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The Microtubule Associated Protein Tau H1 Haplotype and Risk of Essential Tremor

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Abstract

Background—Two recent studies investigated the association of the MAPT H1 haplotype, a known risk factor for neurodegenerative disease including progressive supranuclear palsy and Parkinson's disease (PD), with essential tremor (ET).

Methods—To confirm this association in a different population we analyzed the distribution of allele and genotype frequencies for the MAPT H1/H2 tagging SNP rs1052553 in ET cases and controls enrolled in a clinical-epidemiological study of ET at Columbia University.

Results—Overall, no association was observed between ET and the MAPT H1 haplotype. We also restricted the analysis to clinical subtypes including early-onset (≤40 years of age), Ashkenazi Jewish ancestry, white non-Ashkenazi, or ET cases with a 'definite' or 'probable/possible' diagnosis; none of these stratified analyses showed evidence of association with ET. We also performed a meta-analysis of the H1/H2 tagging SNP rs1052553 in published datasets and the H1 haplotype with risk for ET in the current study and did not find evidence for association.

Conclusions—The inconsistent reports of association of MAPT H1 in three emerging studies (our own and two published studies) may reflect sampling issues and/or clinical heterogeneity in these populations.

Keywords

essential tremor; MAPT; SNPs; case-control study; candidate genes

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Introduction

Essential tremor (ET) is one of the most common movement disorders, with prevalence estimated at 4.6% for individuals age 65 years and older and as high as 20% or more among persons in their 90s and older [1]. Family studies and twin studies have provided strong evidence for a genetic contribution to ET [2,3]. A number of variants in the MAPT gene have been linked with FTD and an increased risk of PSP, PD, and in some studies, with AD, as well as ET more recently [4]. While one study suggests that the MAPT H1 haplotype is associated with increased risk for ET in a North American population [5], a study in Spain did not find evidence for an association between a familial ET and MAPT H1 haplotype [6]. In this study, we evaluated an association between the MAPT H1 haplotype and ET. First, we analyzed the distribution of allele and genotype frequencies for the MAPT H1/H2 tagging SNP ‘rs1052553’ in ET cases and controls. Second, we performed a meta-analysis of one H1/H2 tagging SNP, rs1052553, with available data in published datasets and the current study with risk for ET.

Methods

Study Cohort

A description of the study cohort is provided in Clark et al (2010) [7]. ET cases (n=249) and controls (n=237) were enrolled in a clinical-epidemiological study at the Neurological Institute, Columbia University, New York (2000–2007). All participants underwent a demographic and medical history questionnaire, family history questionnaire (any first- or second-degree relative with nonspecific tremor, ET or PD), and a videotaped neurological examination. Using published research criteria a diagnosis of ET for possible, probable, or definite ET was confirmed (E.D.L.). The clinical characteristics and demographics of genotyped cases and controls is summarized in Table S1

For the current analyses, genotypes for rs1052553 were available for 249 non-Hispanic white cases and 237 non-Hispanic white controls (total N=486).

The study was approved by the CUMC Institutional Review Board. All participants provided signed informed consent.

SNP Genotyping

All genotyping was performed in duplicate and blinded to case control status.

Genotyping for SNP rs1052553 was performed by Taqman allelic discrimination assay (Life Technologies, Carlsbad, California, USA) (‘C_7563736_10’, catalog number 4351376). All samples genotyped successfully by Taqman allelic discrimination and were 100% concordant with H1/H2 haplotype calls recorded by Sequenom genotyping for SNP rs62063857.

Statistical Analysis

The SNP was tested for deviation from Hardy-Weinberg equilibrium (HWE) in PLINK [8]. No deviations from HWE were observed. Association analysis was carried out in PLINK

using chi-squared analysis to assess genotypic and allelic associations. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in PLINK. Meta-analysis was performed for rs1052553 using METAL [9]. In a secondary analysis we also performed a meta analysis using a random and fixed effects model using the program Comprehensive Meta-analysis (CMA) [10]. Power calculations were performed using G* power version 3.1.7 [11].

Results

MAPT H1 Association and ET

Overall, we did not observe an association of the MAPT H1 haplotype and ET by genotyping the MAPT H1 /H2 tagging SNP rs1052553 (Table 1). We also restricted the analysis to clinical subtypes; although the analysis in white non-AJ cases and controls showed a trend towards association (p=0.07) none of the stratified analyses showed evidence of association of the H1 haplotype with risk of ET.

Meta-analysis of MAPT H1/H2 Tagging SNP and Risk of ET—We performed a combined analysis including data for the MAPT H1/H2 tagging SNP rs1052553 from the current study and two published studies; when examined together we found no evidence for association of the 'A' (H1 haplotype) allele with ET (p=0.75; OR=1.03, 95% CI: 0.88–1.20) nor in secondary analyses when we removed samples with AJ ancestry (p=0.07; OR=0.72, 95% CI: 0.50–1.03). We also performed meta analysis in METAL; we again failed to find evidence for association of the MAPT H1 haplotype in our study and published studies (p=0.849 in METAL) (Table 2). In a secondary analysis, using the program CMA we performed meta analysis for rs1052553 using a fixed and random effect model for two datasets and the current study removing controls with a family history of ET or PD and samples with AJ ancestry and again found no evidence for association of the MAPT H1 haplotype (Table S2).

Discussion

We performed an analysis of the MAPT H1 haplotype in a case-control study of ET at Columbia University. Our results suggest that the MAPT H1 haplotype is not a risk factor for ET in a Caucasian sample from North America. We also restricted the analysis to clinical subtypes including early-onset (≤40 years of age), AJ ancestry, white non Ashkenazi, or ET cases with a 'definite' or 'probable/possible' diagnosis; although the analysis in white non-AJ cases and controls showed a trend towards association (p=0.07) the MAPT H1 haplotype was not significantly associated with ET in any of these stratified analyses. A meta-analysis and secondary meta-analysis including a fixed and random effect model, which included our data and two published datasets, also did not provide evidence for association.

We calculated the statistical power for sample sizes in this study, published data [5,6]) and using pooled data from all three studies based on the allele frequencies and the odds ratio reported in the study from Vilarino-Guell *et al*. [5]. Our study had similar power to the published study from Garcia Martin *et al.* [6]. Pooling of data from all three studies shows

that the analysis was adequately powered and the respective values with p=0.05 for one-tailed and two-tailed associations were 98% and 96%.

The inconsistent reports of association of MAPT H1 in three emerging studies (our own and two published studies [5,6]) may reflect sampling issues or clinical heterogeneity in these populations. We note the small sample size in the current study; however meta-analysis with published data [5,6] with a combined sample size of 788 ET cases and 934 controls also does not support association. Further association studies of MAPT in ET populations are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Association between ET and the MAPT H1/H2 tagging SNP rs1052553

SNP	Controls	White non-Hispanic cases		Definite diagnosis cases		Probable/Possible diagnosis cases		Early onset <40 years cases		White non-AJ cases and controls			AJ cases and controls		
rs1052553	Controls (N=237) (Count, freq.)	Cases (N=249) (Count, freq.)	P (OR, 95% CI)	Cases (N=75) (Count, freq.)	P (OR, 95% CI)	Cases (N=174) (Count, freq.)	P (OR, 95% CI)	Cases (N=99) (Count, freq.)	P (OR, 95% CI)	Cases (N=157) (Count, freq.)	Controls (N=180) (Count, freq.)	P (OR, 95% CI)	Cases (N=92) (Count, freq.)	Controls (N=57) (Count, freq.)	P (OR, 95% CI)
Genotype															
AA (H1/H1)	143 (0.60)	140 (0.56)	0.16	40 (0.53)	0.18	100 (0.57)	0.27	59 (0.60)	0.55	88 (0.56)	114 (0.63)	0.12	52 (0.57)	29 (0.51)	0.64
AG (H1/H2)	86 (0.36)	91 (0.37)		29 (0.39)		62 (0.36)		34 (0.34)		58 (0.37)	61 (0.34)		33 (0.36)	25 (0.44)	
GG (H2/H2)	8 (0.03)	18 (0.07)		6 (0.08)		12 (0.07)		6 (0.06)		11 (0.07)	5 (0.03)		7 (0.08)	3 (0.05)	
Allele															
A	372 (0.78)	371 (0.74)	0.14 (0.80, 0.59–1.08)	109 (0.73)	0.14 (0.73, 0.48-	262 (0.75)	0.28 (0.84, 0.60–1.16)	152 (0.77)	0.63 (0.91, 0.61–1.35)	234 (0.75)	289 (0.80)	0.07 (0.72, 0.50–1.03)	137 (0.74)	83 (0.73)	0.75 (1.09, 0.64–1.85)
G	102 (0.22)	127 (0.26)		41 (0.27)		86 (0.25)		46 (0.23)		80 (0.25)	71 (0.20)		47 (0.26)	31 (0.27)	

Table 2

Meta-analysis of the H1/H2 tagging SNP rs1052553 data from the present study and rs1052553 data from Vilariño-Güell et al

and García-Martín et al. Analysis was performed in METAL. Effective sample size is corrected for unequal numbers of cases and controls in METAL.

Study	(White non-Hispanic) Clark et al. (rs1052553)			(White non-AJ) Clark et al. (rs1052553)			Vilariño-Güell et al. (rs1052553)			García-Martín et al. (rs1052553)		
	Cases (N=249) (Count, freq.)	Controls (N=237) (Count, freq.)	P (OR, 95% CI)	Cases (N=157) (Count, freq.)	Controls (N=196) (Count, freq.)	P (OR, 95% CI)	Cases (N=339) (Count, freq.)	Controls (N=406) (Count, freq.)	P (OR, 95% CI)	Cases (N=200) (Count, freq.)	Controls (N=291) (Count, freq.)	P (OR, 95% CI)
Genotype												
AA (H1/H1)	140 (0.56)	143 (0.60)		88 (0.56)	125 (0.64)		221 (0.65)	231 (0.57)		104 (0.52)	158 (0.54)	
AG (H1/H2)	91 (0.37)	86 (0.36)	0.16	58 (0.37)	65 (0.33)	0.13	100 (0.30)	148 (0.36)	0.07	75 (0.38)	111 (0.38)	0.52
GG (H2/H2)	18 (0.07)	8 (0.03)		11 (0.07)	6 (0.03)		18 (0.05)	27 (0.07)		21 (0.11)	22 (0.08)	
Allele												
A	371 (0.74)	372 (0.78)	0.13 (0.80, 0.60–1.07)	234 (0.75)	315 (0.80)	0.06 (0.71, 0.50–1.02)	542 (0.80)	610 (0.75)	0.03 (1.32, 1.03–1.69)	283 (0.71)	427 (0.73)	0.37 (0.88, 0.66–1.17)
G	127 (0.26)	102 (0.22)	0.13 (1.25, 0.93–1.67)	80 (0.25)	77 (0.20)	0.06 (1.41, 0.98–2.00)	136 (0.20)	202 (0.25)	0.03 (0.76, 0.59–0.97)	117 (0.29)	155 (0.27)	0.37 (1.13, 0.86–1.51)

Table 3

Meta association	SNP	Study [a]	Allele1	Allele2	Freq Allele 1	Min Freq	Max Freq	Weight [b]	Z score [c]	P value
White non-Hispanic	rs1052553	1,2,3	A	G	0.74	0.71	0.8	1722	0.19	0.849
White non-AJ	rs1052553	1,2,3	A	G	0.75	0.71	0.8	1573	0.18	0.857
Merged association	**SNP**	**Study**	**Allele1**	**Allele2**	**Freq Allele1 in cases**	**Freq Allele1 in controls**	**OR**	**L95**	**U95**	**P**
White non-Hispanic	rs1052553	1,2,3	A	G	0.76	0.75	1.03	0.88	1.20	0.754
White non-AJ	rs1052553	1,2,3	A	G	0.75	0.80	0.72	0.50	1.03	0.074

Only rs1052553 was genotyped in all studies.

[a] 1, in this study, 2, Vilariño-Güell et al., 3, García-Martín et al.

[b] Weight represents the total number of subjects genotyped

[c] The direction of the Z score represents allelic association with allele 1