The association of *MAOB* and *APOE* single nucleotide polymorphisms in Alzheimer's disease

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INTRODUCTION

The normal functioning of dopaminergic system is compromised during Alzheimer's disease (AD). The activity of monoamine oxidase B (MAOB), enzyme involved in degradation of dopamine, is also disturbed in AD. It was observed that MAOB activity is increased during AD. Also, increased expression of MAOB was detected in hippocampus and cortex of people who suffered from AD. It was observed that *MAOB* rs1799836 polymorphism can affect *MAOB* transcription, consequently influencing also protein translation and MAOB activity. Our recent study showed that the levels of cerebrospinal fluid (CSF) amyloid $\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}$) were decreased in patients carrying A allele in *MAOB* rs1799836 polymorphism. The goal of this study was to compare *MAOB* rs1799836 polymorphism with *APOE*, the only confirmed genetic risk factor for sporadic AD.

MATERIALS AND METHODS

Study included 253 participants of whom 127 suffered from AD, 57 were mild cognitive impairment patients, 11 were healthy controls and 58 suffered from other primary causes of dementia. Genomic DNA was extracted from peripheral blood using the salting-out method. *MAOB* rs1799836 single nucleotide polymorphism (SNP) and *APOE* SNPs (rs7412 and rs429358) were determined using TaqMan SNP Genotyping Assays (Applied Biosystems, Foster City, CA, USA).

RESULTS

There was significant increase in the frequency of *APOE* ε4/ε4 homozygotes among patients carrying AA *MAOB* rs1799836 genotype in comparison to patients carrying other *MAOB* rs1799836 genotypes (**Figure 1**) or G allele carriers (**Figure 1**; **Figure 2**). Also, there was significantly higher frequency of *APOE* ε4 carriers (ε4/ε4 + ε4/εx genotypes) among AA *MAOB* rs1799836 homozygotes (**Figure 3**). Since *MAOB* gene is located on X chromosome, we analysed if distribution of *MAOB* rs1799836 genotypes between patients with different *APOE* genotypes but with *MAOB* rs1799836 genotypes being adjusted for sex (**Table 1**). Logistic regression model revealed that AA *MAOB* rs1799836 genotype had significant association with *APOE* ε4 allele, *APOE* ε4/ε4 and *APOE* ε4/εx genotype even when adjusted for sex (**Table 1**).

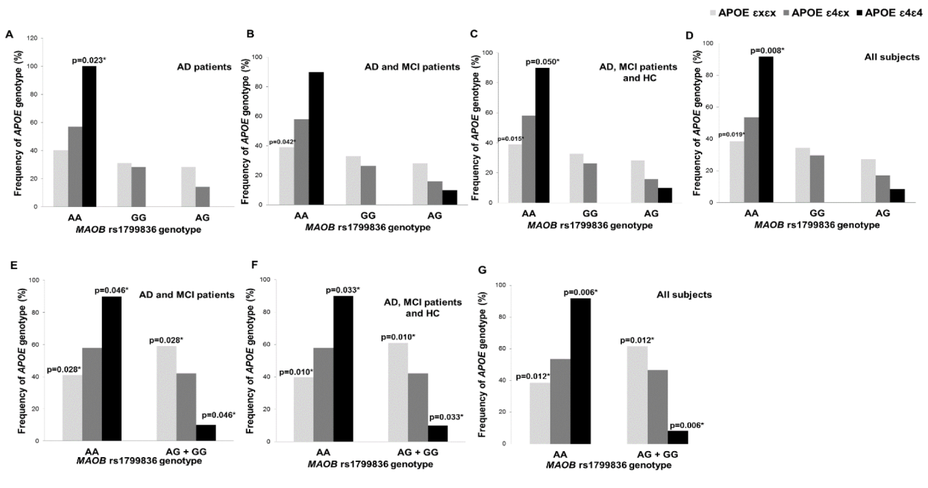

Figure 1. Frequencies of of *MAOB* rs1799836 genotypes (A-D) and *MAOB* rs1799836 alleles (AA vs G allele [AG + GG]) (E-G) in subjects with different *APOE* genotype (divided into three groups; *APOE* εxεx, *APOE* εxε4 and *APOE* ε4ε4, x = 2 or 3). A) χ^2=12.815; df=4; p=0.012, B) χ^2=14.081; df=4; p=0.007, C) χ^2=14.081; df=4; p=0.007, D) χ^2=11.509; df=2; p=0.003, E) χ^2=13.368; df=2; p=0.001, F) χ^2=15.541; df=2; p<0.001, G) χ^2=15.541; df=2; p<0.001.

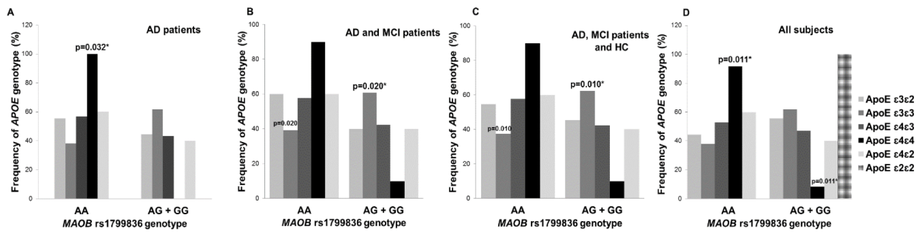

Figure 2. Frequencies of of *MAOB* rs1799836 alleles (AA vs G allele [AG + GG]) in A) AD patients (χ^2=12.744; df=4; p=0.013), B) AD and MCI patients (χ^2=13.094; df=4; p=0.011), C) AD, MCI patients and HC (χ^2=14.535; df=4; p=0.006) and D) all subjects (χ^2=16.502; df=5; p=0.006) with different *APOE* genotypes.

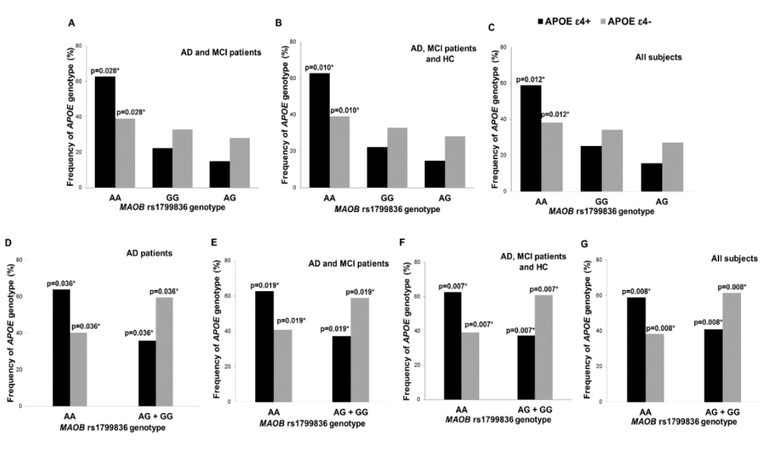

Figure 3. Frequencies of *MAOB* rs1799836 genotypes (A-C) and *MAOB* rs1799836 alleles (AA vs G allele [AG + GG]) (D-G) in subjects with different *APOE* genotype (divided into two groups; *APOE* ε4+ and *APOE* ε4-). A) χ^2=8.076; df=2; p=0.018, B) χ^2=10.086; df=2; p=0.006, C) χ^2=9.828; df=2; p=0.007, D) χ^2=6.835; df=1; p=0.009, E) χ^2=7.999; df=1; p=0.005, F χ^2=9.849; df=1; p=0.002, G) χ^2=9.551; df=1; p=0.002.

Table 1. Multinominal logistic regression analysis in the group of all subjects carrying *APOE* ε4/ε4 and *APOE* ε4/εx genotype in comparison to carriers of *APOE* 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

CONCLUSIONS

The present study sheds light on *MAOB* rs1799836 polymorphism as potential genetic biomarker of AD. We previously proved the association of this polymorphism with $A\beta_{1\text{-}42}$ measured in CSF (Babić Leko et al., J Alzheimers Dis, 2020), and now we also showed the association of *MAOB* rs1799836 polymorphism with *APOE* genotype. In conclusion, the results of this study together with our previous results indicate that the *MAOB* rs1799836 polymorphism could be strong genetic biomarker of AD.

ACKNOWLEDGEMENTS

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