PARK10 is a major locus for sporadic neuropathologically confirmed Parkinson disease

Gary W. Beecham, PhD
Dennis W. Dickson, MD
William K. Scott, PhD
Eden R. Martin, PhD
Gerard Schellenberg, PhD
Karen Nuytemans, PhD
Eric B. Larson, MD
Joseph D. Buxbaum, PhD
John Q. Trojanowski, MD
Vivianna M. Van Deerlin, MD
Howard I. Hurtig, MD
Deborah C. Mash, PhD
Thomas G. Beach, MD
Juan C. Troncoso, MD
Olga Pletnikova, MD
Matthew P. Frosch, MD
Bernardino Ghetti, MD
Tatiana M. Foroud, PhD
Lawrence S. Honig, MD
Karen Marder, MD
Jean Paul Vonsattel, MD
Samuel M. Goldman, MD
Harry V. Vinters, MD
Owen A. Ross, PhD
Zbigniew K. Wszolek, MD
Liyong Wang, PhD
Derek M. Dykxhoorn, PhD
Margaret A. Pericak-Vance
Thomas J. Montine, MD
James B. Leverenz, MD
Ted M. Dawson, MD
Jeffery M. Vance, MD

ABSTRACT

Objective: To minimize pathologic heterogeneity in genetic studies of Parkinson disease (PD), the Autopsy-Confirmed Parkinson Disease Genetics Consortium conducted a genome-wide association study using both patients with neuropathologically confirmed PD and controls.

Methods: Four hundred eighty-four cases and 1,145 controls met neuropathologic diagnostic criteria, were genotyped, and then imputed to 3,922,209 variants for genome-wide association study analysis.

Results: A small region on chromosome 1 was strongly associated with PD (rs10788972; $p = 6.2 \times 10^{-8}$). The association peak lies within and very close to the maximum linkage peaks of 2 prior positive linkage studies defining the *PARK10* locus. We demonstrate that rs10788972 is in strong linkage disequilibrium with rs914722, the single nucleotide polymorphism defining the *PARK10* haplotype previously shown to be significantly associated with age at onset in PD. The region containing the *PARK10* locus was significantly reduced from 10.6 megabases to 100 kilobases and contains 4 known genes: *TCEANC2*, *TMEM59*, *miR-4781*, and *LDLRAD1*.

Conclusions: We confirm the association of a *PARK10* haplotype with the risk of developing idiopathic PD. Furthermore, we significantly reduce the size of the *PARK10* region. None of the candidate genes in the new *PARK10* region have been previously implicated in the biology of PD, suggesting new areas of potential research. This study strongly suggests that reducing pathologic heterogeneity may enhance the application of genetic association studies to PD.

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GLOSSARY

ADGC = Alzheimer Disease Genetics Consortium; **APDGC** = Autopsy-Confirmed Parkinson Disease Genetics Consortium; **CIDR** = Center for Inherited Disease Research; **GWAS** = genome-wide association study; **LD** = linkage disequilibrium; **MAF** = minor allele frequency; **OR** = odds ratio; **PCA** = principal component analysis; **PC1** = principal component 1; **PD** = Parkinson disease; **QC** = quality control; **SNP** = single nucleotide polymorphism.

Family studies have identified multiple Parkinson Disease (PD) genes: α-synuclein (*SNCA*), parkin (*PARK2*), DJ1 (*PARK7*), PTEN induced putative kinase 1 (*PINK1*), and leucine-rich repeat kinase 2 (*LRRK2*); association studies have identified up to 28 loci meeting genome-wide significance.[1–7] However, much of the heritability of PD remains unexplained.

One reason may be the amount of neuropathologic heterogeneity. PD is defined using clinical criteria that can include heterogeneous neuropathologic features, each of which may have a

Correspondence to Dr. Jeffery M. Vance: jvance@med.miami.edu

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Supplemental data at Neurology.org

From the John P. Hussman Institute for Human Genomics (G.W.B., W.K.S., E.R.M., K.N., L.W., D.M.D., M.A.P.-V., J.M.V.) and University of Miami Brain Endowment Bank (D.C.M.), Miller School of Medicine, University of Miami, FL; Departments of Neuroscience (D.W.D., O.A.R.) and Neurology (Z.K.W.), Mayo Clinic Florida, Jacksonville; Department of Pathology & Laboratory Medicine (G.S., J.Q.T., V.M.V.D., H.I.H.), Perelman School of Medicine, Center for Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia; Group Health Research Institute (E.B.L.), Seattle, WA; Departments of Psychiatry, and Genetics and Genomic Sciences (J.D.B.), Mount Sinai School of Medicine, New York, NY; Arizona Alzheimer's Consortium (T.G.B.), Phoenix; Sun Health Research Institute (T.G.B.), Sun City, AZ; Division of Neuropathology, Department of Pathology (J.C.T., O.P.), and Department of Neurology and the Solomon H. Snyder Department of Neuroscience (T.M.D.), Johns Hopkins University School of Medicine, Baltimore, MD; Kubik Laboratory for Neuropathology (M.P.F.), Massachusetts General Hospital and Harvard Medical School, Charlestown, MA; Department of Pathology and Laboratory Medicine, Indiana Alzheimer Disease Center (B.G.), and Department of Medical and Molecular Genetics (T.M.F.), Indiana University School of Medicine, Indianapolis; Departments of Neurology (L.S.H., K.M.) and Psychiatry (K.M.), Gertrude H. Sergievsky Center, and Taub Institute for Research on Alzheimer's Disease and the Aging Brain, New York; Department of Pathology and Cell Biology (J.P.V.), Taub Institute for Research on Alzheimer's Disease and the Aging Brain, New York, NY; The Parkinson's Institute (S.M.G.), Sunnyvale, CA; Departments of Pathology and Laboratory Medicine (Neuropathology) and Neurology (H.V.V.), David Geffen School of Medicine at University of California Los Angeles; Department of Pathology (T.J.M.), University of Washington School of Medicine, Seattle; VA Puget Sound Health Care System (J.B.L.), Seattle, WA.

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distinct genetic architecture.[8–11] Earlier PD autopsy studies[10,12] reported that approximately 75% of clinically diagnosed PD cases had neuropathic evidence of Lewy body disease. However, both of these predate modern imaging studies.[13] Indeed, more recent analyses[11] suggest that concordance of the neuropathologic diagnosis with the clinical diagnosis of PD can approach 90%. These layers of causal, pathologic heterogeneity in PD reduce the statistical power of genetic association tests and, as a result, limit the ability to find disease genes. This is particularly true as the samples in large PD genome-wide association studies (GWAS) have been collected over many years, often predating routine use of modern clinical diagnostic methods such as the advanced imaging of today.

To reduce potential pathologic heterogeneity, the Autopsy-Confirmed Parkinson Disease Genetics Consortium (APDGC) collected a set of individuals with PD that have neuropathologic confirmation of Lewy body PD pathology, as well as a set of "autopsy-confirmed" control individuals with no evidence of PD neuropathology. These neuropathologically confirmed cases and controls provided a level of pathologic homogeneity unavailable in previous GWAS.

METHODS

Sample selection. To be included in the study, all autopsy cases were required to have a diagnosis of PD documented by a neurologist. All patient samples and a subset of the controls used in the analysis were contributed by 12 APDGC centers, which are listed in text e-1 on the *Neurology*® Web site at Neurology.org.

Ascertainment of cases into the APDGC was primarily through existing autopsy cases of patients diagnosed with PD available at the participating center, referred to neuropathologists for autopsy by neurologists, or recruited from families whose affected relative were participants in existing PD studies. Participants from the Miami Udall were enrolled prospectively for autopsy studies. APDGC controls were volunteers, often spouses of patients with PD, without symptoms of parkinsonism. The Alzheimer Disease Genetics Consortium (ADGC) provided neuropathologically examined control samples for this study as well; ADGC contributing centers and affiliate members are described in text e-1 and the contributors supplemental material, respectively.

Before statistical analysis, all neuropathologic reports were reviewed by a single neuropathologist (D.W.D.). Inclusion criteria included clinical diagnosis of PD by a neurologist before death, moderate/severe neuronal loss in the substantia nigra, and the presence of Lewy bodies. Cases were excluded if they had prominent dementia within 1 year of diagnosis[14] (to minimize the inclusion of Lewy body dementia), had competing pathologic features (e.g., progressive supranuclear palsy rather than PD), or had a Braak neurofibrillary tangle stage >IV. Because of the autopsy-based ascertainment scheme, additional information on PD cases (e.g., family history data, age at onset) was limited. Controls were restricted to samples with no antemortem diagnosis of PD, no more than minimal neuronal loss in the substantia nigra, an absence of Lewy bodies, and a Braak neurofibrillary tangle stage ≤IV. The ADGC controls were previously genotyped (see below). All ADGC controls used for our study met the same neuropathologic criteria as the APDGC.

While 977 APDGC samples were genotyped by the Center for Inherited Disease Research (CIDR), Johns Hopkins University, only 791 samples remained after neuropathologic review (484 cases, 307 controls). Exclusion based on neuropathology included the following: 66 cases without Lewy bodies; 6 with excessive Alzheimer pathology; 7 had parkinsonism with other pathologies; 16 had dementia with Lewy bodies; and 9 cases were withdrawn at the request of the contributing sites. As some sites specifically sent samples that met our entrance criteria, whereas other sites sent samples from a broader set of PD (with or without Lewy bodies), these numbers should not be interpreted as population-level rates of pathologic misclassification/diagnosis. For the ADGC controls set, we requested only genotype data for samples that met our inclusion criteria.[15] However, after examination of this dataset, we excluded 6 samples with pathology consistent with PD, 15 that had other diagnoses that excluded them from the analysis, and 2 controls were withdrawn at the request of the contributing sites. Because this was not a random selection of the ADGC dataset, we do not know the breakdown of the control sample exclusions in the entire ADGC control set.

Standard protocol approvals, registrations, and patient consents. All samples were obtained with appropriate institutional review board approval and informed consent.

Genotyping/quality control. Genotyping for all APDGC samples was performed through CIDR using the Illumina HumanOmni1-Quad beadchip (Illumina, Inc., San Diego, CA). ADGC samples were previously genotyped on a variety of platforms and centers, and are detailed elsewhere.[15] For quality control (QC) purposes, there were 8 HapMap trios and 41 within-study duplicates included in the genotyping. Preliminary QC included checks for sample missingness, sample relatedness, sex inconsistencies, and a principal components analysis (PCA) to infer ancestry.[16] For the PCA, we used only good quality (missingness <5%) and common (minor allele frequency [MAF] >5%) variants in low linkage disequilibrium (LD) with each other ($r^2 < 0.1$) that were not in the major histocompatibility complex regions such as the HLA (human leukocyte antigen), LTR (long terminal repeat), chromosome 7q21-31, and chromosome 8p23.1. Samples that did not cluster with the known European ancestry group were excluded. Initial QC also included review of probe intensity data. The sample-level QC was performed on each sample and was largely independent of the dataset to which the sample belonged. Single nucleotide polymorphism (SNP)-level QC was performed on APDGC and ADGC datasets separately for all steps up to and including imputation. The initial postimputation filtering (removing monomorphic SNPs and those with low IMPUTE info scores, <0.40) was also performed on each set separately. Starting with the comparison of the control groups, all analyses were performed jointly.

The Omni1-Quad beadchip assays more than 1.1 million probes. From these, we removed 123,000 intensity-only probes, 10,000 SNPs failed CIDR's technical filter, 55,000 were monomorphic, and 22,000 showed high SNP missingness rates (>2%). Copy number analysis revealed 2 samples with trisomy-21 that were subsequently excluded. A small number of SNPs (<300) were

removed since they had 2 or more discordant calls among the HapMap trios, study replicates, or had low p values for the Hardy-Weinberg equilibrium test among controls ($p < 1 \times 10^{-5}$). SNPs with MAF <2% were not used in the genotype imputation (141,000). Dropout from genotyping QC was <3%. After all of these QC and filtering steps, 782,456 SNPs remained before imputation.

Genotype imputation and final QC. The IMPUTE version 2 software was used to infer genotypes at additional loci for the cases and both control sets. Data from the 1000 Genomes Project were used as a reference (March 2012 release).[17] Imputation and imputation QC were independently performed within the APDGC samples and within each of the 9 ADGC control cohorts.[18] After imputation, the variants were considered for further analysis if they were not monomorphic, had an IMPUTE info score greater than 0.45, and showed no significant difference in frequencies between the ADGC controls and the APDGC controls (genotypic χ^2 test p value >0.05). Thus, control subgroup discordance or pseudoassociation did not contribute to overall significance levels. In addition, SNPs with missingness >5%, MAF <1%, and positions with PLINK's info score <0.8 were removed from further analysis; for imputed loci, MAF was estimated based on allelic dosage.[19] Initial imputation started with 23,284,435 loci, but after filters, using conservative thresholds to avoid biasing the association results by adding unmatched controls typed with different platforms, a final 3,922,209 variants were used in the association analysis. After all genotype and phenotype-based QC, the primary analysis dataset consisted of 484 neuropathologically confirmed PD cases and 1,145 neuropathologically confirmed control samples (307 controls from the APDGC and 838 controls from the ADGC).

Statistical association. All cohorts were jointly analyzed for association between the SNPs and PD status. Statistical association was performed using logistic regression with age at death, sex, and the first eigenvector for population substructure included as covariates in the model. No additional vectors were used in the analysis because they accounted for only a small proportion of the variation (principal component 1 [PC1] accounted for only 0.4% of variation). Association testing was performed using PLINK.[19]

To test for independent genetic effects in regions with multiple associated variants, a forward-backward selection procedure was used: each SNP was tested for association independently and then the most associated variant was added to the model. Each of the remaining variants was separately added to the model, with the most associated being added to the multiple variable regression models. These "forward" selection steps are interrupted by "backward" selection steps to determine whether variants included in the current model should be removed. In the backward step, any variables in the model that are no longer associated with a p value threshold of 0.05 are removed from the model; this sometimes occurs when a signal of strong effect is better described by 2 moderate effects. When no new SNPs are being added to the model, and no current SNPs are being removed, the model represents the independent effects at the locus. LD calculations were performed using the Haploview software.[20]

RESULTS A description of the characteristics of patients and controls is shown in table 1. Population substructure analysis revealed only minor substructure within this European-descended sample (PC1 accounted for less than 0.4% of the genetic variation) that was not associated with disease (p value between PC1 and disease = 0.53). A plot of the first 2 principal components is shown in figure e-1. The genomic inflation factor (λ value) was 1.12 (see Q-Q plot, figure e-2). This is comparable with typical GWAS (1.05–1.10) and much less than those expected in studies with issues in population substructure (>1.2).

A 100-kilobase (kb) LD block, lying within the 10.6-megabase linkage region of the known PD locus *PARK10* (50,700,000–61,300,000 base pairs [bp]; OMIM: %606852), was found to be strongly associated with the risk of PD (figure 1). The most significant SNP (rs10788972) in this LD block is located within the *TCEANC2* gene (table 2), achieving near genome-wide significance (chr1: 54,572,243, MAF = 0.43; odds ratio [OR] = 0.64, p value = 6.2×10^{-8}). As we have merged control datasets, we tested this SNP using the APDGC dataset alone, and also found strong association (p value = 5×10^{-5}). The association peak lies well within the 2 previous *PARK10* linkage regions, very near the maximum logarithm of odds (LOD) score results (figure 2). Rs10788972 and a second strongly associated marker (rs6588502) are in strong LD (e.g., $r^2 = 0.59$ for rs10788972; $r^2 = 0.77$ for rs6588502) with the marker rs914722, previously reported to be associated with age at onset in PD.[21] This is shown in figure e-3 using data from the 1000 Genomes Project.[17] To confirm the LD in our dataset, we genotyped rs914722 in a subset of our samples (n = 357), and confirmed the LD with rs914722 seen in the 1000 Genomes Project (figures e-4 and e-5). There was no evidence of multiple, independent association signals in the region.

No association test met a stringent genome-wide significance threshold (p value $< 5 \times 10^{-8}$). We did note strong association with several known PD loci, including the *SNCA* locus (rs13140923, OR = 1.45, p value = 0.0005513), the microtubule-associated protein tau (*MAPT*) locus (rs1052553, OR = 0.65, p value = 0.000776), and the *GAK* locus (rs5572858, OR = 0.64, p = 0.000171). Because of poor imputation in the ADGC set at the *MAPT* locus, only data from the APDGC dataset were available for the MAPT-specific analysis. In addition, across the genome, there were 39 variants that showed association with PD with a p value $< 2.5 \times 10^{-6}$ (see table e-1). These loci await validation in a second autopsy-confirmed PD dataset. None of these loci were in a previously identified "PARK" locus.

DISCUSSION This study uses both autopsy-confirmed cases and controls to reduce pathologic heterogeneity and improve the chances of making a novel discovery. We confirm the *PARK10* locus as a contributing risk locus for PD cases with Lewy body pathology. The SNP rs10788972 is close to genome-wide significance, and the association peak lies close to both of the reported maximum linkage LOD score

Table 1 Sample set description

	Case	APDGC controls	ADGC controls	All controls	All samples
No.	484	307	838	1,145	1,629
Age at death, y, mean (SD)	77.78 (7.69)	81.19 (13.03)	80.45 (11.1)	80.65 (11.64)	79.8 (10.7)
Sex, n (%)					
Male	348 (71.9)	150 (48.8)	395 (47.1)	545 (47.6)	893 (54.8)
Female	136 (28.1)	157 (51.2)	443 (52.9)	600 (52.4)	736 (45.2)

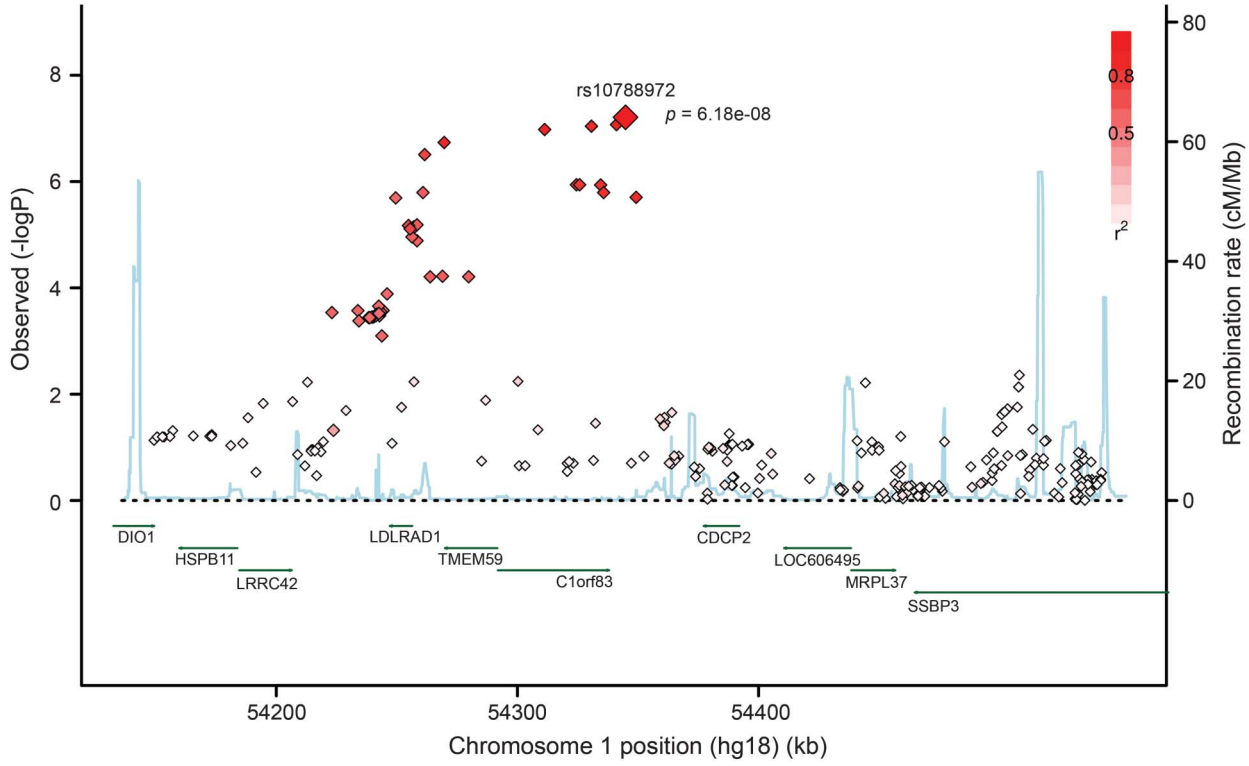
Abbreviations: ADGC = Alzheimer Disease Genetics Consortium; APDGC = Autopsy-Confirmed Parkinson Disease Genetics Consortium.

markers,[22,23] with an OR of 0.64. This effect size is comparable to effect estimates for SNCA and MAPT (SNCA: rs356165, OR = 0.74; MAPT: rs242559, OR = 0.78; in terms of the protective allele). Furthermore, we demonstrate that rs10788972 and other top-associated alleles are in strong LD with rs914722 in the *PARK10* haplotype, which previously demonstrated significant association with age at onset in PD.[21] Thus, multiple independent lines of evidence support the importance of the *PARK10* locus in Lewy body PD.

The first report of linkage for a PD risk locus in this chromosome 1 region was in a large Icelandic family.[22] The authors named the locus *PARK10*. This was followed by a second report[23] of linkage for AAO genes in PD to the same region. The substantial overlap between these 2 linkage peaks is notable (figure 2), suggesting that the *PARK10* locus confers both risk and age at onset effects in PD.

Subsequently, using a dataset independent of the present study, we published an association analysis with age at onset in PD in the *PARK10* region.[21] Two *C1orf8* (*TMEM59*) haplotypes were found to be significantly associated (p = 0.004 and 0.009) with age at onset in PD (rs3766466 [SNP192]-rs914722 [SNP193]-rs2236512 [SNP194], table 10

Figure 1 Regional association plot around rs10788972 on chromosome 1



A regional association plot surrounding the rs10788972 single nucleotide polymorphism (SNP) is shown. The x-axis represents the position in base pair on chromosome 1. The diamond points represent genotyped or imputed variants, with the y-axis denoting −log p value, base 10. The shades of red in the SNP markers show linkage disequilibrium between variants and the top SNP (rs10788972). The blue line shows the recombination rate at different positions across the region.

Table 2 Top 20 *PARK10* SNPs

SNP	Chr	Position	Gene info	A1	A2	Allele frequency	Odds ratio	p Value
rs10788972	1	54,572,243	*TCEANC2*	C	A	0.565	0.6402	6.18E−08
rs4492560	1	54,568,488	*TCEANC2*	G	A	0.5642	0.643	8.49E−08
rs4926619	1	54,558,101	*TCEANC2*	T	C	0.5658	0.6429	9.09E−08
rs12044517	1	54,574,610	*TCEANC2*	G	A	0.5649	0.6445	9.75E−08
rs7537946	1	54,538,700	*TCEANC2*	A	G	0.5668	0.6446	1.05E−07
rs1547467	1	54,497,040	Upstream of *TMEM59*	T	C	0.5674	0.6501	1.84E−07
1-54571318	1	54,571,318	*TCEANC2*	C	CTTTT	0.573	0.6535	2.89E−07
rs6703501	1	54,488,948	Between *TMEM59* and *LDLRAD1*	T	C	0.5924	0.6497	3.11E−07
1-54542674	1	54,542,674	*TCEANC2*	A	AGGG	0.6254	0.6588	8.72E−07
rs7516791	1	54,551,875	*TCEANC2*	G	T	0.6211	0.6657	1.15E−06
rs9651202	1	54,553,207	*TCEANC2*	T	C	0.6211	0.6658	1.15E−06
rs7555099	1	54,561,916	*TCEANC2*	C	T	0.6198	0.6662	1.16E−06
1-54542673	1	54,542,673	*TCEANC2*	A	AAGG	0.6192	0.6664	1.58E−06
rs6588502	1	54,563,156	*TCEANC2*	A	G	0.6185	0.6705	1.61E−06
rs35109297	1	54,488,250	Between *TMEM59* and *LDLRAD1*	A	G	0.5966	0.6673	1.61E−06
rs11206283	1	54,576,639	*TCEANC2*	G	T	0.6181	0.6702	1.98E−06
rs72664117	1	54,476,931	*LDLRAD1*	A	G	0.5979	0.6689	2.03E−06
rs35719463	1	54,487,596	Between *TMEM59* and *LDLRAD1*	G	A	0.576	0.6768	2.92E−06
rs6696554	1	54,487,125	Between *TMEM59* and *LDLRAD1*	A	G	0.5751	0.6831	4.58E−06
rs10888830	1	54,491,802	Upstream of *TMEM59*	T	G	0.6128	0.6795	5.71E−06

Abbreviations: Chr = chromosome; SNP = single nucleotide polymorphism.

in original report). However, examination of these 2 haplotypes reveals that only rs914722 varies between the 2 haplotypes, and is the marker driving the association. Thus, we have confirmed the association with this haplotype in *PARK10* and PD.

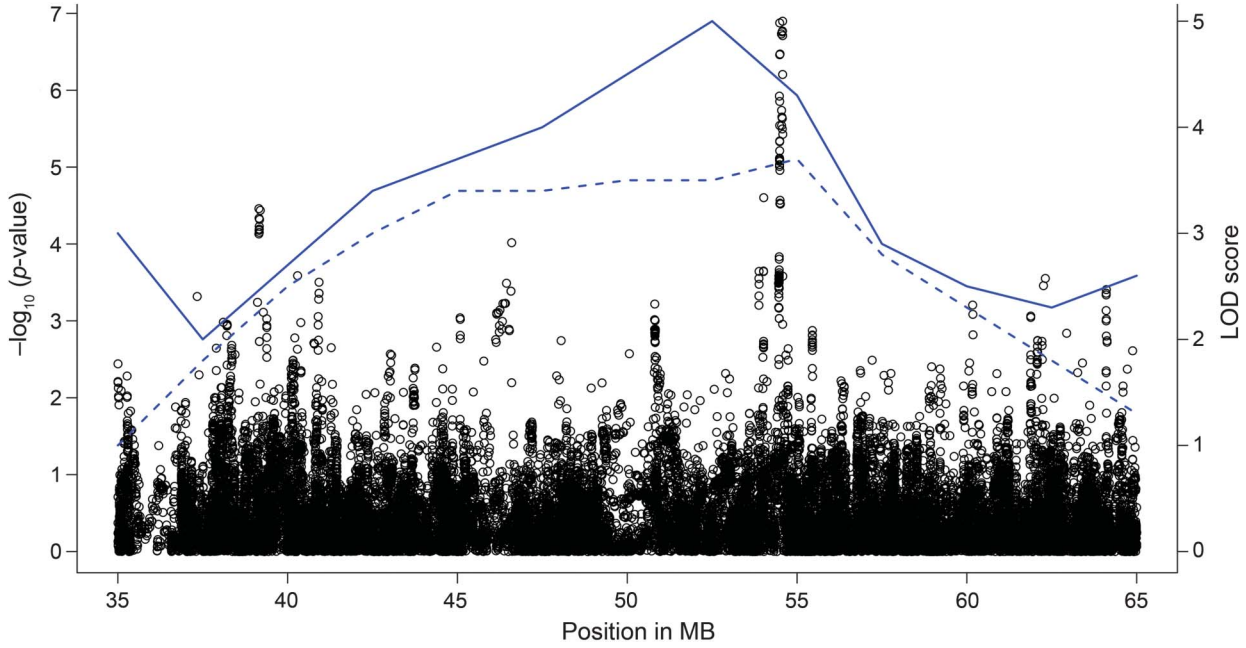
The associated region from this study reduces the size of the *PARK10* locus by 100-fold. No obvious candidate genes are observed in the overall region, and clearly further work is needed to identify any actual *PARK10* risk variant. Four genes are known to lie in this smaller candidate region. None have been previously implicated in the biology of PD: the transcription elongation factor A (SII) N-terminal and central domain containing 2 (*TCEANC2*), transmembrane 59 (*TMEM59* or *C1orf8*), low density lipoprotein receptor class A domain containing protein 1 (*LDLRAD1*) genes and the microRNA *miR-4781* (figure 1). Little is known about *TCEANC2*, but it appears to be involved in RNA processing. *LDLRAD1* is a member of the low-density lipoprotein receptor family involved in the binding site for low-density lipoprotein and calcium. In silico analysis of *miR-4781* targets does not implicate any predicted or known PD target genes.[24,25] *TMEM59* (*C1orf8*) was shown to be overexpressed (3.6-fold) in the substantia nigra of patients with PD compared to controls.[26] Localized in the Golgi body, it is involved in ectodomain shedding of amyloid protein precursor.[27]

To assure that the Alzheimer controls were not solely responsible for the observed association, we repeated the association analysis for *TMEM59* with just the APDGC dataset and detected association ($p = 5 \times 10^{-5}$) in this dataset alone. To look for independent genetic effects in the region, a multiple linear regression was performed using a forward-backward SNP selection scheme. The forward-backward selection did not indicate additional independently associated SNPs in the region (data not shown).

The Web site PDGene (pdgene.org) presents a meta-analysis for risk loci. Examination of these data reveals that the meta-analysis results for these studies generated no significant associations in *TCEANC2*, *TMEM59*, *miR-4787*, and *LDLRAD1*. However, there are nominally significant associations ($p < 0.05$) in the adjacent gene, *CDCP2*, and several others in the *PARK10* interval (50,700,000–61,300,000 bp). These results indicate that there is at least nominal evidence for association at *PARK10* in meta-analyzed GWAS data from PD case-control samples based on clinical diagnosis only.

Why did this autopsy-confirmed GWAS confirm the *PARK10* association while GWAS in clinically

Figure 2 Plot of association results and linkage results



A regional association plot of the *PARK10* locus. The x-axis represents the position in base pair on chromosome 1. The points represent genotyped or imputed variants, with the left y-axis denoting the corresponding −log *p* value, base 10. The solid blue line represents the Parkinson disease age-at-onset linkage peak[23] and the dashed blue line represents a linkage peak from the deCODE Icelandic study.[22] The right y-axis denotes the corresponding logarithm of odds (LOD) score. MB = megabase.

ascertained samples have not? The most likely reason is that we reduced the inherent genetic heterogeneity of the PD phenotype by using a more specific phenotype, i.e., autopsy-confirmed Lewy body PD. It is important to realize that this finding does not suggest any clinical misdiagnosis of these patients; all met the standard PD clinical criteria at the time of their collection. Rather, the results reflect that we limited the pathologic heterogeneity present in the phenotype.

An obvious limitation of our approach is the additional cost to phenotyping and the reduced sample size. While we did see association at SNCA, MAPT, and GAK, the moderate sample size is likely why we did not observe genome-wide *p* values at these loci. We would expect that if these loci are relatively less susceptible to genetic and phenotypic heterogeneity, then an increase in sample size, to increase power, should overcome any additional heterogeneity added by the larger dataset; this principle is at work in large GWAS with unselected control sets for rarer diseases. Finally, while a reduced sample size could increase the impact of population stratification, our PCA and association analyses showed no evidence of differential population substructure between cases and controls.

Unfortunately, because of the autopsy-based ascertainment scheme, age-at-onset data were not available for the majority of our sample, so we could not test the age-at-onset effect. This emphasizes the importance that all centers performing autopsies in collecting a uniform set of historical and clinical data to maximize the usefulness of these efforts for future research.

It is interesting that the 2 previous *PARK10* linkage studies[21,22] and the 2 association studies (including the present study) followed similar patterns. The Icelandic family data identified a risk effect for PD, while the initial association study used multiplex families from primarily North America and found association for age at onset, but not risk. It seems likely that the Icelandic study, like the current study, had reduced genetic heterogeneity by studying a more stringently defined sample (PD in a single, large Icelandic family) than the multiplex and initial association[21] studies. Thus, the studies with less genetic heterogeneity saw a significant risk effect, while those containing more population complexity found an age-at-onset effect. It may be that *PARK10* has a stronger age-at-onset effect relative to other genes, and thus is detected in those studies and not in the more genetically heterogeneous risk effect. However, whatever the reason for this finding, the evidence is strong that *PARK10*, similar to the *APO* ε4 allele in AD, affects both age at onset and risk of PD. The reduction in size of the *PARK10* region makes it an excellent candidate for next-generation sequencing, which should provide insight into the actual variant for *PARK10* and likely new directions for PD research.

AUTHOR CONTRIBUTIONS

Study design: G.W.B., W.K.S., E.R.M., J.Q.T., K.M., T.M.D., J.M.V. Sample/data collection: W.K.S., L.W., G.S., E.B.L., J.D.B., D.W.D., J.Q.T., V.M.V.D., H.I.H., D.C.M., T.G.B., J.C.T., O.P., M.P.F., G.W.B., T.M.F., L.S.H., K.M., J.P.V., S.M.G., H.V.V., Z.K.W., T.J.M., J.B.L., T.J.M., J.M.V. Data analysis: G.W.B., W.K.S., E.R.M., K.N., D.M.D., J.Q.T., M.P.F., J.P.V., B.G., G.S., J.D.B., Z.K.W., T.J.M., J.M.V. Data interpretation: G.W.B., W.K.S., E.R.M., L.W., K.N., D.M.D., J.M.V. Writing: G.W.B., D.D.W., W.K.S., E.R.M., G.S., K.N., E.B.L., J.D.B., J.Q.T., V.M.V., H.I.H., D.C.M., T.G.B., J.C.T., O.P., M.P.F., B.G., T.M.F., L.S.H., K.M., J.P.V., S.M.G., H.V.V., O.A.R., Z.K.W., L.W., D.M.D., M.A.P.-V., T.J.M., J.B.L., T.M.D., J.M.V.

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DISCLOSURE

G. Beecham reports no disclosures relevant to the manuscript. D. Dickson is an editorial board member of *Annals of Neurology*, *Parkinsonism and Related Disorders*, *Journal of Neuropathology & Experimental Neurology*, and *Brain Pathology*. He is editor-in-chief of *American Journal of Neurodegenerative Disease*, and *International Journal of Clinical and Experimental Pathology*. Grant support: P50-AG16574, P50-NS72187, and P01-AG03949. W. Scott receives research funding through NIH (R01 AI068804, R01 EY012118, P50 NS071674), serves on the scientific review board of the Parkinson Study Group, and may accrue revenue on patents submitted by Duke University "Genetic variants increase the risk of age-related macular degeneration" in which he is an inventor. E. Martin reports no disclosures relevant to the manuscript. G. Schellenberg serves on the Medical Scientific Advisory Committee for the Alzheimer's Association, is a stockholder at Genelex (not relevant to the current publication), and receives research funding through NIH grants. K. Nuytemans reports no disclosures relevant to the manuscript. E. Larson received royalties from chapters written for UpToDate. J. Buxbaum reports no disclosures relevant to the manuscript. J. Trojanowski serves as an associate editor of *Alzheimer's & Dementia*. He may accrue revenue on patents submitted by the University of Pennsylvania wherein he is inventor including: Modified avidin-biotin technique, Method of stabilizing microtubules to treat Alzheimer's disease, Method of detecting abnormally phosphorylated tau, Method of screening for Alzheimer's disease or disease associated with the accumulation of paired helical filaments, Compositions and methods for producing and using homogeneous neuronal cell transplants, Rat comprising straight filaments in its brain, Compositions and methods for producing and using homogeneous neuronal cell transplants to treat neurodegenerative disorders

and brain and spinal cord injuries, Diagnostic methods for Alzheimer's disease by detection of multiple MRNAs, Methods and compositions for determining lipid peroxidation levels in oxidant stress syndromes and diseases, Compositions and methods for producing and using homogenous neuronal cell transplants, Method of identifying, diagnosing and treating alpha-synuclein positive neurodegenerative disorders, Mutation-specific functional impairments in distinct tau isoforms of hereditary frontotemporal dementia and parkinsonism linked to chromosome-17: genotype predicts phenotype, Microtubule stabilizing therapies for neurodegenerative disorders, and Treatment of Alzheimer's and related diseases with an antibody. He is coinventor on patents submitted by the University of Pennsylvania wherein he is inventor that have generated income he has received from the sale of Avid to Eli Lilly including: Amyloid plaque aggregation inhibitors and diagnostic imaging agents. 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This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the March 10, 2015, issue of *Neurology*. In the second segment, Dr. Michelle Fullard talks with Dr. Jeffrey Vance about his paper on *PARK 10*, a major locus for sporadic neuropathologically confirmed Parkinson disease. Dr. James Addington then reads the e-Pearl of the week about a mnemonic for the clinical manifestations of CADASIL. In the next part of the podcast, Dr. Michelle Johansen focuses her interview with Dr. Kevin Barrett on the topic of stroke in the setting of renal disease.

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