Published in final edited form as:
Eur J Neurol. 2010 March ; 17(3): 483–486. doi:10.1111/j.1468-1331.2009.02847.x.

Association of the *MAPT* locus with Parkinson's disease

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Abstract

Background and purpose—Whilst an association between the tau gene (*MAPT*)-containing H1 haplotype and supranuclear gaze palsy (PSP) has long been recognized, the effect of H1 on risk for Parkinson's disease (PD) has remained more contentious.

Methods—Herein, we examined the association of H1 and PD in three Caucasian PD patient–control series from Ireland, Norway, and the US (combined: $n = 2619$), by genotyping two H1/H2 single nucleotide polymorphisms (SNPs) in *MAPT* (rs1052553) and in the *Saitohin* gene (rs62063857) and one H1-specific SNP (rs242557).

Results—We identified a significant association between H1/H2 and risk of PD (rs1052553 OR: 1.43, CI: 1.23–1.64; rs62063857 OR: 1.45, CI: 1.27–1.67), but no effect of the H1-specific SNP rs242557 (OR: 0.92, CI: 0.82–1.03).

Conclusions—Our findings show that the H1 haplotype is a significant risk factor for PD. However, one H1-specific SNP (rs242557) previously implicated in PSP did not alter the risk of PD, indicating that distinct H1 sub-haplotypes probably drive the associations with PD and PSP.

Keywords

association studies; genetics; *MAPT*; Parkinson's disease

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Allele and genotype frequencies

Table S2 Estimated frequencies for the three haplotypes involving single nucleotide polymorphisms rs62063857, rs1052553, and rs242557

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Introduction

Tau and α-synuclein are two abundant brain proteins that aggregate in age-related neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease, and progressive supranuclear gaze palsy (PSP) [1]. Evidence suggests that the formation of pathological inclusions containing tau and α-synuclein is promoted by common mechanisms [2] and that the interplay of overlapping genetic factors may determine susceptibility to developing disease [3–5]. Mutations in the tau gene (*MAPT*) cause frontotemporal dementia with parkinsonism linked to chromosome 17, with some patients displaying clinical and pathological features reminiscent of PSP [6,7]. The structurally complex *MAPT* locus on chromosome 17q21.31 contains a *c*. 900-kb inversion polymorphism and occurs as two distinct non-recombinant haplotypes H1 (direct orientation) and H2 (inverted) [8,9]. The major *MAPT*-containing H1 haplotype is associated with increased risk for PSP and other taupathies, as well as PD [10–16]. H2 is found in about 20% of Europeans whereas it is rare in Africans and almost absent from Eastern-Asian populations [17]. In contrast to H2, the H1 extended haplotype is evolutionarily dynamic and contains a number of sub-haplotypes composed of single nucleotide polymorphisms (SNP) highly correlated (i.e. in strong linkage disequilibrium – LD) with each other [13].

Over 20 Caucasian populations of patients and controls have been examined for association of *MAPT* variability and PD, with mostly positive albeit mixed results (available at: http://www.pdgene.org) [3,14–16,18–22]. *Saitohin* (*STH*) is a 1-exon gene located in intron 9 of *MAPT*, in which a coding variant Q7R (rs62063857) was shown to associate with risk of PSP and PD and to be in complete LD with the *MAPT* 238-bp intron 9 deletion that discriminates H1/H2 [16,23]. The two other SNPs included in our study were selected because the first one has been associated with PD (H1/H2-tagging SNP rs1052553) and the second one with PSP (H1-specific SNP rs242557) [10,16]. Herein, we investigate three SNPs in *MAPT* (rs242557 and rs1052553) and *STH* (Q7R, rs62063857) for association with risk of PD in three populations of patients and controls from Ireland, Norway, and the US (combined: 1218 patients and 1401 controls). A subset of the Norwegian patient–control series was reported elsewhere (296 patients and 441 controls) [14,15].

Subjects and methods

Three series of patients with PD and controls were included from Ireland (360 patients, 437 controls), Norway (480 patients, 555 controls), and the US (378 patients, 409 controls). All patients and controls were White and of European ancestry. All patients were examined and observed longitudinally by a movement disorders neurologist and diagnosed with PD according to published criteria [24]. PD was considered familial when ≥1 first- or second-degree relatives were reportedly affected. Unrelated control individuals were free of personal or familial history suggestive of –parkinsonism. The ethical review board at each institution involved approved the study, and all participants provided informed consent.

Genotyping of the three SNPs (rs242557, rs1052553, and rs62063857) was performed on a Sequenom MassArray iPLEX platform (San Diego, CA, USA) (all primer sequences are available on request) and analyzed with Typer 4.0 software. The rate of genotype calls was ≥96% in each population. Numerical variables were summarized with the sample mean, SD, and range. Associations between PD and each SNP were measured by ORs and 95% CIs obtained from logistic regression models adjusted for age, gender, and series (combined series only). In PD cases, associations between age at onset and each marker were examined using linear regression models adjusted for gender and series (combined series only). In controls, the association between rs1052553 and age was examined using linear regression models adjusted for gender and series (combined series only). Both additive and dominant

models were considered for all single marker analyses. Haplotype analysis was performed using SPLUS score tests for association [25], with adjustments made for age and gender; *P*-values were obtained from the asymptotic distribution of the score statistic and haplotypes of <1% were not considered. LD between markers in study controls was measured by pair-wise r^2 values. For each family of statistical tests, multiple testing was adjusted for using single-step minP procedure [26] with 10 000 permutations of case and control labels to determine the level of significance that controls the family-wise error rate at 5%; *P*-values less than or equal to this level were considered statistically significant. Statistical analyses were performed using SPLUS (version 8.0.1; Insightful Corporation, Seattle, WA, USA).

Results

Demographics of the three patient–control series are presented in Table 1. None of the three SNPs departed from Hardy–Weinberg equilibrium in control populations. Two SNPs (rs1052553 and rs62063857) were in high LD with each other ($r^2 \geq 0.91$) but not with rs242557 (r^2: 0.12–0.19). In additive models (Table 2) and dominant models (data not shown), both the H1/H2-tagging SNP (rs1052553) and the *STH* Q7R (rs62063857) displayed significant association with PD in all three series and in the combined series (rs1052553 OR: 1.43, $P < 0.001$; rs62063857 OR: 1.45, $P < 0.001$; $P \leq 0.024$ considered significant after permutation multiple testing adjustment). For both rs1052553 and rs62063857, the frequency of the major A allele (H1) and A-containing genotype was higher in patients than in controls (allele and genotype frequencies for each SNP are provided in Supplementary Tables S1a–c). SNP rs242557 was not associated with PD in any of the individual series ($P \geq 0.13$) or in the combined series (OR: 0.92, 95% CI: 0.82–1.03, $P = 0.16$). Haplotype analysis showed the frequency of one haplotype (G-G-G) was lower in patients than in controls ($P \leq 0.018$) (Supplementary Table S2). A sub-analysis was performed using only those patients and controls homozygous for the A allele of rs1052553 (H1/H1 homozygotes), which showed no association between rs242557 and PD in any series or in the combined series (all *P*-values ≥ 0.50 under additive and dominant models, data not shown). None of the three SNPs displayed a significant association with age at disease onset in the combined series under additive or dominant models ($P \geq 0.13$, data not shown).

We performed a pooled analysis of previous studies combined with our own results (23 Caucasian patient–control series; overall $n = 7736$ patients and 9339 controls), which showed that the H2 allele versus H1 has an estimated overall OR of 0.78 (95% CI: 0.74–0.82).

Discussion

Our data provide strong evidence for an association between the *MAPT* H1 haplotype and risk of PD in three Caucasian populations from Ireland, Norway, and the US. In accordance with previous studies, the two H1/H2 SNPs rs1052553 and rs62063857 were highly correlated with each other and displayed a robust association with PD but not with age at disease onset [15,21]. Pooled analysis using previous studies combined with our data (overall 17 075 Caucasian patients and controls) showed the H2 haplotype versus H1 has an estimated OR of 0.78 (95% CI: 0.74–0.82). In a previous study by Tobin *et al.* [16], the association of SNPs rs1052553 and rs62063857 with PD did not reach statistical significance after correction for multiple testing; however, a 2-SNP H1/H2 haplotype including rs1052553 was highly significant, supporting an association. Whilst the H1-specific SNP rs242557 was not individually associated with risk for PD in our study [19], a 3-SNP haplotype (G-G-G) was significantly less frequent amongst patients than controls. The association of the G-G-G haplotype with PD is probably driven by rs1052553 and rs62063857, and not by rs242557. To examine whether the H1-specific SNP rs242557

influences risk for PD only in H1/H1 homozygotes, a sub-analysis was performed, which did not show any significant association. In our previous study of a subset of the Norwegian population, one H1-specific subhaplotype was strongly associated with PD; however, the sub-haplotype did not include rs242557 [15].

Our results show an excess of H1 in patients compared to controls; however, the association may also reflect a protective effect of H2 which is over-represented in controls. A protective effect of H2 has been hypothesized to account for part of the H1/H2 association with PSP [10]. However, one the most robust association reported in PSP was the H1-specific SNP rs242557 [10], which did not associate with risk of PD in our study. This suggests that, although H1/H2 influences risk for both parkinsonian disorders, the mechanisms involved differ between PD and PSP. To examine whether a putative protective effect of H2 may influence age, we performed an exploratory study in control individuals that did not find an association between H2 and age (data not shown). Future studies comparing centenarians to young subjects will be required to establish whether H2 promotes healthy aging.

Whilst most studies including ours have found an association between the H1 haplotype and PD, the functional variant remains to be identified. H1 contains *MAPT* which is the best candidate, but also other genes such as *CRHR1* and *IMP5* that may account for the association as well. Data from our previous study of the Norwegian population supported the functional variant being located within a *c*. 90-kb interval that contains *MAPT* exons 1–4 [15]; however, the finding was not replicated in an admixed US population [21]. Further studies of large populations from diverse ethnicities will be required to refine the minimum interval and ultimately identify the responsible variant. Given the findings that H1 may act synergistically with variants in the α-synuclein (*SNCA*) and glycogen synthase kinase-3β (*GSK3B*) genes in determining risk for PD [3,27], gene–gene interactions will also be important to consider as they may provide critical insights into mechanisms of disease susceptibility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosure and sources of funding

Mayo Clinic Jacksonville is a Morris K. Udall Parkinson's Disease Research Center of Excellence (NINDS P50 #NS40256) and a Pacific Alzheimer Research Foundation (PARF) grant C06-01 (RJU, ZKW & MJF). ZKW is also partially funded by P01 AG017216, R01 NS057567, R01 AG015866, and CIHR 121849. CW is supported by the Swiss National Science Foundation (PASMP3-123268/1).

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Table 1

Demographic characteristics of the patient–control series

Variable	PD cases	Controls
Irish series (360 cases, 437 controls)		
Age	66.5 ± 10.0 (36, 91)	65.0 ± 24.3 (22, 103)
Gender (male)	216 (60%)	158 (36%)
Age at PD onset	51.8 ± 10.5 (18, 77)	NA
Familial cases	13%	NA
US series (378 cases, 409 controls)		
Age	72.7 ± 11.0 (30, 92)	72.2 ± 10.8 (33, 92)
Gender (male)	215 (57%)	215 (53%)
Age at PD onset	62.0 ± 12.2 (16, 90)	NA
Familial cases	35%	NA
Norwegian series (480 cases, 555 controls)		
Age	72.7 ± 10.8 (45, 99)	70.6 ± 12.5 (43, 106)
Gender (male)	291 (61%)	311 (56%)
Age at PD onset	58.9 ± 11.0 (30, 88)	NA
Familial cases	26%	NA

The sample mean ± SD (minimum, maximum) is given for *age* and *age of PD onset*. Information regarding age at PD onset was unavailable for 107 Irish PD cases (30%) and 10 US PD cases (3%). NA, not applicable; PD, Parkinson's disease.

Table 2

Single single nucleotide polymorphisms associations with Parkinson's disease

	Irish series (360 cases, 437 controls)		US series (378 cases, 409 controls)		Norwegian series (480 cases, 555 controls)		Combined series (1218 cases, 1401 controls)	
Marker	**Estimated OR (95% CI)**	***P*-value**	**Estimated OR (95% CI)**	***P*-value**	**Estimated OR (95% CI)**	***P*-value**	**Estimated OR (95% CI)**	***P*-value**
rs62063857 (A)[a]	1.54 (1.18–2.00)	0.002	1.35 (1.06–1.72)	0.014	1.49 (1.18–1.89)	0.001	1.45 (1.27–1.67)	<0.001
rs1052553 (A)[a]	1.52 (1.16–1.96)	0.002	1.47 (1.15–1.89)	0.002	1.33 (1.05–1.69)	0.018	1.43 (1.23–1.64)	<0.001
rs242557 (G)	0.93 (0.75–1.15)	0.51	0.85 (0.70–1.04)	0.13	0.95 (0.79–1.14)	0.59	0.92 (0.82–1.03)	0.16

[a]The A allele corresponds to the H1 haplotype. Estimated odds ratios and *P*-values result from logistic regression models adjusted for age, gender, and series (combined series only) under an additive model. Estimated odds ratios correspond to an increase of one major allele. Following a single-step minP adjustment for multiple testing, *P*-values ≤ 0.026 (Irish series), 0.021 (US series), 0.022 (Norwegian series), and 0.024 (combined series) are considered statistically significant.