($r^2$) among the SNPs surrounding a lead SNP (SNP with the most significant p-value) in each region and remaining SNPs with $r^2 \geq .8$. This method was based on 1000 Genome Project and performed on FUMA GWAS, which is an online tool that merges those related databases for convenient genetic analysis.

2.6.2 Bayesian fine-mapping

Bayesian methods was performed on PAINTOR by calculating the posterior inclusion probability (PIP), ranking SNPs by their PIP and selecting the top SNPs that with a sum probability of 95% (95% credible sets). Higher weight would be given to SNPs in coding region. Bayesian fine-mapping has advantages compared with other fine-mapping methods and tends to select the minimum set of SNPs as potentially causal SNPs.

2.6.3 Conditional analysis

Conditional analysis was performed before Bayesian fine-mapping to confirm the assumption that only one potential causal SNP exists in each risk region. It means taking the leading SNP as a covariate and running GWAS again to see the p-values of the remaining SNPs. The significant threshold for conditional analysis was $1 \times 10^{-4}$. If there were no significant signals after conditional analysis, this region could be considered as an independent region with only one potential causal SNP. Otherwise, we need to partition the region into smaller ones to ensure no significant signals in addition to the leading SNP.

2.6.4 Functional annotation and eQTL analysis

SNPs were annotated to the nearest gene within $+200$ kB with 1000 Genome Project Phase 3 as reference panel, and ANNOVAR as annotation database. Then, the gene expression level was evaluated from GTEx database in 30 general tissues and 54 tissue types, and the results were presented by a heatmap plot. Those procedures were also conducted on FUMA GWAS.
2.7 | Subgroup analysis

A subgroup analysis was performed on participants without hypertension to reduce the influence of high blood pressure. Hypertension was defined according to diagnosis and blood pressure medication in a health survey.

2.8 | Sensitivity analysis

A looser P threshold was set as $5 \times 10^{-6}$ both in the primary analysis and subgroup analysis to see whether the results were robust.

3 | RESULT

3.1 | Population

Forty-three participants with more than 2% missing SNPs were excluded from 9413 participants, and 9370 participants with 6884260 SNPs were eligible for GWAS analysis. The population had an average age of 55, an average BMI of 26.56, and male proportion of 50.1%. For SBP, the median value, ARV, SD, CV, and SV were 136.83, 3.16, 8.39, 6.17, 11.18 mmHg. For DBP, median value, ARV, SD, CV, and SV were 79.67, 2.45, 5.03, 6.39, 6.60 mmHg. Among those participants, 32% of them were diagnosed with hypertension, 8.6% of them had hypertension medication, and 9.7% participants had BiLEVE genotype array batch. BPV were calculated by four different ways using those BP readings.

3.2 | GWAS and downstream analysis

3.2.1 | GWAS

The whole procedure of GWAS and downstream analysis are shown in Figure 1. The 9370 participants and 6884260 SNPs remained for GWAS analysis after imputation and quality control. Sixty-eight SNPs (on chromosome 3, 7, and 11) achieved genome-wide suggestive significance ($1 \times 10^{-6}$) for SBPV. Among them, 20 SNPs reached significant P-value ($5 \times 10^{-8}$) and the strongest signal was rs574087 (11: 64102948: A: G, $p = 3.19 \times 10^{-10}, \beta = -0.97$). The reference allele was the minor allele G, which means this variant will increase SBPV by 0.97 mmHg compared with major allele. The results were summarized on Manhattan plot (Figure 2 and S1). For DBPV, 15 SNPs (on chromosome 3, 4, 5, and 15) were identified at suggestive significant P-value ($1 \times 10^{-6}$), with the strongest signal of SNP rs1229536170 (3: 11093952, $p = 6.36 \times 10^{-8}, \beta = -0.29$), while there was no SNP reaching significant P-value.

3.2.2 | Fine-mapping

GWAS result with P threshold of $1 \times 10^{-6}$ was used for further downstream analysis. Ninety-five and 62 SNPs were identified respectively for SBPV and DBPV when heuristic fine-mapping was applied on SNPs identified from GWAS. Conditional analyses were performed on different regions, and all P-value were larger than $1 \times 10^{-4}$, which means there was no significant SNP after taking lead SNP as covariates. It
could be assumed that each region had only one potential causal SNP. An example of locusZoom plot was shown in Figure S2.

Then with the one potential causal SNP assumption, Bayesian fine-mapping method was performed on different risk regions. The 95% credible sets had 54 SNPs for SBPV and 62 SNPs for DBPV. The detailed information was displayed in Tables 1 and 2. The strongest signals in SBPV (rs574087) and DBPV (rs1229536170) and the 20 SNPs that reached significant p-value in SBPV GWAS were all remained after fine-mapping.

3.2.3 Functional annotation and eQTL

For SBPV, 54 SNPs mapped 15 genes, and five were in the protein-coding region of gene BAD, CCDC88B, GPR137, PLCB3, and RPS6KA4 on autosome 11. Annotation results are shown in Table 1. The expression of those different genes is displayed in Figure 3. Gene CCDC88B encodes a member of the hook-related protein family and is highly expressed in the brain cerebellar hemisphere and cerebellum, cells EBV transformed lymphocytes and spleen. Gene CPR137 has a broad expression in the testis, brain, and other 24 tissues. Gene RPS6KA4 and BAD are widely expressed in different tissues.

For DBPV, 10 genes were matched by 62 SNPs, and only gene WWC2 was mapped by coding area SNPs (Table 2). Gene WWC2 encodes a member of the WW-and-C2-domain-containing family of proteins. This gene has high expression in lungs, kidneys, and other 23 tissues.

Additionally, annotation was performed on all the SNPs identified from the GWAS result, heuristic fine-mapping, and Bayesian fine-mapping result, ensuring that the fine-mapping methods did not prune essential SNPs.

3.3 Subgroup analysis

There were 3016 hypertensive patients and 6354 hypertension-free participants among 9370 participants. We conducted a subgroup analysis on 6354 hypertension-free participants. The result showed that 14 SNPs reached a suggestive P threshold ($1 \times 10^{-6}$) for SBPV, with three SNPs located in the coding region of gene CCDC88B. For DBPV, 15 SNPs reached a suggestive P threshold ($1 \times 10^{-6}$), but none of them were located in coding regions.

3.4 Sensitivity analysis

A looser significant P threshold was set as $5 \times 10^{-6}$, and the results were shown in Table 3. For SBPV, genes identified by coding region SNPs coincided with the results of a threshold of $1 \times 10^{-6}$ both in the primary and subgroup analysis. For DBPV, gene WWC2 and CCD2D1A were identified in the primary analysis, while gene ZBBX was identified in the subgroup analysis.

4 DISCUSSION

In this GWAS study, 54 SNPs within 15 genes and 62 SNPs within ten genes were related to SBPV and DBPV, respectively. Gene BAD, CCDC88B, GPR137, PLCB3, and RPS6KA4 were identified for SBPV by coding region SNPs, among which the strongest signal of SNP rs574087 mapped gene CCDC88B. Gene WWC2 was associated with DBPV and identified by coding region SNPs. Among these six loci, gene CCDC88B and RPS6KA4 reached a significant P-value ($5 \times 10^{-8}$).

A larger body of evidence showed that 24-h blood pressure varies in response to humoral influences (endothelial), local vasomotor phenomena, arterial stiffness, behavioral factors, and other factors. However, there was little information about the mechanisms of long-term BPV.

Among that incomplete evidence, artery stiffening is one of the potential factors as it was known to be majorly responsible for BP variations with aging. Previous studies reported that the possibly involved genes for arterial stiffness included renin-angiotensin-aldosterone system elastic fiber structural components, apoptosis of endothelial cells and the immune response within the vascular wall. In this GWAS study, the identified genes associated with systolic BP play roles in inflammatory functions, epithelial cell function, and cell death, which were related to arterial stiffness, one of the suspected mechanisms of why blood pressure varies during a longer period.

They were also reported as potential mechanisms of how BPV influences EOD and other diseases. Gene CCDC88B is related to inflammatory functions and has high expression in the brain cerebellar hemisphere and cerebellum (Figure 3). While gene RPS6KA4 encodes proteins that phosphorylate histone H3 to regulate certain inflammatory genes and are also involved in phosphorylation. It is worth noting that phosphorylation was found to be a regulator for vascular tone and blood pressure. Gene GPR137 modulates epithelial cell function and cell apoptosis, and has high expression in the brain (Figure 3). Gene BAD has high expression in almost all tissues and is related to cell death. These findings provide more evidence for the previously proposed mechanisms and provide clues to pathological research, advancing our understanding of BPV and its potential drug targets for the preventing or treating unstable blood pressure.

The previous GWAS study of BPV had a sample size of 3802 and applied VIM as BPV. There were six common methods to calculate blood pressure variation: SD, CV, ARV, SV, VIM, and RSD (Residual Standard Deviation, calculated as residual mean square after fitting a linear regression to blood pressure against time). Several studies discussed the correlation between those different variations and blood pressure levels but lacked evidence for which method could best characterize the “real variation.” This study applied GWAS on SD, CV, ARV, and SV for both SBP and DBP, although VIM and RSD could not be calculated with the limitation of the frequency of BP measurements.

This study also has some limitations due to the difficulty of gaining longitudinal blood pressure readings and genetic data simultaneously. Although in previous observational studies on BPV and other diseases, three times BP measurements were often used even in some large population studies. It does not mean three times of BP measure-
### TABLE 1  Bayesian fine-mapping and annotation results for SBPV (54 SNPs)

| CHR | BP   | SNP            | A1   | p       | β   | BPV   | nearestGene                  | Freq | Function    |
|-----|------|----------------|------|---------|-----|-------|-------------------------------|------|-------------|
| 3   | 11090603 | rs35696236 | C    | 3.25E-07 | −.78 | SV    | SLC6A1                       | .17  | intergenic  |
| 3   | 11092104 | rs2138506   | C    | 1.59E-06 | −.70 | SV    | intergenic                   | .19  | intergenic  |
| 3   | 11092264 | rs11711623 | T    | 1.72E-06 | −.70 | SV    | intergenic                   | .19  | intergenic  |
| 3   | 11093952 | rs1229536170 | T   | 1.71E-07 | −.34 | CV    | intergenic                   | .27  | intergenic  |
| 3   | 11095722 | rs9854512   | A    | 8.48E-07 | −.71 | SV    | intergenic                   | .20  | intergenic  |
| 3   | 11095837 | rs9854424   | A    | 1.25E-06 | −.71 | SV    | intergenic                   | .20  | intergenic  |
| 7   | 47041582 | rs2189926   | G    | 8.76E-07 | .31  | CV    | AC004901.1; AC004870.4; AC004870.3 | .32  | ncRNA_intronic |
| 7   | 47042254 | rs6966942   | G    | 8.00E-07 | .31  | CV    | intergenic                   | .32  | ncRNA_intronic |
| 7   | 47047098 | rs4720569   | C    | 6.87E-07 | .31  | CV    | intergenic                   | .32  | ncRNA_intronic |
| 7   | 47063000 | rs2881492   | T    | 7.17E-07 | .31  | CV    | intergenic                   | .32  | ncRNA_intronic |
| 7   | 47064608 | rs4724529   | G    | 7.17E-07 | .31  | CV    | intergenic                   | .32  | ncRNA_intronic |
| 7   | 72126227 | rs569158324 | G   | 3.01E-07 | .86  | SV    | TYW1B                        | .14  | intronic    |
| 7   | 72126231 | rs55891215 | G    | 3.83E-07 | .85  | SV    | intergenic                   | .14  | intronic    |
| 7   | 156411149 | rs849074  | C    | 4.50E-07 | .37  | CV    | LINC01006                    | .19  | ncRNA_intronic |
| 7   | 156413325 | rs849071  | G    | 6.09E-06 | .48  | SD    | intergenic                   | .20  | ncRNA_intronic |
| 7   | 156416554 | rs1100329 | T    | 5.95E-06 | .48  | SD    | intergenic                   | .20  | ncRNA_intronic |
| 7   | 156416810 | rs1100328 | C    | 5.95E-06 | .48  | SD    | intergenic                   | .20  | ncRNA_intronic |
| 7   | 156423876 | rs77573976 | A    | 1.70E-05 | .45  | SD    | intergenic                   | .20  | ncRNA_intronic |
| 7   | 156427201 | rs1860157  | C    | 3.12E-05 | .44  | SD    | intergenic                   | .20  | ncRNA_intronic |
| 11  | 64109118 | rs647152   | G    | 3.38E-10 | .10  | ARV   | CCDC88B                      | .38  | intergenic  |
| 11  | 64104488 | rs61886886 | T    | 4.68E-10 | .10  | ARV   | intergenic                   | .38  | intergenic  |
| 11  | 64105929 | rs499425   | A    | 5.54E-10 | .10  | ARV   | intergenic                   | .38  | intergenic  |
| 11  | 64106291 | rs1783521  | C    | 5.54E-10 | .10  | ARV   | intergenic                   | .38  | intergenic  |
| 11  | 64106317 | rs11231757 | T    | 5.54E-10 | .10  | ARV   | intergenic                   | .38  | intergenic  |
| 11  | 64109118 | rs647152   | G    | 3.88E-10 | .10  | ARV   | exonicb                      | .38  | exonicb     |
| 11  | 64110668 | rs574835   | A    | 4.02E-10 | .10  | ARV   | exonicb                      | .38  | exonicb     |
| 11  | 64110683 | rs479552   | C    | 3.89E-10 | .10  | ARV   | exonicb                      | .38  | exonicb     |
| 11  | 64110422 | rs11601860 | T    | 3.39E-10 | .10  | ARV   | intronic                     | .38  | intronic    |
| 11  | 64089588 | rs646153   | T    | 3.38E-10 | .10  | ARV   | PRDX5                        | .38  | downstream  |
| 11  | 64039175 | rs2286615  | A    | 2.89E-07 | .10  | ARV   | BAD; GPR137                  | .18  | exonicb     |
| 11  | 64138805 | rs11542299 | C    | 3.67E-07 | .08  | ARV   | RPS6KA4                      | .39  | exonicb     |
| 11  | 64138905 | rs17857342 | G    | 3.67E-07 | .08  | ARV   | exonicb                      | .39  | exonicb     |
| 11  | 64026639 | rs12146487 | A    | 4.75E-07 | .10  | ARV   | PLCB3                        | .18  | exonicb     |
| 11  | 64052447 | rs2510066  | T    | 5.01E-10 | .10  | ARV   | GPR137                       | .38  | UTR5        |
| 11  | 64053157 | rs887314   | G    | 4.50E-10 | .10  | ARV   | intronic                     | .38  | intronic    |
| 11  | 64087642 | rs627425   | T    | 5.39E-10 | .10  | ARV   | PRDX5                        | .38  | intronic    |
| 11  | 64097233 | rs694739   | G    | 6.89E-10 | .10  | ARV   | AP003774.1                   | .38  | upstream    |
| 11  | 79385728 | rs7940535  | T    | 2.28E-06 | .94  | SV    | intergenic                   | .09  | intergenic  |
| 11  | 79391059 | rs34584627 | A    | 9.10E-07 | .97  | SV    | intergenic                   | .09  | intergenic  |
| 11  | 79392577 | rs34705210 | T    | 1.03E-06 | .97  | SV    | intergenic                   | .09  | intergenic  |
| 11  | 79394392 | rs12797948 | A    | 1.03E-06 | .97  | SV    | intergenic                   | .09  | intergenic  |
| 11  | 79395583 | rs7945511  | G    | 1.05E-05 | .90  | SV    | intergenic                   | .09  | intergenic  |
| 11  | 79398748 | rs11237967 | A    | 1.52E-05 | .89  | SV    | intergenic                   | .09  | intergenic  |

(Continues)
### TABLE 1
(Continued)

| CHR | BP   | SNP    | A1  | p         | β  | BPV  | nearestGene | Freq | Function    |
|-----|------|--------|-----|-----------|----|------|-------------|------|-------------|
| 11  | 79399466 | rs11237968 | C   | 1.29E-05  | .89 | SV   | .09 intergenic |
| 11  | 79399607 | rs11237969 | A   | 1.72E-05  | .88 | SV   | .09 intergenic |
| 11  | 79399623 | rs11237970 | A   | 1.29E-05  | .89 | SV   | .09 intergenic |
| 11  | 79400940 | rs7118863  | A   | 1.67E-05  | .88 | SV   | .09 intergenic |
| 11  | 79401271 | rs56118860 | A   | 1.51E-05  | .89 | SV   | .09 intergenic |
| 11  | 79401362 | rs55750340 | A   | 1.69E-05  | .88 | SV   | .09 intergenic |
| 11  | 79401429 | rs56139986 | A   | 1.51E-05  | .89 | SV   | .09 intergenic |
| 11  | 79401612 | rs12363915 | T   | 2.11E-05  | .87 | SV   | .09 intergenic |
| 11  | 79401886 | rs12360999 | A   | 1.69E-05  | .88 | SV   | .09 intergenic |
| 11  | 79404322 | rs11237971 | A   | 2.00E-05  | .87 | SV   | .09 downstream |

| CHR | BP   | SNP    | A1  | p         | β  | BPV  | nearestGene | Freq | Function    |
|-----|------|--------|-----|-----------|----|------|-------------|------|-------------|
| 13  | 31813821 | rs1441067441 | C   | 7.12E-07  | −.79 | SD   | B3GALTL | .08 intronic |

*aThe strongest signal.

bexonic: means coding region.

### TABLE 2
Bayesian fine-mapping and annotation results for DBPV (62 SNPs)

| CHR | BP   | SNP    | A1  | p         | β  | BPV  | nearestGene | Freq | function    |
|-----|------|--------|-----|-----------|----|------|-------------|------|-------------|
| 3   | 11093952a | rs1229536170 | C   | 6.36E-08  | −.29 | SD   | SLC6A1 | .27 intergenic |
| 3   | 56246822 | rs79211524 | C   | 6.39E-07  | −.50 | SD   | ERC2 | .06 intronic |
| 4   | 184190233 | rs11941467 | T   | 2.80E-05  | .46 | SV   | WW2   | .10 exonicb |
| 4   | 21088509 | rs12506214 | A   | 8.15E-07  | .47 | CV   | KCNIP4 | .11 intronic |
| 4   | 21105955 | rs139184666 | A   | 2.33E-07  | .49 | CV   | .11 intronic |
| 4   | 21109682 | rs147216622 | T   | 3.06E-07  | .49 | CV   | .11 intronic |
| 4   | 21111646 | rs11938045 | G   | 4.34E-07  | .48 | CV   | .11 intronic |
| 4   | 21115516 | rs16870400 | C   | 2.96E-07  | .49 | CV   | .11 intronic |
| 4   | 21120875 | rs73802496 | G   | 2.62E-07  | .49 | CV   | .11 intronic |
| 4   | 184194444 | rs75389451 | C   | 6.96E-06  | .49 | SV   | WW2 | .10 intronic |
| 4   | 184197460 | rs79960663 | C   | 3.22E-06  | .51 | SV   | .10 intronic |
| 4   | 184197976 | 4:184197976 | G   | 3.78E-06  | .51 | SV   | .10 intronic |
| 4   | 184200189 | rs528650186 | C   | 3.20E-06  | .51 | SV   | .10 intronic |
| 4   | 184200190 | rs547122124 | A   | 3.20E-06  | .51 | SV   | .10 intronic |
| 4   | 184204777 | rs10520555 | T   | 3.10E-06  | .51 | SV   | .10 intronic |
| 4   | 184207362 | rs3749594 | G   | 3.23E-06  | .51 | SV   | .10 intronic |
| 4   | 184207778 | rs11930293 | C   | 3.23E-06  | .51 | SV   | .10 intronic |
| 4   | 184208522 | rs80202922 | A   | 2.79E-06  | .52 | SV   | .10 intronic |
| 4   | 184211478 | rs60761033 | A   | 3.27E-06  | .51 | SV   | .10 intronic |
| 4   | 184215688 | rs41457144 | T   | 4.02E-06  | .51 | SV   | .10 intronic |
| 4   | 184216958 | rs1000514384 | C   | 3.44E-06  | .51 | SV   | .10 intronic |
| 4   | 184221986 | rs73006721 | A   | 2.60E-06  | .52 | SV   | .10 intronic |
| 4   | 184222034 | rs73006723 | C   | 3.07E-06  | .52 | SV   | .10 intronic |
| 4   | 184222089 | rs73006725 | C   | 2.60E-06  | .52 | SV   | .10 intronic |
| 4   | 184222489 | rs73006729 | A   | 2.60E-06  | .52 | SV   | .10 intronic |
| 4   | 184223548 | rs11932929 | C   | 2.60E-06  | .52 | SV   | .10 intronic |
| 4   | 184224437 | rs17074589 | A   | 2.06E-06  | .52 | SV   | .10 intronic |
| 4   | 184224692 | rs17074592 | A   | 1.89E-06  | .53 | SV   | .10 intronic |

(Continues)
### Table 2 (Continued)

| CHR | BP | SNP       | A1  | p           | β     | BPV | nearestGene | Freq | function       |
|-----|----|-----------|-----|-------------|-------|-----|-------------|------|----------------|
| 4   | 184227801 | rs1299013576 | T   | 1.70E-06   | .53   | SV  | .10         | intronic   |
| 4   | 184229668 | rs76627118   | C   | 1.38E-06   | .53   | SV  | .10         | intronic   |
| 4   | 184234815 | rs17074601   | A   | 2.95E-06   | .52   | SV  | .10         | intronic   |
| 4   | 184236951 | rs73006745   | T   | 2.95E-06   | .52   | SV  | .10         | UTR3       |
| 4   | 184242528 | rs61272231   | A   | 3.95E-06   | .51   | SV  | CLDN24      | .10         | upstream; downstream |
| 4   | 184246068 | rs111959824  | G   | 2.58E-06   | .52   | SV  | .10         | intergenic  |
| 4   | 184249613 | rs1165104995 | G   | 3.32E-06   | .51   | SV  | snoU13      | .10         | upstream |
| 4   | 184251597 | rs10025123   | T   | 3.86E-06   | .51   | SV  | .10         | intergenic  |
| 4   | 184257252 | rs28408355   | G   | 7.16E-07   | .54   | SV  | .10         | intergenic  |
| 5   | 177401368 | rs9329123    | A   | 1.56E-05   | −.40  | SV  | RP11-1252I4.2 | .15         | ncRNA_intronic |
| 5   | 177401382 | rs9329124    | A   | 1.56E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177401509 | rs9329125    | A   | 1.56E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177401630 | rs200303279  | G   | 1.56E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177401779 | rs10050665   | T   | 1.56E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177402307 | rs7719781    | A   | 1.55E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177403389 | rs34022638   | G   | 1.87E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177403407 | rs6885719    | A   | 1.56E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177403484 | rs6861941    | G   | 1.56E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177403622 | rs1772315630 | C   | 1.75E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177404089 | rs7734819    | T   | 1.95E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177404647 | rs12652175   | A   | 1.96E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177404716 | rs11740074   | A   | 1.76E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177404751 | rs11749194   | G   | 1.44E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177404814 | rs11249785   | A   | 1.76E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177405068 | rs6878595    | A   | 1.51E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177405075 | rs12515422   | G   | 1.33E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 5   | 177405145 | rs10065231   | A   | 3.50E-07   | −.43  | SV  | .18         | ncRNA_intronic |
| 5   | 177407687 | rs11746388   | A   | 1.77E-05   | −.40  | SV  | .15         | ncRNA_intronic |
| 15  | 24322045  | rs11630824   | T   | 2.35E-07   | .56   | CV  | PWRN4       | .08         | intergenic   |
| 15  | 71871160  | 15:71871160:TG:T | TG | 8.14E-07   | −.06  | ARV | THSD4       | .26         | in|tronic |
| 15  | 71871754  | rs34865359   | T   | 1.70E-06   | −.06  | ARV | .26         | in|tronic |
| 15  | 71872351  | rs11634676   | A   | 2.73E-06   | −.06  | ARV | .26         | in|tronic |

*aThe strongest signal.
bExonic: means coding region.

ments were enough to measure BPV accurately. Secondly, there is no standard definition for “variation” of blood pressure. Different methods calculated the phenotypes: SD, CV, ARV, SV, and the results of those methods were different (Figure S1). Another limitation is the lack of diversity in genetic samples due to exclusively including white British ancestry. More GWAS studies with larger population and different ancestry population are needed on this topic to further confirm and generalize those findings.

### 5 Conclusion

In summary, by performing a GWAS analysis and downstream analysis on the trait of BPV, several SNPs were identified in coding areas of gene BAD, CCDC88B, GPR137, PLCB3, and RPS6KA4 for SBPV, and WWC2 for DBPV. Gene CCDC88B, GPR137, RPS6KA4, and BAD were involved in inflammatory functions, epithelial cell function, and cell death, which were reported to be potential mechanisms of long-term BPV. These
FIGURE 3  Average expression per label (log2 transformed) for genes identified from fine-mapping. Different tissues are displayed along the X-axis and genes are displayed on the Y-axis. The expression of genes is colored according to average expression per label (log2 transformed) and red represents higher expression.

TABLE 3  Identified coding area genes from different analysis

| Analysis            | Genes identified by coding region SNPs       |
|---------------------|---------------------------------------------|
|                     | Genes identified by coding region SNPs      |
|                     | P threshold       | 5 × 10⁻⁸ | 1 × 10⁻⁶ | 5 × 10⁻⁶ |
| Main analysis (N= 9370) | SBPV       | CCDC88B, RPS6KA4       | BAD, CCDC88B, GPR137, PLCB3, RPS6KA4 | BAD, CCDC88B, GPR137, PLCB3, RPS6KA4 |
|                     | DBPV       | /       | WW2       | WW2, CC2D1A |
| Subgroup analysis (N= 6354) | SBPV       | /       | CCDC88B       | CCDC88B |
|                     | DBPV       | /       | /       | ZBBX |

findings support for further pathological research of BPV and potential drug targets for the prevention or treatment of unstable blood pressure.

AUTHOR CONTRIBUTIONS

Pingping Jia performed the statistical analysis, the interpretation of the results and wrote the original draft of the manuscript. Na Zhan helped to clean the data and do some data analysis. Baker K. K. Bat contributed to cleaning and managing the data. Qi Feng helped to apply UK Biobank data and revise the manuscript for intellectual content. The corresponding author (Kelvin K. F. Tsoi) guided the study, revised, and approved the final version of the manuscript. He attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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