Association between the LRP1B and APOE loci in the development of Parkinson's disease dementia

Raquel Real[1,2,3], Alejandro Martinez-Carrasco[1,2,3], Regina H. Reynolds[3,4], Michael A. Lawton[5], Manuela M. X. Tan[6], Maryam Shoai[7,8], Jean-Christophe Corvol[9,10], Mina Ryten[3,4,11], Catherine Bresner[12], Leon Hubbard[12], Alexis Brice[9,10], Suzanne Lesage[9,10], Johann Faouzi[9,13], Alexis Elbaz[14], Fanny Artaud[14], Nigel Williams[12], Michele T. M. Hu[15,16], Yoav Ben-Shlomo[5], Donald G. Grosset[17], John Hardy[3,7,8,18,19,20], Huw R. Morris[1,2,3]

Abstract

Parkinson's disease is one of the most common age-related neurodegenerative disorders. Although predominantly a motor disorder, cognitive impairment and dementia are important features of Parkinson's disease, particularly in the later stages of the disease. However, the rate of cognitive decline varies among Parkinson's disease patients, and the genetic basis for this heterogeneity is incompletely understood.

To explore the genetic factors associated with rate of progression to Parkinson's disease dementia, we performed a genome-wide survival meta-analysis of 3,923 clinically diagnosed Parkinson's disease cases of European ancestry from four longitudinal cohorts. In total, 6.7% of individuals with Parkinson's disease developed dementia during study follow-up, on average 4.4 ± 2.4 years from disease diagnosis.

We have identified the *APOE* ε4 allele as a major risk factor for the conversion to Parkinson's disease dementia [hazards ratio = 2.41 (1.94–3.00), $P = 2.32\text{x}10^{-15}$], as well as a new locus within the ApoE and APP receptor *LRP1B* gene [hazards ratio = 3.23 (2.17–4.81), $P = 7.07\text{x}10^{-09}$]. In a candidate gene analysis, *GBA* variants were also identified to be associated with higher risk of progression to dementia [hazards ratio = 2.02 (1.21–3.32), $P = 0.007$]. CSF biomarker analysis also implicated the amyloid pathway in Parkinson's disease dementia, with significantly reduced levels of amyloid β_{42} ($P = 0.0012$) in Parkinson's disease dementia compared to Parkinson's disease without dementia.

These results identify a new candidate gene associated with faster conversion to dementia in Parkinson's disease and suggest that amyloid-targeting therapy may have a role in preventing Parkinson's disease dementia.

Author affiliations:

1 Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, London WC1N 3BG, UK

2 UCL Movement Disorders Centre, University College London, London WC1N 3BG, UK

3 Aligning Science Across Parkinson's (ASAP) Collaborative Research Network, Chevy Chase, MD, 20815, USA

4 Genetics and Genomic Medicine, UCL Great Ormond Street Institute of Child Health, University College London, London WC1N 1EH, UK

5 Population Health Sciences, Bristol Medical School, University of Bristol, Bristol BS8 2PS, UK

6 Department of Neurology, Oslo University Hospital, 0424 Oslo, Norway

7 Department of Neurodegenerative Diseases, UCL Queen Square Institute of Neurology, University College London, London WC1N 3BG, UK

8 UK Dementia Research Institute, University College London, London WC1E 6BT, UK

9 Sorbonne Université, Institut du Cerveau et de la Moelle épinière - Paris Brain Institute - ICM, INSERM, CNRS, 75013 Paris, France

10 Assistance Publique Hôpitaux de Paris, Department of Neurology, Hôpital Pitié-Salpêtrière, 75013 Paris, France

11 NIHR Great Ormond Street Hospital Biomedical Research Centre, University College London, London WC1N 1EH, UK

12 Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff CF24 4HQ, UK

13 Centre Inria de Paris, 75012 Paris, France

14 Centre for Research in Epidemiology and Population Health, INSERM U1018, Team "Exposome, heredity, cancer, and health", 94807 Villejuif, France

15 Nuffield Department of Clinical Neurosciences, Division of Clinical Neurology, University of Oxford, Oxford OX3 9DU, UK

16 Oxford Parkinson's Disease Centre, University of Oxford, Oxford OX1 3QU, UK

17 School of Neuroscience and Psychology, University of Glasgow, Glasgow G51 4TF, UK

18 Reta Lila Weston Institute, UCL Queen Square Institute of Neurology, London WC1N 1PJ, UK

19 National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre, London W1T 7DN, UK

20 Institute for Advanced Study, The Hong Kong University of Science and Technology, Hong Kong SAR, China

Correspondence to:

Professor Huw R Morris

Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, Royal Free Hospital, Rowland Hill Street, London NW3 2PF
h.morris@ucl.ac.uk

Dr Raquel Real

Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, Queen Square House, Queen Square, London WC1N 3BG

r.real@ucl.ac.uk

Running title: Genome-wide analysis of Parkinson's disease dementia

Keywords: Parkinson's disease; dementia; genome-wide; survival

Abbreviations: Aβ = Amyloid Beta; APP = Amyloid Precursor Protein; CI = Confidence interval; CPH = Cox Proportional Hazards; eQTL = Expression quantitative trait locus; ER = Endoplasmic reticulum; GRS = Genetic Risk Score; HR = Hazards ratio; HWE = Hardy-Weinberg equilibrium; IQR = Interquartile range; LDL = Low-density lipoprotein; MDS-UPDRS = Movement Disorders Society Unified Parkinson's disease Rating Scale; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; OR = Odds Ratio;

p-Tau181 = Phosphorylated Tau at threonine 181; SNP = Single nucleotide polymorphism; sQTL = Splicing quantitative trait locus; tQTL = Transcript expression quantitative trait locus

Introduction

Parkinson's disease is the second most common neurodegenerative disease, with an estimated worldwide prevalence of 100-200 cases per 100,000 individuals.[1] Although Parkinson's disease is mainly viewed as a motor disorder, the development of dementia in Parkinson's disease is an important determinant of morbidity, mortality and need for social support.[2] The clinico-pathological phenotype of Parkinson's disease dementia can be indistinguishable from dementia with Lewy bodies, although in Parkinson's disease dementia motor symptoms must by definition precede the development of dementia by at least one year.[3] Neuropsychiatric manifestations of Parkinson's disease dementia include cognitive fluctuation with visual misperception, hallucinations, and delusions together with deficits in attention, executive and visuo-spatial function. Cholinergic denervation seems to be important in Parkinson's disease dementia and cholinesterase inhibitors can improve Parkinson's disease dementia symptoms,[4] but there is no treatment for the underlying disease pathology. Identifying the causal mechanisms will be an important step in defining new treatments.

Age is the single most important risk factor for Parkinson's disease dementia. It is estimated that by the age of 90, 80-90% of individuals with Parkinson's disease will have developed dementia.[4] Other clinical predictors of progression to dementia include disease severity and longer disease duration.[5–7] However, the rates of progression to Parkinson's disease dementia vary substantially among individuals, which has important implications for prognosis and quality of life. Several genetic factors have been reported to increase the risk or rate of progression to Parkinson's disease dementia. The most widely reported genetic risk factor associated with increased risk of conversion to Parkinson's disease dementia is the *APOE* ε4 allele.[8–11] A meta-analysis of 17 studies found a significantly higher risk of developing dementia in Parkinson's disease carriers of the ε4 haplotype.[11] Single rare variants in the *GBA* gene increase the risk of developing Parkinson's disease dementia, and the risk may relate to the pathogenicity of the variant.[12–14] Several studies have also reported that the *MAPT* H1 haplotype is associated with dementia,[9,15–17] although this has not been universally replicated.[10] More recently, the *RIMS2 locus* has been described in association with progression to Parkinson's disease dementia, as well as suggestive association signals in *TMEM108* and *WWOX* loci.[18] Genome-wide association studies in neurodegenerative disease have largely defined case-control risk factors for disease susceptibility, but the increasing availability of high-quality longitudinal clinical datasets enables a systematic search for disease modifying

factors. Here, we use a genome-wide survival meta-analysis approach to identify new genetic factors that contribute to the progression to Parkinson's disease dementia.

Materials and methods

Patient cohorts

We have studied four independent longitudinal Parkinson's disease cohorts: Tracking Parkinson's (TPD, www.parkinsons.org.uk/),[19] Oxford Parkinson's Disease Centre Discovery Cohort (OPDC, www.dpag.ox.ac.uk/opdc),[20] Accelerating Medicines Partnership: Parkinson's Disease (AMP-PD v2.5, www.amp-pd.org), which consists of harmonised data from multiple cohorts,[21] and Drug Interaction With Genes in Parkinson's Disease (DIGPD, clinicaltrials.gov/ct2/show/NCT01564992), comprising a total of 3,923 participants after clinical and genetic data cleaning (Supplementary Fig. 1 and Table 1**)**. Each subject provided written informed consent for participation according to the Declaration of Helsinki and all cohort studies were approved by the relevant ethics committee. Methods for clinical data collection, including setting, inclusion criteria and periods of recruitment, are available from the websites of the corresponding cohorts. All participants were diagnosed with Parkinson's disease according to the Queen Square Brain Bank criteria.[22] Participants were excluded from the analysis if an alternative diagnosis was made during the follow-up period (including a diagnosis of dementia with Lewy bodies) and/or the probability of a Parkinson's disease diagnosis as assessed by a clinician at the last available visit was less than 90%. In AMP-PD, only individuals in the Parkinson's disease study arm were included to avoid selection bias of monogenic cases. Criteria for Parkinson's disease dementia was based on the Movement Disorders Society (MDS) taskforce Parkinson's disease dementia diagnostic criteria.[3,18] Specifically, participants were classified as having Parkinson's disease dementia if they had adjusted MoCA (Montreal Cognitive Assessment) scores < 21/30, at least two cognitive domains impaired in the MoCA scale (attention/serial sevens ≤ 2/3; language / verbal fluency 0/1; memory / delayed recall ≤ 4/5; visuospatial/executive ≤ 4/5), a cognitive deficit severe enough to impact on activities of daily living (MDS-Unified Parkinson's disease Rating Scale (UPDRS) part I 1.1 ≥ 2 score), and absence of severe depression (MDS-UPDRS part I 1.3 < 4), except participants from the DIGPD cohort, for whom only MMSE (Mini-Mental State Examination) scores were available together with a clinician assigned diagnosis of dementia. Participants were excluded from the study (left censored) if they met criteria for Parkinson's

disease dementia at study baseline (Supplementary Table 1). Time-to-event was calculated as the number of years from disease diagnosis until the midpoint between the date of the first visit where criteria for Parkinson's disease dementia was met or of study withdrawal due to dementia and the date of the previous available visit. The time interval between the last normal assessment and withdrawal due to dementia was on average 1.66 ± 0.77 years for TPD and 2.57 ± 1.18 years for OPDC. Individuals with missing data regarding time-to-event or event classification were also excluded from the study. Time intervals between visits varied across studies, with assessments being carried out every 18 months in the TPD and OPDC cohorts and every 12 months in the DIGPD and AMP-PD cohorts. Comparisons across cohorts were performed in R (R Project for Statistical Computing, RRID:SCR_001905; version 4.1.3; https://www.R-project.org/) using Pearson's Chi-squared test (*rstatix* package, version 0.7.0; RRID:SCR_021240; https://CRAN.R-project.org/package=rstatix) for categorical variables, and Kruskal-Wallis test with Dunn's test for post hoc multiple pairwise comparisons for continuous variables, with p-values adjusted by the Bonferroni method (*stats* package, version 4.1.3; https://stat.ethz.ch/R-manual/R-devel/library/stats/html/00Index.html). Significance was set at α=0.05.

Data Quality Control

Whole-genome sequence data was available from participants in AMP-PD cohorts. The remainder of samples were genotyped with the Illumina HumanCoreExome array (TPD), Illumina HumanCoreExome-12 v1.1 or Illumina Infinium HumanCoreExome-24 v1.1 arrays (OPDC) and the Illumina Infinium Multi-Ethnic Global (MEGA) array (DIGPD). Sample quality control (QC) included the exclusion of samples with call rates < 98%, samples with excess heterozygosity (defined as samples deviating more than two standard deviations from the mean heterozygosity rate), samples with a mismatch between clinical sex and genetically determined sex from chromosome X heterogeneity, and samples from related individuals (pi-hat > 0.125). Variants with missingness rate > 5%, minor allele frequency (MAF) < 0.01 and Hardy-Weinberg equilibrium (HWE) $P < 1x10^{-05}$ were excluded. To identify the ancestry, variants in linkage disequilibrium were removed and samples clustered against the HapMap3 reference panel, using principal component analysis. Individuals who deviated more than 6 standard deviations from the mean of the first 10 principal components of the HapMap3 CEU+TSI population were excluded from the analysis (Supplementary Fig. 12A). To avoid

inclusion of individuals related to each other across the different cohorts, we merged the genetic data from all cohorts and performed a second relatedness check (pi-hat > 0.125). For each pair of related individuals, the one with the highest missingness rate was excluded from the respective cohort. After extraction of European-ancestry samples and non-related individuals from each cohort, principal components were re-calculated to use as covariates. The genotyping array data was then imputed against the Haplotype Reference Consortium (HRC) reference panel (version r1.1 2016; http://www.haplotype-reference-consortium.org/) in the Michigan Imputation Server (RRID:SCR_017579; https://imputationserver.sph.umich.edu)[23] using Minimac4 (version 1.0.0; https://genome.sph.umich.edu/wiki/Minimac4 version 1.0.0). Imputed variants were excluded if the imputation info R^2 score was ≤ 0.3. Following imputation, variants with missingness > 5% and minor allele frequencies < 1% were also excluded. Data cleaning was performed using PLINK v1.9 (RRID:SCR_001757; https://www.cog-genomics.org/plink/1.9/).[24]

Time-to-event genome-wide survival study and meta-analysis

A time-to-event genome-wide survival study (GWSS) was performed in R (version 4.1.2) in each cohort, using the Cox proportional hazards (CPH) function in the *survival* package (version 3.2.13; RRID:SCR_021137; https://CRAN.R-project.org/package=survival), in which time to Parkinson's disease dementia was regressed against each single nucleotide polymorphism (SNP), with age at onset or diagnosis, sex and first five principal components as covariates. AMP-PD summary statistics were converted from hg38 to hg19 using the binary liftOver tool (RRID:SCR_018160; https://genome.sph.umich.edu/wiki/LiftOver). The summary results from each cohort were then meta-analysed using METAL software in a random effects model, using genomic control correction (version released on the 25/03/2011; RRID:SCR_002013; http://csg.sph.umich.edu//abecasis/Metal/).[25] The genomic inflation factor (λgc) for each cohort varied between 0.863 and 0.9773. After the meta-analysis, the λgc was 1.035 (Supplementary Fig. 12B). Upon completion of the meta-analysis, variants that were not present in all samples were excluded, as well as variants with minor allele frequency variability > 15% across studies. Variants were also excluded if the p-value for the Cochran's Q-test for heterogeneity was less than 0.05 and the I^2 statistic was ≤ 80%. Forest plots of variants of interest were prepared using the R package *forestplot* (version 2.0.1; https://CRAN.R-project.org/package=forestplot). Results of the meta-analysis were annotated

using FUMA (Functional Mapping and Annotation of Genome Wide Association Studies, RRID:SCR_017521; version 1.3.8; https://fuma.ctglab.nl/).[26] Regional association plots were generated in LocusZoom (RRID:SCR_021374; http://locuszoom.org/).[27] LDproxy (https://ldlink.nci.nih.gov/?tab=ldproxy)[28] was used to identify variants in high linkage disequilibrium (LD) with variants of interest.

Tissue and cell-type specificity measures

Specificity represents the proportion of a gene's total expression attributable to one cell type/tissue. To determine specificity of a gene to a tissue or cell-type, specificity values from three independent gene expression datasets were generated. Briefly, these datasets included 1) bulk-tissue RNA-sequencing of 53 human tissues from the Genotype-Tissue Expression consortium (GTEx, version 8; RRID:SCR_013042)[29]; 2) human single-nucleus RNA-sequencing of the middle temporal gyrus from the Allen Institute for Brain Science (AIBS, Allen Cell Types Database - Human MTG Smart-Seq 2018 dataset, available from celltypes.brain-map.org/rnaseq; RRID:SCR_014806)[30]; and 3) human single-nucleus RNA-sequencing of the substantia nigra.[31] Generation of specificity values for GTEx and AIBS were previously described in Chia *et al*.[32] Briefly, specificity values for GTEx were generated using code modified from a previous publication (https://github.com/jbryois/scRNA_disease),[33] to reduce redundancy among brain regions and to include protein- and non-protein-coding genes. Specificity values for the AIBS-derived dataset were generated using gene-level exonic reads and the 'generate.celltype.data' function of the *EWCE* R package (version 1.2.0).[34] Likewise, specificity values from Agarwal *et al.*[31] were generated using *EWCE*. Specificity values for all three datasets and the code used to generate these values are openly available at https://github.com/RHReynolds/MarkerGenes.[35]

Conditional analysis

To understand if one or more genome-wide significant variants at the same locus were contributing to the signal, we performed conditional analysis on single SNPs using a conditional and joint association analysis approach. We used the GWSS meta-analysis summary statistics and the entire AMP-PD cohort (n = 10,418) as the reference sample for linkage disequilibrium estimation. The reference sample was subjected to the same QC steps

as described above. We then used CGTA-COJO software (version 1.93.0 beta for Linux; https://yanglab.westlake.edu.cn/software/gcta/#Overview)[36] to perform association analysis conditional on SNPs of interest.

Colocalization analysis

To investigate whether there is an overlap between Parkinson's disease dementia loci and expression quantitative trait loci (eQTLs), we used the *coloc* R package (version 5.1.0; https://cran.r-project.org/web/packages/colocr/index.html).[37] We also used the R package *colochelpR* (version 0.99.0)[38] to help prepare datasets for use with *coloc*. We took a Bayesian inference approach to test the H4 null hypothesis that there is a shared causal variant associated with both progression to Parkinson's disease dementia and gene expression regulation. The Bayesian inference approach additionally computes the posterior probability (PP) that there is no association with either trait (H0), there is association with the Parkinson's disease dementia trait but not the eQTL trait (H1), there is association with the eQTL trait but not the Parkinson's disease dementia trait (H2), and that there is association with both traits, but the causal variants are independent (H3). We extracted all the genes within 1 Mb of each significant locus in the Parkinson's disease dementia GWSS. *Coloc* was run using default $p_1=10^{-4}$, $p_2=10^{-4}$, and $p_{12}=10^{-5}$ priors (p_1 and p_2 are the prior probability that any random SNP in the region is associated with trait 1 and 2, respectively, while p_{12} is the prior probability that any random SNP in the region is associated with both traits). A PPH4 > 0.9 was considered evidence for the presence of a shared variant between traits, i.e., signal colocalization. *Coloc* calculates Bayes factors under the assumption that a single causal variant exists within a particular locus. This assumption may be relaxed by successively conditioning on the most significant variants for each trait, and testing for colocalisation between each pair of conditioned signals.[39] We therefore performed conditional analysis beforehand to confirm that there were no additional independent signals, thus meeting the assumption of a single causal variant at each locus. Cis-eQTL data were obtained from 1) eQTLGen, comprising bulk blood-derived gene expression from 31,684 individuals (https://www.eqtlgen.org/cis-eqtls.html, accessed on the 07/06/2021) and 2) PsychENCODE, comprising gene expression from bulk RNA sequencing from the prefrontal cortex of 1,387 individuals (http://resource.psychencode.org/, accessed on the 07/06/2021).[40,41] Next, to understand if *LRP1B* or *BBS9* loci regulate alternative splicing, we used a similar approach using frontal cortex and substantia nigra splicing QTLs (sQTLs) data

from the GTEx v8 database containing all variant-gene associations from 183 and 100 individuals, respectively, based on LeafCutter (version 0.2.9; RRID:SCR_017639; https://davidaknowles.github.io/leafcutter/)[42] intron excision phenotypes. For *LRP1B*, we tested the alternative splicing from 8 different introns. In addition, FDR-filtered transcript-per-million (TPM) transcript expression QTLs (tQTLs) (FDR < 0.001) were obtained from PsychENCODE and used to generate regional association plots overlapping with *LRP1B* signals. A full colocalization analysis for tQTLs was not possible due to the unavailability of unfiltered tQTL summary statistics from PsychENCODE.

Signal interaction between APOE and LRP1B

Given the affinity of LRP1B for ApoE carrying lipoproteins, we conducted a survival analysis based on *APOE* ε4 haplotype and *LRP1B* rs80306347 carrier status to understand if the effect of *LRP1B* rs80306347 signal was dependant on *APOE*. *APOE* genotypes were inferred from the imputed genotypes of rs7412 and rs429358 variants. Participants of the combined cohorts (n = 3,923) were grouped according to the presence of the two markers either simultaneously or exclusively, and a Cox proportional hazards model adjusted for age at diagnosis, gender, the first five principal components and a cohort term was performed. We also conditioned the analysis on *APOE* ε4 carrier status by performing a survival analysis of *LRP1B* rs80306347 on *APOE* ε4 carriers and non-carriers separately. We have in addition performed the analysis including an interaction term between *LRP1B* rs80306347 and *APOE* ε4 carrier status.

Candidate loci analysis

We additionally performed a candidate loci analysis of specific loci or variants of interest in the combined cohorts to increase power (n = 3,923), using Cox proportional hazards models adjusted for age at diagnosis, sex, the first five principal components and a cohort term. The regions of interest consisted of genetic variants or loci previously identified in association with cognitive impairment in Parkinson's disease and/or dementia with Lewy bodies: *APOE* ε4 haplotype (rs429358),[8–10] *GBA* variants E365K (or E326K, rs2230288), T408M (or T369M, rs75548401) and N409S (or N370S, rs76763715)[12,13,43], *SNCA* (rs356219, rs7680557, rs7681440, rs11931074, rs7684318),[32,44–46] *MAPT* H1 haplotype (rs1800547),[9,15–17] *RIMS2* (rs182987047), *TMEM108* (rs138073281), and *WWOX* (rs8050111).[18] In addition, participants

from DIGPD and a subset of individuals from the TPD study were Sanger sequenced for *GBA* (n = 1,793). We performed a survival analysis as above based on *GBA* carrier status, for which we defined *GBA* mutation carriers as individuals with at least one Gaucher disease-causing mutation or Parkinson's disease risk factor (Supplementary Table 2).

Genetic risk scores

To understand if there is overlap in the risk of development of Parkinson's disease dementia and the risk of Parkinson's disease or Alzheimer's disease, we performed a genetic risk score (GRS) analysis using PLINK v1.9 software.[24] Scores were calculated using the summary statistics from the largest Parkinson's disease genome-wide association study (GWAS) to date and the 2019 genome-wide association meta-analysis of Alzheimer's disease, respectively.[47,48] Only the independent genome-wide significant risk signals were used in the analysis. Scores were then z-transformed and added as a covariate in a logistic regression model, together with age at diagnosis, sex and the first five principal components. Each cohort was analysed independently, and results were meta-analysed using the *meta* R package (version 5.1-1; RRID:SCR_019055; https://CRAN.R-project.org/package=meta).[49] We conducted the Alzheimer's disease genetic risk score (AD-GRS) analysis also without the *APOE* signal to investigate if the effect of AD-GRS in the risk of developing Parkinson's disease dementia was mediated by factors independent of *APOE*. For the survival analysis based on AD-GRS, individuals were stratified into low-, middle-, and high-risk tertiles of raw AD-GRS. We used Cox proportional hazards models adjusted for age at diagnosis, sex and the first five principal components in each cohort; results were then meta-analysed with the R package *meta*.

Association of clinical phenotype and APOE genotype with CSF biomarkers

A subset of AMP-PD participants (from the BioFIND and PPMI studies) included in the analysis have longitudinal cerebrospinal fluid (CSF) Alzheimer's disease biomarker data available (n = 434). We investigated the association of phenotype (Parkinson's disease dementia vs Parkinson's disease) and *APOE* ε4 carrier status with average levels of amyloid β

(Aβ) 42, total Tau and tau phosphorylated at threonine 181 (p-Tau181) using unpaired two-sample Wilcoxon rank-sum tests (R *stats* package, version 4.1.2) at baseline, 12, 24 and 36 months of follow-up. Significance was set at α=0.05.

Statistical power modelling

The R package *survSNP* (https://cran.r-project.org/web/packages/survSNP/index.html; version 0.25)[50] was used to model statistical power across a range of minor allele frequencies and effect sizes. The time-to-event was fixed at 4.5 years. Modelling took into account the event rates observed in the different cohorts.

Data availability

Meta-analysis summary statistics are available for download from https://pdgenetics.org/resources. TPD data is available upon access request from https://www.trackingparkinsons.org.uk/about-1/data/. BioFIND, PPMI, PDBP and SURE-PD3 cohorts were accessed from Accelerating Medicines Partnership: Parkinson's Disease (AMP-PD) and data is available upon registration at https://www.amp-pd.org/. OPDC data is available upon request from the Dementias Platform UK (https://portal.dementiasplatform.uk/Apply). DIGPD data is available upon request to the principal investigator (JC Corvol, Assistance Publique Hôpitaux de Paris). HapMap phase 3 data (HapMap3) is available for download at ftp://ftp.ncbi.nlm.nih.gov/hapmap/. The Ashkenazi Jewish population panel is accessible at https://www.ncbi.nlm.nih.gov/gds (accession ID: GSE23636). Cis-QTL data were obtained from eQTLGen (https://www.eqtlgen.org/cis-eqtls.html) and PsychENCODE (http://resource.psychencode.org). FDR-filtered tQTL data was obtained from PsychENCODE (http://resource.psychencode.org/). Cortical sQTL data was accessed from the GTEx v8 database (https://gtexportal.org/home/). GTEx bulk-tissue RNA-seq data is available at https://www.gtexportal.org/home/datasets**.** AIBS human single-nucleus RNA-seq data is available at https://portal.brain-map.org/atlases-and-data/rnaseq. Human single-nucleus RNA-seq of the substantia nigra data can be accessed from https://www.ncbi.nlm.nih.gov/geo/ (accession ID: GSE140231). Summary statistics from the Parkinson's disease GWAS (Nalls et al, 2019) used to perform the GRS is analysis available from

https://pdgenetics.org/resources. Code used in the analysis is available from https://github.com/huw-morris-lab/PDD_GWSS (doi:10.5281/zenodo.6535455).

Results

Cohort characterisation

Following data cleaning (Supplementary Fig. 1), a total of 3,923 individuals diagnosed with Parkinson's disease were available for analysis, with an overall mean follow-up time of 43.4 ± 27.7 months. Demographic characteristics of each patient cohort are shown in Table 1. Participants in DIGPD and AMP-PD cohorts were significantly younger at Parkinson's disease diagnosis (Kruskal-Wallis chi-squared value = 348, df = 3, $P < 2x10^{-16}$, post hoc Dunn's multiple comparison test in Supplementary Table 3) and at study baseline (Kruskal-Wallis chi-squared value = 160, df = 3, $P < 2x10^{-16}$, post hoc Dunn's multiple comparison test in Supplementary Table 3), which is probably reflected in the significantly reduced event rates in these two cohorts (Table 1). Adjusted MoCA or MMSE scores over time in Parkinson's disease cases who never developed dementia during the study follow-up remained constant over time, while they were consistently lower and showed greater decline in individuals who went on to develop Parkinson's disease dementia during study follow-up (Supplementary Fig. 2).

Identification of genetic determinants of Parkinson's disease dementia

In our genome wide survival meta-analysis assessing the role of 6,107,418 SNPs in the development of Parkinson's disease dementia, we identified three genome-wide significant genetic loci (Fig. 1 and Table 2; regional association plots in Supplementary Fig. 3). The most significant SNP was the ε4 allele-tagging SNP rs429358 in *APOE* (Hazard Ratio (HR) = 2.41, 95% Confidence Interval (CI) = 1.94-3.00, $P = 2.32 \times 10^{-15}$). *APOE* is the most important genetic risk factor for the development of Alzheimer's disease and has also been shown in multiple studies to contribute to cognitive decline and dementia in Parkinson's disease.[8–10,51]

Conditional analysis on the lead SNP at the *APOE* locus did not reveal any other independent SNPs contributing to the signal at this location (Supplementary Fig. 4A and B).

The second genome-wide significant genetic locus was on chromosome 2. The lead SNP at this locus was rs80306347 (HR = 3.23, 95% CI = 2.17-4.81, $P = 7.07 \times 10^{-09}$). This is an intronic variant located in intron 5 of the *LRP1B* gene (ENSG00000168702). This gene encodes the low-density lipoprotein receptor-related protein 1B, a member of the low-density lipoprotein (LDL) receptor superfamily. LRP1B is a receptor for ApoE-carrying lipoproteins and is highly expressed in the adult human brain (Supplementary Fig. 5A and C).[52] In addition, *LRP1B* was found to be significantly upregulated in excitatory neurons of the anterior cingulate cortex of Parkinson's disease dementia compared to Parkinson's disease and control brain samples (Supplementary Fig. 6).[53] Similar to other LDL receptors, it is involved in the intracellular processing of the amyloid precursor protein (APP).[54] Therefore, *LRP1B* constitutes a promising candidate for regulating the development of dementia in Parkinson's disease. Conditioning on the rs80306347 variant abolished genome-wide significance at the *LRP1B locus*, confirming that a single independent SNP is responsible for the signal at this location (Supplementary Fig. 4C and D).

rs78294974 is an intronic variant in the *BBS9* gene (ENSG00000122507) in chromosome 7 and was associated with progression to dementia with genome-wide significance (HR = 3.90, 95% CI = 2.40-6.32, $P = 3.59 \times 10^{-08}$). This gene is ubiquitously expressed (Supplementary Fig. 5B and D) and encodes the Parathyroid Hormone-Responsive B1 (PTHB1) protein. This protein is part of a stable evolutionary conserved protein complex required for primary cilium biogenesis. The Bardet-Biedl syndrome (BBSome) complex is predominantly responsible for the vesicular trafficking of membrane proteins to the primary cilium, but there is some evidence that it might be involved in other vesicular transport pathways[55]. The BBSome has been shown to bind to Rabin8, which acts as a GTP/GDP exchange factor for the small GTPase Rab8, a substrate of LRRK2. Mutations in *LRRK2* that increase its kinase activity lead to enhanced phosphorylation of RAB GTPases, thus causing RAB-mediated vesicular membrane trafficking and centrosomal defects[56]. Since pathogenic *LRRK2* mutations interfere with primary cilia formation, it has been suggested that defective ciliogenesis could contribute to the pathogenesis of LRRK2-related PD[57]. Interestingly, the BBSome has also been shown to be present at the postsynaptic density of hippocampal neurons and to be important for dendritic spine homeostasis, which could have important implications for cognition[58].

Forest plots of the GWSS meta-analysis (Supplementary Fig. 7A-C) show that the direction of the effect is consistent across cohorts in all the genome-wide significant loci, albeit with smaller contributions from AMP-PD to the *LRP1B* and *BBS9* signals (note that due to reduced number of events in individuals in the DIGPD cohort, infinite estimates were generated by the Cox proportional hazards analysis of this cohort). Several factors could be contributing to these differential observations between cohorts, namely the reduced event rate in the AMP-PD cohort (3.5%) compared to TPD and OPDC (7.2% and 12.4%, respectively). This could in turn be related to the younger age at baseline and shorter follow-up times in the AMP-PD cohorts, since increasing age is the most significant clinical risk factor for the development of dementia in Parkinson's disease (Table 1). To evaluate the effect of the different event rates on the power to detect a genome-wide significant effect on dementia-free survival, we modelled statistical power across a range of minor allele frequencies and effect sizes, assuming a median time to the event of 4.5 years, under an additive genetic risk model (Supplementary Fig. 8). At the current sample size, the detection of an association with genome-wide significance at 80% statistical power requires much more common alleles and/or higher effect sizes at the event rate of the AMP-PD cohort than at the event rates of the TPD and OPDC cohorts. As an example, for a SNP with effect size of the magnitude observed with *LRP1B* rs80306347, only SNPs with minor allele frequency of 0.15 and higher can be detected at the event rate of AMP-PD, while SNPs with a minor allele frequency of 0.05 and 0.03 can be detected at the event rates observed in TPD and OPDC, respectively, thus demonstrating how a low event rate can hinder the ability of the survival analysis to detect significant effects of variants with rarer minor allele frequencies.

Finally, we searched for potential candidate genes with a *P*-value near the genome-wide significance threshold that could be relevant for neurodegeneration. Eighty six variants in 33 independent loci had a suggestive $P < 1x10^{-06}$ (Supplementary Table 4). The nearest genes of some of these variants are involved in pathways known to contribute to neurodegeneration, such as vesicle trafficking (*VTI1A*), ubiquitin signalling (*DDB1*), synaptic homeostasis (*PTPRD*), and endoplasmic reticulum protein quality control and translocation (*UGGT2*, *SSR1*).[59–62] Interestingly, *SSR1* expression has recently been shown to be upregulated in an early Parkinson's disease mouse model and to be highly correlated with the loss of dopaminergic neurons.[63] An intronic variant in *SLC6A3*, which encodes the dopamine transporter (DAT), was also observed to be nominally associated with faster progression to dementia in Parkinson’s disease. This receptor is specifically expressed in nigro-striatal

neurons and is essential in the regulation of dopamine metabolism and neurotransmission. Given its prominent role in the metabolism of dopamine, there has been long-standing interest in this gene in relation to the pathophysiology of Parkinson's disease.[64,65] Future studies with larger samples sizes are needed to enable the identification of associations with suggestive variants of smaller effect sizes and allele frequencies.

Colocalization analysis

We did not identify proxy coding variants in high linkage disequilibrium with the lead variants in *LRP1B* or *BBS9*. To determine if any of the GWSS genome-wide significant signals are involved in the regulation of gene expression, we performed colocalization analysis using eQTLs from eQTLGen[41] and PsychENCODE,[66] which represent large human blood and brain gene expression datasets, respectively. We found no colocalization between Parkinson's disease dementia GWSS loci and eQTLs from either dataset, indicating that there is currently no evidence of shared causal variants driving both gene expression and the three association signals for Parkinson's disease dementia progression (Supplementary Table 5). Of note, *LRP1B* is not expressed in blood, thus no *LRP1B* eQTLs (significant or non-significant) were available from eQTLGen (Supplementary Fig. 5A). Next, we explored whether non-coding GWSS significant signals could have a role in alternative splicing by performing colocalization analysis using cortical and nigral sQTLs from the Genotype-Tissue Expression (GTEx) dataset.[29] Again, we found no colocalization of Parkinson's disease dementia GWSS loci and sQTLs (Supplementary Table 6). We also generated regional associations plots for tQTLs from PsychENCODE and Parkinson's disease dementia GWSS signals in the region surrounding *LRP1B*, which upon visual assessment did not suggest the presence of signal colocalization between *LRP1B* loci and tQTLs (Supplementary Fig. 9). Despite the power limitations of existing QTL datasets, the available data does not currently support *LRP1B* signals regulating the expression of transcript isoforms via alternative splicing.

APOE and LRP1B interaction

One of the ligands of *LRP1B* at the cell surface is *APOE*. To investigate whether the *LRP1B* signal was independent of *APOE* status, we defined four groups of Parkinson's disease patients in the combined cohorts (n = 3,923): non-carriers of either *APOE* ε4 or *LRP1B* rs80306347

alleles, exclusive carriers of *APOE* ε4 allele, exclusive carriers of *LRP1B* rs80306347 allele and carriers of both alleles. We then used a CPH model in the combined cohorts to calculate the hazards of survival dementia-free in each of these groups, adjusting for sex, age at disease onset or diagnosis, the first five principal components and the cohort each individual originated from (Fig. 2A). Compared to non-carriers, participants exclusively carrying the *LRP1B* rs80306347 allele had an increased risk of progressing to Parkinson's disease dementia (HR = 2.33, 95% CI =1.34-4.05, P = 0.00273). In addition, we also performed survival analysis controlling for *APOE* status (Fig. 2B and C). An increased hazard of progression to Parkinson's disease dementia was present in *LRP1B* rs80306347 carriers in both *APOE* ε4 allele carriers (HR = 3.47, 95% CI = 1.96-6.13, $P = 1.82 \times 10^{-05}$) and *APOE* ε4 allele non-carriers (HR = 2.25, 95% CI = 1.29-3.92, P = 0.00422), confirming that the effect of rs80306347 is independent of the effect of *APOE*. Finally, individuals carrying both *APOE* ε4 and *LRP1B* rs80306347 alleles had a much higher hazard of progression to Parkinson's disease dementia than carriers of each allele separately (HR = 8.08, 95% CI = 4.64-14.1, $P = 1.55 \times 10^{-13}$), indicating an increased risk of progression to Parkinson's disease dementia in carriers of both alleles (Fig. 2A). However, the addition of an interaction term in the regression model did not confirm an interaction between the two alleles.

Candidate gene analysis

Several other genes have been suggested to increase the risk of cognitive decline or dementia in Parkinson's disease. One of the most widely reported genes is *GBA*, which has also been described as a risk factor for Parkinson's disease and an earlier age of disease onset.[47,67] The non-Gaucher disease-causing *GBA* Parkinson's disease-risk variants E365K (rs2230288, also known as E326K) has been described in association with cognitive progression in Parkinson's disease.[13,14] We therefore performed a candidate loci survival analysis in the combined cohorts (n = 3,923) based on E365K carrier status, which confirmed a significant hazard ratio for progression to dementia (HR = 2.24, 95% CI = 1.45-3.48, $P = 3.12 \times 10^{-04}$; Fig. 3A and Supplementary Table 7). Conversely, the Parkinson's disease-risk factor T408M (also known as T369M, rs75548401) showed a trend toward a faster rate of cognitive decline that did not reach statistical significance, in keeping with a previous study.[43] The mild GD-causing variant N409S (also known as N370S, rs76763715) has shown inconsistent association with cognitive decline in Parkinson's disease. In our candidate loci analysis, Parkinson's disease patients

carrying this variant had a HR of 4.96 (95% CI = 2.30-10.7, P = 4.42 x10^{-05}) of developing dementia. In addition, *GBA* Sanger sequencing data was available for 1,793 individuals originating from the DIGPD and TPD cohorts. Mutations causing Gaucher's disease and Parkinson's disease risk variants were combined for survival analysis and were present in 9.3% of the cases (Supplementary Table 2). In this subset of patients, *GBA* risk variant and Gaucher's disease-mutation carriers had a HR for progression to Parkinson's disease dementia of 2.02 (95% CI = 1.21-3.32, *P*-value = 0.007), confirming the observation from several previous studies that *GBA* mutations increase the risk of dementia (Supplementary Fig. 10).[12–14] A similar candidate loci approach in the combined cohorts confirmed the strong association of *APOE* ε4 carrier status (HR = 2.56, 95% CI = 2.00-3.28, P = 6.36x10^{-14}) and *LRP1B* rs80306347 carrier status (HR = 2.71, 95% CI = 1.82-4.02, P = 7.71x10^{-07}) with earlier progression to Parkinson's disease dementia (Fig. 3B and C).

Multiplications of *SNCA* can cause autosomal dominant Parkinson's disease that is often associated with a high prevalence of dementia.[68] In addition, common variants in *SNCA* have been reported to increase the risk of cognitive decline or dementia in Parkinson's disease patients, as well as the risk of dementia with Lewy bodies, a related parkinsonism disorder in which dementia is an early feature.[32,44,45] We investigated five *SNCA* variants previously reported in the literature for association with dementia in Parkinson's disease or dementia with Lewy bodies, but none were shown to increase the risk of progression to Parkinson's disease dementia in our longitudinal data (Supplementary Table 7). Some of these variants have only been reported in small studies,[45] while rs356219 has shown inconsistent results across studies,[10,69,70] indicating that there is not enough evidence to support a role for common *SNCA* variants in the risk of cognitive decline or dementia in Parkinson's disease. Importantly, variants identified in dementia with Lewy bodies case-control GWAS studies[44] do not appear to contribute to risk of progression to dementia in Parkinson's disease, suggesting that the mechanisms leading to dementia with Lewy bodies and Parkinson's disease dementia do not entirely overlap.

Some studies have found that the *MAPT* H1 haplotype is a risk factor for cognitive decline in Parkinson's disease and can increase the susceptibility to dementia with Lewy bodies.[9,15–17] However, this finding has not been consistently replicated.[10,18] Similarly, we did not find any association between *MAPT* haplotypes and time to dementia in Parkinson's disease (Supplementary Table 7).

Recently, common variants in *RIMS2*, *TMEM108* and *WWOX* have been suggested to associate with faster progression to Parkinson's disease dementia.[18] Using similar methodology and sample size, we did not replicate these findings (Supplementary Table 7), indicating that further studies are needed to confirm the role of these genes in the risk of cognitive decline in Parkinson's disease.

Alzheimer's disease and Parkinson's disease genetic risk scores in Parkinson's disease dementia

Given the role of both APOE and LRP1B in APP metabolism, we next investigated the overlap between the Alzheimer's disease risk profile with that of Parkinson's disease cases with and without dementia. We calculated the normalised individual-level genetic risk score in each of the cohorts, based on the summary statistics from a recent large-scale GWAS meta-analysis of Alzheimer's disease.[48] A generalised linear model was used to test the association of Alzheimer's disease genetic risk scores with dementia status in each cohort, with results further meta-analysed using a random-effects model (Fig. 4A and Supplementary Fig. 11A). Parkinson's disease dementia was associated with a higher genetic risk score for Alzheimer's disease (Odds Ratio (OR) = 1.48, 95% CI = 1.32-1.66, $P = 4.47 \times 10^{-11}$). In contrast, the normalised genetic risk score for Parkinson's disease, derived from the latest Parkinson's disease GWAS study,[47] was similar between Parkinson's disease dementia and non-demented Parkinson's disease cases (OR = 0.99, 95% CI = 0.82-1.19, $P = 0.9078$; Fig. 4B and Supplementary Fig. 11C). This suggests that the genetic risk of developing Parkinson's disease dementia overlaps with the risk of developing Alzheimer's disease. Interestingly, in a subset of Parkinson's disease samples from the AMP-PD cohort who have been tested for Alzheimer's disease biomarkers in cerebrospinal fluid (CSF), Parkinson's disease dementia cases had decreased $A\beta_{42}$ levels (median ± interquartile range (IQR): 581 ± 493 pg/mL vs 867 ± 478 pg/mL, $P = 0.001193$, Wilcoxon rank-sum test) and increased total Tau (208 ± 129 pg/mL vs 158 ± 70 pg/mL, $P = 0.01617$, Wilcoxon rank-sum test) and p-Tau181 (18.3 ± 14.3 pg/mL vs 13.3 ± 5.84 pg/mL, $P = 0.002544$, Wilcoxon rank-sum test) levels at baseline (Fig. 5A), supporting the hypothesis that APP metabolism is important for the development of Parkinson's disease dementia. In addition, *APOE* ε4 carriers also had significantly decreased CSF $A\beta_{42}$ levels at baseline (median ± IQR: 689 ± 386 pg/mL vs 896 ± 543 pg/mL, $P = 1.7 \times 10^{-06}$, Wilcoxon rank-sum test) and subsequent time points, with no change in total Tau or p-Tau181

levels (Fig. 5B). This is in keeping with results from previous genome-wide association studies of Alzheimer's disease biomarkers, showing an association of *APOE* with abnormal amyloid status in either CSF or PET scans.[71–74]

APOE status is the most significant genetic determinant of the risk of developing Alzheimer's disease,[48] and was also confirmed to be significantly associated with the risk of progression to Parkinson's disease dementia in individuals previously diagnosed with Parkinson's disease. Therefore, to establish that the association between Alzheimer's disease genetic risk score and progression to Parkinson's disease dementia is not exclusively due to the overlap of the *APOE* signal between these two conditions, we adjusted the generalised linear models for *APOE* ε4 carrier status. When adjusting for *APOE* ε4 carrier status, there was no significant association between Parkinson's disease dementia and the genetic risk score for Alzheimer's disease (OR = 1.06, 95% CI = 0.93-1.21, P = 0.374; Supplementary Fig. 11B), indicating that *APOE* ε4 carrier status alone is driving the risk of progression to dementia among Alzheimer's disease GWAS top hits.

Finally, we assessed whether a higher Alzheimer's disease genetic risk score could be contributing to decreased dementia-free survival, i.e., faster progression to Parkinson's disease dementia. We performed survival analysis using CPH models to calculate the hazards of survival dementia-free after stratification of Parkinson's disease individuals into low-, middle-, and high-risk based on Alzheimer's disease genetic risk scores. Individuals in the higher tertile of AD-GRS had faster progression to dementia (HR = 2.38, 95% CI = 1.66-3.40, $P = 1.98 \times 10^{-06}$), but as with the overall risk of Parkinson's disease dementia, faster progression to dementia was abolished after exclusion of the *APOE* signal (HR = 1.16, 95% CI = 0.85-1.60, P = 0.3438, Fig. 4C and D).

Discussion

We have conducted a large genome-wide survival study of progression to dementia in Parkinson's disease patients. *APOE* has consistently been implicated as a risk factor for Alzheimer's disease, Parkinson's disease dementia and dementia with Lewy bodies.[9,32,44,47,51,75] Our results confirm that *APOE* ε4 is also a significant contributing factor in the rate of progression to Parkinson's disease dementia, while a candidate gene approach confirmed the role of non-Gaucher disease-pathogenic *GBA* E365K Parkinson's disease risk

variant and Gaucher disease-pathogenic N409S mutation in accelerating cognitive decline in Parkinson's disease. In addition, we identified a novel locus associated with progression to dementia. These results are in keeping with a recent study with similar sample size, study design and methodology.[18]

LRP1B belongs to the LDL receptor family and is highly expressed in the brain.[52] Several members of the LDL family have been implicated in cellular processes relevant to neurodegeneration, including tau uptake[76] and amyloid precursor protein trafficking, processing, and clearing.[77] Whether APP is processed by beta- and gamma-secretases to Aβ in the amyloidogenic pathway or by alpha-secretases in the non-amyloidogenic pathway depends on its subcellular localisation, as beta-secretase is most active in the acidic pH of the endosome, which appears to be a key site for the production of Aβ.[78] Therefore, modulation of intracellular APP trafficking by LDL receptors with opposing activities is postulated to be a crucial determinant of APP processing and subsequent neurodegeneration.[79] For example, binding of LRP1 and LRAD3 to APP at the cell surface leads to its enhanced endocytic trafficking and increased processing to Aβ.[80,81] In contrast, binding of LRP1B and LRP10 to APP leads to decreased trafficking of APP to the endosome, thus resulting in reduced amyloidogenic processing of APP.[54,82] *LRP10* mutants that disrupt the distribution of LRP10 from the trans-Golgi network to early endosomes lead to increased presence of APP in the endosomes and consequently to increased amyloidogenic processing of APP.[82] Interestingly, loss of function mutations in *LRP10* have recently been implicated in familial Parkinson's disease.[83] Similarly, due to a slower rate of endocytosis which leads to APP accumulation at the cell surface, the binding of APP to LRP1B receptors reduces APP processing into Aβ and increases secretion of soluble APP instead, suggesting that enhanced LRP1B activity could protect against the pathogenesis of Alzheimer's disease.[19] Interestingly, a genome-wide study comparing elderly individuals without cognitive decline and those with late onset Alzheimer's disease identified variants in *LRP1B* as protective against cognitive decline in old age.[84]

It is likely that dementia in Parkinson's disease can be driven by distinct mechanisms. Research in dementia with Lewy bodies, a condition closely related to Parkinson's disease dementia, has shown that *GBA* is more strongly associated with risk of "pure" dementia with Lewy bodies, while *APOE* ε4 is more strongly associated with dementia with Lewy bodies with Alzheimer's disease co-pathology.[85,86] This suggests that the genetic drivers of dementia in α-synucleinopathies are different in cases with and without Aβ co-pathology, with *GBA* predisposing to pure Lewy body pathology and *APOE* predisposing to concomitant Aβ

deposition. While Parkinson's disease neuropathology is primarily characterised by deposition of α-synuclein aggregates, dementia in Parkinson's disease can also be associated with Aβ deposition.[87–89] This leads to the question of whether Aβ metabolism could also play an important role in the development of Parkinson's disease dementia. In fact, increased cortical Aβ deposition has been shown to be associated with a faster progression to dementia in Parkinson's disease[89,90], and a low CSF $A\beta_{42}$-to-total tau ratio at baseline has been associated with cognitive decline in early Parkinson's disease.[91] Our results on Alzheimer's disease CSF biomarkers also suggest that Parkinson's disease dementia is associated with increased Aβ brain pathology, and it is likely that *APOE* ε4 is the main driver of this association. Furthermore, APOE is known to facilitate endocytosis of Aβ via LDL receptors at the cell surface,[92] which could offer a mechanistic link between *APOE* and *LRP1B* and a possible explanation as to why Parkinson's disease carriers of both *APOE* ε4 and *LRP1B* rs80306347-C alleles appear to have a faster progression to dementia. Nonetheless, there is evidence that *APOE* ε4 can also contribute to neurodegeneration by non-amyloidogenic mechanisms: *APOE* ε4 allele carriers can present with “pure" Lewy body dementia; α-synuclein pathology is increased in Lewy body dementia *APOE* ε4 carriers with minimal amyloid pathology, compared to age-matched non-carriers; *APOE* ε4 exacerbates α-synuclein pathology and leads to worse neurodegeneration and cognitive performances in mice.[93,94]

Other genetic variants previously reported in association to dementia in Parkinson’s disease were not confirmed. In particular, a large recent study using a similar genome-wide survival approach identified that a variant in *RIMS2* was a stronger predictor of Parkinson’s disease dementia than *APOE* and *GBA*.[18] We were unable to replicate this finding, which could be the result of small variations in the post-imputation background allele frequencies in different cohorts. Given the relatively rare minor allele frequency of this SNP in the general population, it is possible that small changes in the allele frequency may significantly change the results of the analysis. The apparent discrepancies between studies will likely be resolved as larger longitudinal datasets become available.

Our study has some limitations. First, the analysis was conducted only in individuals of European ancestry, as data from this population was more readily available. It is therefore not possible to generalise our findings to other populations. Future studies including individuals from non-European ancestries are needed. Second, statistical power to detect a significant association is likely to be reduced by the fact that some individuals did not complete the study protocol because of early study withdrawal. It is possible that some individuals who were

censored as non-dementia cases would have developed dementia if the follow-up duration had been longer. To mitigate this, individuals with normal longitudinal assessments who withdrew from the study due to the development of dementia were classified as Parkinson's disease dementia, where this information was available. This creates the potential for a skewed estimation of time-to-dementia in these cases. However, given the relatively short time interval between the last normal assessment and study withdrawal, the risk of disproportionate skewness is reduced. In addition, estimating time-to-dementia using the midpoint between the last normal assessment and withdrawal should further reduce that risk. Statistical power to detect a significant association is a function of sample size and event rates, which for dementia are likely to be influenced by mean age at baseline and duration of follow-up. Two of the cohorts (TPD and OPDC) recruited individuals of similar age to incident cohorts of Northern European ancestry, namely the cohorts included in the Parkinson's Incidence Cohorts Collaboration (PICC).[95] However, the remaining cohorts have a mean younger age than the observed average in incident population-based cohorts, which suggests these cohorts might not be representative of the wider Parkinson's disease population. Given these are non-incident cohorts, it is not possible to know when individuals who met criteria for dementia at baseline developed Parkinson's disease dementia, and so these were excluded from further analysis. It is therefore possible that individuals who develop dementia early in the disease course are not adequately represented in the dataset analysed. Despite being one of the largest genome-wide survival studies of progression to Parkinson's disease dementia, sample size and event rates are relatively small, and larger, incident cohorts with longer follow-up times are needed to detect variants of small effect size. It is nevertheless reassuring that our study has identified some of the same genetic factors associated with higher risk of progression to dementia as large, incident population-based cohorts with long follow-up times such as *APOE* ε4 and *GBA* mutations, despite the potential limitations of large non-incident longitudinal cohorts.[95]

In conclusion, this large genome-wide study identifies several interesting and plausible new gene candidates associated with faster progression to dementia in Parkinson's disease, while also corroborating the importance of the previously described *APOE* and *GBA* variants for cognitive outcomes in Parkinson's disease. In addition, our results provide further evidence that β-amyloid metabolism might play an important role in the pathophysiology of Parkinson's disease dementia, which has important therapeutic implications, as strategies aimed at Alzheimer's disease could also prove effective in Parkinson's disease patients at risk of dementia.

Acknowledgements

Data used in the preparation of this article were obtained from the AMP-PD Knowledge Platform (**https://www.amp-pd.org**). AMP-PD is a public-private partnership managed by the FNIH and funded by Celgene, GSK, Michael J. Fox Foundation for Parkinson's Research, the National Institute of Neurological Disorders and Stroke, Pfizer, and Verily.

Clinical data and biosamples used in preparation of this article were obtained from the Fox Investigation for New Discovery of Biomarkers (BioFIND), the Parkinson's Progression Markers Initiative (PPMI), the Parkinson's Disease Biomarkers Program (PDBP), and the SURE-PD3 Study. BioFIND is sponsored by The Michael J. Fox Foundation for Parkinson's Research (MJFF) with support from the National Institute for Neurological Disorders and Stroke (NINDS).

Data used in the preparation of this article were obtained from the Fox Investigation for New Discovery of Biomarkers ("BioFIND") database (**http://biofind.loni.usc.edu/**). For up-to-date information on the study, visit **michaeljfox.org/news/biofind**.

PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including [list the full names of all of the PPMI funding partners found at **www.ppmi-info.org/fundingpartners**]. The PPMI Investigators have not participated in reviewing the data analysis or content of the manuscript. For up-to-date information on the study, visit **www.ppmi-info.org**.

The Parkinson's Disease Biomarker Program (PDBP) consortium is supported by the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health. A full list of PDBP investigators can be found at **https://pdbp.ninds.nih.gov/policy**. The PDBP Investigators have not participated in reviewing the data analysis or content of the manuscript.

The DIGPD cohort (ClinicalTrials.gov, NCT01564992) is a multicenter longitudinal cohort conducted in four Universities and four General Hospitals in France between 2009 and 2019, sponsored by Assistance Publique Hôpitaux de Paris, funded by a grant from the French Ministry of Health (PHRC 2008, AOR0810) and a grant from the Agence Nationale de Sécurité et des Médicaments (ANSM-2013). We thank the DIGPD Study group which collected the data made available for this work.

Both TPD and OPDC cohorts are primarily funded and supported by Parkinson's UK (**https://www.parkinsons.org.uk/**) and supported by the National Institute for Health Research (NIHR) Dementias and Neurodegenerative Diseases Research Network (DeNDRoN). The TPD study is also supported by NHS Greater Glasgow and Clyde. The

OPDC cohort is also supported by the NIHR Oxford Biomedical Research Centre, based at the Oxford University Hospitals NHS Trust, and the University of Oxford. TPD has multi-centre research ethics approval from the West of Scotland Research Ethics Committee: IRAS 70980, MREC 11/AL/0163 (ClinicalTrials.gov, NCT02881099). OPDC has multi-centre research ethics approval from the South Central Oxford A Research Ethics Committee 16/SC/0108.
The Genotype-Tissue Expression (GTEx) Project was supported by the **Common Fund** of the Office of the Director of the National Institutes of Health, and by NCI, NHGRI, NHLBI, NIDA, NIMH, and NINDS. The data used for the analyses described in this manuscript were obtained from **https://console.cloud.google.com/storage/browser/gtex-resources** on 01/26/2022.

Funding

This research was funded in whole or in part by Aligning Science Across Parkinson's [Grant number: ASAP-000478] through the Michael J. Fox Foundation for Parkinson's Research (MJFF). For the purpose of open access, the author has applied a CC BY public copyright licence to all Author Accepted Manuscripts arising from this submission.

This research was supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. The UCL Movement Disorders Centre is supported by the Edmond J. Safra Philanthropic Foundation.

Competing interests

H.R.M. reports paid consultancy from Roche. Research Grants from Parkinson's UK, Cure Parkinson's Trust, PSP Association, CBD Solutions, Drake Foundation, Medical Research Council (MRC), Michael J. Fox Foundation. Dr Morris is a co-applicant on a patent application related to C9ORF72 - Method for diagnosing a neurodegenerative disease (PCT/GB2012/052140).

D.G.G. has received grants from Michael's Movers, the Neurosciences Foundation, and Parkinson's UK, and honoraria from AbbVie, BIAL Pharma, Britannia Pharmaceuticals, GE Healthcare, and consultancy fees from Acorda Therapeutics and the Glasgow Memory Clinic.

M.T.M.H. received funding/grant support from Parkinson's UK, Oxford NIHR BRC, University of Oxford, CPT, Lab10X, NIHR, Michael J. Fox Foundation, H2020 European

Union, GE Healthcare and the PSP Association. She also received payment for Advisory Board attendance/consultancy for Biogen, Roche, Sanofi, CuraSen Therapeutics, Evidera, Manus Neurodynamica, Lundbeck.

Y.B.-S. has received grant funding from the MRC, NIHR, Parkinson's UK, NIH, and ESRC.

J.C.C. has served on advisory boards for Biogen, Denali, Idorsia, Prevail Therapeutic, Servier, Theranexus, UCB, and received grants from Sanofi and the Michael J. Fox Foundation outside of this work.

A.E. received funding/grant support by Agence Nationale de la Recherche, France Parkinson, and the Michael J. Fox foundation.

J.H. is supported by the UK Dementia Research Institute, which receives its funding from DRI Ltd, funded by the UK Medical Research Council, Alzheimer's Society, and Alzheimer's Research UK. He is also supported by the MRC, Wellcome Trust, Dolby Family Fund, National Institute for Health Research University College London Hospitals Biomedical Research Centre.

All other authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

Appendix

An appendix with the DIGPD Study Group members is available online.

References

1. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. *J Neural Transm*. 2017;124(8):901-905.

2. Szeto JYY, Walton CC, Rizos A, et al. Dementia in long-term Parkinson's disease patients: a multicentre retrospective study. *NPJ Parkinsons Dis*. 2020;6:2.

3. Dubois B, Burn D, Goetz C, et al. Diagnostic procedures for Parkinson's disease dementia: Recommendations from the movement disorder society task force. *Mov Disord*. 2007;22(16):2314-2324.

4. Perez-Lloret S, Barrantes FJ. Deficits in cholinergic neurotransmission and their clinical correlates in Parkinson's disease. *npj Parkinson's Disease*. 2016;2(1):16001-16001.

5. Buter TC, van den Hout A, Matthews FE, Larsen JP, Brayne C, Aarsland D. Dementia and survival in Parkinson disease: A 12-year population study. *Neurology*. 2008;70(13):1017-1022.

6. Hobson P, Meara J. Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. *Mov Disord*. 2004;19(9):1043-1049.

7. Hughes TA, Ross HF, Musa S, et al. A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. *Neurology*. 2000;54(8):1596-1603.

8. Pankratz N, Byder L, Halter C, et al. Presence of an APOE4 allele results in significantly earlier onset of Parkinson's disease and a higher risk with dementia. *Mov Disord*. 2006;21(1):45-49.

9. Tunold JA, Geut H, Rozemuller JMA, et al. APOE and MAPT Are Associated With Dementia in Neuropathologically Confirmed Parkinson's Disease. *Front Neurol*. 2021;12. doi:10.3389/fneur.2021.631145

10. Mata IF, Leverenz JB, Weintraub D, et al. APOE , MAPT , and SNCA Genes and Cognitive Performance in Parkinson Disease. *JAMA Neurol*. 2014;71(11):1405-1405.

11. Pang S, Li J, Zhang Y, Chen J. Meta-Analysis of the Relationship between the APOE Gene and the Onset of Parkinson's Disease Dementia. *Parkinsons Dis*. 2018;2018:9497147.

12. Liu G, Boot B, Locascio JJ, et al. Specifically neuropathic Gaucher's mutations accelerate cognitive decline in Parkinson's. *Ann Neurol*. 2016;80(5):674-685.

13. Davis MY, Johnson CO, Leverenz JB, et al. Association of GBA Mutations and the E326K Polymorphism With Motor and Cognitive Progression in Parkinson Disease. *JAMA Neurol*. 2016;73(10):1217-1217.

14. Mata IF, Leverenz JB, Weintraub D, et al. GBA Variants are associated with a distinct pattern of cognitive deficits in Parkinson's disease. *Mov Disord*. 2016;31(1):95-102.

15. Labbé C, Heckman MG, Lorenzo-Betancor O, et al. MAPT haplotype H1G is associated with increased risk of dementia with Lewy bodies. *Alzheimers Dement*. 2016;12(12):1297-1304.

16. Setó-Salvia N, Clarimón J, Pagonabarraga J, et al. Dementia Risk in Parkinson Disease. *Arch Neurol*. 2011;68(3). doi:10.1001/archneurol.2011.17

17. Goris A, Williams-Gray CH, Clark GR, et al. Tau and α-synuclein in susceptibility to, and

dementia in, Parkinson's disease. *Ann Neurol*. 2007;62(2):145-153.

18. Liu G, Peng J, Liao Z, et al. Genome-wide survival study identifies a novel synaptic locus and polygenic score for cognitive progression in Parkinson's disease. *Nat Genet*. 2021;53(6):787-793.

19. Malek N, Swallow DMA, Grosset KA, et al. Tracking Parkinson's: Study Design and Baseline Patient Data. *J Parkinsons Dis*. 2015;5(4):947-959.

20. Szewczyk-Krolikowski K, Tomlinson P, Nithi K, et al. The influence of age and gender on motor and non-motor features of early Parkinson's disease: Initial findings from the Oxford Parkinson Disease Center (OPDC) discovery cohort. *Parkinsonism Relat Disord*. 2014;20(1):99-105.

21. Iwaki H, Leonard HL, Makarious MB, et al. Accelerating Medicines Partnership: Parkinson's Disease. Genetic Resource. *Mov Disord*. 2021;36(8):1795-1804.

22. Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet*. 2009;373(9680):2055-2066.

23. Das S, Forer L, Schönherr S, et al. Next-generation genotype imputation service and methods. *Nat Genet*. 2016;48(10):1284-1287.

24. Purcell S, Neale B, Todd-Brown K, et al. PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. *Am J Hum Genet*. 2007;81(3):559-575.

25. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*. 2010;26(17):2190-2191.

26. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. *Nat Commun*. 2017;8(1):1826-1826.

27. Boughton AP, Welch RP, Flickinger M, et al. LocusZoom.js: interactive and embeddable visualization of genetic association study results. *Bioinformatics*. 2021;37(18):3017-3018.

28. Machiela MJ, Chanock SJ. LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics*. 2015;31(21):3555-3557.

29. Ardlie KG, Deluca DS, Segrè AV, et al. The Genotype-Tissue Expression (GTEx) pilot analysis: Multitissue gene regulation in humans. *Science*. 2015;348(6235):648-660.

30. Hodge RD, Bakken TE, Miller JA, et al. Conserved cell types with divergent features in human versus mouse cortex. *Nature*. 2019;573(7772):61-68.

31. Agarwal D, Sandor C, Volpato V, et al. A single-cell atlas of the human substantia nigra reveals cell-specific pathways associated with neurological disorders. *Nat Commun*. 2020;11(1):4183-4183.

32. Chia R, Sabir MS, Bandres-Ciga S, et al. Genome sequencing analysis identifies new loci associated with Lewy body dementia and provides insights into its genetic architecture. *Nat Genet*. 2021;53(3):294-303.

33. Bryois J, Skene NG, Hansen TF, et al. Genetic identification of cell types underlying brain complex traits yields insights into the etiology of Parkinson's disease. *Nat Genet*. 2020;52(5):482-493.

34. Skene NG, Grant SGN. Identification of Vulnerable Cell Types in Major Brain Disorders

Using Single Cell Transcriptomes and Expression Weighted Cell Type Enrichment. *Front Neurosci*. 2016;10. doi:10.3389/fnins.2016.00016

35. Reynolds RH. *RHReynolds/MarkerGenes: v0.99.1 - Zenodo Release*.; 2022. doi:10.5281/zenodo.6418605

36. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: A Tool for Genome-wide Complex Trait Analysis. *Am J Hum Genet*. 2011;88(1):76-82.

37. Giambartolomei C, Vukcevic D, Schadt EE, et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS Genet*. 2014;10(5):e1004383.

38. Reynolds RH. *RHReynolds/colochelpR: v0.99.1*.; 2021. doi:10.5281/zenodo.5011869

39. Wallace C. Eliciting priors and relaxing the single causal variant assumption in colocalisation analyses. *PLoS Genet*. 2020;16(4):e1008720.

40. Akbarian S, Liu C, Knowles JA, et al. The PsychENCODE project. *Nat Neurosci*. 2015;18(12):1707-1712.

41. Võsa U, Claringbould A, Westra HJ, et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. *Nat Genet*. 2021;53(9):1300-1310.

42. Li YI, Knowles DA, Humphrey J, et al. Annotation-free quantification of RNA splicing using LeafCutter. *Nat Genet*. 2018;50(1):151-158.

43. Iwaki H, Blauwendraat C, Leonard HL, et al. Genetic risk of Parkinson disease and progression: An analysis of 13 longitudinal cohorts. *Neurol Genet*. 2019;5(4):e348.

44. Guerreiro R, Ross OA, Kun-Rodrigues C, et al. Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study. *Lancet Neurol*. 2018;17(1):64-74.

45. Zheng J, Zang Q, Hu F, Wei H, Ma J, Xu Y. Alpha-synuclein gene polymorphism affects risk of dementia in Han Chinese with Parkinson's disease. *Neurosci Lett*. 2019;706:146-150.

46. Pedersen CC, Lange J, Førland MGG, Macleod AD, Alves G, Maple-Grødem J. A systematic review of associations between common SNCA variants and clinical heterogeneity in Parkinson's disease. *npj Parkinson's Disease*. 2021;7(1):54-54.

47. Nalls MA, Blauwendraat C, Vallerga CL, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet Neurol*. 2019;18(12):1091-1102.

48. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat Genet*. 2019;51(3):414-430.

49. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22(4):153-160.

50. Owzar K, Li Z, Cox N, Jung SH. Power and Sample Size Calculations for SNP Association Studies With Censored Time-to-Event Outcomes. *Genet Epidemiol*. 2012;36(6):538-548.

51. Tan MMX, Lawton MA, Jabbari E, et al. Genome-Wide Association Studies of Cognitive and Motor Progression in Parkinson's Disease. *Mov Disord*. 2021;36(2):424-433.

52. Haas J, Beer AG, Widschwendter P, et al. LRP1b shows restricted expression in human tissues and binds to several extracellular ligands, including fibrinogen and apoE – carrying lipoproteins. *Atherosclerosis*. 2011;216(2):342-347.

53. Feleke R, Reynolds RH, Smith AM, et al. Cross-platform transcriptional profiling identifies common and distinct molecular pathologies in Lewy body diseases. *Acta Neuropathol*. 2021;142(3):449-474.

54. Cam JA, Zerbinatti CV, Knisely JM, Hecimovic S, Li Y, Bu G. The Low Density Lipoprotein Receptor-related Protein 1B Retains β-Amyloid Precursor Protein at the Cell Surface and Reduces Amyloid-β Peptide Production. *J Biol Chem*. 2004;279(28):29639-29646.

55. Nachury MV, Loktev AV, Zhang Q, et al. A core complex of BBS proteins cooperates with the GTPase Rab8 to promote ciliary membrane biogenesis. *Cell*. 2007;129(6):1201-1213.

56. Lara Ordónez AJ, Fernández B, Fdez E, et al. RAB8, RAB10 and RILPL1 contribute to both LRRK2 kinase-mediated centrosomal cohesion and ciliogenesis deficits. *Hum Mol Genet*. 2019;28(21):3552-3568.

57. Dhekne HS, Yanatori I, Gomez RC, et al. A pathway for Parkinson's Disease LRRK2 kinase to block primary cilia and Sonic hedgehog signaling in the brain. *Elife*. 2018;7. doi:10.7554/eLife.40202

58. Haq N, Schmidt-Hieber C, Sialana FJ, et al. Loss of Bardet-Biedl syndrome proteins causes synaptic aberrations in principal neurons. *PLoS Biol*. 2019;17(9):e3000414.

59. Colla E. Linking the Endoplasmic Reticulum to Parkinson's Disease and Alpha-Synucleinopathy. *Front Neurosci*. 2019;13. doi:10.3389/fnins.2019.00560

60. Taylor HBC, Jeans AF. Friend or Foe? The Varied Faces of Homeostatic Synaptic Plasticity in Neurodegenerative Disease. *Front Cell Neurosci*. 2021;0. doi:10.3389/fncel.2021.782768

61. Schmidt MF, Gan ZY, Komander D, Dewson G. Ubiquitin signalling in neurodegeneration: mechanisms and therapeutic opportunities. *Cell Death Differ*. 2021;28(2):570-590.

62. Blackstone C, Elwood F, Plun-Favreau H, Lewis PA. Vesicle trafficking and pathways to neurodegeneration. *Mol Neurodegener*. 2021;16(1):1-4.

63. Zhang W, Shen J, Wang Y, Cai K, Zhang Q, Cao M. Blood SSR1: A Possible Biomarker for Early Prediction of Parkinson's Disease. *Front Mol Neurosci*. 2022;15. doi:10.3389/fnmol.2022.762544

64. Faraone SV, Spencer TJ, Madras BK, Zhang-James Y, Biederman J. Functional effects of dopamine transporter gene genotypes on in vivo dopamine transporter functioning: a meta-analysis. *Mol Psychiatry*. 2014;19(8):880-889.

65. Fazeli G, Oli RG, Schupp N, Stopper H. The Role of the Dopamine Transporter in Dopamine-Induced DNA Damage. *Brain Pathol*. 2011;21(3):237-248.

66. Wang D, Liu S, Warrell J, et al. Comprehensive functional genomic resource and integrative model for the human brain. *Science*. 2018;362(6420). doi:10.1126/science.aat8464

67. Blauwendraat C, Heilbron K, Vallerga CL, et al. Parkinson's disease age at onset genome-wide association study: Defining heritability, genetic loci, and α-synuclein mechanisms. *Mov Disord*. 2019;34(6):866-875.

68. Chartier-Harlin MC, Kachergus J, Roumier C, et al. α-synuclein locus duplication as a cause

of familial Parkinson's disease. *Lancet*. 2004;364(9440):1167-1169.

69. Campêlo CLC, Cagni FC, de Siqueira Figueredo D, et al. Variants in SNCA Gene Are Associated with Parkinson's Disease Risk and Cognitive Symptoms in a Brazilian Sample. *Front Aging Neurosci*. 2017;9:198.

70. Luo N, Li Y, Niu M, et al. Variants in the SNCA Locus Are Associated With the Progression of Parkinson's Disease. *Front Aging Neurosci*. 2019;11:110.

71. Kim S, Swaminathan S, Shen L, et al. Genome-wide association study of CSF biomarkers A 1-42, t-tau, and p-tau181p in the ADNI cohort. *Neurology*. 2011;76(1):69-79.

72. Lee B, Yao X, Shen L. Genome-Wide association study of quantitative biomarkers identifies a novel locus for alzheimer's disease at 12p12.1. *BMC Genomics*. 2022;23(1):85-85.

73. Hong S, Prokopenko D, Dobricic V, et al. Genome-wide association study of Alzheimer's disease CSF biomarkers in the EMIF-AD Multimodal Biomarker Discovery dataset. *Transl Psychiatry*. 2020;10(1):403-403.

74. Ramanan VK, Risacher SL, Nho K, et al. APOE and BCHE as modulators of cerebral amyloid deposition: a florbetapir PET genome-wide association study. *Mol Psychiatry*. 2014;19(3):351-357.

75. Rongve A, Witoelar A, Ruiz A, et al. GBA and APOE ε4 associate with sporadic dementia with Lewy bodies in European genome wide association study. *Sci Rep*. 2019;9(1):7013-7013.

76. Rauch JN, Luna G, Guzman E, et al. LRP1 is a master regulator of tau uptake and spread. *Nature*. 2020;580(7803):381-385.

77. Lane-Donovan C, Philips GT, Herz J. More than Cholesterol Transporters: Lipoprotein Receptors in CNS Function and Neurodegeneration. *Neuron*. 2014;83(4):771-787.

78. Haass C, Kaether C, Thinakaran G, Sisodia S. Trafficking and Proteolytic Processing of APP. *Cold Spring Harb Perspect Med*. 2012;2(5):a006270-a006270.

79. Andersen OM, Willnow TE. Lipoprotein receptors in Alzheimer's disease. *Trends Neurosci*. 2006;29(12):687-694.

80. Cam JA, Zerbinatti CV, Li Y, Bu G. Rapid Endocytosis of the Low Density Lipoprotein Receptor-related Protein Modulates Cell Surface Distribution and Processing of the β-Amyloid Precursor Protein. *J Biol Chem*. 2005;280(15):15464-15470.

81. Ranganathan S, Noyes NC, Migliorini M, et al. LRAD3, A Novel Low-Density Lipoprotein Receptor Family Member That Modulates Amyloid Precursor Protein Trafficking. *Journal of Neuroscience*. 2011;31(30):10836-10846.

82. Brodeur J, Thériault C, Lessard-Beaudoin M, Marcil A, Dahan S, Lavoie C. LDLR-related protein 10 (LRP10) regulates amyloid precursor protein (APP) trafficking and processing: evidence for a role in Alzheimer's disease. *Mol Neurodegener*. 2012;7(1):31-31.

83. Quadri M, Mandemakers W, Grochowska MM, et al. LRP10 genetic variants in familial Parkinson's disease and dementia with Lewy bodies: a genome-wide linkage and sequencing study. *Lancet Neurol*. 2018;17(7):597-608.

84. Poduslo SE, Huang R, Spiro A. A genome screen of successful aging without cognitive decline identifies LRP1B by haplotype analysis. *Am J Med Genet B Neuropsychiatr Genet*. 2009;9999B. doi:10.1002/ajmg.b.30963

85. Kaivola K, Shah Z, Chia R, International LBD Genomics Consortium, Scholz SW. Genetic evaluation of dementia with Lewy bodies implicates distinct disease subgroups. *Brain*. Published online 2021. doi:10.1093/brain/awab402

86. van der Lee SJ, van Steenoven I, van de Beek M, et al. Genetics Contributes to Concomitant Pathology and Clinical Presentation in Dementia with Lewy Bodies. *J Alzheimers Dis*. 2021;83(1):269-279.

87. Kalaitzakis ME, Graeber MB, Gentleman SM, Pearce RKB. Striatal β-Amyloid Deposition in Parkinson Disease With Dementia. *J Neuropathol Exp Neurol*. 2008;67(2):155-161.

88. Lashley T, Holton JL, Gray E, et al. Cortical α-synuclein load is associated with amyloid-β plaque burden in a subset of Parkinson's disease patients. *Acta Neuropathol*. 2008;115(4):417-425.

89. Compta Y, Parkkinen L, O'Sullivan SS, et al. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? *Brain*. 2011;134(5):1493-1505.

90. Smith C, Malek N, Grosset K, Cullen B, Gentleman S, Grosset DG. Neuropathology of dementia in patients with Parkinson's disease: a systematic review of autopsy studies. *J Neurol Neurosurg Psychiatry*. Published online August 2019:jnnp - 2019-321111.

91. Schrag A, Siddiqui UF, Anastasiou Z, Weintraub D, Schott JM. Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study. *Lancet Neurol*. 2017;16(1):66-75.

92. Rebeck GW, LaDu MJ, Estus S, Bu G, Weeber EJ. The generation and function of soluble apoE receptors in the CNS. *Mol Neurodegener*. 2006;1(1):15-15.

93. Tsuang D, Leverenz JB, Lopez OL, et al. APOE ϵ4 Increases Risk for Dementia in Pure Synucleinopathies. *JAMA Neurol*. 2013;70(2):223-228.

94. Zhao N, Attrebi ON, Ren Y, et al. APOE4 exacerbates α-synuclein pathology and related toxicity independent of amyloid. *Sci Transl Med*. 2020;12(529). doi:10.1126/scitranslmed.aay1809

95. Szwedo AA, Dalen I, Pedersen KF, et al. GBA and APOE Impact Cognitive Decline in Parkinson's Disease: A 10-Year Population-Based Study. *Mov Disord*. 2022;37(5):1016-1027.

Figure legends

Figure 1 Manhattan plot representing the results of the GWSS meta-analysis. The GWSS was conducted using a Cox proportional hazards model in each cohort separately, and results were meta-analysed (Parkinson's disease dementia: *n* = 265; Parkinson's disease: *n* = 3,658). Red dots indicate the variant with the lowest *p*-value at each genome-wide significant genetic *locus* and the gene closest to the top variant is indicated. Genome-wide significance was set at $5x10^{-8}$ and is indicated by the dashed line.

Figure 2 Interaction between *APOE* and *LRP1B* rs80306347 signals. (**A**) Kaplan-Meier curve for dementia-free survival based on *APOE* ε4 and *LRP1B* rs80306347 carrier status of Parkinson's disease patients. Compared to non-carriers of either allele, *LRP1B* rs80306347 carriers had an HR of progression to Parkinson's disease dementia of 2.33 (95% CI = 1.34-4.05; *P* = 0.00273), while *APOE* ε4 carriers had an HR of 2.48 (95% CI = 1.91-3.21; *P* = $9.67x10^{-12}$). Carriers of both alleles had the most significant increase in the hazards ratio of progressing to Parkinson's disease dementia (HR = 8.08; 95% CI = 4.64-14.06; *P* = $1.55x10^{-13}$). (**B**) Kaplan-Meier curve for dementia-free survival based on *LRP1B* rs80306347 carrier status in Parkinson's disease *APOE* ε4 carriers. (**C**) Kaplan-Meier curve for dementia-free survival based on *LRP1B* rs80306347 carrier status in Parkinson's disease *APOE* ε4 non-carriers. Statistical analysis was conducted using Cox proportional hazards models in the combined cohorts (*n* = 3,923 individuals) at the specified loci. *HR*, hazard ratio; *CI*, confidence interval; *P*, *p*-value.

Figure 3 Survival curves of candidate gene analysis. (**A**) Kaplan-Meier curve for dementia-free survival based on *GBA* E365K (E362K) and N409S (N370S) carrier status of Parkinson's disease patients. (**B**) Kaplan-Meier curve for dementia-free survival based on *APOE* ε4 carrier status of Parkinson's disease patients. (**C**) Kaplan-Meier curve for dementia-free survival based on *LRP1B* rs80306347 carrier status of Parkinson's disease patients. Statistical analysis was conducted per locus using Cox proportional hazards models in the combined cohorts (*n* = 3,923 individuals). *HR*, hazard ratio; *CI*, confidence interval; *P*, *p*-value; *PD*, Parkinson's disease; *PDD*, Parkinson's disease dementia.

Figure 4 Alzheimer's disease and Parkinson's disease genetic risk scores (GRS). (**A-B**) Violin plots depicting the distribution of the meta-analysis of z-transformed Alzheimer's disease (**A**) and Parkinson's disease genetic risk scores (**B**) in Parkinson's disease and Parkinson's disease dementia. The central line of the boxplots indicates the median, the box limits indicate the first and third quartiles, the whiskers indicate ± 1.5*IQR, and the data points indicate the outliers. (**C-D**) Survival Kaplan-Meier curves for dementia-free survival of Parkinson's disease patients based on the stratification of AD-GRS into low-, middle-, and high-risk tertiles, either including (**C**) or excluding *APOE* (**D**). *PD*, Parkinson's disease; *PDD*, Parkinson's disease dementia.

Figure 5 CSF measurements of Alzheimer's disease biomarkers. Boxplots representing the measurements (in pg/mL) of the CSF biomarkers Aβ42, p-Tau181 and total Tau in a subset of individuals from the AMP-PD cohort (n = 352) across time (M0 = study baseline, M12 = 12 months, M24 = 24 months, M36 = 36 months). (**A**) CSF biomarker levels by phenotype (n = 28 Parkinson's disease dementia and n = 324 Parkinson's disease cases). (**B**) CSF biomarker levels by *APOE* Ɛ4 allele carrier status (n = 86 *APOE* Ɛ4 allele carriers and n = 266 APOE Ɛ4 allele non-carriers). Boxplots display a median line, the box limits indicate the first and third quartiles, the whiskers indicate ±1.5*IQR, and the data points indicate the outliers. The Wilcoxon rank-sum test was used to compare medians across phenotypic groups. Significance threshold: *P <0.05, **P <0.01, ***P <0.001, ****P <0.0001. *PD*, Parkinson's disease; *PDD*, Parkinson's disease dementia.