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Thr105Ile (rs11558538) polymorphism in the histamine *N*-methyltransferase (*HNMT*) gene and risk for Parkinson disease

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background/aims: Several neuropathological, biochemical, and pharmacological data suggested a possible role of histamine in the etiopathogenesis of Parkinson disease (PD). The single nucleotide polymorphism (SNP) rs11558538 in the histamine *N*-methyltransferase (*HNMT*) gene has been associated with the risk of developing PD by several studies but not by some others. We carried out a systematic review that included all the studies published on PD risk related to the rs11558538 SNP, and we conducted a meta-analysis following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Methods: We used several databases to perform the systematic review, the software *Meta-DiSc 1.1.1* to perform the meta-analysis of the eligible studies, and the Q-statistic to test heterogeneity between studies.

Results: The meta-analysis included 4 eligible case–control association studies for the *HNMT* rs11558538 SNP and the risk for PD (2108 patients, 2158 controls). The frequency of the minor allele positivity showed a statistically significant association with a decreased risk for PD, both in the total series and in Caucasians. Although homozygosity for the minor allele did not reach statistical significance, the test for trend indicates the occurrence of a gene–dose effect. Global diagnostic odds ratios (95% confidence intervals) for rs11558538T were 0.61 (0.46–0.81) for the total group, and 0.63 (0.45–0.88) for Caucasian patients.

Conclusion: The present meta-analysis confirms published evidence suggesting that the *HNMT* rs11558538 minor allele is related to a reduced risk of developing PD.

Abbreviations: ABP1 = amiloride binding protein, *ACMSD* = aminocarboxymuconate semialdehyde decarboxylase, *BST1* = bone marrow stromal cell antigen 1, *CCDC62/HIP1R* = coiled-coil domain containing 62/huntingtin interacting protein 1 related, *DGKQ* = diacyl-glycerol-kinase theta, *GAK* = cyclin G-associated kinase, *GBA* = glucocerebrosidase, GWAS = genome-wide association study, *HLA-DRB5* = major histocompatibility complex, class II, DR beta 5, HNMT = histamine *N*-methyltransferase, HR = histamine receptor, *MAPT* = microtubular associated protein tau, *MCCC1/LAMP3* = methylcrotonoyl-CoA carboxylase 1/lysosomal associated membrane protein 3, OR = odds ratio, PD = Parkinson disease, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *RIT2* = Ras-like without CAAX 2, *SNCA* = synuclein alpha, SNP = single nucleotide polymorphism, *STK39* = serine threonine kinase 39, *STX1B* = syntaxin 1b, *SYT11* = synaptotagmin 11.

Keywords: genetics, HNMT polymorphisms, meta-analysis, Parkinson disease

Editor: Xiaolin Zhu.

Funding: This work was supported in part by grants PI12/00241, PI12/00324, PI15/00303, and RETICS RD12/0013/0002 from Fondo de Investigación Sanitaria, Instituto de Salud Carlos III, Spain, and GR15026 from Junta de Extremadura, Spain. It was financed in part with FEDER funds from the European Union.

The authors have no conflicts of interest to disclose.

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Medicine (2016) 95:27(e4147)

Received: 12 February 2016 / Received in final form: 14 April 2016 / Accepted: 13 June 2016

http://dx.doi.org/10.1097/MD.0000000000004147

1. Introduction

Histamine is stored and released in the brain, mainly in mast cells and histaminergic neurons of the tuberomammilary nucleus of the posterior basal hypothalamus. Histaminergic fibers project from this nucleus to many regions of the brain, including the striatum, thalamus, cerebral cortex, hippocampus, and amygdale.[1,2] Histamine acts through 4 metabotropic histamine receptors (HRs), designated as HRH1, HRH2, HRH3, and HRH, which are all G-protein-coupled. HRH3 is implicated in neurotransmitter release in the central nervous system. Histidine decarboxylase is the enzyme responsible for the synthesis of histamine (from its precursor histidine), whereas histamine *N*-methyltransferase (HNMT) and diamine oxidase (or ABP1) are the responsible enzymes in inactivating histamine, respectively, in the brain and in the peripheral tissues (revised in Ref.[3]).

Together with the demonstration that histamine infusion could induce neuronal death and inflammatory phenomena in the *substantia nigra* of rats,[4] recent neuropathological, biochemical, and pharmacological data arisen from studies in patients with Parkinson disease (PD), and in experimental models of

Table 1

Results of studies on brain, CSF, blood, and urine of histamine-related substances in patients with PD, neuropathological data in models of parkinsonism, and pharmacological data in patients with PD and experimental models of parkinsonism related to histamine.

Biochemical findings in patients with PD
Brain
Increased histamine concentrations by 2-fold in the substantia nigra compacta, and lateral and medial globus pallidus, and by 1.6-fold in the putamen, and normal levels of the histamine metabolite tele-methylhistamine in all these regions[5]
Normal histidine decarboxylase activity in the caudate nucleus, substantia nigra compacta, hypothalamus, and frontal cortex,[6], and normality of histidine decarboxylase expression in the tuberomammilary nucleus[7]
Normality of histamine H2 receptor binding sites, as previously described in guinea pigs lesioned with 6-hydroxydopamine[8]
Normality of histamine H3 receptors density, assessed with the ligand [^{3}H]-(*R*)-α-methyl histamine in 1 study,[9] whereas other study using in situ hybridization described increased H3 receptor mRNA expression in the globus pallidus externum and H3 receptor density (assessed by GTP-γ[35*S*]-binding assay) slightly decreased in the substantia nigra and increased in the striatum,[10] and another found a significant decrease in the H3 receptor mRNA expression in the substantia nigra[11]
Increased H4 receptor mRNA expression in the striatum[11]
Increased mRNA levels of histamine *N*-methyltransferase in the substantia nigra (which were negatively correlated with PD duration) and in the putamen[11]
Normal number of large-sized histaminergic neurons in the tuberomammilary nucleus[12]
Increased density of histaminergic fibers in the middle portion of substantia nigra compacta and substantia nigra reticulata, histaminergic fibers thinner and with enlarged varicosities in comparison to controls[13]
CSF
Correlation between CSF levels of pros-methylimidazoleacetic acid (an isomer of the histamine metabolite tele-methylimidazoleacetic acid) and severity of PD[14]
Blood
Increased serum histamine levels in patients with untreated PD (which decrease significantly after therapy with carbidopa/levodopa and even more when anticholinergic drugs are added to this treatment), a normal serum histaminase activity[15]
Urine
Decreased urinary excretion of histamine and 1,4-methylhistamine in patients with PD compared with that in controls, which was more marked after administration of levodopa[16,17]
Neuropathological findings in experimental models of PD
Involvement of histamine neurons of the caudal hypothalamus in the conversion of MPTP in its neurotoxic metabolite MPP^+ after its systemic administration to rats[18]
Increased H3 receptor mRNA expression (assessed by in situ hybridization) and H3 receptor density (assessed by GTP-γ[35*S*]-binding assay) in the ipsilateral substantia nigra and the striatum of 6-hydroxydopamine lesioned rats, whereas histidine decarboxylase mRNA expression was unchanged[19]
Increased histamine concentrations in the hypothalamus, hippocampus, and medulla oblongata induced by intracerebroventricular administration of 6-hydroxydopamine in rats[20]]
Urine of experimental models of PD
Administration of levodopa decreased urinary excretion of histamine and their metabolites 1,4-methylhistamine and 1-methylimidazole-4-acetic acid[16]
Pharmacological data
Improvement of bradyphrenia and motor symptoms with the H2-antagonist famotidine in an open-label study involving 7 patients[21]
Worsening of parkinsonian signs and improvement in choreiform levodopa-induced dyskinesia by H3 receptor agonists in the MPTP lesioned marmoset model of PD[22]
Increase in turning rate and in the loss of tyrosine-hydroxylase immunoreactive neurons induced by 6-hydroxidopamine lesions by pretreatment with the histamine precursor histidine, whereas the irreversible inhibitor of histidine decarboxylase and the histamine H1 receptor antagonist pyrilamine showed the opposite effects, and the H2 receptor antagonist cimetidine did not induce any change[23]
Enhanced histamine H2 receptor-mediated excitation of striatal cholinergic interneurons in mice with levodopa-induced dyskinesia using 2 models (6-hydroxydopamine lesioned mice and mice with the *PITX3 [ak/ak]* mutation; with decreased levodopa-induced dyskinesia after systemic administration of the H2 receptor antagonist famotidine)[24]

CSF = cerebrospinal fluid, MPP^+ = 1-methyl-4-phenyl-pyridinium ion, MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, PD = Parkinson disease.

parkinsonism, which are summarized in Table 1, suggest an implication of histamine in the pathogenesis of PD.[5–24]

The single nucleotide polymorphism (SNP) rs11558538, located in the exon 4 C314T of the *HNMT* gene (chromosome 2q22.1, MIM 605283, gene identity 3176), which causes the amino acid substitution Thr105Ile (related to decreased enzyme activity), has been the matter of several case–control association studies trying to establish its association with the risk of developing PD. However, the results of studies addressing this association have been controversial. For this reason, we performed a systematic review and a meta-analysis of eligible studies, including an estimation of the genetic association of each study and of the pooled data, and investigated the heterogeneity between studies.

2. Materials and methods

2.1. Search strategy

Figure 1 shows the literature search and selection of eligible studies. We crossed the terms "histamine", "HNMT," and "HNMT gene" with "Parkinson's disease," using several databases, to identify the eligible studies for the systematic review and meta-analysis. The search, which included all publications in any language, during the period from 1966 to November 24, 2015, retrieved the following results: PubMed (130 reports), MEDLINE Plus (0 report), EMBASE (38 reports), Science Citation Index Expanded (0 report), National Institute for Health and Care Excellence (0 report), and Cochrane Central Register of Controlled Trials in the Cochrane Library (0 report). We also consulted the PD Gene Data Base (link: http://archive.pdgene.org/). The search using these databases showed 6 case–control association studies on rs11558538 SNPs in the *HNMT* gene and the risk for PD.[25–30] However, we excluded from the review and meta-analyses 2 studies included in the PD Gene Data Base because the genotype and allele frequencies of the analyzed SNP were not available in the respective reports.[26,27] Therefore, only 4 case–control studies were included in the final meta-analysis.[25,28–30]

2.2. Data extraction and analysis

We extracted the following information: journal, publication year, first author, number of cases and controls for each *HNMT* rs11558538 genotype, genotyping method, and demographics,

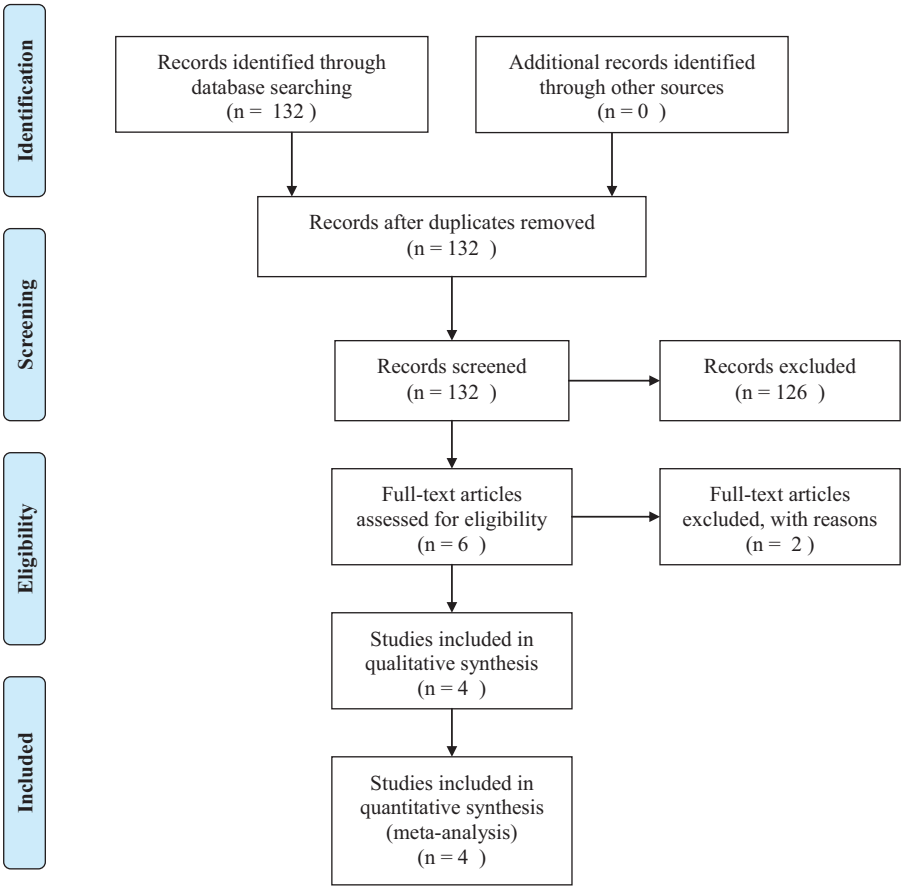

Figure 1. Flowchart of the study selection.

and we calculated allele frequencies, from each study. We also analyzed the statistical significance of the association of *HNMT* rs11558538 alleles and the risk of developing PD for each study to avoid statistical inconsistencies, and indicated all associations as diagnostic odds ratios (ORs) with their corresponding 95% confidence intervals (CIs). Fixed effects of the pooled OR, as well as random pooled OR effects, were estimated, based on individual ORs.

2.3. Statistical analysis

The meta-analyses of the eligible case–control studies regarding association between rs11558538 SNP and PD risk were carried out by using the software *Meta-DiSc 1.1.1* (http://www.hrc.es/investigacion/metadisc.html; Unit of Clinical Statistics, Hospital Ramón y Cajal, Madrid, Spain).[31] The Mantel–Haenszel[32] and the DerSimonian–Laird methods[33] were used, respectively, to calculate the global diagnostic OR when no heterogeneity was observed and when statistically significant heterogeneity existed.

The Q-statistic was used to test heterogeneity between studies.[34] Heterogeneity was considered significant when $P < 0.10$, and was quantified by using the I^2 metric ($I^2 = [Q]$ degrees of freedom [d.f.])/Q), which is independent of the number of studies included in the meta-analysis.[35] I^2 takes values between 0% and 100%, with higher values denoting greater degree of heterogeneity. We also calculated the statistical power for the pooled sample of the eligible studies.

Because this study is a systematic review and meta-analysis, ethical approval was not needed. This work was elaborated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[36]

3. Results

The meta-analysis included a total of 4 eligible studies analyzing the association between the *HNMT* rs1155858 SNP and the risk for PD (2108 patients with PD, 2158 controls). The genotype distribution and the minor allele frequencies from patients with PD and control groups in the eligible studies are summarized in Tables 2 and 3, respectively.

All individual studies on the rs11558538 SNP in PD were at Hardy–Weinberg equilibrium both in the patients with PD and in the control group. The frequency of allele T positivity (CT+TT vs CC) showed a significant association between *HNMT* rs11558538 and the risk for PD, both in the total series and in the series confined to Caucasian populations (Table 2; Fig. 2A and B), whereas homozygosity (TT vs CC+CT) did not show association (Table 2; Fig. 3A and B).

Figure 4A and B represents the results of the diagnostic OR and the 95% CI of all the studies and the pooled samples, which show a significant association between the minor allele of *HNMT* rs11558538 and the risk for PD, both in the total group (Fig. 4A) and in Caucasian patients (Fig. 4A). The diagnostic OR and the 95% CI of the major alleles, represented in Fig. 5A and B for the total series and Caucasians, respectively, showed a milder,

Table 2

Frequency of the genotypes (CC, CT, and TT) of the SNP rs11558538 in the *HNMT* gene in the total series of patients with PD and CONT in different reports with their ORs and 95% CIs.

Authors	Country	Patients with PD, N (M/F)	PD CC, N (%)	PD CT, N (%)	PD TT, N (%)	CONT, N (M/F)	CONT CC, N (%)	CONT CT, N (%)	CONT TT, N (%)	Allele positivity CT+TT versus CC, OR (95% CI); *P*	Homozygosity TT versus CC+CT, OR (95% CI); *P*	Test for trend, OR; *P*
Agúndez et al[25]	Spain	214 (99/115)	193 (90.2)	20 (9.3)	1 (0.5)	295 (135/160)	232 (78.6)	58 (19.7)	5 (1.7)	0.40 (0.24–0.68); 0.00053	0.24 (0.02–2.07); 0.160	0.43; 0.00054
Keeling et al[28]	USA, Canada	417 (190/227)	340 (81.5)	70 (16.8)	7 (1.7)	409 (195/214)	329 (80.4)	72 (17.6)	8 (2.0)	0.93 (0.66–1.32); 0.688	0.85 (0.30–2.36); 0.750	0.93; 0.660
Palada et al[29]	USA	299 (NA)	253 (84.6)	44 (14.7)	2 (0.7)	478 (NA)	350 (72.2)	119 (24.9)	9 (1.9)	0.50 (0.34–0.72); 0.00021	0.31 (0.07–1.44); 0.113	0.52; 0.00019
Palada et al[29]	Croatia, Germany, Slovenia	614 (NA)	503 (81.9)	100 (16.3)	11 (1.8)	480 (NA)	368 (76.6)	101 (21.0)	11 (2.4)	0.73 (0.54–0.97); 0.03227	0.73 (0.31–1.71); 0.467	0.78; 0.04116
Yang et al[30]	China	564 (305/259)	537 (94.2)	27 (4.8)	0	496 (294/202)	452 (91.0)	43 (8.76)	1 (0.2)	0.517 (0.32–0.85); 0.00796	0.28 (0.01–6.91); 0.276	0.52; 0.0064
Total series		2108	1826 (86.6)	261 (12.4)	21 (1.0)	2158	1731 (80.2)	393 (18.2)	34 (1.6)	0.63 (0.53–0.74); 0.0000000188	0.59 (0.34–1.01); 0.053	0.68; 0.00000004
Caucasians		1544	1289 (83.4)	234 (15.2)	21 (1.4)	1662	1279 (77.0)	350 (21.0)	33 (2.0)	0.66 (0.55–0.79); 0.0000037	0.63 (0.36–1.10); 0.100	0.71; 0.000007

CI = confidence interval, CONT = healthy volunteers, NA = not available, OR = odds ratio, PD = Parkinson disease, SNP = single nucleotide polymorphism.

Table 3

Frequency of the allelic variants of the SNP rs11558538 in the *HNMT* gene in the total series of patients with PD and CONT in different reports with their diagnostic ORs and 95% CIs.

Authors	Country	PD, N (M/F)	PD, MAF	CONT, N (M/F)	CONT, MAF	MAF, crude OR (95% CI); *P*	MAF, diagnostic OR (95% CI)
Agúndez et al[25]	Spain	214 (99/115)	0.051	295 (135/160)	0.115	0.42 (0.25–0.68); 0.0004	0.40 (0.24–0.68)
Keeling et al[28]	USA, Canada	417 (190/227)	0.101	409 (195/214)	0.108	0.93 (0.68–1.27); 0.648	0.93 (0.66–1.32)
Palada et al[29]	USA	299 (NA)	0.080	478 (NA)	0.143	0.52 (0.37–0.74); 0.00019	0.50 (0.64–0.72)
Palada et al[29]	Croatia, Germany, Slovenia	614 (NA)	0.099	480 (NA)	0.128	0.75 (0.58–0.98); 0.034	0.73 (0.54–0.97)
Yang et al[30]	China	564 (305/259)	0.025	496 (294/202)	0.042	0.52 (0.32–0.84); 0.0066	0.51 (0.32–0.85)
Total series		2108	0.072	2158	0.107	0.65 (0.56–0.75); 0.000000016	0.61 (0.46–0.81)
Caucasians		1544	0.089	1662	0.125	0.69 (0.58–0.81); 0.0000039	0.63 (0.45–0.88)

CI = confidence interval, CONT = healthy volunteers, MAF = minor allele frequency, NA = not available, OR = odds ratio, PD = Parkinson disease, SNP = single nucleotide polymorphism.

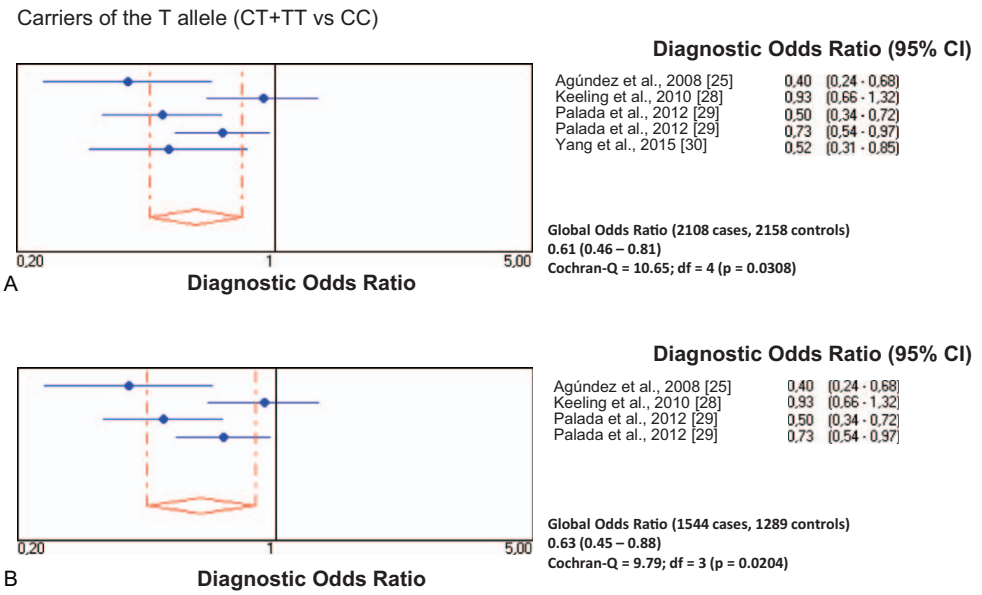

Figure 2. Diagnostic odds ratios and 95% CIs for each study and for pooled samples for carriers of the rs11558538T allele in patients with PD and controls in total series (A) and in Caucasian patients (B). CI = confidence interval, PD = Parkinson disease.

although significant, association between the major allele of *HNMT* rs11558538 and the risk for PD as well. Q-statistic did show a marginally significant heterogeneity between studies, which was due to that by Keeling et al.[28]

The statistical power for the presence of the SNP analyzed in this study was determined from the variant allele frequencies observed in control individuals with a genetic model analyzing the frequency for carriers of the disease gene with a relative risk value = 0.65 ($P = 0.05$). For overall (Caucasian and Asian) patients the power is equal to 99.6% for 1-tailed association and 99.0% for 2-tailed association, and for Caucasian patients it was 97.9% for 1-tailed association and 95.7% for 2-tailed association.

4. Discussion

To date, at least 28 susceptibility loci associated with the risk for PD have been identified in genome-wide association studies (GWAS), the strongest associations related to polymorphisms being in the *MAPT*, *SNCA*, *HLA-DQB1*, *GBA*, *SYT11*, and *GAK-DGKQ* genes, but other genes such as *CCDC62/HIP1R*, *MCCC1/LAMP3*, *ACMSD*, *STK39*, *STX1B*, *RIT2*, and *BST1* have also been found to be associated with the modification of PD risk.[37] Interestingly, meta-analyses of case–control association studies involving SNPs in candidate genes that were not mentioned as possible susceptibility genes in GWAS showed strong associations of many of them with the risk for PD (revised in Ref.[37]). Data suggesting the possible implication of histamine

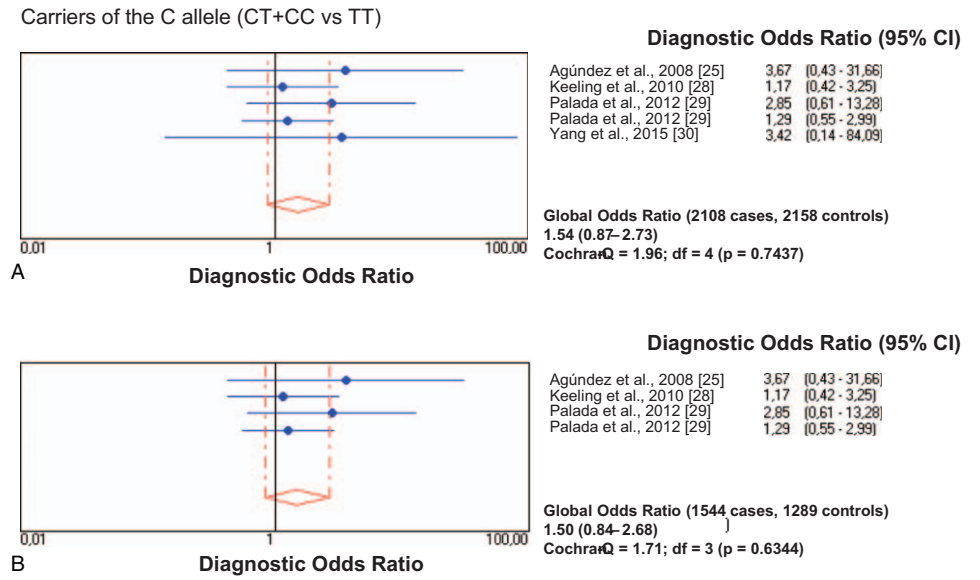

Figure 3. Diagnostic odds ratios and 95% CIs for each study and for pooled samples for carriers of the rs11558538C allele in patients with PD and controls in total series (A) and in Caucasian patients (B). CI = confidence interval, PD = Parkinson disease.

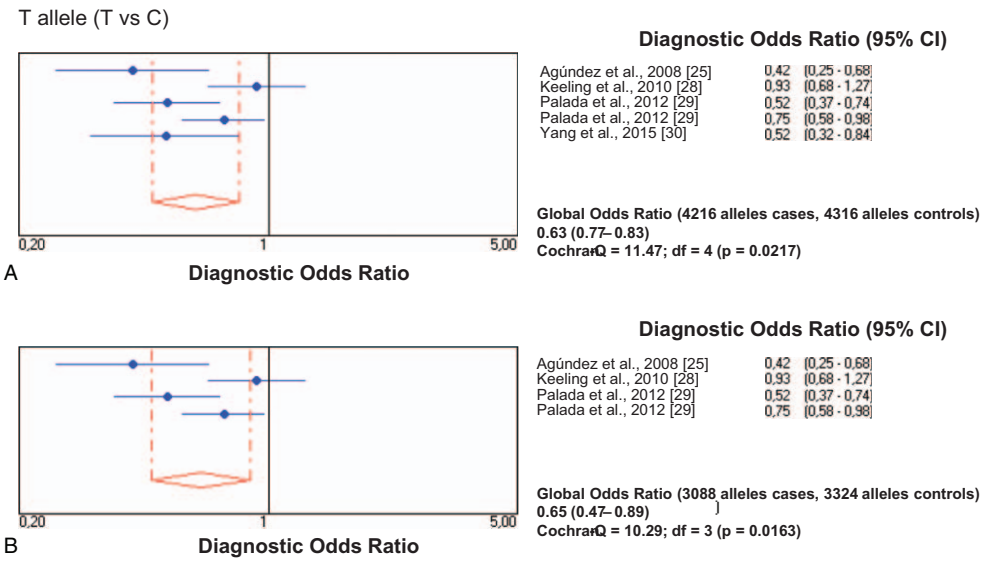

Figure 4. Diagnostic odds ratios and 95% CIs for each study and for pooled samples of rs11558538T allele (minor allele) in patients with PD and controls in total series (A) and in Caucasian patients (B). CI = confidence interval, PD = Parkinson disease.

(summarized in Table 1) in the pathogenesis of PD make reasonable the investigation of the possible role of histamine-related genes in the risk for this disease, despite the fact that none of these have been mentioned among the possible susceptibility genes in GWAS.

Our group described an association between the major allele of the rs1155838 SNP in the *HNMT* gene and the increased risk for PD.[25] Two further studies, 1 involving Caucasian patients[29] and other involving Asian patients,[30] showed similar results, whereas another group reported lack of association.[28] Case–control association studies on other histamine-related genes showed lack of association between the *ABP1* His645Asp polymorphism,[25] the nonsynonymous *HRH1* SNP designated as rs2067470 (Leu449Ser),[38] and the promoter *HRH2* SNP designated as rs2067474 (G1018A)[38] polymorphisms and the risk for PD.

The present systematic review and meta-analysis, which included 4 studies involving 2108 patients with PD and 2158 controls, showed a significantly lower frequency of patients carrying the minor allele of the *HNMT* rs11558538 SNP in patients with PD than in controls, both in the allele positivity analysis and in the comparison of minor allele frequencies, whereas the association of *HNMT* rs11558538TT homozygosity with PD risk did not reach statistical significance because of the low frequency of the homozygous genotype. Nevertheless, the high significance of the test for trend with the number of minor

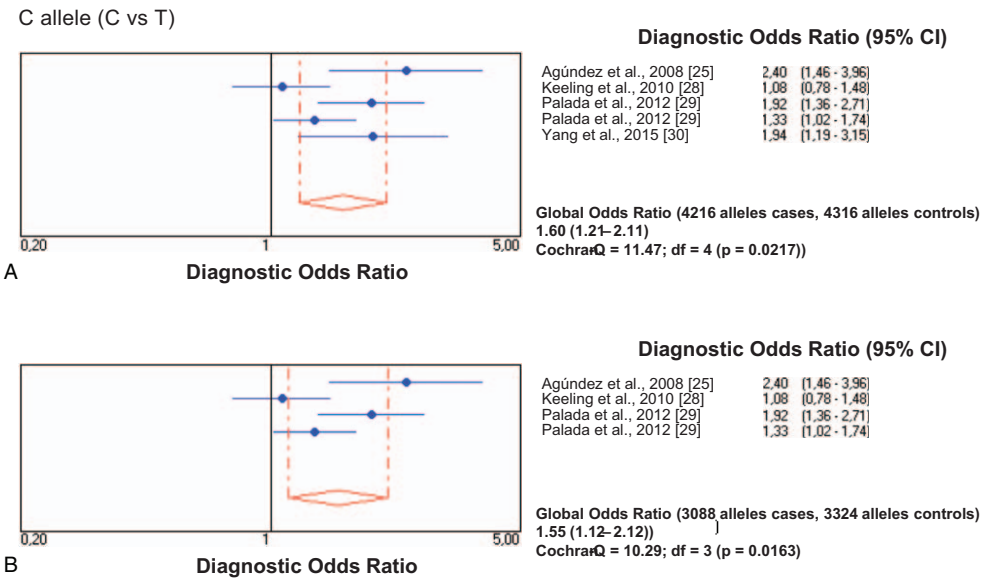

Figure 5. Diagnostic odds ratios and 95% CIs for each study and for pooled samples of rs11558538C allele (major allele) in patients with PD and controls in total series (A) and in Caucasian patients (B). CI = confidence interval, PD = Parkinson disease.

alleles (Table 2) strongly suggests the occurrence of a gene–dose effect.

The mechanism by which HNMT inactivates histamine consists in the transference of a methyl group from *S*-adenosyl-L-methionine (AdoMet) to the $N_{\epsilon 2}$ atom of the imidazole ring, which results in the production of the histamine inactive metabolite *N*-methylhistamine and *S*-adenosyl-L-homocysteine (AdoHcy).[39] Pang et al[40] showed, using a theoretical 3D model of human HNMT, that the polymorphic residue Thr105Ile is located in the turn between an α helix and a β strand on the protein surface away from the active site of HNMT, and that the presence of Ile105 caused destabilization of folded HNMT, leading to the formation of a misfolded protein that is cleared by proteasomes, and therefore to a decreased enzymatic activity. The decreased activity of HNMT in patients carrying the rs11558538 minor allele should hypothetically lead to an increase in brain histamine levels, an increase in brain mRNA levels of HNMT, or both.[41] The results of the present meta-analysis suggest that decreased histamine metabolism in the central nervous system should play a protective role against development of PD.

Despite the fact that our study has as the main limitation the relatively low number of studies on the association between *HNMT* rs11558538 SNP and PD risk that fulfill inclusion criteria, our data point at a protective role of the *HNMT* rs11558538T variant on the risk of developing PD (the calculated statistical power for the mean OR for carriers of the minor allele —0.65—seems to be acceptable), and give support to the hypothesis of a possible role of histamine in the pathogenesis of this disease.

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