

Genome-wide Association and Meta-analysis of Age at Onset in Parkinson Disease

Evidence From the COURAGE-PD Consortium

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Abstract

Background and Objectives

Considerable heterogeneity exists in the literature concerning genetic determinants of the age at onset (AAO) of Parkinson disease (PD), which could be attributed to a lack of well-powered replication cohorts. The previous largest genome-wide association studies (GWAS) identified *SNCA* and *TMEM175* loci on chromosome (Chr) 4 with a significant influence on the AAO of PD; these have not been independently replicated. This study aims to conduct a meta-analysis of GWAS of PD AAO and validate previously observed findings in worldwide populations.

Methods

A meta-analysis was performed on PD AAO GWAS of 30 populations of predominantly European ancestry from the Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease (COURAGE-PD) Consortium. This was followed by combining our study with the largest publicly available European ancestry dataset compiled by the International Parkinson Disease Genomics Consortium (IPDGC).

Results

The COURAGE-PD Consortium included a cohort of 8,535 patients with PD (91.9%: Europeans and 9.1%: East Asians). The average AAO in the COURAGE-PD dataset was 58.9 years (SD = 11.6), with an underrepresentation of females (40.2%). The heritability estimate for AAO in COURAGE-PD was 0.083 (SE = 0.057). None of the loci reached genome-wide

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Glossary

AAO = age at onset; **Chr** = chromosome; **COURAGE-PD** = Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease; **eQTL** = expression quantitative trait locus; **GTE_x** = Genotype-Tissue Expression; **GWAS** = genome-wide association studies; **IPDGC** = International Parkinson Disease Genomics Consortium; **LD** = linkage disequilibrium (LD); **PD** = Parkinson disease; **PRS** = polygenic risk score; **QQ** = quantile-quantile; **SNV** = single-nucleotide variation; **UKBEC** = UK Brain Expression Consortium.

significance ($p < 5 \times 10^{-8}$). Nevertheless, the COURAGE-PD dataset confirmed the role of the previously published *TMEM175* variant as a genetic determinant of the AAO of PD with Bonferroni-corrected nominal levels of significance ($p < 0.025$): (rs34311866: $\beta(\text{SE})_{\text{COURAGE}} = 0.477(0.203)$, $p_{\text{COURAGE}} = 0.0185$). The subsequent meta-analysis of COURAGE-PD and IPDGC datasets ($N_{\text{total}} = 25,950$) led to the identification of 2 genome-wide significant association signals on Chr 4, including the previously reported *SNCA* locus (rs983361: $\beta(\text{SE})_{\text{COURAGE+IPDGC}} = 0.720(0.122)$, $p_{\text{COURAGE+IPDGC}} = 3.13 \times 10^{-9}$) and a novel *BST1* locus (rs4698412: $\beta(\text{SE})_{\text{COURAGE+IPDGC}} = -0.526(0.096)$, $p_{\text{COURAGE+IPDGC}} = 4.41 \times 10^{-8}$).

Discussion

Our study further refines the genetic architecture of Chr 4 underlying the AAO of the PD phenotype through the identification of *BST1* as a novel AAO PD locus. These findings open a new direction for the development of treatments to delay the onset of PD.

In 2019, over 8.51 million individuals (95% uncertainty interval 7.3–9.8) had Parkinson disease (PD) globally.¹ This disease is one of the fastest-growing neurodegenerative diseases with an estimated 30.9% increase in the number of patients with PD in 2019 compared with 2010. However, the

prevalence of a disease depends on both the incidence and duration of disease, making an earlier age at onset (AAO) of PD an essential contributor to the overall burden of the disease. Although less than 5% of patients with PD harbor pathogenic variants in known monogenic PD genes, the

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majority are sporadic with predominantly late AAO.^{2,3} A better understanding of genetic factors influencing variability in AAO in sporadic patients could improve our understanding of PD pathophysiology.

The emergence of genome-wide association studies (GWAS) has resulted in a rapidly expanding list of loci harboring disease-susceptibility variants for the sporadic form of the disorder.^{4,6} To date, genetic variants at 78 loci have been identified for sporadic PD.⁶ Despite advances in understanding the genetic basis of PD, the heritability underlying PD AAO remains largely unexplained. A recent global effort involving 28,568 patients with sporadic PD of European ancestry led to the identification of 2 loci, *SNCA* and *TMEM175*, as risk factors for an earlier AAO, both of which are also known to play a role in α -synuclein-linked mechanisms underlying PD pathology.^{1,7,8} More recently, a meta-analysis including 5,166 Chinese patients with PD led to the identification of another locus *NDN/PWRN4*.⁹ Despite the large disparity in sample size and the genetic loci identified by the 2 studies, both works estimated a similar total heritability of the AAO of 10%–14%.^{7,9} They also showed an indirect correlation between a polygenic risk score (PRS) and AAO based on risk loci for PD on individuals of similar ancestry, suggesting an overlap between the pathways underlying disease susceptibility and AAO in PD.

Recent studies have underscored the relevance of inclusion of ethnic diversity in genomic research.^{9,10} The COMprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease (COURAGE-PD) is a worldwide collaboration consortium comprising 35 PD study cohorts, which aims to address this disparity to some extent in PD research.¹¹ This study aims to perform an AAO GWAS in COURAGE-PD and to investigate the validity of previously observed loci by conducting one of the largest meta-analysis of PD AAO GWAS to date by combining previous International Parkinson Disease Genomics Consortium (IPDGC) AAO GWAS ($n = 17,415$) with newly generated COURAGE-PD AAO GWAS ($n = 8,535$), resulting in a combined dataset of 25,950 patients with PD. Finally, we investigate the influence of a PD PRS on PD AAO to dissect the potential overlapping etiology.

Methods

Study Cohorts and Participants

The COURAGE-PD Consortium comprises data from 15,849 patients with PD and 11,444 controls of predominantly European ancestry from 35 cohorts with a major contribution from the Genetic Epidemiology of Parkinson's Disease Consortium (geopd.net). Quality control (QC) of genome-wide data was performed in each COURAGE-PD study cohort. See eMethods, [links.lww.com/WNL/C87](https://www.lww.com/WNL/C87), for more details, including collected phenotypic data. AAO was defined based on the initial manifestation of motor symptoms associated with

PD, as described elsewhere.⁶ After imputation, only patients with potential sporadic PD with data available on AAO and not overlapping with previous IPDGC AAO GWAS were included in this study, leaving 8,535 samples from 30 cohorts. These comprised 26 European and 4 East Asian ancestry cohorts.

Genotype–Phenotype Analysis

Regression Analysis and Meta-analysis of Study-specific Estimates

Linear regression analysis of imputed dosages with AAO was performed in each study cohort using an additive model, implemented in *rvtests*, correcting for gender and the first 5 principal components.¹² The selection of 5 principal components was based on study cohort–specific scree plots. The scree plot flattened out after the third factor for most study cohorts, with few exceptions, where 5 factors explained the highest proportion of the total variance. This was followed by combining study-specific results through inverse variance–weighted fixed-effect meta-analyses conducted using METAL.^{13,14} In addition, only those variants that were successfully genotyped in at least 2/3rd of study cohorts were included for further interpretation. Similarly, the variants with I^2 statistic $\geq 50\%$ were considered to have substantial heterogeneity and were excluded from further interpretation. We also used additive random-effect meta-analyses using the DerSimonian-Laird estimator to check the influence of heterogeneity on our findings.¹⁵ The quantile-quantile (QQ) plot was generated using R to judge the potential influence of population stratification on the overall significance of the effect estimates. We considered $p < 5 \times 10^{-8}$ as genome-wide significant and $p < 1 \times 10^{-6}$ as suggestive evidence for a potential association.⁹ We also considered Bonferroni-corrected $p < 0.025$ for reporting replication signals originating from 2 single-nucleotide variations (SNVs [formerly SNPs]; rs356203 [*SNCA*] and rs34311866 [*TMEM175*]) that reached a genome-wide significance in the previous largest meta-analysis of the AAO of PD.⁷ The results were visualized using R generated Manhattan and LocusZoom generated regional association plots.¹⁶ We conducted linkage disequilibrium (LD) score regression with LDSC (using summary-level data) to estimate heritability explained by the PD AAO GWAS.¹⁷ We also performed a meta-analysis of COURAGE-PD AAO ($n = 8,535$) with the previous largest AAO meta-analysis comprising IPDGC dataset ($n = 17,415$) to discover potentially new loci and improve heritability estimates.⁷

Correlation Between Case-Control GWAS and AAO GWAS

We used 2 approaches to assess the correlation between PD case-control GWAS meta-analysis and COURAGE-PD AAO GWAS meta-analysis. First, we computed the genome-wide genetic correlation between PD status and PD AAO in COURAGE-PD dataset using the cross-trait LD score regression method.¹⁷ Second, we used effect estimates of significant genetic variants ($p < 5 \times 10^{-8}$) identified by combining

the COURAGE-PD case-control GWAS meta-analysis dataset with the IPDGC-PD case-control GWAS meta-analysis dataset to generate individual-specific PRSs in the COURAGE-PD AAO population, using PRSice2.¹⁸ Linear regression analysis of the PRS with AAO was performed, correcting for gender and the first 5 principal components.

Subgroup Analysis and Power Computation

A subgroup analysis was performed to explore the influence of ethnicity and gender on the AAO GWAS and the correlation between case-control and AAO GWAS meta-analyses. The power was estimated using QUANTO 1.2.4.¹⁹

Expression Quantitative Trait Loci Analysis

We further explored the potential influence of novel variants identified in this study on the expression traits using the gene expression data from the Genotype-Tissue Expression Project using the Genotype-Tissue Expression (GTEx) portal (gtexportal.org, Data Source: GTEx Analysis Release V8 (dbGaP Accession phs000424.v8.p2)) and the UK Brain Expression Consortium (UKBEC) using the Braineac portal (braineac.org).^{20,21}

Standard Protocol Approvals, Registrations, and Patient Consents

This study was conducted at the University of Tübingen, and the ethical approval was obtained by the local institutional review board of the respective study sites. All the study participants provided signed informed consent.

Data Availability

Summary statistics of COURAGE-PD AAO GWAS used in the meta-analysis are available from the corresponding author on reasonable request. In addition, IPDGC summary statistics for AAO GWAS were downloaded from the IPDGC website (pdgenetics.org/resources). Significant SNVs of the risk of PD based on the meta-analysis of COURAGE-PD and IPDGC datasets used in the PRS calculation can be found in the original publication (Grover et al. in preparation). Relevant programming scripts used for the present work are available at the GitHub website of the Center for Genetic Epidemiology at Tübingen (github.com/CGEatTuebingen/Ageatonsset_GWAS_Courage-PD).

Results

Main Study Outcome Variable

The final cohort after QC included a total of 8,535 patients with PD, 7,847 of European ancestry (91.9%) and 688 of East Asian ancestry (9.1%). The average AAO in the COURAGE-PD dataset was 58.9 years (SD = 11.6), with an underrepresentation of females (40.2%) (eTable 1, links.lww.com/WNL/C88). We did not observe any major influence of gender or ethnicity on AAO. Furthermore, the average AAO was slightly lower than that reported in the

IPDGC dataset (62.1 years; SD = 12.1), a difference that was statistically significant ($p < 0.05$).

Genetic Heritability of the Study Outcome

Using summary-level data, the total estimated heritability (h^2) in the COURAGE-PD dataset was 0.083 (SE = 0.057). Similar heritability estimates were observed in the European subcohort ($h^2 = 0.079$, SE = 0.061). However, the heritability estimates in the Asian subcohort could not be reliably computed because of an insufficient number of patients. In addition, we failed to achieve any improvement in heritability estimates, although with improved accuracy by combining COURAGE-PD with the IPDGC dataset ($h^2 = 0.078$, SE = 0.018).

Genome-wide Meta-analysis

COURAGE-PD

GWAS meta-analysis

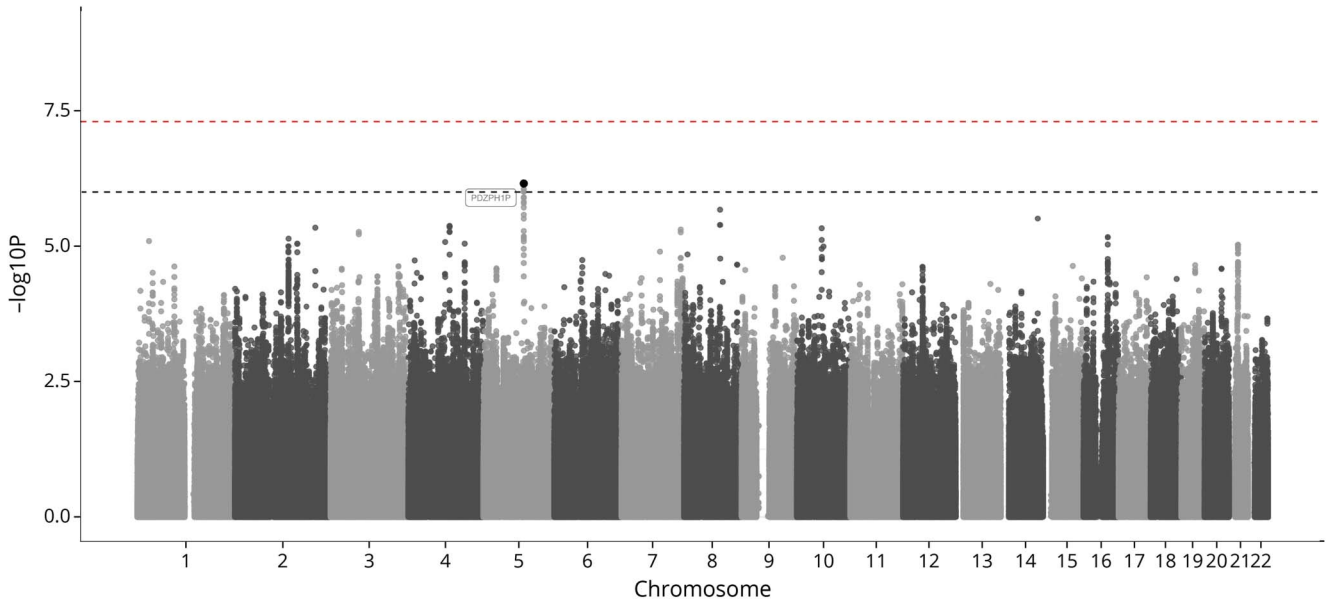
The genomic inflation factor λ was 1.016 (see eFigure 1, links.lww.com/WNL/C86, for the QQ plot). None of the loci reached genome-wide significance (Figure 1). We observed 1 locus reaching the suggestive genome-wide significance level, *PDZPH1P* (Chr 5) ($\beta(\text{SE})_{\text{COURAGE}} = -1.456(0.293)$, $p_{\text{COURAGE}} = 6.91 \times 10^{-7}$). However, stratifying the analyses by ethnicities, we did not observe any suggestive involvement of *PDZPH1P* locus in the European subcohort (eTable 2, links.lww.com/WNL/C88). Of interest, despite being a smaller subcohort, *SUGCT* locus on chromosome (Chr) 7 was detected as a suggestive locus in the East Asian subcohort ($\beta(\text{SE})_{\text{COURAGE-EASIAN}} = 13.681(2.769)$, $p_{\text{COURAGE-EASIAN}} = 7.80 \times 10^{-7}$). Furthermore, the stratified analysis provided suggestive evidence of 3 loci, *RHEB* (Chr 8) in males ($\beta(\text{SE})_{\text{COURAGE-M}} = -1.112(0.222)$, $p_{\text{COURAGE-M}} = 5.15 \times 10^{-7}$), *MTHFD1L* (Chr 6) in females ($\beta(\text{SE})_{\text{COURAGE-F}} = -1.995(0.402)$, $p_{\text{COURAGE-F}} = 6.78 \times 10^{-7}$), and *KNH3* (Chr 12) in females ($\beta(\text{SE})_{\text{COURAGE-F}} = 2.176(0.432)$, $p_{\text{COURAGE-F}} = 4.59 \times 10^{-7}$) (eTable 2, links.lww.com/WNL/C88).

In the replication of previously reported variants, only the *TMEM175* variant (rs34311866: $\beta(\text{SE})_{\text{COURAGE}} = 0.477(0.203)$, $p_{\text{COURAGE}} = 0.018$) reached Bonferroni-corrected nominal levels of significance in the COURAGE-PD dataset. Nevertheless, the *SNCA* variant also showed a trend toward association (rs356203: $\beta(\text{SE})_{\text{COURAGE}} = 0.362(0.172)$, $p_{\text{COURAGE}} = 0.035$).

Meta-analysis of COURAGE-PD and IPDGC Datasets

The meta-analysis of COURAGE-PD and IPDGC datasets led to the identification of 2 loci that reached genome-wide significance (eTable 2, links.lww.com/WNL/C88; Figure 2). The *SNCA* variant, rs983361, was the most strongly associated SNV, with the presence of allele T (frequency = 0.204) leading to an average delay in AAO by 0.72 years ($\beta(\text{SE})_{\text{COURAGE+IPDGC}} = 0.720(0.122)$, $p_{\text{COURAGE+IPDGC}} = 3.13 \times 10^{-9}$). This association, however, appeared to be driven by the strong association reported by the IPDGC dataset, with negligible effect

Figure 1 Manhattan Plot of COURAGE-PD Age-at-Onset GWAS

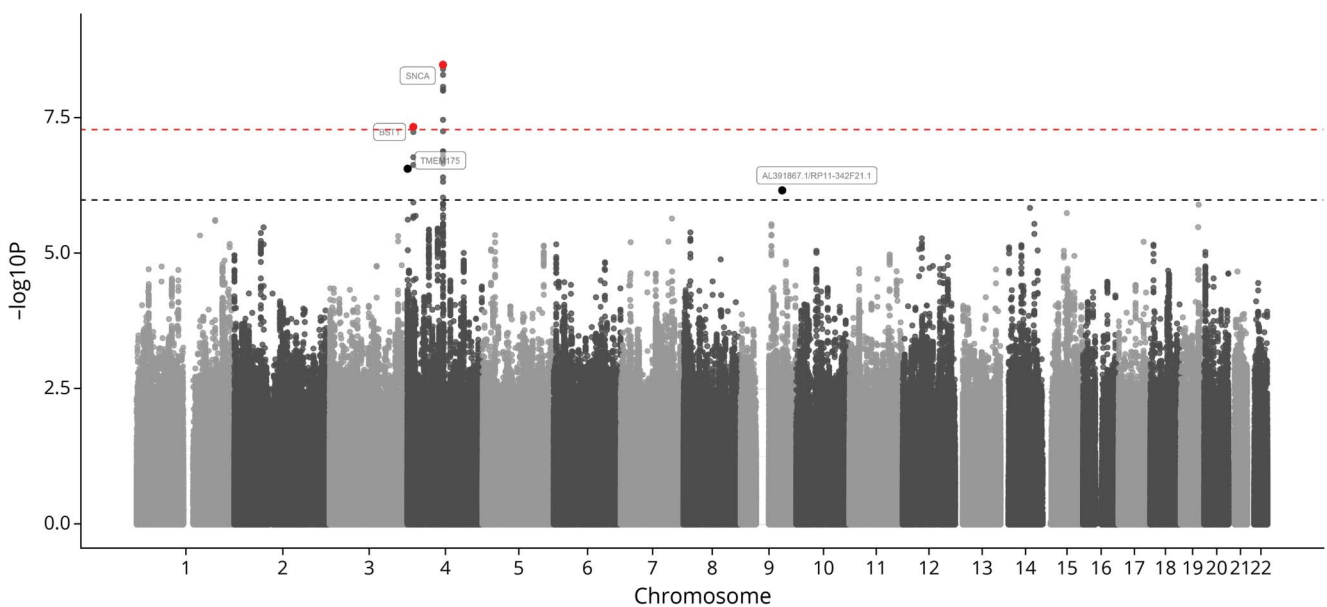


COURAGE-PD = Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease; GWAS = genome-wide association studies.

detected in the COURAGE-PD dataset ($p_{\text{COURAGE/COURAGE-EUR}}(\text{rs983361}) = 0.022$; not detected in the East Asian sub-population) (eFigure 2A, links.lww.com/WNL/C86), which was also reflected in the loss of genome-wide significance, when using an additive random effect model ($p = 2.98 \times 10^{-6}$). On the other hand, another independent locus on the same

chromosome, *BST1* (rs4698412), showed similar effects in COURAGE-PD and IPDGC datasets ($\beta(\text{SE})_{\text{COURAGE}} = -0.633(0.175)$, $p_{\text{COURAGE}} = 2.95 \times 10^{-4}$; $\beta(\text{SE})_{\text{IPDGC}} = -0.480(0.115)$, $p_{\text{IPDGC}} = 3.04 \times 10^{-5}$), and the combination of both estimates resulted in the identification of a novel genome-wide significant *BST1* locus for AAO ($\beta(\text{SE})_{\text{COURAGE+IPDGC}} =$

Figure 2 Manhattan Plot of the Meta-analysis of COURAGE-PD and IPDGC Age-at-Onset GWAS



COURAGE-PD = Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease; GWAS = genome-wide association studies; IPDGC = International Parkinson Disease Genomics Consortium.

Table 1 eQTL Lookup of *BST1* SNV rs4698412 From GTEx and UKBEC in Brain Tissue

Database		Gene symbol	p Value	NES	Tissue
GTEx	ENSG00000004468	<i>CD38</i>	3.3e-16	-0.44	Caudate (basal ganglia)
	ENSG00000004468	<i>CD38</i>	5.5e-15	-0.39	Cortex
	ENSG00000004468	<i>CD38</i>	1.4e-13	-0.39	Nucleus accumbens (basal ganglia)
	ENSG00000004468	<i>CD38</i>	1.4e-11	-0.32	Putamen (basal ganglia)
	ENSG00000004468	<i>CD38</i>	6.6e-6	-0.21	Frontal cortex (BA9)
	ENSG00000237765	<i>FAM200B</i>	1.0e-5	0.23	Cerebellar hemisphere
	ENSG00000004468	<i>CD38</i>	1.2e-5	-0.26	Anterior cingulate cortex (BA24)
	ENSG00000237765	<i>FAM200B</i>	1.4e-5	0.23	Cortex
	ENSG00000004468	<i>CD38</i>	1.4e-5	-0.22	Hypothalamus
UKBEC	ENSG00000118564	<i>FBXL5</i>	5.1e-7	NA	Occipital cortex
	ENSG00000004468	<i>CD38</i>	7.1e-6	NA	Putamen (basal ganglia)
	ENSG00000004468	<i>CD38</i>	2.1e-5	NA	Hippocampus
	ENSG000001137449	<i>CPEB2</i>	2.4e-5	NA	Medulla

Abbreviations: eQTL = expression quantitative trait locus; GTEx = Genotype-Tissue Expression Project; NA = not available; UKBEC = UK Brain Expression Consortium.

-0.526(0.096), $p_{\text{COURAGE+IPDGC}} = 4.41 \times 10^{-8}$) (eFigure 2B, links.lww.com/WNL/C86). The rs4698412 allele A (frequency = 0.562) at the locus led to an average earlier AAO of 0.526 years in patients with PD. No genetic heterogeneity was detected in the observed association ($I^2 = 0$; heterogeneity $p = 0.465$). Furthermore, we did not observe any change in the effect estimates, when using the additive random effect model ($p = 4.41 \times 10^{-8}$).

The previously reported *TMEM175* (rs34311866) showed a suggestive association in the combined analysis ($\beta(\text{SE})_{\text{COURAGE+IPDGC}} = 0.589(0.114)$, $p_{\text{COURAGE+IPDGC}} = 2.64 \times 10^{-7}$) that appeared to be driven by previously reported findings in the IPDGC dataset ($\beta(\text{SE})_{\text{IPDGC}} = 0.642(0.139)$, $p_{\text{IPDGC}} = 3.72 \times 10^{-6}$) (eFigure 2C, links.lww.com/WNL/C86). Another locus *AL391867.1/RP11-342F21.1* (rs62582905), a locus of unknown biological significance, also crossed the threshold of a suggestive association in the same analysis ($\beta(\text{SE})_{\text{COURAGE+IPDGC}} = -1.456(0.293)$, $p_{\text{COURAGE}} = 6.62 \times 10^{-7}$) (eTable 2, links.lww.com/WNL/C88). However, unlike the *TMEM175* association, the association with *AL391867.1/RP11-342F21.1* was observed to be stronger in the COURAGE-PD dataset ($\beta(\text{SE})_{\text{COURAGE}} = -1.925(0.447)$, $p_{\text{COURAGE}} = 1.64 \times 10^{-5}$).

We performed a sensitivity analysis by excluding the Asian subcohort from the COURAGE dataset, followed by combining with the IPDGC dataset. Similar findings were observed for the 2 genome-wide significant loci (*SNCA* rs983361: $p_{\text{COURAGE-EUR+IPDGC}} = 3.13 \times 10^{-9}$, *BST1* rs4698412: $p_{\text{COURAGE-EUR+IPDGC}} = 6.27 \times 10^{-8}$) (eTable 2, links.lww.com/WNL/C88). A similar sensitivity analysis for the previously

reported *APOE* $\epsilon 4$ locus also showed a suggestive association with PD AAO (*APOE* rs429358: $\beta(\text{SE})_{\text{COURAGE-EUR+IPDGC}} = 0.711(0.145)$, $p_{\text{COURAGE-EUR+IPDGC}} = 9.33 \times 10^{-7}$). However, the association was primarily driven by highly significant findings in the IPDGC dataset ($\beta(\text{SE})_{\text{IPDGC}} = 0.754(0.171)$, $p_{\text{IPDGC}} = 9.86 \times 10^{-6}$; $\beta(\text{SE})_{\text{COURAGE-EUR}} = 0.599(0.275)$, $p_{\text{COURAGE-EUR}} = 0.029$).

Correlation Between Genetic Risk for PD and PD AAO

Using complete GWAS summary datasets for COURAGE-PD case-control and COURAGE-PD AAO, we observed a nonsignificant negative genetic correlation between PD and PD AAO ($r_g = -0.291$, $\text{SE} = 0.224$; $p = 0.186$). Furthermore, a slightly stronger genetic correlation was observed when restricting our correlation analysis to European subcohorts alone ($r_g = -0.315$; $\text{SE} = 0.252$; $p = 0.211$).

When using the PRS based on the significant loci detected in the meta-analysis of COURAGE-PD and IPDGC European datasets, as reported elsewhere, we observed that each unit increase in SD in the PRS leads to a significant decrease in AAO in COURAGE-PD by 0.58 years ($\beta(\text{SE})_{\text{COURAGE}} = -0.581(0.149)$, $p_{\text{COURAGE}} = 9.35 \times 10^{-5}$). Despite the significant findings, the PRS explained only 0.59% of the genetic proportion of PD heritability.

Expression Quantitative Trait Analysis of Novel *BST1* Locus

The mining of the GTEx portal showed that rs4698412 representing the *BST1* locus is a highly significant expression quantitative trait locus (eQTL) for *CD38* in the basal ganglia (caudate, nucleus accumbens, and putamen) and cortex

(NES = -0.32 – 0.44 ; $p < 1 \times 10^{-10}$) (Table 1). The expression analysis also showed a strong dosage effect with a consistent lower expression in the presence of AA genotype compared with GG genotype with a higher expression, irrespective of the brain tissue type. In addition, we also found that SNV modulates the expression of *BST1* in whole blood. However, the effect was considerably lower in comparison with that observed on *CD38* expression levels in brain tissues (NES = -0.071 ; $p = 1.7 \times 10^{-6}$). The follow-up of the association of rs4698412 with expression in brain tissues in the UKBEC database further confirmed the role of basal ganglia, with *CD38* as the most significantly associated expressed gene in the putamen ($p = 7.1 \times 10^{-6}$) (Table 1).

Discussion

The identification of genetic determinants that modify the disease progression will not only help to increase our understanding of PD etiopathogenesis but also enable the development of strategies that could be used for therapeutic intervention for at-risk carriers. Our study not only validates previously reported AAO PD loci in the COURAGE-PD dataset, but our meta-analysis with IPDGC data also provides the first genome-wide significant evidence that the known *BST1* PD risk locus affects AAO. Of interest, the variant, rs4698412, representing the *BST1* locus, showed a similar large effect in COURAGE-PD and IPDGC, providing strong evidence that this is a bona fide genetic locus for PD AAO. Finally, using significant SNVs from the meta-analysis of COURAGE-PD and IPDGC case-control datasets, we demonstrate an inverse association between a PD PRS and AAO of PD.

Numerous genetic loci for familial and sporadic PD have been well characterized. The existence of overlapping loci between familial and sporadic PD suggests a complex but interconnected relationship between PD and age. Several meta-analyses of candidate genes and GWAS have previously recognized the *BST1* locus as a locus that could influence the development of sporadic late-onset PD.^{6,22-24} Notably, the *BST1* locus has been demonstrated to play a role in both Asian and European PD populations.^{6,22-24} The genome-wide significant *BST1* variant, rs4698412 observed in our AAO meta-analysis, is also identical to the top *BST1* variant reported in the latest PD GWAS meta-analysis.⁶ Of interest, regional plots showed that the genome-wide significant variant, rs4694812, was neither the top genetic variant in the *BST1* locus in IPDGC nor COURAGE AAO PD datasets. Although rs4694819 (r^2 with rs4694812 < 0.6) was the most significant variant in the COURAGE AAO dataset, rs11724635 (r^2 with rs4698412 = 1.0) was the most significant variant in the IPDGC AAO dataset (eFigure 2B, links.lww.com/WNL/C86).

BST1 was first identified as a gene encoding a cell surface receptor on bone marrow stromal cells (bone marrow stromal cell antigen 1) with a role in promoting the growth of hematopoietic stromal cells.²⁵ In addition to its role as a receptor,

it also exhibits ADP-ribosyl cyclase activity, leading to the generation of cyclic ADP-ribose, with a role in intrinsic Ca^{2+} regulation.²⁶ The dual functional protein, a highly conserved glycosylphosphatidylinositol-anchored glycoprotein (also known as *CD157*), is now known to be expressed in a wide variety of tissues, including the vascular endothelium and follicular dendritic cells, with an ability to perform a wide variety of immune system- and inflammation-related cellular functions.²⁷ The initial identification of *BST1/CD157* as a potential risk locus for sporadic late-onset PD in a GWAS in the Japanese population led to several functional studies aimed at deciphering its potential neuronal role in influencing the PD phenotype.²² Several knockout mouse model studies have shown that *BST1* can influence social behavior. However, the studies failed to demonstrate any influence on motor functioning, the cardinal feature that is impaired in patients with PD.^{28,29} The eQTL analysis demonstrated a highly significant effect of the *BST1* locus, rs4694812, on gene expression, with the A allele resulting in a decreased expression of *CD38*, a paralog of *CD157*, in a dose-dependent manner. *CD38* and *CD157* are contiguous gene duplicates, which belong to the same gene family with a similar role of dual functional protein and an ability to modulate social behavior.^{30,31} Of interest, unlike *CD157*, *CD38* knockout mice have been shown to have higher locomotor activity.³² Furthermore, the highly significant increased expression of *CD38* was mainly observed in the striatum, a region directly implicated in motor dysfunction in PD. Of interest, a statistically underpowered brain imaging study in humans suggested that allele A of *BST1* SNV rs4698412 leads to deficits in the right lingual gyrus region in the brain during the progression of PD.³³ This brain region is known to play a role in spatial orientation and visuospatial information processing. However, specific molecular and neuronal pathways influenced by altered *CD38* expression in basal ganglia, with a potential role in triggering earlier AAO in sporadic PD, remain unclear.

SNCA is one of the most consistently observed significant loci in both early- and late-onset PD and has been suggested to play a critical role in the age-related hierarchy of disease onset. Although monogenic PD, often with relatively early onset, is attributed to rare point mutations and multiple copies of the *SNCA* gene, susceptibility to late-onset PD is attributed to common variants.^{6,10,34-36} In addition to being a leading locus in the largest GWAS of sporadic PD to date, the locus was also recently reported to be a top locus in influencing AAO in Europeans in meta-analyses comprising IPDGC and 23andMe datasets ($n = 28,568$).⁷ An SNV present toward the 3' end (rs356203) of the *SNCA* gene was observed as the strongest genome-wide significant variant originating from the region ($p = 1.9 \times 10^{-12}$). Based on the conditional analysis, the study also identified an independent signal at the 5' end of the gene, rs983361 ($p = 6.8 \times 10^{-6}$). A recent GWAS of AAO in 5,166 East Asian (Chinese) patients with PD further reported a slightly weaker signal originating from another independent *SNCA* variant, rs3775458 ($p = 9.92 \times 10^{-7}$).⁹ Using the 1000 genome phase 3 dataset, we failed to detect any

LD among the 3 variants in both European and East Asian populations (data not shown here). On screening the *SNCA* locus in the COURAGE-PD dataset, we observed nominal significance of all the 3 variants ($P_{\text{COURAGE}}(\text{rs356203}) = 0.035$, $P_{\text{COURAGE}}(\text{rs3775458}) = 0.005$, and $P_{\text{COURAGE}}(\text{rs983361}) = 0.022$), possibly suggesting a consistence influence of different loci around the *SNCA* region in determining AAO in different worldwide PD populations. The combination of our dataset with IPDGC further showed an independent genome-wide significant signal originating from the 3' end of the *SNCA* gene (rs983361), as shown in the Results section above. Notably, we also observed an independent signal at the 5' end (rs356203). However, the variant was excluded for further interpretation because of high heterogeneity observed when combining IPDGC and COURAGE datasets ($\beta(\text{SE})_{\text{COURAGE+IPDGC}} = -0.591(0.097)$, $P_{\text{COURAGE+IPDGC}} = 9.28 \times 10^{-10}$; $I^2 = 61.9\%$).

Another PD locus, *TMEM175*, was previously shown to reach genome-wide significance in an AAO study.³⁷ Similar to *SNCA*, our study also demonstrated replication of the *TMEM175* locus in the COURAGE-PD AAO dataset with a nominal level of significance ($p = 0.018$). The subsequent combination of the nonsynonymous coding variant, rs3431186 (p.M393T), representing the genome-wide significant locus, in the IPDGC dataset with the COURAGE-PD, resulted in the suggestive level of association without any underlying heterogeneity ($P_{\text{COURAGE+IPDGC}} = 2.64 \times 10^{-7}$; $I^2 = 0.0$). On the contrary, a recent East Asian GWAS failed to observe any signal originating from the locus, possibly suggesting the contribution of the locus mainly in the European populations.⁹ A previous study also reported a borderline significant association of the variant rs429358, representing the *APOE* $\epsilon 4$ locus with PD-AAO ($p = 5.69 \times 10^{-8}$) in a combined dataset ($n = 28,568$) comprising IPDGC and 23andMe datasets.⁷ The study, however, suggested that the association at the locus could be an age-related effect, with a highly significant association with the age of controls ($p = 1.49 \times 10^{-5}$). The variant also resulted in a suggestive association on merging of the COURAGE-PD European dataset only with the IPDGC dataset ($p = 9.3 \times 10^{-7}$). These findings are consistent with the failure to detect the association of *APOE* $\epsilon 4$ locus with PD-AAO in the recently reported East Asian GWAS.⁹ However, being a longevity marker, the suggestive finding of the *APOE* $\epsilon 4$ locus in Europeans must be interpreted with caution.

Our study has several strengths and limitations. Our study provides the largest independent dataset for testing the reliability of previously discovered AAO loci in a highly diverse and predominantly European population. Another strength of our study was the availability of data on AAO on all the study participants as opposed to the age at diagnosis, often used as a proxy for AAO. One of the significant limitations of our findings was the lack of ready access to the recently published East Asian AAO GWAS dataset that prevented us from drawing any conclusion on the validity of the novel *BST1* locus in the East Asian population. Likewise, the unavailability of the 23andMe dataset to us has precluded us from making an unequivocal claim on our *BST1* findings. Hopefully, the inclusion of other datasets, such as 23andMe and East Asian

GWAS datasets, will help further to refine the signals originating from the *BST1* locus. We also suggest that loci identified through meta-analysis in the COURAGE-PD dataset (*PDZPH1P*) and subsequent stratification by gender (*RHEB*, *MTHFD1L*, and *KNH3*) and ethnicity (*MOAPI/TMEM251* and *SUGCT*) be meta-analyzed with these unavailable datasets. Another limitation was our inability to conduct gene-gene interaction because of the limited sample size in this study. The possibility of complex interactions among various loci on Chr 4 in modulating AAO cannot be ruled out. A recent study showed the association of several genome-wide significant loci on the X Chr with PD.³⁸ It is also possible that some of these variants may also modulate AAO. However, owing to potential analytic challenges from calling and imputation of X Chr genotypes, to model uncertainty associated with random X Chr inactivation, we excluded the X Chr variants from the present analysis.³⁹ And finally, it is hoped that in the future, the availability of a larger dataset would enable us to integrate additional layers of genetic data, including rare and copy number variants.⁴⁰

Our findings clearly highlight the importance of combining GWAS from diverse populations, representative of worldwide populations, to refine the genetic architecture underlying a complex trait such as AAO. Our COURAGE-PD dataset suggests a role for additional pathways in addition to α -synuclein mechanisms of modulating PD pathogenesis and influencing AAO in worldwide PD populations.

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Disclosure

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Appendix (continued)

Name	Location	Contribution
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Appendix (continued)

Name	Location	Contribution
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Name	Location	Contribution
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