α-synuclein genetic variability: a biomarker for dementia in Parkinson's disease

Ilaria Guella PhD[1], Daniel M. Evans BSc[1], Chelsea Szu-Tu MSc[1], Ekaterina Nosova PhD[1], Stephanie F. Bortnick BSc[1], *SNCA* Cognition study group[2], Jennifer G. Goldman MD, MS[3], John Dalrymple-Alford PhD[4], Gert J. Geurtsen PhD[5], Irene Litvan MD[6], Owen A. Ross PhD[7], Lefkos T. Middleton MD[8], Laura Parkkinen PhD[9], Matthew J. Farrer PhD[1]*.

[1]Centre for Applied Neurogenetics (CAN), Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada;
[2]A list of members appears at the end of the paper;
[3]Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA;
[4]New Zealand Brain Research Institute, Christchurch, New Zealand;
[5]Department of Neurology, Academic Medical Center Amsterdam, The Netherlands;
[6]Department of Neurosciences University of California, Movement Disorder Center, San Diego, CA, USA;
[7]Department of Neuroscience, Mayo Clinic, Jacksonville, FL 32224, USA;
[8]School of Public Health, Faculty of Medicine, Imperial College, St. Mary's Campus, London, UK;
[9] Oxford Parkinson's Disease Centre, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK.

* Corresponding Author:
Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada, V6T 1Z3. Tel: (604) 822 7753. Fax: (604) 822-0361; E-mail: mfarrer@can.ubc.ca

Running head: *SNCA* variability and cognitive decline

Keywords: *SNCA,* cognitive decline, Lewy body disorders.

Title character count (with spaces): 80, Running head character count: 38

Abstract word count: 250, Text word count: 3584; Tables: 2; Figures: 2; Supplementary tables 7 ;

References: 51

Abstract

Objective

The relationship between Parkinson's disease (PD), PD with dementia (PDD) and dementia with Lewy bodies (DLB) is long 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 world-wide 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 multi-national cohort of patients with PD, PDD, DLB and healthy controls.

Results

An analysis of 43 tagging single nucleotide polymorphisms across the *SNCA* locus shows two distinct association profiles for symptoms of parkinsonism and/or dementia, respectively towards 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 aetiologies 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.

Introduction

Parkinson's disease (PD) has been traditionally defined by characteristic clinical motor hallmarks of bradykinesia, tremor, muscular rigidity and postural instability. However, the non-motor 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-MCI) [1, 2] and approximately 80% of longitudinally followed patients with PD develop 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 (i.e. diagnosis of DLB is assigned when motor symptoms and dementia appear together or within one 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, since the burden of cortical Lewy bodies and neurites is often indistinguishable [7, 9-12]. Recent studies suggest increased cortical LB and Aβ deposition in temporal and parietal regions may be distinguishing features of DLB, compared to PDD [13], and may potentially be mediated by APOE ϵ4 [14]. The aetiopathogenic 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 world-wide populations *SNCA* genetic variability remains the most reproducible risk factor for idiopathic PD. However, only few investigators have looked at *SNCA* variability in terms of these different clinico-pathological groups. In this study, we have used targeted high-throughput sequencing

to comprehensively characterize the 135kb *SNCA* locus in a large multi-national cohort of patients with PD, PDD, DLB and healthy controls.

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 1492 PD, 922 DLB and 971 healthy controls (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 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 (MDS) Task Force criteria [6], or using Montreal Cognitive Assessments (MoCA) taking into account the mean score, minimum score and at score 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/ICL: PD Brain Bank). Controls were individuals with no evidence of neurological disease, including movement disorders or dementia at the time of examination.

Genetic screening

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

High Throughput Sequencing (HTS)

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, Carlsbad, CA, USA) as previously described [23]. Mapping, sequence alignment, duplicate removal, 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.

SNPs 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 (version 0.1.18) [26] was used to generate genotype calls from individual BAM files. Genotypes with depth of coverage less than 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, CA). PCR amplification, shrimp alkaline phosphatase (SAP) 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 manufacturers 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 more than 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. Odd ratios (ORs) and 95% confidence intervals (CI) are calculated for the minor allele.

The linkage disequilibrium (LD) structure of the *SNCA* locus was assessed with the software package Haploview version 4.1 [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 1492 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 HC. 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 1366 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%, MAF>5% and were in HWE in control subjects. After LD pruning (r2>0.8) 22 SNPs were selected for single SNP association analysis (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 p-values are reported in Supplementary table 3. Results are displayed in Figure 1. After correction for multiple testing, six SNPs (rs356220, rs356225, rs3857057, rs10018362, rs2737029, rs7689942) showed a significant association with PD, and three 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 1067 (72%) of 1492 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 ~~were~~ reached the statistical significance ~~t~~ after Bonferroni correction, and rs10018362 remained significant after covariate adjustment. In the PDD group three SNPs (rs10018362, rs7689942, rs1348224) showed a statistically significant association, ~~that~~ and rs10018362 and rs7689942 remained significant after covariate adjustment.

Further, haplotype-based association analysis was performed for SNPs within LD blocks (Figure 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 HC; OR [95% CI]= 1.67 [1.32-2.11], $p=6.34x10^{-5}$, $p\text{-perm}=2.00x10^{-4}$, OR [95% CI]= 1.71 [1.29-2.28], $p=6.00x10^{-4}$, $p\text{-perm}=0.0031x10^{-4}$ 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, rs2737029-C. Two alternative 11kb haplotypes in *SNCA* intron 4 were also significantly associated with increased risk of PDD (rs62306323-C rs7689942-T; frequency: 9.1% in PDD, 4.9% in HC; OR [95%CI]=2.01 [1.33-3.04], $p=9.18\ x10^{-4}$, p-perm=0.01) or DLB (rs62306323-T, 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 (1366 PD, 122 DLB and 490 HC). A total of 79 SNVs were identified of which 45 had a 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). Haplotypes reconstruction identified 21 distinct haplotypes of which 11 had a frequency >0.01 (Figure 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 HC; 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 non-carriers.

Four repeated elements (AluJb, chr4:90716499-90716796; AluSx1, chr4:90717144-90717436; $TTTC_n$ repeat, chr4:90723737-90723915; THE1D, chr4:90724732-90725112) within the 11 kb region could not be examined by HTS (Figure 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 540 individuals (239 PD, 281 HC) showed that every haplotype is associated with a specific repeat size (ranging from 289bp to 301bp), with the exception of the PDD risk haplotype which is associated with larger expanded repeat sizes (all >309bp) (Figure 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 345 bp). Nevertheless, among PDD haplotype carriers the distribution of the repeat sizes was not different between diagnostic groups (Supplementary table 7).

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 two distinct association profiles for symptoms of parkinsonism and/or dementia respectively, towards 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 a disease continuum have distinct genetic aetiologies albeit within one locus.

Cognitive decline is one of the most debilitating manifestations of disease progression in PD and it has an important influence on patient management and prognosis. The incidence rate of dementia is estimated to be at least fourfold higher among patients with PD than in the general population [3]. However, only 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 74 kb 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], $p=6.34x10^{-5}$, p-perm=$2.00x10^{-4}$). 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], $p=6.00x10^{-4}$, 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 two diseases. The top DLB associated SNP (rs1348224, OR [95% CI]=0.71 [0.61-0.83], $p=1.1x10^{-5}$) is located 2.5 kb upstream

the *SNCA* gene. This SNP is in almost complete LD (r2>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 1063bp apart (chr4:90760883-90761946) and show comparable odds ratios in the same direction. However, they are frequent (MAF_{HC}=0.50) and tag a common ancestral haplotype. Higher-resolution nucleotide sequencing 5' 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 (Figure 2). Nevertheless, while 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] (Figure 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 *SNCA* variability affects gene expression [41-43]. Some efforts have also been made to investigate potential regulatory elements. Sterling and colleagues [44] analyzed conserved non-coding 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 an intronic CT-rich region in *SNCA* intron 4 increased risk of developing Lewy body pathology in Alzheimer's 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 (r2>0.96)).

Limitations of this cross-sectional study are that phenotype data related to PD and cognition were analysed at one point in time, and originate from several studies and sites (Table 1). Clinical data on *post-mortem* cases were obtained by retrospective chart review. In contrast, *de-novo* subjects within the PPMI Consortium are prospectively followed and may yet develop cognitive impairment and dementia. While more detailed, prospective, cognitive data are available for the PD-MCI Consortium, these samples represent a smaller subset of patients and may also go on to develop dementia. We accounted for predictors of cognitive function by including demographic characteristics (e.g., 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] which 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 high throughput sequencing at single nucleotide resolution. Rather than a continuum we show 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 [49]). Longitudinal studies investigating rates of progression in motor and cognitive decline, and *SNCA* variability, are ongoing. While genetic results for PD, PDD and DLB show aspects of alpha-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* cases are now warranted.

Acknowledgement:

We very much wish to thank all the individuals and families who generously participated in this research. We appreciate the technical contribution from T. Candido, C. Thompson, V. Silva, and F. T. Pishotta.

Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (http://www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org. Biospecimens used in the analyses presented in this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) (www.ppmi-info.org/specimens). As such, the investigators within PPMI contributed to the design and implementation of PPMI and/or provided data and collected biospecimens but did not participate in the analysis or writing of this report. The complete list of PPMI Investigators can be found at http://www.ppmi-info.org/Authorslist. PPMI –a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including Abbott, Avid Radiopharmaceuticals, Biogen Idec, Covance, Elan Corporation, plc, GE Healthcare, Genentech, GlaxoSmithKline, Eli Lilly and Company, Merck, Pfizer Inc., Roche CNS group, and UCB (~~[list the full names of all of the PPMI funding partners found at~~ www.ppmi-info.org/fundingpartners~~)]~~.

This research was undertaken, in part, thanks to funding from Michael J. Fox Foundation (Cognitive Biomarkers RFA)~~,~~ the Canada Excellence Research Chairs program, and the Cundill Foundation.~~,~~ Leading Edge Endowment Funds provided by the Province of British Columbia, LifeLabs, and Genome BC support the Dr. Donald Rix BC Leadership Chair~~, and the Cundill Foundation~~. We acknowledge the Oxford Brain Bank, supported by the Medical Research Council (MRC), Brains for Dementia Research (BDR) (Alzheimer Society and Alzheimer Research UK), Autistica UK and the NIHR Oxford Biomedical Research Centre. The Mayo Clinic Jacksonville is a Morris K. Udall Parkinson's Disease Research Center of Excellence (NINDS P50 #NS072187) and is supported by The Little Family Foundation

and the Mangurian Foundation for Lewy body research. This work is also supported by NINDS R01 NS078086, R01 ES10751, NIA R01 AG015866, and P50 AG016574 (Alzheimer's Disease Research Center).

Author Contributions:

Study concept and design: IG, JGG, JDA, GJG, IL, LTM, LP, MJF; data acquisition and analysis: IG, DME, EN, CST, SFB, OAR; drafting the manuscript or figures: IG. In addition, the following teams contributed to the acquisition of clinical data without which the study would not have been possible:

***SNCA* Cognition study group:**

CAN – (CI: Mattew J Farrer); Silke Appel-Cresswell MD, Joseph K Tsui MD, Martin J McKeown MD, A. Jon Stoessl MD: Pacific Parkinson's Research Centre, Department of Medicine (Neurology) and Djavad Mowafaghian Centre for Brain Health, University of British Columbia Vancouver, BC, Canada; Jan O. Aasly MD: Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway; Department of Neurology, St. Olav's Hospital, Trondheim, Norway; Alex Rajput MD, Ali H. Rajput MD: Division of Neurology, University of Saskatchewan and Saskatoon Health Region, Saskatoon, SK, Canada.

Mayo Foundation – (CI: Owen A. Ross); Alexandra I. Soto-Ortolaza BSc, Dennis W. Dickson MD: Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA; Tanis Ferman PhD: Department of Psychiatry and Psychology, Mayo Clinic, Jacksonville, FL, USA; Zbigniew K. Wszolek MD: Department of Neurology, Mayo Clinic, Jacksonville, FL, USA; Bradley F. Boeve MD: Department of Neurology, Mayo Clinic, Rochester, MN, USA.

MDS PD-MCI Study Group – (CIs: Jennifer G. Goldman - USA; John Dalrymple-Alford - New Zealand; Gert J. Geurtsen - CARPA; Irene Litvan); Jeroen Hoogland MD, Rob M. A. de Bie MD, PhD: Department of Neurology, Academic Medical Center Amsterdam, The Netherlands.

Parkinson UK – (CIs: Lefkos T. Middleton - ICL; Laura Parkkinen - OPDC); Hazal Haytural MSc: Oxford Parkinson's Disease Centre, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK.

Potential Conflicts of Interest

None

References

1. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology. 2005 Oct 25;65(8):1239-45.
2. Litvan I, Aarsland D, Adler CH, et al. MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. Movement disorders : official journal of the Movement Disorder Society. 2011 Aug 15;26(10):1814-24.
3. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Archives of neurology. 2003 Mar;60(3):387-92.
4. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Movement disorders : official journal of the Movement Disorder Society. 2008 Apr 30;23(6):837-44.
5. Rosenthal E, Brennan L, Xie S, et al. Association between cognition and function in patients with Parkinson disease with and without dementia. Movement disorders : official journal of the Movement Disorder Society. 2010 Jul 15;25(9):1170-6.
6. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2007 Sep 15;22(12):1689-707; quiz 837.
7. Lippa CF, Duda JE, Grossman M, et al. DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. Neurology. 2007 Mar 13;68(11):812-9.
8. McKeith IG. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. Journal of Alzheimer's disease : JAD. 2006;9(3 Suppl):417-23.
9. Ballard C, Ziabreva I, Perry R, et al. Differences in neuropathologic characteristics across the Lewy body dementia spectrum. Neurology. 2006 Dec 12;67(11):1931-4.
10. Guo L, Itaya M, Takanashi M, Mizuno Y, Mori H. Relationship between Parkinson disease with dementia and dementia with Lewy bodies. Parkinsonism & related disorders. 2005 Aug;11(5):305-9.
11. Harding AJ, Halliday GM. Cortical Lewy body pathology in the diagnosis of dementia. Acta neuropathologica. 2001 Oct;102(4):355-63.
12. Jellinger KA. Morphological substrates of parkinsonism with and without dementia: a retrospective clinico-pathological study. Journal of neural transmission Supplementum. 2007(72):91-104.
13. Howlett DR, Whitfield D, Johnson M, et al. Regional Multiple Pathology Scores Are Associated with Cognitive Decline in Lewy Body Dementias. Brain pathology. 2015 Jul;25(4):401-8.
14. Ruffmann C, Calboli FC, Bravi I, et al. Cortical Lewy bodies and Abeta burden are associated with prevalence and timing of dementia in Lewy body diseases. Neuropathol Appl Neurobiol. 2015 Nov 3.
15. Poulopoulos M, Levy OA, Alcalay RN. The neuropathology of genetic Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2012 Jun;27(7):831-42.
16. Rajput AH, Rozdilsky B, Rajput A. Accuracy of clinical diagnosis in parkinsonism--a prospective study. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques. 1991 Aug;18(3):275-8.
17. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Archives of neurology. 1999 Jan;56(1):33-9.
18. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. Journal of neurology, neurosurgery, and psychiatry. 1992 Mar;55(3):181-4.

19. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. 2005 Dec 27;65(12):1863-72.
20. Dalrymple-Alford JC, MacAskill MR, Nakas CT, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. Neurology. 2010 Nov 9;75(19):1717-25.
21. Hu MT, Szewczyk-Krolikowski K, Tomlinson P, et al. Predictors of cognitive impairment in an early stage Parkinson's disease cohort. Movement disorders : official journal of the Movement Disorder Society. 2014 Mar;29(3):351-9.
22. Johnson J, Hague SM, Hanson M, et al. SNCA multiplication is not a common cause of Parkinson disease or dementia with Lewy bodies. Neurology. 2004 Aug 10;63(3):554-6.
23. Steele JC, Guella I, Szu-Tu C, et al. Defining neurodegeneration on Guam by targeted genomic sequencing. Annals of neurology. 2015 Mar;77(3):458-68.
24. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic acids research. 2010 Sep;38(16):e164.
25. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics. 2005 Jan 15;21(2):263-5.
26. Li H, Handsaker B, Wysoker A, et al. The Sequence Alignment/Map format and SAMtools. Bioinformatics. 2009 Aug 15;25(16):2078-9.
27. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. American journal of human genetics. 2007 Sep;81(3):559-75.
28. Nalls MA, Pankratz N, Lill CM, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nature genetics. 2014 Sep;46(9):989-93.
29. Satake W, Nakabayashi Y, Mizuta I, et al. Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. Nature genetics. 2009 Dec;41(12):1303-7.
30. Maraganore DM, de Andrade M, Elbaz A, et al. Collaborative analysis of alpha-synuclein gene promoter variability and Parkinson disease. Jama. 2006 Aug 9;296(6):661-70.
31. Mata IF, Shi M, Agarwal P, et al. SNCA variant associated with Parkinson disease and plasma alpha-synuclein level. Archives of neurology. 2010 Nov;67(11):1350-6.
32. Winkler S, Hagenah J, Lincoln S, et al. alpha-Synuclein and Parkinson disease susceptibility. Neurology. 2007 Oct 30;69(18):1745-50.
33. Bras J, Guerreiro R, Darwent L, et al. Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. Hum Mol Genet. 2014 Dec 1;23(23):6139-46.
34. Nishioka K, Wider C, Vilarino-Guell C, et al. Association of alpha-, beta-, and gamma-Synuclein with diffuse lewy body disease. Archives of neurology. 2010 Aug;67(8):970-5.
35. Heintzman ND, Hon GC, Hawkins RD, et al. Histone modifications at human enhancers reflect global cell-type-specific gene expression. Nature. 2009 May 7;459(7243):108-12.
36. Gymrek M, Willems T, Guilmatre A, et al. Abundant contribution of short tandem repeats to gene expression variation in humans. Nature genetics. 2015 Dec 7.
37. Beyer K, Ispierto L, Latorre P, Tolosa E, Ariza A. Alpha- and beta-synuclein expression in Parkinson disease with and without dementia. Journal of the neurological sciences. 2011 Nov 15;310(1-2):112-7.
38. Chiba-Falek O, Lopez GJ, Nussbaum RL. Levels of alpha-synuclein mRNA in sporadic Parkinson disease patients. Movement disorders : official journal of the Movement Disorder Society. 2006 Oct;21(10):1703-8.
39. Kingsbury AE, Daniel SE, Sangha H, Eisen S, Lees AJ, Foster OJ. Alteration in alpha-synuclein mRNA expression in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2004 Feb;19(2):162-70.

40. Neystat M, Lynch T, Przedborski S, Kholodilov N, Rzhetskaya M, Burke RE. Alpha-synuclein expression in substantia nigra and cortex in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 1999 May;14(3):417-22.
41. Fuchs J, Tichopad A, Golub Y, et al. Genetic variability in the SNCA gene influences alpha-synuclein levels in the blood and brain. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2008 May;22(5):1327-34.
42. Linnertz C, Saucier L, Ge D, et al. Genetic regulation of alpha-synuclein mRNA expression in various human brain tissues. PloS one. 2009;4(10):e7480.
43. Sotiriou S, Gibney G, Baxevanis AD, Nussbaum RL. A single nucleotide polymorphism in the 3'UTR of the SNCA gene encoding alpha-synuclein is a new potential susceptibility locus for Parkinson disease. Neuroscience letters. 2009 Sep 18;461(2):196-201.
44. Sterling L, Walter M, Ting D, Schule B. Discovery of functional non-coding conserved regions in the alpha-synuclein gene locus. F1000Research. 2014;3:259.
45. Lutz MW, Saul R, Linnertz C, Glenn OC, Roses AD, Chiba-Falek O. A cytosine-thymine (CT)-rich haplotype in intron 4 of SNCA confers risk for Lewy body pathology in Alzheimer's disease and affects SNCA expression. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2015 Jun 13.
46. Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. Brain : a journal of neurology. 2010 Jun;133:1755-62.
47. Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain : a journal of neurology. 2009 Nov;132(Pt 11):2958-69.
48. Levy G, Tang MX, Cote LJ, et al. Motor impairment in PD: relationship to incident dementia and age. Neurology. 2000 Aug 22;55(4):539-44.
49. Chen-Plotkin AS. Unbiased approaches to biomarker discovery in neurodegenerative diseases. Neuron. 2014 Nov 5;84(3):594-607.
50. Parkinson Progression Marker I. The Parkinson Progression Marker Initiative (PPMI). Progress in neurobiology. 2011 Dec;95(4):629-35.
51. Geurtsen GJ, Hoogland J, Goldman JG, et al. Parkinson's disease mild cognitive impairment: application and validation of the criteria. Journal of Parkinson's disease. 2014;4(2):131-7.

Figure 1: Regional association plot and linkage disequilibrium structure for the *SNCA* locus

A) Logistic regression, adjusting for age, gender, site and APOE dosage, was performed for each group (PD, PD-noCI, PDD, DLB) versus HC (n=971). P values for the 22 tagging SNPs are plotted (as −log10 P) against their physical position on chromosome 4 (NCBI 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, ORs and p-values (after 10000 permutations) are also shown. SNPs defining the haplotypes are underlined and the corresponding alleles are indicated with capital letters. LD map 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 of black represent greater r^2 values).

Figure 2: Analysis of the 11kb DLB/PDD associated haplotype

Schematic representation of the *SNCA* gene showing the relative position of the 11kb haplotype (grey 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 SNPs with MAF>0.1 is indicated. Haplotypes (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 SNPs set are shaded in darker grey. The $TTTC_n$ repeat length is also shown for each haplotype, a short repeat expansion (size 309bp to 345bp, in bold and shaded) is associated with the PDD risk haplotype.

Table 1: Cohort description

	CI	PD (n)	DLB (n)	HC (n)
UBC	MJF	421	67	556
PPMI[50]		465		209
CARPA: PD-MCI [51]	GJG	110		
USA: PD-MCI [51]	JGG	75		
New Zealand: PD-MCI [51]	JDA	143		55
Mayo	OAR	84	798	91
UK/ICL: PD Brain Bank	LTM	194	5	
UK/OPDC: Oxford Brain Bank	LP		52	60
TOTAL		1492	922	971

CI, coordinating investigator for each site; HC, Healthy controls; PD, Parkinson's disease; DLB, Dementia with Lewy body. UBC, University of British Columbia; ICL, Imperial College London; OPDC Oxford Parkinson's Disease Centre.

Table 2: Sample Demographics

Diagnosis	n	Neuropath diagnosis	Gender (Male %)	Age/ Age at Death	Age at Onset	Disease duration
PD	1492	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*	10.8 ± 4.9*
HC	971	115	53.4	72.0 ± 12.6	-	-

mean ± SD; * data only available for 468 subjects
HC, Healthy controls; PD, Parkinson's disease; PD-noCI, PD with no cognitive impairment; PDD, PD dementia; DLB, Dementia with Lewy body.

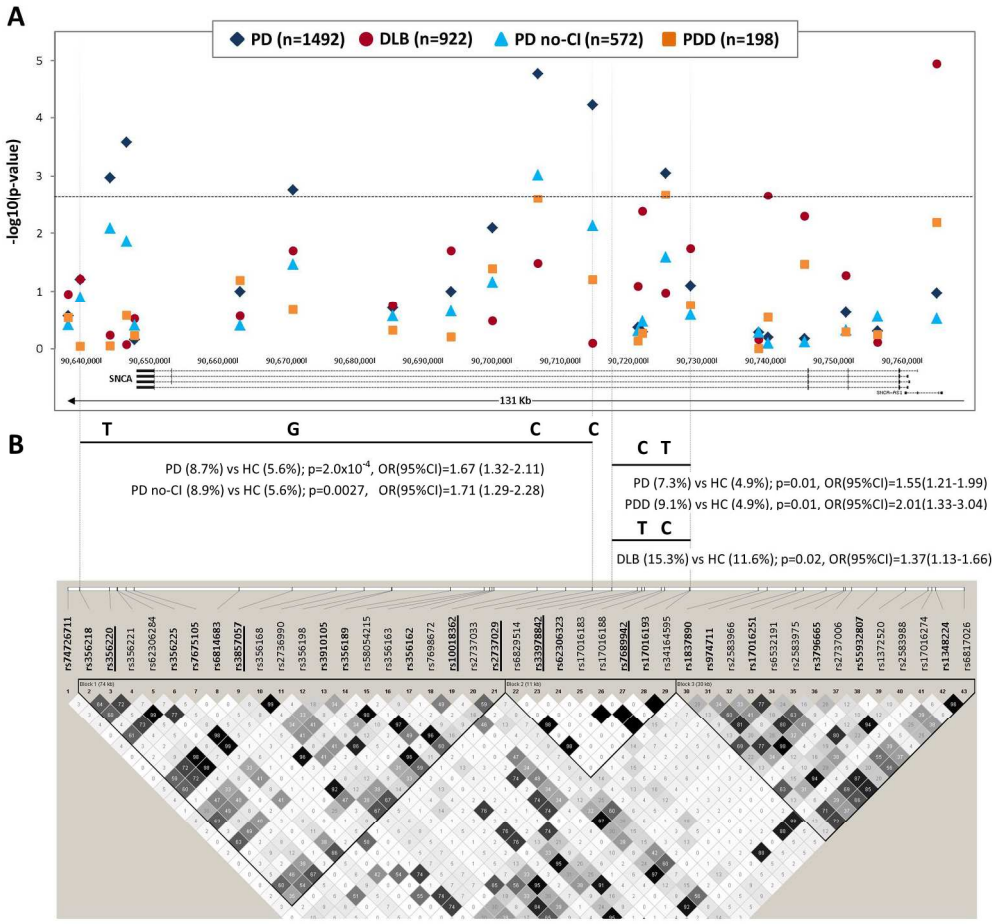


Figure 1: Regional association plot and linkage disequilibrium structure for the SNCA locus
190x177mm (300 x 300 DPI)

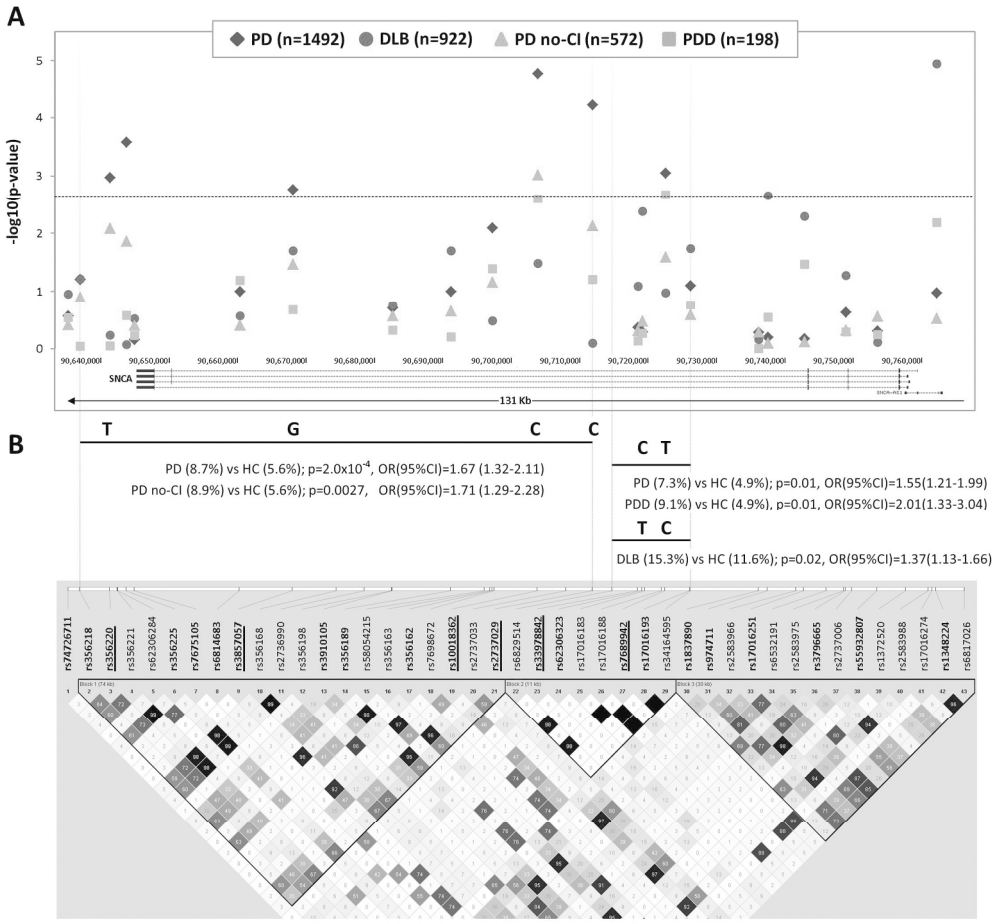
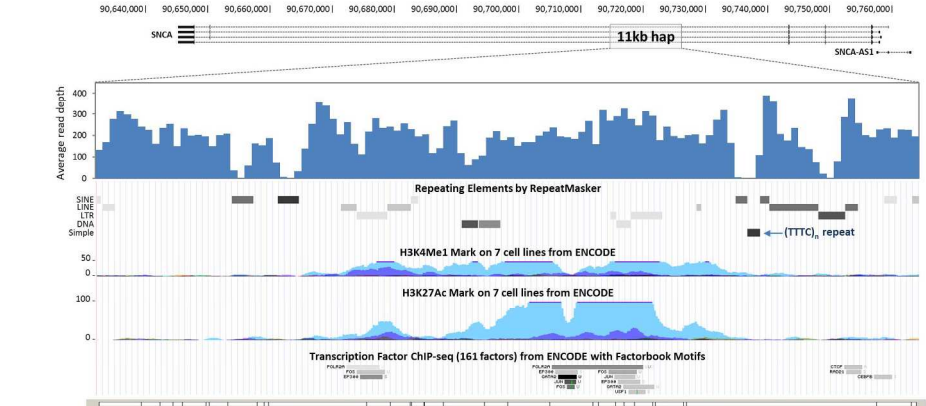
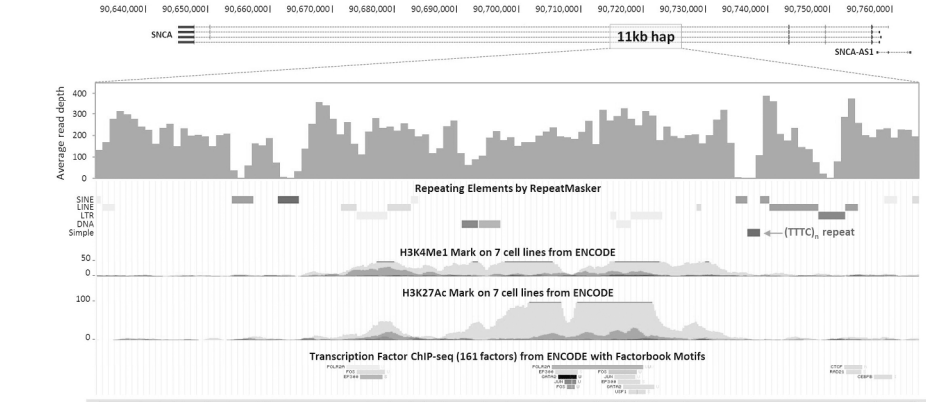


Figure 1: Regional association plot and linkage disequilibrium structure for the SNCA locus
190x177mm (300 x 300 DPI)



HAP	F_HC	rs6829514	rs3775442	rs139854705	rs3775443	rs141076413	rs3906824	rs9956651	rs10516847	rs3889917	rs3889916	rs2737028	rs33978842	rs2572318	rs62306323	rs56270968	rs2737025	rs6532190	rs17016183	rs1145312224	rs2583958	rs3756055	rs2737024	rs2583959	rs17016188	rs7684892	rs7684637	rs7689942	rs2619373	rs17016190	rs6848726	rs34683772	rs35540244	rs17016193	rs34164595	(TTTC)n size (bp)
1	0.28	A	C	C	T	T	C	C	G	T	C	G	G	T	C	G	G	A	T	T	T	A	A	C	T	G	A	C	G	A	T	T	T	T	C	297
	0.20	A	C	C	T	T	C	C	G	T	C	G	G	T	C	G	G	A	T	T	C	A	G	G	T	G	A	C	A	A	C	T	T	T	C	293
	0.18	A	C	C	T	T	C	C	G	T	C	A	G	C	C	G	A	A	T	T	T	A	A	C	T	G	A	C	G	A	C	T	T	T	C	301
	0.02	A	C	C	T	T	C	C	G	T	C	A	G	C	C	G	A	A	T	A	T	A	A	C	T	G	A	C	G	A	C	T	T	T	C	301
	0.01	A	C	C	T	C	C	C	G	T	C	A	G	C	C	G	A	A	T	T	T	A	A	C	T	G	A	C	G	A	C	T	T	T	C	301
	0.01	A	C	T	T	T	C	C	G	T	C	G	G	T	C	G	G	A	T	T	C	A	G	G	T	G	A	C	A	A	C	T	T	T	C	293
2 (DLB)	0.12	A	C	C	T	T	C	C	G	T	C	G	G	T	T	G	G	A	T	T	T	A	A	C	T	G	A	C	G	A	T	T	T	T	C	297
3 (PDD)	0.05	G	C	C	G	T	G	C	G	C	T	G	G	T	C	T	G	A	C	T	T	G	A	C	T	A	C	T	G	G	C	T	T	T	C	309-345
4	0.04	A	C	C	T	T	C	G	G	T	C	G	G	T	C	G	G	T	T	T	T	A	A	C	C	G	A	C	G	A	C	T	T	G	A	289
	0.01	A	T	C	T	T	C	C	C	T	C	G	G	T	C	G	G	T	T	T	T	A	A	C	C	G	A	C	G	A	C	C	G	G	A	297
5	0.05	A	C	C	T	T	C	C	G	T	C	G	C	T	C	G	G	A	T	T	C	A	G	G	T	G	A	C	A	A	C	T	T	T	C	293

Figure 2: Analysis of the 11kb DLB/PDD associated haplotype
209x152mm (300 x 300 DPI)



HAP	F_HC	rs6829514	rs3775442	rs139854705	rs3775443	rs141076413	rs3906824	rs9995651	rs10516847	rs3889917	rs3889916	rs2737028	rs33978842	rs2572318	rs62306323	rs56270968	rs2737025	rs6532190	rs17016183	rs1145312224	rs2583958	rs3756055	rs2737024	rs2583959	rs17016188	rs7684892	rs7684637	rs7689942	rs2619373	rs17016190	rs6848726	rs34683772	rs35540244	rs17016193	rs34164595	(TTTC)n size (bp)
1	0.28	A	C	C	T	T	C	C	G	T	C	G	G	T	C	G	G	A	T	T	T	A	A	C	T	G	A	C	G	A	T	T	T	T	C	297
	0.20	A	C	C	T	T	C	C	G	T	C	G	G	T	C	G	G	A	T	T	C	A	G	G	T	G	A	C	A	A	C	T	T	T	C	293
	0.18	A	C	C	T	T	C	C	G	T	C	A	G	C	C	G	A	A	T	T	T	A	A	C	T	G	A	C	G	A	C	T	T	T	C	301
	0.02	A	C	C	T	T	C	C	G	T	C	A	G	C	C	G	A	A	T	A	T	A	A	C	T	G	A	C	G	A	C	T	T	T	C	301
	0.01	A	C	C	T	C	C	C	G	T	C	A	G	C	C	G	A	A	T	T	T	A	A	C	T	G	A	C	G	A	C	T	T	T	C	301
	0.01	A	C	T	T	T	C	C	G	T	C	G	G	T	C	G	G	A	T	T	C	A	G	G	T	G	A	C	A	A	C	T	T	T	C	293
2 (DLB)	0.12	A	C	C	T	T	C	C	G	T	C	G	G	T	T	G	G	A	T	T	T	A	A	C	T	G	A	C	G	A	T	T	T	T	C	297
3 (PDD)	0.05	G	C	C	G	T	G	C	G	C	T	G	G	T	C	T	G	A	C	T	T	G	A	C	T	A	C	T	G	G	C	T	T	T	C	309-345
4	0.04	A	C	C	T	T	C	G	G	T	C	G	G	T	C	G	G	T	T	T	T	A	A	C	C	G	A	C	G	A	C	T	T	G	A	289
	0.01	A	T	C	T	T	C	C	C	T	C	G	G	T	C	G	G	T	T	T	T	A	A	C	C	G	A	C	G	A	C	C	G	G	A	297
5	0.05	A	C	C	T	T	C	C	G	T	C	G	C	T	C	G	G	A	T	T	C	A	G	G	T	G	A	C	A	A	C	T	T	T	C	293

Figure 2: Analysis of the 11kb DLB/PDD associated haplotype
209x152mm (300 x 300 DPI)

Supplementary Table 1: List of 43 *SNCA* SNPs

rsID	Chr:Position	Alleles (A/B)	MAF	HWE P	Success rate
rs74726711	**4:90635286**	**G/A**	**0.06**	**0.36**	**0.95**
rs356218	**4:90637010**	**A/G**	**0.34**	**0.23**	**0.98**
rs356220	**4:90641340**	**T/C**	**0.38**	**0.24**	**0.95**
rs356221	4:90642464	A/T	0.46	0.19	0.96
rs62306284	**4:90642531**	**G/A**	**0.08**	**0.82**	**0.94**
rs356225	**4:90643757**	**C/G**	**0.46**	**0.15**	**0.96**
rs7675105	4:90644960	T/C	0.06	0.27	0.98
rs6814683	4:90660294	G/A	0.04	0.25	0.96
rs3857057	4:90668019	G/A	0.07	0.04	0.98
rs356168	4:90674431	G/A	0.47	0.07	0.95
rs2736990	4:90678541	G/A	0.46	0.14	0.98
rs356198	4:90682504	T/C	0.18	0.32	0.98
rs3910105	**4:90682571**	**G/A**	**0.46**	**0.55**	**0.96**
rs356189	**4:90691132**	**T/C**	**0.29**	**0.82**	**0.98**
rs58054215	4:90696036	C/T	0.07	0.21	0.98
rs356163	4:90696827	A/C	0.29	1.00	0.98
rs356162	**4:90697157**	**C/T**	**0.20**	**0.68**	**0.97**
rs7698672	4:90697466	C/T	0.06	1.00	0.91
rs10018362	**4:90703753**	**C/T**	**0.10**	**0.58**	**0.97**
rs2737033	4:90707947	C/T	0.27	0.16	0.94
rs2737029	**4:90711770**	**C/T**	**0.40**	**0.39**	**0.98**
rs6829514	4:90714635	G/A	0.05	0.72	0.91
rs33978842	**4:90718390**	**C/G**	**0.05**	**1.00**	**0.97**
rs62306323	**4:90718995**	**T/C**	**0.12**	**1.00**	**0.98**
rs17016183	4:90719460	C/T	0.05	0.72	0.97
rs17016188	4:90721880	C/T	0.06	0.39	0.98
rs7689942	**4:90722400**	**T/C**	**0.05**	**0.72**	**0.98**
rs17016193	**4:90726022**	**G/T**	**0.06**	**0.39**	**0.98**
rs34164595	4:90726089	A/C	0.06	0.39	0.97
rs1837890	**4:90736006**	**A/C**	**0.25**	**0.61**	**0.96**
rs974711	**4:90737327**	**A/G**	**0.46**	**0.52**	**0.97**
rs2583966	4:90741519	A/G	0.29	0.88	0.98
rs17016251	**4:90742639**	**C/G**	**0.45**	**0.48**	**0.98**
rs6532191	4:90745930	C/T	0.49	0.61	0.97
rs2583975	4:90748488	T/C	0.19	0.40	0.98
rs3796665	**4:90748710**	**A/G**	**0.40**	**0.69**	**0.97**
rs2737006	4:90749686	G/A	0.29	0.76	0.98
rs55932807	**4:90753339**	**T/A**	**0.05**	**0.72**	**0.97**
rs1372520	4:90757505	T/C	0.21	0.37	0.94
rs2583988	4:90760828	T/C	0.28	0.48	0.98
rs17016274	4:90761357	A/T	0.06	0.55	0.97
rs1348224	**4:90761946**	**G/A**	**0.50**	**0.75**	**0.97**
rs6817026	4:90766069	C/T	0.51	0.75	0.96

Chr, chromosome; position, NCBI Build 37 (hg19); A, minor allele; B, major allele; MAF, minor allele frequency; HWE P, Hardy-Weinberg equilibrium in healthy controls. SNPs with r2<0.8 (tSNPs) are marked in bold.

Supplementary table 2: APOE allele and genotype frequencies by groups.

	Genotype Frequency						Allele Frequency			
Group	ε2/ε2	ε2/ε3	ε3/ε3	ε2/ε4	ε3/ε4	ε4/ε4	ε1	ε2	ε3	ε4
HC	1.2	10.9	57.4	2.3	25.9	2.3	0.0	7.7	75.8	16.4
PD	0.9	12.7	58.8	2.0	23.3	2.3	0.1	8.4	76.7	14.9
PD-noCI	1.3	14.1	59.0	1.1	22.9	1.6	0.2	9.0	77.2	13.6
PDD	1.0	9.3	54.1	2.1	28.9	4.6	0.0	6.7	73.2	20.1
DLB	0.1	5.9	37.8	4.1	41.0	11.0	0.0	5.1	61.3	33.6

HC, Healthy controls; PD, Parkinson's disease; PD-noCI, PD with no cognitive impairment; PDD, PD dementia; DLB, Dementia with Lewy body

Supplementary Table 3: Logistic regression analysis of *SNCA* tagging SNPs

		PD				PD-noCI				PDD				DLB			
rsID	MAF HC	MAF	UNADJUSTED OR (95%CI)	p	ADJUSTED OR (95%CI)	p	MAF	UNADJUSTED OR (95%CI)	p	ADJUSTED OR (95%CI)	p	MAF	UNADJUSTED OR (95%CI)	p	ADJUSTED OR (95%CI)	p	MAF	UNADJUSTED OR (95%CI)	p	ADJUSTED OR (95%CI)	p
rs74726711	0.06	0.05	0.88 (0.68-1.14)	0.337	0.86 (0.65-1.13)	0.268	0.04	0.77 (0.54-1.09)	0.141	0.84 (0.58-1.24)	0.382	0.06	1.14 (0.72-1.80)	0.587	1.30 (0.80-2.11)	0.288	0.07	1.27 (0.97-1.65)	0.086	1.29 (0.94-1.77)	0.111
rs356218	0.34	0.37	1.13 (1.00-1.28)	0.050	1.13 (0.99-1.29)	0.062	0.38	1.17 (1.00-1.37)	0.047	1.14 (0.96-1.35)	0.126	0.33	0.94 (0.74-1.19)	0.578	0.98 (0.76-1.27)	0.896	0.32	0.90 (0.79-1.03)	0.135	0.86 (0.73-1.01)	0.061
rs356220	0.38	0.42	**1.23 (1.09-1.39)**	**0.001**	**1.25 (1.09-1.42)**	**0.001**	0.43	**1.29 (1.10-1.51)**	**0.002**	1.26 (1.06-1.49)	0.008	0.38	1.01 (0.80-1.27)	0.965	1.02 (0.79-1.31)	0.890	0.37	0.98 (0.86-1.12)	0.762	0.96 (0.82-1.12)	0.580
rs356225	0.46	0.52	**1.26 (1.11-1.41)**	**$2.0x10^{-4}$**	**1.27 (1.12-1.44)**	**$2.6x10^{-4}$**	0.51	1.25 (1.07-1.46)	0.004	1.23 (1.04-1.45)	0.014	0.49	1.11 (0.89-1.39)	0.353	1.15 (0.90-1.47)	0.266	0.46	1.00 (0.88-1.14)	0.956	0.98 (0.85-1.14)	0.840
rs7675105	0.06	0.06	0.94 (0.74-1.18)	0.577	0.95 (0.74-1.22)	0.684	0.07	1.07 (0.80-1.43)	0.638	1.14 (0.84-1.55)	0.388	0.07	1.05 (0.68-1.61)	0.843	0.87 (0.54-1.42)	0.588	0.08	1.30 (1.02-1.66)	0.033	1.16 (0.87-1.55)	0.301
rs6814683	0.04	0.06	1.29 (0.98-1.70)	0.066	1.27 (0.95-1.70)	0.100	0.05	1.19 (0.84-1.69)	0.324	1.17 (0.81-1.70)	0.392	0.07	1.60 (1.00-2.56)	0.050	1.62 (0.97-2.72)	0.064	0.05	1.18 (0.87-1.61)	0.293	1.23 (0.85-1.76)	0.269
rs3857057	0.07	0.09	**1.39 (1.13-1.72)**	**0.002**	**1.43 (1.15-1.79)**	**0.002**	0.09	1.30 (1.00-1.70)	0.054	1.36 (1.02-1.82)	0.034	0.09	1.38 (0.95-2.00)	0.096	1.30 (0.86-1.95)	0.209	0.09	1.30 (1.03-1.63)	0.027	1.38 (1.05-1.80)	0.020
rs3910105	0.46	0.44	0.93 (0.83-1.05)	0.246	0.92 (0.81-1.04)	0.197	0.43	0.90 (0.78-1.05)	0.178	0.91 (0.78-1.07)	0.270	0.49	1.12 (0.90-1.39)	0.319	1.09 (0.86-1.38)	0.476	0.49	1.11 (0.98-1.26)	0.115	1.11 (0.95-1.29)	0.175
rs356189	0.29	0.31	1.10 (0.96-1.24)	0.162	1.12 (0.98-1.28)	0.100	0.31	1.10 (0.93-1.29)	0.259	1.11 (0.94-1.33)	0.221	0.27	0.89 (0.70-1.14)	0.371	0.93 (0.72-1.22)	0.615	0.26	0.87 (0.75-1.00)	0.049	0.82 (0.69-0.97)	0.020
rs356162	0.20	0.17	0.84 (0.72-0.97)	0.018	0.81 (0.69-0.95)	0.008	0.18	0.88 (0.73-1.07)	0.197	0.83 (0.68-1.02)	0.069	0.15	0.74 (0.55-0.99)	0.046	0.72 (0.52-0.99)	0.041	0.18	0.88 (0.75-1.04)	0.138	0.91 (0.75-1.10)	0.329
rs10018362	0.10	0.14	**1.49 (1.24-1.80)**	**$3.2x10^{-5}$**	**1.54 (1.27-1.88)**	**$1.7x10^{-5}$**	0.13	**1.46 (1.15-1.84)**	**0.002**	**1.52 (1.19-1.95)**	**$9.5x10^{-4}$**	0.15	**1.77 (1.28-2.45)**	**$5.9x10^{-4}$**	**1.74 (1.21-2.48)**	**0.002**	0.12	1.24 (1.01-1.53)	0.041	1.30 (1.02-1.66)	0.033
rs2737029	0.40	0.45	**1.26 (1.12-1.42)**	**$1.5 x10^{-4}$**	**1.30 (1.14-1.47)**	**$6.0x10^{-5}$**	0.44	1.22 (1.04-1.42)	0.013	1.25 (1.06-1.47)	0.007	0.44	1.20 (0.96-1.50)	0.108	1.26 (0.99-1.60)	0.062	0.40	1.01 (0.89-1.15)	0.841	0.98 (0.84-1.14)	0.798
rs33978842	0.05	0.05	0.93 (0.72-1.22)	0.613	0.89 (0.68-1.18)	0.430	0.05	0.92 (0.65-1.29)	0.625	0.88 (0.61-1.26)	0.484	0.05	0.99 (0.60-1.63)	0.969	0.91 (0.52-1.57)	0.727	0.04	0.76 (0.55-1.04)	0.083	0.72 (0.50-1.04)	0.081
rs62306323	0.12	0.12	1.06 (0.88-1.26)	0.557	1.07 (0.88-1.29)	0.513	0.13	1.12 (0.90-1.41)	0.318	1.13 (0.89-1.43)	0.332	0.14	1.20 (0.87-1.66)	0.270	1.12 (0.78-1.60)	0.538	0.15	**1.35 (1.12-1.64)**	**0.002**	1.39 (1.11-1.74)	0.004
rs7689942	0.05	0.07	**1.58 (1.23-2.03)**	**$3.5x10^{-4}$**	**1.56 (1.20-2.03)**	**$8.8x10^{-4}$**	0.07	1.44 (1.05-1.97)	0.022	1.46 (1.05-2.03)	0.025	0.09	**2.10 (1.39-3.17)**	**$4.1x10^{-4}$**	**2.04 (1.30-3.22)**	**0.002**	0.06	1.25 (0.94-1.66)	0.130	1.32 (0.94-1.84)	0.105
rs17016193	0.06	0.07	1.23 (0.98-1.55)	0.080	1.25 (0.97-1.59)	0.080	0.07	1.17 (0.87-1.58)	0.285	1.20 (0.88-1.65)	0.255	0.08	1.37 (0.91-2.05)	0.127	1.35 (0.88-2.09)	0.174	0.08	1.36 (1.06-1.75)	0.015	1.42 (1.06-1.90)	0.018
rs1837890	0.25	0.25	0.99 (0.86-1.12)	0.825	0.96 (0.83-1.10)	0.520	0.25	0.99 (0.84-1.17)	0.919	0.94 (0.79-1.13)	0.522	0.26	1.02 (0.79-1.32)	0.854	1.00 (0.76-1.32)	0.976	0.24	0.92 (0.80-1.07)	0.298	0.96 (0.81-1.15)	0.685
rs974711	0.46	0.45	0.97 (0.87-1.09)	0.596	0.97 (0.86-1.10)	0.631	0.45	0.96 (0.83-1.11)	0.553	0.98 (0.84-1.14)	0.794	0.50	1.15 (0.93-1.43)	0.202	1.14 (0.90-1.43)	0.284	0.51	**1.22 (1.07-1.38)**	**0.002**	**1.26 (1.09-1.46)**	**0.002**
rs17016251	0.45	0.45	1.03 (0.92-1.16)	0.618	1.03 (0.91-1.16)	0.666	0.45	1.00 (0.86-1.16)	0.989	1.03 (0.87-1.20)	0.757	0.52	1.31 (1.05-1.62)	0.017	1.29 (1.02-1.63)	0.033	0.49	1.20 (1.05-1.36)	0.006	1.24 (1.07-1.44)	0.005
rs3796665	0.40	0.38	0.93 (0.83-1.05)	0.222	0.93 (0.82-1.05)	0.235	0.38	0.93 (0.80-1.08)	0.311	0.94 (0.80-1.11)	0.479	0.42	1.09 (0.87-1.35)	0.462	1.08 (0.85-1.37)	0.514	0.43	1.13 (0.99-1.28)	0.061	1.16 (1.00-1.35)	0.053
rs55932807	0.05	0.05	1.12 (0.87-1.46)	0.379	1.10 (0.83-1.45)	0.495	0.06	1.26 (0.91-1.74)	0.169	1.22 (0.86-1.73)	0.273	0.04	0.77 (0.44-1.35)	0.370	0.84 (0.46-1.53)	0.568	0.05	1.02 (0.75-1.38)	0.900	1.06 (0.74-1.50)	0.761
rs1348224	0.50	0.48	0.91 (0.81-1.02)	0.091	0.90 (0.8-1.020)	0.104	0.49	0.95 (0.82-1.10)	0.483	0.92 (0.79-1.08)	0.298	0.41	**0.69 (0.55-0.86)**	**0.001**	0.72 (0.57-0.91)	0.007	0.43	**0.74 (0.65-0.85)**	**$6.5x10^{-6}$**	**0.71 (0.61-0.83)**	**$1.1x10^{-5}$**

HC, Healthy controls; PD, Parkinson's disease; PD-noCI, PD with no cognitive impairment; PDD, PD dementia; DLB, Dementia with Lewy body; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval. The p-values (p) were obtained by logistic regression analysis (unadjusted) or adjusted by age, gender, site and APOE dosage. Significant p-values after Bonferroni correction ($p < 0.002$) are marked in bold.

Supplementary Table 4: Haplotype Association Analysis

LD BLOCK		HAPLOTYPE	Freq HC	PD				PD-noCI				PDD				DLB			
				Freq	OR(95%CI)	p	p-perm	Freq	OR(95%CI)	p	p-perm	Freq	OR(95%CI)	p	p-perm	Freq	OR(95%CI)	p	p-perm
1	1	GCTAGCAAAACGCTCTTTTT	0.32	0.30	0.83 (0.72-0.95)	0.10	0.61	0.29	0.75 (0.63-0.90)	0.05	0.29	0.33	1.09 (0.83-1.42)	0.72	1.00	0.32	1.03 (0.88-1.20)	0.84	1.00
	2	ATAACCAAGGCATTATTTCC	0.26	0.28	1.20 (1.04-1.38)	0.08	0.57	0.29	1.22 (1.02-1.46)	0.14	0.77	0.24	0.85 (0.65-1.12)	0.43	1.00	0.23	0.79 (0.68-0.93)	0.039	0.36
	3	**GCTAGCAAAATACTCCTTTT**	**0.14**	**0.11**	**0.75 (0.63-0.89)**	**0.006**	**0.04**	0.12	0.84 (0.67-1.06)	0.20	0.87	0.09	0.61 (0.42-0.89)	0.023	0.21	0.11	0.78 (0.64-0.95)	0.034	0.34
	4	**GTAACCAGGGCACCCTCCTC**	**0.06**	**0.09**	**1.67 (1.32-2.11)**	**6.34×10^{-5}**	**2.00×10^{-4}**	**0.09**	**1.71 (1.29-2.28)**	**6.00×10^{-4}**	**0.003**	0.09	1.74 (1.16-2.60)	0.012	0.13	0.07	1.30 (1.00-1.70)	0.07	0.50
	5	**GCTGGTAAAACGCTCTTTTT**	0.06	0.06	0.99 (0.77-1.27)	0.93	1.00	0.07	1.14 (0.84-1.55)	0.44	1.00	0.06	1.10 (0.70-1.73)	0.71	1.00	**0.08**	**1.46 (1.13-1.89)**	**0.007**	**0.048**
	6	GCAACCGAGGCGCTCTTCTC	0.04	0.05	1.30 (0.97-1.76)	0.09	0.59	0.04	1.16 (0.79-1.69)	0.47	1.00	0.06	1.69 (1.03-2.77)	0.046	0.35	0.04	1.19 (0.85-1.65)	0.33	0.99
	7	ATAACCAAGGTACTCCTTTT	0.04	0.04	0.86 (0.64-1.15)	0.34	0.98	0.05	1.04 (0.72-1.49)	0.84	1.00	0.03	0.63 (0.33-1.21)	0.17	0.81	0.04	0.90 (0.65-1.25)	0.55	1.00
	8	ACAACCAAGGCGCTCCTTTT	0.02	0.02	0.89 (0.57-1.39)	0.62	1.00	0.01	0.60 (0.31-1.16)	0.13	0.72	0.02	0.89 (0.37-2.13)	0.79	1.00	0.02	1.07 (0.66-1.73)	0.78	1.00
	9	ACAACCAAGGCATTATTTCC	0.01	0.01	0.97 (0.58-1.63)	0.92	1.00	0.01	0.78 (0.38-1.59)	0.50	1.00	0.01	0.63 (0.19-2.06)	0.46	1.00	0.01	1.09 (0.63-1.91)	0.76	1.00
2	1	**AGCTTCTC**	**0.72**	**0.68**	**0.82(0.72-0.93)**	**0.002**	**0.04**	0.69	0.84(0.71-0.98)	0.029	0.4	**0.64**	**0.66(0.53-0.83)**	**4.56×10^{-4}**	**0.007**	**0.68**	**0.79(0.69-0.91)**	**0.001**	**0.024**
	2	**AGTTTCTC**	0.12	0.12	1.06(0.87-1.29)	0.55	1.00	0.13	1.12(0.90-1.40)	0.31	1.00	0.14	1.20(0.87-1.66)	0.27	0.99	**0.15**	**1.37(1.13-1.66)**	**0.001**	**0.02**
	3	**GGCCTTTC**	**0.05**	**0.07**	**1.55(1.21-1.99)**	**5.99×10^{-4}**	**0.01**	0.07	1.42(1.04-1.93)	0.026	0.36	**0.09**	**2.01(1.33-3.04)**	**9.18×10^{-4}**	**0.015**	0.05	1.14(0.85-1.53)	0.39	1.00
	4	AGCTCCGA	0.06	0.07	1.23(0.98-1.55)	0.08	0.75	0.07	1.17(0.87-1.57)	0.29	1.00	0.08	1.41(0.94-2.11)	0.09	0.77	0.07	1.29(1.00-1.66)	0.049	0.60
	5	ACCTTCTC	0.05	0.05	0.93(0.71-1.21)	0.58	1.00	0.05	0.92(0.65-1.30)	0.63	1.00	0.05	0.99(0.60-1.63)	0.97	1.00	0.04	0.77(0.56-1.05)	0.10	0.84
3	1	CAGCTCAAACCTAT	0.4	0.38	0.94(0.83-1.05)	0.29	1.00	0.38	0.92(0.79-1.08)	0.31	1.00	0.44	1.12(0.90-1.39)	0.31	1.00	0.44	1.19(1.04-1.36)	0.009	0.16
	2	AGGCTCGAACCTAT	0.04	0.06	1.35(1.02-1.79)	0.035	0.48	0.05	1.19(0.84-1.69)	0.33	1.00	0.07	1.76(1.10-2.81)	0.018	0.25	0.05	1.24(0.91-1.69)	0.17	0.96
	3	CGAGCCGGACTTGC	0.24	0.25	1.03(0.89-1.20)	0.70	1.00	0.24	1.00(0.85-1.17)	0.98	1.00	0.22	0.86(0.66-1.13)	0.28	1.00	0.2	0.79(0.67-0.92)	0.003	0.05
	4	AGGGCTGAATCTGC	0.19	0.16	0.83(0.71-0.97)	0.018	0.28	0.17	0.90(0.74-1.09)	0.28	1.00	0.14	0.68(0.50-0.94)	0.020	0.28	0.16	0.83(0.70-0.99)	0.03	0.46
	5	CGAGCCGGTCTTGC	0.05	0.05	1.07(0.80-1.42)	0.64	1.00	0.06	1.22(0.87-1.71)	0.25	0.99	0.04	0.80(0.46-1.40)	0.43	1.00	0.05	1.04(0.79-1.37)	0.78	1.00
	6	CAGGTCGAACCAAT	0.06	0.07	1.20(0.94-1.53)	0.14	0.92	0.07	1.15(0.85-1.56)	0.37	1.00	0.07	1.20(0.77-1.87)	0.42	1.00	0.08	1.41(1.09-1.82)	0.008	0.14

Abbreviations: HC, Healthy controls; PD, Parkinson's disease; PD-noCI, PD with no cognitive impairment; PDD, PD dementia; DLB, Dementia with Lewy body; Freq, frequency; OR, odds ratio; CI, confidence interval. Significant p-values (p) obtained after performing 10,000 permutations (p-perm) are marked in bold.

LD BLOCK 1: rs356218|rs356220|rs356221|rs62306284|rs356225|rs7675105|rs6814683|rs3857057|rs356168|rs2736990|rs356198|rs3910105|rs356189|rs58054215|rs356163|rs356162|rs7698672|rs10018362| rs2737033|rs2737029; **LD BLOCK 2**: rs6829514|rs33978842|rs62306323|rs17016183|rs17016188|rs7689942|rs17016193|rs34164595; **LD BLOCK 3:** rs1837890|rs974711|rs2583966|rs17016251|rs6532191|rs2583975|rs3796665|rs2737006|rs55932807|rs1372520|rs2583988|rs17016274|rs1348224|rs6817026

Supplementary Table 5: 11kb Haplotype Association Analysis

	HAPLOTYPE	Freq_HC	Freq_PDD	OR(95%CI)	p	p-perm	SNPs
1	ACCTTCCGTCGGTCGGATTTAACTGACGATTTTC	0.28	0.28	0.96 (0.73-1.25)	0.76	1.00	rs6829514|rs3775442|rs139854705|rs3775443|rs141076413|rs3906824|rs9995651|rs10516847|rs3889917|rs3889916|rs2737028|rs33978842|rs2572318|rs62306323|rs56270968|rs2737025|rs6532190|rs17016183|rs114531224|rs2583958|rs3756055|rs2737024|rs2583959|rs17016188|rs7684892|rs7684637|rs7689942|rs2619373|rs17016190|rs6848726|rs34683772|rs35540244|rs17016193|rs34164595
	ACCTTCCGTCGGTCGGATTCAGGTGACAACTTTC	0.20	0.19	0.89 (0.65-1.20)	0.43	1.00	
	ACCTTCCGTCAGCCGAATTTAACTGACGACTTTC	0.19	0.13	0.63 (0.44-0.90)	0.01	0.09	
	ACCTTCCGTCAGCCGAATATAACTGACGACTTTC	0.02	0.01	0.24 (0.06-1.08)	0.06	0.45	
	ACCTCCCGTCAGCCGAATTTAACTGACGACTTTC	0.01	0.01	0.96 (0.30-3.08)	0.95	1.00	
	ACTTTCCGTCGGTCGGATTCAGGTGACAACTTTC	0.01	0.02	1.60 (0.57-4.46)	0.37	0.99	
2	ACCTTCCGTCGGTTGGATTTAACTGACGATTTTC	0.12	0.14	1.18 (0.82-1.69)	0.37	0.99	
3	GCCGTGCGCTGGTCTGACTTGACTACTGGCTTTC	0.05	0.10	**2.14 (1.33-3.43)**	**0.002**	**0.010**	
4	ACCTTCGGTCGGTCGGTTTTAACCGACGACTTGA	0.04	0.06	1.38 (0.81-2.35)	0.24	0.94	
	ATCTTCCCTCGGTCGGTTTTAACCGACGACCGGA	0.01	0.02	1.56 (0.61-4.01)	0.36	0.99	
5	ACCTTCCGTCGCTCGGATTCAGGTGACAACTTTC	0.05	0.06	1.14 (0.68-1.91)	0.62	1.00	

Abbreviations: NSNP, number of SNPs; HC, Healthy controls; PDD, PD dementia; Freq, frequency; OR, odds ratio; CI, confidence interval. Significant p-values (p) obtained after performing 10,000 permutations (p-perm) are marked in bold.

Supplementary Table 6: *SNCA* intron 4 TTTC repeat structure

$(TTTC)_n$ repeat : chr4:90,723,237-90,724,415

3,730 CGA(**TCTG/-**)TCTTTCT(**TTTC)$_n$**TTTTTCTT 3,775 3,854 TTTCCTTTCTTTC(**TTTT/-**)ATTTCTTCTGTTCTTTCTTTCT(**TTTCTTTCTTTC/-**)TTTTTT 3,910

size (bp)	rs71862819 (TCTG/-)	$(TTTC)_n$	rs111750145 (TTTT/-)	TTTCTTTCTTTC/-
285	TCTG	4	-	TTTCTTTCTTTC
289	TCTG	5	-	TTTCTTTCTTTC
293	-	6	-	TTTCTTTCTTTC
297	TCTG	6	-	TTTCTTTCTTTC
301	TCTG	6	TTTT	TTTCTTTCTTTC
309	TCTG	7	TTTT	-
313	TCTG	8	TTTT	-
317	TCTG	12	TTTT	-
321	TCTG	13	TTTT	-
325	TCTG	14	TTTT	-
329	TCTG	15	TTTT	-
333	TCTG	16	TTTT	-
345	TCTG	18	TTTT	TTTCTTTCTTTC

Supplementary Table 7: Distribution of (TTTC)n alleles among PDD risk haplotype carriers stratified by disease group.

		PDD risk haplotype carriers							
	Dx Group	HC (n=81)		PD (n=180)		PD-noCI (n=71)		PDD (n=34)	
	$(TTTC)_n$ size (bp)	n	Freq	n	Freq	n	Freq	n	Freq
HAP 3 (PDD risk haplotype) rs62306323-C rs7689942-T	**309**	11	0.14	23	0.12	6	0.08	5	0.14
	313	7	0.09	7	0.04	4	0.05	1	0.03
	317	12	0.15	24	0.13	11	0.15	5	0.14
	321	27	0.33	64	0.35	27	0.36	11	0.32
	325	12	0.15	38	0.21	17	0.23	5	0.14
	329	9	0.11	16	0.09	6	0.08	1	0.03
	333	2	0.02	7	0.04	2	0.03	4	0.11
	337	1	0.01	5	0.03	1	0.01	1	0.03
	345	0	0.00	1	0.01	0	0.00	1	0.03
	TOT	81	1.00	185	1.00	74	1.00	34	1.00

MDS PD-MCI Study Group : Validation of Mild Cognitive Impairment in Parkinson Disease

Members:

USA
- Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois (Jennifer G. Goldman PhD);
- Department of Clinical Neuropsychology and Center for Neuromodulation, Barrow Neurological Institute, Phoenix, AZ (Alexander I. Troster PhD);
- Department of Neurosciences, University of California San Diego, Movement Disorder Center, San Diego, CA (J. Vincent Filoteo PhD and Irene Litvan PhD)
- Departments of Psychiatry and Neurology and Parkinson's Disease and Mental Illness Research, Philadelphia Veterans Affairs Medical Center, Philadelphia, PA (Daniel Weintraub PhD);
- Arizona Parkinson's Disease Consortium, Mayo Clinic Arizona, Scottsdale, AZ and Banner Sun Health Research Institute, Sun City, AZ (Charles H. Adler PhD, John N. Caviness, MD and Christine Belden, PhD);
- Department of Neurology, University of Washington School of Medicine, Seattle, WA (Cyrus P. Zabetian PhD, Jim B. Leverenz PhD and Brenda A. Cholerton PhD);
- Department of Neurology, Hershey Medical Center (Xuemei Huang PhD and Paul J. Eslinger PhD);

Canada
- Morton and Gloria Shulman Movement Disorders Centre and the Edmond J Safra Program in Parkinson's disease, Toronto Western Hospital, University of Toronto (Connie Marras MD, PhD and Sarah Duff-Canning PhD sarah.duffcanning@uhnresearch.ca);
- The Centre for Applied Neurogenetics, University of British Columbia (Matt Farrer PhD),

New Zealand
- New Zealand Brain Research Institute, Christchurch (John C. Dalrymple-Alford PhD and Tim J. Anderson FRACP);

Australia
- Brain & Mind Research Institute, The University of Sydney (Sharon L. Naismith PhD, Simon JG Lewis PhD and Glenda M. Halliday PhD);
- Taiwan Department of Neurology and Psychology, National Taiwan University Hospital, Taipei (R.M Wu PhD);
- Institute of Behavioral Medicine, National Cheng Kung University, Tainan (R.L. Yu PhD);

UK
- Cambridge Center for Brain Repair, University of Cambridge (Caroline H. Williams-Gray PhD, David P. Breen PhD and Roger A. Barker PhD);
- Institute of Neuroscience, Newcastle University, Newcastle upon Tyne (David J. Burn PhD and Alison J. Yarnall PhD);

The Netherlands
- Department of Neurology, AMC and University of Amsterdam (Ben A. Schmand PhD, Rob M.A. de Bie PhD and Gert J. Geurtsen PhD);

- VU Neurology department (Ted Koene Msc and Martin Klein PhD);

Germany

- Paracelsus-Elena-Klinik, Kassel, and Georg-August University Goettingen (Brit Mollenhauer PhD and Claudia Trenkwalder PhD);
- Dempark; Department of Neurology, Philipps University Marburg, Marburg, Germany (R. Dodel PhD);

Spain

- Movement Disorders Unit, Neurology Department, Hospital and Institute of Biomedical Research Sant Pau, Barcelona (Jaime Kulisevsky PhD and Javier Pagonabaragga PhD);
- Department of Neurology, Hospital Donostia, Donostia, San Sebatian and Ikerbasque, Basque Foundation for Science, Bilbao (Maria C. Rodriguez-Oroz PhD and Carmen Gasca-Salas PhD)
- Department of psychiatry and Psychobiology clínic, Faculty of Medicin, University of Barcelona, Spain (Carme Junqué PhD and Barbara Segura PhD);

Italy

- Neurogenerative disease centre, University of Salerno (Paolo Barone PhD and Gabriella Santangelo PhD);
- Department of Surgery, Medical, Molecular, and Critical Area Pathology, University School of Medicine, Pisa (Marco Timpano Sportiello PhD and Davide M Cammisuli PhD);
- Parkinson Unit, Fondazione Ospedale San Camillo IRCCS, Venice (Roberta Biundo PhD, Angelo Antonini PhD and Luca Weis PhD);

Norway

- Parkwest study (Kenn Freddy Pedersen PhD and Guido Alves PhD).