A transcriptome-wide association study identifies susceptibility genes for Parkinson’s disease

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Genome-wide association study (GWAS) has seen great strides in revealing initial insights into the genetic architecture of Parkinson’s disease (PD). Since GWAS signals often reside in non-coding regions, relatively few of the associations have implicated specific biological mechanisms. Here, we aimed to integrate the GWAS results with large-scale expression quantitative trait loci (eQTL) in 13 brain tissues to identify candidate causal genes for PD. We conducted a transcriptome-wide association study (TWAS) for PD using the summary statistics of over 480,000 individuals from the most recent PD GWAS. We identified 18 genes significantly associated with PD after Bonferroni corrections. The most significant gene, LRRC37A2, was associated with PD in all 13 brain tissues, such as in the hypothalamus (P = 6.12 × 10−22) and nucleus accumbens basal ganglia (P = 5.62 × 10−21). We also identified eight conditionally independent genes, including four new genes at known PD loci: CD38, LRRC37A2, RNF40, and ZSWIM7. Through conditional analyses, we demonstrated that several of the GWAS significant signals on PD could be driven by genetically regulated gene expression. The most significant TWAS gene LRRC37A2 accounts for 0.855 of the GWAS signal at its loci, and ZSWIM7 accounts for all the GWAS signals at its loci. We further identified several phenotypes previously associated with PD by querying the single nucleotide polymorphisms (SNPs) in the final model of the identified genes in phenome databases. In conclusion, we prioritized genes that are likely to affect PD by using a TWAS approach and identified phenotypes associated with PD.

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INTRODUCTION
Parkinson’s disease (PD) is the second most common age-related neurodegenerative disorder after Alzheimer’s disease, characterized by the loss of nigrostriatal neurons in the substantia nigra. PD is more common in the elderly, and the prevalence increased from 1% in people over 60 years to 3–4% in those over 80 years. Based on twin and family studies, the heritability of PD has been estimated to be at least 27% and up to 60%3,4, suggesting a substantial proportion of genetic risk factors uncharacterized6. A substantial proportion of genetic risk factors uncharacterized6. Genotype-phenotype correlation studies on PD have modest effect sizes, and it is difficult to identify them via a typical individual SNP-based GWAS study, even with a considerable sample size. Transcriptome-wide association studies (TWAS) that systematically investigate the relationship between genetically predicted gene expression and disease risk, providing a powerful approach to identify disease risk genes and uncovering possible causal genes at loci identified previously by GWAS16−20. Considering the essential role of epigenetic features in predicting gene expression, we developed an epigenetic element-based TWAS21. Briefly, for a given gene, we used eQTL data to impute the total expression across a large cohort of genotyped individuals with the epigenetic features as prior, followed by a test of association with disease risk. Compared with the single SNP-based GWAS study, TWAS can increase power in identifying disease-related genes, either by reducing the burden of multiple comparisons or by aggregating multiple expression-altering variants into a single test.

In the current study, we carried out a TWAS to prioritize candidate PD genes and to better understand the primary and complex disease. Expression quantitative trait locus (eQTL) analysis seeks to identify genetic variants that affect the gene expression; several studies have successfully used this approach to identify putative susceptibility genes at GWAS risk loci for PD12. The enrichment of eQTLs of trait-associated variants also showed the importance of gene expression regulation13,14. Recent studies have reported that regulatory variants may account for a large proportion of disease heritability that has not yet been identified through GWAS15. Many of these variants may have modest effect sizes, and it is difficult to identify them via a typical individual SNP-based GWAS study, even with a considerable sample size. Transcriptome-wide association studies (TWAS) that systematically investigate the relationship between genetically predicted gene expression and disease risk, providing a powerful approach to identify disease risk genes and uncovering possible causal genes at loci identified previously by GWAS16−20. Considering the essential role of epigenetic features in predicting gene expression, we developed an epigenetic element-based TWAS21. Briefly, for a given gene, we used eQTL data to impute the total expression across a large cohort of genotyped individuals with the epigenetic features as prior, followed by a test of association with disease risk. Compared with the single SNP-based GWAS study, TWAS can increase power in identifying disease-related genes, either by reducing the burden of multiple comparisons or by aggregating multiple expression-altering variants into a single test.

In the current study, we carried out a TWAS to prioritize candidate PD genes and to better understand the primary...
mechanisms that underlie PD genetic risk factors using the largest PD cohort currently available with 15,056 PD cases, 18,618 proxies, and 449,056 controls. We prioritized 18 genes whose predicted expression is significantly associated with PD risk, comprising 67 associations, after Bonferroni corrections. Through conditional analyses, we demonstrated that several of the GWAS significant signals on PD could be driven by genetically regulated gene expression. We identified eight conditionally independent genes, including LRRC37A2, MMRN1, CD38, RNF40, GPNMB, ZSWIM7, GAK, and CPLX1. We observed that ZSWIM7 accounts for all the signals at its loci (rs4566208 lead SNP, GWAS $P = 3.90 \times 10^{-8}$, conditioned on ZSWIM7 lead SNP, GWAS $P = 0.17$, accounting for 0.855 of the variances) (Fig. 3a). Similarly, conditioning on LRRC37A2 accounts for most of the signal at its loci (rs199452 lead SNP, GWAS $P = 4.80 \times 10^{-21}$, conditioned on LRRC37A2 lead SNP, GWAS $P = 0.17$, accounting for 0.855 of the variances) (Fig. 3b). Conditioning on RNF40 accounts for most of the loci's variance (rs4662208 lead SNP, GWAS $P = 3.90 \times 10^{-8}$, conditioned on RNF40 lead SNP, GWAS $P = 4.80 \times 10^{-21}$, conditioned on RNF40 lead SNP, GWAS $P = 0.066$, accounting for 0.713 of the variances) (Fig. 3c). We also found that conditioned on the expression GPNMB accounts for 0.8 of the variances (rs466225 lead SNP, GWAS $P = 3.90 \times 10^{-8}$, conditioned on GPNMB lead SNP, GWAS $P = 4.80 \times 10^{-21}$, conditioned on GPNMB lead SNP, GWAS $P = 0.066$, accounting for 0.713 of the variances).

Conditionally testing GWAS signals
Since most of the TWAS-identified genes overlapped with GWAS PD loci, we performed the conditional and joint analyses to check whether these signals were due to multiple associated features and how much GWAS signal remains after the gene expression is removed. We identified eight conditionally independent genes, including LRRC37A2, MMRN1, CD38, RNF40, GPNMB, ZSWIM7, GAK, and CPLX1. We observed that ZSWIM7 accounts for all the signals at its loci (rs4566208 lead SNP, GWAS $P = 3.90 \times 10^{-8}$, conditioned on ZSWIM7 lead SNP, GWAS $P = 0.17$, accounting for 0.855 of the variances) (Fig. 3a). Similarly, conditioning on LRRC37A2 accounts for most of the signal at its loci (rs199452 lead SNP, GWAS $P = 4.80 \times 10^{-21}$, conditioned on LRRC37A2 lead SNP, GWAS $P = 0.17$, accounting for 0.855 of the variances) (Fig. 3b). Conditioning on RNF40 accounts for most of the loci's variance (rs4662208 lead SNP, GWAS $P = 3.90 \times 10^{-8}$, conditioned on RNF40 lead SNP, GWAS $P = 4.80 \times 10^{-21}$, conditioned on RNF40 lead SNP, GWAS $P = 0.066$, accounting for 0.713 of the variances) (Fig. 3c). We also found that conditioned on the expression GPNMB accounts for 0.8 of the variances (rs466225 lead SNP, GWAS $P = 3.90 \times 10^{-8}$, conditioned on GPNMB lead SNP, GWAS $P = 4.80 \times 10^{-21}$, conditioned on GPNMB lead SNP, GWAS $P = 0.066$, accounting for 0.713 of the variances).
Phenome-wide association studies

We identified 166 phenotypes associated with the SNPs in the final model of the TWAS-identified conditionally independent genes, including activities such as neurological, psychiatric, and cognitive (Supplementary Fig. 1). We further conducted the genetic correlation between PD and 122 identified traits with currently available GWAS data to determine their relationship. The latest GWAS summary statistics are listed in Supplementary Table 4. We found that the age at first sexual intercourse positively correlated with PD (Fig. 5). We also reported five phenotypes negatively correlated with PD, including three impedance measures, heel bone mineral density, and current tobacco smoking (Fig. 5). Importantly, tobacco use disorder and bone mineral density have been identified through GAD disease enrichment analyses.

DISCUSSION

PD is a long-term movement disorder that affects approximately seven million people globally. Although recent GWAS has seen great strides in identifying risk loci associated with PD, the functional significance of these associations remains elusive. We conducted a PD TWAS using the summary statistics of over 480,000 individuals from the most recent PD GWAS. This approach creates genotype-expression reference panels using public consortia through Lasso and Elastic Net with epigenetic annotations as prior, allowing for imputation and association testing of independent large-scale data. We identified 18 genes associated with PD after Bonferroni corrections, comprising 67 associations localized to seven different regions in the genome.

Conditional and joint analyses identified eight independent genes and demonstrated that the TWAS expression signals were driving the significance for several previously implicated PD loci. For example, the most significant TWAS gene LRR37A2 accounts for 0.855 of the GWAS signal at its loci, and ZSWIM7 accounts for all the GWAS signals at its loci. These results imply a limited residual association signal from the genetic variant in the GWAS locus after considering these predicted expression signals. Our identifications provide further support for three genes previously implicated by GWAS, whose expression was significantly associated with a possible causal change in PD risk by summary-based Mendelian randomization, including MMKN1, GPNMB, and GAK. Another gene, CPLX1, was possibly associated with at least one QTL in public reference datasets but did not pass the Bonferroni corrections.

Additionally, our TWAS implicates four new genes at known PD loci, including CD38, LRR37A2, RNF40, and ZSWIM7. For instance, CD38 encodes the cluster of differentiation 38, also known as cyclic ADP ribose hydrolase, a glycoprotein on many immune cells’ surfaces. CD38 strongly expressed in brain cells, including neurons, astrocytes, and microglial cells. Of note, several data tend to
Fig. 3  Regional association of TWAS hits. a Chromosome 17 regional association plot (part 1). b Chromosome 17 regional association plot (part 2). c Chromosome 16 regional association plot. d Chromosome 7 regional association plot. The marginally associated TWAS genes are shown in blue, and the conditionally significant genes are shown in green. The bottom panel shows a regional Manhattan plot of the GWAS data before (gray) and after (blue) conditioning on the green genes’ predicted expression.
indicate that CD38 expression increase in the brain as a consequence of aging23,24, the primary risk factor associated with the vast majority of neurodegenerative diseases, including PD. Moreover, several experimental data demonstrated that CD38 knockout mice are protected from neurodegenerative and neuroinflammatory insults35,26. Future studies could interrogate whether expression differences of other candidate genes are consistent with our findings.

In parallel to ours, Kia and colleagues27 conducted TWAS using expression weights from the CommonMind Consortium (CMC) dorsolateral prefrontal cortex to identify genes associated with PD. While considering the essential role of epigenetic features in predicting gene expression, our approach integrated the epigenetic information in the original TWAS to find gene-trait associations. Among the 18 genes we identified, eight genes (MMRN1, CD38, NUPL2, GPNNB, RNFL40, VKORC1, ZSWIM7, and CENPV) were significantly heritable in CMC dorsolateral prefrontal cortex and qualified for the TWAS analyses. According to the published results, seven of the above eight genes associated with PD risk at an FDR level of 0.05 (Supplementary Table 5), including two genes (CD38, and GPNNB) with solid evidence for colocalization (PPH4 > 0.75)27. At the same time, numerous previously reported PD risk loci did not implicate in our TWAS. For example, Li and colleagues28 found the predicted gene expression of SNCA was associated with PD in peripheral monocytes, and published experimental data demonstrated that SNCA was associated with PD-related clinical outcomes in PD29,30. The most significant gene we identified, LRRC37A2, was located at the end of the MAPT locus, and the second most significant finding is MMRN1 at the SNCA locus. However, MAPT and SNCA were not included in this project since they were not significantly heritable in any brain tissues at current sample sizes. Considering the previous evidence and the fact that we did not perform these associations in our project, we cannot determine the driver genes of PD at these loci, which can be regarded as one of the limitations of TWAS. Further studies with a larger sample size of reference data are needed to identify the driver genes of PD at these loci.

The GAD disease enrichment analyses of TWAS-identified genes detected six GAD diseases, including PD itself. Other enriched phenotypes, such as tobacco use disorder, cholesterol, and bone mineral density, also have been reported to be associated with PD. For example, tobacco use disorder, also known as nicotine dependence, is a chronic, relapsing disease defined as a compulsive craving to use it, despite harmful social consequences31. Epidemiological studies show that smoking is associated with a lower incidence of PD32. Moreover, nicotine stimulates striatal dopamine neurons that are damaged in PD and protect against neuronal insults in experimental models. Besides, previous researches have suggested that higher total- and LDL-cholesterol levels may be associated with lower risk and beneficial outcomes in PD33,34. Bone mineral density is the most widely used predictor for osteoporosis, and increasing evidence suggests that neurological conditions, including PD, are associated with an excess rate of osteoporosis and fracture risk35.

KEGG pathway enrichment analyses identified three pathways, including the mTOR signaling pathway, PPAR signaling pathway, and selenocompound metabolism. mTOR is a serine/threonine kinase that is the central component of mTORC1 and mTORC2 multiprotein complexes. mTOR regulates many integrated physiological functions of the nerve system, including neuronal development, synaptic plasticity, memory storage, and cognition36. The deregulation of mTOR signaling appears to be a common hallmark of human neurological disorders, including PD37, and mTORC1-induced transcripts enriched in a cluster of genes related to PD38. We also identified multiple GO terms that had been reported to be associated with PD. For example, above we have discussed the correlation between PD and osteoporosis, and three GO terms associated with osteoporosis were detected, such as regulation of bone remodeling, regulation of bone remodeling, and bone resorption. In summary, by using the TWAS method that we generated recently, we identified 18 genes associated with PD after Bonferroni corrections, comprising 67 associations localized to seven different regions in the genome. We identified eight conditionally independent genes, and we demonstrated that several of the GWAS significant signals on PD could be driven by genetically regulated gene expression. Our TWAS implicates four new genes at known PD loci: CD38, LRRC37A2, RNFL40, and ZSWIM7. We further identified seven phenotypes associated with PD by querying the SNPs in the final model of identified genes in phenome databases. In conclusion, we prioritized genes that are likely to affect PD by using a TWAS approach and identified phenotypes associated with PD.
**METHODS**

**GWAS summary statistics**

**Discovery GWAS data.** We used the most recent GWAS summary statistics for PD. Details on participant ascertainment and quality control were previously reported by Nalls et al.\(^5\). The summary statistics comprising 15,056 PD cases, 18,618 UK Biobank proxy-cases (individuals who do not have PD but have a first-degree relative that does), and 449,056 controls. Since our approach depends on having dense summary-level data to overlap with the expression weights closely, we did not prune SNPs in the summary data.

**Replicate GWAS data.** Another GWAS summary statistic of PD, comprising 4238 PD cases and 4239 controls, was used as the replication data of this study. Details about ascertainment and quality control were previously reported by Pankratz et al.\(^3\). Similarly, all datasets employed standard UK Brain Bank criteria\(^4\) for the diagnosis of PD, with a modification to allow the inclusion of cases that had a family history of PD, since familial PD.

**RESULTS**

**Pathway enrichment results of TWAS-identified genes.** a) GAD disease enrichment analyses of TWAS genes. b) KEGG pathway enrichment analyses of TWAS genes, including biological processes (c), cellular component (d), and molecular function (e). f) GWAS Catalog enrichment analyses of TWAS genes. The histogram shows the expected number of genes with \(P < 0.01\) based on 10,000 random permutations. The large red point shows the observed number of previously known PD genes that fall below this threshold.

**Genetic correlation between PD and phenotypes associated with top PD eQTLs.** \(P < 0.05/122, \quad \text{**} P < 0.01/122, \) error bars indicate standard error of the genetic correlations.
cases may have a more substantial genetic contribution than sporadic PD, making them potentially more informative for genetic studies.

Transcriptome-wide association study
We used transcriptome and high-density genotyping data of European descendent from the Genotype-Tissue Expression (GTEx) study Pilot Project V8 (dbGap accession: phs000424.v8.p2) to establish gene expression prediction models41. In this project, we used genotyping and transcriptome data from 13 brain tissues to build epigenetic-based gene expression prediction models.

As described in our previously reported method21, we performed a TWAS using reference panels derived from tissue-specific gene expression coupled with genotypic data with the epigenetic features. For each gene x, we trained and evaluated the models for gene expression prediction in each round y of ten-fold cross-validation using the following steps. (a) We performed eQTL analyses with SNPs located within 1 Mb of the transcription start/end sites of the gene using the training data; (b) We then annotated the SNPs with epigenetic annotations. For each SNP, an epigenomic feature was labeled if the SNP overlapped with the feature. (c) We obtained multiple SNP sets according to the eQTL P-value threshold and epigenetic annotation. (d) For each SNP set z, we built an expression prediction model in the training dataset by using the Lasso and the Elastic Net (α = 0.5) methods as implemented in the glmnet R package. For each model, we evaluated its prediction performance by the coefficient of determination R² between the predicted gene expression and the observed gene expression of the testing data, and averaged all the cross-validation data. For each gene x, the model with the highest mean R² in the testing data was selected as the best model. Based on the parameters of the best model, we performed the eQTL analyses again using all the samples in the reference data and constructed each gene’s final prediction model. We estimated the associations between predicted expressions and PD with the combination of SNP-trait effect sizes while accounting for linkage disequilibrium among SNPs via Functional Summary-based Imputation (FUSION, http://gusevlab.org/projects/fusion/).

Since highly heritable genes were significantly enriched in trait associations19,20, we only focused on genes whose heritability did not overlap with zero with 95% confidence interval. We used a strict Bonferroni-corrected study-wise threshold with P = 2.55 × 10⁻⁶ (0.05/19,632, the total number of highly heritable genes across tissues). We applied the 1000 Genomes v3 LD panel for the TWAS. To assess the possibility of inflated association statistics from TWAS, we performed a permutation test. We shuffled the eQTL weights (n = 10,000) and recomputed an empirical association statistics conditional on the GWAS effects at the locus via FUSION.

Conditional analyses
We performed conditional and joint analyses at each genome-wide Bonferroni-corrected TWAS genes to determine how much GWAS signal remains after the expression association from TWAS is removed. Moreover, for regions where TWAS identified multiple associated features, we jointly modeled these genes to determine the independent signals. Each PD GWAS association was conditioned on the joint gene model, one SNP at a time. We set the overlapping genes in the range of 1 Mb around each SNP, and the defined regions included only the transcribed region of the genes. We used the FUSION tool to perform the conditional and joint analyses with the cis-genetic component of expression we generated.

Partitioned heritability estimation
The partitioned analysis is to quantify the heritability directly explained by SNPs in each functional category using the summary statistics compared with the null expectation, equal to the percentage of SNPs in the gene set. We estimated the partitioned heritability of PD by SNPs around TWAS-identified genes to see whether the identified genes significantly contribute to the PD heritability. Partitioned heritability of PD was estimated using LD score regression (LDSC) following the previously described methodology42. We partitioned the heritability explained by TWAS-identified genes with a less stringent threshold (P < 0.01) in each tissue by SNPs within 2 kb of the genes. We generated the LD score files using the open-source software available at https://github.com/bulik/lensc/wiki/Partitioned-Heritability.

Gene set enrichment analyses
To demonstrate TWAS’s ability to identify PD-related genes, we performed the GAD disease enrichment analyses via the Database for Annotation, Visualization, and Integrated Discovery (DAVID) tool (https://david.ncifcrf.gov/home.jsp) using default settings. A relaxed threshold of 0.01, rather than Bonferroni-correction, was used for GAD disease enrichment analyses since Bonferroni-correction assumes independence while genes tend to correlate due to co-expression. More genes will allow for better recapitulation and prioritization of appropriate pathways. We performed the GO and pathway enrichment analyses using the clusterProfiler R package. The GO terms (including biological processes, cellular components, and molecular functions) and pathways from KEGG (https://www.genome.jp/kegg/) were analyzed in this study.

GWAS Catalog enrichment analyses
We tested whether the TWAS-identified genes enriched known PD-associated genes. The reported PD genes derived from the NHGRI GWAS Catalog43 identified using GWAS were regarded as the set of known PD-associated genes. We excluded studies that included the discovery dataset to make sure our known gene list was independent of the current analysis. We then counted the number of known disease-associated genes that had a TWAS P-value below 0.01. We compared this count to the null expectation based on 10,000 randomly drawn gene sets of similar size to the known disease gene set to derive an enrichment P-value.

Phenome-wide association studies
To identify phenotypes that may be associated with PD, we conducted a phenome-wide association study (pheWAS) for each SNP in the final model of the identified genes. We reported the first five phenotypes (excluding PD) through public data provided by GWASAtlas (https://atlas.cglab.nl) according to the P-values. We further conducted the genetic correlation between PD and identified traits with currently available GWAS data to determine their relationship. The analyses were carried out using LDSC at https://github.com/bulik/lensc. The latest GWAS summary statistics were used for the correlation.

Standard protocol approvals and participant consents
This study protocol was approved by the Ethics Committee of Hunan Brain Hospital. The study based on GWAS summary statistics does not require informed consent from all study participants. The methods were carried out in accordance with the approved guidelines.

Reporting summary
Further information on research design is available in the Nature Research Reporting Summary linked to this article.

DATA AVAILABILITY
The discovery GWAS summary statistic of PD was obtained from the link (https://bit.ly/2ofzGrk) shared by Nalls and colleagues1. The replicate GWAS summary statistic was obtained from the Genome-Wide Repository of Associations Between SNPs and Phenotypes database (https://grasp.nhlbi.nih.gov/FullResults.aspx). Other data that support the findings of this study are available from the corresponding author upon reasonable request.

CODE AVAILABILITY
The source code is available at https://github.com/studentyaoshi/etwas.

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