α-Synuclein Genetic Variability: A Biomarker for Dementia in Parkinson Disease

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Objective: The relationship between Parkinson disease (PD), PD with dementia (PDD), and dementia with Lewy bodies (DLB) has long been debated. Although PD is primarily considered a motor disorder, cognitive impairment is often present at diagnosis, and only ~20% of patients remain cognitively intact in the long term. Alpha-synuclein (*SNCA*) was first implicated in the pathogenesis of the disease when point mutations and locus multiplications were identified in familial parkinsonism with dementia. In worldwide populations, *SNCA* genetic variability remains the most reproducible risk factor for idiopathic PD. However, few investigators have looked at *SNCA* variability in terms of cognitive outcomes.
Methods: We have used targeted high-throughput sequencing to characterize the 135kb *SNCA* locus in a large multinational cohort of patients with PD, PDD, and DLB and healthy controls.
Results: An analysis of 43 tagging single nucleotide polymorphisms across the *SNCA* locus shows 2 distinct association profiles for symptoms of parkinsonism and/or dementia, respectively, toward the 3′ or the 5′ of the *SNCA* gene. In addition, we define a specific haplotype in intron 4 that is directly associated with PDD. The PDD risk haplotype has been interrogated at single nucleotide resolution and is uniquely tagged by an expanded $TTTC_n$ repeat.
Interpretation: Our data show that PD, PDD, and DLB, rather than a disease continuum, have distinct genetic etiologies albeit within one genomic locus. Such results may serve as prognostic biomarkers to these disorders, to inform physicians and patients, and to assist in the design and stratification of clinical trials aimed at disease modification.

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Parkinson disease (PD) has been traditionally defined by characteristic clinical motor hallmarks of bradykinesia, tremor, muscular rigidity, and postural instability. However, the nonmotor aspects of PD, including cognitive impairment, are now increasingly recognized as a common feature of the disease. At the time of diagnosis, approximately 24% of PD patients have mild cognitive impairment (PD with mild cognitive impairment [PD-MCI]),[1,2]

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Members of the *SNCA* Cognition Study Group and MDS PD-MCI Study Group are available as online supplementary files.

Additional supporting information can be found in the online version of this article

TABLE 1. Cohort Description

Cohort	CI	PD, No.	DLB, No.	HC, No.
UBC	M.J.F.	421	67	556
PPMI[50]		465		209
CARPA: PD-MCI[51]	G.J.G.	110		
USA: PD-MCI[51]	J.G.G.	75		
New Zealand: PD-MCI[51]	J.C.D.-A.	143		55
Mayo	O.A.R.	84	798	91
UK/ICL: PD Brain Bank	L.T.M.	194	5	
UK/OPDC: Oxford Brain Bank	L.P.		52	60
Total		1,492	922	971

CARPA = Comorbidity and Aging in Rehabilitation Patients: The Influence on Activities; CI = coordinating investigator for each site; DLB = dementia with Lewy bodies; HC = healthy controls; ICL = Imperial College London; MCI = mild cognitive impairment; OPDC = Oxford Parkinson's Disease Centre; PD = Parkinson disease; PPMI = Parkinson's Progression Markers Initiative; UBC = University of British Columbia.

and approximately 80% of longitudinally followed patients with PD develop dementia (PD with dementia [PDD]) during the course of the disease.[3,4] The presence of cognitive impairment in patients with PD is associated with lower quality of life, increased nursing home placement, and mortality.[5] Clinically, the cognitive features of PDD are similar to and often indistinguishable from dementia with Lewy bodies (DLB).[6,7] The two dementia syndromes are differentiated based on the timing of the motor PD signs relative to the onset of dementia (ie, diagnosis of DLB is assigned when motor symptoms and dementia appear together or within 1 year of each other).[8] However, overlap in these clinical presentations often causes difficulty in the diagnostic process. In addition to the clinical phenotypic similarities, PDD and DLB also share common neuropathological features, because the burden of cortical Lewy bodies and neurites is often indistinguishable.[7,9–12] Recent studies suggest increased cortical Lewy body and amyloid β deposition in temporal and parietal regions may be distinguishing features of DLB, compared to PDD,[13] and may potentially be mediated by apolipoprotein E (APOE) ϵ4.[14] The etiopathogenic mechanisms of DLB and PDD still remain unclear, and they are often considered as two manifestations of one continuous spectrum of disease. Genetic factors may play a role in the expression of cognitive deficits in PDD and DLB, as suggested by dominant familial forms of PDD/DLB. Notably, missense mutations in the α-synuclein gene (*SNCA*) and locus multiplications are associated with clinical and pathological phenotypes ranging from PD to PDD to DLB.[15] In worldwide populations, *SNCA* genetic variability remains the most reproducible risk factor for idiopathic PD. However, only a few investigators have looked at *SNCA* variability in terms of these different clinicopathological groups. In this study, we have used targeted high-throughput sequencing to comprehensively characterize the 135kb *SNCA* locus in a large multinational cohort of patients with PD, PDD, and DLB and healthy controls.

Subjects and Methods

Subjects

All sites received approval from an ethical standards committee on human experimentation before study initiation and obtained written informed consent for research from all individuals participating in the study. A total of 1,492 PD, 922 DLB, and 971 healthy control (HC) samples, originating from 8 cohorts, were included in the study (Table 1). All samples are of self-declared European or North American ancestry. Clinical examinations were performed by movement disorders specialty-trained neurologists, and diagnoses were made using established criteria,[16,17] the UK Brain Bank Criteria for PD,[18] and the DLB Consortium.[19] PD patients were classified without cognitive impairment (noCI) or with dementia (PDD) according to the Movement Disorder Society Task Force criteria,[6] or using Montreal Cognitive Assessment (MoCA), taking into account the mean score, minimum score, and score at last examination.[20,21] Patients with raw MoCA scores >21 but <26 were considered to have some degree of cognitive impairment, and were not used in stratified cognitive analyses. When quantitative scores were unavailable, a qualitative diagnosis of PDD was made on the basis of longitudinal evaluations and clinical impression ($n = 57$, UK Imperial College London, PD Brain Bank). Controls were individuals with no evidence of neurological disease, including movement disorders or dementia, at the time of examination.

TABLE 2. Sample Demographics

Diagnosis	No.	Neuropath Diagnosis	Gender, Male %	Age/Age at Death, yr	Age at Onset, yr	Disease Duration, yr
PD	1,492	314	65.3	71.5 ± 11.3	60.3 ± 10.2	9.6 ± 6.0
PD-noCI	572	7	60.7	67.4 ± 10.4	58.5 ± 9.6	8.3 ± 4.8
PDD	198	57	68.2	76.6 ± 7.8	63.2 ± 9.8	13.3 ± 6.8
DLB	922	518	63.7	81.5 ± 9.2	73.2 ± 8.1[a]	10.8 ± 4.9[a]
HC	971	115	53.4	72.0 ± 12.6	—	—

Mean ± standard deviation.
[a]Data only available for 468 subjects.
DLB = dementia with Lewy bodies; HC = healthy controls; noCI = no cognitive impairment; PD = Parkinson disease; PDD = PD with dementia.

Genetic Screening

SNCA gene dosage was assessed by quantitative real-time polymerase chain reaction (PCR).[22] Short tandem repeat genotyping was performed using fluorescent-labeled primer PCR reaction with capillary electrophoresis on an ABI3730xl Genome Analyzer and analyzed with Genemapper software (Life Technologies, Carlsbad, CA). All subjects were genotyped for *APOE* ϵ2/ϵ3/ϵ4 using a TaqMan SNP Genotyping Assay (Life Technologies).

High-Throughput Sequencing

The entire 135kb *SNCA* genomic locus (chr4:90,635,215-90,769,364) was sequenced as part of a custom designed high-throughput sequencing (HTS) panel, capturing the exonic regions of candidate genes previously associated or linked to neurodegenerative disease. Pair-end sequencing was performed on a SOLiD 5500xl platform (Life Technologies) as previously described.[23] Mapping, sequence alignment, duplicate removal, single nucleotide polymorphism (SNP) calling, and indel detection were performed by Lifescope v2.5.1 (Life Technologies). Annotation was performed with ANNOVAR,[24] using NCBI Build 37 (hg19) as the reference genome.

SNP Selection

Forty-four SNPs (Supplementary Table 1) were selected for the *SNCA* locus using the TAGGER program as implemented in HaploView 4.1,[25] with parameters of minor allele frequency (MAF) > 5% and pairwise r^2 threshold of 0.8.

Genotyping

SAMtools (v0.1.18)[26] was used to generate genotype calls from individual BAM files. Genotypes with depth of coverage < 10 were set as missing. Additional genotyping of 43 SNPs was carried out by Sequenom MassArray iPLEX system (Sequenom, San Diego, CA). Sequenom primers were designed using MassARRAY Designer 4.0 software (Sequenom). PCR amplification, shrimp alkaline phosphatase treatment, and single-base extension and desalting were performed in 384-well microplates (Thermo Fisher Scientific, Fremont, CA) using Sequenom PCR reagents according to the manufacturer's protocol. Reproducibility was assessed by comparing replicated samples both within and across platforms. A genotype call rate > 95% and a $p > 0.01$ for test of deviation from Hardy–Weinberg equilibrium (HWE) were used as quality-control criteria. Samples with > 5% missing genotypes were removed from the study.

Statistical Analysis

Highly polymorphic genetic variability in candidate genes (MAF > 0.2), beyond the *SNCA* locus, was used in a factor analysis to generate eigenvectors and correct for potential population stratification, as previously described.[23] HWE was tested in PLINK,[27] and markers that deviated from expectation ($p < 0.001$) were excluded. Association testing was performed using the logistic regression function in PLINK, using gender, age/age at death, site, and *APOE* dosage as covariates. Pairwise linkage disequilibrium (LD) was calculated for all 43 *SNCA* SNPs. Twenty-one markers in disequilibrium ($r^2 > 0.8$) were excluded from the Bonferroni correction, and the significance level was set to 0.05/22 = 0.002. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated for the minor allele.

The LD structure of the *SNCA* locus was assessed with the software package Haploview v4.1.[25] For each block, only haplotypes with frequency > 0.01 were considered. Logistic regression analysis implemented in PLINK was used to test for association, and multiple testing was adjusted for using the max(T) permutation procedure (n = 10,000).[27]

Results

The final study population consisted of 1,492 PD, 922 DLB, and 971 HC samples; demographic and clinical characteristics, including those with autopsy, are summarized in Table 2. All subjects were wild-type for *SNCA* multiplication and without pathogenic mutations in known genes for parkinsonism. *APOE* genotypes and allele frequencies observed in the samples are reported in Supplementary Table 2. There was no significant difference in allele or genotype distribution between patients

with PD and HCs. However, an overrepresentation of the *APOE* ϵ4 allele in both PDD (OR [95% CI] = 1.28 [1.11–1.48], $p = 0.09$) and DLB (OR [95% CI] = 2.50 [2.29–2.70], $p < 0.001$) groups was observed.

Genotypes for 43 SNPs (MAF > 5%) spanning the entire *SNCA* locus were obtained for the cohort. Sequencing of the *SNCA* locus was performed in 1,366 PD, 122 DLB, and 490 HC samples, selected as they had the most detailed history and sufficient DNA. Overall, 92% of the *SNCA* locus was sequenced with a minimum average depth >20×, across all the samples. Regions with no coverage were found to be in or near repetitive elements. An additional 126 PD, 800 DLB, and 488 HC samples were genotyped for the 43 *SNCA* SNPs using Sequenom technology. All SNPs had a genotyping call rate > 90% and MAF > 5% and were in HWE in control subjects. After LD pruning ($r^2 > 0.8$), 22 SNPs were selected for single SNP association analysis (see Supplementary Table 1). Logistic regression analysis was used to test for association between the 22 tagging SNPs and disease status (PD, PD-noCI, PDD, or DLB vs HC) with and without adjusting for the following covariates; age, gender, site, and APOE ϵ4 dosage. Allele frequencies, ORs, and probability values are reported in Supplementary Table 3. Results are displayed in Figure 1. After correction for multiple testing, 6 SNPs (rs356220, rs356225, rs3857057, rs10018362, rs2737029, rs7689942) showed a significant association with PD, and 3 SNPs (rs62306323, rs974711, rs1348224) reached statistical significance in the DLB samples. All SNPs except rs62306323 remained significantly associated after adjusting for covariates. Cognitive assessments were available for 1,067 (72%) of 1,492 patients with PD; 572 patients were classified as PD-noCI and 198 as PDD. The remaining 297 patients were considered to have some degree of cognitive impairment, and were not included in subsequent analyses. In the PD-noCI group, rs356220 and rs10018362 reached statistical significance after Bonferroni correction, and rs10018362 remained significant after covariate adjustment. In the PDD group, 3 SNPs (rs10018362, rs7689942, rs1348224) showed a statistically significant association, and rs10018362 and rs7689942 remained significant after covariate adjustment.

Furthermore, haplotype-based association analysis was performed for SNPs within LD blocks (see Fig 1 and Supplementary Table 4). A significant risk haplotype was identified in both the PD and PD-noCI groups (frequency: 8.7% in PD, 8.9% in PD-noCI, 5.6% in HCs; OR [95% CI] = 1.67 [1.32–2.11], $p = 6.34 \times 10^{-5}$, p-perm = 2.00×10^{-4}, OR [95% CI] = 1.71 [1.29–2.28], $p = 6.00 \times 10^{-4}$, p-perm = 0.0031×10^{-4} in PD and PD-noCI, respectively). The risk haplotype, spanning approximately 74kb from intron 4 to the 3′ end of *SNCA*, is tagged by rs356220-T, rs3857057-G, rs10018362-C, and rs2737029-C. Two alternative 11kb haplotypes in *SNCA* intron 4 were also significantly associated with increased risk of PDD (rs62306323-C and rs7689942-T; frequency: 9.1% in PDD, 4.9% in HC; OR [95% CI] = 2.01 [1.33–3.04], $p = 9.18 \times 10^{-4}$, p-perm = 0.01) or DLB (rs62306323-T and rs7689942-C; frequency: 15.3% in DLB, 11.6% in HC; OR [95% CI] = 1.37 [1.13–1.66], $p = 0.001$, p-perm = 0.02). Both haplotypes remain as significant after covariate adjustment.

To identify the complete set of DNA variants in the 11kb associated haplotype in *SNCA* intron 4, all variants within this region were extracted for the samples that underwent HTS (1,366 PD, 122 DLB, and 490 HC). A total of 79 single nucleotide variants were identified, of which 45 had an MAF < 0.01 and 15 were novel relative to dbSNP build 142. Of the 79 variants in the interval, 11 are in complete LD ($r^2 > 0.98$) with the PDD-associated SNP (rs7689942), whereas none is in LD ($r^2 > 0.5$) with the DLB-associated SNP (rs62306323). Haplotype reconstruction identified 21 distinct haplotypes, of which 11 had a frequency > 0.01 (Fig 2). Remarkably, both the DLB and PDD risk haplotypes were uniquely tagged by SNPs included in the initial set of 43 SNPs. Haplotype association analysis showed a significant association between the rs62306323-C rs7689942-T haplotype and PDD (frequency: 9.7% in PDD, 5.0% in HCs; OR [95% CI] = 2.14 [1.33–3.43], $p = 0.002$, p-perm = 0.01; Supplementary Table 5). The number of rare variants in the 11kb region was no different between PDD risk haplotype carriers and noncarriers.

Four repeated elements (AluJb, chr4:90716499-90716796; AluSx1, chr4:90717144-90717436; $TTTC_n$ repeat, chr4:90723737-90723915; THE1D, chr4:90724732-90725112) within the 11kb region could not be examined by HTS (see Fig 2). These regions were Sanger sequenced in homozygote subjects for each of the 5 common haplotypes (frequency > 0.5). Three repeated elements (AluJb, AluSx1, THE1D) were univariate in size (wild-type) in all subjects. However, a variable number of $TTTC_n$ repeats was observed for different haplotypes (see Supplementary Table 6 for a detailed description of the repeat structure). Genotyping of the repeat in 520 individuals (239 PD, 281 HC) showed that every haplotype is associated with a specific repeat size (ranging from 289 to 301bp), with the exception of the PDD risk haplotype, which is associated with larger expanded repeat sizes (all > 309bp; see Fig 2). Subsequent genotyping of all the PDD risk haplotype carriers (81 HC and 180 PD) revealed that the PDD risk allele is uniquely tagged by an expanded $TTTC_n$ repeat (size ranging from 309 to 345bp). Nevertheless, among PDD haplotype carriers the distribution of the repeat sizes was not different between diagnostic groups (Supplementary Table 7).

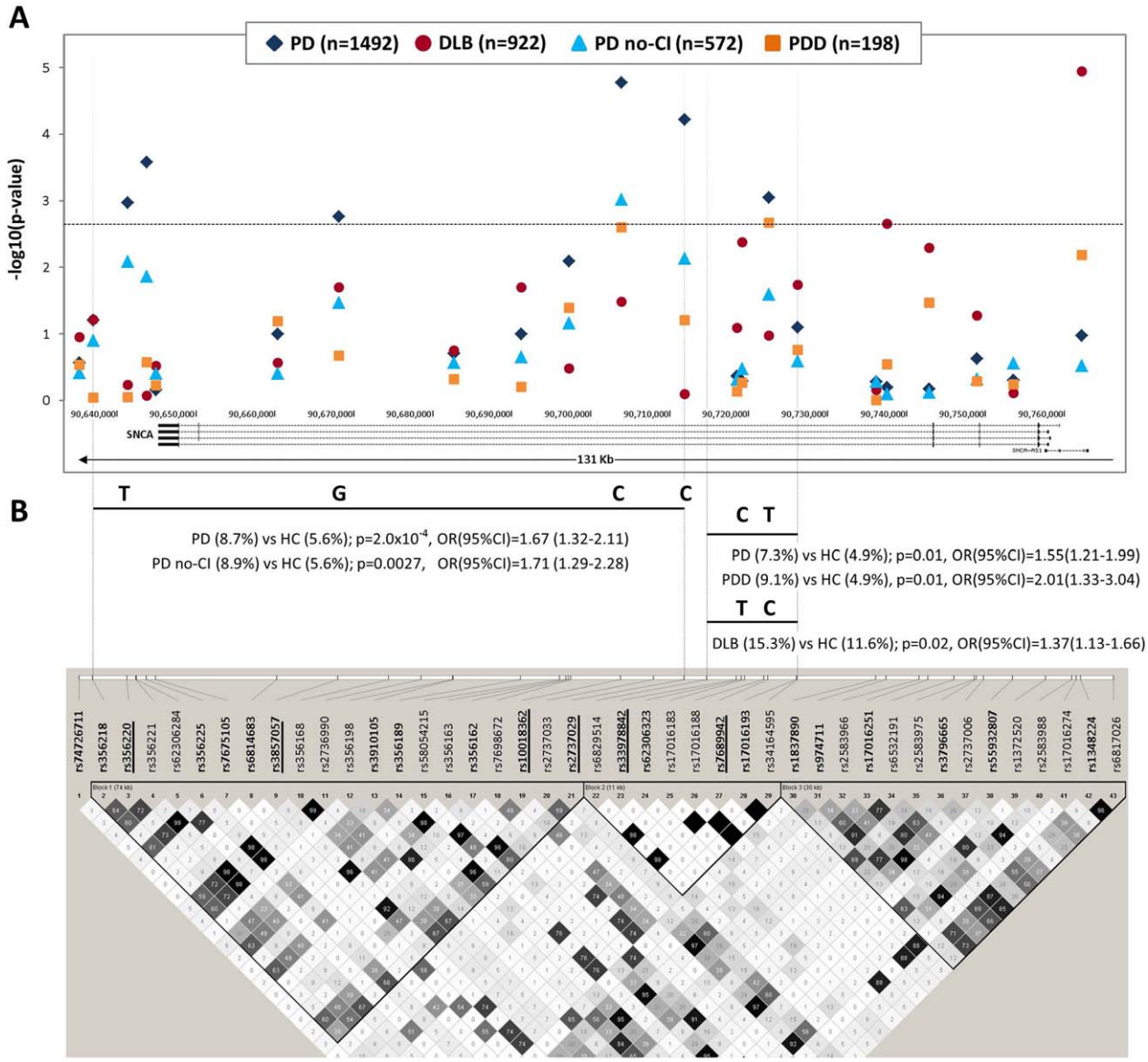

FIGURE 1: Regional association plot and linkage disequilibrium structure for the *SNCA* locus. (A) Logistic regression, adjusting for age, gender, site, and apolipoprotein E dosage, was performed for each group (Parkinson disease [PD], PD without cognitive impairment [PD no-CI], PD with dementia [PDD], dementia with Lewy bodies [DLB]) versus healthy controls (HC; n = 971). Probability values for the 22 tagging single nucleotide polymorphisms (SNPs) are plotted (as −log10 P) against their physical position on chromosome 4 (National Center for Biotechnology Information Build 37). The locations of known genes in the region are also shown. The black dotted line represents Bonferroni correction threshold of 0.002. (B) Disease-associate haplotypes are indicated by black lines. Frequencies, odds ratios (ORs), and probability values (after 10,000 permutations) are also shown. SNPs defining the haplotypes are underlined, and the corresponding alleles are indicated with capital letters. The linkage disequilibrium map is based on r^2 values in the associated regions using genotyping results for all the 43 SNPs in HC, as derived by Haploview software (darker shades represent greater r^2 values). CI = confidence interval. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

Discussion

In the present study, we have explored the contribution of *SNCA* genetic variability to PD, PD-noCI, PDD, and DLB. These disorders share similarities in motor and cognitive dysfunction, and are characterized by Lewy body pathology. Results from an analysis of 43 tagging SNPs spanning the entire *SNCA* locus show 2 distinct association profiles for symptoms of parkinsonism and/or dementia, respectively, toward the 3′ or the 5′ of the *SNCA* gene. In addition, we identify a specific haplotype in *SNCA* intron 4 that is directly associated with PDD. Collectively, our results suggest that PD, PDD, and DLB, rather than representing a disease continuum, have distinct genetic etiologies, albeit within one locus.

Cognitive decline is one of the most debilitating manifestations of disease progression in PD, and it has

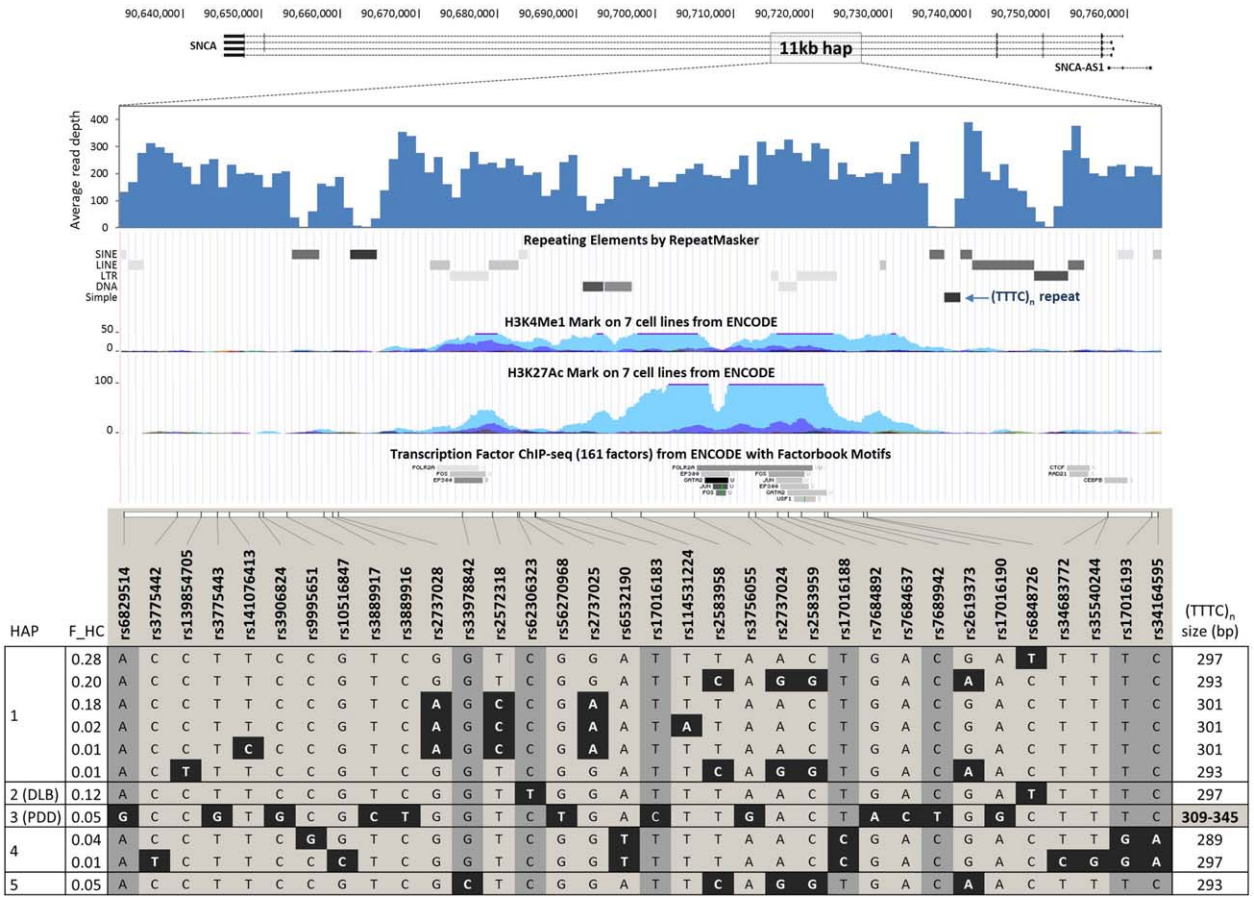

FIGURE 2: Analysis of the 11kb dementia with Lewy bodies (DLB)/Parkinson disease with dementia (PDD)-associated haplotype. Schematic representation of the *SNCA* gene show the relative position of the 11kb haplotype *(gray box)*. The average read depth across the interval in 100bp bins is shown. Repeated elements in the region (RepeatMasker), and ENCODE regulatory tracks (including H3K4Me1, H3K27Ac, and transcription factor binding sites) are annotated. The position of single nucleotide polymorphisms (SNPs) with minor allele frequency > 0.1 is indicated. Haplotypes (HAP; frequency > 0.1) are displayed and numbered (1–5) accordingly to Supplementary Table 5. The frequency in controls (F_HC) is given next to each haplotype. Alternative alleles are highlighted in black, and SNPs originally included in the 43-SNP set are shaded in darker gray. The $TTTC_n$ repeat length is also shown for each haplotype; a short repeat expansion (size = 309–345bp, in bold and shaded) is associated with the PDD risk haplotype. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

an important influence on patient management and prognosis. The incidence rate of dementia is estimated to be at least 4-fold higher among patients with PD than in the general population.[3] However, only a few genetic studies have been conducted in this area and the specific genetic contributions to cognitive impairment are still poorly understood. Herein, we have looked at *SNCA* variability in patients with PD at two extremes of the cognitive spectrum. Genetic variability within the *SNCA* gene has been unequivocally associated with sporadic PD susceptibility.[28,29] Initial results highlighted 5′ promoter variability (REP1, D4S3481),[30] but several independent association signals have been identified across the locus.[31,32] REP1 was not associated with disease in this study (data available on request). However, our results show a 74kb haplotype, from intron 4 to the 3′ end of *SNCA*, is associated with increased risk of PD (OR [95% CI] = 1.67 [1.32–2.11], $p = 6.34 \times 10^{-5}$, p-perm = 2.00×10^{-4}). The association profile in PD without cognitive impairment overlaps the one observed for all patients with PD (OR [95% CI] = 1.71 [1.29–2.28], $p = 6.00 \times 10^{-4}$, p-perm = 0.003).

In agreement with previous studies,[33,34] our results show significant association of the *SNCA* locus with PD and DLB, and show that alleles conferring that risk are different in these 2 diseases. The top DLB-associated SNP (rs1348224, OR [95% CI] = 0.71 [0.61–0.83], $p = 1.1 \times 10^{-5}$) is located 2.5kb upstream of the *SNCA* gene. This SNP is in almost complete LD ($r^2 > 0.95$; LD calculation based on genotypes extracted from the samples that underwent *SNCA* locus HTS) with rs894280, the top SNP recently reported by Bras et al.[33] rs894280 and rs1348224 are 1,063bp apart (chr4:90760883–90761946) and show comparable ORs in the same direction. However, they are frequent ($MAF_{HC} = 0.50$) and tag a common ancestral haplotype. Higher-resolution nucleotide sequencing of the 5′ flanking region of the *SNCA* gene is now

warranted in additional patients with DLB to precisely define the functional variant(s).

Extending prior studies, our analysis reveals a significant association between an 11kb haplotype located more 5′ in intron 4 in both PDD and DLB, albeit on alternate alleles. Within this region, using HTS, we have defined the genetic variability at single nucleotide resolution. Complementary analysis of repeated elements also found a novel, informative $TTTC_n$ for which the largest, expended alleles are associated with PDD risk (see Fig 2). Nevertheless, although these alleles are associated with twice the risk of PDD, only a small number of PDD cases (9.1%) carry them. Of note, the 11kb haplotype contains major histone modifications, H3K4Me1 and H3K27Ac marks, that denote an active enhancer[35] (see Fig 2). Hence, single nucleotide and tandem repeat variability may jointly contribute to cis-regulation of *SNCA* expression.[36]

Several studies have reported dysregulation of *SNCA* expression in sporadic PD brains,[37–40] and suggest that *SNCA* variability affects gene expression.[41–43] Some efforts have also been made to investigate potential regulatory elements. Sterling and colleagues[44] analyzed conserved noncoding genomic regions across the *SNCA* locus and identified 12 cis-regulatory regions that modulate expression of a reporter; the element with the highest fold change (2.5-fold) is located within the PDD/DLB-associated haplotype (chr4: 90721509–90721763). Lutz and colleagues[45] found that an intronic CT-rich region in *SNCA* intron 4 increased risk of developing Lewy body pathology in Alzheimer disease, influencing histone modification and *SNCA* transcriptional regulation. However, no association was detected in our study of PD or DLB (employing rs17016193 as a surrogate for rs2298728 in LD [$r^2 > 0.96$]).

Limitations of this cross-sectional study are that phenotype data related to PD and cognition were analyzed at 1 point in time, and originate from several studies and sites (see Table 1). Clinical data on postmortem cases were obtained by retrospective chart review. In contrast, de novo subjects within the Parkinson's Progression Markers Initiative Consortium are prospectively followed and may yet develop cognitive impairment and dementia. Although more detailed, prospective, cognitive data are available for the PD-MCI Consortium, these samples represent a smaller subset of patients, who may also go on to develop dementia. We accounted for predictors of cognitive function by including demographic characteristics (eg, age, gender, and *APOE* ϵ4 dosage) in the regression models, age being the most prominent risk factor for PDD.[46,47] However, cognitive impairment in PD also correlates with the severity of motor disability[48] and cognitive tests scores should be corrected for education[21]; these were not available for most of the subjects. Despite these caveats, all diagnoses were made by movement disorders specialty-trained neurologists using established criteria, and within and among sites the study protocols were well defined and have common clinical elements that facilitated post hoc data harmonization.

SNCA was the first locus implicated in PD and confers the highest population-attributable risk in genome-wide meta-analyses.[31] It remains the only gene unequivocally associated with disease susceptibility, progression, and pathology. Here, we precisely define and dissect genetic variability within the *SNCA* locus using HTS at single nucleotide resolution. Rather than a continuum, we show that PD, PDD, and DLB have overlapping but unique genetic architectures, albeit within the same genomic region. Such genetic predictors of cognitive decline may now optimize stratification in clinical trials and advance clinical care (reviewed by Chen-Plotkin[49]. Longitudinal studies investigating rates of progression in motor and cognitive decline, and *SNCA* variability, are ongoing. Although genetic results for PD, PDD, and DLB show that aspects of α-synuclein biology will overlap, the results predict several mechanisms will be specific. Analyses of *SNCA* expression and aggregate protein pathology in PD without cognitive impairment (and of long disease duration), PDD, and DLB in *SNCA* genotype-defined *case*s are now warranted.

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Author Contributions

Study concept and design: I.G., J.G.G., J.C.D.-A., G.J.G., I.L., L.T.M., L.P., M.J.F.; data acquisition and analysis: I.G., D.M.E., E.N., C.S.-T., S.F.B., O.A.R.; drafting the manuscript and figures: I.G.

See online supplementary file for members of *SNCA* Cognition Study Group teams that contributed to the acquisition of clinical data, without which the study would not have been possible.

Potential Conflicts of Interest

Nothing to report.

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