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 Radijojvko-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. Hadjiegeorgiou, MD, Efthimos Dardiotis, MD, Leonidas Stefanis, MD, PhD, Athina Maria Simitsi, MD, PhD, Enza Maria Valente, MD, PhD, Simona Petrucci, 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 Aaslø, 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, 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, Reijo Krüger, 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

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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
In 2019, over 8.51 million individuals (95% uncertainty interval 7.3–9.8) had Parkinson disease (PD) globally. 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 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.
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 I2 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 × 10−8 as genome-wide significant and p < 1 × 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 × 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 Brainiac 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 (h²) in the COURAGE-PD dataset was 0.083 (SE = 0.057). Similar heritability estimates were observed in the European subcohort (h² = 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 (h² = 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) (β(SE)COURAGE = −1.456(0.293), PCOURAGE = 6.91 × 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 (β(SE)COURAGE-EASIAN = 13.681(2.769), PCOURAGE-EASIAN = 7.80 × 10⁻⁷). Furthermore, the stratified analysis provided suggestive evidence of 3 loci, RHEB (Chr 8) in males (β(SE)COURAGE-M = −1.112(0.222), PCOURAGE-M = 5.15 × 10⁻⁷), MTHFD1L (Chr 6) in females (β(SE)COURAGE-F = −1.995(0.402), PCOURAGE-F = 6.78 × 10⁻⁷), and KNH3 (Chr 12) in females (β(SE)COURAGE-F = 2.176(0.432), PCOURAGE-F = 4.59 × 10⁻⁷) (eTable 2, links.lww.com/WNL/C88).

In the replication of previously reported variants, only the TMEM175 variant (rs34311866: β(SE)COURAGE = 0.477(0.203), PCOURAGE = 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: β(SE)COURAGE = 0.362(0.172), PCOURAGE = 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 (β(SE)COURAGE+IPDGC = 0.720(0.122), PCOURAGE+IPDGC = 3.13 × 10⁻⁵). This association, however, appeared to be driven by the strong association reported by the IPDGC dataset, with negligible effect.
detected in the COURAGE-PD dataset ($p_{\text{COURAGE/COURAGE-EUR}} = 0.022$; 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, $\text{BST1 (rs4698412)}$, showed similar effects in COURAGE-PD and IPDGC datasets ($\hat{\beta}(SE)_{\text{COURAGE}} = -0.633(0.175), p_{\text{COURAGE}} = 2.95 \times 10^{-4}; \hat{\beta}(SE)_{\text{IPDGC}} = -0.480(0.115), p_{\text{IPDGC}} = 3.04 \times 10^{-5}$), and the combination of both estimates resulted in the identification of a novel genome-wide significant $\text{BST1}$ locus for AAO ($\hat{\beta}(SE)_{\text{COURAGE+IPDGC}} = $...
The previously reported TMEM175 (rs34311866) showed a suggestive association in the combined analysis (β(SE)COURAGE+IPDGC = 0.589(0.114), PCOURAGE+IPDGC = 2.64 × 10⁻⁷) that appeared to be driven by previously reported findings in the IPDGC dataset (β(SE)IPDGC = 0.642(0.139), pIPDGC = 3.72 × 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 (β(SE)COURAGE+IPDGC = −1.456(0.293), pCOURAGE = 6.62 × 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 (β(SE)COURAGE = −1.925(0.447), pCOURAGE = 1.64 × 10⁻³).

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: PCOURAGE-EUR+IPDGC = 3.13 × 10⁻⁷, BST1 rs4698412: PCOURAGE-EUR+IPDGC = 6.27 × 10⁻⁸) (eTable 2, links.lww.com/WNL/C88). A similar sensitivity analysis for the previously reported APOE e4 locus also showed a suggestive association with PD AAO (APOE rs429358: β(SE)COURAGE+EUR+IPDGC = 0.711(0.145), pCOURAGE+EUR+IPDGC = 9.33 × 10⁻⁷). However, the association was primarily driven by highly significant findings in the IPDGC dataset (β(SE)IPDGC = 0.754(0.171), pIPDGC = 9.86 × 10⁻⁸; β(SE)COURAGE-EUR = 0.599(0.275), pCOURAGE-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 (β(SE)COURAGE = −0.581(0.149), pCOURAGE = 9.35 × 10⁻³). 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.

| 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.
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 × 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 × 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, rs4698412, was neither the top genetic variant in the BST1 locus in IPDGC nor COURAGE AAO PD datasets. Although rs4698419 (r^2 with rs4698412 < 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, rs4698412, 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 × 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 × 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 × 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 (PCOURAGE \(= 0.035\), PCOURAGE \(= 0.005\), and PCOURAGE \(= 0.022\)), 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 \((r9833611)\), as shown in the Results section above. Notably, we also observed an independent signal at the 5’ end \((r536203)\). However, the variant was excluded for further interpretation because of high heterogeneity observed when combining IPDGC and COURAGE datasets \(\beta(\text{SE})_{\text{COURAGE+IPDGC}} = -0.591(0.097)\), PCOURAGE+IPDGC = \(9.28 \times 10^{-15}\), \(I^2 = 61.9\%\).

Another PD locus, TMEM175, was previously shown to reach genome-wide significance in an AAO study. 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, \(r53431186\) \((p.M393T)\), 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 \(\text{PCOURAGE+IPDGC} = 2.64 \times 10^{-7}; I^2 = 0.0\). 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. A previous study also reported a borderline significant association of the variant \(r5429358\), representing the APOE e4 locus with PD-AAO \((p = 5.69 \times 10^{-5})\) in a combined dataset \((n = 28,568)\) comprising IPDGC and 23andMe datasets. 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 e4 locus with PD-AAO in the recently reported East Asian GWAS. However, being a longevity marker, the suggestive finding of the APOE e4 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 SUGC1) 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. 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. 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.

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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program, funded by the European Commission, outside the submitted work; in addition, T. Gasser has a Patent Number: EP1802749 (A2) KASPP (LRRK2) gene, its production and use for the detection and treatment of neurodegenerative disorders issued. D. Krainc is the Founder of Lysosomal Therapeutics Inc. and Vanqua Bio; serves on the scientific advisory boards of the Silverstein Foundation, Vanqua Bio, Intellia Therapeutics, and Prevail Therapeutics; and is a Venture Partner at OrbiMed. BvdW received research support from Radboud University Medical Center, ZonMw, Gossweiler Foundation, and Hersenstichting and has served on a scientific advisory board of uniQure. The remaining authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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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 |
| Cléo 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 Tübingen; 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 |
| 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 |
| 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) Unite 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) Unite 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) Unite 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-Harin, 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. Deuschlender, 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, Egnition 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, Egnition 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 |

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, Italy                                                                                                         | 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, Italy                                                                                                         | 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), Tubingen; 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                                                          |
| 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 Clinic 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 Mutua 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 Mutua 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, 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 Tübingen; German Center for Neurodegenerative Diseases (DZNE), Tübingen | Drafting/revision of the manuscript for content, including medical writing for content |

Continued
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39. Din D, Liu HX, Hirai H, et al. CD38 is critical for social behaviour by regulating oxytocin secretion. Nature. 2007;446(7131):41-45.
40. Shen YT, Wang JW, Wang M, et al. BST1 rs4698412 allelic variant increases the risk of Parkinson disease in Chinese. Exp Neurol. 2019;319:403-412.
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43. Quatrano V, Zaccarello G, Chillemi A, et al. CD38 and CD157: a long journey from activation markers to multifunctional molecules. Cytometry B Clin Cytom. 2013;84(2):207-217.
44. Higashida H, Liang M, Yoshihara T, et al. An immunohistochemical, enzymatic, and behavioral study of CD157/BST-1 as a neuroregulator. BMC Neurosci. 2017;18(1):35-35.
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