Published in final edited form as:

Ann Neurol. 2011 May ; 69(5): 778–792. doi:10.1002/ana.22321.

Independent and joint effects of the *MAPT* and *SNCA* genes in Parkinson's disease

Alexis Elbaz, MD, PhD^{1,2,*}, Owen A. Ross, PhD^{3,*}, John P.A. Ioannidis, MD, PhD^{4,5}, Alexandra I Soto-Ortolaza, BSc³, Frédéric Moisan, MSc^{1,2}, Jan Aasly, MD⁶, Grazia Annesi, PhD⁷, Maria Bozi, MD⁸, Laura Brighina, MD, PhD⁹, Marie-Christine Chartier-Harlin, PhD^{10,11}, Alain Destée, MD, PhD^{10,11,12}, Carlo Ferrarese, MD, PhD⁹, Alessandro Ferraris, MD, PhD¹³, J. Mark Gibson, MD¹⁴, Suzana Gispert, PhD¹⁵, Georgios M. Hadjigeorgiou, MD^{16,17}, Barbara Jasinska-Myga, MD, PhD¹⁸, Christine Klein, MD¹⁹, Rejko Krüger, MD, PhD²⁰, Jean-Charles Lambert, PhD²¹, Katja Lohmann, PhD¹⁹, Simone van de Loo, MD¹⁵, Marie-Anne Lorient, Pharm, PhD^{22,23,24}, Timothy Lynch, MD, FRCPI²⁵, George D. Mellick, MD, PhD^{26,27,28}, Eugénie Mutez, MD^{10,11,12}, Christer Nilsson, MD, PhD²⁹, Grzegorz Opala, MD, PhD¹⁸, Andreas Puschmann, MD^{29,30}, Aldo Quattrone, MD³¹, Manu Sharma, MD²⁰, Peter A. Silburn, MD, PhD^{26,27,28,32}, Leonidas Stefanis, MD, PhD³³, Ryan J. Uitti, MD³⁴, Enza Maria Valente, MD, PhD¹³, Carles Vilariño-Güell, PhD^{3,37}, Karin Wirdefeldt, MD, PhD³⁵, Zbigniew K. Wszolek, MD³⁴, Georgia Xiomerisiou, MD^{16,17}, Demetrius M. Maraganore, MD³⁶, and Matthew J. Farrer, PhD^{3,37} on behalf of the Genetic Epidemiology Of Parkinson's Disease (GEO-PD) consortium

¹ INSERM, Unit 708, Neuroepidemiology, F-75013, Paris, France ² UPMC Univ Paris 06, UMR-S 708, F-75005, Paris, France ³ Division of Neurogenetics, Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA ⁴ Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece ⁵ Tufts Clinical and Translational Science Institute, Tufts Medical Center, and Tufts University School of Medicine, Boston, Massachusetts, USA ⁶ Department of Neurology; St Olav Hospital, Trondheim, Norway ⁷ Institute of Neurological Sciences, National Research Council, Cosenza, Italy ⁸ General Hospital of Syros, Syros, and Second Department of Neurology, University of Athens Medical School, Greece ⁹ Dept of Neurology and Neuroscience, Univ of Milano-Bicocca, Ospedale San Gerardo, Monza, Italy ¹⁰ Inserm, U837, F-59045, Lille, France ¹¹ Univ Lille Nord de France, F-59000, Lille, France ¹² CHRU, F-59037, Lille, France ¹³ Mendel Laboratory, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy ¹⁴ Department of Neurology, Royal Victoria Hospital, Belfast, Ireland ¹⁵ Dept. Neurology, Goethe University Frankfurt am Main, Germany ¹⁶ Department of Neurology, Laboratory of Neurogenetics, Faculty of Medicine, University of Thessaly, Larissa, Greece ¹⁷ Institute of Biomedical Research & Technology, CERETETH, Larissa, Greece ¹⁸ Department of Neurology, Medical University of Silesia, Katowice, Poland ¹⁹ Section of Clinical and Molecular Neurogenetics at the Department of Neurology, University of Luebeck, Germany ²⁰ Center of Neurology and Hertie-Institute for Clinical Brain Research, University of Tübingen, and German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany ²¹ INSERM U744, Institut Pasteur de Lille, Université Lille Nord de France, UDSL, Lille, France ²² INSERM, UMR-S 775, Bases moléculaires de la réponse aux xénobiotiques, 45 rue des Saints-Pères, 75270 Paris Cedex 06, France ²³ Université Paris Descartes, F-75005, Paris, France ²⁴ Assistance-Publique Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Biochimie, Pharmacogénétique et Oncologie Moléculaire, 20 rue

Corresponding author's contact information: Alexis Elbaz, Inserm U708, Hôpital de la Salpêtrière, 47 boulevard de l'Hôpital, 75651 Paris Cedex 13, France. Phone : +33 - 1 42 16 25 66. Fax : +33 - 1 42 16 25 41. alexis.elbaz@upmc.fr.

*Both authors contributed equally to this work.

Leblanc, 75908 Paris Cedex 15, France ²⁵ Dublin Neurological Institute at the Mater Misericordiae University Hospital, and Conway Institute of Biomolecular & Biomedical Research, University College Dublin, Ireland ²⁶ National Centre for Adult Stem Cell Research, ESKITIS Institute for Cell and Molecular Therapies, Griffith University, Brisbane, Queensland, Australia ²⁷ Department of Neurology, Princess Alexandra Hospital, Brisbane, Queensland, Australia ²⁸ Neurology Research Centre, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia ²⁹ Department of Clinical Science, Section of Geriatric Psychiatry, Lund University, Sweden ³⁰ Department of Neurology, Skåne University Hospital, Lund, Sweden ³¹ Institute of Neurology, University Magna Graecia, Catanzaro, and Neuroimaging Research Unit, National Research Council, Germaneto, Italy ³² School of Medicine and Centre for Clinical Research, University of Queensland, Brisbane, Australia ³³ Division of Basic Neurosciences, Biomedical Research Foundation of the Academy of Athens, and Second Department of Neurology, University of Athens Medical School, Greece ³⁴ Department of Neurology, Mayo Clinic, Jacksonville, FL, USA ³⁵ Department of Clinical Neuroscience and Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden ³⁶ Department of Neurology, NorthShore University HealthSystem, Evanston, IL, USA ³⁷ Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, V5Z4H4 BC, Canada

Abstract

Objective—We studied the independent and joint effects of the genes encoding alpha-synuclein (*SNCA*) and microtubule associated protein tau (*MAPT*) in Parkinson's disease (PD) as part of a large meta-analysis of individual data from case-control studies participating in the Genetic Epidemiology of Parkinson's Disease (GEO-PD) consortium.

Methods—Participants of Caucasian ancestry were genotyped for a total of four *SNCA* (rs2583988, rs181489, rs356219, rs11931074) and two *MAPT* (rs1052553, rs242557) SNPs. Individual and joint effects of *SNCA* and *MAPT* SNPs were investigated using fixed- and random-effects logistic regression models. Interactions were studied both on a multiplicative and an additive scale, and using a case-control and case-only approach.

Results—Fifteen GEO-PD sites contributed a total of 5302 cases and 4161 controls. All four *SNCA* SNPs and the *MAPT* H1-haplotype defining SNP (rs1052553) displayed a highly significant marginal association with PD at the significance level adjusted for multiple comparisons. For *SNCA*, the strongest associations were observed for SNPs located at the 3' end of the gene. There was no evidence of statistical interaction between any of the four *SNCA* SNPs and rs1052553 or rs242557, neither on the multiplicative nor on the additive scale.

Interpretation—This study confirms the association between PD and both *SNCA* SNPs and the H1 *MAPT* haplotype. It shows, based on a variety of approaches, that the joint action of variants in these two loci is consistent with independent effects of the genes without additional interacting effects.

Keywords

Parkinson disease; *SNCA*; *MAPT*; genetics; interaction; case-control

Background

The microtubule associated protein tau and α -synuclein are two abundant brain proteins that aggregate in neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer disease, and progressive supranuclear palsy (PSP). There is evidence that the formation of pathological inclusions containing tau and α -synuclein is promoted by common

mechanisms,¹ and there are reports of concurrence of α -synuclein and tau brain pathology in autosomal dominant parkinsonism.^{2,3}

There is increasing evidence that genetic susceptibility contributes to the etiology of PD. Using a candidate-gene approach, genetic association studies pointed towards an association between PD and both the α -synuclein (*SNCA*)⁴⁻⁶ and microtubule-associated protein tau (*MAPT*) genes.⁷⁻¹⁰ More recently, genome-wide association studies (GWAS) confirmed that *SNCA* and *MAPT* were two of the main common contributors to PD genetic susceptibility among Caucasians.¹¹⁻¹⁴ The *MAPT* locus (17q21.31) contains a c.900-kb inversion polymorphism with two distinct haplotypes, H1 and H2; the major H1 haplotype is associated with PD, PSP, and other tauopathies. The *SNCA* gene lies in a region of relatively high linkage disequilibrium (LD) with SNPs at both 3'- and 5'-ends of the gene associated with PD. Given the multiple associations at this locus, it remains unclear whether they result from a single functional variant or whether there are different functional variants at both ends.⁵ Given the over-expression hypothesis for *SNCA*, there may well be multiple variants affecting transcription factor binding sites at the promoter or miRNA sites in the 3'UTR.¹⁵

Although the functional variant(s) have not been identified, the association between PD and both the *SNCA* and *MAPT* genes is well established. These findings raise the question of a possible gene-gene interaction between *SNCA* and *MAPT*, but few studies have investigated this question and with inconsistent findings.¹⁶⁻¹⁸

Sample sizes needed to detect interactions between two variables are larger than for marginal effects of similar size;^{19,20} therefore, larger studies are needed to investigate whether *SNCA* and *MAPT* interact and collaborative efforts are needed to reach sufficient sample sizes. We invited teams involved in the Genetic Epidemiology of Parkinson's Disease (GEO-PD) consortium to undertake a collaborative effort in order to investigate the joint effects and potential interactions between *SNCA* and *MAPT* in conferring susceptibility to PD in a large sample of cases and controls.

Methods

Study population

The aim of the GEO-PD consortium is to conduct collaborative studies of genetic risk factors in PD. Since its creation in 2004, the consortium has regularly met in order to organize scientific collaborations between participating teams. During the meeting held in Tuebingen (Germany) in 2009 and following the presentation at scientific meetings of the results of PD GWAS, attending teams were invited to participate to a collaborative effort in order to study the joint effects of *SNCA* and *MAPT*.

All studies were approved by the local ethical committees following the procedures of each country.

Genotyping methods

Participating sites were asked to contribute 250 nanograms of DNA. DNA was sent to a central laboratory (Mayo Clinic, Jacksonville, USA) where genotypes were determined blinded to case-control status.

Four *SNCA* (rs2583988, rs181489, rs356219, rs11931074) and two *MAPT* (rs1052553, rs242557) SNPs were selected for genotyping. We identified *SNCA* SNPs at the 5'- (rs2583988, 5'-6) or 3'-ends (rs181489, 5'-21 rs356219, 6'-13-17 rs11931074, 11'-13-21) of the gene which had been previously associated with PD. In addition, rs11931074 (located approximately 7Kb downstream from the 3'-end) has been associated with multiple system

atrophy (MSA).²² We did not select the REP1 polymorphism in the *SNCA* promoter because the 263 bp allele, which is more strongly associated with PD, is rare (<10%) thus leading to insufficient power for interaction analyses.

The rs1052553 A-allele defines the *MAPT* H1 haplotype; rs242557 highlights the *MAPT* H1c sub-haplotype associated with progressive supranuclear palsy (PSP).²³

Genotyping was performed on a Sequenom MassArray iPLEX platform (San Diego, CA); primer sequences are available upon request.

Statistical methods

We used exact tests to assess among controls of each site whether genotype distributions for each SNP violated Hardy-Weinberg equilibrium (HWE).²⁴ Sites with a nominally significant ($p < 0.05$) deviation from HWE were excluded. All participants were of Caucasian ancestry.

We investigated the marginal association between PD and the six SNPs by site using fixed-effects logistic regression. For *SNCA* SNPs, the reference allele was the major frequency allele; for *MAPT* SNPs we considered the minor allele as the reference in order to be in agreement with previous papers.¹⁰ Odds ratios (OR), 95% confidence intervals (CI), and p -values were computed using a dummy-coding of the genotypes (model-free analysis), as well as additive, dominant, and recessive models. The Akaike information criterion (AIC) was computed; the lowest AIC indicates the best model when both goodness of fit and parsimony are considered.

Our primary analyses of the interaction between SNPs were performed by estimating ORs for individual and joint effects and by including multiplicative terms in the models to test for statistical multiplicative interaction.²⁵ We also tested interactions on an additive scale by estimating the relative excess risk due to interaction (RERI, also known as the interaction contrast ratio), the attributable proportion due to interaction (AP), and the synergy index (SI); $RERI = AP = 0$ and $SI = 1$ indicate lack of interaction on an additive scale.^{26,27} For interaction analyses, our primary analyses focused on *MAPT* rs1052553; we tested the interaction between each of the four *SNCA* SNPs and rs1052553. Additional analyses involving the other *MAPT* SNP (rs242557) were also performed and reported as supplementary data. Analyses unadjusted and adjusted for age and gender were performed.

The results of analyses by site are displayed as forest plots and were used to estimate between-site heterogeneity. We tested for between-site heterogeneity with the χ^2 -based Q statistic (significant for $p < 0.10$) and quantified its extent with I^2 , which ranges from 0% to 100% and represents the proportion of between-study variability ascribed to heterogeneity rather than to chance.^{28,29} Values for I^2 of 0–24% suggest little heterogeneity, 25–49% reflect moderate heterogeneity, 50–74% reflect large heterogeneity, and >75% reflect very large heterogeneity.

For quantitative syntheses, we used fixed- and random-effects logistic regression models. In the presence of heterogeneity, random-effects syntheses are preferable;³⁰ because there was evidence of heterogeneity in some analyses, our primary analyses are based on random-effects models and we present the results of analyses based on fixed-effects models as supplementary data. Fixed-effects models assume that ORs are constant across sites and that observed differences are due to chance; they were implemented by including site as a categorical covariate in the models. Random-effects models allow that results might be genuinely heterogeneous across sites and take into account between-study heterogeneity by including random effects for genotypes; they were implemented using multilevel regression

models.³¹⁻³⁴ For analyses of gene-gene interactions, regression models included several random effects and we used an unstructured variance-covariance matrix for the random effects.

Gene-gene multiplicative interactions were also investigated by looking at the association of *SNCA* and *MAPT* genotypes among cases-only using fixed- and random-effects logistic regression (secondary analysis). If genotypes are independent among controls, this approach has generally increased power compared to case-control analyses.²⁰⁻³⁵

SNCA haplotypes were defined using Thesias software, that allows to test interactions with covariates.³⁶ We tested the interaction between *SNCA* haplotypes and rs1052553 or rs242557. The relative effect of *SNCA* SNPs was explored using a unified stepwise regression procedure.³⁷

Among cases, we followed a similar strategy as described above to investigate, with fixed- and random-effects linear regression models, the effect of SNPs and their interaction on age at onset (AAO) of PD as a continuous outcome.

Both for case-control and case-only analyses, a Bonferroni correction was used to take into account multiple testing. In marginal-effects analyses, we considered four models for six SNPs; $p \leq 0.0021$ (0.05/24) was considered as statistically significant. For analyses of joint effects, three multiplicative interaction models (model-free, dominant, or additive coding of *SNCA* SNPs) were considered for four SNPs; $p \leq 0.0042$ (0.05/12) was considered as statistically significant.

The sample size needed to detect interactions on a multiplicative scale was investigated for different gene frequencies, genetic models, and effects (supplementary figure 1). For instance, to detect an interaction OR of 1.5, and assuming that the marginal OR for a *SNCA* SNP with a frequency of 15% is 1.20 (additive model) and that the marginal OR for a *MAPT* SNP with a frequency of 80% is 1.25 (recessive model), a case-control study (1:1 matching) would need to include ~1700 cases in order to reach 80% power at the two-sided 0.05 significance level. At the 0.0042 significance level, ~2900 cases would be necessary to reach 80% power.

Analyses were performed using SAS 9.1 (Cary, NC, USA) and STATA 11.0 (College Station, TX, USA).

Results

Fifteen sites contributed a total of 5302 cases and 4161 controls. Their demographic and clinical characteristics are shown in table 1; 16% of the cases reported a positive history of PD among first-degree relatives. The distributions by site of the six SNPs in cases and controls are shown in supplementary table 1. HW equilibrium was tested among controls for each SNP and site; rs1052553 was the only SNP for which a significant departure ($p=0.0008$) was identified in site K. We excluded participants from this site and retained the remaining 5199 cases and 4059 controls. Genotyping call-rates were > 95% for all SNPs and sites. One site (P) contributed only cases; they were included in case-only analyses (therefore based on 5272 cases).

Table 2 shows the association between each SNP and PD using random-effects logistic regression, together with heterogeneity estimates; results from fixed-effects models are shown in supplementary table 2. Supplementary figure 2 shows forest plots under additive, dominant, and recessive genetic models. There was evidence of heterogeneity for some *SNCA* SNPs (rs181489, additive and dominant model; rs356219, recessive model;

rs2583988, additive and dominant model; table 2), while no heterogeneity was detected for *MAPT* SNPs. Fixed- and random-effects models yielded similar conclusions. All *SNCA* SNPs displayed a highly significant association with PD at the Bonferroni-corrected significance level. For rs181489, rs356219, and rs2583988, both heterozygotes and homozygotes for the minor allele were significantly more frequent in cases than controls, but ORs increased with the number of minor alleles and the additive model displayed the lowest AIC value. For rs11931074, the association pattern was more consistent with a dominant model, but the additive model was also very close in AIC. The strongest associations were detected for rs181489 followed by rs356219 (both located at the 3' end of the gene). Adjustment for age and sex yielded similar findings (not shown).

When all *SNCA* SNPs together with all possible pair-wise interactions were included in the same model and after using a backward selection procedure (supplementary table 3), main effects remained highly significant for the 3' SNPs, indicating that they were independently associated with PD. The direction of the independent association between PD and rs356219 was reversed in this analysis compared to univariate analyses (table 2); it is likely that the strong linkage disequilibrium between SNPs in the *SNCA* gene leads to confounding in univariate analyses and that an independent effect of rs356219 is not apparent in univariate analyses due to its strong association with rs181489. In addition, there was a trend in favor of an interaction between rs11931074 and rs181489, suggesting that the effect of rs11931074 decreased with the number of rs181489 alleles. The main effect for rs2583988 (5'-end) was not significant once 3'-end SNPs were included in the model; however, there was a trend in favor of interaction between rs2583988 and rs356219, suggesting that rs2583988 has a small effect among carriers of the minor rs356219 allele.

We found a highly significant association between PD and the H1-tagging allele of rs1052553 with the same AIC values for additive and recessive models; the GA rs1052553 genotype was not associated with PD and it was only the AA genotype (i.e., carriers of the H1/H1 haplotype) that was positively associated with PD. A weaker association was found for rs242557 (dominant model). Adjustment for age and sex yielded similar findings (data not shown). After Bonferroni correction, rs1052553 remained significantly associated with PD while rs242557 did not. When both rs1052553 (recessive) and rs242557 (dominant) were included in the same model, the association between PD and rs1052553 remained virtually unchanged (fixed-effects, OR=1.25, 95% CI=1.14-1.37) while the association with rs242557 disappeared (fixed-effects, OR=0.95, 95% CI=0.84-1.08).

The genotype counts for the cross-tabulation of rs1052553 and each of the *SNCA* SNPs are presented in supplementary table 4 by study. Figure 1 includes forest plots of ORs corresponding to the multiplicative interaction between the H1/H1 *MAPT* haplotype (defined by rs1052553) and each *SNCA* SNP (additive coding); supplementary figure 3 shows the same analysis using a dominant coding of *SNCA* SNPs. Depending on the SNPs, heterogeneity measures suggested weak (rs356219, rs11931074), moderate (rs181489) or large (rs2583988) heterogeneity.

Table 3 presents the results of interaction analyses between each *SNCA* SNP and *MAPT* rs1052553; because of the large sample size, we were able to investigate the interaction between carriers of the H1/H1 *MAPT* haplotype and each of the genotypes of *SNCA* SNPs. Multiplicative interaction was tested using different codings of *SNCA* SNPs. All interaction tests were far from nominal significance: while both *SNCA* and *MAPT* SNPs independently increased the risk of PD, their joint effects were not different from that expected under a multiplicative model. Fixed-effects models (supplementary table 5) and adjustment for age and gender (data not shown) yielded the same conclusions. For the analyses presented in figure 2, we used a dominant coding for *SNCA* SNPs to show that there was no interaction

using alternative codings of *SNCA* SNPs. In addition, RERI and AP were not different from 0 and SI was not different from 1 in all instances, thus showing that there was no interaction on an additive scale. There was no evidence of interaction using a recessive coding for *SNCA* SNPs¹⁷ (data not shown). No multiplicative interactions were observed between *MAPT* rs242557 and *SNCA* SNPs (supplementary table 6); there was no evidence of additive interaction either (not shown). Finally, we defined *SNCA* haplotypes and tested their interaction with rs1052553 or rs242557; no interactions were detected both on multiplicative or additive scales (not shown). Analyses restricted to sporadic cases yielded the same conclusions (data not shown).

Supplementary table 7 shows the association between *MAPT* rs1052553 and *SNCA* SNPs stratified by disease status. There was no association between either rs1052553 or rs242557 (not shown) and any *SNCA* SNP among controls or cases.

We performed additional analyses restricted to cases in order to investigate whether *SNCA* and *MAPT* SNPs influenced AAO. Table 4 shows the marginal association between each SNP and AAO. There was no significant association between any SNP and AAO at the Bonferroni-corrected significance level. Table 5 shows individual and joint effects of *SNCA* SNPs and rs1052553 on AAO; there was no evidence of departure from additivity in linear regression models. No interaction between *SNCA* SNPs and rs242557 was seen for AAO (not shown).

Discussion

SNCA and *MAPT* have been confirmed by recent GWAS as two of the main contributors to genetic susceptibility in PD among Caucasians.¹¹⁻¹⁴ α -synuclein is one of the main protein components of Lewy bodies and it has been reported that common mechanisms promote the aggregation of α -synuclein and tau,¹ supporting findings of concurrent α -synuclein and tau brain pathology in autosomal dominant parkinsonism.^{2,3} These observations raise the possibility of an interaction between *SNCA* and *MAPT*.

In this large case-control study, we confirmed the association between PD and four SNPs distributed across the *SNCA* gene as well as with the H1 *MAPT* haplotype. All *SNCA* SNPs and the *MAPT* H1 defining variant (rs1052553) affected PD susceptibility. Neither *SNCA* nor *MAPT* SNPs influenced AAO among cases. The large sample size allowed us to address the important question of whether there is a *SNCA*-by-*MAPT* interaction. We did not find any evidence in favor of interaction for susceptibility to PD or AAO.

Previously, Mamah et al.¹⁶ genotyped 557 case-control pairs for the REP1 polymorphism in the *SNCA* promoter and *MAPT* H1 haplotype, and found a marginal association between PD and both the 261/261 REP1 genotype and the H1/H1 *MAPT* haplotype. They investigated individual and joint effects by implementing several genetic models, without formally testing for statistical interaction, and concluded that the most likely model was one that forced the regression parameters to be equal for individual gene effects and their combination. According to this model, the combined effect of the genes is smaller than expected under a multiplicative model. A subsequent study of the relation between REP1 and PD found that it was not the 261 allele, but the less-frequent 263 allele that was associated with PD.⁴ Goris et al.¹⁷ genotyped 659 PD cases and 2176 controls for the H1 *MAPT* haplotype and one 3' *SNCA* SNP (rs356219). They found a marginal association between PD and both H1/H1 *MAPT* and GG rs356219. In addition, there was evidence of a multiplicative interaction ($p=0.03$): the combined OR for H1/H1 *MAPT* and GG rs356219 (OR=2.14) was greater than expected under a multiplicative model given their individual ORs (H1/H1 *MAPT*, OR=1.23; GG rs356219, OR=1.00). As a part of another study that

looked at several gene-gene and gene-environment interactions (932 cases, 664 controls), McCulloch et al.¹⁸ did not find evidence of an interaction between the H1 *MAPT* haplotype and *REP1*. Finally, a GWAS did not detect an epistatic interaction between *SNCA* and *MAPT*, but without further information about the interaction models that were tested.¹¹

Interestingly, for all *SNCA* SNPs except rs11931074, the best fitting marginal model was an additive model and PD risk increased with the number of minor alleles. As duplications and triplications of *SNCA* have been identified in families, overdosage has been postulated as a potential mechanism. In addition, additive models are typically the best-fitting for GWAS-discovered SNPs.³⁸ For rs11931074, the best-fitting model was the dominant one, but the difference in AIC from the additive model was minimal, and it was recently associated with PD in two GWAS using an additive coding.^{11,12} In agreement with previous studies,^{5,6,11} our analysis of the relative effects of *SNCA* SNPs suggests that the causal variant may be located towards the 3'-end and could affect post-transcriptional RNA processing or stability, and thus gene/protein expression; however, we cannot exclude that the 5'-end may also play a role, and additional genomic capture and sequencing studies are needed to identify the causal variant(s).

Mutations in the *MAPT* gene cause frontotemporal dementia with parkinsonism and there is consistent evidence that PSP is associated with the *MAPT* H1 haplotype.^{23,39} There is increasing evidence from candidate gene studies¹⁰ and GWAS¹¹⁻¹⁴ that the H1 *MAPT* haplotype is also associated with PD among Caucasians. In agreement with these studies, we found a strong association with rs1052553. The rs242557 A-allele defines the H1c PSP-associated haplotype and a recent study reported that PD may be associated with the opposite G-rs242557 allele,⁴⁰ but in our study, the association between PD and rs242557 was not significant after correction for multiple testing and is likely to be accounted for by its LD with rs1052553, as demonstrated by analyses in which both SNPs were included in the same model.

One of the main strengths of our study is its large sample size that conferred sufficient power to detect even small interactions. Smaller studies suffer from insufficient numbers of subjects jointly exposed to the two variables investigated, which leads to reduced power and unstable interaction estimates with large confidence intervals. Additional strengths involve the centralized genotyping in a single laboratory, the consideration of several SNPs in the *SNCA* gene located both at its 5' and 3' ends (compared to previous studies on *SNCA*-by-*MAPT* interaction that considered single SNPs), and implementation of complementary approaches to test for interaction.

The relevant scale to test for statistical interaction has been a subject of intense debate in the epidemiological community and there is no consensus about the most appropriate method.^{41,42} The multiplicative scale has been most often used for dichotomous outcomes mainly due to an easier implementation using logistic regression. It has been argued, however, that biologic interactions are more likely to lead to departure from additive effects of two variables.^{25,26,43} As we were concerned that we may have failed to detect an interaction on the additive scale, we investigated additive interactions and found that the pattern of association was not suggestive of an interaction on this scale either. In addition, it has been pointed out that the same word, epistasis, i.e., interaction between genes, has been used in the literature to describe different concepts,⁴⁴ and Phillips⁴⁵ recently described three main categories: functional, compositional, and statistical epistasis. The extent to which statistical interaction implies functional or compositional epistasis, and vice-versa, is unclear,^{44,45} but empirical tests have been proposed as a way to detect compositional epistasis (also termed epistasis in the sense of masking);^{46,47} our RERI estimates were clearly not in agreement with this type of mechanism either.

Weaknesses of our study include lack of standardized inclusion/exclusion criteria for cases or controls, different diagnostic criteria across studies, and lack of standard definition of AAO; however, random-effects models, which take into account heterogeneity between studies, yielded the same results as fixed-effects models and analyses stratified by diagnostic criteria showed no differences across strata.

In conclusion, this study confirms the association between PD and both *SNCA* SNPs and the H1 *MAPT* haplotype, with similar size effects as previous studies, and it shows, based on a variety of approaches, that the association between PD and *SNCA* is not modified by *MAPT*, and vice-versa. Thus, the joint action of variants in these two loci is consistent with independent effects. While these findings do not support a strong gene-gene interaction between *MAPT* and *SNCA* at the level of epidemiological risk, they do not rule out functional interactions at the protein level and further in vitro and in vivo studies will be necessary to address this question.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors acknowledge the following GEO-PD collaborators and funding sources: **France:** Philippe Amouyel (Inserm, U744, Lille, France); Christophe Tzourio (Inserm, U708, Paris, France); Claire Mulot (Inserm, U775; CRB Epigenetec, Paris, France). Funding: Agence Nationale de la Recherche (Sant-environnement 2005, Maladies neurologiques, 2009), Agence franaise de scurit sanitaire de l'environnement et du travail (Afsset), France Parkinson. **USA:** Justin A. Bacon, BS, and Stephanie A. Cobb, BA (Mayo Clinic, Jacksonville). Funding: The Michael J. Fox Foundation (O.A. Ross & M.J. Farrer); American Parkinson's Disease Association Research Grant (O.A. Ross); Mayo Clinic Jacksonville is a Morris K. Udall Parkinson's Disease Research Center of Excellence (NINDS P50 #NS40256); NIH grant 2R01ES10751 (D.M. Maraganore). **Greece/USA:** Funding: Scientific support for this project to J.P.A. Ioannidis was provided through the Tufts Clinical and Translational Science Institute (Tufts CTSI) under funding from the National Institute of Health/National Center for Research Resources (UL1 RR025752, PI: Harry Selker). Points of view or opinions in this paper are those of the authors and do not necessarily represent the official position or policies of the Tufts CTSI. **Australia (site A):** Greg T. Sutherland, Gerhard A. Siebert, Nadeeka Dissanayaka, John D. O'Sullivan, Richard S. Boyle. Funding: National Health and Medical Research Council (Australia) Project Grant #401537; Geriatric Medical Foundation of Queensland; Princess Alexandra Hospital; Royal Brisbane and Women's Hospital Foundations. **France (site B):** Florence Pasquier and Rgis Bordet (Steering Committee of the Paradigme study); Jean-Philippe Legendre (CHRU-Lille). Funding: Fondation de la Recherche Mdicale (Convergence 2006/413), PHRC (Parkfanord 005/1913, Paradigme 2002/1918), Univ Lille 2 (Synucleothque), Inserm-French Research Ministry for support for the biological resources centers (CHRU Lille and Institut Pasteur de Lille). **Germany (site C):** Georg Auburger; Rdiger Hilker; Nadine Abahuni (Goethe University Frankfurt); Christof Geisen (Blood Bank Frankfurt). Funding: BMBF NGFNplus 01GS08138. **Germany (site D):** Susen Winkler, BS. Funding: Volkswagen Foundation and Hermann and Lilly Schilling Foundation. **Germany (site E):** Thomas Gasser, Olaf Riess, Daniela Berg, Claudia Schulte. Funding: Germany: Work of was supported by grants from the German Research Council [DFG, KR2119/3-2] to R. Krger; the Federal Ministry for Education and Research [BMBF, NGFNplus; 01GS08134] to R. Krger, T. Gasser, O. Riess; and the Michael J Fox Foundation to M. Sharma, R. Krger, T. Gasser. **Greece (site F):** Demitris Vassilatis, Eleftherios Stamboulis. Funding: Hellenic Secretariat of Research and Technology (IENE 2003). **Greece (site G):** Efthimios Dardiotis, Department of Neurology, Faculty of Medicine, University of Thessaly, Larissa, Greece); Ioanna Patramani, MD (Department of Neurology, Faculty of Medicine, University of Thessaly, Larissa, Greece); Persa-Maria Kountra, MD (Department of Neurology, Laboratory of Neurogenetics, Faculty of Medicine, University of Thessaly, Larissa, Greece); Christina Vogiatzi (Department of Neurology, Faculty of Medicine, University of Thessaly, Larissa, Greece); Katerina Markou, MD (Department of Neurology, Faculty of Medicine, University of Thessaly, Larissa, Greece). Funding: University of Thessaly, Research Committee (Code: 2845); Institute of Biomedical Research & Technology, CERETETH (Code: 01-04-207). **Italy (site I):** Patrizia Tarantino, Ferdinando Annesi (Institute of Neurological Sciences, National Research Council, Cosenza, Italy). **Italy (site J):** Anna Rita Bentivoglio, MD, PhD; Arianna Guidubaldi, MD; Matilde Caccialupi, MD; Francesca De Nigris, MD (Institute of Neurology, Catholic University, Rome, Italy). Funding: Italian Ministry of Health (Ricerca Corrente 2010; Ricerca Finalizzata 2006; Progetto Giovani Ricercatori 2008). **Italy (site K):** Chiara Riva, PhD (Department of Neuroscience and Biomedical Technologies, University of Milano-Bicocca, Monza, Italy). Funding: FIRB 2003 GENOPOLIS Project; grant number: RBLA038RMA_003. **Norway (site L):** Funding: The Research Council of Norway, Project 10314000. **Sweden (site N):** Nancy L Pedersen. Funding: National Institutes

of Health (ES10758), the Swedish Research Council, the Swedish Society for Medical Research, the Swedish Society of Medicine, funds from the Karolinska Institutet, and the Parkinson Foundation in Sweden. **Sweden (site P):** Other contributors: Karin Nilsson, RN (Department of Clinical Science, Section of Geriatric Psychiatry, Lund University, Sweden); Jan Reimer, RN (Department of Neurology, Skåne University Hospital, Lund, Sweden; Region Skåne Competence Centre, Skåne University Hospital, Malmö, Sweden). Funding: Swedish Parkinson Academy, AFA Insurance Research Grant (Sweden), Elsa Schmitz Foundation (Sweden), Apotekare Hedberg's Foundation for Medical Research (Sweden), The Swedish Parkinson Fund, The Royal Physiographic Society in Lund (Sweden), Lund University Hospital Research Fund (Sweden). **USA (site O):** Jay Van Gerpen, MD; Jennifer Lash; Jill Searcy; Audrey Strongosky. Funding: Mayo Clinic Jacksonville Morris K. Udall Parkinson's Disease Research Center of Excellence NIH/NINDS P50 #NS40256, NIH/NINDS R01 NS057567, NIH/NINDS RC2 NS070276-01, Mayo Clinic Florida Research Committee CR programs, and gift from Carl Edward Bolch, Jr. and Susan Bass Bolch.

References

1. Giasson BI, Forman MS, Higuchi M, et al. Initiation and synergistic fibrillization of tau and alpha-synuclein. *Science*. 2003; 300:636–640. [PubMed: 12714745]
2. Wszolek ZK, Pfeiffer RF, Tsuboi Y, et al. Autosomal dominant parkinsonism associated with variable synuclein and tau pathology. *Neurology*. 2004; 62:1619–1622. [PubMed: 15136696]
3. Duda JE, Giasson BI, Mabon ME, et al. Concurrence of alpha-synuclein and tau brain pathology in the Contursi kindred. *Acta Neuropathol*. 2002; 104:7–11. [PubMed: 12070658]
4. Maraganore DM, De Andrade M, Elbaz A, et al. Collaborative analysis of the alpha-synuclein gene promoter variability and Parkinson's disease. *JAMA*. 2006; 296:661–670. [PubMed: 16896109]
5. Winkler S, Hagenah J, Lincoln S, et al. Alpha-synuclein and Parkinson disease susceptibility. *Neurology*. 2007; 69:1745–1750. [PubMed: 17872362]
6. Mueller JC, Fuchs J, Hofer A, et al. Multiple regions of alpha-synuclein are associated with Parkinson's disease. *Ann Neurol*. 2005; 57:535–541. [PubMed: 15786467]
7. Farrer M, Skipper L, Berg M, et al. The Tau H1 haplotype is associated with Parkinson's disease in the Norwegian population. *Neurosci Lett*. 2002; 322:83–86. [PubMed: 11958849]
8. Levecque C, Elbaz A, Clavel J, et al. Association of polymorphisms in the Tau and Saitohin genes with Parkinson's disease. *J Neurol Neurosurg Psychiatr*. 2004; 75:478–480. [PubMed: 14966169]
9. Healy DG, bou-Sleiman PM, Lees AJ, et al. Tau gene and Parkinson's disease: a case-control study and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2004; 75:962–965. [PubMed: 15201350]
10. Wider C, Vilarino-Guell C, Jasinska-Myga B, et al. Association of the MAPT locus with Parkinson's disease. *Eur J Neurol*. 2010; 17:483–486. [PubMed: 19912324]
11. Simon-Sanchez J, Schulte C, Bras JM, et al. Genome-wide association study reveals genetic risk underlying Parkinson's disease. *Nat Genet*. 2009; 41:1308–1312. [PubMed: 19915575]
12. 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. *Nat Genet*. 2009; 41:1303–1307. [PubMed: 19915576]
13. Pankratz N, Wilk JB, Latourelle JC, et al. Genomewide association study for susceptibility genes contributing to familial Parkinson disease. *Hum Genet*. 2009; 124:593–605. [PubMed: 18985386]
14. Edwards TL, Scott WK, Almonte C, et al. Genome-Wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for Parkinson disease. *Ann Hum Genet*. 2010; 74:97–109. [PubMed: 20070850]
15. Ross OA, Braithwaite AT, Skipper LM, et al. Genomic investigation of alpha-synuclein multiplication and parkinsonism. *Ann Neurol*. 2008; 63:743–750. [PubMed: 18571778]
16. Mamah CE, Lesnick TG, Lincoln SJ, et al. Interaction of alpha-synuclein and tau genotypes in Parkinson's disease. *Ann Neurol*. 2005; 57:439–443. [PubMed: 15732111]
17. Goris A, Williams-Gray CH, Clark GR, et al. Tau and alpha-synuclein in susceptibility to, and dementia in, Parkinson's disease. *Ann Neurol*. 2007; 62:145–153. [PubMed: 17683088]
18. McCulloch CC, Kay DM, Factor SA, et al. Exploring gene-environment interactions in Parkinson's disease. *Hum Genet*. 2008; 123:257–265. [PubMed: 18210157]
19. Smith PG, Day NE. The design of case-control studies: the influence of confounding and interaction effects. *Int J Epidemiol*. 1984; 13:356–365. [PubMed: 6386716]

20. Gauderman WJ. Sample size requirements for association studies of gene-gene interaction. *Am J Epidemiol.* 2002; 155:478–484. [PubMed: 11867360]
21. Ross OA, Gosal D, Stone JT, et al. Familial genes in sporadic disease: common variants of alpha-synuclein gene associate with Parkinson's disease. *Mech Ageing Dev.* 2007; 128:378–382. [PubMed: 17531291]
22. Scholz SW, Houlden H, Schulte C, et al. SNCA variants are associated with increased risk for multiple system atrophy. *Ann Neurol.* 2009; 65:610–614. [PubMed: 19475667]
23. Rademakers R, Melquist S, Cruts M, et al. High-density SNP haplotyping suggests altered regulation of tau gene expression in progressive supranuclear palsy. *Hum Mol Genet.* 2005; 14:3281–3292. [PubMed: 16195395]
24. Guo SW, Thompson EA. Performing the exact test of Hardy-Weinberg proportion for multiple alleles. *Biometrics.* 1992; 48:361–372. [PubMed: 1637966]
25. Knol MJ, Egger M, Scott P, et al. When one depends on the other: reporting of interaction in case-control and cohort studies. *Epidemiology.* 2009; 20:161–166. [PubMed: 19034025]
26. Rothman, KJ.; Greenland, S.; Lash, TL. *Modern epidemiology.* Philadelphia, USA: Lippincott, Williams & Wilkins; 2008.
27. Zou GY. On the estimation of additive interaction by use of the four-by-two table and beyond. *Am J Epidemiol.* 2008; 168:212–224. [PubMed: 18511428]
28. Chalmers I, Hedges LV, Cooper H. A brief history of research synthesis. *Eval Health Prof.* 2002; 25:12–37. [PubMed: 11868442]
29. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002; 21:1539–1558. [PubMed: 12111919]
30. Trikalinos TA, Salanti G, Zintzaras E, et al. Meta-analysis methods. *Adv Genet.* 2008; 60:311–334. [PubMed: 18358326]
31. Turner RM, Omar RZ, Yang M, et al. A multilevel model framework for meta-analysis of clinical trials with binary outcomes. *Stat Med.* 2000; 19:3417–3432. [PubMed: 11122505]
32. Whitehead A, Omar RZ, Higgins JP, et al. Meta-analysis of ordinal outcomes using individual patient data. *Stat Med.* 2001; 20:2243–2260. [PubMed: 11468762]
33. Higgins JP, Whitehead A, Turner RM, et al. Meta-analysis of continuous outcome data from individual patients. *Stat Med.* 2001; 20:2219–2241. [PubMed: 11468761]
34. Bagos PG, Nikolopoulos GK. A method for meta-analysis of case-control genetic association studies using logistic regression. *Stat Appl Genet Mol Biol.* 2007; 6 Article17.
35. Khoury MJ, Flanders WD. Nontraditional epidemiologic approaches in the analysis of gene-environment interaction: Case-control studies with no controls! *Am J Epidemiol.* 1996; 144:207–213. [PubMed: 8686689]
36. Tregouet DA, Garelle V. A new JAVA interface implementation of THESIAS: testing haplotype effects in association studies. *Bioinformatics.* 2007; 23:1038–1039. [PubMed: 17308338]
37. Cordell HJ, Clayton DG. A unified stepwise regression procedure for evaluating the relative effects of polymorphisms within a gene using case/control or family data: Application to HLA in type 1 diabetes. *Am J Hum Genet.* 2002; 70:124–141. [PubMed: 11719900]
38. Salanti G, Southam L, Altshuler D, et al. Underlying genetic models of inheritance in established type 2 diabetes associations. *Am J Epidemiol.* 2009; 170:537–545. [PubMed: 19602701]
39. Baker M, Litvan I, Houlden H, et al. Association of an extended haplotype in the tau gene with progressive supranuclear palsy. *Hum Mol Genet.* 1999; 8:711–715. [PubMed: 10072441]
40. Ezquerra M, Pastor P, Gaig C, et al. Different MAPT haplotypes are associated with Parkinson's disease and progressive supranuclear palsy. *Neurobiol Aging.* 2009; 30:1016–1021. [PubMed: 19090111]
41. Rothman KJ. Synergy and antagonism in cause-effect relationships. *Am J Epidemiol.* 1974; 99:385–388. [PubMed: 4841816]
42. Rothman KJ, Greenland S, Walker AM. Concepts of interaction. *Am J Epidemiol.* 1980; 112:467–470. [PubMed: 7424895]
43. Vanderweele TJ. Sufficient cause interactions and statistical interactions. *Epidemiology.* 2009; 20:6–13. [PubMed: 19234396]

44. Cordell HJ. Detecting gene-gene interactions that underlie human diseases. *Nat Rev Genet.* 2009; 10:392–404. [PubMed: 19434077]
45. Phillips PC. Epistasis--the essential role of gene interactions in the structure and evolution of genetic systems. *Nat Rev Genet.* 2008; 9:855–867. [PubMed: 18852697]
46. Vanderweele TJ. Empirical tests for compositional epistasis. *Nat Rev Genet.* 2010; 11:166. [PubMed: 20084088]
47. Vanderweele TJ. Epistatic interactions. *Stat Appl Genet Mol Biol.* 2010; 9:1–22.

FIGURE 1.

Forest plots of the interaction ORs between rs1052553 and each of the *SNCA* SNPs (additive coding) by participating site.

Multiplicative interaction ORs were computed using an additive coding of *SNCA* SNPs.

They compare the OR for an increase in one minor allele of *SNCA* SNPs in carriers of the AA genotype for rs1052553 and in non-carriers. Heterogeneity measures (I^2 , p -value) are shown. Supplementary figure 3 shows the same analysis using a dominant coding of *SNCA* SNPs.

FIGURE 2.

Individual and joint effects of *MAPT* rs1052553 and each of the *SNCA* SNPs (dominant model) estimated using random-effects logistic regression.

The solid line corresponds to ORs for *SNCA* SNPs in carriers of *MAPT* rs1052553 AA, while the dotted line corresponds to ORs in non carriers.

Tests of interaction on the additive scale are shown (RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, synergy index). Tests of multiplicative interaction were as follows: rs181489, $p=0.93$; rs356219, $p=0.75$; rs2583988, $p=0.80$; rs11931074, $p=0.72$.

TABLE 1

Characteristics of Study Participants by Site

Site	Country	Study PI	Cases				Controls					
			N	Male sex %	Mean age at onset (SD)	Mean age at study (SD)	Family history, n ^a	Diagnostic criteria	N	Male sex %	Mean age at study (SD)	Source
A	Australia	Mellick ^b	929	62	59.4 (11.4)	72.3 (10.2)	118	Bower	713	36	66.6 (9.9)	Electoral rolls; spouses; unaffected siblings
B	France	Chartier-Harlin ^b	563	54	54.7 (11.5)	63.8 (10.4)	243	Gelb	143	45	65.2 (11.0)	Friends
C	Germany	Auburger	232	51	56.2 (10.8)	71.9 (11.4)	20	UKPDBB	47	64	58.8 (9.8)	Blood donors
D	Germany	Klein	522	58	43.9 (12.9)	61.5 (12.3)	0	UKPDBB	289	47	54.9 (13.9)	Spouses
E	Germany	Kruger	335	59	-	52.1 (12.5)	NA	UKPDBB	339	55	53.2 (12.2)	Population-based
F	Greece	Bozi	135	59	66.4 (10.7)	72.6 (10.4)	24	Gelb	95	44	71.3 (9.5)	Spouses; hospital
G	Greece	Hadjiageorgiou ^b	322	50	64.6 (9.4)	68.8 (9.1)	0	Bower	315	50	70.0 (8.6)	Hospital
H	Ireland	Lynch ^c	361	58	51.4 (10.4)	67.4 (10.2)	49	UKPDBB	445	36	66.6 (24.2)	Hospital
I	Italy	Annesi; Quattrone	190	53	61.3 (9.4)	71.8 (9.4)	0	UKPDBB	168	46	53.6 (9.1)	Population-based
J	Italy	Valente; Bentivoglio	189	51	58.4 (8.2)	67.6 (8.5)	7	UKPDBB	95	45	69.0 (9.8)	Population-based
K	Italy	Ferrares ^b	103	53	62.3 (10.4)	67.8 (9.6)	22	Gelb	102	62	62.1 (6.6)	Spouses; blood donors
L	Norway	Aasly ^{b,c}	603	58	59.3 (10.9)	73.5 (10.7)	136	UKPDBB	526	56	71.3 (12.5)	Blood donors; societies for retired persons
M	Poland	Opala	349	62	57.1 (11.6)	70.1 (10.6)	57	UKPDBB	340	46	64.3 (15.7)	Population-based
N	Sweden	Wirdefeldt	91	56	65.7 (11.0)	75.6 (8.8)	7	Gelb	180	44	73.7 (10.1)	Population-based
O	USA	Wszolek; Uitti	378	55	62.1 (11.9)	71.0 (11.2)	146	UKPDBB	364	52	72.9 (10.8)	Spouses; friends; neighbors
P	Sweden	Nilsson; Puschmann	73	62	-	71.1 (9.8)	24	UKPDBB	-	-	-	-

UKPDBB: United Kingdom Parkinson's Disease Brain Bank (the exclusion criterion "more than one affected relative" was not included); NA: not available.

^aFamily history of PD among first-degree relatives.

^bPart of the samples had been previously included in a study of the marginal association between the REPI (SNCA) polymorphism and PD (Reference 4: Maraganore et al, 2006).

^cPart of the samples had been previously included in a study of the marginal association between the MAPT gene and PD (Reference 10: Wider et al, 2010).

TABLE 2
Marginal Association Between SNPs in the *SNCA* and *MAPT* Genes and Parkinson's Disease (Random-Effects Models)

SNP	Genotype	OR (95% CI) ^a	p ^a	AIC ^{a,b}	Heterogeneity	
					I ² % (95% CI)	p
SNCA						
rs181489 (5043 cases, 3910 controls)	CC	1.00 (reference)	-	-	-	-
	CT	1.14 (1.04-1.26)	0.0054	-	31 (0-64)	0.13
	TT	1.67 (1.43-1.96)	1.1E-10	11825	33 (0-64)	0.11
	Additive (T vs C) ^c	1.24 (1.16-1.33)	2.0E-09	11824 ^b	41 (0-69)	0.054
	Dominant (CT+TT vs CC)	1.23 (1.13-1.34)	1.7E-06	11844	39 (0-68)	0.065
	Recessive (TT vs CC+CT)	1.57 (1.36-1.80)	3.4E-10	11827	24 (0-60)	0.20
rs356219 (5131 cases, 3995 controls)	AA	1.00 (reference)	-	-	-	-
	AG	1.16 (1.06-1.28)	0.0020	-	0 (0-55)	0.58
	GG	1.53 (1.31-1.79)	8.3E-08	12062	29 (0-63)	0.15
	Additive (G vs A) ^c	1.22 (1.15-1.29)	2.6E-10	12059 ^b	23 (0-59)	0.21
	Dominant (AG+GG vs AA)	1.25 (1.14-1.36)	1.1E-06	12076	0 (0-55)	0.53
	Recessive (GG vs AA+AG)	1.41 (1.21-1.64)	9.0E-06	12066	41 (0-69)	0.053
rs11931074 (5159 cases, 4032 controls)	GG	1.00 (reference)	-	-	-	-
	GT	1.35 (1.20-1.52)	8.7E-07	-	0 (0-55)	0.88
	TT	1.33 (0.79-2.23)	0.28	12175	0 (0-55)	0.99
	Additive (T vs G) ^c	1.32 (1.18-1.47)	1.1E-06	12169	0 (0-55)	0.81
	Dominant (GT+TT vs GG)	1.35 (1.20-1.52)	5.4E-07	12168 ^b	0 (0-55)	0.84
	Recessive (TT vs GG+GT)	1.27 (0.76-2.13)	0.3575	12192	0 (0-55)	0.99
rs2583988 (5161 cases, 4015 controls)	CC	1.00 (reference)	-	-	-	-
	CT	1.25 (1.11-1.39)	0.0001	-	44 (0-70)	0.041
	TT	1.48 (1.23-1.78)	2.7E-05	12141	39 (0-68)	0.067
	Additive (T vs C) ^c	1.23 (1.13-1.34)	2.5E-06	12134 ^b	53 (0-74)	0.011
	Dominant (CT+TT vs CC)	1.29 (1.15-1.43)	7.5E-06	12138	51 (0-74)	0.014
	Recessive (TT vs CC+CT)	1.32 (1.13-1.55)	0.0005	12156	23 (0-59)	0.21
MAPT						

SNP	Genotype	OR (95% CI) ^a	p ^a	AIC ^{a,b}	Heterogeneity		
					I ² % (95% CI)	p	
rs1052553 (5199 cases, 4059 controls)	GG	1.00 (reference)	-	-	-	-	-
	GA	1.12 (0.90-1.40)	0.31	-	0 (0-55)	0.86	
	AA	1.38 (1.12-1.71)	0.0028	12267	0 (0-55)	0.91	
	Additive (A vs G) ^c	1.21 (1.12-1.30)	5.4E-07	12261 ^b	0 (0-55)	0.70	
	Dominant (GA+AA vs GG)	1.29 (1.05-1.60)	0.0173	12280	0 (0-55)	0.90	
	Recessive (AA vs GG+GA)	1.25 (1.15-1.37)	7.0E-07	12261 ^b	0 (0-55)	0.57	
rs242557 (5159 cases, 4008 controls)	AA	1.00 (reference)	-	-	-	-	-
	AG	0.87 (0.77-0.99)	0.0340	-	24 (0-60)	0.19	
	GG	0.86 (0.76-0.98)	0.0285	12162	0 (0-55)	0.79	
	Additive (G vs A) ^c	0.94 (0.89-1.00)	0.0687	12158	0 (0-55)	0.93	
	Dominant (AG+GG vs AA)	0.87 (0.77-0.98)	0.0214	12156 ^b	0 (0-55)	0.45	
	Recessive (GG vs AA+AG)	0.96 (0.88-1.05)	0.36	12160	0 (0-55)	0.81	

AIC: Akaike information criterion.

^aORs (95% CI) and the corresponding p-values and AIC were computed using random-effects logistic regression.

^bThe lowest value of the AIC indicates a better fit.

^cThe OR is computed for an increase of one minor allele.

TABLE 3
Individual and Joint Effects of rs1052553 (MAPT) and Each of the SNPs in the SNCA Gene for Parkinson's Disease and Corresponding Tests of Multiplicative Interaction (Random-Effects Models): Case-Control Analysis

SNCA SNP		MAPT rs1052553	OR (95% CI) ^a	p ^a	Tests of interaction			
					OR (95% CI) ^{a,b}	p ^{a,b}	OR (95% CI) ^{a,c}	p ^{a,c}
rs181489 (5043 cases, 3910 controls)								
CC	GG or GA	1.00 (reference)	-					
CT	GG or GA	1.15 (0.81-1.63)	0.43					
TT	GG or GA	1.75 (1.15-2.64)	0.0082					
CC	AA	1.21 (0.91-1.62)	0.19					
CT	AA	1.45 (1.07-1.96)	0.0164	1.04 (0.78-1.38)	0.81			
TT	AA	1.93 (1.35-2.75)	0.0003	0.96 (0.61-1.52)	0.88	0.99 (0.78-1.25)	0.92	
rs356219 (5131 cases, 3995 controls)								
AA	GG or GA	1.00 (reference)	-					
AG	GG or GA	1.20 (0.97-1.49)	0.0994					
GG	GG or GA	1.71 (1.18-2.48)	0.0049					
AA	AA	1.27 (1.05-1.54)	0.0152					
AG	AA	1.50 (1.23-1.84)	7.5E-05	1.00 (0.72-1.40)	0.98			
GG	AA	1.92 (1.54-2.39)	4.8E-09	0.87 (0.56-1.34)	0.53	0.95 (0.77-1.17)	0.60	
rs11931074 (5159 cases, 4032 controls)								
GG	GG or GA	1.00 (reference)	-					
GT	GG or GA	1.43 (1.11-1.84)	0.0053					
TT	GG or GA	1.45 (0.47-4.44)	0.52					
GG	AA	1.26 (1.14-1.39)	3.4E-06					
GT	AA	1.67 (1.43-1.96)	2.3E-10	0.94 (0.73-1.22)	0.65			
TT	AA	1.79 (0.72-4.48)	0.21	1.06 (0.26-4.43)	0.93	0.95 (0.75-1.20)	0.65	
rs2583988 (5161 cases, 4015 controls)								
CC	GG or GA	1.00 (reference)	-					
CT	GG or GA	1.24 (0.95-1.62)	0.11					
TT	GG or GA	1.79 (1.19-2.70)	0.0052					
CC	AA	1.23 (1.03-1.46)	0.0201					

Tests of interaction							
SNCA SNP	MAPT rs1052553	OR (95% CI) ^a	p ^a	OR (95% CI) ^{a,b}	p ^{a,b}	OR (95% CI) ^{a,c}	p ^{a,c}
CT	AA	1.54 (1.26-1.88)	2.1E-05	1.01 (0.70-1.46)	0.96		
TT	AA	1.66 (1.25-2.19)	0.0004	0.75 (0.44-1.29)	0.30	0.92 (0.71-1.20)	0.54

^aORs (95% CI) and the corresponding p-values were computed using random-effects logistic regression.

^bThe ORs for the interaction terms compare the effect of heterozygotes and homozygotes for the minor allele of the SNCA SNPs in carriers of the AA genotype of MAPT rs1052553 and in non-carriers.

^cInteraction test under an additive coding of the SNCA SNPs. The ORs compare the OR for an increase in one minor allele of SNCA SNPs in carriers of the AA genotype for rs1052553 and in non-carriers.

TABLE 4

Age at Onset of Parkinson's Disease among Cases: Marginal Association with Each of the SNPs in the *SNCA* and *MATP* Genes (Random-Effects Models)

SNP	Genotype	Beta ^a	SE ^a	p ^a	AIC ^b	Heterogeneity p
<i>SNCA</i>						
rs181489 (4357 cases)	CC	0.0 (ref)	-	-	-	-
	CT	-0.472	0.489	0.34	-	0.0468
	TT	-1.039	0.509	0.0414	33319	0.86
	Additive (T vs C) ^c	-0.439	0.274	0.11	33317	0.35
	Dominant (CT+TT vs CC)	-0.588	0.453	0.19	33316 ^c	0.0754
	Recessive (TT vs CC+CT)	-0.679	0.491	0.17	33317	0.94
rs356219 (4420 cases)	AA	0.0 (ref)	-	-	-	-
	AG	-0.165	0.372	0.66	-	0.36
	GG	-0.553	0.531	0.30	33833	0.53
	Additive (G vs A) ^c	-0.252	0.264	0.34	33784	0.37
	Dominant (AG+GG vs AA)	-0.343	0.411	0.40	33783 ^b	0.26
	Recessive (GG vs AA+AG)	-0.343	0.420	0.41	33783 ^b	0.92
rs11931074 (4439 cases)	GG	0.0 (ref)	-	-	-	-
	GT	-0.432	0.412	0.29	-	0.99
	TT	0.573	2.356	0.81	33981	0.43
	Additive (T vs G) ^c	-0.167	0.401	0.68	33929	0.99
	Dominant (GT+TT vs GG)	-0.258	0.429	0.55	33928	0.99
	Recessive (TT vs GG+GT)	1.246	2.067	0.55	33925 ^b	0.42
rs2583988 (4445 cases)	CC	0.0 (ref)	-	-	-	-
	CT	-0.314	0.435	0.47	-	0.21
	TT	0.174	0.565	0.76	34035	0.80
	Additive (T vs C) ^c	-0.068	0.251	0.79	33975	0.70
	Dominant (CT+TT vs CC)	-0.223	0.375	0.55	33974	0.37
	Recessive (TT vs CC+CT)	0.323	0.547	0.55	33973 ^b	0.70
<i>MATP</i>						

SNP	Genotype	Beta ^a	SE ^a	p ^a	AIC ^b	Heterogeneity p
rs1052553 (4478 cases)	GG	0.0 (ref)	-	-	-	-
	GA	0.347	0.977	0.72	-	0.79
	AA	1.015	1.013	0.32	34280	0.55
	Additive (A vs G) ^c	0.634	0.313	0.0427	34225	0.35
	Dominant (GA+AA vs GG)	0.721	0.958	0.45	34226	0.61
	Recessive (AA vs GG+GA)	0.765	0.350	0.0287	34224 ^b	0.53
rs242557 (4447 cases)	AA	0.0 (ref)	-	-	-	-
	AG	-1.154	0.503	0.0218	-	0.57
	GG	-1.395	0.683	0.0410	34047	0.0586
	Additive (G vs A) ^c	-0.593	0.345	0.0861	33983	0.0357
	Dominant (AG+GG vs AA)	-1.213	0.526	0.0211	33982 ^b	0.25
	Recessive (GG vs AA+AG)	-0.519	0.478	0.28	33986	0.0376

SE: standard error. AIC: Akaike information criterion.

^aLinear regression coefficients (beta) and SE were computed using random-effects linear regression.

^bThe lowest value of the AIC indicates a better fit.

^cThe regression coefficient is computed for an increase of one minor allele.

TABLE 5
Age at Onset of Parkinson's Disease among Cases: Individual and Joint Effects of rs1052553
(MAPT gene) and Each of the SNPs in the SNCA Gene and Corresponding Tests of Interaction (Random-Effects Models)

SNCA SNP	MAPT rs1052553	Beta ^a	SE ^a	p ^a	Tests of interaction					
					Beta ^{a,b}	SE ^{a,b}	p ^{a,b}	Beta ^{a,c}	SE ^{a,c}	p ^{a,c}
rs181489	(4357 cases)									
CC	GG or GA	0.0 (ref)	-	-						
CT	GG or GA	-0.591	1.427	0.68						
TT	GG or GA	-0.078	1.511	0.96						
CC	AA	0.986	1.229	0.42						
CT	AA	0.539	1.197	0.65	0.261	1.096	0.81			
TT	AA	-0.390	1.219	0.75	-1.268	1.370	0.35	-0.352	0.655	0.59
rs356219	(4420 cases)									
AA	GG or GA	0.0 (ref)	-	-						
AG	GG or GA	-0.088	1.271	0.94						
GG	GG or GA	0.852	1.367	0.53						
AA	AA	1.567	1.261	0.21						
AG	AA	1.071	1.210	0.38	-0.312	1.309	0.81			
GG	AA	0.290	1.256	0.82	-2.020	1.473	0.17	-0.879	0.724	0.22
rs11931074	(4439 cases)									
GG	GG or GA	0.0 (ref)	-	-						
GT	GG or GA	0.256	2.334	0.91						
TT	GG or GA	2.621	4.158	0.53						
GG	AA	1.016	2.197	0.64						
GT	AA	0.517	2.230	0.82	-0.823	2.402	0.73			
TT	AA	2.251	3.341	0.51	-1.118	5.002	0.82	-1.233	0.967	0.20
rs2583988	(4445 cases)									
CC	GG or GA	0.0 (ref)	-	-						
CT	GG or GA	-0.104	1.331	0.94						
TT	GG or GA	2.016	1.521	0.19						
CC	AA	1.218	1.159	0.29						

Tests of interaction									
SNCA SNP	MAPT rs1052553	Beta ^a	SE ^a	p ^a	Beta ^{a,b}	SE ^{a,b}	p ^{a,b}	Beta ^{a,c}	SE ^{a,c} p ^{a,c}
CT	AA	0.736	1.201	0.54	-0.312	1.357	0.82		
TT	AA	0.585	1.222	0.63	-2.466	1.576	0.12	-0.933	0.711 0.19

SE: standard error.

^aThe relation between the SNPs and age at PD onset was studied using random-effects linear regression models. We present the linear regression coefficients (beta) and their SE with the corresponding p-values.

^bThe regression coefficients for the interaction terms compare the effect of heterozygotes and homozygotes for the minor allele of the SNCA SNPs in carriers of the AA genotype of MAPT rs1052553 and in non-carriers.

^cInteraction test using an additive coding of the SNCA SNPs. The regression coefficients compare the change in age at onset associated with an increase in one minor allele of SNCA SNPs in carriers of the AA genotype for rs1052553 and in non-carriers.