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Relationships of Cerebrospinal Fluid Alzheimer's Disease Biomarkers and *COMT*, *DBH*, and *MAOB* Single Nucleotide Polymorphisms

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Abstract. The noradrenergic and dopaminergic systems are affected in Alzheimer's disease (AD). Polymorphisms in genes encoding enzymes and proteins that are components of these systems can affect products of transcription and translation and lead to altered enzymatic activity and alterations in overall dopamine and noradrenaline levels. Catechol-*O*-methyltransferase (*COMT*) and monoamine oxidase B (*MAOB*) are the enzymes that regulate degradation of dopamine, while dopamine β -hydroxylase (*DBH*) is involved in synthesis of noradrenaline. *COMT* Val158Met (rs4680), *DBH* rs1611115 (also called –1021C/T or –970C/T), and *MAOB* rs1799836 (also called A644G) polymorphisms have been previously associated with AD. We assessed whether these polymorphisms are associated with cerebrospinal fluid (CSF) AD biomarkers including total tau (t-tau), phosphorylated tau proteins (p-tau₁₈₁, p-tau₁₉₉, and p-tau₂₃₁), amyloid- β ₄₂ (A β ₄₂), and visinin-like protein 1 (*VILIP-1*) to test possible relationships of specific genotypes and pathological levels of CSF AD biomarkers. The study included 233 subjects: 115 AD, 53 mild cognitive impairment, 54 subjects with other primary causes of dementia, and 11 healthy controls. Significant decrease in A β ₄₂ levels was found in patients with GG compared to AG *COMT* Val158Met genotype, while t-tau and p-tau₁₈₁ levels were increased in patients with AA compared to AG *COMT* Val158Met genotype. A β ₄₂ levels were also decreased in carriers of A allele in *MAO-B* rs1799836 polymorphism, while p-tau₁₈₁ levels were increased in carriers of T allele in *DBH* rs1611115 polymorphism. These results indicate that *COMT* Val158Met, *DBH* rs1611115, and *MAOB* rs1799836 polymorphisms deserve further investigation as genetic markers of AD.

Keywords: Alzheimer's disease, biomarkers, *COMT*, *DBH*, dopamine, *MAOB*, noradrenaline, polymorphisms

INTRODUCTION

Neuropathological changes of monoaminergic systems are considered an early and clinically important feature of Alzheimer's disease (AD) (for a review, see [1, 2]). Dopamine β -hydroxylase (*DBH*)

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is an enzyme involved in the synthesis of norepinephrine, whereas catechol-*O*-methyltransferase (COMT) and monoamine oxidase B (MAOB) regulate the degradation of dopamine. Polymorphisms in genes for these enzymes can lead to altered transcription and translation products, and their dysfunctional enzymatic activity consequently leads to changes in dopamine and norepinephrine levels. It is therefore not surprising that single nucleotide polymorphisms (SNPs) in genes for COMT, DBH, and MAOB are associated with neuropsychiatric disorders [3–7]. The possible association of *COMT* Val158Met (rs4680), *DBH* rs1611115 (also called –1021C/T or –970C/T), and *MAOB* rs1799836 (also called A644G) polymorphisms with cerebrospinal fluid (CSF) AD biomarkers has not yet been evaluated. CSF AD biomarkers can serve as intermediate quantitative traits (endophenotypes, proxy variables) of AD as they can reflect AD-related pathology [8]. Increased deposition of amyloid in brain is reflected in reduced concentration of CSF amyloid- β_{42} (A β_{42}) [9], while phosphorylated tau proteins [10] positively correlate with formation of neurofibrillary tangles, thus reflecting the extent of neurofibrillary degeneration. Total tau (t-tau) and visinin-like protein 1 (VILIP-1) are also increased in CSF during neurodegeneration and their levels positively correlate with the cognitive impairment [11–13]. In order to determine if pathological levels of CSF biomarkers are more likely to occur in patients with certain genotypes, we measured the levels of CSF AD biomarkers (A β_{42} , t-tau, p-tau₁₈₁, p-tau₁₉₉, p-tau₂₃₁, and VILIP-1) and assessed whether they differed between patients with *COMT*

Val158Met, *DBH* rs1611115, and *MAOB* rs1799836 genotypes.

MATERIALS AND METHODS

Subjects

The study included 233 Croatian Caucasian subjects recruited at the University Hospital Center Zagreb. While this population is clearly representative of a European ethnic group, by which it may not be entirely comparable to US populations investigated in comparable contexts, it is nonetheless purely Caucasian. Of note, assessing our Croatian population using a Croatian version of the Mini-Mental State Examination (MMSE) yielded outcomes entirely comparable to other population similarly assessed worldwide [14]. Out of 233 subjects recruited, 115 were AD patients, 53 had mild cognitive impairment (MCI), 54 were patients with other primary causes of dementia (14 patients had dementia due to vascular cognitive dementia [AD+VaD], three had dementia with Parkinson's disease [PD], 7 had dementia with Lewy bodies [DLB], 23 had frontotemporal dementia [FTD], and one had corticobasal syndrome [CBS]). Eleven subjects were healthy controls (HC) (Table 1). AD was clinically diagnosed using criteria of the National Institutes on Aging - Alzheimer's Association (NIA-AA) [15]. VaD was diagnosed by using the criteria of National Institute for Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINCDS-AIREN) [16] and the Hachinski Ischemic Score [17]. FTD diagnosis was

Table 1

Frequency of *COMT* Val158Met, *DBH* rs1611115, and *MAOB* rs1799836 genotypes in AD and MCI patients, HC, and in patients with other causes of dementia

	<i>COMT</i>			<i>DBH</i>			<i>MAOB</i>			MMSE Mean \pm SD	Age Median (25–75th percentile)	Gender M/F
	AA	GG	AG	CC	TT	CT	AA	GG	AG			
AD	32	23	59	77	5	33	57	34	24	19.9 \pm 4.5	73 (67–77)	53/62
MCI	9	14	30	35	3	15	23	18	12	25.1 \pm 2.9	70 (59–74)	26/27
HC	8	1	2	3	1	7	2	3	6	27.8 \pm 1.9	54 (45–61)	4/7
VaD	5	4	5	8	2	4	7	2	5	22.2 \pm 5.0	71 (63–77)	8/6
FTD	5	3	15	13	1	8	8	11	3	16.7 \pm 5.2	61 (56–64)	12/11
DLB	1	6	7	4	1	2	3	3	1	19.3 \pm 3.9	70 (68–75)	5/2
AD + VaD		1	2	2		1	2	1		19.3 \pm 4.0	78	3/0
PD		1	2	1		2	1	1	1	22.5 \pm 10.6	65	2/1
CBS	1					1			1	27	51	0/1
ND		1	2	2		1		2	1	20.7 \pm 5.5	68	1/2

AD, Alzheimer's disease; AD + VaD, mixed dementia; CBS, corticobasal syndrome; COMT, catechol-*O*-methyltransferase; DBH, dopamine β -hydroxylase; DLB, dementia with Lewy bodies; F, female; FTD, frontotemporal dementia; HC, healthy controls; M, male; MAOB, monoamine oxidase B; MCI, mild cognitive impairment; ND, nonspecific dementia; PD, Parkinson's disease; SD, standard deviation; VaD, vascular dementia.

made by using the criteria of Neary et al. [18], while MCI was diagnosed using criteria of Albert et al. [19] and Petersen et al. [20]. Before the enrolment in the study, patients gave informed consent for lumbar puncture and for participation in the study. They were tested neuropsychologically using the MMSE, Montreal Cognitive Assessment (MoCA), and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog). In addition to thorough neurological examination, each patient went through complete blood tests, including serology for Lyme's disease and syphilis, thyroid function, and levels of vitamin B12 and folic acid (B9). All procedures performed within this study were in accord with the Helsinki Declaration [21] and approved by the Central Ethical Committee of the University of Zagreb Medical School (case no. 380-59-10106-18-111/126, class 641-01/18-02/01 from June 20, 2018) and Ethical Committee of the Clinical Hospital Center Zagreb (case no. 02/21 AG, class 8.1-18/82-2 from April 24, 2018).

Analysis of CSF biomarkers

CSF was collected by lumbar puncture between intervertebral spaces L3/L4 or L4/L5. After lumbar puncture, CSF was centrifuged for 10 min at 2,000 g and stored in polypropylene tubes at -80°C . CSF biomarkers were measured using the following enzyme-linked immunosorbent assays (ELISA): $\text{A}\beta_{42}$ (Innotest β -amyloid1-42, Fujirebio, Gent, Belgium), p -tau₂₃₁ (Tau [pT231] Phospho-ELISA Kit, Human, Thermo Fisher Scientific, Waltham, MA, USA), p -tau₁₉₉ (TAU [pS199] Phospho-ELISA Kit, Human, Thermo Fisher Scientific), p -tau₁₈₁ (Innotest Phospho-Tau [181P], Fujirebio), t -tau (Innotest hTau Ag, Fujirebio), and VILIP-1 (VILIP-1 Human ELISA, BioVendor, Brno, Czech Republic) according to the manufacturers' instructions.

DNA analysis

Venous blood was collected in plastic syringes with 1 ml of acid citrate dextrose as an anticoagulant. Isolation of DNA from the peripheral blood was done by the salting-out method [22]. TaqMan SNP Genotyping Assays (Applied Biosystems, Foster City, CA, USA) were used for determination of *COMT* Val158Met (rs4680), *DBH* rs1611115 (also called -1021C/T or -970C/T), and *MAOB* rs1799836 SNPs. Analysis of SNPs was done using ABI Prism

7300 Real Time PCR System apparatus (Applied Biosystems).

Statistical analysis

SPSS 19.0.1 (SPSS, Chicago, IL, USA) was used for statistical analyses with level of statistical significance set at $\alpha=0.05$. Normality of data was tested using the Kolmogorov-Smirnov test. Because some groups contained small number of subjects, non-parametric statistics were also used. Non-parametric Kruskal-Wallis test was used for comparison of the CSF biomarkers' levels among the groups. *Post-hoc* non-parametric test with calculation of the corrected p value was used for pairwise comparisons. One limitation of our study was the small number of HC available ($n=11$). Statistical analysis was performed in all subjects combined ($n=233$). Additionally, association of CSF biomarkers with SNPs was tested separately in AD subjects, MCI patients, a mixed group of AD, MCI, and HC subjects, as well as in a mixed group of MCI and HC subjects. Only statistically significant associations were reported.

RESULTS

COMT Val158Met (rs4680)

Levels of t -tau (H test = 7.657, $df=2$, $p=0.022$) and p -tau₁₈₁ (H test = 6.348, $df=2$, $p=0.042$) were significantly different in patients with different *COMT* Val158Met genotype (in all subjects with different diagnoses; AD, MCI, VaD, FTD, DLB, AD+VaD, CBS, ND, PD, and healthy controls). Levels of t -tau (Kruskal-Wallis *post hoc* $p=0.017$) and p -tau₁₈₁ (K-W *post hoc* $p=0.035$) were significantly increased in patients with AA compared to AG *COMT* Val158Met genotype (Fig. 1). $\text{A}\beta_{42}$ levels were significantly different in all subjects with AD, MCI, and HC grouped together with different *COMT* Val158Met genotype (H test = 7.354, $df=2$, $p=0.025$). More precisely, $\text{A}\beta_{42}$ levels were significantly decreased in patients with GG compared to AG *COMT* Val158Met genotype (KW *post hoc* $p=0.038$) (Fig. 2). Patients with AG genotype had normal levels of CSF biomarkers (t -tau, p -tau₁₈₁, and $\text{A}\beta_{42}$), while patients with AA and GG genotype have pathological levels of CSF biomarkers (increased t -tau and p -tau₁₈₁ levels and decreased $\text{A}\beta_{42}$ levels) (Figs. 1 and 2).

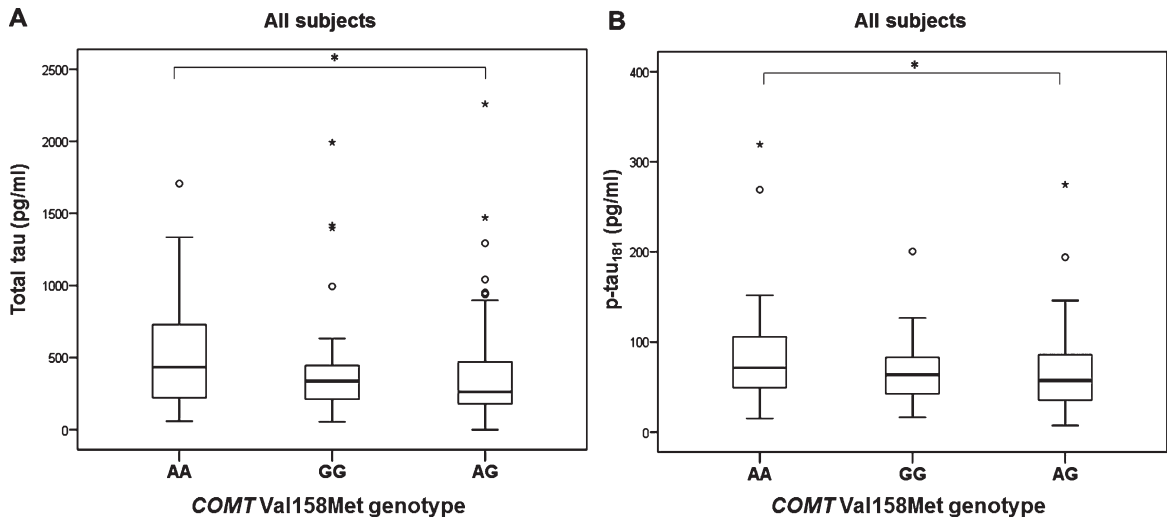


Fig. 1. Levels of A) *t*-tau and B) *p*-tau₁₈₁ in patients with different *COMT* Val158Met genotype. **p* < 0.05.

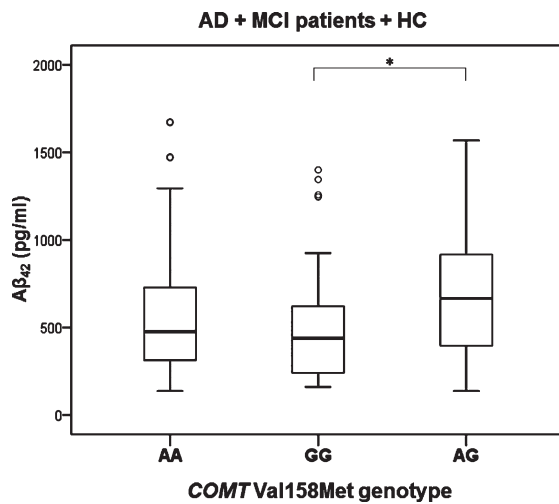


Fig. 2. Levels of Aβ₄₂ in AD, MCI patients and HC with different *COMT* Val158Met genotype. **p* < 0.05.

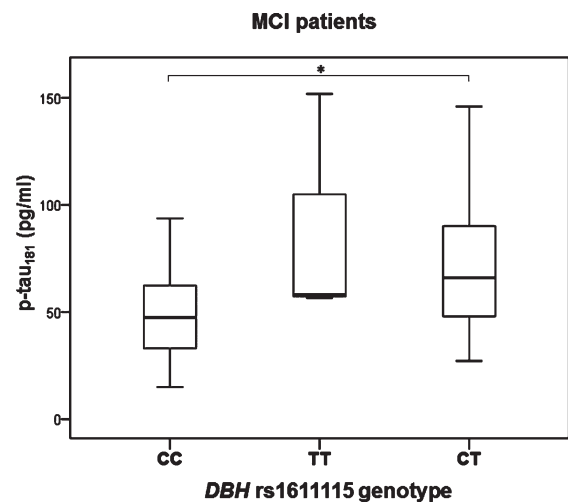


Fig. 3. Levels of *p*-tau₁₈₁ in MCI patients with different *DBH* rs1611115 genotype. **p* < 0.05.

DBH rs1611115

Significant difference in the levels of *p*-tau₁₈₁ was observed in MCI patients with different *DBH* rs1611115 genotype (H test = 8.377, *df* = 2, *p* = 0.015). Namely, *p*-tau₁₈₁ levels were significantly increased in patients with CT compared to CC *DBH* rs1611115 genotype (K-W *post hoc p* = 0.036) (Fig. 3). *P*-tau₁₈₁ levels were also significantly increased in MCI patients with TT and CT compared to CC *DBH* rs1611115 genotype (U = 146, Z = -2.857, *p* = 0.004) (Fig. 4).

MAO-B rs1799836

Aβ₄₂ levels were significantly decreased in MCI patients with AA and AG compared to GG *MAO-B* rs1799836 genotype (U = 206, Z = -2.047, *p* = 0.041) (Fig. 5). These results were confirmed when MCI patients and HC were grouped together (U = 313, Z = -1.980, *p* = 0.048) (Fig. 5).

DISCUSSION

In this study we showed that *COMT* Val158Met, *DBH* rs1611115, and *MAOB* rs1799836

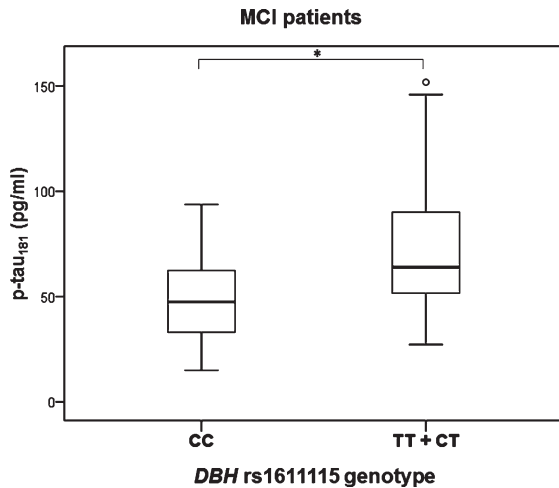


Fig. 4. Levels of $p\text{-tau}_{181}$ in MCI patients with different *DBH* rs161115 genotype. Subjects with TT and CT genotypes are grouped together. $*p < 0.05$.

polymorphisms deserve further investigation as genetic markers of AD. Future research in this direction is also motivated by the occurrence of significant neuropathological alterations of noradrenergic and dopaminergic systems in AD [2, 23–26]. For example, up to 70% of locus coeruleus (LC) neurons are lost in AD brains [27–29]. A postmortem analysis of 118 brains showed that >20% of Braak stage 0 and all of Braak stage I cases have substantial neurofibrillary changes in dorsal raphe nucleus (the earliest site of neurofibrillary pathology in 6% of all AD cases) and LC (the earliest site of neurofibrillary pathology in 8% of

all AD cases) [30]. These findings are paralleled by clinicopathological correlations. For example, in a retrospective review of 100 autopsy-confirmed AD cases, it was found that, on average, depression, mood change, social withdrawal, confusion, disorientation, agitation, disturbed wake-sleep cycle, and other behavioral and psychological symptoms of dementia (BPSD) were documented more than 2 years before the diagnosis of AD, whereas the first non-cognitive symptom appeared, on average, 33 months before the diagnosis [31]. Another study of 235 patients with early probable AD reported that only 8.5% of them were free of BPSD during the first three years of follow-up [32]. Perhaps the most impressive confirmation of the importance of the LC integrity to memory and cognition in aging was a recent *in vivo* study of Dahl and collaborators [33]. Using high-resolution, neuromelanin-sensitive magnetic resonance imaging (MRI), these authors found that individual differences across a variety of memory tasks in both 66 younger and 228 older adults strongly correlated with integrity of rostral LC [33].

Experimental work has shown that LC input to hippocampal CA3 drives single-trial learning of a novel context [26]. However, besides its role in memory consolidation and synaptic plasticity, LC neurons modulate many other different processes, such as sleep-wake cycle, blood-brain barrier permeability, and neuronal metabolism, all functions that have been impaired in AD [34, 35]. Over the past 40 years Aston-Jones and colleagues have elucidated many of the roles of noradrenaline that regulate behavior

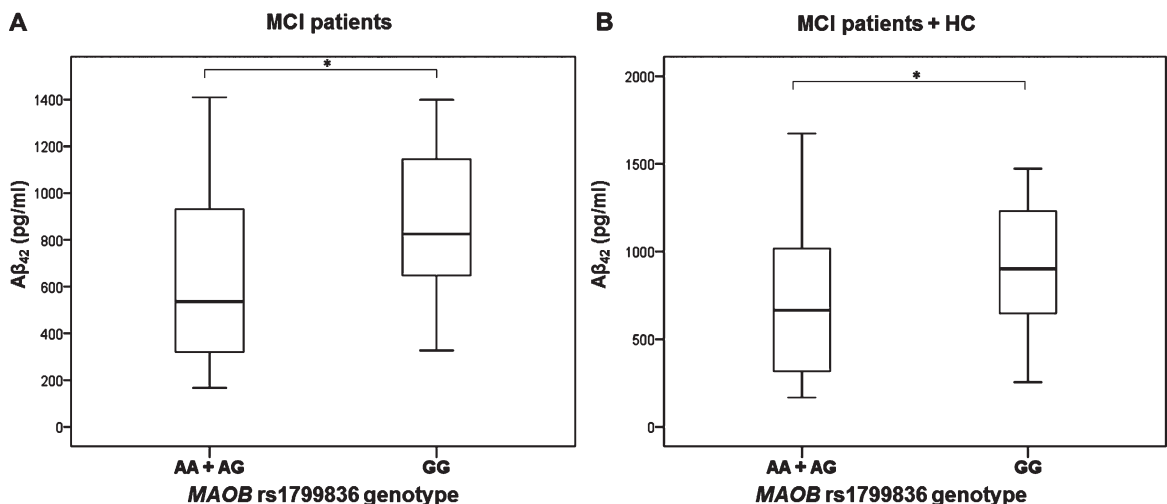


Fig. 5. Levels of $A\beta_{42}$ in A) MCI patients and B) MCI patients and HC with different *MAO-B* rs1799836 genotype. $*p < 0.05$.

(for a review, see [36]). One of these roles is that noradrenaline is released from LC when a subject is engaged in cognitive and motor tasks in relation to novelty, interest, excitement, or effort [24]. As noradrenaline regulates the phagocytosis of A β by microglia and acts as a neuroprotective and anti-inflammatory agent [37], it is not surprising that enhanced noradrenergic transmission in the brain results in reduced neuroinflammation and reduced cognitive decline [35]. It was also observed that enhancement of dopaminergic transmission ameliorates cognitive deficits in AD [38, 39]. Decrease in dopamine, dopamine metabolites, and number of dopamine receptors has been reported in AD [40, 41]. Animal models of AD also showed decrease in dopamine levels in the brain [42, 43]. Also, polymorphisms in genes for the dopaminergic system proteins are associated with characteristic BPSD in early AD [44, 45].

In this study, we compared the levels of six AD CSF biomarkers (A β ₄₂, *t*-tau, *p*-tau₁₈₁, *p*-tau₁₉₉, *p*-tau₂₃₁, and VILIP-1) in patients with different *COMT* Val158Met (rs4680), *DBH* rs1611115 (also called -1021C/T or -970C/T), and *MAOB* rs1799836 (also called A644G) polymorphisms. We observed that the levels of *t*-tau and *p*-tau₁₈₁ are increased in patients with AA compared to AG *COMT* Val158Met genotype, while A β ₄₂ levels are decreased in patients with GG compared to AG *COMT* Val158Met genotype. *P*-tau₁₈₁ levels are also increased in carriers of T allele in *DBH* rs1611115 polymorphism, while A β ₄₂ levels are decreased in carriers of A allele in *MAOB* rs1799836 polymorphism.

As *COMT* is involved in degradation of dopamine, functional polymorphisms in its gene can lead to different transcription and translation products that can affect its enzymatic activity and consequently dopamine levels in the brain. Val158Met polymorphism in *COMT* gene involves substitution at codon 158 of amino acid Val by Met [46]. Met/Met homozygotes have four times lower *COMT* enzymatic activity than Val/Val homozygotes. Val allele (G allele) in *COMT* gene that results in lower dopamine levels in synaptic cleft was associated with increased risk for AD [47]. *COMT* Val158Met polymorphism was compared with genetic biomarkers of AD, such as apolipoprotein E (*APOE*) [48–51], and with neuroimaging biomarkers of AD [52–54]. However, the association of *COMT* Val158Met polymorphism with CSF AD biomarkers was not previously tested, and case-control studies on association of *COMT* Val158Met polymorphism and AD yielded incon-

sistent results. The G allele in *COMT* Val158Met polymorphism was associated with increased risk for AD (mostly in synergy with the effect of *APOE* ϵ 4) [48, 49, 54–56], risk of psychosis in AD [45, 57, 58], and higher alcohol consumption in AD [52]. Several studies showed no association between *COMT* Val158Met polymorphism and AD [59–62], while others showed that *COMT* Val158Met A allele is, in fact, associated with AD [63, 64, 7]. The meta-analysis of Lee and Song [47] showed association between G allele in *COMT* Val158Met polymorphism and AD, while other meta-analyses [6, 65, 66] found no association between *COMT* Val158Met polymorphism and AD. The results of our study suggest that heterozygosity in *COMT* Val158Met polymorphism could be protective against AD as the patients with the AA genotype had pathological levels of CSF *t*-tau and *p*-tau₁₈₁, while patients with the GG genotype had pathological levels of A β ₄₂.

The presence of a T allele in the rs1611115 *DBH* polymorphism contributes to a decrease in plasma DBH (pDBH) activity [67]. Decrease in DBH activity has been detected in both brain [68, 69] and plasma [70] of AD patients. Given that pDBH activity decreases in early AD regardless of rs1611115 *DBH* genotype [70], AD patients carrying a T allele in rs1611115 *DBH* polymorphism may have even more pronounced decrease in DBH activity and consequently in noradrenaline synthesis. Combarros et al. [71] and Belbin et al. [72] reported an association between T allele in rs1611115 *DBH* polymorphism and AD. However, this association of rs1611115 *DBH* polymorphism and AD has not been confirmed in other studies [70, 73–75], although Mateo et al. [73] showed that T/T rs1611115 *DBH* genotype, in addition to the risk genotypes in -889 *IL-1 α* and -174 *IL6* polymorphisms, increases the risk of AD. Synergy between *DBH* rs1611115 and *BDNF* rs6265 polymorphisms was also observed, and this synergistic interaction contributed to a greater risk for AD [72]. The meta-analysis of Tang et al. [76] showed no association between rs1611115 *DBH* polymorphism and AD. The association of rs1611115 *DBH* polymorphism with CSF AD biomarkers was not previously tested. The results of our study agree with evidence of increased risk of AD in carriers of the T allele in rs1611115 *DBH* polymorphism and are supported by the finding of pathological CSF *p*-tau₁₈₁ levels in patients carrying this allele.

It has been proposed that *MAOB* rs1799836 polymorphism affects *MAOB* transcription and translation, enzyme's activity and consequently

concentration of monoamines in synapses [77]. However, studies investigating influence of *MAOB* rs1799836 polymorphism on MAOB activity yielded conflicting results. Namely, both A allele [78] and G allele [79] in *MAOB* rs1799836 polymorphism were associated with lower MAOB activity. Lower MAOB activity was associated with poor impulse control, risky behavior, and behavioral disinhibition [80]. However, other studies [81–83] and a meta-analysis [4] found no association between *MAOB* rs1799836 polymorphism and MAOB activity. Because MAOB activity is influenced by smoking, aging, gender, ethnicity, and various medicaments [81–88], it was proposed [89] that MAOB could be a molecular link between lifestyle and AD pathogenesis. As environmental and lifestyle factors may influence epigenetic mechanisms [90], lifestyle factors could affect *MAOB* expression epigenetically through one-carbon metabolism that causes reduced methylation of its promoter [91]. Although there are many indices of increased MAOB activity in AD [92–95], the distribution of *MAOB* rs1799836 genotypes in AD patients and controls had not been analyzed. Veitinger et al. [89, 96] reported that platelet MAOB could even represent a peripheral biomarker of AD with high sensitivity and specificity. The present results and existing evidence indicate that additional investigations should consider more closely the distribution of *MAOB* rs1799836 genotypes between AD patients and HC, as well as the association of *MAOB* rs1799836 polymorphism with neuroimaging AD biomarkers and *APOE* genotype.

In conclusion, our study shows that carriers of different genotypes in *COMT* Val158Met (rs4680), *DBH* rs1611115 (–1021C/T or –970C/T), and *MAOB* rs1799836 (A644G) polymorphisms have altered levels of CSF AD biomarkers. As persons with specific genotypes in *COMT*, *DBH*, and *MAOB* genes are more prone to develop AD pathology (as reflected by their levels of CSF AD biomarkers), the potential of these polymorphisms as genetic biomarkers of AD is significant and should be further assessed in larger cohorts of AD patients and healthy controls.

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