RESEARCH ARTICLE

Association of Histamine N-Methyltransferase Thr105Ile Polymorphism with Parkinson’s Disease and Schizophrenia in Han Chinese: A Case-Control Study

Xinglong Yang1☯, Chuanxin Liu2,3☯, Jinxiang Zhang4☯, Hongying Han5, Xiuyan Wang6, Zhoulin Liu7, Yanming Xu1*  

1 Department of Neurology, West China Hospital, Sichuan University, 37 Guo Xue Xiang, Chengdu, Sichuan Province, 610041, PR China, 2 College of Basic and Forensic Medicine, Sichuan University, Chengdu, Sichuan Province, 610041, PR China, 3 Department of Psychiatry, Jining Medical College, Jining, Shandong Province, 272051, PR China, 4 Department of Psychiatry, Jining Mental Hospital, Jining, Shandong Province, 272051, PR China, 5 Department of Psychiatry, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong Province, 510630, PR China, 6 Institute of Mental Health, The Second Xiangya Hospital, Central South University, Changsha, Hunan Province, 410011, PR China, 7 Department of Neurology, First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong Province, 510080, PR China

☯ These authors contributed equally to this work.
* neuroxym999@163.com

Abstract

Parkinson’s disease (PD) and schizophrenia (SCZ) are frequent central nervous disorders that have unclear etiologies but that show similarities in their pathogenesis. Since elevated histamine levels in the brain have been associated with PD and SCZ, we wanted to explore whether the Thr105Ile substitution in the histamine N-methyltransferase gene (HNMT-Thr105Ile), which impairs histamine degradation, is associated with either disease. We used the ligase detection reaction to genotype a case-control cohort of Han Chinese patients with PD or SCZ and healthy controls at the HNMT-Thr105Ile locus. The Ile allele was associated with reduced risk of PD (OR 0.516, 95%CI 0.318 to 0.838, p = 0.007) and of SCZ (OR 0.499, 95%CI 0.288 to 0.865, p = 0.011). Genotype frequencies and minor allele frequencies were similar between patients and controls when we compared males with females or early-onset patients with late-onset ones. Genotype and allele frequencies were not significantly different between PD patients with dyskinesia and PD patients without dyskinesia. Our results suggest that the heterozygous Thr/Ile genotype at the HNMT-Thr105Ile locus and the minor Ile105 allele protect against PD and SCZ in Han Chinese.

Introduction

Parkinson’s disease (PD) and schizophrenia (SCZ) are devastating central nervous disorders and despite decades of research, their etiology remains unclear. However, numerous studies...
have documented similarities in the pathogenesis of both diseases. The risk of both PD and SCZ is higher in patients with the Val158Met polymorphism in the gene for catechol-O-methyltransferase (COMT) [1,2], the rs1799836 polymorphism in the gene for monoamine oxidase B (MAOB) [1,3], or the C(-1562)T polymorphism in the gene encoding matrix metalloprotease-9 (MPP-9) [4,5]. Dysregulation of several neurotransmitters, including dopamine and histamine, is associated with PD and SCZ [6,7]. In fact, substantial evidence indicates an association of the dopamine metabolism pathway with PD and SCZ, and the main treatments for PD and SCZ are based on the dopamine pathway [8,9].

Like the dysregulation of dopamine, dysregulation of histamine levels in the brain may be another unifying element in the pathogenesis of both PD and SCZ. Histamine can selectively damage dopaminergic neurons of the substantia nigra pars compacta (SNc), leading to the increased inflammation that is characteristic of PD pathology [10]. Patients with SCZ show lower density of histamine H1 receptors in the frontal, prefrontal, and cingulate cortex than do controls [11]. In addition, levels of the histamine metabolite tele-methylhistamine in the cerebrospinal fluid are 2.6-fold higher in SCZ patients than in healthy individuals, suggesting abnormally high histamine turnover [12]. Histamine H2 antagonist therapy has shown clinical benefits for patients with SCZ without significant adverse effects in a recent placebo-controlled randomized clinical trial [13]. The same type of therapy has proven effective at treating levodopa-induced dyskinesia in an animal model of PD and in patients with PD [6,14]. These findings suggest that histamine levels and histamine metabolism may influence onset and progression of PD and SCZ.

The enzymes histamine N-methyltransferase (HNMT) and diamine oxidase (DAO) degrade histamine, with HNMT playing the leading role in histamine metabolism in the central nervous system. The HNMT gene has even been proposed as a genetic biomarker for PD [15]. A sequence variant of the HNMT gene, exon 4(C314T), causes the amino acid substitution Thr105Ile in the enzyme, reducing its activity and increasing histamine levels in the brain [16]. This Thr105Ile mutation is the only functional mutation identified so far in the HNMT coding region in Chinese populations [17]. Several studies have examined a possible association between the HNMT-Thr105Ile polymorphism and PD, but the results have been inconsistent [18–20]. At the same time, we are aware of only one published study examining the association between HNMT-Thr105Ile and risk of SCZ, which found no association [21]. That study involved a relatively small sample of 185 patients with SCZ and 189 healthy controls, and the subjects came from several ethnicities; both factors may have significantly affected the outcome.

To help resolve the controversy over whether the HNMT-Thr105Ile variant is associated with risk of PD and SCZ, we performed a case-control study in a relatively large, single-ethnicity cohort of Han Chinese.

Materials and Methods

Materials

A total of 564 Han Chinese patients with sporadic PD (305 males, 259 females) were consecutively recruited from two movement disorder centers: West China Hospital of Sichuan University, located in southwest China; and First Affiliated Hospital of Sun Yat-sen University, located in southeast China. PD was diagnosed in all patients by two independent movement disorder specialists based on the UK Parkinson’s Disease Society Brain Bank criteria for idiopathic PD [22]. Patients with at least one relative with PD were excluded from the study. As controls, 496 healthy Han Chinese (294 males, 202 females) unrelated to the PD cohort were recruited. Average age was 62.75±12.84 yr for PD patients, and 61.91±11.51 yr for healthy
controls (Table 1). Patients who were younger than 50 years at onset were classified as having early-onset PD (EOPD; n = 167; mean age at onset, 44.37±5.35 yr); others were defined as having late-onset PD (LOPD; n = 397; mean age at onset, 63.05±6.59 yr). Patients were further divided into those with dyskinesia (n = 124) and those without it (n = 440).

Patients with SCZ were recruited from four centers: The Second Xiangya Hospital of Central South University, located in central China; West China Hospital of Sichuan University, located in southwest China; and the Third Affiliated Hospital of Sun Yat-sen University and Jining Mental Hospital, both located in east China. A total of 423 Han Chinese patients were recruited (180 males, 243 females; mean age, 36.11±13.61 yr). All patients were diagnosed by two psychiatrists based on the Structured Clinical Interview for DSM Disorders (SCID) and DSM-IV criteria [23]. Patients who were older than 18 at SCZ onset were classified as having late-onset SCZ (LOSCZ; n = 287; mean age at onset, 25.99±6.77 yr); others were classified as having early-onset SCZ (EOSCZ; n = 136; mean age at onset, 15.35±2.13 yr) [24]. The control group for SCZ patients comprised 457 Han Chinese (193 males, 264 females; mean age, 36.69±10.86 yr).

Control individuals were screened for mental disorders and for family history of mental disease. The corresponding controls were well-matched with SCZ patients in terms of age and gender. To take into account the different age distributions between our PD and SCZ groups, we recruited a healthy control population for the SCZ cohort that was entirely different from that of the PD cohort. Each control group was well-matched with PD or SCZ patients in terms of age and gender (Table 1).

The protocol of the study was approved by the ethics committees of West China Hospital of Sichuan University, the First Affiliated Hospital of Sun Yat-sen University, the Second Xiangya Hospital of Central South University, the Third Affiliated Hospital of Sun Yat-sen University, and Jining Mental Hospital. Written informed consent was obtained from all subjects.

Genotyping

Genomic DNA was obtained from peripheral leukocytes by classical phenol- chloroform extraction. All genotyping was performed by the Shanghai BioWing Applied Biotechnology Company using the ligase detection reaction (LDR) [25]. Briefly, this method involved the following steps. Target DNA in the HNMT gene was amplified using a multiplex PCR method using the forward primer 5'-GCAAGCA AACTTTACGTTC-3' and the reverse primer 5'-TGATGGTGTTGACCTCCTTC-3'. Then amplifications were mixed with 1 μl of proteinase K (20 mg/ml), incubated at 70°C for 10 min and then at 94°C for 15 min. Ligation reactions (20 μl) were set up with 20 mM Tris-HCl (pH 7.6), 25 mM potassium acetate, 10 mM magnesium acetate, 10 mM DTT, 1 mM NAD, 0.1% Triton X-100, 10 μl of ampiclon, 1 pmol of each discriminant primer, 1 pmol of each universal primer and 0.5 μl of 40 U/μl Taq DNA ligase (New England Biolabs, USA). Ligation was performed using 40 cycles at 94°C for 30 s and 63°C for 4 min. Fluorescent ligation products were analyzed on an ABI Sequencer 377.

Several measures were taken to ensure accurate genotyping. First, the technicians performing the genotyping were blinded to the case or control status of the samples. Second, a random
selection of 20% of the samples was genotyped independently by other technicians; the results of this second round of testing were identical in all cases to the initial results. Third, we selected 10 samples for each variant genotype obtained in the ligase detection reaction and we sequenced them directly using an automated sequencer (ABI Prism 3730); in all cases, the expected sequences were obtained.

Statistical analysis

All statistical analyses were performed using SPSS 17.0 (IBM, Chicago, USA). Age was reported as mean±SD, while gender, allele and genotype frequencies were reported as percentages. Allele and genotype frequencies were determined by direct counting of HNMT alleles. Concordance between genotype distributions was verified by comparison with the predictions of Hardy-Weinberg equilibrium (HWE); differences were assessed using the chi-squared test. Associations among gender, allele and genotype were assessed using the chi-squared test. Intergroup differences in age at the time of the study and in age at onset were assessed using the t test. A two-tailed P value < 0.05 was defined as the threshold of statistical significance.

Result

The genotype distribution at the HNMT-Thr105Ile locus and frequencies of individual alleles in patients with PD and the corresponding control group are shown in Table 2. The genotype distribution was in accordance with HWE for patients (χ² = 0.34, p = 0.56) and controls (χ² = 0.0005, p = 0.98). The Thr/Ile+Ile/Ile genotype was significantly less frequent among patients than controls (OR 0.53, 95%CI 0.322 to 0.871, p = 0.013), as was the Ile105 allele (OR 0.516, 95%CI 0.318 to 0.838, p = 0.007). We also examined whether patients and controls differed significantly in genotype frequencies or minor allele frequency when we compared males with females, early-onset patients with late-onset ones or patients with dyskinesia and patients without dyskinesia. Frequencies were similar between patients and controls in all these subgroup analyses (Table 3).

The genotype distribution at the HNMT-Thr105Ile locus and frequencies of individual alleles in patients with SCZ and the corresponding control group are shown in Table 2. The genotype distribution was in accordance with HWE for patients (χ² = 0.20, p = 0.65), and for controls (χ² = 0.91, p = 0.34). The Thr/Ile genotype was significantly less frequent among patients than controls (OR 0.499, 95%CI 0.268 to 0.847, p = 0.010), as was the Ile105 allele (OR

| Variant | PD      | Control | Comparison** | SCZ      | Control | Comparison** |
|---------|---------|---------|--------------|---------|---------|--------------|
| Genotype |         |         |              |         |         |              |
| Thr/Thr | 537 (94.2) | 452 (91.03) | 0.53;0.322–0.871; 0.013*** | 405 (95.7) | 418 (91.47) | 0.499;0.268–0.847; 0.010*** |
| Thr/Ile | 27 (4.8) | 43 (8.76) | 18 (4.3) | 39 (8.53) |          |
| Ile/Ile | 0 | 1 (0.2) | 0 | 0 |          |
| Allele |         |         |              |         |         |              |
| Thr     | 1101 | 947 | 0.516;0.318–0.838;0.007 | 828 (97.75) | 875 (95.73) | 0.499;0.288–0.865; 0.011 |
| Ile     | 27 | 45 | 18 (2.25) | 39 (4.27) |          |

* Values for the PD, SCZ and control groups are reported as n (%).
**Unless otherwise indicated, the values refer to OR; 95%CI; P value.
***Ile/Ile+Thr/Ile vs Thr/Thr

doi:10.1371/journal.pone.0119692.t002
0.499, 95%CI 0.288 to 0.865, p = 0.011). Genotype frequencies and MAF were similar between patients and controls in subgroup analyses based on gender or age at onset (Table 3).

Discussion

Our results suggest that the HNMT-Thr105Ile locus is associated with risk of both PD and SCZ in Han Chinese, with the heterozygous genotype Thr/Ile and the minor Ile105 allele conferring a protective effect against both disorders. To the best of our knowledge, this is the first study to relate variations at the HNMT-Thr105Ile locus to PD and SCZ in an Asian population.

We detected the Ile/Ile allele in only one of 496 subjects in the control group matched to PD patients; a similarly low frequency was also reported in a previous study of HNMT-Thr105Ile polymorphism in Chinese [26]. The frequencies of the heterozygous genotype Thr/Ile and the Ile allele are significantly lower in our population than in European and North American populations [18]. However, PD and SCZ appear to be less prevalent among Asians than in these other populations [27,28], contrary to what one might predict if the Thr/Ile genotype and Ile allele protect against these disorders. This apparent paradox presumably reflects the strong influence of gene-gene and gene-environment interactions in determining the overall risk of disease.

Such influences may also help explain why we failed to detect significant differences in genotype distribution between PD patients with dyskinesia and PD patients without it, even though histamine H2 antagonist therapy has proven effective at treating levodopa-induced dyskinesia in an animal model of PD and in patients [6,14]. Since our findings are based on only 124 patients with dyskinesia, larger studies are needed to verify this result.

The HNMT gene, located at 2q22.1, encodes an enzyme that methylates histamine in the extracellular space of the central nervous system. Histamine is an important neurotransmitter in the brain, and HNMT-mediated methylation is the only way to deactivate it, since the mammalian brain lacks a histamine reuptake system [29]. Numerous lines of evidence suggest that histamine hypermetabolism is associated with the pathophysiology of PD. This hypermetabolism may involve increased synthesis to compensate for a relatively rapid deactivation [add here the Agundez et al. reference]. Elevated serum levels of histamine have been detected in patients

| Subgroup | Genotype / MAF | Comparison* |
|----------|---------------|-------------|
| **Patients with SCZ** | | |
| Males | 180 Thr/Thr 170 10 10 0.571; 0.221–1.478; 0.243 a | |
| Females | 243 Thr/Thr 235 8 8 1.707; 0.667–4.370; 0.259 b | |
| EOSCZ | 136 Thr/Thr 128 8 8 1.731; 0.668–4.490; 0.254 a | |
| LOSCZ | 287 Thr/Thr 277 10 10 1.709; 0.667–4.380; 0.259 b | |
| **Patients with PD** | | |
| Male | 305 Thr/Thr 293 12 12 1.501; 0.690–3.267; 0.303 a | |
| Female | 259 Thr/Thr 244 15 15 0.637; 0.312–1.451; 0.309 b | |
| EOPD | 167 Thr/Thr 161 6 6 0.637; 0.312–1.451; 0.309 b | |
| LOPD | 397 Thr/Thr 376 21 21 0.673; 0.312–1.451; 0.309 b | |
| With dyskinesia | 124 Thr/Thr 121 3 3 1.876; 0.556–6.332; 0.303 a | |
| Without dyskinesia | 540 Thr/Thr 516 24 24 1.856; 0.554–6.213; 0.308 b | |

*Values indicate: OR; 95%CI; P value. Results marked with “a” refer to the genotype distribution; results marked with “b” refer to MAF distribution.

doi:10.1371/journal.pone.0119692.t003

Table 3. Distributions of minor allele frequency (MAF) in Han Chinese patients with SCZ or PD, stratified by gender or age of onset.
with PD [30], and non-medicated patients with mild to moderate PD show elevated levels of
the histamine metabolite pros-methylimidazole acid in the cerebrospinal fluid[31]. Autopsy
studies of patients with PD have revealed elevated levels of histamine in areas associated with
motor behavior, including the caudate nucleus, putamen, internal and external globus pallidus
and the SNC. Autopsy studies have also shown that histaminergic fibers, where the neurotrans-
mitter is synthesized, are denser in patients with PD than in controls, and that a greater pro-
portion of these fibers have enlarged varicosities, where histamine is stored [32]. Post-mortem
studies have shown higher levels of HNMT mRNA in the SNC and putamen of patients than of
healthy individuals, and the precise mRNA level may correlate with PD severity [33]. Adminis-
tering an irreversible inhibitor of histamine synthesis to a rat model of PD produced significant
protection against neuronal loss [34]. Histamine hypermetabolism may contribute to PD
pathophysiology by inhibiting dopamine activity: in a rat model of PD, a selective H3 receptor
agonist attenuated dopamine release in the striatum [35]. Together, the findings suggest that el-
levated histamine metabolism may promote PD onset and/or progression, perhaps by disturb-
ing dopamine signaling, whereas reduced histamine metabolism may exert a protective effect.
Consistent with this literature, we found in the present study that the minor allele Thr105Ile,
which reduces HNMT-mediated histamine deactivation, helps reduce risk of PD. This may be
because the reduction in deactivation causes a compensatory reduction in synthesis, which
should be tested in future studies.

Whether SCZ involves a similar disruption of histamine homeostasis is unclear, but several
pieces of evidence point in that direction. Autopsy studies of patients with SCZ show that the
density of histamine H1 receptors in the frontal cortex is lower in patients with SCZ than in
controls [11]. In addition, levels of histamine metabolites in the cerebrospinal fluid are higher
in patients with SCZ, suggesting histamine hypermetabolism similar to that in PD[12]. It may
be no coincidence that antipsychotic drugs such as clozapine and olanzapin act, in least in part,
through histamine receptors [36]. Indeed, a new generation of non-dopaminergic drugs to
treat both PD and SCZ bind to histamine H2 receptors[6,13].

Our results provide strong evidence that the HNMT gene is associated with PD and SCZ,
with a power of 0.955 for the PD association and 0.912 for the SCZ association. These findings
extend the list of diseases already associated with the gene, including alcoholism [37], essential
tremor [38], allergic rhinitis [39], asthma [40], and myasthenia gravis [41]. Future studies
should explore to what extent histamine dysregulation is important in the onset or progression
of these disorders.

Our observation of an association between the HNMT-Thr105Ile polymorphism and PD
risk is consistent with previous studies in Caucasians from Spain [16] and from Europe and the
US [20], but at least one study, on Caucasians from North America, concluded that there was
no association [19]. These discrepancies may reflect strong influence of different genetic back-
grounds in different ethnicities. It may also reflect differences in gene-gene or gene-environ-
mental interactions. The HNMT-Thr105Ile polymorphism would not be the first to show
different effects on PD risk as a function of ethnicity or environment. The rs11724635 poly-
morphism in the BST1 gene increases the risk of PD to a significantly greater extent in Asians
than in Caucasians. Another BST1 polymorphism, rs11724635, is not by itself associated with
PD in ethnic Taiwanese, but when carriers drink well water, it does increase the risk of the dis-
ease[42]. Future studies should examine the extent to which other genes and environment may
affect the influence of the HNMT-Thr105Ile polymorphism on PD and SCZ.

The results of our study should be interpreted with caution given its limitations. Although
we examined a relatively large study population, the low minor allele frequency reduced the
overall statistical power. In addition, we focused on the one functional SNP in the HNMT gene,
leading us to neglect SNPs in other regions of the gene that may be playing a disease role. Thus,
future studies should examine more \textit{HNMT} variants in a larger study population in order to gain a more complete picture of the potential association of this gene with PD and SCZ.

In conclusion, our multi-center study shows that the \textit{HNMT}-Thr105Ile polymorphism is associated with PD and SCZ in Han Chinese. Nevertheless, these associations should be verified in larger studies of other ethnicities. Future studies are also needed to understand how \textit{HNMT} polymorphism affects histamine homeostasis, and how histamine dysregulation contributes to PD, SCZ and potentially other motor disorders.

**Author Contributions**

Conceived and designed the experiments: XLY CXL JXZ YMX. Performed the experiments: XLY CXL JXZ HYH XYW ZLL. Analyzed the data: XLY YMX. Contributed reagents/materials/analysis tools: XLY CXL JXZ HYH XYW ZLL. Wrote the paper: XLY YMX.

**References**

1. Kiyohara C, Miyake Y, Koyanagi M, Fujimoto T, Shirasawa S, et al. (2011) Genetic polymorphisms involved in dopaminergic neurotransmission and risk for Parkinson’s disease in a Japanese population. BMC Neuro 11:89. doi:10.1186/1471-2377-11-89 PMID: 21781348
2. Voisey J, Swagell CD, Hughes IP, Lawford BR, Young RM, et al. (2012) HapMap tag-SNP analysis confirms a role for COMT in schizophrenia risk and reveals a novel association. Eur Psychiatry 27:372–376. doi:10.1016/j.eurpsy.2010.08.004 PMID: 20934310
3. Wei YL, Li CX, Li SB, Liu Y, Hu L (2011) Association study of monoamine oxidase A/B genes and schizophrenia in Han Chinese. Behav Brain Funct, 7, 42. doi:10.1186/1744-9081-7-42 PMID: 21978760
4. Han H, He X, Tang J, Liu W, Liu K, et al. (2011) The C(-1562)T polymorphism of matrix metalloproteinase-9 gene is associated with schizophrenia in China. Psychiatry Res 190: 163–164. doi: 10.1016/j.psychres.2011.04.026 PMID: 21620482
5. He X, Zhang L, Yao X, Hu J, Yu L, et al. (2013) Association studies of MMP-9 in Parkinson’s disease and amyotrophic lateral sclerosis. PLoS One 8:e73777. doi: 10.1371/journal.pone.0073777 PMID: 24040066
6. Kalia LV, Brotchie JM, Fox SH (2013) Novel nondopaminergic targets for motor features of Parkinson’s disease: review of recent trials. Mov Disord 28:131–144. doi: 10.1002/mds.25273 PMID: 23225267
7. Brisch R, Saniotis A, Wolf R, Bielau H, Bernstein HG, et al. (2014) The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: old fashioned, but still in vogue. Front Psychiatry 5:47. doi: 10.3389/fpsycho.2014.00047 PMID: 24904438
8. Abi-Dargham A, Meyer JM (2014) Schizophrenia: the role of dopamine and glutamate. J Clin Psychiatry 75:274–275. doi: 10.4088/JCP.13078co7c PMID: 24717380
9. Miyasaki JM (2010) Evidence-based initiation of dopaminergic therapy in Parkinson’s disease. J Neurol 257(Suppl 2):S309–313. doi: 10.1007/s00415-010-5718-x PMID: 21080195
10. Vizuete ML, Merino M, Venero JL, Santiago M, Cano J, et al. (2000) Histamine infusion induces a selective dopaminergic neuronal death along with an inflammatory reaction in rat substantia nigra. J Neurochem 75:540–552. PMID: 10899929
11. Iwabuchi K, Ito C, Tashiro M, Kato M, Kano M, et al. (2005) Histamine H1 receptors in schizophrenic patients measured by positron emission tomography. Eur Neuropsychopharmacol 15:185–191. PMID: 15690663
12. Prell GD, Green JP, Kaufmann CA, Khandelwal JK, Morishow AM, et al. (1995) Histamine metabolites in cerebrospinal fluid of patients with chronic schizophrenia: their relationships to levels of other aminergic transmitters and ratings of symptoms. Schizophr Res 14:93–104. PMID: 7711000
13. Meskenen K, Ekelund H, Laitinen J, Neuvonen PJ, Haukka J, et al. (2013) A randomized clinical trial of histamine 2 receptor antagonist in treatment-resistant schizophrenia. J Clin Psychopharmacol 33:472–478. doi: 10.1097/JCP.0b013e3182970490 PMID: 23764683
14. Johnston TH, van der Meij A, Brotchie JM, Fox SH (2010) Effect of histamine H2 receptor antagonism on levodopa-induced dyskinesia in the MPTP-macaque model of Parkinson’s disease. Mov Disord 25:1379–1390. doi: 10.1002/mds.23069 PMID: 20510030
15. Alonso-Navarro H, Jimenez-Jimenez FJ, Garcia-Martin E, Agundez JA (2014 Genomic and pharmacogenomic biomarkers of Parkinson’s disease. Curr Drug Metab 15:129–181. PMID: 24694231
16. Pang YP, Zheng XE, Weinshilboum RM. (2001) Theoretical 3D model of histamine N-methyltransferase: insights into the effects of a genetic polymorphism on enzymatic activity and thermal stability. Biochem Biophys Res Commun 287:204–208. PMID: 11549275

17. García-Martín E, Ayuso P, Martínez C, Blanca M, Agündez JA (2009) Histamine pharmacogenomics. Pharmacogenomics 10: 867–883. doi: 10.2217/pgs.09.26 PMID: 19450133

18. Agündez JA, Luengo A, Herráez O, Martínez C, Alonso-Navarro H, et al. (2008) Nonsynonymous polymorphisms of histamine-metabolising enzymes in patients with Parkinson’s disease. Neuromolecular Med 10:10–16. PMID: 17985251

19. Keeling BH, Vilariño-Güell C, Soto-Ortolaza AI, Ross OA, Uitti RJ, et al. (2010) Histamine N-methyltransferase Thr105Ile is not associated with Parkinson’s disease or essential tremor. Parkinsonism Relat Disord 16:112–114. doi: 10.1016/j.parkreldis.2009.08.011 PMID: 19773194

20. Palada V, Terzić J, Mazzulli J, Bwala G, Hagenah J, et al. (2012) Histamine N-methyltransferase Thr105Ile polymorphism is associated with Parkinson’s disease. Neurobiol Aging 33:836 e831–833.

21. Yan L, Szumlanski CL, Rice SR, Sobell JL, Lachman HM, Weinshilboum RM (2000) Histamine N-methyltransferase functional polymorphism: lack of association with schizophrenia. Am J Med Genet 96:404–406. PMID: 10898922

22. Calne DB, Snow BJ, Lee C (1992) Criteria for diagnosing Parkinson’s disease. Ann Neurol 32 Suppl: S125–127. PMID: 1510370

23. First MB, Donovan S, Frances A (1996) Nosology of chronic mood disorders. Psychiatr Clin North Am 19: 29–39. PMID: 8677218

24. Rapoport JL, Addington AM, Frangou S, Psych MR (2005) The neurodevelopmental model of schizophrenia: update 2005. Mol Psychiatry 10:434–449. PMID: 15700048

25. Thomas G, Sinville R, Sutton S, Farquar H, Hammer RP, et al. (2004) Capillary and microelectrophoretic separations of ligase detection reaction products produced from low-abundant point mutations in genomic DNA. Electrophoresis 25:1668–1677. PMID: 15188256

26. Chen GL, Xu ZH, Wang W, Wang GP, Zhou G, et al. (2002) Analysis of the C314T and A595G mutations in histamine N-methyltransferase gene in a Chinese population. Clin Chim Acta 326:163–167. PMID: 12417108

27. Pringsheim T, Jette N, Frolikis A, Steeves TD (2014) The prevalence of Parkinson’s disease: a systematic review and meta-analysis. Mov Disord 29:1583–1590. doi: 10.1002/mds.25945 PMID: 24975103

28. Saha S, Chant D, Welham J, McGrath J (2005) A systematic review of the prevalence of schizophrenia. PLoS Med 2:e141. PMID: 15916472

29. Duch DS, Bowers SW, Nichol CA (1978) Elevation of brain histamine levels by diaminopyrimidine inhibitors of histamine N-methyl transferase. Biochem Pharmacol 27:1507–1509. PMID: 697892

30. Coelho MH, Silva IJ, Azevedo MS, Manso CF (1991) Decrease in blood histamine in drug-treated Parkinsonian patients. Mol Chem Neuropathol 14:77–85. PMID: 1910360

31. Prell GD, Green JP (1991) Histamine metabolites and pros-methylimidazoleacetic acid in human cerebrospinal fluid. Agents Actions Suppl 33:343–363. PMID: 1828934

32. Anichtchik OV, Rinne JO, Kalimo H, Panula P (2000) An altered histaminergic innervation of the substantia nigra in Parkinson’s disease. Exp Neurol 163:20–30. PMID: 10785440

33. Shan L, Bossers K, Luchetti S, Balesar R, Lethbridge N, et al. (2012) Alterations in the histaminergic system in the substantia nigra and striatum of Parkinson’s patients: a postmortem study. Neuropath Aging 33:1488 e1481–1413.

34. Langlais PJ, Zhang SX, Wellersbacher G, Hough LB, Barke KE (1994) Histamine-mediated neuronal death in a rat model of Wernicke’s encephalopathy. J Neurosci Res 38:565–574. PMID: 7529327

35. Nowak P, Bortel A, Dabrowska J, Biedka I, Slomian G, et al. (2008) Histamine H(3) receptor ligands modulate L-dopa-evoked behavioral responses and L-dopa derived extracellular dopamine in dopamine-denervated rat striatum. Neurotox Res 13:231–240. PMID: 18522092

36. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, et al. (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353:1209–1223. PMID: 16172203

37. Orosz G, Enoch MA, Chun J, Virkkunen M, Goldman D (2005) Thr105Ile, a functional polymorphism of histamine N-methyltransferase, is associated with alcoholism in two independent populations. Alcohol Clin Exp Res 29:303–309. PMID: 15770103

38. Ledesma MC, García-Martín E, Alonso-Navarro H, Martínez C, Jiménez-Jiménez FJ, et al. (2008) The nonsynonymous Thr105Ile polymorphism of the histamine N-methyltransferase is associated to the risk of developing essential tremor. Neuromolecular Med 10:356–361. doi: 10.1007/s12017-008-8040-3 PMID: 18543121
39. García-Martín E, García-Menaya J, Sánchez B, Martínez C, Rosendo R, et al. (2007) Polymorphisms of histamine-metabolizing enzymes and clinical manifestations of asthma and allergic rhinitis. Clin Exp Allergy 37:1175–1182. PMID: 17651147

40. Yan L, Galinsky RE, Bernstein JA, Liggett SB, Weinshilboum RM (2000) Histamine N-methyltransferase pharmacogenetics: association of a common functional polymorphism with asthma. Pharmacogenetics 10:261–266. PMID: 10803682

41. Kellermayer B, Polgar N, Pal J, Banati M, Maasz A, et al. (2013) Association of myasthenia gravis with polymorphisms in the gene of histamine N-methyltransferase. Hum Immunol 74:1701–1704. doi: 10.1016/j.humimm.2013.07.016 PMID: 23932992

42. Chen ML, Lin CH, Lee MJ, Wu RM (2014) BST1 rs11724635 interacts with environmental factors to increase the risk of Parkinson’s disease in a Taiwanese population. Parkinsonism Relat Disord 20:280–283. doi: 10.1016/j.parkreldis.2013.11.009 PMID: 24342025