Independent and Joint Effects of the *MAPT* and *SNCA* Genes in Parkinson Disease

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Objective: We studied the independent and joint effects of the genes encoding alpha-synuclein (*SNCA*) and microtubule-associated protein tau (*MAPT*) in Parkinson 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 4 *SNCA* (rs2583988, rs181489, rs356219, rs11931074) and 2 *MAPT* (rs1052553, rs242557) single nucleotide polymorphism (SNPs). Individual and joint effects of *SNCA* and *MAPT* SNPs were investigated using fixed- and random-effects logistic regression models. Interactions were studied on both a multiplicative and an additive scale, and using a case–control and case-only approach.
Results: Fifteen GEO-PD sites contributed a total of 5,302 cases and 4,161 controls. All 4 *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 4 *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 2 loci is consistent with independent effects of the genes without additional interacting effects.

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The microtubule-associated protein tau and α-synuclein are 2 abundant brain proteins that aggregate in neurodegenerative diseases such as Parkinson 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 toward 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 (GWASs) confirmed that *SNCA* and *MAPT* were 2 of the main common contributors to PD genetic susceptibility among Caucasians.[11–14] The *MAPT* locus (17q21.31) contains a ~900kb inversion polymorphism with 2 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 single nucleotide polymorphisms (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 overexpression hypothesis for *SNC*A, there may well be multiple variants affecting transcription factor binding sites at the promoter or miRNA sites in the 3′ untranslated region.[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 2 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 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.

Subject and 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 to organize scientific collaborations between participating teams. During the meeting held in Tübingen, Germany in 2009 and following the presentation at scientific meetings of the results of PD GWASs, attending teams were invited to participate in a collaborative effort to study the joint effects of *SNCA* and *MAPT*.

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

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

Genotyping Methods

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

Four *SNCA* (rs2583988, rs181489, rs356219, rs11931074) and 2 *MAPT* (rs1052553, rs242557) SNPs were selected for genotyping. We identified *SNCA* SNPs at the 5′ (rs2583988[5,6]) or 3′ ends (rs181489,[5,6] 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.[22] We did not select the REP1 polymorphism in the *SNCA* promoter, because the 263bp 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[10]; rs242557 highlights the *MAPT* H1c subhaplotype associated with 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 6 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 to be in agreement with previous papers.[10] Odds ratios (OR), 95% confidence intervals (CIs), 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[10]; we tested the interaction between each of the 4 *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 chi-square–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 to 24% suggest little heterogeneity, 25 to 49% reflect moderate heterogeneity, 50 to 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). When 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 which allows testing 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 4 models for 6 SNPs; $p \leq 0.0021$ (0.05/24) was considered statistically significant. For analyses of joint effects, 3 multiplicative interaction models (model-free, dominant, or additive coding of *SNCA* SNPs) were considered for 4 SNPs; $p \leq 0.0042$ (0.05/12) was considered statistically significant.

The sample size needed to detect interactions on a multiplicative scale was investigated for different gene frequencies, genetic models, and effects (Supporting Information Fig 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 ~1,700 cases to reach 80% power at the 2-sided 0.05 significance level. At the 0.0042 significance level, ~2,900 cases would be necessary to reach 80% power.

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

Results

Fifteen sites contributed a total of 5,302 cases and 4,161 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 6 SNPs in cases and controls are shown in Supporting Information Table 1. HWE 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 5,199 cases and 4,059 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 5,272 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 Supporting Information Table 2. Supporting Information 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; see Table 2), whereas 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 (Supporting Information 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 (see Table 2); it is likely that the strong LD between SNPs in the *SNCA* gene leads to confounding in univariate analyses, and that an independent effect of rs356219 was confounded 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 (ie, 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, whereas 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), whereas 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 Supporting Information 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); Supporting Information 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

TABLE 1: Characteristics of Study Participants by Site

Site	Country	Study PI	Cases						Controls			
			No.	Male Sex, %	Mean Age at Onset, yr (SD)	Mean Age at Study, yr (SD)	Family History, No.[a]	Diagnostic Criteria	No.	Male Sex, %	Mean Age at Study, yr (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	Auberger	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	Hadjigeorgiou[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[b]	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	Ferrarese[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	—	—	—	—

[a]Family history of PD among first-degree relatives.
[b]Part of the samples had been previously included in a study of the marginal association between the REP1 (*SNCA*) polymorphism and PD (Maraganore et al[4]).
[c]Part of the samples had been previously included in a study of the marginal association between the *MAPT* gene and PD (Wider et al[10]).
PI = principal investigator; SD = standard deviation; UKPDBB = United Kingdom Parkinson's Disease Brain Bank (the exclusion criterion ">1 affected relative" was not included); NA = not available; PD = Parkinson disease.

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

SNP	Genotype	OR (95% CI)[a]	p[a]	AIC[a,b]	Heterogeneity	
					I^2 % (95% CI)	p
SNCA						
rs181489 (5,043 cases, 3,910 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	11,825	33 (0–64)	0.11
	Additive (T vs C)[c]	1.24 (1.16–1.33)	2.0E-09	11,824[b]	41 (0–69)	0.054
	Dominant (CT+TT vs CC)	1.23 (1.13-1.34)	1.7E-06	11,844	39 (0-68)	0.065
	Recessive (TT vs CC+CT)	1.57 (1.36–1.80)	3.4E-10	11,827	24 (0–60)	0.20
rs356219 (5,131 cases, 3,995 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	12,062	29 (0–63)	0.15
	Additive (G vs A)[c]	1.22 (1.15–1.29)	2.6E-10	12,059[b]	23 (0–59)	0.21
	Dominant (AG+GG vs AA)	1.25 (1.14–1.36)	1.1E-06	12,076	0 (0–55)	0.53
	Recessive (GG vs AA+AG)	1.41 (1.21–1.64)	9.0E-06	12,066	41 (0–69)	0.053
rs11931074 (5,159 cases, 4,032 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	12,175	0 (0–55)	0.99
	Additive (T vs G)[c]	1.32 (1.18–1.47)	1.1E-06	12,169	0 (0–55)	0.81
	Dominant (GT+TT vs GG)	1.35 (1.20–1.52)	5.4E-07	12,168[b]	0 (0–55)	0.84
	Recessive (TT vs GG+GT)	1.27 (0.76–2.13)	0.3575	12,192	0 (0–55)	0.99
rs2583988 (5,161 cases, 4,015 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	12,141	39 (0–68)	0.067
	Additive (T vs C)[c]	1.23 (1.13–1.34)	2.5E-06	12,134[b]	53 (0–74)	0.011
	Dominant (CT+TT vs CC)	1.29 (1.15–1.43)	7.5E-06	12,138	51 (0–74)	0.014
	Recessive (TT vs CC+CT)	1.32 (1.13–1.55)	0.0005	12,156	23 (0–59)	0.21
MAPT						
rs1052553 (5,199 cases, 4,059 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	12,267	0 (0–55)	0.91
	Additive (A vs G)[c]	1.21 (1.12–1.30)	5.4E-07	12,261[b]	0 (0–55)	0.70
	Dominant (GA+AA vs GG)	1.29 (1.05–1.60)	0.0173	12,280	0 (0–55)	0.90
	Recessive (AA vs GG+GA)	1.25 (1.15–1.37)	7.0E-07	12,261[b]	0 (0–55)	0.57
rs242557 (5,159 cases, 4,008 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	12,162	0 (0–55)	0.79
	Additive (G vs A)[c]	0.94 (0.89–1.00)	0.0687	12,158	0 (0–55)	0.93
	Dominant (AG+GG vs AA)	0.87 (0.77–0.98)	0.0214	12,156[b]	0 (0–55)	0.45
	Recessive (GG vs AA+AG)	0.96 (0.88–1.05)	0.36	12,160	0 (0–55)	0.81

[a]ORs (95% CI) and the corresponding p values and AIC were computed using random-effects logistic regression.
[b]The lowest value of the AIC indicates a better fit.
[c]The OR is computed for an increase of 1 minor allele.
SNP = single nucleotide polymorphism; OR = odds ratio; CI = confidence interval; AIC = Akaike information criterion.

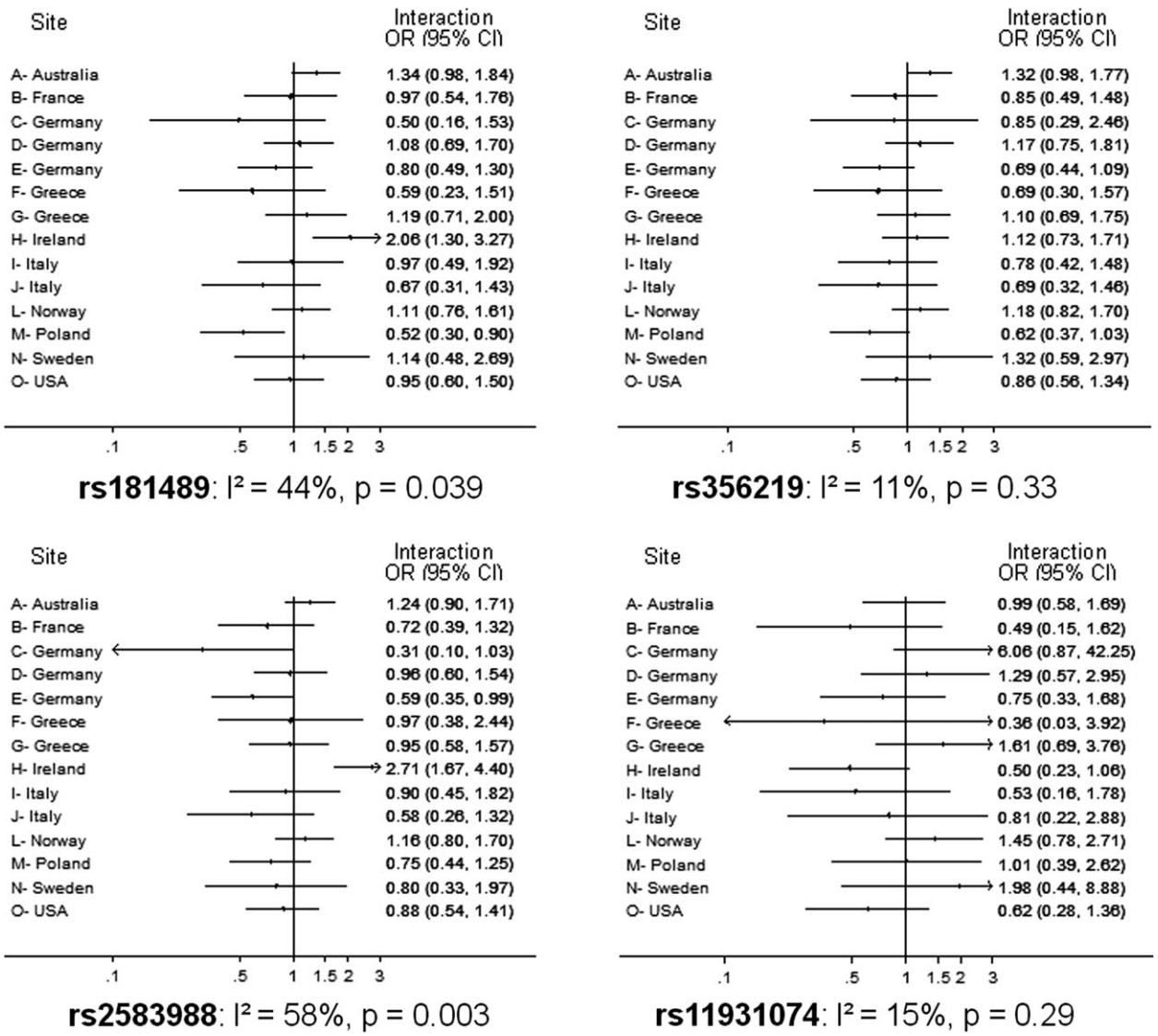


FIGURE 1: Forest plots of the interaction odds ratios (ORs) between rs1052553 and each of the *SNCA* single nucleotide polymorphisms (SNPs; additive coding) by participating site. Multiplicative interaction ORs were computed using an additive coding of *SNCA* SNPs. They compare the OR for an increase in 1 minor allele of *SNCA* SNPs in carriers of the AA genotype for rs1052553 and in noncarriers. Heterogeneity measures (I^2, *p* value) are shown. Supporting Information Figure 3 shows the same analysis using a dominant coding of *SNCA* SNPs. CI = confidence interval.

SNCA SNPs. All interaction tests were far from nominal significance; although 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 (Supporting Information 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* SNPs[17] (data not shown). No multiplicative interactions were observed between *MAPT* rs242557 and *SNCA* SNPs (Supporting Information 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 on either multiplicative or additive scales (not shown). Analyses restricted to sporadic cases yielded the same conclusions (data not shown).

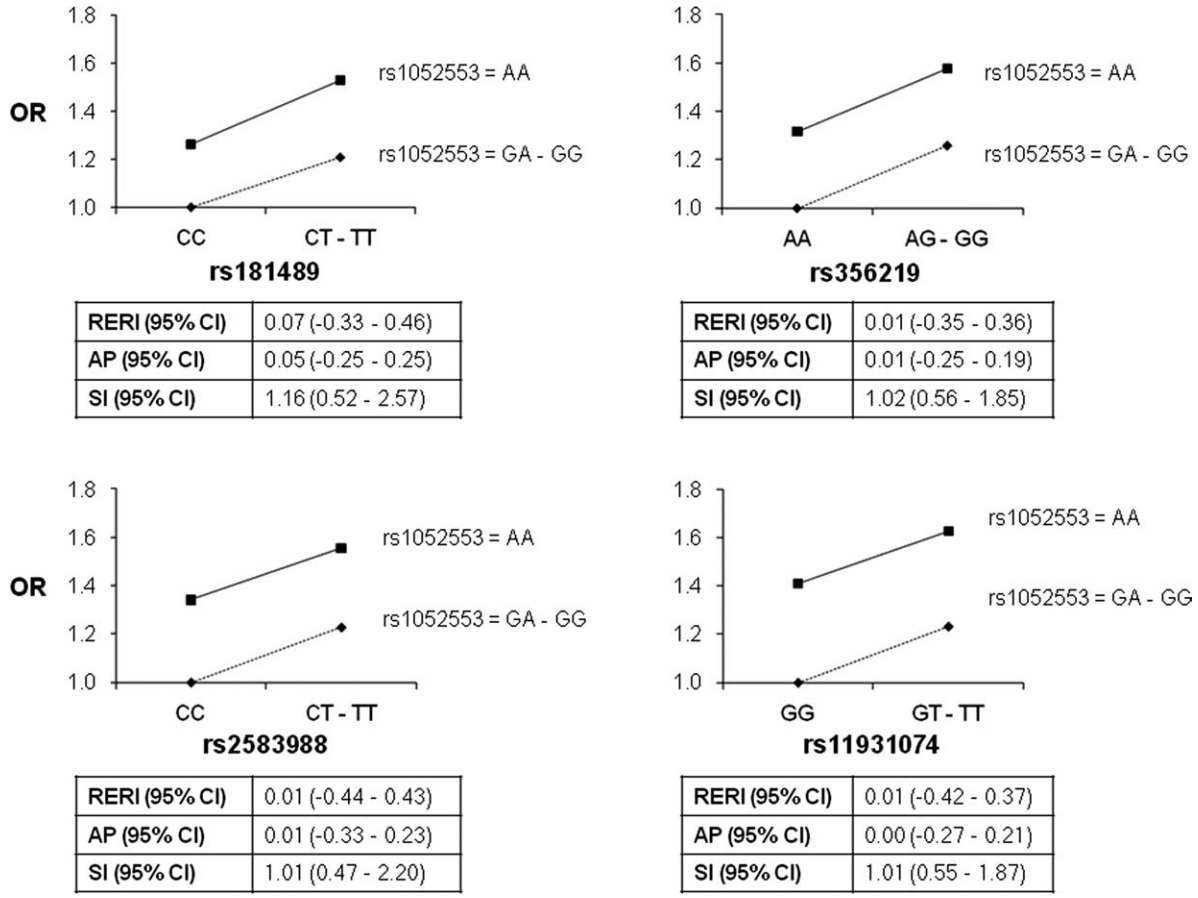
Supporting Information Table 7 shows the association between *MAPT* rs1052553 and *SNCA* SNPs stratified by disease status. There was no association between either rs1052553 or rs242557 (not shown) and any *SNCA* SNP among controls or cases.

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

SNCA	*MAPT*			Tests of Interaction			
SNP	**rs1052553**	**OR (95% CI)[a]**	***p*[a]**	**OR (95% CI)[a,b]**	***p*[a,b]**	**OR (95% CI)[a,c]**	***p*[a,c]**
rs181489 (5,043 cases, 3,910 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 (5,131 cases, 3,995 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 (5,159 cases, 4,032 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 (5,161 cases, 4,015 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				
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

[a]ORs (95% CI) and the corresponding *p* values were computed using random-effects logistic regression.
[b]The 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 noncarriers.
[c]Interaction test under an additive coding of the *SNCA* SNPs. The ORs compare the OR for an increase in 1 minor allele of *SNCA* SNPs in carriers of the AA genotype for rs1052553 and in noncarriers.
SNP = single nucleotide polymorphism; OR = odds ratio; CI = confidence interval.

We performed additional analyses restricted to cases 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



RERI (95% CI)	0.07 (-0.33 - 0.46)
AP (95% CI)	0.05 (-0.25 - 0.25)
SI (95% CI)	1.16 (0.52 - 2.57)

RERI (95% CI)	0.01 (-0.35 - 0.36)
AP (95% CI)	0.01 (-0.25 - 0.19)
SI (95% CI)	1.02 (0.56 - 1.85)

RERI (95% CI)	0.01 (-0.44 - 0.43)
AP (95% CI)	0.01 (-0.33 - 0.23)
SI (95% CI)	1.01 (0.47 - 2.20)

RERI (95% CI)	0.01 (-0.42 - 0.37)
AP (95% CI)	0.00 (-0.27 - 0.21)
SI (95% CI)	1.01 (0.55 - 1.87)

FIGURE 2: Individual and joint effects of *MAPT* rs1052553 and each of the *SNCA* single nucleotide polymorphisms (SNPs; dominant model) estimated using random-effects logistic regression. Solid lines correspond to ORs for *SNCA* SNPs in carriers of *MAPT* rs1052553 AA, whereas dotted lines correspond to ORs in noncarriers. Tests of interaction on the additive scale are shown. Tests of multiplicative interaction were as follows: rs181489, $p = 0.93$; rs356219, $p = 0.75$; rs2583988, $p = 0.80$; rs11931074, $p = 0.72$. RERI = relative excess risk due to interaction; CI = confidence interval; AP = attributable proportion due to interaction; SI = synergy index.

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 GWASs 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 4 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

TABLE 4: Age at Onset of Parkinson Disease among Cases: Marginal Association with Each of the SNPs in the *SNCA* and *MAPT* Genes (Random-Effects Models)

SNP	Genotype	Beta[a]	SE[a]	*p*[a]	AIC[b]	Heterogeneity, *p*
SNCA						
rs181489 (4,357 cases)	CC	0.0 (reference)	—	—	—	—
	CT	−0.472	0.489	0.34	—	0.0468
	TT	−1.039	0.509	0.0414	33,319	0.86
	Additive (T vs C)[c]	−0.439	0.274	0.11	33,317	0.35
	Dominant (CT+TT vs CC)	−0.588	0.453	0.19	33,316[b]	0.0754
	Recessive (TT vs CC+CT)	−0.679	0.491	0.17	33,317	0.94
rs356219 (4,420 cases)	AA	0.0 (reference)	—	—	—	—
	AG	−0.165	0.372	0.66	—	0.36
	GG	−0.553	0.531	0.30	33,833	0.53
	Additive (G vs A)[c]	−0.252	0.264	0.34	33,784	0.37
	Dominant (AG+GG vs AA)	−0.343	0.411	0.40	33,783[b]	0.26
	Recessive (GG vs AA+AG)	−0.343	0.420	0.41	33,783[b]	0.92
rs11931074 (4,439 cases)	GG	0.0 (reference)	—	—	—	—
	GT	−0.432	0.412	0.29	—	0.99
	TT	0.573	2.356	0.81	33,981	0.43
	Additive (T vs G)[c]	−0.167	0.401	0.68	33,929	0.99
	Dominant (GT+TT vs GG)	−0.258	0.429	0.55	33,928	0.99
	Recessive (TT vs GG+GT)	1.246	2.067	0.55	33,925[b]	0.42
rs2583988 (4,445 cases)	CC	0.0 (reference)	—	—	—	—
	CT	−0.314	0.435	0.47	—	0.21
	TT	0.174	0.565	0.76	34,035	0.80
	Additive (T vs C)[c]	−0.068	0.251	0.79	33,975	0.70
	Dominant (CT+TT vs CC)	−0.223	0.375	0.55	33,974	0.37
	Recessive (TT vs CC+CT)	0.323	0.547	0.55	33,973[b]	0.70
MAPT						
rs1052553 (4,478 cases)	GG	0.0 (reference)	—	—	—	—
	GA	0.347	0.977	0.72	—	0.79
	AA	1.015	1.013	0.32	34,280	0.55
	Additive (A vs G)[c]	0.634	0.313	0.0427	34,225	0.35
	Dominant (GA+AA vs GG)	0.721	0.958	0.45	34,226	0.61
	Recessive (AA vs GG+GA)	0.765	0.350	0.0287	34,224[b]	0.53
rs242557 (4,447 cases)	AA	0.0 (reference)	—	—	—	—
	AG	−1.154	0.503	0.0218	—	0.57
	GG	−1.395	0.683	0.0410	34,047	0.0586
	Additive (G vs A)[c]	−0.593	0.345	0.0861	33,983	0.0357
	Dominant (AG+GG vs AA)	−1.213	0.526	0.0211	33,982[b]	0.25
	Recessive (GG vs AA+AG)	−0.519	0.478	0.28	33,986	0.0376

[a]Linear regression coefficients (beta) and SEs were computed using random-effects linear regression.
[b]The lowest value of the AIC indicates a better fit.
[c]The regression coefficient is computed for an increase of 1 minor allele.
SNP = single nucleotide polymorphism; SE = standard error; AIC = Akaike information criterion.

TABLE 5: Age at Onset of Parkinson 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 (4,357 cases)										
CC	GG or GA	0.0 (reference)	—	—						
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 (4,420 cases)										
AA	GG or GA	0.0 (reference)	—	—						
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 (4,439 cases)										
GG	GG or GA	0.0 (reference)	—	—						
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 (4,445 cases)										
CC	GG or GA	0.0 (reference)	—	—						
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						
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

[a]The relation between the SNPs and age at Parkinson disease onset was studied using random-effects linear regression models. We present the linear regression coefficients (beta) and their SEs with the corresponding *p* values.
[b]The 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 noncarriers.
[c]Interaction test using an additive coding of the *SNCA* SNPs. The regression coefficients compare the change in age at onset associated with an increase in 1 minor allele of *SNCA* SNPs in carriers of the AA genotype for rs1052553 and in noncarriers.
SNP = single nucleotide polymorphism; SE = standard error.

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 2,176 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 model, but the difference in AIC from the additive model was minimal, and it was recently associated with PD in two GWASs 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 toward 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 studies[10] and GWASs[11–14] 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 2 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, that is, interaction between genes, has been used in the literature to describe different concepts,[44] and Phillips[45] recently described 3 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 a 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 2 loci is consistent with independent effects. Although 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.

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A.E. and O.A.R. contributed equally to this work.

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