Replication of a Novel Parkinson’s Locus in a European Ancestry Population

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ABSTRACT: Background: A recently published East Asian genome-wide association study of Parkinson’s disease (PD) reported 2 novel risk loci, SV2C and WBSCR17.

Objectives: The objective of this study was to determine whether recently reported novel SV2C and WBSCR17 loci contribute to the risk of developing PD in European and East Asian ancestry populations.

Methods: We report an association analysis of recently reported variants with PD in the COURAGE-PD cohort (9673 PD patients; 8465 controls) comprising individuals of European and East Asian ancestries. In addition, publicly available summary data (41,386 PD patients; 476,428 controls) were pooled.

Results: Our findings confirmed the role of the SV2C variant in PD pathogenesis (rs246814, COURAGE-PD European = 6.64 × 10⁻⁴, pooled PD P = 1.15 × 10⁻¹¹). The WBSCR17 rs6386816 was observed as a significant risk marker in the East Asian pooled population only (P = 1.16 × 10⁻⁸).

Conclusions: Our comprehensive study provides an up-to-date summary of recently detected novel loci in different PD populations and confirmed the role of SV2C locus as a novel risk factor for PD irrespective of the population or ethnic group analyzed. © 2021 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Parkinson’s disease (PD) is a complex neurodegenerative disease characterized by the predominant loss of nigrostriatal dopaminergic neurons and the formation of Lewy bodies.1 The majority of underlying genetic causes for both familial and sporadic forms of PD have been identified in the European ancestry population.2-4 These discoveries, nonetheless, have considerably improved our understanding of PD, yet there remains a concern for genetic transferability of these loci in other ethnically distinct populations.5,6 To unravel the genetic spectrum of PD, it is essential to catalogue the genetic architecture of PD in ethnically diverse populations.

In a recent study Foo et al performed a large genome-wide association study (GWAS) in PD patients of East Asian ancestry.5 The study not only replicated 9 loci previously reported in European populations but also discovered 2 novel loci (SV2C and WBSCR17). SV2C encodes a synaptic vesicle protein known to be involved in
doamine transmission with a role in PD, and WBSCR17 encodes an N-acetylgalactosaminyltransferase enzyme with a potential role in membrane trafficking.5,8 However, it is critical to replicate the newly reported loci in different independent populations, given the variability in allele frequencies, linkage disequilibrium (LD) patterns, and effect estimates.5

Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson’s Disease (COURAGE-PD) is one such collaborative initiative, which aims to uncover the complex genetic architecture of PD in different ethnic groups including European and East Asian ancestry populations.9 In the present article, we aimed to replicate the findings for the recently detected novel loci SV2C and WBSCR17 using the newly generated COURAGE-PD data set and provide an up-to-date summary by pooling different publicly available PD data sets.

Methods

COURAGE-PD Project

As part of the COURAGE-PD project, 27,538 individuals comprising 35 independent cohorts were genotyped with the NeuroChip.9 Quality control (QC) was conducted independently for each cohort according to standard procedures (Supplementary methods). This was followed by imputation using the HRC reference panel. After conducting QC and imputation procedures, a total of 9673 PD cases and 8465 controls comprising 26 independent cohorts across 17 countries were finally included in the present study (Supplementary methods, eTable S1). The association analysis was performed in each cohort assuming an additive genetic model adjusted for sex and different independent populations, given the variability in allele frequencies, linkage disequilibrium (LD) patterns, and effect estimates.5

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Meta-Analysis of COURAGE-PD and Other PD Data Sets

We employed weighted Z-score meta-analysis of odds ratios (ORs) and standard errors (SEs) as implemented in the METAL software to combine summary statistics across all the COURAGE-PD cohorts for the variants identified in the recent East Asian meta-GWAS.11 We also extracted summary data for the novel loci identified in the same study from recently published meta-analysis of GWAS data sets to provide updated pooled summary estimates for rs246814 and rs9638616 stratified by European and East Asian ancestry subpopulations. For the European meta-analysis, we combined the summary statistics from the COURAGE-PD European ancestry data set with those from the largest publicly available PD GWAS of European ancestry comprising of 36,674 PD patients, and 449,056 controls from the International Parkinson’s Disease Genomics Consortium (IPDGC), and UK Biobank (UKB)2 using the same methodology as described above. For the East Asian meta-analysis, we combined the summary statistics from the COURAGE-PD East Asian data sets with those reported by Foo et al and Satake et al2,3,6 using the same methodology as described above. We considered a Bonferroni-corrected threshold of 1.92 × 10⁻³ (number of independent tests, 26) for a replication study in our COURAGE-PD data set (eTable 2). We further considered a significance level of P < 1 × 10⁻⁵ as evidence of suggestive association in the pooled meta-analysis of the latest publicly available data sets (http://www.pdgene.org/methods).

AUC/ROC Analysis in COURAGE-PD European Ancestry Data Set

The proportion of the genetic heritability in PD risk explained by single-nucleotide polymorphisms (SNP entered in the PRS model was estimated by calculating Nagelkerke’s pseudo R² using the R package fmsb. Receiver operating characteristic (ROC) curves and area under the curve (AUC) estimates were plotted using the R package pROC.

Regional Association Plots

Regional association plots were drawn for a 5-kb region around the SNPs of interest and the top candidate SNPs by the web-based LocusZoom (http://locuszoom.sph.umich.edu/locuszoom).

Results

Meta-Analysis of COURAGE-PD Data Sets

The study population included 9673 PD cases and 8465 controls. The frequencies of the novel variants in our data set are 8.3% and 31.5% for SV2C rs246814 T and WBSCR17 rs9638616 T, respectively. A single-marker analysis showed a significant overrepresentation of SV2C rs246814 T-allele in PD cases compared with controls in the European ancestry population data set.
TABLE 1. A meta-analysis of novel loci detected in a recent study in the latest PD data sets with European ancestry

| SNP  | Chr | Pos     | EA | OA       | Nearest gene | PD cases (n) | Controls (n) | OR (95% CI) | β      | SE    | P      | I2, % | Het P |
|------|-----|---------|----|----------|--------------|--------------|--------------|-------------|--------|-------|--------|------|-------|
| OR European | 1.165; 95% CI, 1.067–1.273; P European = 6.64 × 10⁻⁶; eTable 2. On the other hand, we did not observe any association of WBSCR17 rs9638616 T allele with PD in the COURAGE-PD European ancestry data set (OR European, 1.020; 95% CI, 0.969–1.073; P European = 0.4552; eTable 2). We did not detect the same variant in the COURAGE-PD East Asian data set.

Meta-Analysis of COURAGE-PD and Other PD Data Sets

We further pooled the COURAGE-PD GWAS data set with the available summary statistics of GWASs of PD in European and East Asian ancestry populations (Table 1). Our meta-analysis confirmed the association of SV2C rs246814 in the pooled data set (eTable 3). We
also confirmed the validity of WBSCR17 rs9638616 as a risk marker in the East Asian population (eTable 4).

Polygenic Risk Scores and AUC/ROC Analysis in COURAGE-PD European Ancestry Data Set

The overall contribution of 9 of the 11 loci in the COURAGE-PD European ancestry data set is shown in eTable 2. The distribution of PRS scores in both PD cases and healthy population controls is shown in Figure 1. Compared with individuals within the bottom 5% and 10% PRS values, individuals with PRS values within the top 5% and 10% values showed 2.30 (95% CI, 1.88–2.81; $P_{\text{European}} < 2.2 \times 10^{-16}$) and 1.92 (95% CI, 1.67–2.21; $P_{\text{European}} < 2.2 \times 10^{-16}$) fold higher risk in the COURAGE-PD European ancestry data set (Fig. 1A). The variants further explained 1.06% of PD heritability with an AUC of 55.1% (Fig. 1B).

Regional Association Plots

Regional association plots were drawn for the SV2C locus in both European and East Asian ancestry COURAGE-PD data sets. Although the most significant SNP in the European data set was located in the downstream region of SV2C genes (rs2937736 or Chr5:75636408, $P_{\text{European}} = 7.74 \times 10^{-6}$), the most significant SNP in the Asian data set was identified in the nearby IQGAP2 gene (rs4704337 or chr5:75869457, $P_{\text{Asian}} = 0.014$). However, both the variants did not show LD with SV2C rs246814 in the respective data sets.

Discussion

To the best of our knowledge, this is the first study that comprehensively assessed the role of 2 novel risk loci in different PD populations and confirmed the role of SV2C in PD pathogenesis.

Our findings in the COURAGE-PD European ancestry data set are consistent with the previous largest publicly available meta-analysis of PD in European ancestry data set (IPDGC + UKB; eTable 2). Although the associations observed for SV2C rs246814 T in both data sets did not surpass Bonferroni threshold for genome-wide significance, by pooling the various PD data sets our meta-analysis showed that the variant could improve the genetic prediction of PD risk (Table 1). In contrast, no association was detected for WBSCR17 rs9638616 in the COURAGE-PD and IPDGC+UKB data sets. On the other hand, the meta-analysis of WBSCR17 rs9638616 in a pooled PD population comprising COURAGE-PD and the latest large publicly available PD data sets provided weak evidence of the involvement of WBSCR17 in PD (eTables 3 and 4). However, the effect appeared to be mainly driven by the East Asian subpopulation, as suggested by the presence of high heterogeneity in the observed association.

The SV2C variant (rs246814) was also observed to be in strong LD with a missense variant, p.Asp543Asn (rs321444); $r^2_{\text{European}} = 0.99$. It has been further hypothesized that the missense variant may effect N-linked glycosylation of the extracellular or luminal domain of SV2C and possibly modulates dopamine release in basal ganglia and dopaminergic neurons in PD cases.7,12 Our findings thereby suggest p.Asp543Asn (rs321444) as a common putative functional SNP in European and East Asian ancestry populations. The regional association plots further ruled out the role of any nearby genes in driving the association observed in the present study. The predictive value of the top locus in the European ancestry population showed a limited predictive power in the European ancestry population (AUC, 55.1%) compared with the Foo et al study (AUC, 60.4%); see Figure 1.

There were limitations in our study as well. The main limitation of the present study was our inability to adjust for age in the COURAGE-PD data set. This was attributed to the availability of sparse data on age in some of our participating study cohorts. Another limitation could be a lack of adjustment for a study-cohort-specific population substructure. The possibility of a slight over- or underadjustment in some of the study cohorts cannot be ruled out. Nevertheless, the strong association observed for SV2C in our COURAGE-PD data set and retention of the association after pooling our data set with other worldwide data sets provides compelling evidence for the novel locus’s role in PD pathogenesis.

In summary, our study showed the relevance of cohorts with different ancestries to test the validity of newly defined PD loci.

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Author contributions

Grover and Kumar-Sreelatha Ashok contributed equally to this work. Kumar-Sreelatha had full access to all the data in the study and takes responsibility for the integrity of the data. Grover, Kumar-Sreelatha and Bobbili take responsibility for accuracy of the data analysis.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.