Alzheimer’s disease risk and polymorphisms of the DHCR24 gene
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BACKGROUND

The presence of extracellular senile plaques composed of amyloid-β (Aβ) peptid is the major pathologic characteristic of Alzheimer’s disease (AD). The amount of cell cholesterol has a major impact on Aβ generation and cell resistance against Aβ toxicity. The 24-dehydrocholesterol reductase (DHCR24) gene at locus 1p33-p31.1 encodes Seladin1 (Selective AD Indicator) that catalyses the conversion of desmosterol to cholesterol. Seladin1 also has other relevant biological effects: it confers resistance against Aβ and oxidative stress induced apoptosis and affects the Aβ generation via the modulation of membrane cholesterol content.

We tested the hypothesis that the rs638944 (G/T nucleotide change in intron 2) and the rs600491 (C/T nucleotide change in intron 5) polymorphisms of the DHCR24 gene influence the risk for developing AD.

DHCR24: 24-dehydrocholesterol reductase gene encodes Seladin1 (Selective AD Indicator) catalyses the conversion of desmosterol to cholesterol
rs638944: G/T nucleotide change in intron 2
rs600491: C/T nucleotide change in intron 5

RESULTS

A total of 440 Hungarian Caucasian subjects were enrolled in this study. (Table 1.) The diagnosis of the 236 AD patients fulfilled the criteria for NINCDS-ADRDA. As a healthy control (HC) group we studied 204 elderly, cognitively intact, healthy individuals. MMSE was used as a measure of global cognitive performance. Genomic DNA was extracted from peripheral blood leukocytes. The genotypes of the rs638944 polymorphism were determined by PCR amplification with allele specific primers. Genotyping of the rs600491 polymorphism was assessed by PCR amplification and enzymatic digestion with restriction enzyme AoI.

Fisher’s exact and Pearson’s χ2 tests were used to compare gender, Hardy-Weinberg equilibrium (HWE), allele and genotype frequencies between the AD and HC groups. The mean age of the AD and HC groups was compared by using the t-test for independent samples. Analysis of variance was carried out to determine possible effect of the different genotypes on age at onset of AD.

236 patients with AD: clinical diagnosis (NINCDS-ADRDA)
204 elderly, cognitively intact healthy control individuals

Table 1. Characteristics of the probands

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<th>AD (n=236)</th>
<th>HC (n=204)</th>
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<tr>
<td>Age (mean years ± SD)</td>
<td>75.6 ± 7.4</td>
<td>71.2 ± 6.9</td>
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<td>Male/female (%)</td>
<td>32/68</td>
<td>31/69</td>
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<td>MMSE (mean scores ± SD)</td>
<td>17.4 ± 5.9</td>
<td>29.1 ± 0.9</td>
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<tr>
<td>APOE*4 allele carriers (%)</td>
<td>46.4</td>
<td>13.8</td>
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AD: Alzheimer’s disease
HC: healthy control
MMSE: Mini Mental State Exam
APOE*4 allele: apolipoprotein E4 allele

Men with the T/T genotype had a significantly increased risk for AD (OR=4.37; p=0.009) as compared to those men carrying the C/C genotype. (Figure 4.)

CONCLUSION

We failed to support the hypothesis that DHCR24 rs638944 polymorphism influences the predisposition to AD.

Our results indicate a gender dependent effect of the DHCR24 rs600491 polymorphism on the susceptibility to AD, since a statistically significant association was found between the T/T genotype and the risk for AD in men, but nor in women or in the whole population.

This work was supported by grants from Hungarian Scientific Research Fund 60589/2006 and Hungarian Ministry of Health 052-07/2009.