Genome-wide survival study identifies a novel synaptic locus and polygenic score for cognitive progression in Parkinson’s disease

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A key driver of patients’ well-being and clinical trials for Parkinson’s disease (PD) is the course that the disease takes over time (progression and prognosis). To assess how genetic variation influences the progression of PD over time to dementia, a major determinant for quality of life, we performed a longitudinal genome-wide survival study of 11.2 million variants in 3,821 patients with PD over 31,053 visits. We discover RIMS2 as a progression locus and confirm this in a replicate population (hazard ratio (HR) = 4.77, \( P = 2.78 \times 10^{-16} \)) of 7,821 patients with PD over 31,053 visits. We discover RIMS2 as a progression locus and confirm this in a replicate population (hazard ratio (HR) = 4.77, \( P = 2.78 \times 10^{-16} \)), identify suggestive evidence for TMEM108 (HR = 2.86, \( P = 2.09 \times 10^{-9} \)) and WWOX (HR = 2.12, \( P = 2.37 \times 10^{-8} \)) as progression loci, and confirm associations for GBA (HR = 1.93, \( P = 0.0002 \)) and APOE (HR = 1.48, \( P = 0.001 \)). Polygenic progression scores exhibit a substantial aggregate association with dementia risk, while polygenic susceptibility scores are not predictive. This study identifies a novel synaptic locus and polygenic score for cognitive disease progression in PD and proposes diverging genetic architectures of progression and susceptibility.

The past decade has seen success in identifying genetic variants linked to susceptibility for common disease from genome-wide association studies (GWAS) through time-static, two-group comparisons of unaffected controls and cases captured in one single snapshot of time1−5. The genetic architecture of progression and prognosis, which is fundamental for patients, has not been established. Which genes determine whether a patient will have an aggressive or benign course, and which variants influence who will develop dementia? To shift from the genetics of susceptibility to precision medicine, longitudinal designs are needed that examine the critical time dimension and provide information about individual change.6

The number of patients with PD is projected to double to 14 million worldwide by 2040 (ref. 7). The pace of progression varies considerably between patients8−10. Parkinson’s disease dementia (PDD) is one of the most debilitating manifestations of disease progression in PD with the greatest influence on quality of life, caregivers and health costs11. In clinical trials, the heterogeneity of progression rates obfuscates drug effects. None of the existing PD therapies slow the underlying neuropathology, which relentlessly advances from brainstem to cortex1−7 and clinically correlates with progression from motor to cognitive symptoms.

Limited evidence exists on the genetic architecture of cognitive decline in PD beyond the GBA (β-galactocerebrosidase) locus established by us6,7,13 and others14. APOE (apolipoprotein E) is implicated chiefly based on cross-sectional studies15. Evidence for other candidate genes and GWAS-derived susceptibility variants is controversial (for example, LRRK216, SNCA17−18, MAPT19,20 and others21−23). We determined the effects of 11.2 million deeply imputed variants on cognitive decline in 4,872 patients with PD in 15 cohorts1−3 from North America and Europe between 1986 and 2017, who were prospectively assessed with 36,123 study visits (Supplementary Fig. 1 and Supplementary Table 1). We evaluated thousands more patients, tens of thousands more follow-up visits and millions more SNPs than previous longitudinal explorations24−26, and confirmed associations in an independent replicate population. We performed whole-genome genotyping on our cohorts with the new-generation, high-density Illumina Infinium Multi-Ethnic Global Array that harnesses content from Phase 3 of the 1000 Genomes Project27 and transancestry tagging strategies to maximize imputation accuracy for low-frequency variants. Imputation28−30 provides power of detection comparable to whole-genome sequencing (WGS) for low frequency (minor allele frequency (MAF) of \( \geq 1\% \) but \(< 5\% \))13 and common variants31. We genotyped 1.8 million variants and imputed 11.2 million variants (Methods and Supplementary Fig. 2). Concordance of imputation compared to WGS was 99.4% based on 562 samples probed with both methods (Supplementary Fig. 3).
A total of 4,491 samples passed genotyping quality control. Patients were left-censored, and those with missing or non-quality clinical data were excluded (n=670, Extended Data Fig. 1). To identify genetic variants associated with progression from PD to PDD (Supplementary Table 2), we performed a longitudinal genome-wide survival study (GWSS) (Fig. 1 and Methods) on the remaining 3,821 patients. We assigned 2,650 patients and 11,744 visits to the discovery population (n=3,821 cases with PD tracked in 31,053 longitudinal visits for up to 12 years). Each point represents a SNP. The dashed red line corresponds to the genome-wide significance threshold. Covariate-adjusted survival curves for patients with PD without the RIMS2 rs182987047 variant (light blue line) and for those carrying the variant (dashed magenta line). Cox PH model with two-sided Wald test. Adjusted mean MMSE scores across time predicted from the estimated fixed-effect parameters in the LMM analysis are shown for cases carrying the RIMS2 rs182987047 variant (magenta) and cases without the variant (non-carriers; light blue) adjusting for covariates. Shaded ribbons indicate ± standard error of the mean (s.e.m.) across time. P values from LMM.

Fig. 1 | Within-cases longitudinal GWSS identifies three loci associated with progression to PDD. a, Manhattan plot of the GWSS. −log10[P value] from the Cox proportional hazards (Cox PH) model with two-sided Wald test for 12-year survival free of dementia are plotted against chromosomal position for the combined population (n=3,821 cases with PD tracked in 31,053 longitudinal visits for up to 12 years). Each point represents a SNP. The dashed red line corresponds to the genome-wide significance threshold. b, Covariate-adjusted survival curves for patients with PD without the RIMS2 rs182987047 variant (light blue line) and for those carrying the variant (dashed magenta line). Cox PH model with two-sided Wald test. c, Adjusted mean MMSE scores across time predicted from the estimated fixed-effect parameters in the LMM analysis are shown for cases carrying the RIMS2 rs182987047 variant (magenta) and cases without the variant (non-carriers; light blue) adjusting for covariates. Shaded ribbons indicate ± standard error of the mean (s.e.m.) across time. P values from LMM.
patients who were non-carriers, with $P = 0.0014$ (Fig. 1c) in the LMM adjusting for fixed covariates of age, sex, disease duration upon enrollment, years of education, ten principal components, and random effects (Methods). The RIMS2 variant was not associated with motor progression (Supplementary Fig. 5), possibly due to power and design limitations (confounding from PD medications, which treat motor symptoms but not dementia).

RIMS2 (chromosome 8) encodes the regulating synaptic membrane exocytosis 2 protein, a RIM family member, which is involved in docking and priming of presynaptic vesicles\(^\text{41,42}\). Mutations in RIMS2 cause cone-rod synaptic disorder syndrome (MIM 618970)\(^\text{43}\). In mice, knockout of the RIMS2 ortholog leads to critical defects in memory\(^\text{44}\). The paralogs RIM1 (chromosome 6) is a PD susceptibility locus\(^\text{45}\) that was not associated with progression. Human RIMS2 showed preferential expression in brain compared to 53 tissues (GTEx\(^\text{45}\); Extended Data Fig. 4) with high expression in dopamine and pyramidal neurons laser-captured from 86 and 13 human brains, respectively (BRAINcode\(^\text{46}\); Extended Data Fig. 5).

Two suggestive association signals were located in transmembrane protein 108 (TMEM108, NC_000003.11:g.132985956A>C) and WW domain containing oxidoreductase (WWOX; NC_000016:9:g.78281160A>G) loci, respectively (Fig. 1a). These loci achieved genome-wide significance ($P < 5 \times 10^{-8}$) in the combined analysis of discovery and replicate populations with suggestive $P < 5 \times 10^{-5}$ in the discovery and $P < 0.05$ in the replication cohort (Table 1). These two loci can now be prioritized for further evaluation. Six additional loci reached genome-wide significance in the discovery cohort but were not replicated (Supplementary Table 3 and Supplementary Fig. 4). The rs138073281 variant in the TMEM108 locus, which is implicated in synaptic spine formation\(^\text{47}\) and cognition\(^\text{48}\), was associated with cognitive progression\(^\text{48}\), was asso-

Table 1 | Variants linked to progression from PD to PDD

| Chr. | Position (Mb) | SNP | Risk allele | RAF | HR | 95% CI | $P$ discovery | $P$ replication | $P$ combined | Nearest gene |
|------|--------------|-----|-------------|-----|-----|--------|--------------|----------------|---------------|--------------|
| 8    | 105.25       | rs182987047 | T   | 0.013 | 4.77 | 3.01-7.56 | 1.16 x 10^{-9} | 4.14 x 10^{-5} | 2.78 x 10^{-11} | RIMS2       |
| 3    | 132.99       | rs138073281 | C   | 0.017 | 2.86 | 1.98-4.13 | 3.43 x 10^{-5} | 4.23 x 10^{-5} | 2.09 x 10^{-8} | TMEM108     |
| 16   | 78.28        | rs8050111  | G   | 0.066 | 2.12 | 1.63-2.75 | 1.08 x 10^{-6} | 0.01           | 2.37 x 10^{-8} | WWOX        |

Hazard ratio for developing PDD in patients with PD carrying a risk allele. Three variants were imputed, and imputation accuracy was confirmed by WGS. Bold font, replicated association; regular font, suggestive associations. Chr., chromosome; RAF, risk allele frequency; HR, hazard ratio from the combined analysis. $P$ values from Cox proportional hazards models with two-sided Wald test.

It has been assumed that GWAS-derived susceptibility variants constitute progression drivers with limited evidence (for example, ref. \(^\text{55}\)). The aggregate effect of 90 GWAS-derived susceptibility loci\(^\text{56}\) can be captured in a polygenic risk score (PRS) (Methods) that estimates the cumulative genetic susceptibility for PD\(^\text{56}\). We tested the PRS for association with dementia prognosis in our longitudinal PD cohorts. Contrary to expectation, no statistically significant association between PRS and progression to PDD was found in the Cox analysis (HR = 0.95, 95% CI, 0.80–1.13, $P = 0.57$). The area under the curve (AUC) for 10-year prediction of PDD was 0.496 (95% CI 0.444–0.548; Table 2 and Fig. 3a), which was not different from chance. Furthermore, we compared patients in the highest PRS quartile to those in the lowest PRS quartile using survival curves (Fig. 3b, $P = 0.91$) and LMM (Extended Data Fig. 6) and detected no appreciable differences. Individually, none of the 90 susceptibility variants achieved multiple-testing-corrected significance thresholds for predicting PDD (Supplementary Table 5). They were also not significantly linked to motor progression in PD as measured by transition to HY (Hoehn and Yahr) stage 3 using Cox model analysis and change in the MDS-UPDRS (Movement Disorder Society–sponsored revision of the unified Parkinson’s disease rating scale) part III subscale score by LMM model analysis, respectively, adjusting for covariates (Supplementary Data 1). There was no correlation between the statistical power to detect effects at these SNPs and the observed $P$ values (Pearson correlation $r^2 = 0.016, P = 0.88$). This suggests that genetic variants and scores linked to susceptibility are not significantly associated with cognitive progression.

We then used the lead variant from each of the three prognosis loci to develop an innovative cognitive polygenic hazard score (PHS) to predict PD dementia (Methods). The HR was 2.54 (95% CI 2.10–3.08) with $P = 4.51 \times 10^{-20}$ for a one-unit value increase in PHS. The PHS was associated with prediction of PDD with a 10-year cumulative AUC of 0.589 (95% CI 0.552–0.626; Fig. 3a). Out of 3,821 cases with PD, 688 (18%) carried at least one of the three novel progression alleles (rs182987047, rs138073281, rs8050111), of which 639 cases carried only one progression allele, 47 cases carried two risk alleles, and two cases carried three risk alleles. Cox proportional hazards analysis stratified for carriers of 1, 2 (either homozygous
or heterozygous for two loci) and 3 risk alleles compared to non-carrier cases indicated an additive effect with HRs of 2.79 (95% CI 2.12–3.67) with $P = 2.70 \times 10^{-13}$, 5.65 (95% CI 3.27–9.74) with $P = 4.81 \times 10^{-10}$, and 30.4 (95% CI 3.77–245.4), respectively.

We evaluated different genetic Cox proportional hazards models for prediction of PDD in the combined population (Table 2, Fig. 3a and Methods). The most robust genetic hazard model included the three new prognosis loci plus GBA and APOE (model concordance = 0.618). This PHS was a significant predictor of PDD in the new cohorts. The PRS was again not predictive of PDD in the new cohorts. AUCs in the independent development and validation stages were consistent; for example, 0.623 (95% CI 0.576–0.670) and 0.668 (95% CI 0.519–0.817), respectively (Table 2). Similarly, stratified covariate-adjusted survival analysis comparing cases scoring in the highest quartile of PHS with cases scoring zero on the PHS were consistent in development and validation stages, with HR $P = 0.623 (0.576–0.670)$ and 0.668 (0.519–0.817), respectively (Table 2). Similarly, stratified covariate-adjusted survival analysis comparing cases scoring in the highest quartile of PHS with cases scoring zero on the PHS were consistent in development and validation stages, with HR $P = 0.623 (0.576–0.670)$ and 0.668 (0.519–0.817), respectively (Table 2).

This study uncovered genetic variation linked to cognitive progression in PD with substantial effect sizes. These progression variants were not associated with susceptibility. Susceptibility variants and scores did not appear to predict progression. This is consistent with the hypothesis that disease initiation and progression may, in part, be governed by diverging genetics and mechanisms. Cognitive progression in PD strongly correlates with cortical spread of Lewy bodies and neurites. Furthermore, amyloid plaques and tangles present in up to one-third of patients. Our study indicates...
that genetic drivers of PD progression may comprise PD-specific loci (for example, *RIMS2* and potentially *TMEM108*), loci shared with dementia with Lewy bodies (for example, *APOE* and *GBA*), and possibly loci shared with Alzheimer’s disease (for example, *APOE* and *WWOX*). Analyses of larger longitudinal populations will be required to detect variants with small effect sizes, to increase statistical power for motor phenotypes confounded by PD medications, and to systematically decode the divergent and convergent features of the genetic architecture underlying susceptibility, progression and dementia.

These results suggest a new paradigm for drug development. Disease-modifying drugs that target the genetic drivers of disease progression could potentially turn fast progressors into slow progressors and substantially improve quality of life. Clinically, this study provides a polygenic score that could be used to enrich trials with patients who have a more aggressive disease course and are therefore likely to show the greatest benefits from interventions.

This may be useful because ascertaining therapeutic efficacy in patients who naturally progress slowly is exceedingly difficult.

**Online content**

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41588-021-00847-6.

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Methods

Study participants. Supplementary Table 1 describes the cohorts included in this work.

Discovery, replication and PHS development stages. We used 15 cohorts from North America and Europe to discover and replicate progression variants and to build the PHS. The 15 cohorts comprised a total of 4,872 patients with PD (with available genotyping data), who were longitudinally assessed with 36,123 study visits between 1986 and 2017 (Supplementary Fig. 1).

Written informed consent for DNA collection and phenotyping data collection for secondary research use for each cohort was obtained from the participants, with approval from the local ethics committees. The institutional review board of Partners HealthCare approved the current genotyping and analyses. For the Parkinson’s Progression Markers Initiative (PPMI), approval was obtained to download and analyze the publicly accessible WGS and clinical data. Patients with a diagnosis of PD were enrolled according to modified UK PD Society Brain Bank diagnostic criteria, as previously reported, who were recruited to 13 cohorts. In DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism), the eligibility criteria required a clinical diagnosis of early, idiopathic PD (HY stages 1 or 2) with patients not on anti-parkinsonian medications. For the Arizona Study of Aging/Brain and Body Donation Program, all subjects had come to autopsy and had full neuropathological examinations. Medications were excluded. For the Arizona Study of Aging/Brain and Body Donation Program, NET-PD LS1, CamPaIGN (Cambridgeshire Parkinson’s Disease Biomarkers Program) and PPMI cohorts and converted to MMSE scores according to published formulas. SCOPA-COG (scales for outcomes in Parkinson’s disease-cognition) were collected in PROPARK (Profiling Parkinson’s Disease Biomarkers Program) and PROPARK-C cohorts comprised the discovery population and 21 patients were excluded due to left-censoring. Thus, a total of 404 patients with 1,028 visits were used in the PHS validation stage.

Genotype imputation. Genotype imputation was performed using Minimac3 (v1.0.1.0; on the Michigan online mapping server). The haplotype reference consortium (HRC version r1.1) was selected as the reference panel. This consists of 64,940 haplotypes of predominantly European ancestry with ~39.2 million SNPs, all with an estimated minor allele count of ≥50. Eagle2 (v2.30) with 20-Mb chunk size was used to estimate haplotype phasing: pipeline details, including quality check, phasing and imputation, are available at https://imputationserver.sph.umich.edu. Samples from all discovery and replication cohorts were prephased and imputed in a single batch to avoid batch effects attributable to the imputation process: Multi-Ethnic Genotyping Array (MEGA) data of 4,020 subjects with PD with 1,635,580 SNPs at autosomes were used as input for the online server. To estimate imputation accuracy, imputed genotype calls for 1,052,012 SNPs were compared to directly genotyped data using Empir to calculate the proportion between the true genotyped values and the imputed values from the output of Minimac3. Mean R2 was 0.996 and Empir was 0.997 for variants with MAF ≥ 0.1% (Supplementary Fig. 2). Imputed variants with MAF < 0.1% and/or R2 < 0.05 were excluded. In total, 11,120,132 imputed SNPs remained for further analysis (Supplementary Fig. 2). In addition, we removed 2,785 variants with discordant of 6.7 years (interquartile range, 4.2 years). We therefore focused our survival analyses on the 12-year time frame from disease onset. In total, 3,821 samples passed genotyping and clinical data quality control (Extended Data Fig. 1). Patients were left-censored and those with missing or non-quality clinical data were excluded (n = 670; Extended Data Fig. 1). Specifically, 24 were excluded for whom clinical data were not available. Another 646 patients were excluded owing to missing critical individual data points or left-censoring (Extended Data Fig. 1) (for example, 138 participants already had PDD at the baseline visit and were left-censored; 39 subjects had missing data for age at onset or age at the baseline visit; 238 subjects had a first study visit that occurred more than 12 years from disease onset; and 231 were missing dementia ascertainment data). To identify genetic variants associated with progression from PD to PDD, we performed a longitudinal GWSS on these 3,821 patients, of whom 2,650 (and 11,744 visits) were assigned to the discovery population, and 1,171 (and 19,309 visits) were assigned to the replicate population.

PPMI and HBS whole-genome sequencing datasets. The PPMI and HBS data sets containing 86,998 LD-independent SNPs were merged with the 1000 Genomes Project data set. Principal component analysis (smartPCA) was used to identify and exclude the geographical outliers.

Genotyping and data quality control and processing. Quality control steps to discovery or replication cohorts to achieve an approximately two-thirds to one-third split in the two stages. (for example, 138 participants already had PDD at the baseline visit and were left-censored; 39 subjects had missing data for age at onset or age at the baseline visit; 238 subjects had a first study visit that occurred more than 12 years from disease onset; and 231 were missing dementia ascertainment data). To identify genetic variants associated with progression from PD to PDD, we performed a longitudinal GWSS on these 3,821 patients, of whom 2,650 (and 11,744 visits) were assigned to the discovery population, and 1,171 (and 19,309 visits) were assigned to the replicate population.

Genotyping and data quality control and processing. Quality control steps were collected in PDBP (Parkinson’s Disease Biomarkers Program) and PPMI cohorts and converted to MMSE scores according to a published formula. SCOPA-COG (scales for outcomes in Parkinson’s disease-cognition) were collected in PROPARK (Profiling Parkinson’s Disease Biomarkers Program) and PROPARK-C (PROPARK-cross sectional cohort) and NET-PD Long term study (LS1) cohorts and converted to MMSE scores. Cohort-specific definitions of PDD were used (Supplementary Table 2). For seven cohorts, operationalized level 1 diagnostic criteria for PDD according to the Movement Disorders Society Task Force were available; PreCEPT (Parkinson Research Examination of CEP-1347 Trial) and DATATOP used distinct definitions. PreCEPT defined PDD as a score of 4 on the UPDRS subscale 1 item 1 defined as ‘cognitive dysfunction’ [that] precludes the patient’s ability to carry out normal activities and social interactions. For DATATOP published criteria for cognitive impairment leading to functional impairment were used. Depression status was defined according to cohort-specific assessments. Ancestry was self-reported. For several cohorts, this was also evaluated previously collected longitudinal phenotypic data: for the active HBS, PDBP and DGGP (Drug Interaction with Genes in Parkinson’s Disease) cohorts, both retrospectively and prospectively collected longitudinal data elements were included. HBS, Arizona Study of Aging/Brain and Body Donation Program, NET-PD LS1, CamPaIGN (Cambridgeshire Parkinson’s Incidence from GP to Neurologist), PICNICS (Parkinsonism: Incidence, Cognitive and Non-motor symptoms in the Community), INGPD, PDBP, PDBP-Park, PROCEP and PROCEP-C comprised the discovery population and DATATOP, PPMI, PreCEPT and Tartu the replicate population.

PHS validation stage. To avoid overfitting, we tested the performance of the pre-specified PHS in 520 patients from three independent cohorts with detailed longitudinal clinical phenotyping; DeNoPa, EPIPARK and HBS2 (Supplementary Table 1), from Germany and the United States. These three longitudinal PD cohorts were not used to discover and replicate progression variants, or to build the PHS. PD was diagnosed in these cohorts according to modified UK PD Society Brain Bank diagnostic criteria. Cohort-specific definitions of PDD are listed in Supplementary Table 2.

Genotyping and data quality control and processing. Quality control steps are shown in Extended Data Fig. 1. In brief, the DNA of patients with PD was quality controlled on an Agilent 2100 Bioanalyzer. DNA was quantified against an eight-point standard curve using the Quanti-IT Picogreen dsDNA Assay Kit (Life Technologies, P7589) with a SpectraMax Gemini plate reader from Molecular Devices. Sample were genotyped at the Translational Genomics Core of Partners HealthCare using the Illumina Multi-Ethnic Genotyping Array (MEGA A1), which includes 1,779,819 markers (MEGA array kit, Illumina, WG-316–1001). DNA was amplified using a whole-genome amplification process. After fragmentation of the DNA, the sample was hybridized to 50-mer probes attached to the BeadChips, stopping one base before the interrogated base. Single base extension was then carried out to incorporate fluorescently labeled nucleotides with contained allowing the nucleotide to be detected by the iSCAN reader. Data from the iSCAN were collected in the Illumina LIMS and automated conversion to genotype occurred using AutoCall v2.0.1. In total, 4,510 PD samples were genotyped with the MEGA array; 512 PD samples from the PPMI had whole-genome sequences available.

We used PLINK (v1.90 beta) and in-house scripts to conduct genotyping data processing and perform rigorous subject and SNP quality control (Extended Data Fig. 1). SNPs with overall missingness > 0.05 were excluded. Samples with mismatched sex were excluded. Samples with a genotype missingness > 0.05 or heterozygote rate > 4.0 s.d. from the mean were also excluded. To check relatedness among samples, 279,933 LD-independent SNPs were selected and pairwise identity by descent was estimated using PLINK routine ‘--indep 50 5 2’. For any related sample (pi-hat between 0.1875 to 0.9) , one case with higher genotyping call rate was selected and kept, and the others were excluded. For those sample pairs with pi-hat > 0.9, both cases were excluded. To identify geographical outliers, a pruned data set containing 86,998 LD-independent SNPs were merged with the 10,000 Genomes Project data set . Principal component analysis (smartPC) was used to identify and exclude the geographical outliers.

For 4,491 patients with PD, 31,885 (95.4%) of visits occurred within 12 years of diagnosis follow-up visit. For 520 independent patients from DeNoPa, EPIPARK and HBS2, the same genotyping quality control was performed, and 425 samples passed quality control and 21 patients were excluded due to left-censoring. Thus, a total of 404 patients with 1,028 visits were used in the PHS validation stage.

Download the data

Acknowledgements

We thank all PD patients and their families who participated in the studies, as well as study nurses, research coordinators, and other study personnel. We thank A. Singleton for collecting and managing the PPMI and HBS whole-genome sequencing datasets. We thank the Illumina TruSeq PCR Free DNA sample Preparation Guide. The libraries were sequenced using a Illumina HiSeq X Ten Sequencer. Detailed methods are available at https://ida.loni.ucla.edu/pages/access/geneticData.jsp.
Candidate loci GBA and APOE. GBA gene variants were defined as described, and included pathogenic mutations associated with Gaucher's disease as well as the PD-association coding risk variants (E326K, T369M and E388K). We previously reported that the GBA gene variants are primarily based on targeted resequencing (128–128k (2013)).

We performed a genome-wide association study (GWAS) of 2,625 of the 4,491 patients with PD included here. For the remaining 1,866 patients with PD, GBA variants and mutations were identified based on the MEGA array. Participants were classified as carriers (with one or more GBA mutations) or non-carriers (no GBA mutation) as reported.

APOE alleles ε2 ε3 and ε4 were identified based on rs7412 and rs429358 from MEGA chip plus imputation data (14 cohorts) or WGS (PPMI cohort). We compared imputed APOE alleles of 313 HBS patients with PD to the results of a TaqMan SNP genotyping assay for the two SNPs. The concordance rate was 98.7%. We classified the 4,491 patients with PD into three groups for downstream analysis: 81 homozygous ε4 carriers (ε4/ε4), 1,068 heterozygous ε4 carriers (ε2/ε4, ε3/ε4), and 3,342 non-ε4 carriers (ε2/ε2, ε2/ε3, ε3/ε3).

Statistical analysis. The Cox proportional hazards statistic was used to estimate the influence of each genotype on time (years from onset of PD) to reaching the endpoint of PDD. Age at onset of PD, sex, years of education, and the top ten principal components of population substructure were included as covariates in the Cox analyses. For the meta-analyses across cohorts, a 'cohort' term was included as a random effect (a random effects Cox model is often termed a 'frailty' model). Regarding 'cohort' as a random term will permit inferences about study level variance among a hypothetical universe of studies in the reference population. For 4,491 patients with PD, 51,885 (95.4%) of visits occurred within 12 years of longitudinal follow-up from disease onset with a median follow-up time of 6.7 years (interquartile range, 4.2 years). We therefore focused our survival analyses on the 12-year time frame from disease onset. Cox proportional hazards analyses were performed using the coxph function in the Survival package (v2.38–1) in R, and the 'Breslow' method was used for handling observations that have tied survival times. P values of less than or equal to 5 × 10−8 were considered indicative of genome-wide significance.

Generalized longitudinal mixed fixed and random effects analysis (LMM) of cognitive decline was performed using serial MMSE scores longitudinally assessed (enrollment visit and multiple longitudinal follow-up visits) in the combined data set. The PROPARK-C and Tartu cohorts were excluded from the LMM because no longitudinal MMSE scores were available. The MMSE score was the dependent variable and the primary predictors were group status (for example, genotype carrier status or alleles), time in the study (years), and their interaction. An intercept term and linear rate of change in time per subject were the random terms (permitted to be correlated). Subject-level fixed covariates were age at baseline, sex, years of education, duration of PD illness at baseline, as well as ten principal components. A study term was included as a random effect. The significance, direction and effect size of the group × time terms answers the question of differential progression for the carriers, compared to the non-carrier group. To avoid problems with somewhat non-normal residuals for MMSE, P values were obtained by penalized quasi-likelihood ratio tests of the full model with the effect in question contrasted with the model without the effect in question. This analysis was performed using the glmmPQL function in the MASS package (v7.3–37). All analyses were conducted in the R statistical environment, v3.3.1. Nominal P values (not adjusted for multiple testing) were shown except where indicated otherwise. Evidence for genome-wide significance in the discovery population was defined as P ≤ 5 × 10−8; P values ≤ 0.05 were considered evidence of significance in the replicate population and in the PHS validation population. Associations for previously established candidate loci were considered significant if they met Bonferroni-adjusted significance thresholds (for example, 0.05/number of established candidates evaluated).

Polygenic risk score. A PRS was calculated as the weighted sum of the number of risk alleles possessed by an individual, in which the weight was taken as the natural log of the odds ratio associated with each individual SNP. We used 90 lead GWAS variants associated with susceptibility for PD and the odds ratios from a recent meta-analysis study21 to calculate the PRS (Supplementary Table 5).

Polygenic hazard score. For each patient in this study, we calculated a PHS using a similar method to that described in ref. 21. We used the hazard ratios of the lead associated SNPs (from the combined data set) in each of the three prognosis loci to calculate the PHS. In brief, we added the number of risk alleles (0, 1 or 2) for a lead variant multiplied by the effect size (natural log of hazard ratio from combined dataset) for that variant. In other versions of the PHS, we additionally included one of the candidates for cognitive prognosis genes (GBA mutation status and APOE ε4 allele haplotype). To evaluate the performance of the PHS models, the cumulative or dynamic receiver operating characteristic (ROC), AUCs, confidence intervals of the AUC (simulation method), and comparisons between two AUCs were calculated using the timeROC package (v0.2.7) in R with the inverse probability of censoring weights method used to compute the weights.

Characterization of genomic risk loci. We used FUMA (http://fuma.ctglab.nl) to characterize the cognitive prognosis loci. Tag SNPs with suggestive P < 1 × 10−6 were input; additional SNPs in high LD with a tag SNP (with r2 > 0.6 and independent from each other with r2 < 0.6) were identified using the 1000 Genomes Phase 3 reference panel for Europeans. If LD blocks of independent single nucleotide polymorphisms (SNPs) were closely located to each other (r2 < 0.5 based on the most right and left SNPs from each LD block), they were merged into one genomic locus.

Gene expression analysis. Gene expression profiles of the three significant loci included tissues was imaged directly from GTEx portal v7 (https://gtexportal.org/). Downloaded gene expression profiles were normalized. Detailed processing methods can be found in the GTEx portal v7. Human brain cell type-specific expression of the three cognitive prognosis loci was evaluated using the BRAINcode dataset and portal (http://www.humanbraincode.org).

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability
A Nature Research Reporting Summary is available for this paper. Human brain cell type-specific expression data from BRAINcode RNA-seq data are accessible through a user-friendly webportal at http://www.humanbraincode.org and individual-level data through dbGaP (accession no. phs001556.v1.p1). The gene expression profiles of human tissues used in this study can be downloaded from the GTEx Portal v7 (https://gtexportal.org/). The GWSS summary statistics for the combined analysis of discovery and replicate populations are publicly accessible through the EGA database at https://ega-archive.org/ (accession no. EGAS000010005110). Individual-level genetic data for the NIH-funded Illumina MultiEthnic Genotyping Array analyses of the HBS2 and EPIPARK cohorts are accessible in dbGaP with accession no. phs002328.v1.p1 in accordance with NIH Genomic Data Sharing Policy. The WGS and clinical data for PPMI included in this study are publicly available upon request to pppi@ioni.usc.edu through a PPMI Whole Genome Sequencing Data Agreement. Clinical data for PDDB included in this study are publicly available through https://pdhp.nds.nih.gov. Clinical longitudinal data for the other cohorts included are accessible through appropriate data sharing agreements that protect patient privacy with the institutions that conducted or are conducting study consents and clinical assessments under local institutional review board approvals.

Code availability
Analysis code is available at https://github.com/sixguns1984/GWSS.PDD.

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Author contributions

C.R.S. conceived and designed the study. G.L. contributed to the study design, and carried out the statistical and bioinformatics analyses with J.P., J.J.L. and C.R.S. X.D. contributed to the analysis. Z.L. and S.S.A. performed genotyping. Patient samples and phenotypic data were collected by J.-C.C., F.Z., J.M., G.M.C.C., A.E., S.L., A.B., G.M., J.H.G., A.Y.H., M.A.S., M.T.H., A.-M.W., T.M.H., B.R., I.S., S.K., P.T., T.G.B., F.C.-D., G.A., O.-R.T., J.S.P., P.H., J.J.v.H., R.A.B., C.H.W.-G., J.M., M.K., C.K., C.T., B.M. and C.R.S. C.R.S. and G.L. drafted the manuscript. All authors reviewed, edited and approved the manuscript prior to submission.

Competing interests

Brigham and Women's Hospital holds a US provisional patent application on the PHS for predicting PD progression, on which C.R.S. is named as inventor. Outside this work, C.R.S. has served as consultant, scientific collaborator or on scientific advisory boards for Sanofi, Berg Health, Pfizer and Biogen, and has received grants from the NIH, US Department of Defense, American Parkinson Disease Association, and the Michael J Fox Foundation (MJFF). G.L., J.J.L., J.M., A.E., J.H.G., A.Y.H., S.K., P.T., S.A., J.S.P. and M.C.C. report no relevant financial or other conflicts of interest in relation to this study. M.A.S. has no conflict of interest related to this work. Outside this work, M.A.S. has received grants from NINDS, DoD, MJFF, Farmer Family Foundation, and has served as a consultant to commercial programs for Eli Lilly & Co (data monitoring committee), Prevail Therapeutics (scientific advisory board), Denali Therapeutics (scientific advisory board), NQ Medical (scientific advisory board), Chase Therapeutics (scientific advisory board) and Partner Therapeutics (scientific advisory board). A.-M.W. has received research funding from the ALS Association, the Parkinson’s Foundation, has participated in clinical trials funded by Acorda, Biogen, Bristol-Myers Squibb, Sanofi/Genzyme, Pfizer and Abbvie, and received consultant payments from Mitsubishi Tanabe and from Accordant. T.M.H. has no conflict of interest related to this work. Outside this work, he has received honoraria for consulting in advisory boards for Boston Scientific and Medtronic, J.-C.C. has no conflict of interest related to this work. Outside this work, J.C.C. has received honoraria for consulting in advisory boards for Abbvie, Actelion, Air Liquide, Biogen, BMS, BrainEve, Clevelex, Denali, Pfizer, Theranexus and Zambon. B.R. is an employee of and holds equity in Praxis Precision Medicines and is advisor for Caraway Therapeutics and Bram Neurotherapy Bio. I.S. is Principal Investigator of a MJFF Computational Science Grant (2017–19). S.K. is supported by Multiple Sclerosis of Western-Australia (MSWA) and the Perrin Institute. P.H. is a Scientific Advisor of Neuron23. J.J.v.H. has no conflict of interest related to this work. Outside this work, J.J.v.H. has received grants from the Alkemade-Keuls Foundation, Stichting Parkinson Fonds, Parkinson Vereniging, the Netherlands Organisation for Health Research and Development, the Netherlands Organisation for Scientific Research, Hersenstichting, AbbVie, MJFF, and research support from Hoffmann-La Roche, Lundbeck and the Centre of Human Drug Research. B.M. has no conflict related to this work. Outside this work, B.M. has received honoraria for consultancy from Roche, Biogen, AbbVie, Servier and Amprion. B.M. is member of the executive steering committee of the Parkinson Progression Marker Initiative and Principal Investigator of the Systemic Synchronisation Sampling Study of the MJFF for Parkinson's Research and has received research funding from the Deutsche Forschungsgemeinschaft (DFG), EU (Horizon2020), Parkinson Fonds Deutschland, Deutsche Parkinson Vereinigung, Parkinson’s Foundation and MJFF. R.A.B. has no conflict of interest related to this work. Outside this work, R.A.B. has received consultancy monies from LCT, FCDI, Novo Nordisk, Cellino, Sana, UC, has received royalties from Wiley and Springer Nature, grant funding from CPT, NIHR Cambridge Brainimaging Research Centre and the UK Medical Research Council (MRC), Wellcome Trust (201511Z/16/Z) and Rosettes Trust (A1519 M654). C.H.W.-G. has no conflict of interest related to this work. C.H.W.-G. is supported by a RCUK UKRI Research Innovation Fellowship awarded by the MRC (MR/R007461/1) and the NIHR Cambridge Brainimaging Research Centre, and receives grant support from MJFF; the Evelyn Trust, the Cure Parkinson’s Trust, Parkinson’s UK, the Rosettes Trust and the Centre Cambridge for Parkinson-Plus. C.H.W.-G. has received honoraria from Lundbeck and consultancy payments from Modus Outcomes and Evidera. C.T. is supported by EU Grant Horizon 2020/propag-ageing and the MJFF. C.K. serves as a medical advisor to Centogene for genetic testing reports in the fields of movement disorders and dementia, excluding Parkinson’s disease.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41588-021-00847-6.

Supplementary information

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Peer review information

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Extended Data Fig. 1 | Genotyping pipeline for discovery and replication cohorts. Quality control (QC) steps outlined in blue were performed using PLINK v1.90beta7. Note that 509 samples with WGS from the PPMI cohort (after removing three with gender mismatches) were added in Step 10.
Extended Data Fig. 2 | Characteristics of loci associated with cognitive progression in PD. **a**, RIMS2 locus. **b**, TMEM108 locus. **c**, WWOX locus. Top, chromosomal position; middle, -log10(P values) for individual SNPs at each locus (left y-axis) with the rate of recombination indicated by the red line (right y-axis); bottom, gene positions with the locus. Each point represents a SNP colored according to LD with the lead associated variant. Figure panels were generated with LocusTrack and \( r^2 \) values were calculated based on CEU population in the 1000 Genomes Project data set.
Extended Data Fig. 3 | Associations between a second RIMS2 variant rs116918991, TMEM108 rs138073281, and WWOX rs8050111 with cognitive PD progression. a,c,e, Covariate-adjusted survival curves for PD patients without the indicated variant (blue line) and for those carrying the indicated variant (heterozygotes and homozygotes; red dashed line) are shown. P values Cox PH models with two-sided Wald test. b,d,f, Adjusted mean MMSE scores across time predicted from the estimated fixed-effect parameters of the LMM analysis are shown for cases carrying the variant (heterozygotes and homozygotes; red) and cases without the variant (non-carriers; blue) adjusting for covariates. Shaded ribbons indicate ± s.e.m. around predicted MMSE scores across time. Note that a second RIMS2 variant rs116918991 (correlated with $r^2 = 0.49$ with the lead variant rs182987047; Fig. 1) is shown in a and b, and that the HR and P values shown here for TMEM108 rs138073281 and WWOX rs8050111 are different from the HR and P values from the main analysis (Table 1), where variant alleles were coded as 0, 1, 2. P values from LMM analysis with two-sided t-test.
Extended Data Fig. 4 | RIMS2, TMEM108, and WWOX are expressed in human brain. Gene expression profiles were downloaded directly from the GTEx Portal V7\textsuperscript{e}. Expression values are shown in Transcript per Million (TPM), calculated from a gene model with isoforms collapsed to a single gene. Box plots visualize first, third quartiles and medians; the ends of the whiskers represent the lowest (or highest) value still within 1.5-times the interquartile range. Outliers are displayed as dots, if they are above or below 1.5-times the interquartile range. \( n \) indicates number of individuals for each tissue analyzed in GTEx V7.
Extended Data Fig. 5 | Cell-type specific expression of RIMS2, TMEM108, and WWOX in human brain. Cell type-specific transcriptomes were assayed using laser-capture RNA sequencing (lcRNAseq) as we reported\(^4\). Gene expression (FPKM) profiles of RIMS2, TMEM108, and WWOX are from BRAINcode consortium (http://www.humanbraincode.org). \(n\) indicates the number of individuals assayed for each cell type. SNDA, indicates dopamine neurons laser-captured from human substantial nigra pars compacta; MCPY, pyramidal neurons from human motor cortex; TCPY, pyramidal neurons from human temporal cortex; PBMC, human peripheral blood mononuclear white cells; FB, primary human fibroblasts. Box plots visualize first, third quartiles, and medians; the ends of the whiskers represent the lowest (or highest) value still within 1.5-times the interquartile range. Each dot represents a sample.
Extended Data Fig. 6 | The polygenic hazard score (PHS) is associated with decline in serial MMSE scores. a, PD cases scoring in the highest quartile (red) of a polygenic risk score (PRS based on 90 susceptibility variants \(^45\)) compared to PD cases scoring in the lowest quartile of the PRS (blue) are shown. b, PD cases scoring in the highest quartile (red) of the PHS (comprising \(\text{GBA} + \text{APOE} \varepsilon 4 + \) the 3 novel progression variants) compared to PD cases scoring zero on the PHS (blue) are shown. For a and b, adjusted mean MMSE scores across time predicted from the estimated fixed-effect parameters in the LMM analysis for the combined data set comprising discovery and replication populations are shown. The shaded ribbons indicate ± s.e.m. around predicted MMSE scores across time. The \(P\) values from LMM analysis with two-sided \(t\)-tests.
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- For null hypothesis testing, the test statistic (e.g. F, t, r) with confidence intervals, effect sizes, degrees of freedom and P value noted
- For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
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**Software and code**

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**Data collection**

- No software was used for data collection.

**Data analysis**

Genotype imputation was performed using Minimac3 (v2.0.1) on the Michigan online imputation server. The SnpSift tool (v4.0) was used to evaluate the concordance between imputed SNPs (based on the MEGA array) and SNPs directly called from whole genome sequencing in 562 individuals from HBS for which both assays were available. Cox proportional hazards analyses were performed using the coxph function in the Survival package (version 2.38-1). Generalized longitudinal mixed fixed and random effects analysis was performed using the glmmPQL function in the MASS package (version 7.3-37) in R (version 3.3.1). R version 3.3.1 was also used to compute polygenic hazard and polygenic risk scores as described in the methods. Analysis code is made available in https://github.com/sixguns1984/GWSS.PDD. To evaluate the performance of the PHS models, the cumulative/dynamic receiver operating characteristic (ROC) curves, area under curves (AUC), confidence intervals of the AUC (simulation method), and comparisons between two AUCs were calculated using the timeROC package (Version 0.2) in R (version 3.3.1). FUMA (v1.3.3; http://fuma.ctglab.nl) was used to evaluate prognosis loci.

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A Life Sciences Reporting Summary for this paper is available. Human brain cell type-specific expression data from BRAINcode. RNAseq data are accessible through a user-friendly webportal at www.humanbraincode.org and individual-level data through dbGAP (acc. number phs001556.v1.p1). The gene expression profiles of
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All studies must disclose on these points even when the disclosure is negative.

Sample size

| No sample size calculations were performed. Sample sizes were chosen based on availability of cohorts. |

Data exclusions

| Sample and variant quality control was performed as outlined in the methods. Samples not meeting Q/C criteria were excluded as shown in Extended Data Figure 1. The exclusion criteria of genotyping Q/C were pre-established. In genome-wide survival analysis, total 6/10 patients were left-censored and those with missing or non-quality clinical data were excluded. |

Replication

| Progression variants meeting genome-wide significance in the discovery phase were evaluated in an independent replication population once. Moreover, an exploratory joint phase (combined discovery and replication populations) meta analysis was conducted. The PHS score was developed in the PHS Development Stage population (combined discovery and replication populations) and evaluated in an independent PHS Validation Population once. All attempts at replication were successful. |

Randomization

| In this within cases longitudinal cohort study, PD patients were enrolled and longitudinally assessed; neither patients nor investigators were aware of an individual's whole genome genotyping status; after completion of longitudinal follow-up assessments, PD patients were assigned to carrier and non-carrier groups based on genotypes. |

Blinding

| Patients and investigators were blinded to the participants' whole genome genotyping data during enrollment and longitudinal follow-up. |

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

| n/a
| Involved in the study
| Antibodies
| Eukaryotic cell lines
| Palaeontology
| Animals and other organisms
| Human research participants
| Clinical data |

Methods

| n/a
| Involved in the study
| ChiP-seq
| Flow cytometry
| MRI-based neuroimaging |

Human research participants

| Policy information about studies involving human research participants |

Population characteristics

| Characteristics of the cohorts are described in Supplementary Table 1 and Supplementary Fig. 1. |

Recruitment

| All participants were recruited into individual cohorts as part of previous studies. The cohorts include population-based, incident cohort studies; purpose-built biomarkers studies with carefully standardized, highly comparable clinical and biospecimens collection methods; and carefully phenotyped, failed Phase III clinical trials. Genetic analyses were performed at the end of the clinical longitudinal follow-up period. Physicians therefore recruited and longitudinally assessed the participants without knowledge of their genotypes. This cohort study design is thought to be less vulnerable to recruitment and ascertainment bias than case-control studies. The population-based cohorts included in the analysis were designed to guard against self-selection bias, which may affect clinical trial cohorts. |
Written informed consent for DNA collection and phenotypic data collection for secondary research use for each cohort was obtained from the participants with approval from the local ethics committees. The Institutional Review Board of Partners HealthCare approved the current genotyping and analyses. For PPM, approval was obtained to download and analyze the publicly available WGS and clinical data.

Note that full information on the approval of the study protocol must also be provided in the manuscript.