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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 5×10^{-8} and 1×10^{-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 (1×10^{-6}). Among them, gene *CCDC88B* and *RPS6KA4* reached the significant P threshold (5×10^{-8}), with the strongest signal of SNP *rs1229536170* ($P = 6.36 \times 10^{-8}$, $\beta = -.29$). 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.[1] Accumulating evidence demonstrated that BPV might contribute to end-organ damage (EOD) independent of blood pressure levels,[2–4] increasing the risk of cardiovascular disease, cerebrovascular disease, and dementia.[5–8] In clinical settings, the necessity of hypertension treatment was widely accepted for preventing EOD and avoiding consequent lethal complications associated with hypertension,[9] while BPV is seldom considered. However, observational studies suggested that hypertensive persons with high BPV had a higher risk of EOD,[10] and some animal studies indicated that BPV might play a more critical role than blood pressure level in EOD.[2–4] Both genetic and environmental factors can influence BPV,[11] 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,[12,13] and only one GWAS study explored the genetic factor of BPV.[14] 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 all 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.[15] 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 based 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 constructed from height and weight measured during the initial Assessment Centre visit. If either height or weight readings were omitted, BMI would be estimated by impedance 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

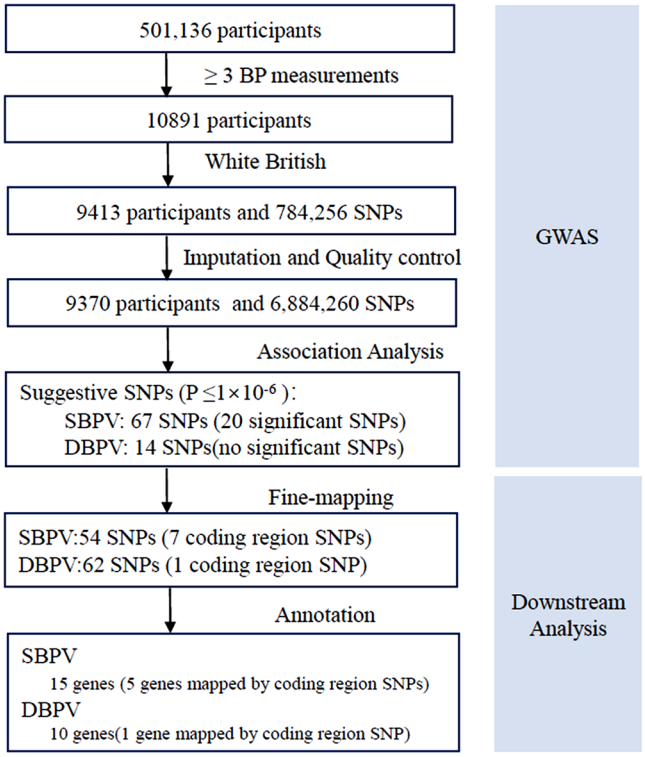

FIGURE 1 The flow chart of GWAS and downstream analysis

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 1×10^{-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.[16,17] 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.[18] 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.[19] 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 5×10^{-8}, and the suggestive significant *p*-value was 1×10^{-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.[20] 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 $r^2 \geq .8$.[20,21] This method was based on 1000 Genome Project[17] and performed on FUMA GWAS,[22] 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[23] 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[15,20,21,24] and tends to select the minimum set of SNPs as potentially causal SNPs.[25,26]

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 1×10^{-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.[17,27] Then, the gene expression level was evaluated from GTEx database[28] 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.[22]

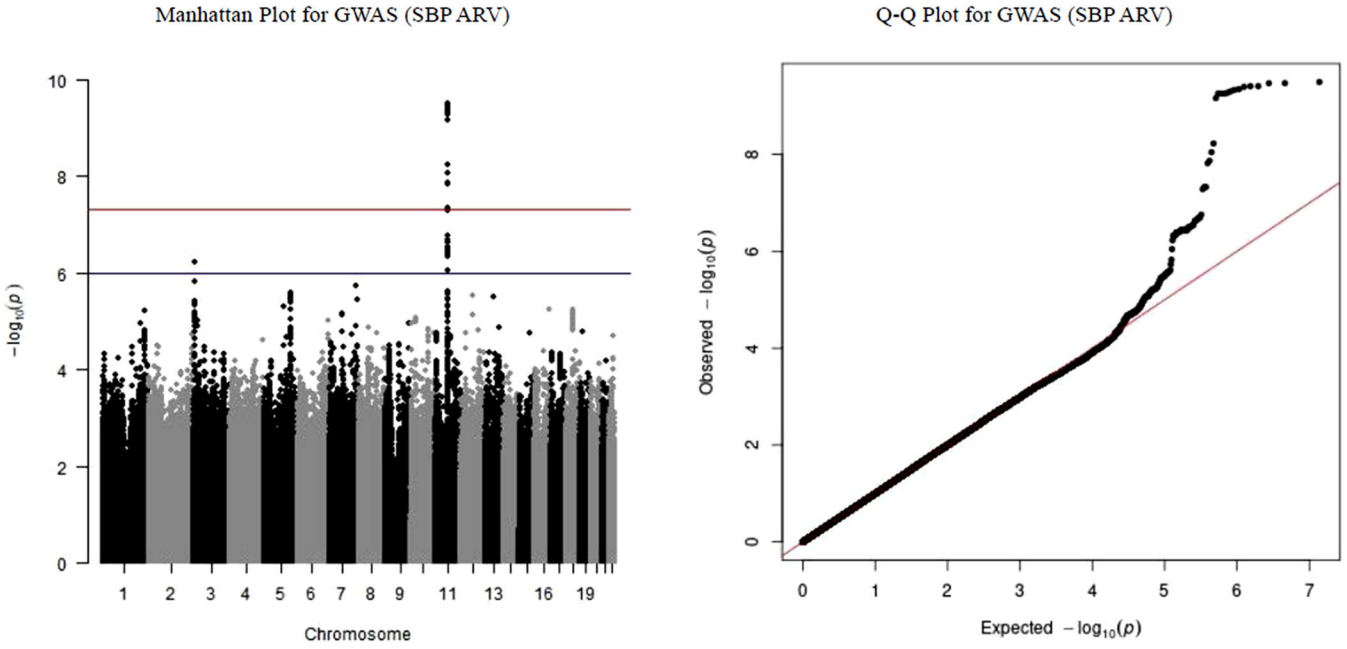

FIGURE 2 Manhattan Plots and Q-Q plot for SBP ARV. Each dot signifies a single nucleotide polymorphism (SNP). Different chromosomes are displayed along the X-axis and the negative logarithm of the association *p*-values are displayed on the Y-axis. The red line represents significant threshold of *p*-value (5×10^{-8}), and blue line represents suggestive significant threshold (1×10^{-6})

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 5×10^{-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 6 884 260 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 6 884 260 SNPs remained for GWAS analysis after imputation and quality control. Sixty-eight SNPs (on chromosome 3, 7, and 11) achieved genome-wide suggestive significance (1×10^{-6}) for SBPV. Among them, 20 SNPs reached significant *p*-value (5×10^{-8}) and the strongest signal was *rs574087* (11: 64102948: A: G, $p = 3.19 \times 10^{-10}$, $\beta = -.097$). The reference allele was the minor allele G, which means this variant will increase SBPV by .097 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 (1×10^{-6}), with the strongest signal of SNP *rs1229536170* (3: 11093952, $p = 6.36 \times 10^{-8}$, $\beta = -.29$), while there was no SNP reaching significant *p*-value.

3.2.2 | Fine-mapping

GWAS result with P threshold of 1×10^{-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 1×10^{-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 (1×10^{-6}) for SBPV, with three SNPs located in the coding region of gene *CCDC88B*. For DBPV, 15 SNPs reached a suggestive P threshold (1×10^{-6}), but none of them were located in coding regions.

3.4 | Sensitivity analysis

A looser significant P threshold was set as 5×10^{-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 1×10^{-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 (5×10^{-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.[29] However, there was little information about the mechanisms of long-term BPV.[29] 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.[29,30] 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.[31] In this GWAS study, the identified genes associated with systolic BPV 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.[32] They were also reported as potential mechanisms of how BPV influences EOD and other diseases.[9,33] Gene *CCDC88B* is related to inflammatory functions[34,35,36] 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.[37,38,39,40] It is worth noting that phosphorylation was found to be a regulator for vascular tone and blood pressure.[41] Gene *GPR137* modulates epithelial cell function and cell apoptosis,[42] and has high expression in the brain (Figure 3). Gene *BAD* has high expression in almost all tissues and is related to cell death.[43] 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.[14] 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).[44] Several studies discussed the correlation between those different variations and blood pressure levels[45] 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,[46–48] 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		.19	intergenic
3	11092264	rs11711623	T	1.72E-06	−.70	SV		.19	intergenic
3	11093952	rs1229536170	T	1.71E-07	−.34	CV		.27	intergenic
3	11095722	rs9854512	A	8.48E-07	−.71	SV		.20	intergenic
3	11095837	rs9854424	A	1.25E-06	−.71	SV		.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		.32	ncRNA_intronic
7	47047098	rs4720569	C	6.87E-07	.31	CV		.32	ncRNA_intronic
7	47063000	rs2881492	T	7.17E-07	.31	CV		.32	ncRNA_intronic
7	47064608	rs4724529	G	7.17E-07	.31	CV		.32	ncRNA_intronic
7	72126227	rs569158324	G	3.01E-07	.86	SV	TYW1B	.14	intronic
7	72126231	rs55891215	G	3.83E-07	.85	SV		.14	intronic
7	156411149	rs849074	C	4.50E-07	.37	CV	LINC01006	.19	ncRNA_intronic
7	156413325	rs849071	G	6.09E-06	.48	SD		.20	ncRNA_intronic
7	156416554	rs1100329	T	5.95E-06	.48	SD		.20	ncRNA_intronic
7	156416810	rs1100328	C	5.95E-06	.48	SD		.20	ncRNA_intronic
7	156423876	rs77573976	A	1.70E-05	.45	SD		.20	ncRNA_intronic
7	156427201	rs1860157	C	3.12E-05	.44	SD		.20	ncRNA_intronic
11	64102948[a]	rs574087	G	3.19E-10	−.10	ARV	CCDC88B	.38	intergenic
11	64104488	rs61886886	T	4.68E-10	−.10	ARV		.38	intergenic
11	64105929	rs499425	A	5.54E-10	−.10	ARV		.38	intergenic
11	64106291	rs1783521	C	5.54E-10	−.10	ARV		.38	intergenic
11	64106317	rs11231757	T	5.54E-10	−.10	ARV		.38	intergenic
11	64109118	rs647152	G	3.88E-10	−.10	ARV		.38	exonic[b]
11	64110668	rs574835	A	4.02E-10	−.10	ARV		.38	exonic[b]
11	64110683	rs479552	C	3.89E-10	−.10	ARV		.38	exonic[b]
11	64110422	rs11601860	T	3.39E-10	−.10	ARV		.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	exonic[b]
11	64138805	rs11542299	C	3.67E-07	−.08	ARV	RPS6KA4	.39	exonic[b]
11	64138905	rs17857342	G	3.67E-07	−.08	ARV		.39	exonic[b]
11	64026639	rs12146487	A	4.75E-07	−.10	ARV	PLCB3	.18	exonic[b]
11	64052447	rs2510066	T	5.01E-10	−.10	ARV	GPR137	.38	UTR5
11	64053157	rs887314	G	4.50E-10	−.10	ARV		.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		.09	intergenic
11	79391059	rs34584627	A	9.10E-07	.97	SV		.09	intergenic
11	79392577	rs34705210	T	1.03E-06	.97	SV		.09	intergenic
11	79394392	rs12797948	A	1.03E-06	.97	SV		.09	intergenic
11	79395583	rs7945511	G	1.05E-05	.90	SV		.09	intergenic
11	79398748	rs11237967	A	1.52E-05	.89	SV		.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	rs56013986	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
13	31813821	rs1441067441	C	7.12E-07	−.79	SD	B3GALTL	.08	intronic

[a]The strongest signal.
[b]exonic: 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	11093952[a]	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	WWC2	.10	exonic[b]
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	rs147216662	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	184194442	rs75389451	C	6.96E-06	.49	SV	WWC2	.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	184216588	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
4	184262171	rs28669318	T	1.01E-06	.51	SV		.11	intergenic
5	150250368	rs1277463	A	4.75E-07	−.39	SD	IRGM	.11	intronic
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	intronic
15	71871754	rs34865359	T	1.70E-06	−.06	ARV		.26	intronic
15	71872351	rs11634676	A	2.73E-06	−.06	ARV		.26	intronic

[a]The strongest signal.
[b]Exonic: 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

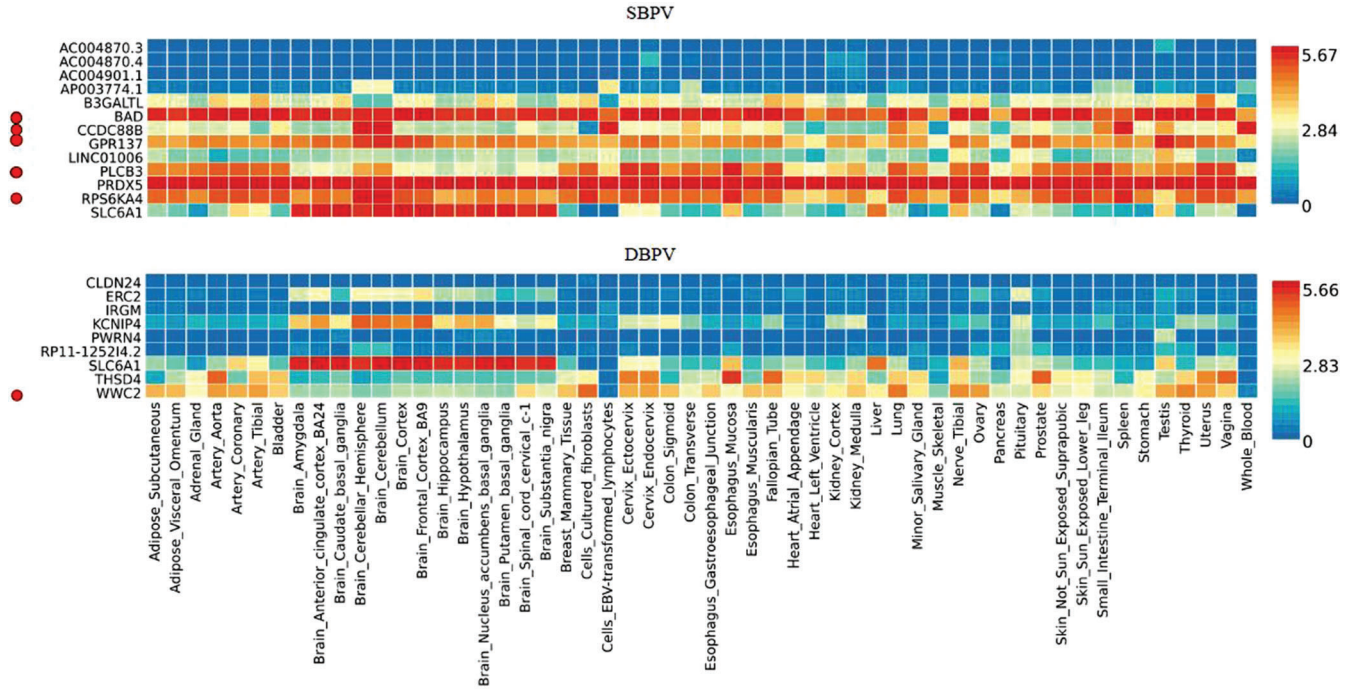

FIGURE 3 Average expression per label (log2 transformed) for genes identified from fine-mapping. Different tissues are displayed along the X-axis and genes are displayed on the Y-axis. The expression of genes is colored according to average expression per label (log2 transformed) and red represents higher expression

TABLE 3 Identified coding area genes from different analysis

	Genes identified by coding region SNPs		
	P threshold		
Analysis	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	/	WWC2	WWC2, 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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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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