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Genomic determinants of motor and cognitive outcomes in Parkinson's disease

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Abstract

Background—Little is known regarding genetic factors associated with motor or cognitive outcomes in Parkinson's disease (PD).

Objective—To identify common genetic variants associated with motor and cognitive outcomes in PD.

Methods—The sample consisted of 443 PD cases included in the first genome-wide association study (GWAS) of PD. Methods included telephone interview assessments of motor and cognitive outcomes, a median 9 years following the initial clinical assessments. Analyses included Cox proportional hazard models to study the association of 198,345 single nucleotide polymorphisms (SNPs) with survival free of Hoehn-Yahr Stage ≥4 (motor outcome), and either TICS-M ≤27 or AD-8 ≥2 (cognitive outcomes).

Results—The SNP rs10958605 in the *C8orf4* gene had the smallest *p*-value in analyses of the motor outcome (HR = 1.81; 95% CI = 1.42 – 2.31; $p = 1.51 \times 10^{-6}$). The SNP rs6482992 in the *CLRN3* gene had the smallest *p*-value in analyses of the cognitive outcome (HR = 2.03, 95% CI 1.47–2.79, $p = 4.08 \times 10^{-6}$). However, no SNP associations were significant after Bonferroni correction. The *C8orf4* gene had small *p*-values for both motor and cognitive outcomes, highlighting inflammation as a possible pathogenesis mechanism for progression in PD.

Conclusions—This study suggests that common variants in several genes may be associated with motor and cognitive outcomes in PD, with biological plausibility.

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Keywords

Genome wide association studies; Parkinson's disease; outcomes

INTRODUCTION

Parkinson's disease (PD) is characterized by progressive motor and cognitive impairment, resulting in a seven-fold increased risk of nursing home placement and a two-fold increased risk of death [1]. There is limited information regarding the long-term progression of motor and cognitive impairment in PD. A community-based prevalence cohort of 245 Norwegian PD cases was re-examined over 12 years [2, 3]. The mean annual decline in Hoehn and Yahr stage was 3.2% and correlated well with mean annual declines in the Unified Parkinson's Disease Rating Scale (UPDRS) and Schwab and England Scale of Capacity for Daily Living. By eight years, the mean annual decline in Mini Mental State Examination (MMSE) score was 1.1 points or a 3.9% change overall. By 12 years, dementia was documented in 60% of PD cases. A cohort of 149 Australian PD cases enrolled in a clinical trial was re-examined several times over 20 years [4, 5]. By 15 years, the mean Hoehn and Yahr stage was 4. By 15 years dementia was documented in 48% of cases, and by 20 years dementia was documented in 77% of cases. In both studies, there was considerable variability in the rates of progression of motor and cognitive impairment in PD. Factors associated with faster rates of motor and cognitive progression included older age at onset and akinetic-rigid subtype of PD [6].

There is also limited information regarding the genomic factors associated with survival free of motor and cognitive outcomes in PD. The few candidate gene studies of cognitive outcomes in PD employed small samples, considered only a few genes and variants, were mostly cross-sectional, and yielded non-significant, mixed, or non-replicated results [7–9]; there have been no candidate gene studies of longitudinal motor outcomes in PD. To our knowledge this is the first genome wide association study (GWAS) of motor and cognitive outcomes in PD.

METHODS

Subjects

We included 443 PD cases from the discovery phase ("tier 1") of a prior GWAS [10]. The sampling methods are as previously reported by that study. All cases were enrolled prospectively from the clinical practice of the Department of Neurology of the Mayo Clinic in Rochester, MN, from June 1996 through May 2004. They all resided within Minnesota or one of the surrounding four states (Wisconsin, Iowa, South Dakota, or North Dakota). All cases underwent a standardized clinical assessment performed by a neurologist sub-specialized in movement disorders. Cases had at least two of four cardinal signs of parkinsonism (rest tremor, rigidity, bradykinesia, and/or postural instability) and no features atypical for PD (such as unexplained upper motor neuron signs or cerebellar signs) [11]. The institutional review board of the Mayo Clinic approved the study, and all subjects provided written informed consent.

Genotyping

The genotyping methods were previously reported [10]. For each case, DNA was individually genotyped for a set of 248,535 single nucleotide polymorphisms (SNPs) with unique positions on National Center for Biotechnology Information (NCBI) build 34.

For the 248,535 SNPs selected, the genotyping call rate was >80% for 220,143 SNPs. Of these SNPs, 205,031 (93%) were polymorphic within the study sample. The Hardy-Weinberg equilibrium (HWE) *p* value was >0.001 for 198,345 SNPs (97% of polymorphic SNPs, with an average gap between adjacent SNPs of 12,363 bp) [10]. For these 198,345 informative SNPs, the genotype call rate was 98.1%. We regenotyped in triplicate 96 SNPs for each subject, with 99.8% concordance of genotypes. The concordance of genotypes called by the oligonucleotide array platform, as compared with genotypes called by other platforms employed as part of the multicenter HapMap project, was 99.5% [12].

Outcome measurements

For this study we designed scripted telephone interview questionnaires to collect motor, cognitive, and other outcome data for the 443 PD cases from the previous study (or to their proxy when incapacitated or deceased). The direct interview questionnaire collected demographic characteristics (marital status, place of residence including nursing home or assisted living and dates of admission, education and income levels), the Telephone Interview of Cognitive Status-Modified (TICS-M) [13], and Unified Parkinson's Disease Rating Scale (UPDRS) milestones (selected items from Parts 1 and 2, including hallucinations, falls, freezing, and inability to stand or walk unassisted, with start dates). We asked for permission and contact information to retrieve copies of medical records from care providers other than the Mayo Clinic. The proxy questionnaires collected the same information, with the exception of screening for dementia using the Alzheimer's Disease Dementia Screening Interview (AD-8) [14] rather than the TICSM because AD-8 is a brief informant-based measure that reliably differentiates between non-demented and demented individuals and is sensitive to the earliest signs of cognitive change as reported by a proxy informant. For deceased subjects, we obtained the date of death and a copy of their death certificates.

We measured the motor outcome at baseline via clinical assessment using the Hoehn and Yahr stage; we defined the motor outcome as Hoehn and Yahr stage 4 or 5 [15]. We measured the motor outcome at follow up via telephone interview; we defined the motor outcome as "no" in response to the question: "Are you able to stand or walk without someone else helping you or without a cane or walker?" (or appropriately reworded for proxy interviews). We considered a "no" response to the question as corresponding to Hoehn and Yahr stage 4 or 5. When the response was "no" we also asked: "At what age were you no longer able to stand or walk without assistance?" (or as appropriately reworded for proxy interviews). We measured the cognitive outcome at baseline via clinical assessment using the MMSE; we defined the cognitive outcome as MMSE <26. We measured the cognitive outcome at follow-up via telephone interview using the TICS-M (direct interviews) or the AD8 (proxy interviews); we defined the cognitive outcome as TICS-M score ≤27 or AD-8 score ≥2.

Statistical analysis

We performed survival analyses using Cox proportional hazard models. All models were adjusted for sex, disease duration at baseline, and type of interview (direct or proxy). We performed analyses primarily with a log additive genotype coding scheme and also with dominant or recessive coding schemes. Analyses of motor outcomes were also adjusted for LDOPA treatment at baseline, and analyses of cognitive outcomes were also adjusted for education. For each genetic variant we calculated a hazard ratio (HR), a 95% confidence interval (CI), and a two-tailed *p*-value. The *p*-values from primary analyses were assessed for significance using a Bonferroni correction. Manhattan plots and quantile-quantile (Q–Q) plots of *p*-values for 198,345 SNPs passing quality control were constructed for analyses of motor and cognitive outcomes. For SNPs showing greatest evidence of association with time

to motor or cognitive outcomes, the assumption of Cox's proportional hazards model was assessed by the analysis of scaled Schoenfeld residuals. There was no evidence of violation of the assumption of Cox's proportional hazards model in the cognitive outcome analyses. However, the proportional hazard assumption was violated (at a 0.05 significance level) for two SNPs (rs1412907 and rs1861114) in the analyses of motor impairment. Among the variables included as covariates in the models, the type of interview (direct or proxy) showed evidence of non-proportionality ($p<0.05$). Therefore, for the top SNPs in the motor and cognitive outcomes analyses, sensitivity analyses were performed using stratified Cox regression models that included the type of interview as a stratifying variable. In these analyses, the two SNPs rs1412907 and rs1861114 still violated the proportional hazard assumption (at the 0.05 level); the results for these two SNPs should therefore be interpreted with caution. Finally, sensitivity analyses that included age of onset as a covariate, in addition to the previously included covariates, were performed.

The statistical packages SAS® (version 9.2; SAS Institute Inc., Cary, NC) and R (version 2,14; R Development Core Team (2011). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/) were used for all analyses.

RESULTS

The demographic and clinical features of cases are described in Table 1. The 443 PD cases included 271 men (61.2%) and 172 women (38.8%). The median duration of PD at baseline was 3.5 years. The cases were primarily Caucasian of European origin.

At time of follow-up, 184 PD cases were contacted, as well as proxies for 103 incapacitated patients and 155 deceased patients. Only one case was lost to contact. Of the 184 PD cases that were contacted, 9 refused to participate. Four out of 103 proxies of incapacitated cases refused participation, and 12 out of 155 proxies of deceased cases refused participation. Thus, the overall participation rate for the telephone interview was 94.1% (95.1% direct, 96.1% proxy for incapacitated patients, and 91.7% proxy for deceased patients) (Supplementary Fig. 1). At follow-up telephone assessment, 44 directly interviewed PD cases had cognitive impairment (TICS-M ≤27), and they underwent repeated interviews (proxy interviews for incapacitated patients) in order to obtain dates of onset of motor and cognitive outcomes. Of the 417 cases that participated in the follow up study (via direct or proxy interview), 32 (7.7%) had motor outcomes (Hoehn and Yahr ≥4) at baseline, 31 (7.4%) had cognitive outcomes (MMSE <26) at baseline, and one did not have a baseline MMSE score available. They were removed from the motor or cognitive outcome survival analyses, respectively. The median lag time from baseline to follow-up assessment was 9 years (range, 4.7 – 12.6 years). The Kaplan-Meier curves for survival free of motor and cognitive outcomes in PD stratified by sex are shown in Supplementary Fig. 2. By 10 years following initial assessment, approximately 50% of PD cases assessed for at least 10 years survived free of Hoehn and Yahr stage ≥4 (motor outcome) and approximately 40% of PD cases assessed for 10 years survived free of TICS-M ≤27 or AD-8 ≥2 (cognitive outcome). There was significant difference in the survival free of cognitive outcomes between men and women: higher proportion of women survived free of cognitive outcomes than men (χ^2 = 5.9, p value = 0.015). In contrast, there was no significant difference in the survival free of motor outcomes between men and women (p value = 0.91).

We studied the association of 198,345 genomic SNPs with motor and cognitive outcomes, primarily using a log additive genotype coding scheme. The Q–Q plot for analyses of motor outcome shows an excess of likely true positives near the tail of the distribution, with no genomic inflation of the statistics (genetic control inflation factor, λ_{GC} = 0.995), while the

Q–Q plot for analyses for cognitive outcome demonstrates some evidence of genomic inflation (λ_{GC} = 1.10) (Supplementary Fig. 3). For survival free of motor outcomes, 9,857 SNPs had *p* values <0.05; this is consistent with the 9,917 associations with *p* values <0.05 expected by chance. None of these SNP associations were significant after Bonferroni correction. For survival free of cognitive outcomes, 12,199 SNPs were associated at *p* values <0.05; this is in excess of the 9,918 associations with *p* values <0.05 expected by chance. However, none of these SNP associations were significant after Bonferroni correction.

The Manhattan plots of the *p* values from both the motor and cognitive outcome analyses are shown in Fig. 1. Of the nominally significant SNPs in analyses for motor outcome, the most significant finding was for SNP rs10958605, which maps to the *C8orf4* gene (HR = 1.81, 95% CI = 1.42 – 2.31, $p = 1.51 \times 10^{-6}$). However, this SNP rs10958605 did not remain significant after Bonferroni correction. Other genes with low *p* values ($\leq 5 \times 10^{-5}$) include *RPS17P6, CACNB4, ANK2, ACTR3B, COL1A2, STARP1, EPB41L3, MAGI2, SNX6*, and *PLCB4* (Table 2). None of these genes or loci was previously highlighted by GWAS studies of PD.

Of the nominally significant SNPs in analyses for cognitive outcome, the most significant finding was for SNP rs6482992, which maps to the *CLRN3* gene (HR = 2.03, 95% CI = 1.47 – 2.79, $p = 4.08 \times 10^{-6}$). However, this SNP rs6482992 did not remain significant after Bonferroni correction. Other genes with low *p* values ($\leq 5 \times 10^{-5}$) include *C4orf26, LMNB1, C17orf68, RNU7-2P, TRPM3, C8orf4, ODF4, C9orf135, ITPR2, LOC100130088, FOXK2, SH3BGRL2, PRL, CAST,* and *NFYAP1* (Table 3). None of these genes or loci was previously highlighted by GWAS studies of PD susceptibility. Notably, SNPs in the APOE gene were not associated with cognitive outcomes. Only the *C8orf4* gene was associated with survival free of both motor and cognitive outcomes.

Sensitivity analyses with age at onset as a covariate demonstrated similar results to those obtained without age at onset in the model (Supplemental Tables 1 and 2). However, in the cognitive outcome analysis adjusted for age at onset, there was evidence of inflation of the association test statistics ($\lambda = 1.2$). Hence, we focus our report on findings from the analysis without age at onset in the model.

DISCUSSION

This is the first GWAS of motor and cognitive outcomes in PD. Prior GWAS evaluated PD susceptibility but not outcomes (http://www.genome.gov). Similarly, candidate gene studies and meta-analyses of genetic and genomic studies have focused on PD susceptibility but not outcomes (http://www.pdgene.org). Instead, we aimed to discover common genomic variants associated with motor and cognitive outcomes in PD, because the development of molecular prognostic tests and molecular targets for disease-modifying therapies are major unmet needs.

Although none of the SNPs that we studied were significantly associated with motor and cognitive outcomes in PD after correction for multiple testing, the SNPs with suggestive evidence of association should be investigated in independent samples. Regarding the motor outcome, the SNP rs10958605 in the *C8orf4* gene had the smallest *p*-value ($p = 1.51 \times 10^{-6}$). Another SNP in the *C8orf4* gene (rs7014749) also had a small *p*-value with respect to cognitive outcomes ($p = 1.2 \times 10^{-5}$). The *C8orf4* gene has not been previously implicated in PD. *C8orf4* is located on chromosome 8p11.2 and encodes a small, monomeric, predominantly unstructured protein that functions as a positive regulator of the Wnt/beta-catenin signaling pathway [16]. Interestingly, *C8orf4* gene is up-regulated by IL-1β, TNF-α, and diverse cellular stresses through activation of NF-κB in various cells, and is a regulator

of heat shock response [17]. Inflammatory mechanisms may contribute to the cascade of events leading to neuronal degeneration in PD [18–20]. Epidemiological studies support a role of inflammatory processes in the progression of PD [21]. Perhaps genetic variants in the *C8orf4* gene might affect the basal level of the inflammatory status and the response to inflammatory stimuli in PD, increasing the effect of inflammation on dopaminergic neuronal cell death. If replicated, our findings for the *C8orf4* gene might support the use of anti-inflammatory drugs to slow the progression of PD.

The SNP rs3768653 in the *CACNB4* gene also had a low *p* value (1.2×10^{-5}) in analyses of motor outcome. *CACNB4* is located on chromosome 2q22–23 and encodes a member of the beta subunit family of voltage-dependent Ca^{2+}-channel complex proteins. A recent clinical study reported a potential neuroprotective role for centrally acting Ca^{2+}-channel blockers of the dihydropyridine class in PD [23]. If replicated, our finding for the *CACNB4* gene might support the use of calcium channel blocking drugs to slow the progression of PD.

Regarding cognitive outcomes, SNPs with small *p*-values highlighted several genes. Our most significant finding was for the *CLRN3* gene. While the biological plausibility for the association of that gene with cognitive outcomes in PD is unclear, other SNPs with small *p*-values highlighted several other genes with biological plausibility. The *TRPM3* (9q21.12) encoded protein inhibits the activity of Akt protein kinases and is promoted by endoplasmic reticulum (ER) stress [24]. Similarly, the *ITPR2* gene (12p11) encodes a calcium channel on the ER that is primarily responsible for controlling intracellular calcium concentrations in neurons [25]. If replicated, our findings for the *TRPM3* and *ITPR2* genes might similarly support the use of calcium-channel blocking and anti-apoptotic therapies in PD.

Interestingly, a higher proportion of women PD patients survived free of cognitive outcomes than men. This sex difference in the cognitive outcomes may be due to neuroprotective effects of female sex hormone such as estrogen. We previously reported that women who underwent oophorectomy before menopause showed increased risk of cognitive impairment or dementia [26]. Further studies with adequate statistical power will be warranted to perform analyses of cognitive outcomes in sex specific strata.

Sensitivity analyses with age at onset as a covariate demonstrated similar results to those obtained in the primary analysis without age at onset. In particular, of the top association results that were the focus of our discussion, only the *CACNB4* SNP and *ITPR2* SNP did not have *p*-values $< 5 \times 10^{-5}$ in the adjusted analysis ($p = 5.9 \times 10^{-5}$ for association of CI with rs7302093 in *ITPR2*, and $p = 9.3 \times 10^{-5}$ for association of motor outcome with rs3768653 in *CACNB4*).

Our study is not only innovative, but it also has methodological strengths. First, our PD cases were well characterized at baseline and at follow up with respect to motor and cognitive outcomes. Second, our participation rates at baseline (~83%) and at follow up (~94%) were high and only one of 443 cases was lost to follow up. This degree of participation and follow up are exceptional for clinical studies. Third, the duration of the longitudinal follow up was long (about a decade). Fourth, we used outcome measures that are well validated and widely employed. Therefore it will be possible for others to generalize our findings to their patients and also to perform replication studies of our findings.

Our study also has methodological limitations. First, our sample size was small by comparison to recent GWAS of PD susceptibility. However, this is to our knowledge the only longitudinal cohort of PD with available GWAS data [27]. The effect sizes of SNPs associated with PD outcomes at the genomic significance level, and the necessary sample sizes to detect such associations, are empirically undefined. Second, the number of

genotyped SNPs was small by comparison to recent GWAS of PD susceptibility. However, this is to our knowledge the only GWAS of PD with available longitudinal data; imputation methods may also increase the genomic coverage provided by our SNPs. Third, our PD cohort was referral-based and the cases had variable lengths of PD duration at the time of enrollment. We tried to limit sampling bias by recruiting cases prospectively from a defined geographic region (the upper Midwest, USA) [11, 28]. We also included disease duration at baseline as a covariate in statistical models. Fourth, we used different screening tools for cognition at baseline and at follow up. However, the TICS-M or AD-8 used at follow up had been well validated and highly correlated with the MMSE used at baseline [13, 14]. Fifth, we did not study gene-gene or gene-environment interactions (beyond the scope of this initial exploratory study). Finally, we did not replicate our suggestive findings (e.g., SNPs with p-values $\leq 1 \times 10^{-5}$) in independent samples. Large-scale replications of GWAS of PD susceptibility are feasible within existing large consortia [29]. However, we are not aware of any PD consortia that are conducting large-scale longitudinal studies of PD or GWAS of PD outcomes. Although the Parkinson's Progression Biomarkers Initiative will enroll 400 newly diagnosed PD cases and follow them prospectively (http://www.ppmi-info.org/); only 35% of the cases were enrolled as of December 1, 2011 and with only one year follow up. Our study may prove useful in informing the design of large-scale GWAS of PD outcomes for the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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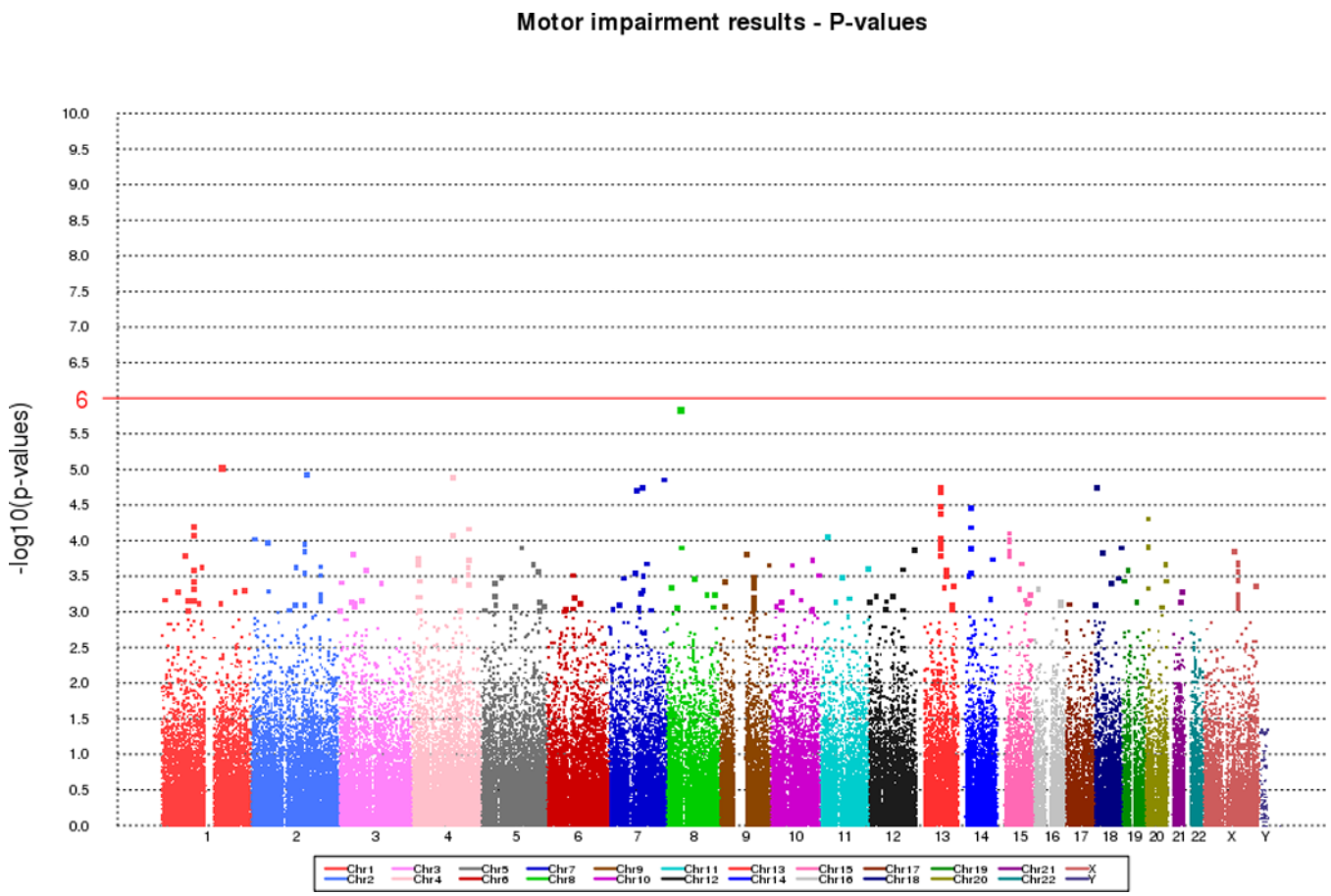

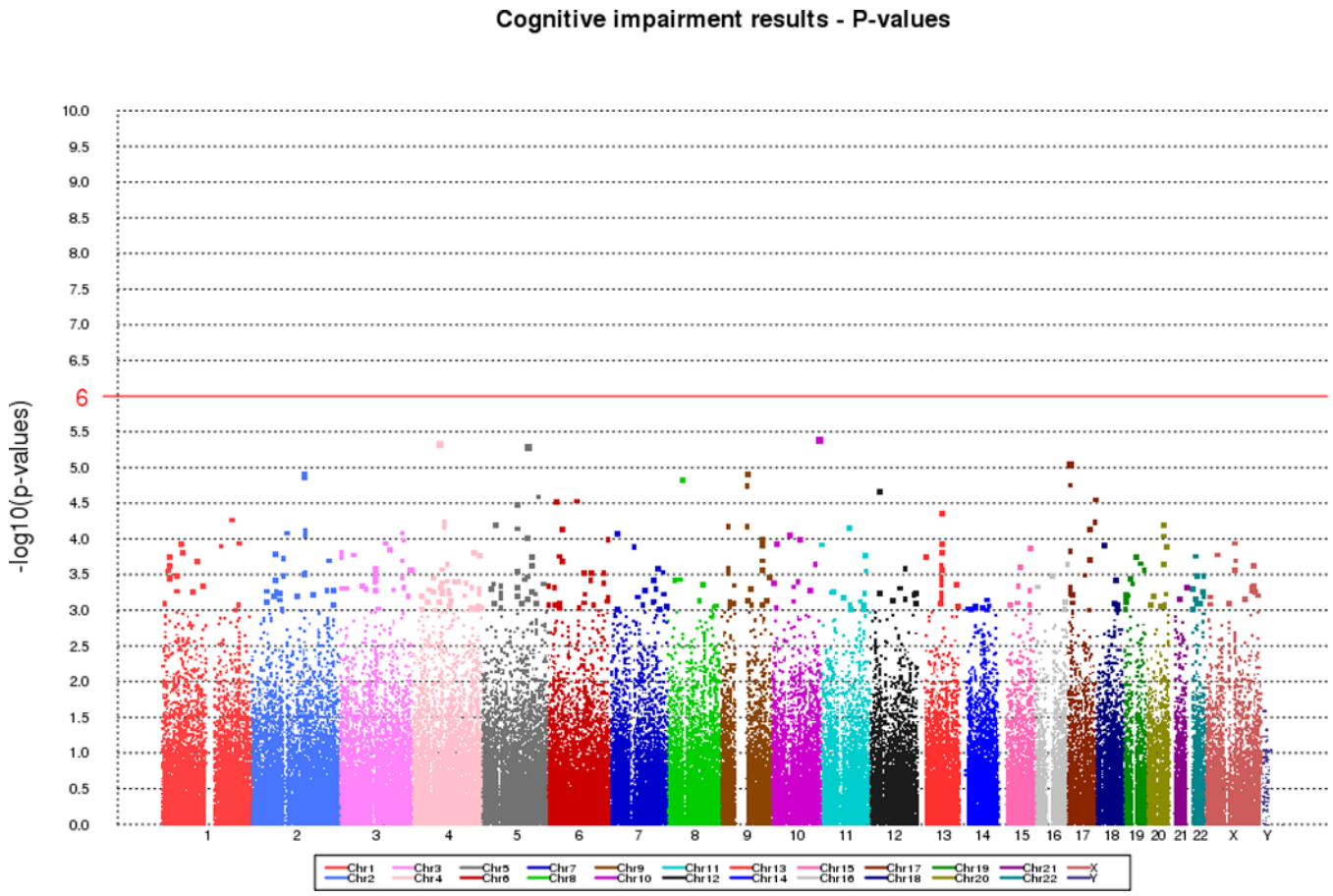

Figure 1.

Genome-wide association *p* values. The Manhattan plot shows the *p* value for association of 198,345 SNPs with motor (A) and cognitive (B) outcomes in Parkinson's disease. *P* values are log transformed (y axis) and plotted against chromosomal position (x axis). The red line indicates the Bonferroni-corrected significance threshold.

Table 1

Demographic and clinical characteristics of subjects

Characteristics	Findings for Subjects
Total sample, n	443
Men, n (%)	271 (61.2)
Women, n (%)	172 (38.8)
Age at onset of PD, median year (range)	61 (31 – 94)
Age at study, median year (range)[a]	68 (33 – 96)
Time period between baseline and follow-up assessment (n = 417), median year (range)	9.0 (4.7 – 12.6)
Percentage of subjects with family history of PD[b]	20.5
Region of origin of parents[c]	
Both parents of European origin, n (%)	381 (86.0)
Both parents Northern European, n (%)	111 (29.1)
Both parents Central European, n (%)	145 (38.1)
Both parents Southern European, n (%)	3 (0.8)
Both parents European, mixed region, n (%)	122 (32.0)
Only one parent of European origin, n (%)[d]	39 (8.8)
One parent declared “American”, n (%)[e]	2 (0.5)
Both parents declared “American”, n (%)[e]	18 (4.1)
Both parents Asian, n (%)	-
Unknown, n (%)	3 (0.7)

[a]Age at blood draw.

[b]Family history was defined as having at least one affected first-degree relative; 90/439 cases had a family history of PD (information was missing for 4).

[c]Self-reported by subjects. “Northern European” includes Scandinavian, Swedish, Norwegian, Finnish, Danish, Irish, or British origins. “Central European” includes French, Belgian, Dutch, Swiss, Luxemburgian, German, Austrian, Hungarian, Polish, Czechoslovakian, or Russian origins. “Southern European” includes Italian, Spanish, Portuguese, Greek, or Yugoslavian origins.

[d]Includes subjects for whom origin of one parent is unknown.

[e]These subjects were all Caucasians and not Native Americans.

Table 2

Genomic single nucleotide polymorphisms most significantly associated ($p \leq 5.0 \times 10^{-5}$) with motor outcome in Parkinson's disease[a]

Gene	SNP	Chromosome	Position[b]	Location Relative to Gene	Allele	Minor Allele Frequency (%)	Log Additive Model HR (95% CI)	Log Additive Model *P* Value[c]
C8orf4	rs10958605	8	40053605	3' downstream	C>A	0.452	1.81 (1.42 – 2.31)	0.00000151
RPS17P6	rs10918653	1	167143896	5' upstream	G>A	0.337	0.57 (0.44 – 0.74)	0.00000957
CACNB4	rs3768653	2	152716628	intronic SNP	C>A	0.184	1.90 (1.44 – 2.49)	0.0000121
ANK2	rs6819908	4	113887737	intronic SNP	C>G	0.232	1.76 (1.38 – 2.25)	0.0000133
ACTR3B	rs11773902	7	152501825	intronic SNP	A>G	0.377	1.75 (1.35 – 2.26)	0.000014
COL1A2	rs1861114	7	93883599	5' upstream	T>G	0.076	0.36 (0.21 – 0.62)	0.000018
STARP1	rs1412907	13	65919459	5' upstream	T>C	0.415	0.61 (0.48 – 0.77)	0.0000183
EPB41L3	rs1785423	18	5610882	5' upstream	G>A	0.447	0.61 (0.49 – 0.77)	0.0000185
MAGI2	rs12534352	7	77643059	3' downstream	A>G	0.251	1.66 (1.33 – 2.07)	0.0000201
STARP1	rs1333169	13	65907951	5' upstream	G>A	0.116	2.07 (1.52 – 2.83)	0.0000207
STARP1	rs9317493	13	65832729	3' downstream	A>G	0.416	0.62 (0.49 – 0.78)	0.0000334
SNX6	rs17524152	14	35067542	intronic SNP	T>A	0.434	0.63 (0.50 – 0.78)	0.0000347
STARP1	rs9571383	13	65939434	5' upstream	G>T	0.443	1.62 (1.28 – 2.05)	0.0000415
PLCB4	rs4813881	20	8968642	5' upstream	A>T	0.362	0.61 (0.48 – 0.78)	0.0000495

[a]The SNPs are listed in order of decreasing statistical significance as indicated by the uncorrected *p* values.

[b]NCBI build 37.1 of the human genome.

[c]uncorrected *p* values.

SNP = single nucleotide polymorphism; UTR = untranslated region; HR = hazard ratio; CI = confidence interval

Table 3

Genomic single nucleotide polymorphisms significantly associated ($p \leq 5.0 \times 10^{-5}$) with cognitive outcome in Parkinson's disease[a]

Gene	SNP	Chromosome	Position[b]	Location Relative to Gene	Allele	Minor Allele Frequency (%)	Log Additive Model HR (95% CI)	Log Additive Model *P* value[c]
CLRN3	rs6482992	10	129678674	intronic SNP	C>T	0.236	2.03 (1.47 – 2.79)	0.00000408
C4orf26	rs17000647	4	76481730	intronic SNP	C>A	0.025	5.58 (3.00 – 10.38)	0.00000483
LMNB1	rs959573	5	126181862	3' downstream	C>T	0.258	0.52 (0.40 – 0.67)	0.00000527
C17orf68	rs3027247	17	8130867	intronic SNP	A>C	0.260	0.53 (0.40 – 0.71)	0.00000927
RNU7-2P	rs12621515	2	146780097	5' upstream	C>A	0.109	2.26 (1.61 – 3.16)	0.0000123
RNU7-2P	rs16825922	2	146772505	5' upstream	C>T	0.107	2.27 (1.62 – 3.18)	0.0000124
TRPM3	rs4143736	9	73517105	intronic SNP	G>A	0.250	0.51 (0.37 – 0.70)	0.0000124
RNU7-2P	rs16825883	2	146748264	5' upstream	A>G	0.109	2.26 (1.61 – 3.17)	0.0000138
C8orf4	rs7014749	8	39943820	5' upstream	A>G	0.025	6.08 (3.05 – 12.13)	0.000015
ODF4	rs2313148	17	8251845	3' downstream	T>C	0.366	0.57 (0.44 – 0.74)	0.0000177
C9orf135	rs10511973	9	72466275	intron SNP	A>G	0.361	1.73 (1.35 – 2.21)	0.0000179
ITPR2	rs7302093	12	26602682	intron SNP	C>T	0.104	2.41 (1.53 – 3.79)	0.0000216
LOC100130088	rs12657212	5	154653619	5' upstream	A>C	0.093	2.53 (1.70 – 3.76)	0.0000257
FOXK2	rs6502124	17	80545156	intron SNP	G>A	0.048	4.02 (1.91 – 8.47)	0.0000283
SH3BGRL2	rs9443691	6	80441475	3' downstream	G>A	0.155	0.44 (0.30 – 0.67)	0.0000297
PRL	rs9379382	6	22289461	intron SNP	T>C	0.477	1.79 (1.36 – 2.36)	0.0000305
CAST	rs11745122	5	96060738	intron SNP	T>C	0.120	0.48 (0.33 – 0.70)	0.0000335
NFYAP1	rs1508938	13	64755699	5' upstream	A>T	0.404	1.64 (1.29 – 2.09)	0.0000445

[a] The SNPs are listed in order of decreasing statistical significance as indicated by the uncorrected *p* values.

[b] NCBI build 37.1 of the human genome.

[c] uncorrected *p* values.

SNP = single nucleotide polymorphism; UTR = untranslated region; HR = hazard ratio; CI = confidence interval