Identifying susceptibility genes for essential hypertension by transcriptome-wide association study

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ABSTRACT

Hypertension is a leading risk factor of cardiovascular disease and mortality in the population worldwide. Recently, hundreds of genomic loci were reported for hypertension by GWAS, however, the most SNPs are located in intergenic regions of genome, where a functional cause is difficult to determine. In the current study, a TWAS of hypertension was conducted using 452,264 individuals including 84,640 patients. KEGG and GO enrichment analyses were performed for the hypertension-related genes identified via TWAS. PPI network analysis based on the STRING database was also performed to detect TWAS-identified genes in hypertension. We have identified 18,420 genes from the GWAS summary data, and of those 1010 non-overlapping genes expression were significantly associated with hypertension after FDR correction (PFDR <0.05) in four tissues (left heart ventricle, aorta, whole blood, and peripheral blood). The KEGG and GO terms were mostly related to autoimmune mechanisms, and the autoimmune-related pathways have also been enriched using GO analysis for PPI genes. We further performed Mendelian randomization analysis, and the results supported a significant association between autoimmunity and hypertension. Moreover, 15 novel hypertension-susceptible genes were identified in all tissues, and five of the genes (RBM6, HLA-DRB5, UHRF1BP1, LYZ, and TMEM116) were associated with autoimmune system, which provide further evidence supporting an autoimmune mechanism in hypertension. In summary, our study supports that an autoimmune mechanism plays an important role in the development of hypertension, and these findings will provide new biological insights that will assist in deciphering the molecular etiology of hypertension.

1. Introduction

Hypertension refers to a clinical syndrome characterized by increased systemic arterial blood pressure (BP), which may be accompanied by functional or organic damage to organs such as the heart, brain, and kidneys, and is the most common chronic disease [1,2]. It is a leading risk factor of cardiovascular disease and mortality, affecting approximately 27% of the population worldwide [3,4]. Genetic, estimated to have a 30–60% heritability, and environmental factors and their interaction determinate the hypertension risk for an individual [5].

In 2009, two large-scale meta-analyses of genome-wide association studies (GWAS) have identified 13 genomic loci significantly associated with blood pressure variation [6,7]. Subsequently, the International Consortium for Blood Pressure Genome-Wide Association Studies and Kato et al. identified 16 novel loci and four new loci, respectively, in different populations [2,8]. The UK Biobank Cardio-metabolic Traits Consortium Blood Pressure Working Group reported 107 independent loci and related biological pathways for BP in 2017 [9]. To date, hundreds of genomic loci have been reported for hypertension by GWAS [4, 10–12]. Unfortunately, the most associated single nucleotide polymorphism (SNP) markers of GWAS are not located in or near genes but rather in intergenic regions of genome, where the functional role of these variants is difficult to elucidate. Integrating gene expression or other omics may be a better way to investigate underlying biological mechanisms while overcoming the challenges in GWAS [13]. Recently, transcriptome-wide association studies (TWAS) integrating GWAS and expression quantitative trait loci (eQTLs) data have been proposed to identify gene-trait associations [14,15]. Gusev et al. performed a TWAS...
integrating the schizophrenia GWAS with expression data from brain, blood and adipose tissues, and identified 35 novel genes which were involved in 157 TWAS significant genes [16]. TWAS has been utilized to interrogate the genetics of many diseases including prostate cancer, ankylosing spondylitis, low-density-lipoprotein cholesterol, Crohn’s, and may be more useful in prioritizing candidate causal genes than GWAS [15,17–19].

In the current study, a large-scale hypertension GWAS data set was utilized to identify genetic loci that may be associated with hypertension by TWAS. Integrating of bioinformatic analysis including enrichment analysis, protein-protein interaction (PPI) network analysis, and Mendelian randomization (MR) analysis, were performed on candidate genes to identify hypertension-related genes and biological pathways. This study has discovered new genetic loci related to hypertension and provided new clues for understanding the molecular mechanism of hypertension.

2. Materials and methods

This study was approved by the Medical Ethics Committee of Xi’an Jiaotong University (Xi’an, China).

2.1. GWAS data for hypertension

GWAS summary data for essential hypertension was obtained from UK Biobank samples (UK Biobank field: 20002). Briefly, information on hypertension phenotypes was collected from each participant in the UK Biobank samples (UK Biobank field: 20002). Briefly, information on hypertension phenotypes was collected from each participant in the UK Biobank samples (UK Biobank field: 20002). Each feature expanded in 100,000 loci estimates, and the IMPUTE4 program was used to perform the imputation (http://jmarchini.org/software/).

2.2. TWAS of hypertension

We used the FUnctional Summary-based ImputatiON (FUSION) method (http://gusevlab.org/projects/fusion/) for TWAS analysis of hypertension [14]. To measure significant SNP-trait associations, all GWAS summary data for essential hypertension was obtained from UK Biobank samples (UK Biobank field: 20002). Briefly, information on hypertension phenotypes was collected from each participant in the UK Biobank cohort, which included a total of 452,264 white British individuals, including 84,640 patients with essential hypertension. All study subjects had blood samples taken at the subject’s visit to the UK Biobank Assessment Centre, and DNA extraction and genotyping were done at the Affymetrix Research Services Laboratory. This dataset contains 9,113,133 filtered imputation variants and the IMPUTE4 program was used to perform the imputation (http://jmarchini.org/software/).

Details on subjects, genotyping, attribution and quality control can be found in previous publication [20].

2.3. Functional exploration analysis

We used the FUSION method (http://gusevlab.org/projects/fusion/) for TWAS analysis of hypertension [14]. To measure significant SNP-trait associations, all GWAS summary data for essential hypertension was obtained from UK Biobank samples (UK Biobank field: 20002). Briefly, information on hypertension phenotypes was collected from each participant in the UK Biobank cohort, which included a total of 452,264 white British individuals, including 84,640 patients with essential hypertension. All study subjects had blood samples taken at the subject’s visit to the UK Biobank Assessment Centre, and DNA extraction and genotyping were done at the Affymetrix Research Services Laboratory. This dataset contains 9,113,133 filtered imputation variants and the IMPUTE4 program was used to perform the imputation (http://jmarchini.org/software/).

Details on subjects, genotyping, attribution and quality control can be found in previous publication [20].

To identify articles that study the relationship between 15 over 250 hypertension-related outcomes [29]. In this study, MR analysis was used to evaluate the causal relationship between autoimmune diseases (exposure, ID: finn-b-AUTOIMMUNE) and hypertension (outcome). We carried out inverse variance weighted (IVW) methods. The significant dietary pattern identified by LDSC analysis were checked and included in the subsequent analysis. The SNPs were included as instrumental variables after filtering out SNPs whose distance was within 10,000 kb and \( r^2 > 0.001 \). The number of SNPs included and the effect values (confidence intervals) and P values were reported. MR analysis, heterogeneity and multiple validity tests were conducted by R packages, including “Two-SampleMR”, “RVAideMemoire”, and “MRPPRESSO”. P values < 0.05 were considered significant.

2.4. MR analysis

MR analysis refers to the use of genetic variants in observational epidemiology to infer the variable risk factors for the disease and health-related outcomes [29]. In this study, MR analysis was used to evaluate the causal relationship between autoimmune diseases (exposure, ID: finn-b-AUTOIMMUNE) and hypertension (outcome). We carried out inverse variance weighted (IVW) methods. The significant dietary pattern identified by LDSC analysis were checked and included in the subsequent analysis. The SNPs were included as instrumental variables after filtering out SNPs whose distance was within 10,000 kb and \( r^2 > 0.001 \). The number of SNPs included and the effect values (confidence intervals) and P values were reported. MR analysis, heterogeneity and multiple validity tests were conducted by R packages, including “Two-SampleMR”, “RVAideMemoire”, and “MRPPRESSO”. P values < 0.05 were considered significant.

2.5. Further analysis for TWAS-identified genes overlapped in four tissues

To identify articles that study the relationship between 15 overlapped TWAS-identified genes and autoimmune, PUBMED (http://www.ncbi.nlm.nih.gov), and SCOPUS (http://www.scopus.com) (up to July 2022) were surveyed with “gene name”, “autoimmunity” as keywords. The articles were read entirely to assess their appropriateness for cited in this study. We also collected the expression information of these 15 identified genes in different tissues in Genecard database (https://www.genecards.org/).

3. Results

3.1. TWAS analysis of hypertension

TWAS analysis identified 18,420 genes from the GWAS summary data, and of those 1387 genes expression were significantly associated with hypertension after FDR correction (\( P_{FDR} < 0.05 \)), including 422 genes from the left heart ventricle (Fig. 1A), 509 genes in aorta (Figs. 1B), 283 genes in whole blood (Figs. 1C), and 173 genes in peripheral blood (Fig. 1D). Finally, a total of 1010 non-overlapping differentially expressed genes were selected for subsequent analysis after eliminating overcounted genes.

3.2. Functional exploration of TWAS-identified genes associated with hypertension

We performed an overlap analysis of the significantly associated genes in different tissues to identify the most representative genes, as every tissue have unique gene-expression profile. Fig. 2A shows the
result of the Venn diagram, which indicates the number of genes expressed in one or more tissues. Finally, 15 novel hypertension-susceptible genes were identified by TWAS in all tissues, and they were Glutamine-Fructose-6-Phosphate Transaminase 1 (GFPT1), RNA-binding motif protein 6 (RBM6), Zinc Finger Protein 589 (ZNF589), Major Histocompatibility Complex, Class II, DR Beta 5 (HLA-DRB5), UHRF1 Binding Protein 1 (UHRF1BP1), Nei Like DNA Glycosylase 2 (NEIL2), NOP2/Sun RNA Methyltransferase 6 (NSUN6), Sideroflexin 4 (SFXN4), Fast Skeletal Type, Troponin T3 (TNNT3), Lysozyme (LYZ), Transmembrane Protein 116 (TMEM116), Cell Division Cycle 16 (CDC16), Exosome Component 6 (EXOSC6), Cytokine Receptor Like Factor 3 (CRLF3), Zinc Finger Protein 100 (ZNF100) (Table 1). The expression information of these 15 identified genes in different tissues were shown in Supplementary File 1.

We subjected the 1010 TWAS-identified associated genes to KEGG and GO analysis (Fig. 2B). The significantly enriched KEGG and GO terms including MHC protein complex, MHC class II protein complex, MHC class II receptor activity, type I diabetes mellitus, asthma, inflammatory bowel disease, rheumatoid arthritis, fatty acid metabolism, intestinal immune network for IgA production. Furthermore, the P values for GO and KEGG analyses were shown in Supplementary Table 1.

3.3. PPI network of the TWAS-identified genes

1010 hypertension-associated genes were used for PPI analysis, and 736 protein-coding genes were successfully revealed. The PPI genes were used for enrichment analysis (Fig. 3). Several autoimmune-related pathways have been enriched, such as adaptive immune system, regulation of cellular response to stress, cellular responses to stimuli, regulation of hormone levels. Furthermore, PPI network of the 736 TWAS-identified genes was shown in Supplementary Fig. 1.

3.4. Causal relationships between autoimmune diseases and hypertension

We also identified causal relationships between autoimmune diseases and hypertension using MR (odds ratio (OR) = 1.1134, 95% confidence interval (CI) = (1.059, 1.171), P value = 2.48E-05) (Table 1). Our study suggested that autoimmune diseases play varied roles in the progression of hypertension (Fig. 4). The result did not satisfy heterogeneity and pleiotropy after testing.

Fig. 1. Manhattan plots of the association results from the hypertension transcriptome-wide association study. The dashed horizontal lines represent $P = 5.00 \times 10^{-2}$. The solid horizontal lines represent $P = 1.00 \times 10^{-3}$. Each dot represents the genetically predicted expression of one specific gene in the left heart ventricle, aorta, whole blood, and peripheral blood. The X axis represents the chromosome (Chr) encoding the corresponding gene, and the Y axis represents the negative logarithm of the association $P_{TWAS}$ value. A: Gene-expression weights for the left heart ventricle. B: Gene-expression weights for the aorta. C: Gene-expression weights for the whole blood. D: Gene-expression weights for the peripheral blood.
3.5. Five TWAS-identified genes were reported to associate with autoimmune

Five TWAS-identified genes (RBM6, HLA-DRB5, UHRF1BP1, LYZ, and TMEM116) were identified to associate with autoimmunity by the combined search, which is shown in Table 2.

4. Discussion

The genetic architecture of BP includes more than 30 genes and 1400 common SNPs to date. The related signaling pathways involve the renin-angiotensin-aldosterone system and the adrenal glucocorticoid pathway. Most of the BP SNPs identified by GWAS show pleiotropic associations, and the effect of each SNP on BP is small. Further
investigation of these loci may identify novel targets for the molecular etiology of hypertension and the prevention of cardiovascular disease [12,30].

In the current study, we have identified 1010 susceptibility genes of essential hypertension with four tissues (left heart ventricle, aorta, whole blood, and peripheral blood) from 18,420 candidate genes of GWAS utilizing a TWAS framework. To our knowledge, this is the first systematic TWAS for essential hypertension.

The enrichment analysis was carried out to identify and confirm related signaling pathways of TWAS-identified genes. The KEGG and GO terms were mostly related to autoimmune mechanisms, including MHC protein complex, MHC class II protein complex, MHC class II receptor activity, type I diabetes mellitus, asthma, inflammatory bowel disease, rheumatoid arthritis, fatty acid metabolism, intestinal immune network for IgA production, which is consistent with the report of Wolf et al. [31]. Evidence supporting a role for immunity and inflammation in the development of hypertension began as early as the late 1950s [32]. With the emergence and development of gene editing technology, the study of the immune system using knockout mice has developed rapidly [33]. Further understanding of immune factors, immune cells, and the role of the immune system in hypertension has also been gained [34]. Research findings show that long-term low-intensity inflammatory response and persistent activation of the immune system play an important role in the development of hypertension [35]. In addition, the accumulation of immune cells in blood vessels, kidneys, heart, and brain promotes chronic inflammatory responses that impair blood pressure regulation in these organs, and can also lead to hypertension [36-39].

In this study, 15 novel hypertension-susceptible genes (GFPT1, RBM6, ZNF589, HLA-DRB5, UHRF1BP1, NEIL2, NSUN6, SFXN4, TNNT3, LYZ, TMEM116, CDC16, EXOSC6, CRLF3, and ZNF100) were identified by TWAS in all tissues, and the genes (RBM6, HLA-DRB5, UHRF1BP1, Table 1

| Exposure                | Outcome   | Number of SNP | Method | OR (95% CI)     | P value |
|-------------------------|-----------|---------------|--------|-----------------|---------|
| Autoimmune Diseases     | Hypertension | 44            | IVW    | 1.1134 (1.059–1.171) | 2.48E-05 |
|                         |           |               | WM     | 4.30E-04         | 0.04    |
|                         |           |               | MR     | 5.83E-04         | 0.03    |

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|                         |           |               | WM     | 4.30E-04         | 0.04    |
|                         |           |               | MR     | 5.83E-04         | 0.03    |

Fig. 3. PPI network and functional exploration. A: PPI enrichment analysis, colored by cluster ID, where nodes that share the same cluster ID are typically close to each other. B: PPI enrichment analysis, colored by P-value, where terms containing more genes tend to have a more significant P-value.
Fig. 4. MR analysis results. A: Scatter plot of MR. B: Forest plot of MR. C: Funnel plot of MR.
LYZ, and TME116) were associated with the autoimmune, which provide further evidence supporting the involvement of an autoimmune mechanism in hypertension. While studying the role of somatic mutations in an autoimmune disease, multiple sclerosis (MS), Valori et al. found that the RBM6 plays an important role in autoimmunity, providing an interesting and unexplored role for subsequent research. HLA-DRB5 was reported to regulate T1r1, T1r2, and T1r17 cell differentiation signaling pathways in T cells in primary Sjögren’s syndrome (pSS), which is one of the most common autoimmune diseases that mainly affect middle-aged and older women [41]. As a chronic autoimmune disease with heterogeneous presentation and complex etiology, systemic lupus erythematosus (SLE) was studied by GWASs, and UHFR1BP1 and TME116 were identified as new susceptibility loci in different studies, although the role of these genes in SLE was unknown [42,43]. Graves’ disease (GD) is an autoimmune inflammatory disease of the eye, and Fairfax et al. found that the level of LYZ in the tears of patients was significantly increased, which provided a new marker for differentiating the degree of clinical symptoms in patients [44].

Further GO enrichment analysis of PPI genes also detected several GO terms with autoimmunity, such as the adaptive immune system, regulation of hormone levels. This supports the important role of autoimmunity in hypertension. Moreover, we performed MR analysis, and the results also supported a significant association between autoimmunity and hypertension [29].

Finally, our results should be used with caution as the GWAS data in this study are predominantly from the UK Biobank cohort with European ancestry, therefore, limiting the generalisability of the findings. In addition, there are few studies on the five autoimmune-related hypertension susceptibility genes identified by TWAS, and the link between them cannot be well elucidated.

In summary, we integrated the GWAS datasets of hypertension from the UK Biobank and mRNA expression profiling together to complete a TWAS in four tissues, and our results support that an autoimmune mechanism plays an important role in the development of hypertension. Our findings will provide new biological insights into BP control and help us to further untangle the molecular etiology of hypertension.

Data availability statement

The datasets analyzed during the current study are available from the Database of Genomic Variants (http://projects.tcag.ca/variation/); the URLs for Consortia and Groups (https://www.preventcd.com); the BioGPS (http://biogps.gnf.org); and the UK biobank (http://geneatlas.roslin.ed.ac.uk/) (fields: 20002).

Author contributions

LH: data collection and analysis, manuscript drafting; QZ: data collection, KEGG and Go analysis; RV: conceptualization, manuscript revision; JX: PPI analysis and interpretation; FY: bioinformatic analysis, and data representation; JM: conceptualization, manuscript drafting and revision.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrep.2022.101387.

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