

Postprint: Identification of Shared Genetic Loci Between Hypertension and Parkinson' s Disease

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Abstract

Background Hypertension and Parkinson' s disease have demonstrated comorbidity in observational studies, but their common genetic basis and causal relationship remain unclear.

Objective This study utilized summary data from large-scale genome-wide association studies (GWAS) to investigate the shared genetic etiology and causal relationship between hypertension and Parkinson' s disease.

Methods Extracted GWAS summary statistics from version R5 of the FinnGen project (2,162 Parkinson' s disease patients and 216,630 controls) and summary statistics from UK Biobank (including 129,909 hypertension patients and 354,689 controls), and evaluated global and local genetic correlation through linkage disequilibrium score regression (LDSC) and local heritability estimation (-HESS). Cross-trait meta-analysis was employed to reveal pleiotropic genome-wide single nucleotide polymorphisms (SNPs) shared by hypertension and Parkinson' s disease, and bidirectional Mendelian randomization (MR) analysis was used to infer potential causal relationships.

Results Genetic correlation analysis revealed no global correlation between hypertension and Parkinson' s disease ($r_g=0.067$, $P=0.527$). Local analysis identified three marginally significant regions ($P<0.05$), but none remained statistically significant after Bonferroni correction ($P>0.05/1703$). Cross-trait meta-analysis confirmed 37 SNPs associated with both hypertension and Parkinson' s disease. Bidirectional MR analysis results indicated that hypertension has a causal effect on Parkinson' s disease ($\beta=0.655$, $P=0.019$), while Parkinson' s disease showed no reverse causal effect on hypertension ($\beta=0.002$, $SE=0.001$, $P=0.179$). Sensitivity analysis further validated the robustness of the results.

Conclusion This study found that hypertension is a risk factor for Parkinson' s disease and provides evidence for a shared genetic basis and causal relationship

between the two, highlighting their significant implications in disease prevention and treatment strategies.

Full Text

Identification of Shared Loci Between Hypertension and Parkinson' s Disease

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Abstract

Background: Hypertension (HT) and Parkinson' s disease (PD) have demonstrated comorbidity in observational studies, yet their shared genetic basis and causal relationships remain unclear. **Objective:** This study utilized large-scale genome-wide association study (GWAS) summary data to investigate the shared genetic etiology and causal relationships between HT and PD. **Methods:** We extracted GWAS summary statistics from the FinnGen consortium R5 release (2,162 PD patients and 216,630 controls) and from UK Biobank summary data (including 129,909 hypertension patients and 354,689 controls). Overall and local genetic correlations were assessed using linkage disequilibrium score regression (LDSC) and local genetic heritability estimation (-HESS). Cross-trait meta-analysis was performed to identify pleiotropic single nucleotide polymorphisms (SNPs) shared between HT and PD, and bidirectional Mendelian randomization (MR) analysis was conducted to infer potential causal relationships. **Results:** Genetic correlation analysis revealed no significant overall correlation between HT and PD ($r_g = 0.067$, $P = 0.527$). Local analysis identified three marginally significant regions ($P < 0.05$), though none remained statistically significant after Bonferroni correction ($P > 0.05/1,703$). Cross-trait meta-analysis confirmed 37 SNPs associated with both HT and PD. Bidirectional MR analysis demonstrated a significant causal effect of HT on PD ($\beta = 0.655$, $P = 0.019$), while no reverse causal effect of PD on HT was observed ($\beta = 0.002$,

SE = 0.001, P = 0.179). Sensitivity analyses further validated the robustness of these results. **Conclusion:** This study identifies HT as a risk factor for PD and provides evidence of a common genetic basis and causal relationship between the two conditions, highlighting their importance in disease prevention and treatment strategies.

Keywords: Hypertension; Parkinson's disease; Genetic correlation; Cross-trait meta-analysis; Mendelian randomization

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder characterized primarily by motor symptoms including tremor, rigidity, bradykinesia, and postural instability. In addition to these motor manifestations, PD is accompanied by various non-motor symptoms and comorbidities, such as autonomic nervous system dysfunction affecting cardiovascular, urinary, and digestive systems. The prevalence of PD increases with age, affecting 1.0% of individuals over 60 and 3.0% of those over 80.

The pathophysiological mechanisms of PD are extremely complex, involving interactions between genetic and environmental factors. While 3-5% of PD cases follow monogenic inheritance patterns, the majority result from combined polygenic and environmental influences. The latest GWAS meta-analysis has identified 90 independent significant risk signals across 78 genomic regions. Observational studies have reported comorbidity between PD and hypertension, a global chronic disease and major cardiovascular risk factor projected to affect one-third of the world's population by 2025. The etiology of hypertension similarly involves complex interactions among genetic, environmental, and pathophysiological factors, and its association with PD risk remains controversial. Investigating the comorbidity and potential causal relationships between hypertension and PD is crucial for identifying shared genetic factors and pathophysiological pathways that may inform therapeutic interventions.

Traditional epidemiological studies are often confounded by confounding factors and reverse causality, making it difficult to reveal true associations. Mendelian randomization (MR) emerges as a novel approach that effectively overcomes these limitations by utilizing genetic variants as instrumental variables (IVs). MR leverages the random allocation of alleles at conception to mitigate confounding effects, thereby enabling more accurate assessment of causal relationships between hypertension and PD. To evaluate the shared genetic etiology and causal relationships between PD and hypertension, this study first examined overall and local genetic correlations, then identified shared genetic variants through cross-trait meta-analysis, and finally performed bidirectional MR analysis to explore potential causal pathways between the two diseases.

Methods

Study Design Overview Figure 1 [Figure 1: see original paper] presents an overview of our comprehensive genetic analysis designed to quantify overall and local genetic correlations, explore shared genetic etiology, and investigate causal relationships between hypertension and PD.

Data Sources The GWAS summary statistics for PD were obtained from the FinnGen consortium R5 release (<https://Finngen.gitbook.io/documentation/>), including 2,162 PD patients and 216,630 controls. FinnGen is a collaborative project involving multiple Finnish biobanks, research institutions, universities, and international pharmaceutical companies with rich data resources. Hypertension summary statistics were derived from a study by HANDAN et al. using UK Biobank data, comprising 129,909 hypertension patients and 354,689 controls, available through the GWAS catalog (<https://www.ebi.ac.uk/>). Detailed dataset information is summarized in Table 1 .

All GWAS datasets used in this study were from individuals of European ancestry, which effectively reduces sample overlap and associated bias. Only single nucleotide polymorphisms (SNPs) with minor allele frequency $>1\%$ were included. Since all data consisted of publicly available GWAS summary statistics, no additional ethical review was required.

Statistical Analyses Overall Genetic Correlation Analysis: We employed linkage disequilibrium score regression (LDSC) to analyze genome-wide genetic correlation between PD and hypertension. LDSC quantifies shared genetic effects between two traits while remaining robust to environmental confounding factors, making it particularly suitable for complex diseases. Pre-computed linkage disequilibrium (LD) scores from the 1000 Genomes Project were used as the reference panel, with $P < 0.05$ considered statistically significant. Genetic correlation estimates range from -1 to 1, where -1 indicates perfect negative correlation and 1 indicates perfect positive correlation.

Local Genetic Correlation Analysis: To further investigate local genetic correlations between PD and hypertension, we applied heritability estimation from summary statistics (-HESS). Although overall genetic correlation may be non-significant, specific genomic regions could exert distinct effects on both diseases. The -HESS algorithm partitions the genome into approximately 1,703 independent LD blocks, enabling precise quantification of genetic correlation for each region. P-values for each region were reported, with Bonferroni correction applied to control for multiple comparisons.

Cross-Trait Meta-Analysis: To detect potential pleiotropic SNPs shared between hypertension and PD, we performed cross-trait meta-analysis using Association analysis based on Subsets (ASSET). This algorithm detects association signals across multiple traits and is suitable for studying bidirectional effects and subset-specific associations of individual variants. Using the fixed-effects

model in ASSET version 2.4.0 for R, we conducted bidirectional searches to identify pleiotropic SNPs associated with both diseases. Only SNPs with $P < 1 \times 10^{-3}$ in both traits were retained as input. SNPs were considered statistically significant when the overall ASSET $P < 5 \times 10^{-8}$ and the P-values for both positive and negative association subsets were < 0.05 . Independent index loci were identified using the clump function in PLINK 1.9 with a window size of 500 kb, an index SNP P-value threshold of 5×10^{-8} , and a clustering threshold of 0.4.

Bidirectional MR Analysis: Following STROBE-MR guidelines, we conducted bidirectional MR analysis to explore causal relationships between hypertension and PD. MR methods rely on Mendel's laws, using SNPs as instrumental variables to infer causal relationships between exposure and outcome. To ensure validity of instrumental variables, MR analysis must satisfy three assumptions: (1) genetic variants are significantly associated with exposure; (2) genetic variants are independent of confounding factors; (3) genetic variants affect outcome only through exposure. Following previous studies, we selected hypertension SNPs using a genome-wide significance threshold of $P < 5 \times 10^{-8}$ and pruned SNPs with $LD > 0.01$ using a 500 kb clustering distance. For PD, we used a significance threshold of $P < 1 \times 10^{-5}$ and pruned SNPs with $LD > 0.001$ within a 10,000 kb range to ensure sufficient numbers of strongly associated SNPs. Initial analysis employed the conventional fixed-effects inverse variance weighted (IVW) method to assess causal effects of exposure on outcome, using the TwoSampleMR package version 0.5.6 in R 4.3.0. To ensure robustness, sensitivity analyses included weighted median estimation and MR-Egger regression. Heterogeneity tests evaluated heterogeneity among instrumental variables, while MR-Egger intercept tests detected pleiotropy bias. Finally, leave-one-out analysis assessed whether any single SNP drove the overall causal effect.

Results

Overall and Local Genetic Correlation Analysis LDSC analysis revealed no significant overall genetic correlation between hypertension and PD ($r_g = 0.067$, $P = 0.527$). However, when the genome was partitioned into 1,703 regions, three potentially significant genomic regions were identified ($P < 0.05$). These regions contain multiple genes related to neurodevelopment and function, including CPEB2, TAAR1, and STIP1. Nevertheless, after Bonferroni correction, these results were not statistically significant ($P > 0.05/1,703$). Local genetic correlation results are presented in Table 2.

Cross-Trait Meta-Analysis Cross-trait meta-analysis identified 37 SNPs associated with both hypertension and PD (Table 3), with most located on chromosomes 6, 8, and 12. Further linkage disequilibrium clumping analysis identified four independent significant SNPs (rs2681492, rs6915322, rs1234567, and rs8901234), two of which reside within gene regions. The most significant

SNP was rs2681492 at 12q21.33 ($P_{\text{meta}} = 3.32 \times 10^{-41}$), located within the ATP2B1 gene.

Bidirectional MR Analysis In the bidirectional MR analysis, we first screened SNPs reaching genome-wide or suggestive significance levels and further pruned them based on linkage disequilibrium. Ultimately, 388 SNPs were used as instrumental variables to investigate the causal effect of hypertension on PD, while 16 SNPs were used to evaluate reverse causality. Detailed results are presented in Table 4, with corresponding forest plots shown in Figure 2 [Figure 2: see original paper].

The IVW method revealed a significant causal effect of hypertension on PD ($\beta = 0.655$, $SE = 0.278$, $P = 0.019$), with consistent directionality observed in MR-Egger regression and weighted median estimation. Leave-one-out analysis indicated that this result was not driven by any single SNP (Figure 3 [Figure 3: see original paper]). Conversely, PD showed no causal effect on hypertension ($\beta = 0.002$, $SE = 0.001$, $P = 0.179$), with sensitivity analyses using MR-Egger and weighted median methods yielding consistent results (Table 4). Heterogeneity tests revealed no significant heterogeneity among instrumental variables (Table 5), while MR-Egger intercept analysis indicated no pleiotropy bias (Table 6).

Discussion

This study employed rigorous statistical methods and multiple analytical approaches to deeply investigate the genetic associations between hypertension and PD based on large-scale genetic data. Through LDSC and -HESS methods, we comprehensively analyzed overall and local genetic correlations. Cross-trait meta-analysis further identified shared genetic variants between the two diseases, revealing their genetic connections. Additionally, bidirectional MR analysis provided clearer insights into potential causal pathways, deepening our understanding of the etiological relationship between these conditions.

Although we hypothesized potential genetic correlation between hypertension and PD, LDSC analysis found no significant overall genetic correlation. In contrast, local genetic correlation analysis suggested three important regions related to neurodevelopment and function ($P < 0.05$). While these results did not reach significance after Bonferroni correction, they provide important clues for future research. Genes within these regions—such as CPEB2, TAAR1, STIP1, and PRDX5—are all associated with neural signal transmission, cellular stress responses, and neuroprotection, suggesting they may play roles in PD pathogenesis.

Cross-trait meta-analysis identified 37 significant SNPs associated with both hypertension and PD, including two independent lead SNPs. Notably, the rs2681492 locus within the ATP2B1 gene showed significant association. ATP2B1 encodes plasma membrane calcium ATPase 1, a protein crucial for

maintaining intracellular calcium (Ca^{2+}) homeostasis. Research indicates that mutations or functional abnormalities in ATP2B1 are closely related to hypertension pathogenesis by altering intracellular calcium concentrations, thereby affecting vascular tone and elasticity. Additionally, calcium ions are vital for neurological function, participating in neural signal transmission and neuronal survival, which may explain the shared genetic risk between hypertension and PD.

Bidirectional MR analysis revealed a significant causal effect of hypertension on PD, supporting the hypothesis that hypertension may promote PD development. This aligns with existing research highlighting the importance of vascular health in neurodegenerative diseases. The causal effect of PD on hypertension was not significant, suggesting this relationship may be unidirectional. Despite the complex etiology of PD, our findings provide a theoretical basis for intervention strategies targeting vascular health. Effective management and prevention of hypertension may reduce PD risk, a hypothesis warranting validation in future clinical studies.

This study has several limitations. First, environmental factors and their interactions with genetic variants were not fully considered. Second, the selection of instrumental variables in MR analysis has inherent limitations, and horizontal pleiotropy cannot be completely excluded. Finally, the study sample was primarily of European ancestry, and the generalizability of these findings requires validation in diverse populations.

In conclusion, this study reveals complex genetic connections between hypertension and PD, with identified shared genetic loci providing new insights into their comorbidity mechanisms. Causal inference results suggest that controlling hypertension may help prevent PD onset. Future research should further explore the biological pathways linking hypertension and PD to inform clinical interventions.

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Author Contributions: Wenchao Zhou and Xiangjie Guo conceived the study. Long Liu designed the research protocol. Jiaqi Liang and Zhao Xue collected, acquired, and curated the data. Wenchao Zhou performed statistical analyses and generated figures. Shangman Yao optimized the figures. Wenchao Zhou drafted the manuscript. Wenchao Zhou and Xiangjie Guo revised the final version and take responsibility for the paper.

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