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Letter to the Editor

Association study of the *ABCA7* rs3752246 polymorphism in Alzheimer's disease

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ABSTRACT

The ATP-binding cassette, sub-family A, member 7 (*ABCA7*) gene has been identified as a strong genetic risk locus for Alzheimer's disease (AD). Our case-control study (416 AD patients and 302 controls) provides further data on the rs3752246 polymorphism in AD in the Hungarian population that has not been investigated so far regarding the *ABCA7* gene variants. A modest, marginally significant association of the G allele containing genotypes with AD was observed ($p = 0.054$). In line with the previous results in other populations, the G allele carriers had an increased risk for developing AD considering C/C genotype as reference category.

1. Introduction

Alzheimer's disease (AD), the leading cause of dementia worldwide, is a multifactorial neurodegenerative disease with complex genetic background. So far the most prognostic genetic susceptibility factor for late-onset AD is the ε4 variant of the apolipoprotein E (*APOE*; MIM#107741; 19q13.32) gene.

Genome-wide association studies (GWAS) provided evidence for the association of the ATP-binding cassette (ABC) transporter family A member 7 (*ABCA7*; OMIM #605414; 19p13.3) gene variants with the risk for developing late-onset AD. The top findings include rs3764650, rs3752246 and rs115550680 which were confirmed in independent studies (Hollingworth et al., 2011; Naj et al., 2011; Reitz et al., 2013); additionally, susceptibility variant rs4147929 was identified in a large meta-analysis (Lambert et al., 2013).

ABCA7 gene encodes a multispan transmembrane protein that is expressed in the brain. Like ABCA1, whom with ABCA7 shares a high degree of sequence homology, it promotes efflux of phospholipids and cholesterol across cell membranes. Although *ABCA7* polymorphisms have been shown to confer elevated risk for AD, our knowledge on the impact of these polymorphisms on ABCA7 function and AD is limited.

ABCA7 rs3752246 within exon 33 is the only missense variant to be identified by GWASs: it results in a Glycine to Alanine mutation at position 1527 (G1527A) that may alter the function. The present study aimed to support the previous reports on associations between rs3752246 polymorphism and AD and to give further data in the Hungarian population that has not been investigated yet regarding the *ABCA7* gene variants. Taking into account the involvement of both *APOE* and *ABCA7* in cholesterol metabolism, we assumed a possible interaction effect as well.

2. Subjects and methods

A total of 716 participants of Hungarian Caucasian origin were enrolled in our case-control study including 416 AD patients (74.8 ± 6.7 years of age (mean ± SD), men 34.6%) and 302 cognitively healthy, elderly control individuals (74.2 ± 7.3 years of age (mean ± SD), men 36.0%).

The diagnoses of probable AD (minimum age at onset: 65 years) were established according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria. All recruitment and protocols were conducted with the approval of the Ethics Committee of the Hungarian Council on Science and Health. The Mini-Mental State Examination (MMSE) was applied to measure global cognitive performance: the mean MMSE score in the AD group was 17.5 ± 5.6 (mean ± SD), while in the control group MMSE scores were higher than 28 points and none of the control individuals had any verified symptoms of dementia.

The investigated polymorphisms were genotyped by applying commercial TaqMan single-nucleotide polymorphism assays (Thermo Fisher Scientific, Waltham, Massachusetts, USA). Categorical variables were analyzed by Fisher exact and Pearson $\chi 2$-tests, while continuous parameters were compared by *t* test for independent samples. Binary logistic regression model was used to test for interaction between the *ABCA7* and *APOE* polymorphisms (variables were defined on the basis of the presence or absence of the probable risk factors: *APOE* ε4 allele and *ABCA7* G allele), and to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Hardy-Weinberg equilibrium (HWE) were tested by Pearson chi-square test. Genotype frequencies in both cases and controls conformed to HWE.

Post-hoc power calculations were conducted using G*Power 3.0 software. Detecting differences in rs3752246 genotype frequencies between the two investigated groups, our study population has a power of 95.4% at the significance level of 0.05 based on the calculated effect size ($w = 0.149$).

3. Results

No significant differences were found between the AD cases and controls in mean age or in the male to female ratio. The *APOE* ε3/ε4 and ε4/ε4 genotypes occurred with statistically significantly higher frequency in the AD as compared to the control group (ε3/ε4: AD: 38.7%; C: 17.2%; ε4/ε4 AD: 7.2%, C: 0.3%; $\chi^2 = 73.890$ (5) $p < 0.001$). The ε4

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Table 1
Genotype frequencies of the *ABCA7* rs3752246 polymorphism.

Genotypes	AD patients	Controls	Genotypic model	Recessive model
rs3752246			0.141	0.054
C/C	236 (56.7%)	193 (63.9%)		
C/G	159 (38.2%)	98 (32.5%)		
G/G	21 (5.1%)	11 (3.6%)		

AD: Alzheimer's disease, *ABCA7:* ATP-binding cassette transporter subfamily A member 7.

allele carriers had a significantly increased risk for AD (OR: 3.980; 95% CI: 2.814–5.628; $p < 0.001$).

Genotype distributions of the investigated *ABCA7* polymorphism are summarized in Table 1. The rs3752246 C/G and G/G genotypes occurred with higher frequency in the AD group (C/G: AD: 38.2%, C: 32.5%; G/G: 5.1%, C: 3.6%), while the C/C genotype was more prevalent among the controls (AD: 56.7%, C: 63.9%); however, the difference did not reach statistical significance ($\chi 2 = 3.912$ (2) $p = 0.141$).

Based on the observed genotype frequencies and tendencies, a recessive model was also applied and a clear tendency to significance was found; however, the p value was slightly above 0.05 (Fisher exact test: $p = 0.054$). Carriers of the rs3752246 G allele had an increased risk for developing AD considering C/C genotype as reference category (OR = 1.350; 95% CI = 0.996–1.831; $p = 0.053$). The logistic regression analysis did not show a significant interaction effect for the combinations of the *APOE ε4* allele and the *ABCA7* G allele on the risk for AD ($p = 0.890$).

4. Discussion

Association between *ABCA7* rs3752246 polymorphism and the risk for developing AD was examined in a well-characterized Hungarian sample. Minor allele frequency of the rs3752246 polymorphism may vary in different ethnicities. The observed minor allele frequency in our control sample is comparable to earlier reports on other populations of European origin (Cuyvers et al., 2015). The detected effects of the rs3752246 polymorphism on the risk for developing AD also differed through ethnicities, being more modest in the European ancestry populations (1.1–1.3-fold) as opposed to the reported risk in the African ancestry populations (1.8-fold) (Lambert et al., 2013; Reitz et al., 2013). Our results in the Hungarian population of European origin is in line with these findings.

A modest, marginally significant effect of the *ABCA7* rs3752246 minor G allele on AD risk was observed. We cannot conclude a clear strong association of the *ABCA7* rs3752246 polymorphism with AD from our data set; however, since our results showed a trend very close to significance and our OR is in the same direction as in the previous findings, we cannot conclude a negative result either. Our findings should be considered in light of some limitations due to our medium sample size. Notwithstanding, we provided data in an independent sample of a so far not investigated ethnics, which could strengthen the earlier results and could contribute to a later meta-analysis.

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Conflict of interest

The authors have no conflict of interest to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.01.081.

References

Cuyvers, E., De Roeck, A., Van den Bossche, T., Van Cauwenberghe, C., Bettens, K., Vermeulen, S., Mattheijssens, M., Peeters, K., Engelborghs, S., Vandenbulcke, M., Vandenberghe, R., De Deyn, P.P., Van Broeckhoven, C., Sleegers, K, 2015. Mutations in ABCA7 in a Belgian cohort of Alzheimer's disease patients: A targeted resequencing study. Lancet Neurol. 14, 814–822.

Hollingworth, P., Harold, D., Sims, R., Gerrish, A., Lambert, J.C., Carrasquillo, M.M., Abraham, R., Hamshere, M.L., Pahwa, J.S., Moskvina, V., Dowzell, K., Jones, N., Stretton, A., Thomas, C., Richards, A., et al., 2011. Common variants at *ABCA7, MS4A6A/MS4A4E, EPHA1, CD33* and *CD2AP* are associated with Alzheimer's disease. Nat. Genet. 43, 429–435.

Lambert, J.C., Ibrahim-Verbaas, C.A., Harold, D., Naj, A.C., Sims, R., Bellenguez, C., DeStafano, A.L., Bis, J.C., Beecham, G.W., Grenier-Boley, B., Russo, G., Thorton-Wells, T.A., Jones, N., Smith, A.V., Chouraki, V., et al., 2013. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat. Genet. 45, 1452–1458.

Naj, A.C., Jun, G., Beecham, G.W., Wang, L.S., Vardarajan, B.N., Buros, J., Gallins, P.J., Buxbaum, J.D., Jarvik, G.P., Crane, P.K., Larson, E.B., Bird, T.D., Boeve, B.F., Graff-Radford, N.R., De Jager, P.L., et al., 2011. Common variants at MS4A4/ MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat. Genet. 43, 436–441.

Reitz, C., Jun, G., Naj, A., Rajbhandary, R., Vardarajan, B.N., Wang, L.S., Valladares, O., Lin, C.F., Larson, E.B., Graff-Radford, N.R., Evans, D., De Jager, P.L., Crane, P.K., Buxbaum, J.D., Murrell, J.R., Raj, T., Ertekin-Taner, N., Logue, M., Baldwin, C.T., Green, R.C., Barnes, L.L., Cantwell, L.B., Fallin, M.D., Go, R.C., Griffith, P., Obisesan, T.O., Manly, J.J., Lunetta, K.L., Kamboh, M.I., Lopez, O.L., Bennett, D.A., Hendrie, H., Hall, K.S., Goate, A.M., Byrd, G.S., Kukull, W.A., Foroud, T.M., Haines, J.L., Farrer, L.A., Pericak-Vance, M.A., Schellenberg, G.D., Mayeux, R., Alzheimer Disease Genetics Consortium., 2013. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E ε4,and the risk of late-onset Alzheimer disease in African Americans. JAMA 309, 1483–1492.

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