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Do interactions between *SNCA*, *MAPT*, and *LRRK2* genes contribute to Parkinson's disease susceptibility?

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Abstract

Background—Polymorphisms in *SNCA*, *MAPT* and *LRRK2* genes have recently been confirmed as risk factors for Parkinson's disease (PD), although with small individual attributable risk. Here we investigated the association of PD with interactions between variants of these genes.

Methods—As part of a previous study of PD susceptibility genes 119 *SNCA*, *MAPT*, and *LRRK2* haplotype tagging single nucleotide polymorphisms (SNPs) and two variable number tandem repeats (VNTRs) were genotyped in 1,098 PD cases from the upper Midwest, USA and 1,098 matched controls. Twenty-six of these SNPs were selected for SNP-SNP (or SNP-VNTR or VNTR-VNTR) interaction analysis (256 interaction pairs). Case-control analyses were performed to study association of pairwise SNP interactions with PD susceptibility.

Results—Out of the 256 interaction pairs investigated, 10 had uncorrected p-values <0.05. These represented six *SNCA-LRRK2* pairs, three *SNCA-MAPT* pairs, and one *MAPT-LRRK2* pair. However, none of these pairwise interactions were significant after correction for multiple testing. Secondary analyses in strata defined by type of control (sibling or unrelated), sex, or age at onset of the case also did not reveal any significant interactions after accounting for multiple testing.

Conclusions—This study provides no statistically significant evidence of gene-gene interaction effects for the three confirmed genetic susceptibility loci for PD. However, this does not exclude the possibility that other genomic loci or environmental risk factors interact with these genes.

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Keywords

Parkinson's disease; gene-gene interaction; alpha-synuclein; microtubule associated protein tau; leucine rich repeat kinase 2

Introduction

Parkinson's disease (PD) is of unknown etiology, but is generally assumed to have complex substrates, both genetic and environmental. Numerous factors associated with PD have been reported, but the attributable risk of each is small; no single genetic or environmental factor appears to make a substantial contribution to PD risk. Although individual factors operating independently account for little PD risk, the contribution from interactions between such factors could be more substantial.

The association of three genes with PD risk has been reproducibly documented in four recent and independent genome-wide association studies (GWAS) in large PD cohorts: alpha-synuclein (*SNCA*)[1–4], microtubule associated protein tau (*MAPT*)[1, 3, 4], and leucine rich repeat kinase 2 (*LRRK2*)[2, 3]. Although each of these three genes has small attributable PD risk, they all have substantial biologic plausibility from additional lines of evidence. Firstly, linkage studies revealed that pathogenic point mutations in *SNCA*[5] or *LRRK2*[6] result in familial Parkinson's disease with phenotypic fidelity to sporadic PD; and *SNCA* triplications or duplications similarly cause familial PD[7]. Secondly, candidate gene studies revealed that polymorphisms of *SNCA*[8] and *MAPT*[9] each confer increased PD risk. Thirdly, immunohistochemical studies revealed that the neuropathologic hallmark of PD, the Lewy body, contains not only alpha-synuclein, but also MAPT[10] and LRRK2[11] proteins.

Interactions between the products of these three genes might conceivably amplify their individual pathogenic contributions to PD. Laboratory evidence suggests that such interactions may indeed occur. It has been shown that MAPT induces fibrillization of alpha-synuclein[12]; such fibrillization is proposed to be an initial step in the generation of PD-pathogenic alpha-synuclein aggregates. Alpha-synuclein not only interacts with tau protein in vitro[13], it also binds to tau and stimulates its phosphorylation; hyperphosphorylation destabilizes tau and impairs protein transport[14]. LRRK2, which is thought to be an upstream factor in the neurodegenerative pathway[15], induces SNCA expression[16]. Whereas tau is a microtubule-associated protein, LRRK2 is known to interact with microtubules[17]. Finally, in vivo studies suggest that tau and alpha-synuclein may interact to promote aggregation and accumulation of each protein[18].

Human post-mortem studies also suggest interactions among these three genes. Namely, there is a robust correlation between alpha-synuclein-labeled Lewy bodies and MAPT-labeled neurofibrillary tangles in sporadic PD[19] Moreover, whereas most cases of LRRK2 parkinsonism display alpha-synuclein-labeled Lewy bodies, occasionally LRRK2 cases are marked by MAPT-positive tangles[15].

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While the main effects of *SNCA*, *MAPT* and *LRRK2* as causal or risk factors for PD are well established, there has been only limited study of the joint effects or statistical interaction of the effects of these genes in PD. The causal variants in these genes are rare and have limited attributable risk and the common susceptibility variants in these genes have small effect sizes. We hypothesized, however, that the interactions of common variants in the *SNCA*, *MAPT*, and *LRRK2* genes may have substantially larger effect sizes and therefore result in appreciable attributable risk in PD.

Specifically in this study we assessed whether *SNCA*, *MAPT*, and *LRRK2* genes have not simply additive effects on the log odds of PD, but rather multiplicative effects on PD susceptibility. Thus, we comprehensively assessed the association of PD with pairwise SNP or VNTR interactions of these three genes in a large case-control study.

Subjects and Methods

Study subjects

The Institutional Review Board of the Mayo Clinic approved the study, and all subjects provided written informed consent. The enrollment of matched cases and controls has been previously described[20, 21]. PD cases were recruited from patients seen at the Department of Neurology of the Mayo Clinic in Rochester, MN between 1996 and 2007. All cases were residents of Minnesota or one of the surrounding four states (Wisconsin, Iowa, South Dakota, and North Dakota). The diagnosis of PD was made by movement disorders specialists using established criteria[22]. The age at onset of PD was defined as the time of the first observed cardinal motor sign (rest tremor, bradykinesia, rigidity, or postural instability), as reported by the patient or a family member at the time of clinical assessment for the study. Controls included unaffected siblings of cases or unrelated controls when there were no siblings available. Potential controls were screened for parkinsonism using a validated telephone instrument[23]. Only potential controls who screened negative for PD, or who were confirmed not to have PD via clinical assessment (despite having screened positive by telephone interview), were included in the study. Cases were matched to a single participating sibling first by sex (when possible) and then by closest age. Cases without an available sibling were matched to unrelated controls living in the same 5-state region and of same sex and age (same year of birth ± 2 years). Initially 1,103 cases and matched controls were enrolled in the study[20, 21]. Genomic DNA was collected, extracted, and stored as previously described[20]. Five cases were subsequently excluded because of indeterminate diagnoses. Thus 1,098 cases and matched controls were used in the analyses.

Genotyping

Single nucleotide polymorphisms (SNPs) in species-conserved regions of 13 PARK locus or related genes, including *SNCA*, *MAPT* and *LRRK2*, were detected via sequencing in 25 cases and 25 controls (see Chung et al.[21] for details). Additional tag SNPs were then selected for these genes from the HapMap database using the LDSelect program with a linkage disequilibrium (LD) r^2 threshold of 0.8 and minor allele frequencies (MAF) > 0.05. Two tag SNPs were selected for each LD bin when the number of SNPs in the bin was 10 or more. In total, 19 SNPs in *SNCA*, 35 in *MAPT*, and 65 in *LRRK2* were successfully genotyped using a

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bead array platform (Illumina GoldenGate). In addition two variable number tandem repeats (VNTRs) (*SNCA* REP1, *MAPT* H1/H2 haplotype) were genotyped using a sequencing platform (Applied Biosystems).

Selection of SNPs for gene-gene interaction analysis

Variants with MAF < 0.05 or showing departures from Hardy-Weinberg equilibrium ($p < 0.001$) were excluded from the analyses. Kooperberg and LeBlanc[24] demonstrated that testing for SNP-SNP interactions in a subset of SNPs selected using a screening step based on univariate SNP analysis (i.e. single SNP effects) tends to be more powerful than the alternative strategy of testing all possible pairs of SNPs. To determine the optimal p-value threshold for the screening step, we used the Splus library *powerGWASinteraction* (http://cran.r-project.org/web/packages/powerGWASinteraction/index.html), a program for estimating power under a range of scenarios corresponding to different screening-step *p*-value thresholds. Based on these calculations we selected $p=0.2$ in the single SNP analysis as the threshold for inclusion of SNPs in the interaction analysis. This strategy excludes SNPs with no evidence of single-SNP association with PD (based on the threshold $p>0.2$) while retaining SNPs with significant marginal effects. Using the threshold of $p=0.2$ attempts to retain SNPs that have weak marginal associations that are not detectable at traditionally used significance levels with the available sample size. Finally, to avoid redundancy of tests due to testing of SNPs in high LD, and to reduce the total number of tests performed, we further applied a tag-SNP selection strategy to the resulting SNP list. Tagging SNP selection was performed using the pairwise Tagger algorithm with $r^2=0.9$ implemented in Haploview 4.2[25].

This procedure resulted in the selection of 10 SNPs in *SNCA*, 8 SNPs in *MAPT*, and 8 SNPs in *LRRK2* that had p-values<0.2 in a trend test for association with PD (i.e. marginal test of association with PD under the assumption of log-additive allele effects). In addition, *SNCA* REP1 (coded based on the number of 259 bp alleles and the number of 263 bp alleles) and the *MAPT* VNTR that distinguishes the H1/H2 haplotype were included in the analyses, as these variables also showed marginal evidence of association at the $p<0.2$ level. The polymorphisms examined in the interaction analyses are listed in Table 1. LD plots for the three genes highlighting the SNPs and VNTRs used for the interaction analysis are shown in Figure 1 in the supplement.

Statistical Analyses

Pairwise interactions between genetic variants in *SNCA*, *MAPT*, and *LRRK2* were assessed using conditional logistic regression analyses. To identify interactions between rather than within genes, only pairs of SNPs in two different genes were considered in the primary analysis. Thus a total of 256 pairwise interactions were tested. For SNPs, a log-additive genotype coding scheme was used, while for *SNCA* REP1 genotypes were converted to scores ranging from 0 to 4 as previously described[20]. Namely, the score for the REP1 genotype was calculated as the sum of two allele scores, with each 259 bp allele contributing 0 points, each 261 bp allele contributing 1 point, and each copy of a 263 bp allele contributing 2 points. In addition, the REP1 genotype coded both as the number of 259 alleles and the number of 263 alleles was used in the interaction analyses. All analyses were

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adjusted for age at study and sex. For each genetic variant we calculated the odds ratio (OR), 95% confidence interval (CI), and *p* value for the univariate effect in the conditional logistic regression model. In addition, the coefficient for the multiplicative interaction term and the associated *p* value were calculated.

We performed similar analyses of gene-gene interactions in subgroups, restricting either to case-unaffected sibling or case-unrelated control pairs, to men–men or women–women pairs, or to younger or older pairs as defined by median age at onset in the cases.

Finally, to understand the joint effects of variants within each of the three investigated genes, we tested for SNP-SNP or SNP-VNTR interactions within *SNCA* (63 pairs), within *MAPT* (28 pairs), and within *LRRK2* (28 pairs) using the same conditional logistic regression approach.

The statistical packages SAS (version 9.1; SAS Institute Inc., Cary, NC) and S-Plus (version 8.0.1; MathSoft, Seattle, WA) were used for all analyses. In addition to the uncorrected *p* values, a Bonferroni correction was applied to correct *p* values for the number of tests performed.

Results

The demographic characteristics of the sample of 1,098 cases and 1,098 controls included in the study (653 case-unaffected sibling pairs and 445 case-unrelated control pairs) are summarized in Table 2.

After correction for multiple testing, there were no significant pairwise interactions between the selected *SNCA*, *MAPT* and *LRRK2* variants. Ten of the 256 interaction pairs were associated with PD susceptibility at the uncorrected $p < 0.05$ level (Table 3). This included six *SNCA-LRRK2* pairs, three *SNCA-MAPT* pairs, and one *MAPT-LRRK2* pair. None of these interaction effects were significantly associated with PD susceptibility after Bonferroni correction for multiple comparisons. Supplementary Table 1 provides detailed results of the interaction tests for the entire sample.

The 10 nominally significant interactions included interactions of *LRRK2* SNP rs17484286 with four *SNCA* variants, including REP1 coded based on the number of 263 bp alleles, and the three SNPs rs3775423, rs3775439, and rs9995651. LD between the *SNCA* SNPs rs3775423 and rs3775439 is r^2=0.65, while for rs3775423 and rs9995651 r^2=0.53. The *SNCA* SNP rs3775423 showed nominal evidence of interaction with one *LRRK2* SNP, as well as two *MAPT* SNPs (rs2435211 and rs8079215). These two *MAPT* SNPs are not in very strong LD (r^2 = 0.18). There was also nominal evidence of interaction between the *MAPT* SNP rs2435211 and both a *SNCA* SNP as well as a *LRRK2* SNP.

Stratified analyses also did not identify any significant interactions after adjustment for multiple comparisons. Supplementary Table 2 shows results for all interaction pairs for subgroups defined by type of control, gender, and age at onset. Analysis of 653 cases with matched sibling controls detected 19 nominally significant interactions, while analysis of the 445 cases with unrelated controls detected eight nominally significant interactions. Analyses

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of 553 men-men pairs detected 11 nominally significant interactions, while analyses of 329 women-women pairs detected five nominally significant interactions. Finally, analysis of 548 early age at onset cases (age at onset ≤median) with their matched controls detected 17 nominally significant interactions, while analysis of 548 late age at onset cases (age at onset >median) with their matched controls detected 16 nominally significant interactions. Median age at onset for cases was 62.16 years. Note that none of the interactions that were nominally significant in the overall sample were also significant in both of two complimentary strata (e.g. in both men and women strata, or in both case-unrelated control and case sibling strata, or in both early and late age at onset strata). However, several of the interactions were significant in more than one of the non-complimentary strata. For example, the interaction between the *MAPT* SNP rs2435211 and the *SNCA* SNP rs3775423 was nominally significant in the stratum of men, in the case-sib stratum, and in the stratum containing cases with early age at onset.

Analyses of interaction pairs within each of the three genes of interest showed that seven of the 119 interaction pairs were associated with PD susceptibility at the uncorrected $p < 0.05$ level (Supplemental Table 3). This included two *LRRK2* pairs, three *MAPT* pairs, and two *SNCA* pairs. None of these interaction effects were significantly associated with PD susceptibility after Bonferroni correction for multiple comparisons.

Discussion

Previous studies have provided compelling evidence that polymorphisms in *SNCA*, *MAPT*, and *LRRK2* genes confer susceptibility to PD (main effects). Our study indicates that pairwise interactions between common variations in these genes have limited association with PD susceptibility.

Few prior studies have investigated the joint effects of PARK locus genes and related PD susceptibility genes[26–29]. One study observed significant joint effects on PD susceptibility for the *MAPT* H1 haplotype and *SNCA* 3′ SNP variants, with a synergistic interaction of the risk alleles[26]. We previously investigated joint effects for *MAPT* H1 haplotype and *SNCA* REP1 variants with PD susceptibility and found that the main effects of the variants were separate and equal with no significant pairwise interactions[27]. Here we extended those analyses of joint effects to include multiple SNPs in *SNCA*, *MAPT*, and *LRRK2*, but again we did not observe any significant pairwise interactions. Recently, a whole-genome conditional two-locus analysis identified SNPs that interacted with SNPs in PARK locus genes[30]. In agreement with our results, that study also failed to detect significant pairwise interactions for *SNCA*, *LRRK2*, and *MAPT* SNPs.

Although none of the interactions were significant after correction for multiple testing in our study, the pairs with suggestive evidence of interaction could be investigated in independent samples. In particular, several of the investigated SNPs or VNTRs were involved in multiple interactions that were significant at the nominal 0.05 significance level. These interactions are good candidates for further investigation.

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We focused on the three genes that have been confirmed as playing a role in PD susceptibility by candidate gene and genome-wide association studies (*SNCA*, *MAPT*, and *LRRK2*). Rather than restricting the analyses to the few SNPs with the strongest evidence for association in prior GWAS, we studied a number of variants in each gene (including VNTRs)[21]. Restricting our interaction analyses to the three genes that have recently been confirmed as PD susceptibility loci allowed us to investigate the joint effects of these variants while limiting the multiple testing burden. However, focusing exclusively on these three genes also limited our ability to discover novel genetic risk factors for PD. Nevertheless an assessment of interactions for the three established PD susceptibility genes was an important step towards understanding their joint effects and their full contribution to PD.

Although we had a large sample size of 1,098 PD cases and 1,098 controls, this sample size may still be inadequate for detecting interaction effects, particularly involving rare alleles. We estimated power to detect the interaction of the two genetic variants of primary interest (*SNCA* REP1 and *MAPT* H1/H2 variation). The power calculations were performed using the software Quanto [31] (http://hydra.usc.edu/GxE/), with an alpha level of 0.0002, which takes into account the fact that 256 interactions were tested. We used the observed allele frequencies in our calculations, and assumed dominant effects of the 259 allele of *SNCA* REP1 and the H2 haplotype of *MAPT*. We considered models with marginal effect sizes consistent with those observed in our data (with both the 259 REP1 allele and the H2 *MAPT* haplotype having protective effects, with marginal odds ratios of approximately 0.80 and 0.75, respectively). Under these assumptions the power was estimated to be 80% to detect an interaction effect size (which represents a ratio of odds ratios) of 0.40 for the combination of protective genotypes at the two loci, or 2.5 for the combination of high-risk genotypes. Smaller interaction effects may exist, and samples sizes that are currently being used for association studies of main effects may not provide adequate power for analyses of joint effects. Design of gene-gene interaction studies is complicated by the fact that sample size requirements depend on the true effect sizes of interactions, which at this point remain unknown. Collaborative analyses of our suggestive interaction findings within a global genetics consortium may yield more definitive evidence of interactions[8].

Another limitation of our study stems from the use of sibling controls for some of the cases, which may reduce power relative to a sample with unrelated controls. Sibling controls were selected when possible to ensure close matching on ethnicity, and thus avoid population stratification effects. The disadvantage of using sibling controls is that because siblings share a considerable proportion of genetic background, the power for detecting genetic associations (both main effects and interactions) is reduced. However, the reduction in power to detect gene-gene interactions is usually quite small, as shown by Gauderman [31]. Gauderman's power calculations demonstrate that while larger sample sizes are often needed to detect gene-gene interactions in case-sib studies than in case-unrelated-control studies, the sample size requirements are not substantially different, usually requiring no more than a 20% increase in sample size for the case-sib design. Gauderman also showed some scenarios for which the case-sib design had greater power to detect gene-gene interactions than did the case-unrelated-control design.

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Finally, we note that our study only considered SNPs and VNTRs. Additional interaction variables to consider in the study of PD include copy number variations, and environmental and epigenetic variations. Studies that include measurement of multiple types of variations in samples from multiple diverse populations may ultimately uncover the complex causes of PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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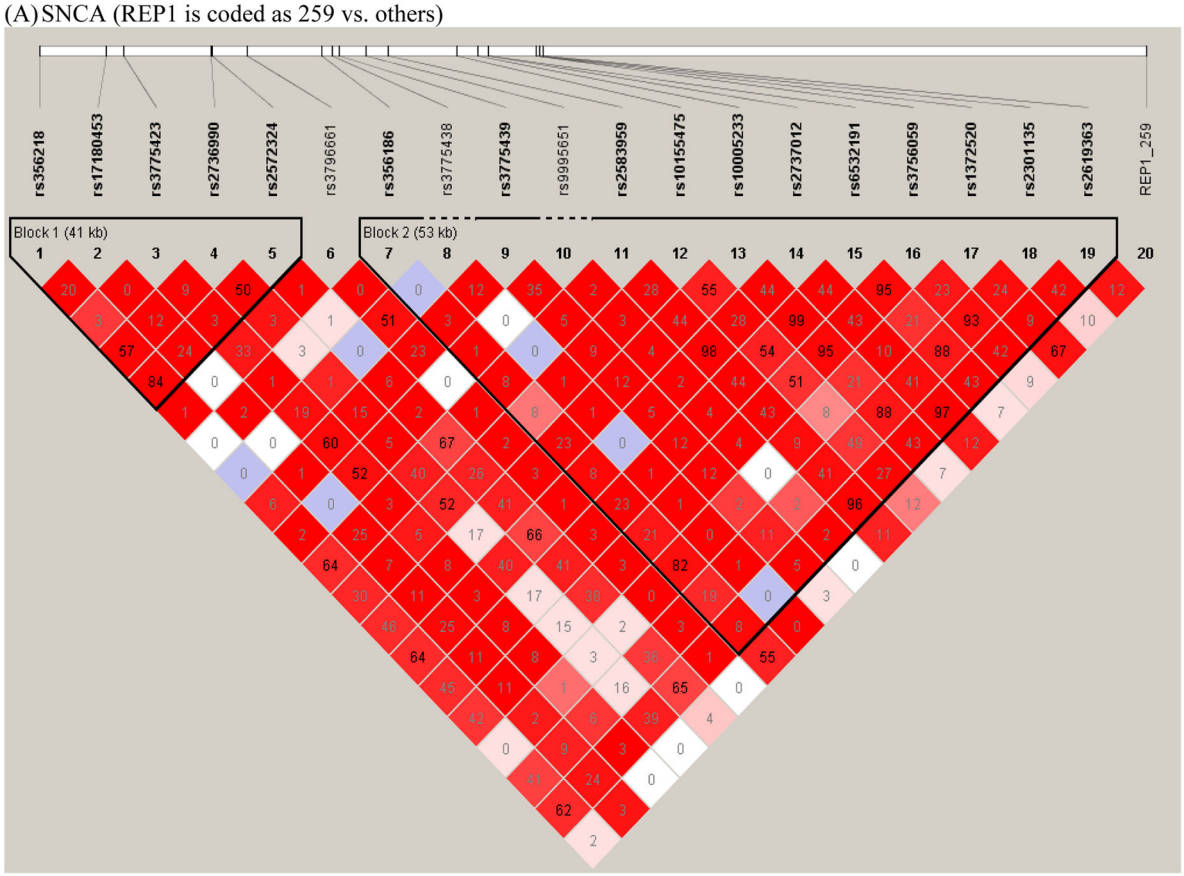
(A) SNCA (REP1 is coded as 259 vs. others)



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(B) MAPT

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(C) LRRK2

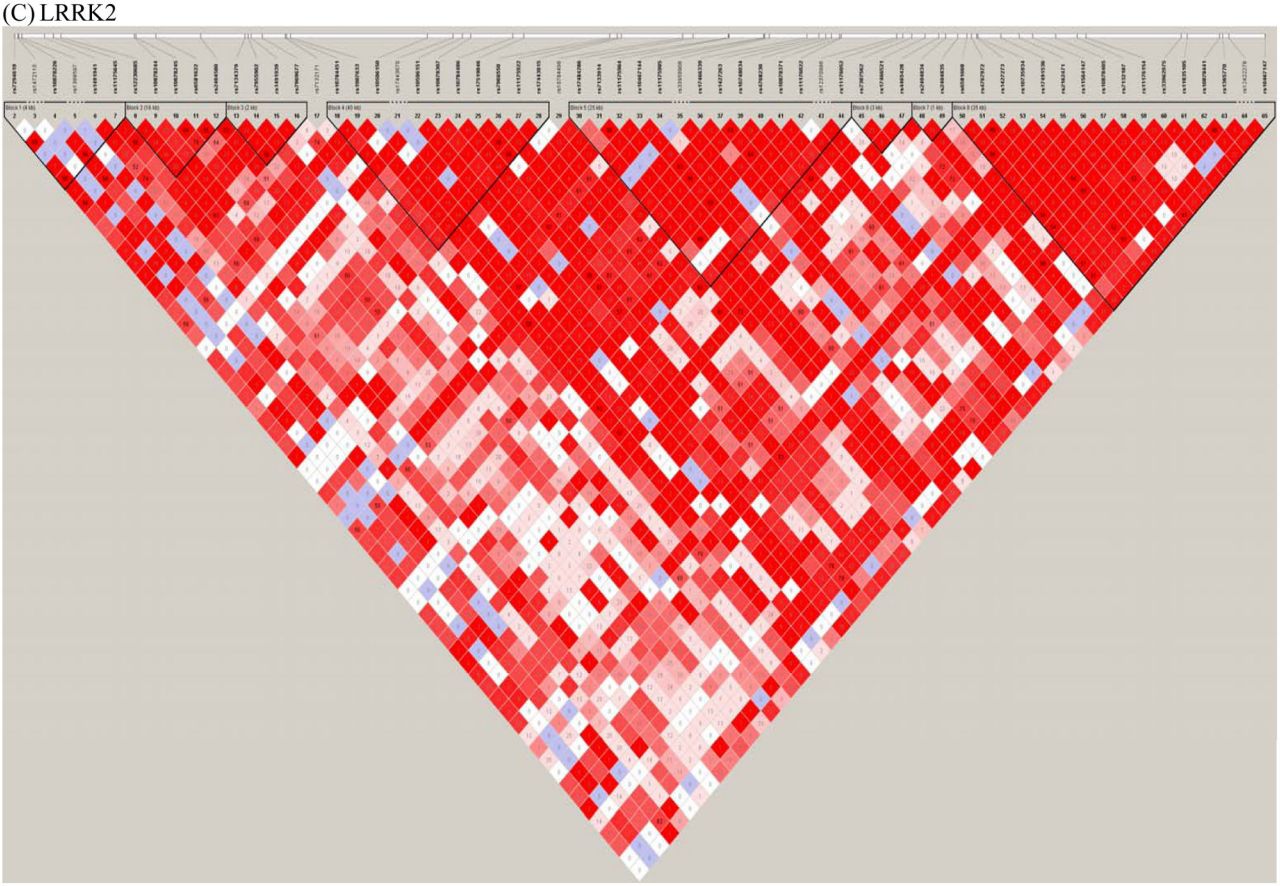

Figure 1. Linkage disequilibrium plots

Plots of the linkage disequilibrium (LD) structure of the *SNCA* (Figure 1A), *MAPT*, (Figure 1B), and *LRRK2* (Figure 1C) genes are shown. For the *SNCA* gene, the multiallelic VNTR REP1 was coded as 259 bp vs. others. The LD values as measured using r^2 are given by numbers and the LD values as measured by D′ are given by color intensity (red squares indicate strong LD, pink squares indicate intermediate LD, and white squares indicate low LD, with evidence for ancestral recombination; blue indicates limited data). SNPs used in the interaction analyses are listed in Table 1.

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Table 1

Genetic variants used in gene-gene interaction analysis

GENE	VARIANT	SNP location or known function	MINOR ALLELE FREQUENCY	P-VALUE[3]
SNCA	rs1372520	intron	0.1848	0.0056
	rs2572324	intron; associated with the extent of neurofibrillary pathology	0.3226	0.0090
	rs2583959	intron	0.3013	0.0506
	rs2736990	intron	0.4902	0.0017
	rs356186	intron	0.1686	0.0119
	rs356218	3′ downstream	0.3545	0.0419
	rs3775423	intron	0.0903	0.0090
	rs3775439	intron	0.1290	0.0716
	rs9995651	intron	0.0519	0.1097
	REP1-259[1]	regulates SNCA gene expression	0.2413	0.0345
	REP1-263[2]	regulates SNCA gene expression	0.0749	0.0465
	REP1 score	regulates SNCA gene expression	n.a.	0.0118
MAPT	rs16940758	intron; regulates MAPT gene expression	0.1745	0.0844
	rs16940806	3′ UTR	0.1800	0.0059
	rs2435200	Intron	0.3968	0.0001
	rs2435211	intron; regulates MAPT gene expression	0.3012	0.0856
	rs4792891	intron	0.3016	0.0036
	rs8079215	intron	0.2945	0.0660
	rs878918	intron	0.3329	0.1437
	MAPT H1/H2	regulates MAPT gene expression	0.1793	0.0042
LRRK2	rs10784486	intron	0.3140	0.1691
	rs11175922	intron	0.4877	0.1736
	rs1491939	intron	0.0601	0.1521
	rs17466521	intron	0.2546	0.1961
	rs17484286	intron	0.0927	0.0128
	rs2404835	intron	0.3255	0.0872
	rs6581668	intron	0.4727	0.1814
	rs7307562	intron	0.4070	0.1669

[1] REP1-259 denotes the *SNCA* VNTR REP1 coded as the number of 259 bp alleles

[2] REP1-263 denotes the *SNCA* VNTR REP1 coded as the number of 263 bp alleles

[3] P-value for trend test for association with PD. P-values are not corrected for multiple testing.

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Table 2

Demographic Characteristics of Parkinson's Disease (PD) Cases, Siblings, and Unrelated Controls

	PD Case – Sibling Pairs		PD Case-Unrelated Control Pairs		All PD Case- Control Pairs	
General characteristics	**PD Cases**	**Sibling Controls**	**PD Cases**	**Unrelated Controls**	**PD Cases**	**All Controls**
Total sample, n	653	653	445	445	1,098	1,098
Men, n (%)	417 (63.8)	329 (50.4)	288 (64.7)	288 (64.7)	705 (64.2)	617 (56.2)
Women, n (%)	236 (36.1)	324 (49.6)	157 (35.3)	157 (35.3)	393 (35.8)	481 (43.8)
Age at onset of PD, median (range)	60.4 (28.2–86.9)	--	64.6 (23.3–88.0)	--	62.2 (23.3–88.0)	--
Age at study, median (range)[1]	66.3 (30.8–91.4)	65.1 (32.0–90.4)	70.3 (44.5–90.4)	71.8 (44.9–92.8)	68.0 (30.8–91.4)	67.6 (32.0–92.8)
Ethnicity:						
Both parents of European origin, n(%)	570 (87.3)	557 (85.3)	357 (80.2)	388 (87.2)	927 (84.4)	945 (86.1)
One parents of European origin, n(%)	52 (8.0)	60 (9.2)	60 (13.5)	41 (9.2)	112 (10.2)	101 (9.2)
Family History of PD						
First degree family history of PD, n (%)	73 (16.4)	--	106 (16.2)	--	179 (16.3)	--
At least third degree family history of PD, n (%)	112 (27.4)	--	193 (29.6)	--	315 (28.7)	--

[1] Age at blood draw

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Table 3

SNP-SNP Interactions with Marginal Evidence of Association with PD Susceptibility (uncorrected p < 0.05)

SNP1	Gene1	SNP1 OR (95% CI)	SNP1 P value	SNP2	Gene2	SNP2 OR (95% CI)	SNP2 P value	Interaction P value
rs16940758	*MAPT*	1.21 (0.99 – 1.47)	0.0595	rs2583959	*SNCA*	1.18 (1.00 – 1.39)	0.0492	0.0049
rs2435211	*MAPT*	1.16 (0.99 – 1.35)	0.0677	rs3775423	*SNCA*	1.38 (1.07 – 1.79)	0.0136	0.0105
rs17484286	*LRRK2*	0.73 (0.57 – 0.94)	0.0143	rs3775423	*SNCA*	1.42 (1.10 – 1.85)	0.0071	0.0117
rs17484286	*LRRK2*	0.72 (0.56 – 0.92)	0.0093	rs3775439	*SNCA*	1.21 (0.97 – 1.50)	0.0914	0.0192
rs8079215	*MAPT*	1.16 (0.99 – 1.36)	0.0713	rs3775423	*SNCA*	1.41 (1.09 – 1.82)	0.0083	0.0214
rs17484286	*LRRK2*	0.73 (0.57 – 0.94)	0.0142	REP1-263	*SNCA*	1.35 (1.02 – 1.78)	0.0348	0.0233
rs7307562	*LRRK2*	1.11 (0.96 – 1.29)	0.1658	rs9995651	*SNCA*	1.31 (0.92 – 1.86)	0.1270	0.0383
rs17466521	*LRRK2*	0.88 (0.75 – 1.05)	0.1522	rs2572324	*SNCA*	1.23 (1.05 – 1.44)	0.0120	0.0416
rs17484286	*LRRK2*	0.73 (0.57 – 0.94)	0.0142	rs9995651	*SNCA*	1.33 (0.93 – 1.88)	0.1138	0.0445
rs10784486	*LRRK2*	0.89 (0.76 – 1.05)	0.1660	rs2435211	*MAPT*	1.15 (0.98 – 1.35)	0.0770	0.0490

P-values are not corrected for multiple testing. For consistency, all results in a given row are based on the same sample that contributed to the interaction analysis, with complete data at both SNPs under consideration.