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

Evidence From the COURAGE-PD Consortium

Sandeep Grover, PhD, Ashwin Ashok Kumar Sreelatha, MTech, Lasse Pihlstrom, MD, Cloé Domenighetti, PhD, Claudia Schulte, MSc, Pierre-Emmanuel Sugier, PhD, Milena Radivojkov-Blagojevic, MSc, Peter Lichtner, PhD, Océane Mohamed, MSc, Berta Portugal, PhD, Zied Landoulsi, PhD, Patrick May, PhD, Dheeraj Bobbili, PhD, Connor Edsall, PhD, Felix Bartusch, MSc, Maximilian Hanussek, MSc, Jens Krüger, PhD, Dena G. Hernandez, PhD, Cornelis Blauwendraat, PhD, George D. Mellick, PhD, Alexander Zimprich, MD, Walter Pirker, MD, Manuela Tan, MSC, Ekaterina Rogaeva, PhD, Anthony Lang, MD, Sulev Koks, MD, PhD, Pille Taba, MD, PhD, Suzanne Lesage, PhD, Alexis Brice, Jean-Christophe Corvol, MD, PhD, Marie-Christine Chartier-Harlin, PhD, Eugenie Mutez, MD, PhD, Kathrin Brockmann, MD, Angela B. Deutschländer, MD, Georges M. Hadjigeorgiou, MD, Efthimos Dardiotis, MD, Leonidas Stefanis, MD, PhD, Athina Maria Simitsi, MD, PhD, Enza Maria Valente, MD, PhD, Simona Petrucci, MD, PhD, Letizia Straniero, PhD, Anna Zecchinelli, MD, Gianni Pezzoli, MD, Laura Brighina, MD, PhD, Carlo Ferrarese, MD, PhD, Grazia Annesi, PhD, Andrea Quattrone, MD, Monica Gagliardi, PhD, Lena F. Burbulla, PhD, Hirotaka Matsuo, MD, PhD, Yusuke Kawamura, MD, Nobutaka Hattori, MD, PhD, Kenya Nishioka, MD, PhD, Sun Ju Chung, MD, PhD, Yun Joong Kim, MD, PhD, Lukas Pavelka, MD, Bart P.C. van de Warrenburg, MD, PhD, Bastiaan R. Bloem, MD, PhD, Andrew B. Singleton, PhD, Jan Aasly, MD, Mathias Toft, MD, PhD, Leonor Correia Guedes, MD, PhD, Joaquim J. Ferreira, MD, PhD, Soraya Bardien, PhD, Jonathan Carr, PhD, Eduardo Tolosa, MD, PhD, Mario Ezquerra, PhD, Pau Pastor, MD, PhD, Monica Diez-Fairen, MSc, Karin Wirdefeldt, MD, PhD, Nancy L. Pedersen, PhD, Caroline Ran, PhD, Andrea C. Belin, PhD, Andreas Puschmann, MD, PhD, Clara Hellberg, MD, Carl E. Clarke, MD, Karen E. Morrison, MD, Dimitri Krainc, MD, PhD, Matt J. Farrer, PhD, Rejko Kruger, MD, Alexis Elbaz, PhD, Thomas Gasser, MD, and Manu Sharma, PhD, and the Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease (COURAGE-PD) Consortium

Correspondence
Dr. Sharma
manu.sharma@uni-tuebingen.de

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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; **GTEx** = 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: $\beta(SE)_{COURAGE} = 0.477(0.203)$, $p_{COURAGE} = 0.0185$). The subsequent meta-analysis of COURAGE-PD and IPDGC datasets ($N_{total} = 25{,}950$) led to the identification of 2 genome-wide significant association signals on Chr 4, including the previously reported *SNCA* locus (rs983361: $\beta(SE)_{COURAGE+IPDGC} = 0.720(0.122)$, $p_{COURAGE+IPDGC} = 3.13 \times 10^{-9}$) and a novel *BST1* locus (rs4698412: $\beta(SE)_{COURAGE+IPDGC} = -0.526(0.096)$, $p_{COURAGE+IPDGC} = 4.41 \times 10^{-8}$).

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

From the Centre for Genetic Epidemiology (S.G., A.A.K.S., M.S.), Institute for Clinical Epidemiology and Applied Biometry, University of Tubingen, Germany; Department of Neurology (L. Pihlstrom, M.T.), Oslo University Hospital, Norway; Université Paris-Saclay (C.D., P.E.S., O.M., B.P., A.E.), UVSQ, Univ. Paris-Sud, Inserm, Team "Exposome, heredity, cancer and health," CESP, Villejuif, France; Department for Neurodegenerative Diseases (C.S., K.B., T.G., M.S.), Hertie Institute for Clinical Brain Research, University of Tubingen; German Center for Neurodegenerative Diseases (DZNE) (C.S., L.F.B., T.G.), Tübingen; Institute of Human Genetics (M.R.B., P.L.), Helmholtz Zentrum München, Neuherberg, Germany; Luxembourg Centre for Systems Biomedicine (LCSB) (Z.L., P.M., D.B., R.K.), University of Luxembourg, Esch-sur-Alzette, Luxembourg; Molecular Genetics Section (C.E., D.G.H., C.B., A.B.S.,), Laboratory of Neurogenetics, NIA, NIH, Bethesda, MD; Group of Applied Bioinformatics (F.B., M.H., J.K.), University of Tübingen; High Performance and Cloud Computing Group ZDV (F.B., M.H.), University of Tübingen, Germany; Griffith Institute for Drug Discovery (G.D.M.), Griffith University, Don Young Road, Nathan, Queensland, Australia; Department of Neurology (A.Z.), Medical University of Vienna; Department of Neurology (W.P.), Wilhelminenspital, Austria; Department of Clinical and Movement Neurosciences (M.T.), UCL Queen Square Institute of Neurology, University College London, London, UK; Tanz Centre for Research in Neurodegenerative Diseases (E.R, A.L.), University of Toronto; Edmond J. Safra Program in Parkinson's Disease (A.L.), Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN; Division of Neurology (A.L.), University of Toronto; Krembil Brain Institute (A.L.), Toronto, Ontario, Canada; Centre for Molecular Medicine and Innovative Therapeutics (S.K.), Murdoch University, Murdoch, Australia; Perron Institute for Neurological and Translational Science (S.K.), Nedlands, Western Australia, Australia; Department of Neurology and Neurosurgery (P.T.), University of Tartu; Neurology Clinic, Tartu University Hospital (P.T.), Estonia; Sorbonne Université (SU) Unité Mixte de Recherche (UMR) 1127 (S.L., A.B., J.C.C.), Institut du Cerveau et de la Moelle épinière, ICM; Assistance Publique Hôpitaux de Paris (J.C.C.), Department of Neurology, CIC Neurosciences, Paris, France; Univ. Lille (M.C.C.H., E.M.), Inserm, CHU Lille, UMR-S 1172—JPArc—Centre de Recherche Lille Neurosciences & Cognition, Lille, France; Department of Neurology (A.B.D.), Ludwig Maximilians University of Munich; Department of Neurology (A.B.D.), Max Planck Institute of Psychiatry, Munich, Germany; Department of Neurology and Department of Clinical Genomics (A.B.D.), Mayo Clinic Florida, Jacksonville, FL; Department of Neurology (G.M.H.), Medical School, University of Cyprus, Nicosia, Cyprus; Department of Neurology (G.M.H., E.D.), Laboratory of Neurogenetics, University of Thessaly, University Hospital of Larissa, Larissa, Greece; Center of Clinical Research (L.S.), Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens; 1st Department of Neurology (L.S, A.M.S.), Eginition Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece; Department of Molecular Medicine (E.M.V.), University of Pavia; Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Mondino Foundation (E.M.V.), Pavia; UOC Medical Genetics and Advanced Cell Diagnostics (S.P.), S. Andrea University Hospital; Department of Clinical and Molecular Medicine (S.P.), University of Rome, Italy; Department of Biomedical Sciences—Humanitas University (L.S.); Humanitas Clinical and Research Center (L.S.), IRCCS, Via Manzoni 56, Milan, Italy; Parkinson Institute (A.Z., G.P.), Azienda Socio Sanitaria Territoriale (ASST) Gaetano Pini/CTO, Milano, Italia; Department of Neurology (L.B., C.F.), San Gerardo Hospital, Milan; Center for Neuroscience (L.B., C.F.), University of Milano Bicocca, Monza; Institute for Biomedical Research and Innovation (G.A., M.G.), National Research Council, Mangone, Cosenza; Institute of Neurology (A.Q.), Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy; Department of Neurology (L.F.B., D.K.), Northwestern University Feinberg School of Medicine, Chicago, IL; Metabolic Biochemistry (L.F.B.), Biomedical Center (BMC), Faculty of Medicine, Ludwig-Maximilians University; Munich Cluster for Systems Neurology (SyNergy) (L.F.B.), Munich, Germany; Department of Integrative Physiology and Bio-Nano Medicine (H.M., Y.K.), National Defense Medical College, Saitama; Department of Neurology (N.H., K.N.), Juntendo University School of Medicine, Bunkyo-ku, Tokyo, Japan; Department of Neurology (S.J.C.), Asan Medical Center, University of Ulsan College of Medicine; Department of Neurology (Y.J.K.), Yonsei University College of Medicine, Seoul, South Korea; Luxembourg Centre for Systems Biomedicine (L. Pavelka), University of Luxembourg, Belval, Luxembourg; Radboud University Medical Centre (B.P.C.v.d.W., B.R.B.), Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, Nijmegen, The Netherlands; Department of Neurology (J.A.), St Olav's Hospital and Norwegian University of Science and Technology, Trondheim, Norway; Instituto de Medicina Molecular João Lobo Antunes (L.C.G., J.J.F.), Faculdade de Medicina, Universidade de Lisboa; Department of Neurosciences and Mental Health (L.C.G.), Neurology, Hospital de Santa Maria, Centro Hospitalar Universitario Lisboa Norte (CHULN); Laboratory of Clinical Pharmacology and Therapeutics (J.J.F.), Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal; Division of Molecular Biology and Human Genetics (S.B.), Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University; Division of Neurology (J.C.), Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa; Parkinson's disease & Movement Disorders Unit, Neurology Service (E.T.), Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona; Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED: CB06/05/0018-ISCIII) Barcelona (E.T.), Spain; Lab of Parkinson Disease and Other Neurodegenerative Movement Disorders (M.E.), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Institut de Neurociències, Universitat de Barcelona, Catalonia; Fundació per la Recerca Biomèdica i Social Mútua Terrassa (P.P., M.D.F.); Movement Disorders Unit (P.P., M.D.F.), Department of Neurology, Hospital Universitari Mutua de Terrassa, Barcelona, Spain; Department of Clinical Neuroscience (K.W.), Karolinska Institutet; Department of Medical Epidemiology and Biostatistics (K.W., N.L.P.), Karolinska Institutet; Department of Neuroscience, Karolinska Institutet (C.R., A.C.B.), Stockholm; Lund University (A.P., C.H.), Skåne University Hospital, Department of Clinical Sciences Lund, Neurology, Lund, Sweden; University of Birmingham and Sandwell and West Birmingham Hospitals NHS Trust (C.E.C.); Faculty of Medicine, Health and Life Sciences (K.E.M.), Queens University, Belfast, United Kingdom; Department of Neurology (M.J.F.), McKnight Brain Institute, University of Florida, Gainesville, FL; Parkinson Research Clinic (R.K.), Centre Hospitalier de Luxembourg; Transversal Translational Medicine, Luxembourg Institute of Health (LIH) (R.K.), Strassen; and Neurology (R.K.), Centre Hospitalier de Luxembourg, Luxembourg.

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 lead 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, 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 ≥ 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/Ageatonset_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

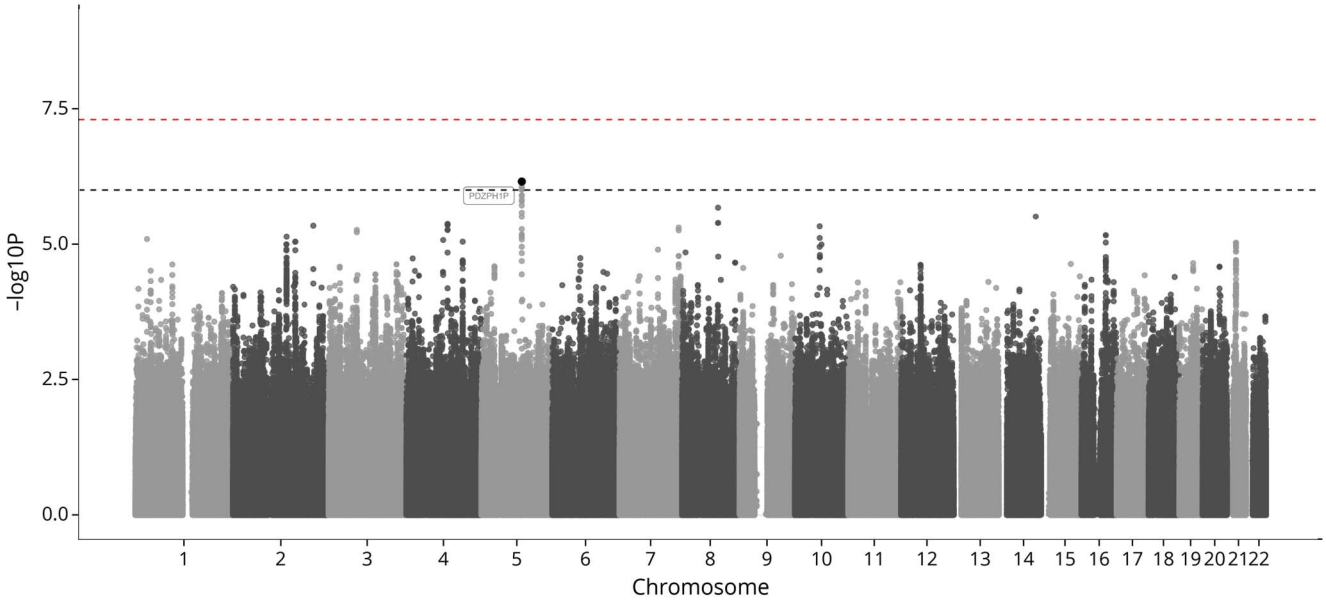
The genomic inflation factor λ was 1.016 (see eFigure 1, links.lww.com/WNL/C86, for the QQ plot). None of the loci reached genome-wide significance (Figure 1). We observed 1 locus reaching the suggestive genome-wide significance level, *PDZPH1P* (Chr 5) ($\beta(SE)_{COURAGE} = -1.456(0.293)$, $p_{COURAGE} = 6.91 \times 10^{-7}$). 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 ($\beta(SE)_{COURAGE\text{-}EASIAN} = 13.681(2.769)$, $p_{COURAGE\text{-}EASIAN} = 7.80 \times 10^{-7}$). Furthermore, the stratified analysis provided suggestive evidence of 3 loci, *RHEB* (Chr 8) in males ($\beta(SE)_{COURAGE\text{-}M} = -1.112(0.222)$, $p_{COURAGE\text{-}M} = 5.15 \times 10^{-7}$), *MTHFD1L* (Chr 6) in females ($\beta(SE)_{COURAGE\text{-}F} = -1.995(0.402)$, $p_{COURAGE\text{-}F} = 6.78 \times 10^{-7}$), and *KNH3* (Chr 12) in females ($\beta(SE)_{COURAGE\text{-}F} = 2.176(0.432)$, $p_{COURAGE\text{-}F} = 4.59 \times 10^{-7}$) (eTable 2, links.lww.com/WNL/C88).

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

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 ($\beta(SE)_{COURAGE+IPDGC} = 0.720(0.122)$, $p_{COURAGE+IPDGC} = 3.13 \times 10^{-9}$). This association, however, appeared to be driven by the strong association reported by the IPDGC dataset, with negligible effect

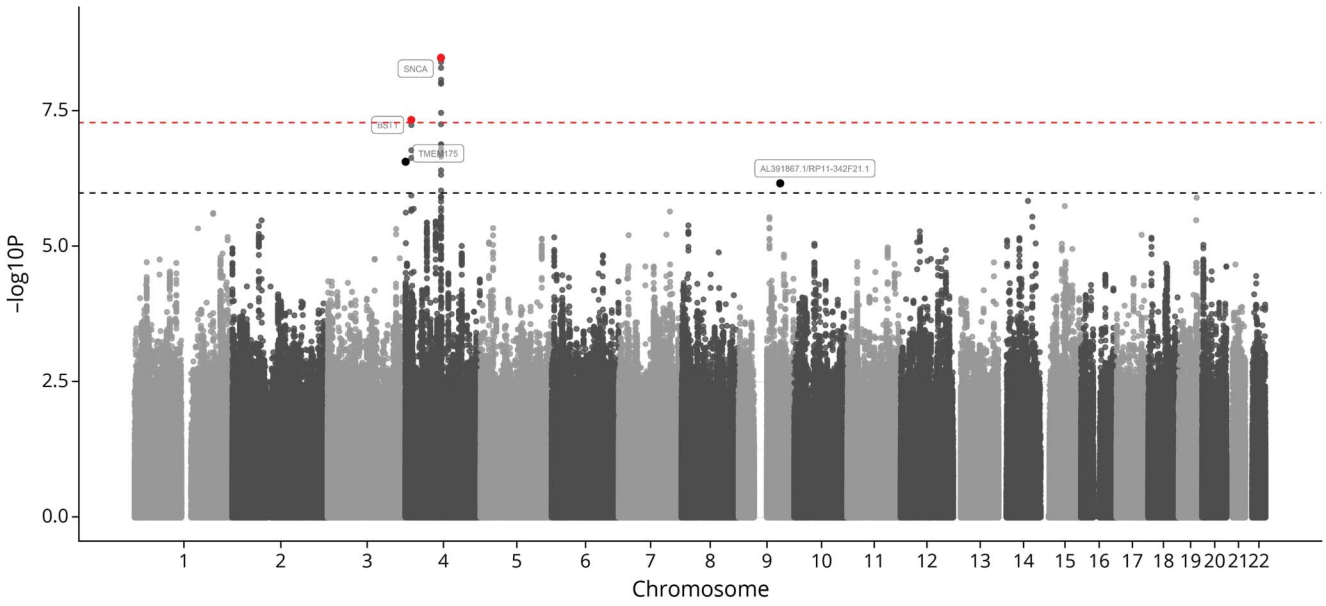
Figure 1 Manhattan Plot of COURAGE-PD Age-at-Onset GWAS



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 ($p_{\text{COURAGE/COURAGE-EUR (rs983361)}} = 0.022$; not detected in the East Asian subpopulation) (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	*CD38*	3.3e-16	−0.44	Caudate (basal ganglia)
	ENSG00000004468	*CD38*	5.5e-15	−0.39	Cortex
	ENSG00000004468	*CD38*	1.4e-13	−0.39	Nucleus accumbens (basal ganglia)
	ENSG00000004468	*CD38*	1.4e-11	−0.32	Putamen (basal ganglia)
	ENSG00000004468	*CD38*	6.6e-6	−0.21	Frontal cortex (BA9)
	ENSG00000237765	*FAM200B*	1.0e-5	0.23	Cerebellar hemisphere
	ENSG00000004468	*CD38*	1.2e-5	−0.26	Anterior cingulate cortex (BA24)
	ENSG00000237765	*FAM200B*	1.4e-5	0.23	Cortex
	ENSG00000004468	*CD38*	1.4e-5	−0.22	Hypothalamus
UKBEC	ENSG00000118564	*FBXL5*	5.1e-7	NA	Occipital cortex
	ENSG00000004468	*CD38*	7.1e-6	NA	Putamen (basal ganglia)
	ENSG00000004468	*CD38*	2.1e-5	NA	Hippocampus
	ENSG00000137449	*CPEB2*	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* ε4 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 (rg = −0.291, SE = 0.224; $p = 0.186$). Furthermore, a slightly stronger genetic correlation was observed when restricting our correlation analysis to European subcohorts alone (rg = −0.315; 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 ($P_{COURAGE\ (rs356203)} = 0.035$, $P_{COURAGE\ (rs3775458)} = 0.005$, and $P_{COURAGE\ (rs983361)} = 0.022$), 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 ($\beta(SE)_{COURAGE+IPDGC} = -0.591(0.097)$, $P_{COURAGE+IPDGC} = 9.28 \times 10^{-10}$; $I^2 = 61.9\%$).

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 ($P_{COURAGE+IPDGC} = 2.64 \times 10^{-7}$; $I^2 = 0.0$). 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* ε4 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* ε4 locus with PD-AAO in the recently reported East Asian GWAS.[9] However, being a longevity marker, the suggestive finding of the *APOE* ε4 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 (*MOAP1/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 Authors

Name	Location	Contribution
Sandeep Grover, PhD	Centre for Genetic Epidemiology, Institute for Clinical Epidemiology and Applied Biometry, University of Tubingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Ashwin Ashok Kumar Sreelatha, MTech	Centre for Genetic Epidemiology, Institute for Clinical Epidemiology and Applied Biometry, University of Tubingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data and analysis or interpretation of data
Lasse Pihlstrom, MD	Department of Neurology, Oslo University Hospital, Norway; Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Belval, Luxembourg	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Cloé Domenighetti, MSc	Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, Team "Exposome, heredity, cancer and health," CESP, Villejuif, France	Drafting/revision of the manuscript for content, including medical writing for content
Claudia Schulte, MSc	Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tubingen; German Center for Neurodegenerative Diseases (DZNE), Tübingen	Drafting/revision of the manuscript for content, including medical writing for content
Pierre-Emmanuel Sugier, PhD	Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, Team "Exposome, heredity, cancer and health," CESP, Villejuif, France	Drafting/revision of the manuscript for content, including medical writing for content
Milena Radivojkov-Blagojevic, MSc	Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Peter Lichtner, PhD	Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Océane Mohamed, MSc	Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, Team "Exposome, heredity, cancer and health," CESP, Villejuif, France	Drafting/revision of the manuscript for content, including medical writing for content
Berta Portugal, PhD	Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, Team "Exposome, heredity, cancer and health," CESP, Villejuif, France	Drafting/revision of the manuscript for content, including medical writing for content
Zied Landoulsi, PhD	Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Esch-sur-Alzette, Luxembourg	Drafting/revision of the manuscript for content, including medical writing for content
Patrick May, PhD	Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Esch-sur-Alzette, Luxembourg	Drafting/revision of the manuscript for content, including medical writing for content
Dheeraj Bobbili, PhD	Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Esch-sur-Alzette, Luxembourg	Drafting/revision of the manuscript for content, including medical writing for content
Connor Edsall, PhD	Molecular Genetics Section, Laboratory of Neurogenetics, NIA, NIH, Bethesda, MD	Drafting/revision of the manuscript for content, including medical writing for content
Felix Bartusch, MSc	Group of Applied Bioinformatics, University of Tübingen; High Performance and Cloud Computing Group ZDV, University of Tübingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Maximilian Hanussek, MSc	Group of Applied Bioinformatics, University of Tübingen; High Performance and Cloud Computing Group ZDV, University of Tübingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Jens Krüger, PhD	Group of Applied Bioinformatics, University of Tübingen	Revision of the manuscript for content
Dena G. Hernandez, PhD	Molecular Genetics Section, Laboratory of Neurogenetics, NIA, NIH, Bethesda, MD	Drafting/revision of the manuscript for content, including medical writing for content
Cornelis Blauwendraat, PhD	Molecular Genetics Section, Laboratory of Neurogenetics, NIA, NIH, Bethesda, MD	Drafting/revision of the manuscript for content, including medical writing for content

Appendix *(continued)*

Name	Location	Contribution
George D. Mellick, PhD	Griffith Institute for Drug Discovery, Griffith University, Don Young Road, Nathan, Queensland, Australia	Drafting/revision of the manuscript for content, including medical writing for content
Alexander Zimprich, MD	Department of Neurology, Medical University of Vienna	Drafting/revision of the manuscript for content, including medical writing for content
Walter Pirker, MD	Department of Neurology, Wilhelminenspital, Austria	Drafting/revision of the manuscript for content, including medical writing for content
Manuela Tan, MSc	Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, London, UK	Drafting/revision of the manuscript for content, including medical writing for content
Ekaterina Rogaeva, PhD	Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto	Drafting/revision of the manuscript for content, including medical writing for content
Anthony Lang, MD	Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto; Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN; Division of Neurology, University of Toronto; Krembil Brain Institute, Toronto, Ontario, Canada	Drafting/revision of the manuscript for content, including medical writing for content
Sulev Koks, MD, PhD	Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Murdoch, Australia; Perron Institute for Neurological and Translational Science, Nedlands, Western Australia, Australia	Drafting/revision of the manuscript for content, including medical writing for content
Pille Taba, MD, PhD	Department of Neurology and Neurosurgery, University of Tartu; Neurology Clinic, Tartu University Hospital, Estonia	Drafting/revision of the manuscript for content, including medical writing for content
Suzanne Lesage, PhD	Sorbonne Université (SU) Unité Mixte de Recherche (UMR) 1127, Institut du Cerveau et de la Moelle épinière, ICM	Drafting/revision of the manuscript for content, including medical writing for content
Alexis Brice	Sorbonne Université (SU) Unité Mixte de Recherche (UMR) 1127, Institut du Cerveau et de la Moelle épinière, ICM	Drafting/revision of the manuscript for content, including medical writing for content
Jean-Christophe Corvol, MD, PhD	Sorbonne Université (SU) Unité Mixte de Recherche (UMR) 1127, Institut du Cerveau et de la Moelle épinière, ICM; Assistance Publique Hôpitaux de Paris, Department of Neurology, CIC Neurosciences, Paris, France	Drafting/revision of the manuscript for content, including medical writing for content
Marie-Christine Chartier-Harlin, PhD	Univ. Lille, Inserm, CHU Lille, UMR-S 1172—JPArc—Centre de Recherche Lille Neurosciences & Cognition, Lille, France	Drafting/revision of the manuscript for content, including medical writing for content
Eugenie Mutez, MD, PhD	Univ. Lille, Inserm, CHU Lille, UMR-S 1172—JPArc—Centre de Recherche Lille Neurosciences & Cognition, Lille, France	Drafting/revision of the manuscript for content, including medical writing for content
Kathrin Brockmann, MD	Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tubingen	Drafting/revision of the manuscript for content, including medical writing for content
Angela B. Deutschländer, MD	Department of Neurology, Ludwig Maximilians University of Munich; Department of Neurology, Max Planck Institute of Psychiatry, Munich, Germany; Department of Neurology and Department of Clinical Genomics, Mayo Clinic Florida, Jacksonville, FL	Drafting/revision of the manuscript for content, including medical writing for content
Georges M. Hadjigeorgiou, MD	Department of Neurology, Medical School, University of Cyprus, Nicosia, Cyprus; Department of Neurology, Laboratory of Neurogenetics, University of Thessaly, University Hospital of Larissa, Larissa, Greece	Drafting/revision of the manuscript for content, including medical writing for content
Efthimos Dardiotis, MD	Department of Neurology, Laboratory of Neurogenetics, University of Thessaly, University Hospital of Larissa, Larissa, Greece	Drafting/revision of the manuscript for content, including medical writing for content
Leonidas Stefanis, MD, PhD	Center of Clinical Research, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens; 1st Department of Neurology, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece	Drafting/revision of the manuscript for content, including medical writing for content
Athina Maria Simitsi, MD, PhD	1st Department of Neurology, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece	Drafting/revision of the manuscript for content, including medical writing for content
Enza Maria Valente, MD, PhD	Department of Molecular Medicine, University of Pavia; Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Mondino Foundation, Pavia	Drafting/revision of the manuscript for content, including medical writing for content

Continued

Appendix *(continued)*

Name	Location	Contribution
Simona Petrucci, MD, PhD	UOC Medical Genetics and Advanced Cell Diagnostics, S. Andrea University Hospital; Department of Clinical and Molecular Medicine, University of Rome, Italy	Drafting/revision of the manuscript for content, including medical writing for content
Letizia Straniero, PhD	Department of Biomedical Sciences—Humanitas University; Humanitas Clinical and Research Center, IRCCS, Via Manzoni 56, Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content
Anna Zecchinelli, MD	Parkinson Institute, Azienda Socio Sanitaria Territoriale (ASST) Gaetano Pini/CTO, Milano, Italia	Drafting/revision of the manuscript for content, including medical writing for content
Gianni Pezzoli, MD	Parkinson Institute, Azienda Socio Sanitaria Territoriale (ASST) Gaetano Pini/CTO, Milano, Italia	Drafting/revision of the manuscript for content, including medical writing for content
Laura Brighina, MD, PhD	Department of Neurology, San Gerardo Hospital, Milan; Center for Neuroscience, University of Milano Bicocca, Monza	Drafting/revision of the manuscript for content, including medical writing for content
Carlo Ferrarese, MD, PhD	Department of Neurology, San Gerardo Hospital, Milan; Center for Neuroscience, University of Milano Bicocca, Monza	Drafting/revision of the manuscript for content, including medical writing for content
Grazia Annesi, PhD	Institute for Biomedical Research and Innovation, National Research Council, Mangone, Cosenza	Drafting/revision of the manuscript for content, including medical writing for content
Andrea Quattrone, MD	Institute of Neurology, Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy	Drafting/revision of the manuscript for content, including medical writing for content
Monica Gagliardi, PhD	Institute for Biomedical Research and Innovation, National Research Council, Mangone, Cosenza	Drafting/revision of the manuscript for content, including medical writing for content
Lena F. Burbulla, PhD	German Center for Neurodegenerative Diseases (DZNE), Tübingen; Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL; Metabolic Biochemistry, Biomedical Center (BMC), Faculty of Medicine, Ludwig-Maximilians University; Munich Cluster for Systems Neurology (SyNergy), Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Hirotaka Matsuo, MD, PhD	Department of Integrative Physiology and Bio-Nano Medicine, National Defense Medical College, Saitama	Drafting/revision of the manuscript for content, including medical writing for content

Appendix *(continued)*

Name	Location	Contribution
Yusuke Kawamura, MD	Department of Integrative Physiology and Bio-Nano Medicine, National Defense Medical College, Saitama	Drafting/revision of the manuscript for content, including medical writing for content
Nobutaka Hattori, MD, PhD	Department of Neurology, Juntendo University School of Medicine, Bunkyo-ku, Tokyo, Japan	Drafting/revision of the manuscript for content, including medical writing for content
Kenya Nishioka, MD, PhD	Department of Neurology, Juntendo University School of Medicine, Bunkyo-ku, Tokyo, Japan	Drafting/revision of the manuscript for content, including medical writing for content
Sun Ju Chung, MD, PhD	Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine	Drafting/revision of the manuscript for content, including medical writing for content
Yun Joong Kim, MD, PhD	Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea	Drafting/revision of the manuscript for content, including medical writing for content
Lukas Pavelka, MD	Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Belval, Luxembourg	Drafting/revision of the manuscript for content, including medical writing for content
Bart P.C. van de Warrenburg, MD, PhD	Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, Nijmegen, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content
Bastiaan R. Bloem, MD, PhD	Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, Nijmegen, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content
Andrew B. Singleton, PhD	Molecular Genetics Section, Laboratory of Neurogenetics, NIA, NIH, Bethesda	Drafting/revision of the manuscript for content, including medical writing for content
Jan Aasly, MD	Department of Neurology, St Olav's Hospital and Norwegian University of Science and Technology, Trondheim, Norway	Drafting/revision of the manuscript for content, including medical writing for content
Mathias Toft, MD, PhD	Department of Neurology, Oslo University Hospital, Norway	Drafting/revision of the manuscript for content, including medical writing for content
Leonor Correia Guedes, MD, PhD	Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa; Department of Neurosciences and Mental Health, Neurology, Hospital de Santa Maria, Centro Hospitalar Universitario Lisboa Norte (CHULN)	Drafting/revision of the manuscript for content, including medical writing for content

Appendix *(continued)*

Name	Location	Contribution
Joaquim J. Ferreira, MD, PhD	Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa; Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal	Drafting/revision of the manuscript for content, including medical writing for content
Soraya Bardien, PhD	Division of Molecular Biology and Human Genetics, Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University	Drafting/revision of the manuscript for content, including medical writing for content
Jonathan Carr, PhD	Division of Neurology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa	Drafting/revision of the manuscript for content, including medical writing for content
Eduardo Tolosa, MD, PhD	Parkinson's disease & Movement Disorders Unit, Neurology Service, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona; Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED: CB06/05/0018-ISCIII) Barcelona, Spain	Drafting/revision of the manuscript for content, including medical writing for content
Mario Ezquerra, PhD	Lab of Parkinson Disease and Other Neurodegenerative Movement Disorders, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Institut de Neurociències, Universitat de Barcelona, Catalonia	Revision of the manuscript for content, including medical writing for content
Pau Pastor, MD, PhD	Fundació per la Recerca Biomèdica i Social Mútua Terrassa; Movement Disorders Unit, Department of Neurology, Hospital Universitari Mutua de Terrassa, Barcelona, Spain	Drafting/revision of the manuscript for content, including medical writing for content
Monica Diez-Fairen, MSc	Fundació per la Recerca Biomèdica i Social Mútua Terrassa; Movement Disorders Unit, Department of Neurology, Hospital Universitari Mutua de Terrassa, Barcelona, Spain	Drafting/revision of the manuscript for content, including medical writing for content
Karin Wirdefeldt, MD, PhD	Department of Clinical Neuroscience, Karolinska Institutet; Department of Medical Epidemiology and Biostatistics, Karolinska Institutet	Drafting/revision of the manuscript for content, including medical writing for content
Nancy L. Pedersen, PhD	Department of Medical Epidemiology and Biostatistics, Karolinska Institutet	Drafting/revision of the manuscript for content, including medical writing for content
Caroline Ran, PhD	Department of Neuroscience, Karolinska Institutet, Stockholm	Drafting/revision of the manuscript for content, including medical writing for content
Andrea C. Belin, PhD	Department of Neuroscience, Karolinska Institutet, Stockholm	Drafting/revision of the manuscript for content, including medical writing for content
Andreas Puschmann, MD, PhD	Lund University, Skåne University Hospital, Department of Clinical Sciences Lund, Neurology, Lund, Sweden	Drafting/revision of the manuscript for content, including medical writing for content
Clara Hellberg, MD	Lund University, Skåne University Hospital, Department of Clinical Sciences Lund, Neurology, Lund, Sweden	Drafting/revision of the manuscript for content, including medical writing for content
Carl E. Clarke, MD	University of Birmingham and Sandwell and West Birmingham Hospitals NHS Trust	Drafting/revision of the manuscript for content, including medical writing for content
Karen E. Morrison, MD	Faculty of Medicine, Health and Life Sciences, Queens University, Belfast, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content
Dimitri Krainc, MD, PhD	Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL	Drafting/revision of the manuscript for content, including medical writing for content
Matt J. Farrer, PhD	Department of Neurology, McKnight Brain Institute, University of Florida, Gainesville, FL	Drafting/revision of the manuscript for content, including medical writing for content
Rejko Kruger, MD	Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Esch-sur-Alzette, Luxembourg; Parkinson Research Clinic, Centre Hospitalier de Luxembourg; Transversal Translational Medicine, Luxembourg Institute of Health (LIH), Strassen; and Neurology, Centre Hospitalier de Luxembourg, Luxembourg	Drafting/revision of the manuscript for content, including medical writing for content
Alexis Elbaz, PhD	Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, Team "Exposome, heredity, cancer and health," CESP, Villejuif, France	Drafting/revision of the manuscript for content, including medical writing for content
Thomas Gasser, MD	Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tubingen; German Center for Neurodegenerative Diseases (DZNE), Tübingen	Drafting/revision of the manuscript for content, including medical writing for content

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Appendix *(continued)*

Name	Location	Contribution
Manu Sharma, PhD	Centre for Genetic Epidemiology, Institute for Clinical Epidemiology and Applied Biometry, University of Tubingen, Germany; Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tubingen	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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