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ORIGINAL ARTICLE

Association of the *MAOB* rs1799836 Single Nucleotide Polymorphism and *APOE* ε4 Allele in Alzheimer's Disease

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Abstract: Background: The dopaminergic system is functionally compromised in Alzheimer's disease (AD). The activity of monoamine oxidase B (MAOB), the enzyme involved in the degradation of dopamine, is increased during AD. Also, increased expression of MAOB occurs in the postmortem hippocampus and neocortex of patients with AD. The *MAOB* rs1799836 polymorphism modulates *MAOB* transcription, consequently influencing protein translation and MAOB activity. We recently showed that the cerebrospinal fluid levels of amyloid β_{1-42} are decreased in patients carrying the A allele in *MAOB* rs1799836 polymorphism. **Objective:** The present study compares *MAOB* rs1799836 polymorphism and *APOE*, the only confirmed genetic risk factor for sporadic AD. **Method:** We included 253 participants, 127 of whom had AD, 57 had mild cognitive impairment, 11 were healthy controls, and 58 suffered from other primary causes of dementia. *MAOB* and *APOE* polymorphisms were determined using TaqMan SNP Genotyping Assays. **Results:** We observed that the frequency of *APOE* ε4/ε4 homozygotes and *APOE* ε4 carriers is significantly increased among patients carrying the AA *MAOB* rs1799836 genotype. **Conclusions:** These results, together with the results of our previous study, indicate that the *MAOB* rs1799836 polymorphism is a potential genetic biomarker of AD.

Key words: Alzheimer's disease, MAOB, APOE, polymorphisms, genetic biomarkers, mild cognitive impairment

1. INTRODUCTION

The only confirmed genetic risk factor for sporadic Alzheimer's disease (AD) that comprises over 99% of all AD cases, is the apolipoprotein E gene (*APOE*) ε4 variant [1,2]. The APOE protein is mainly produced by astrocytes and is involved in transport of cholesterol to neurons [3]. Two single nucleotide polymorphisms (SNP) in the *APOE* gene that affect *APOE* transcription and translation result in three common APOE variants (APOE ε2, ε3 and ε4) [4]. While *APOE* ε2 variant is considered to have protective effect in AD [5], *APOE* ε4 heterozygotes have a 5-time increased risk, and *APOE* ε4 homozygotes a 20-time increased risk of developing AD [6]. Several other genes have been recently associated with the increased risk for development of sporadic AD, such as *ABCA7*, *BIN1*, *CD33*, *CD2AP*, *CLU*, *CR1*, *MS4A6A*, *MS4A4E*, *PICALM* [7–12], *PLD3* [13], *TREM2* [14] among others. However, the influence that these genes have on increasing the risk of AD is far less than that of the *APOE* gene.

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Monoamine oxidase B (MAOB) is the enzyme bound to the outer mitochondrial membrane responsible for the degradation of dopamine. MAOB activity is increased in AD [15–18], contributing to decreasing dopamine levels [19–21]. Moreover, it was proved that MAOB inhibitors increase dopamine levels in the brain (reviewed in [22]). Some polymorphisms within the *MAOB* gene can also affect MAOB activity. The *MAOB* rs1799836 SNP (A644G) modifies *MAOB* transcription and translation leading to altered activity [23]. In fact, we recently observed that cerebrospinal fluid (CSF) amyloid $\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}$) levels are decreased in patients carrying the A allele in *MAOB* rs1799836 polymorphism [24]. Here, we assess the potential association of this polymorphism with *APOE* genotype variants in AD.

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2. MATERIALS AND METHOD

2.1. Subjects

The study included a total of 253 subjects recruited at the University Hospital Center Zagreb, Croatia. The subjects presented with various types of dementia, including AD, mild cognitive impairment (MCI), vascular cognitive impairment/vascular dementia (VaD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), mixed dementia (AD+VaD), corticobasal syndrome (CBS), non-specific dementia (ND) and Parkinson's disease (PD). AD was diagnosed in 127 patients using the criteria of the National Institutes on Aging - Alzheimer's Association (NIA-AA) [25]. MCI was diagnosed in 57 patients using the criteria of Petersen *et al.* [26] and Albert *et al.* [27]. FTD was diagnosed in 25 patients using the criteria of Neary *et al.* [28], while VaD was diagnosed in 15 patients using the criteria of National Institute for Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINCDS-AIREN) [29] and the Hachinski Ischemic Score [30]. Additionally, 11 subjects were healthy controls (HC), 8 suffered from DLB, 3 from AD+VaD, 3 from PD, 1 from CBS, and 3 had ND (**Table 1**). All participants were neurologically examined. Complete blood tests including determination of vitamin B12 and folic acid (B9) levels, thyroid function, serology for Lyme's disease and syphilis were obtained for each patient. They were also tested neuropsychologically using the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog), Mini-Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA). Informed consent for participation was obtained from all patients and HC, and all procedures were 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) and done in accord with the Helsinki Declaration [31].

2.2. DNA analysis

Genomic DNA was extracted from peripheral blood using the salting-out method [32]. *MAOB* rs1799836 and *APOE* rs7412 and rs429358 (for *APOE* variants ε2, ε3, and ε4) SNPs were determined using primers and probes purchased from Applied Biosystems as TaqMan® SNP Genotyping Assays (C_8878790_10 for rs1799836, C_904973_10 for rs7412 and C_3084793_20 for rs429358)on an ABI Prism 7300 Real Time PCR System apparatus (Applied Biosystems). *APOE* ε2 variant is determined by both rs429358 and rs7412 T allele, the ε4 variant is determined by both rs429358 and rs7412 C allele, while ε3 variant is determined by rs429358 T allele and rs7412 C allele. All genotyping procedures were done by a researcher who was blind to all clinical data according to the procedures described by Applied Biosystems. Out of 253, 74 samples (29%) were genotyped again as a quality control for genotyping analyses.

2.3. Statistical analysis

The frequencies of *APOE* genotypes and alleles among subjects with different *MAOB* rs1799836 genotypes and alleles was analyzed using a χ^2-test. A correction for

pairwise comparisons was applied. Correction for sex was done using binary and multinominal logistic regression analysis. All statistical analyses were done using SPSS 19.0.1 (SPSS, Chicago, IL, USA) with the level of statistical significance set at $\alpha = 0.05$.

3. RESULTS

There was a significant increase in the frequency of *APOE* ε4/ε4 homozygotes among patients carrying the AA *MAOB* rs1799836 genotype in comparison to patients carrying other *MAOB* rs1799836 genotypes [in the group of AD patients (χ^2=12.815; df=4; p=0.012), in the group of AD and MCI patients and HC (χ^2=14.081; df=4; p=0.007), and in the group of all subjects (χ^2=16.316; df=4; p=0.003)] (**Figure 1**) or G allele [in the group of AD and MCI patients (χ^2=11.509; df=2; p=0.003), in the group of AD and MCI patients and HC (χ^2=13.368; df=2; p=0.001), and in the group of all subjects (χ^2=15.541; df=2; p<0.001)] (**Figure 1**; **Figure 2**). Also, frequency of *APOE* εx/εx genotype (x = 2 or 3) (**Figure 1E-G**) and *APOE* ε3/ε3 genotype (**Figure 2**) is increased among carriers of G allele in *MAOB* rs1799836 polymorphism. There was significantly higher frequency of *APOE* ε4 carriers (ε4/ε4 + ε4/εx genotypes) among AA *MAOB* rs1799836 homozygotes [**Figures 3A-C**; in the group of AD and MCI patients (χ^2=8.076; df=2; p=0.018), in the group of AD and MCI patients and HC (χ^2=10.086; df=2; p=0.006), and in the group of all subjects (χ^2=9.828; df=2; p=0.007), **Figures 3D-G**; in the group of AD patients (χ^2=6.835; df=1; p=0.009), in the group of AD and MCI patients (χ^2=7.999; df=1; p=0.005), in the group of AD and MCI patients and HC (χ^2=9.849; df=1; p=0.002), and in the group of all subjects (χ^2=9.551; df=1; p=0.002)]. Also, significantly higher frequency of *APOE* ε4 non-carriers was observed among carriers of G allele in *MAOB* rs1799836 polymorphism (**Figures 3D-G)**.

Since *MAOB* gene is located on X chromosome, it is not surprising that we observed statistically significant difference in distribution of *MAOB* rs1799836 genotypes between males and females (χ^2=69.974; df=2; p<0.001). Thus, we tested distribution of *MAOB* rs1799836 genotypes between patients with different *APOE* genotypes but with *MAOB* rs1799836 genotypes being adjusted for sex (**Table 2**). Logistic regression model revealed that AA *MAOB* rs1799836 genotype had significant association with *APOE* ε4 allele (p=0.002) (**Table 2**), *APOE* ε4/ε4 (p=0.022) and *APOE* ε4/εx genotype (p=0.015) even when adjusted for sex (**Table 3**). No significant association between sex and *APOE* genotype was detected (p=0.781) (**Table 2**).

We also tested if *MAOB* and *APOE* polymorphisms are good predictors of AD using logistic regression. Neither *MAOB* nor *APOE* were proved as good predictors of AD (**Supplementary table 1**). However, possible cause for these results is because we included only 11 HCs in this study. Thus, these results should be verified on the bigger cohort.

4. DISCUSSION

The goal of this study was to test whether *MAOB* rs1799836 polymorphism is associated with *APOE* genotype. This polymorphism affects *MAOB* transcription and consequently influences the amount of the produced protein [23]. We showed that the frequency of *APOE* ε4/ε4 homozygotes and *APOE* ε4 carriers was significantly increased among patients carrying AA *MAOB* rs1799836 genotype.

The dopaminergic system is affected in AD and in animal models of AD [33–36]. The degeneration of main dopaminergic nuclei, the ventral tegmental area (VTA) [37] and the substantia nigra pars compacta [38] has also been observed in animal models of AD. Altered connectivity between the VTA and other brain regions implicated in AD pathology have been observed [39], further supporting dopaminergic system dysregulation in AD. It was even suggested that VTA volume could represent early neuroimaging biomarker of neurodegeneration [40,41]. Krashia et al. suggested that dopaminergic neurons in VTA could be more prone to cell death than other neuronal cells since they have long unmyelinated axons that innervate cortex and also since due to their autonomous pacemaker activity [self-generated activity that maintains dopamine levels in the brain [42]] they require high levels of energy and efficient mitochondrial function [36]. Levels of dopamine, dopamine metabolites, activity of dopamine β-

hydroxylase (DBH), expression and availability of dopamine receptors are decreased in AD [19–21,43–47]. Additionally, polymorphisms in genes encoding proteins and enzymes of the dopaminergic system are associated with behavioral and psychological symptoms of dementia observed in early AD [48,49].

Increased activity of MAOB has been reported in AD [15–18]. MAOB activity is influenced by various medications, smoking, ethnicity, gender, and ageing [50–57]. Thus, it was suggested that MAOB represents a molecular link between AD pathogenesis and lifestyle [58]. It was proposed that MAOB might serve as peripheral biomarker of AD in view of high levels of sensitivity and specificity in differentiating AD patients and HC [58,59]. Also, neuroimaging study of Rodriguez-Vieitez et al. showed potential of MAOB as an early biomarker of AD since binding of MAOB ligand (11C-deuterium-l-deprenyl) was increased in presymptomatic early-onset familial AD cases [60]. MAOB expression is increased in the neocortex and hippocampus in postmortem AD brains [61–63]. An increase in MAOB expression was detected in reactive astrocytes around amyloid plaques [64]. Such increases in expression or activity result in higher production of H_2O_2 — a by-product of MAOB activity -— and of reactive oxygen species-induced oxidative stress [65]. Increased MAOB activity also contributes to mitochondrial dysfunction in AD [66]. Additionally, Schedin-Weiss et al. showed that MAOB is ɣ-secretase associated protein that can regulate levels of $A\beta_{1\text{-}42}$. They proved that MAOB silencing by siRNA reduces intraneuronal $A\beta_{1\text{-}42}$ levels, while MAOB overexpression leads to increase in $A\beta_{1\text{-}42}$ levels [18]. MAOB inhibitors were in fact tested as potential therapeutics in AD (selegiline, lazabemide, sembragiline) with purpose to reduce cognitive decline [67–69]. Additionally, several multi-target drugs have been designed to inhibit MAOB in AD. For example, ASS234 inhibits both monoamine oxidases (MAO-A/MAO-B) and cholinesterases [70] as do PF1901N [71], M30D [72] and ladostigil [73]. Since AD is product of various factors, such as age, genetic predisposition, lifestyle and environmental risk factors, it is not surprising that in addition to age and lifestyle factors that affect MAOB activity, some genetic factors could also change enzyme's activity. It was reported that *MAOB* rs1799836 polymorphism can affect *MAOB* transcription and translation. Thus, this polymorphism could affect enzyme's activity that could lead to altered concentration of dopamine in synapses [23]. However, conflicting results were obtained in the studies with both A [74] and G [75] allele in *MAOB* rs1799836 polymorphism being associated with increased MAOB activity. Possible cause of discrepancies between these studies is that Balciuniene et al. [74] measured MAOB activity in the brain, while Garpenstrand et al. [75] measured platelet MAOB activity. Additional two studies that measured platelet MAOB activity [76] and dopamine turnover in the brain [77] observed the association of A allele in *MAOB* rs1799836 polymorphism with increased MAOB activity. However, some studies failed to confirm the association of *MAOB* rs1799836 polymorphism and MAOB activity [53,56,57,78]. There is a little information in the literature on the interaction between APOE and MAOB. However, Veitinger et al. reached high levels of specificity and sensitivity in differentiating AD patients and HC when combining platelet MAOB activity and *APOE* ε4 allele [58]. Also, recent study of Quartey et al. showed that MAOB activity was increased in hippocampus and cortex of AD donors who carried *APOE* ε4 allele in comparison to *APOE* ε4 non-carriers. They also proved that *in vitro* overexpression of human APOE4 in C6 and in HT-22 cell cultures increases MAOB activity. Since MAOB activity was increased in C6 and in HT-22 cells without changes in MAOB protein levels, authors suggested that APOE4 might through post-translational mechanisms influence MAOB function [63]. Since the results of our study showed that the frequency of *APOE* ε4/ε4 homozygotes and *APOE* ε4 carriers was significantly increased among patients carrying AA *MAOB* rs1799836 genotype (and by taking into account conflicting results of previous studies on the influence of *MAOB* rs1799836 polymorphism on MAOB activity), it should be further validated in the cohort of AD patients if *MAOB* rs1799836 polymorphism affects MAOB activity.

CONCLUSION

The present study provides more support for *MAOB* rs1799836 polymorphism as a potential genetic biomarker of

AD. We previously reported an association of this polymorphism with $A\beta_{1-42}$ measured in CSF [24], and now we also showed its association with *APOE* ε4 genotype. By taking these studies into account, we suggest that patients carrying the AA *MAOB* rs1799836 genotype could have a higher risk for AD development. However, further longitudinal studies should test if MCI patients carrying AA *MAOB* rs1799836 genotype would actually develop AD. Also, further studies should investigate the distribution of *MAOB* rs1799836 genotypes between AD, MCI patients and HC and also the association of this polymorphism with neuroimaging biomarkers of AD. In conclusion, the present results together with our previous observations [24] indicate that the *MAOB* rs1799836 polymorphism could be an important genetic biomarker of AD.

LIST OF ABBREVIATIONS

Aβ, amyloid β protein; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; APOE, apolipoprotein E; CBS, corticobasal syndrome; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; HC, healthy control; HIS, Hachinski Ischemic Score; MAOB, monoamine oxidase B; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; ND, nonspecific dementia; NINCDS-AIREN, National Institute for Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences; PD, Parkinson's disease; SNP, single nucleotide polymorphisms; VaD, vascular dementia; VTA, ventral tegmental area.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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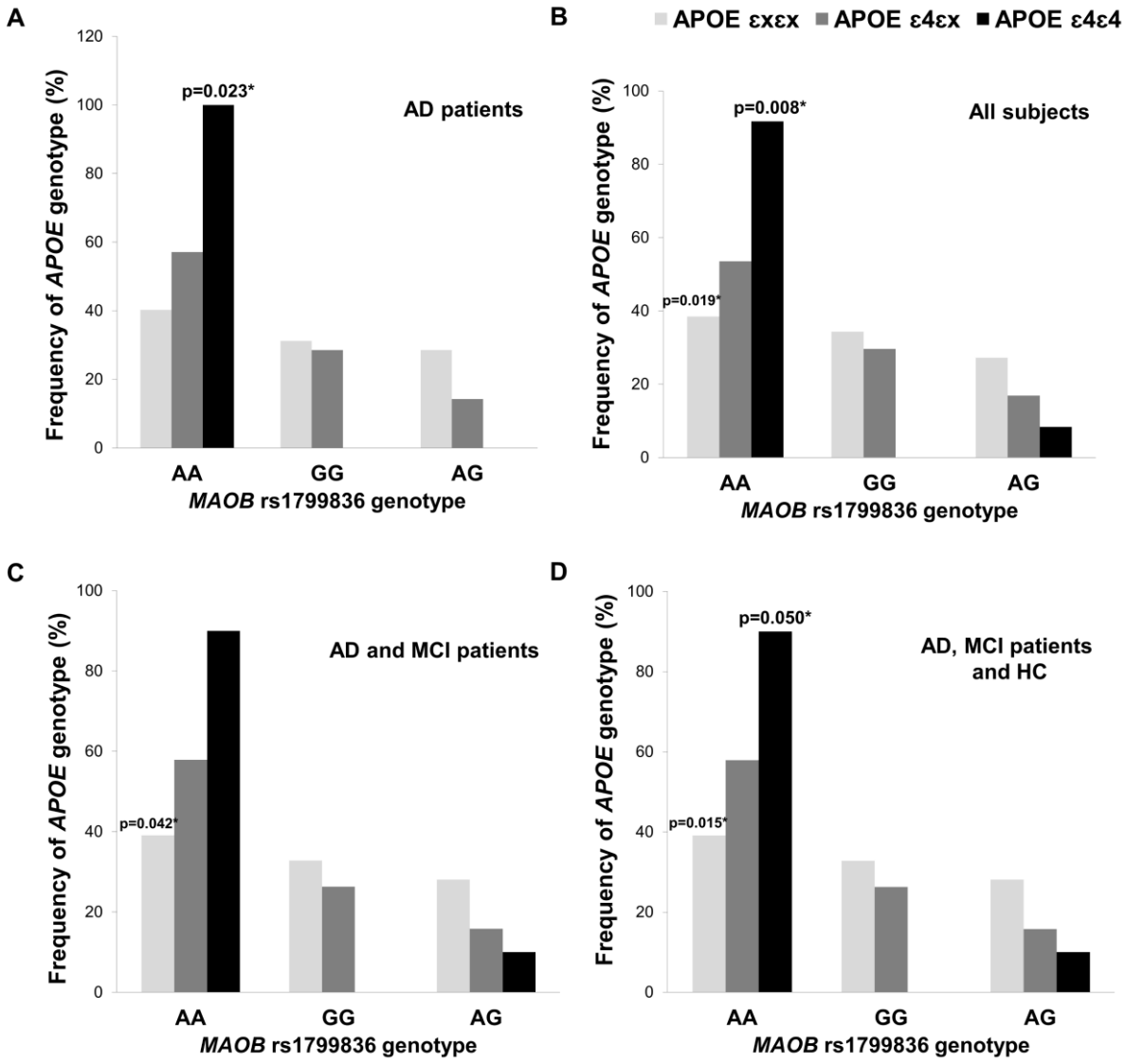
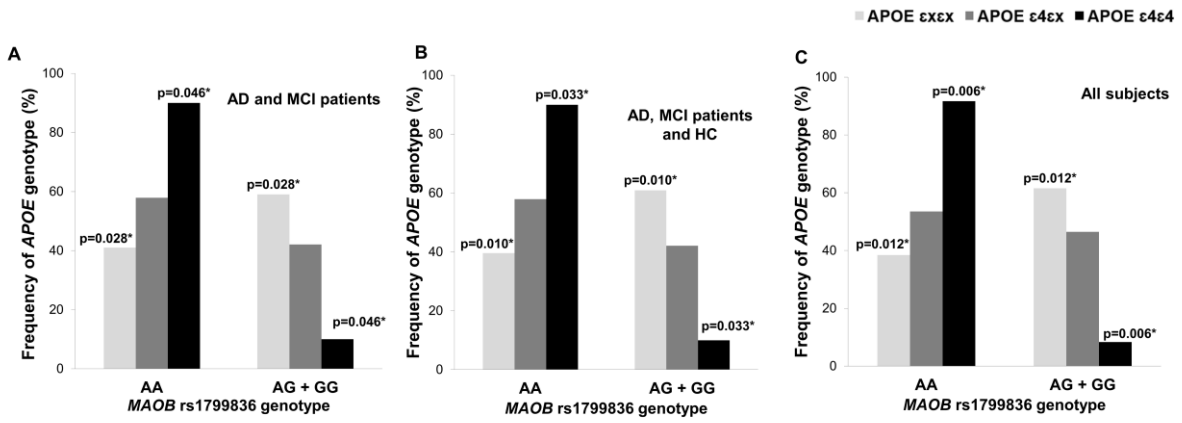
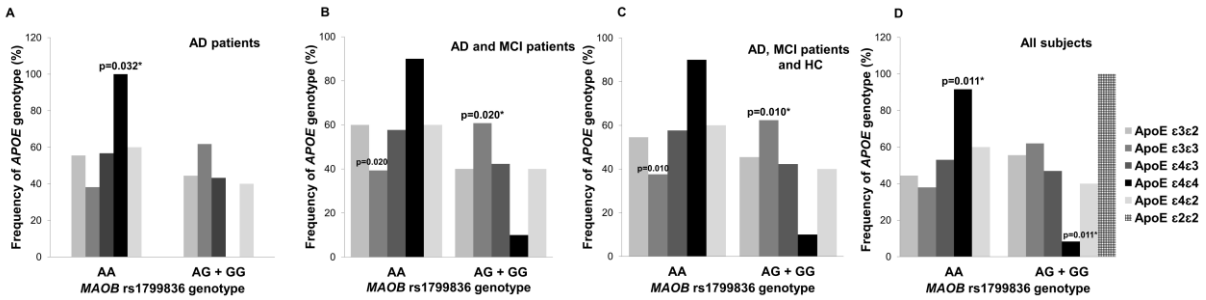

A
B
APOE εxεx
APOE ε4εx
APOE ε4ε4
Frequency of APOE genotype (%)
p=0.023*
AD patients
p=0.008*
All subjects
p=0.019*
AA
GG
AG
MAOB rs1799836 genotype
C
D
AD and MCI patients
p=0.042*
p=0.050*
AD, MCI patients and HC
p=0.015*


APOE εxεx
APOE ε4εx
APOE ε4ε4
A
B
C
Frequency of APOE genotype (%)
AD and MCI patients
AD, MCI patients and HC
All subjects
p=0.028*
p=0.046*
p=0.028*
p=0.046*
p=0.010*
p=0.033*
p=0.010*
p=0.033*
p=0.012*
p=0.006*
p=0.012*
p=0.006*
AA
AG + GG
MAOB rs1799836 genotype


A
AD patients
p=0.032*
Frequency of APOE genotype (%)
AA
AG + GG
MAOB rs1799836 genotype
B
AD and MCI patients
p=0.020*
p=0.020*
C
AD, MCI patients and HC
p=0.010*
p=0.010*
D
All subjects
p=0.011*
p=0.011*
ApoE ε3ε2
ApoE ε3ε3
ApoE ε4ε3
ApoE ε4ε4
ApoE ε4ε2
ApoE ε2ε2

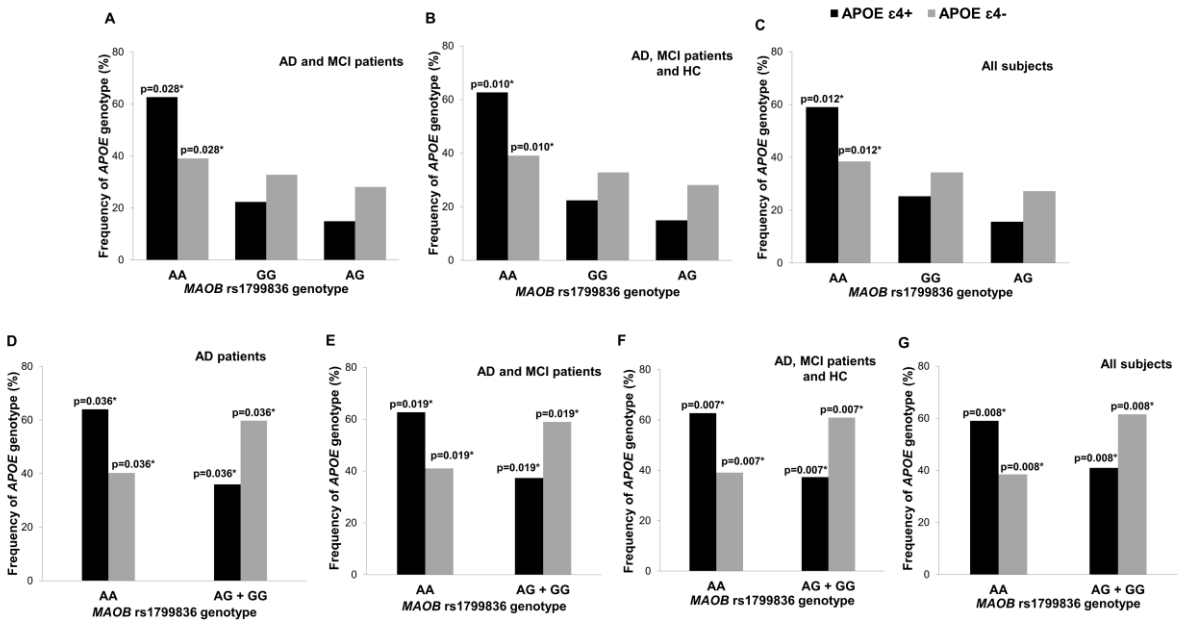

A
AD and MCI patients
B
AD, MCI patients and HC
C
APOE ε4+
APOE ε4-
All subjects
Frequency of APOE genotype (%)
p=0.028*
p=0.010*
p=0.012*
AA
GG
AG
MAOB rs1799836 genotype
D
AD patients
E
AD and MCI patients
F
AD, MCI patients and HC
G
All subjects
p=0.036*
p=0.019*
p=0.007*
p=0.008*
AG + GG

Table 1. Number of *MAOB* rs1799836 and *APOE* genotypes in AD and MCI patients, HC, and in patients with other causes of dementia.

	MAOB			*APOE*						Age	Sex	MMSE	Years of education
	AA	**AG**	**GG**	**ε3ε2**	**ε3ε3**	**ε4ε3**	**ε4ε4**	**ε4ε2**	**ε2ε2**	**Median (25–75th percentile)**	**F/M**	**Mean ± SD**	**Median (25–75th percentile)**
AD	63	28	36	9	68	37	8	5		73 (66-77)	68/59	19.9 ± 4.8	12 (8-14)
MCI	27	12	17	1	39	15	2			69 (58-74)	30/27	25.3 ± 3	12 (11-16)
HC	2	6	3	1	10					54 (45-61)	7/3	26.8 ± 2.5	12 (9-17)
VaD	7	5	3	2	8	4	1			72 (63-77)	6/7	23.1 ± 4.8	15 (9-16)
FTD	9	3	12	2	16	6	1			61 (56-66)	12/13	17.0 ± 5.7	12 (11-13)
DLB	3	2	3	1	5	2				71 (68-75)	3/5	20.4 ± 4.3	12 (4-16)
AD + VaD	2		1		2	1				78	0/3	19.3 ± 4.0	12
PD	1	1	1	1	1	1				65	1/2	15	8
CBS		1		1						51	1/0	24.0 ± 1.4	6
ND		1	2		2				1	68	2/1	20.7 ± 5.5	12

AD, Alzheimer's disease; AD + VaD, mixed dementia; APOE, apolipoprotein E; CBS, corticobasal syndrome; DLB, dementia with Lewy bodies; F, female; FTD, frontotemporal dementia; HC, healthy controls; M, male; MAOB, monoamine oxidase B; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; ND, nonspecific dementia; PD, Parkinson's disease; SD, standard deviation; VaD, vascular dementia.

Table 2. Binary logistic regression analysis using *MAOB* rs1799836 genotype and *MAOB* genotype adjusted for sex as predictors of *APOE* genotype (carriers of ε4 allele vs ε4 non-carriers).

	***APOE* ε4 allele**							
Predictor	χ2, df, p	N	B	SE	Wald	p	OR	95% CI
	Univariate model							
MAOB rs1799836 AA genotype	χ2=9.518, df=1, p=0.002	252	-0.835	0.274	9.329	**0.002***	0.434	0.254-0.741
Sex	χ2=0.078, df=1, p=0.781	250	-0.075	0.270	0.077	0.781	0.928	0.546-1.575
	Multivariate model							
MAOB rs1799836 AA genotype[a]	χ2=9.638, df=1, p=0.002	249	-0.846	0.275	9.453	**0.002***	0.429	0.250-0.736

[a]adjusted for sex. APOE, apolipoprotein E; MAOB, monoamine oxidase B. *p<0.05

Table 3. Multinominal logistic regression using *MAOB* rs1799836 genotype adjusted for sex as a predictor of *APOE* genotype (ε4/ε4, ε4/εx and εx/εx genotype [x = 2 or 3]).

Predictor	χ2, df, p	N	B	SE	Wald	p	OR	95% CI
	***APOE* ε4/ε4 genotype**							
MAOB rs1799836 AA genotype[a]	χ2=21.501, df=6, p=0.001	249	2.542	1.109	5.256	**0.022***	12.709	1.446-111.695
	***APOE* ε4/εx genotype**							
MAOB rs1799836 AA genotype[a]	χ2=21.501, df=6, p=0.001	249	1.056	0.432	5.961	**0.015***	2.874	1.231-6.707

[a]adjusted for sex. APOE, apolipoprotein E; MAOB, monoamine oxidase B. *p<0.05

Supplementary Table 1. Binary logistic regression analysis using *MAOB* rs1799836 genotype and *APOE* genotype as predictors of AD.

			Diagnosis – AD vs HC							
No.	Predictor		$\chi2$, df, p	N	B	SE	Wald	p	OR	95% CI
			Univariate models							
1.	*MAOB* rs1799836 genotype	AA	$\chi2$=6.041, df=2, p=0.049	138			5.403	0.067		
		GG			-1.910	0.847	5.077	0.024*	0.148	0.028-0.780
		AG			-0.944	0.751	1.583	0.208	0.389	0.089-1.694
2.	*MAOB* rs1799836 AA vs AG + GG genotype		$\chi2$=4.362, df=1, p=0.037	138	-1.488	0.802	3.447	0.063	0.226	0.047-1.086
3.	*APOE* genotype	εxεx	$\chi2$=10.433, df=2, p=0.005	138			0.000	1.000		
		ε4εx			19.257	14210.4	0.000	0.999	230782167	
		ε4ε4			0.000	15504.8	0.000	1.000	1.000	
4.	*APOE* genotype ε4+ vs ε4-		$\chi2$=10.433, df=1, p=0.001	138	-19.257	5684.14	0.000	0.997	0.000	
			Multivariate models							
1.	*MAOB* rs1799836 genotype	AA	$\chi2$=13.722, df=4, p=0.008	138			3.051	0.218		
		GG			-1.442	0.863	2.792	0.095	0.237	0.044-1.283
		AG			-0.780	0.766	1.037	0.309	0.458	0.102-2.058
	APOE genotype	εxεx					0.000	1.000		
		ε4εx			18.462	14210.37	0.000	0.999	104224200	
		ε4ε4			-0.510	15459.19	0.000	1.000	0.600	
2.	*MAOB* rs1799836 AA vs AG + GG genotype		$\chi2$=12.633, df=2, p=0.002	138	-1.109	0.816	1.851	0.174	0.330	0.067-1.631
	APOE genotype ε4+ vs ε4-				-18.976	5584.8	0.000	0.997	0.000	

AD, Alzheimer's disease; APOE, apolipoprotein E; HC, healthy controls; MAOB, monoamine oxidase B; No, number of models. *p<0.05