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Histamine N-methyltransferase Thr105Ile is not associated with Parkinson's disease or essential tremor

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Abstract

A functional variant in the *Histamine N-Methyltransferase* gene (*HNMT* – rs11558538) resulting in a threonine to isoleucine substitution (Thr105Ile), has been shown to impair histamine degradation. Two recent studies reported that the threonine allele of this polymorphism might be a risk factor for Parkinson disease (PD) and essential tremor (ET) development. Although PD and ET are considered different entities, they share some clinical and pathological features, suggesting a possible joint etiology. In this study we assess the role of the Thr105Ile variant in PD and ET development, genotyping the variant in a North American Caucasian PD and ET case-control series. Statistical analysis did not identify any significant association between this variant and PD or ET; therefore, our findings do not support the HNMT Thr105Ile variant as a factor in disease development or a genetic link between the disorders.

Keywords

Parkinson Disease; Essential Tremor; Histamine; HNMT

Introduction

Parkinson disease (PD) is a progressive neurodegenerative condition caused by neuron dysfunction and cell death resulting in dopamine depletion. This reduction in dopamine is responsible for the hallmark PD motor symptoms: bradykinesia, resting tremor, postural instability, and rigidity. PD affects >1% of the population by age 65 and increases to 4-5% by age 85 [1]. Essential tremor (ET) is the most common tremor disorder, affecting 4% of the population above age 40 [2] and characterized by a postural and kinetic tremor that worsens with movement [3-5]. While the pathogenesis of ET remains widely disputed [4,5], there is a

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compelling argument for a possible genetic link between ET and PD due to a 4 fold increased incidence of PD among ET patients, increased frequency of ET among relatives of PD patients, some overlapping pathological features, and presence of action tremor preceding the onset of PD [6,7].

The threonine allele of histamine N-methyltransferase (HNMT - rs11558538) has been nominated as a risk factor for both PD and ET development, particularly in late onset forms of these conditions [8,9]. The threonine residue (polar) causes a more accessible conformation of substrate binding residues than the isoleucine variant (non-polar), resulting in higher HNMT enzymatic activity, the primary mechanism by which histamine is degraded in the central nervous system [8-11]. Histamine is involved in a wide variety of functions including allergy and anaphylaxis, digestive regulation, and neurotransmission [10]. Although the histaminergic system has not been extensively studied with regard to diseases affecting dopaminergic neurons such as PD, post-mortem analysis of PD patients has shown increased density of histaminergic fibers and considerable interaction between histaminergic fibers and dopaminergic neurons in the substantia nigra [12]. While the exact nature of the interaction between the histaminergic and dopaminergic systems is unknown, it is generally accepted that increased histamine is related to dopaminergic neuron loss in both animal models [13,14] and in humans [12]. Given the findings of these studies and the complex relationship between PD and ET, we set out to evaluate this single nucleotide polymorphism (SNP) in a case-control series of PD and ET patients from North America.

Methods

In our study, we included 417 PD cases, 338 ET cases and 409 controls. Average age of PD patients was 72.6 years (range 30-92) with mean age at onset of 62.1 ± 12.0 years (range 16-85) and a 1:1.2 female to male ratio. Average age of ET cases was 70.9 years (range 18-93) with mean age at onset of 52.5 ± 19.3 years (range 5-88) and a 1:0.8 female to male ratio. The control subjects, collected at Mayo Clinic Florida outpatient clinic and consisting of spouses and unrelated individuals identified as free of any evidence of PD or ET by a movement disorder neurologist (Z.K.W., R.J.U.), had an average age of 72.2 years (range 33-92) and a 1:1.1 female to male ratio. All patients were selected consecutively from examination and observed longitudinally, with nine to twelve month follow-up, by a movement disorder neurologist (Z.K.W., R.J.U., or A.R.) and diagnosed according to standard criteria [15,16]. The ethical review board of each institution approved the study and all participants provided informed consent. Genotyping of *HNMT* rs11558538 was performed on a Sequenom MassArray iPLEX platform (San Diego, CA); all primer sequences are available on request. Associations between PD and ET with rs11558538 were measured by odds ratios (OR), corresponding 95% confidence intervals (CI) and chi-square test. With a recessive model of inheritance and a disease prevalence of 1%, our case-control populations have 96% (PD) and 94% (ET) power to detect a positive association at a nominal significance level of 0.05, assuming an odds ratio of 2.0 and the previously reported disease allele frequency (0.88) [8].

Results

The genotype and allele frequencies and statistical analysis for rs11558538 in PD and ET are given in Table 1. Cases and controls were in Hardy-Weinberg equilibrium and frequencies of controls were similar to previous reports [8,9]. Statistical analysis did not identify a difference between PD or ET cases and controls ($p > 0.05$). Stratified analysis of patients both above and below the median age of onset revealed no difference in genotype or allele frequencies compared to controls (Table 2). A previous study reported a significantly protective association in female PD patients with the minor allele (Ile) [8]; however, we found no difference between female PD cases and controls ($p = 0.62$).

Discussion

We assessed the role of a missense variant in *HNMT* (rs11558538) in a North American PD and ET case-control series. The common allele of this variant (Thr) was found to be overrepresented in cohorts of Spanish PD and ET patients, in particular among those with late onset (PD, AAO > 68 years; ET, AAO > 54 years). This association led the authors to suggest that the presence of the threonine allele possibly triggers a mechanism enhancing histamine synthesis and density of histaminergic fibers contributing to PD development [8]. However, it has not been determined whether the observed increase in histaminergic innervation in post-mortem PD brains occurs before the degeneration of dopaminergic neurons contributing to PD, or is a compensatory mechanism unrelated to disease development following neuronal death [12].

In contrast to previous reports, statistical analysis revealed no difference between the case and control frequencies for either disease ($p > 0.05$). Likewise, further analysis evaluating only patients with late onset PD or ET (defined as patients with onset above the median age at onset) failed to identify statistically significant differences. The discrepancy in our findings might be attributed to different ethnic background between populations, and additional studies in ethnically matched series may be warranted; however, since the genotype and allele frequencies for our North American control subjects were similar to those reported in the Spanish population, this seems unlikely [8,9]. In conclusion, while our study focused on the reported functional SNP in *HNMT* and cannot rule out the possibility that other variants within the *HNMT* locus affect risk of disease, our results suggest that the Thr105Ile variant in HNMT plays no role in PD or ET development in the North American population and is unlikely to be a genetic link between these two conditions.

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Table 1

Genotype frequencies and statistical analysis for *HNMT* rs11558538 patient and controls. OR, odds ratio. CI, confidence interval. P value calculated by chi-square test

	Controls		PD		Intergroup comparison Values		ET		Intergroup comparison Values	
Genotype	**No.**	**%**	**No.**	**%**	**OR (95% CI)**	**p Value**	**No.**	**%**	**OR (95% CI)**	**p Value**
Thr/Thr	329	80.44	340	81.53	1.07 (0.76-1.52)	0.69	270	79.88	0.97 (0.67-1.39)	0.85
Thr/Ile	72	17.60	70	16.79	1.06 (0.74-1.51)	0.76	64	18.93	1.09 (0.75-1.59)	0.64
Ile/Ile	8	1.96	7	1.68	0.86 (0.31-2.38)	0.77	4	1.18	0.60 (0.18-2.01)	0.40
Allele										
Thr	730	89.24	750	89.93	1.08 (0.79-1.48)	0.65	604	89.35	1.01 (0.73-1.41)	0.95
Ile	88	10.76	84	10.07	0.93 (0.68-1.27)		72	10.65	0.99 (0.71-1.38)	

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Table 2

Age related analysis of *HNMT* rs11558538 in patients and controls. OR, odds ratio. CI, confidence interval. P value calculated by chi-square test. PD median age at onset = 64 years. ET median age at onset = 56 years

PD	**Age at Onset ≤ 64 years**				**Age at Onset > 64 years**			
	N = 202, 404 alleles				**N = 202, 404 alleles**			
Genotype	**No.**	**%**	**OR (95% CI)**	**p Value**	**No.**	**%**	**OR (95% CI)**	**p Value**
Thr/Thr	170	84.16	1.29 (0.82-2.03)	0.26	158	78.22	0.87 (0.58-1.32)	0.37
Thr/Ile	30	14.85	0.82 (0.51-1.30)	0.39	39	19.31	1.12 (0.73-1.73)	0.61
Ile/Ile	2	0.99	0.50 (0.11-2.38)	0.38	5	2.48	1.27 (0.41-3.94)	0.68
Alleles								
Thr	370	91.59	1.31 (0.87-1.99)	0.20	355	87.87	0.87 (0.60-1.27)	0.47
Ile	34	8.42	0.76 (0.50-1.15)		49	12.13	1.14 (0.79-1.66)	

ET	**Age at Onset ≤ 56 years**				**Age at Onset > 56 years**			
	N = 153, 306 alleles				**N = 152, 304 alleles**			
Genotype	**No.**	**%**	**OR (95% CI)**	**p Value**	**No.**	**%**	**OR (95% CI)**	**p Value**
Thr/Thr	125	81.70	1.09 (0.67-1.75)	0.74	117	76.97	0.81 (0.52-1.27)	0.52
Thr/Ile	28	18.30	1.05 (0.65-1.70)	0.85	31	20.39	1.20 (0.75-1.92)	0.45
Ile/Ile	0	0	0	0.08	4	2.63	1.35 (0.40-4.57)	0.62
Alleles								
Thr	278	90.85	1.20 (0.77-1.87)	0.43	265	87.17	0.82 (0.55-1.22)	0.33
Ile	28	9.15	0.84 (0.53-1.31)		39	12.83	1.22 (0.82-1.83)	