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ORIGINAL PAPER

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Lack of association between schizophrenia and the apolipoprotein E ε4 allele

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Abstract The association between the ε4 allele of the apolipoprotein E (APOE) gene and Alzheimer's disease (AD) has been reported. In order to examine if the ε4 allele may play a role also in schizophrenia, another mental disorder, patients (n = 87) and control subjects (n = 57) were genotyped for APOE. No significant difference was found between the groups. The data indicate that the APOE gene is not of major importance for the genesis of schizophrenia.

Key words Schizophrenia · Apolipoprotein E · Association study · Psychiatric genetics · Alzheimer's disease

Introduction

Family, twin and adoption studies suggest that genetic factors play a role in the aetiology of schizophrenia (Kendler and Diehl 1993). Apolipoprotein E (apoE) is a lipid-transport-associated protein with three common isoforms designated E2, E3 and E4. They differ by one or two amino acids, and are products of three alleles, ε2, ε3 and ε4. ApoE is produced by astrocytes and probably plays an important role in nerve cell injury and regeneration (Boyles et al. 1985). The APOE gene is located on chromosome 19q13.2. Allelic associations have been demonstrated between the APOE ε4 allele and both familial and sporadic late-onset Alzheimer's disease (AD) and Creutzfeld-Jacob disease (Poirer et al. 1993; Saunders et al. 1993; Strittmatter et al. 1993; Amouyel et al. 1994; Lannfelt et al. 1994; Liu et al. 1995). Subjects heterozygous for the ε4 allele have three to four times higher risk for AD and homozygotes eight times higher risk (Corder et al. 1993). However, the mechanisms by which the apoE E4 protein increases the risk for AD is not understood, but a recent report demonstrates that apoE and the amyloid precursor protein are internalised by the same receptor (Kounnas et al. 1995). In a subpopulation of schizophrenic patients the clinical course has similarities to neurodegenerative disorders, and Kraepelin (1919) suggested the term dementia praecox. The prevalence of neuropathological changes consistent with AD was found to be considerably higher in schizophrenic patients than in the general population in an analysis of 544 autopsied schizophrenic subjects (Prohovnik et al. 1993). In a few studies neuropathological, cerebrospinal and immunological findings have suggested similarities between schizophrenia and Alzheimer's disease (Aksenova et al. 1991; Shinitzky et al. 1991; Johnson et al. 1992). However, most recent neuropathological and neuropsychological studies have not detected similarities, but instead differences suggesting alternative mechanisms underlying the dementia in elderly schizophrenic patients and AD cases (El-Mallakh et al. 1991; Casanova et al. 1993; Purohit et al. 1993; Arnold et al. 1994; Gabriel et al. 1994; Haroutunian et al. 1994; Heaton et al. 1994; Sarter 1994; Goldsmith and Joyce 1995; for review see Harrison 1995). In order to examine if the ε4 allele may play a role in schizophrenia we have genotyped Swedish schizophrenic patients and control subjects for APOE.

Subjects and methods

All subjects were unrelated Caucasian individuals living in Stockholm. They were assessed for psychiatric morbidity (DSM-III-R), family history of psychosis in first-, or second-degree relatives and geographical origin as previously described (Jönsson et al. 1993). The patients (n = 87) were also evaluated regarding age at first hospitalisation, abuse of alcohol, solvents or drugs, previous suicide attempts, response to neuroleptic drug treatment, extrapyramidal side effects (EPS) and treatment with anticholinergic drugs. All patients (56 men and 31 women) fulfilled a DSM-III-R diagnosis of schizophrenia. Their age range was 20–90 years (mean 46.8 years). They had their first hospitalisation at the age of 15–56 (mean 25.9 years). Genealogical reports indicated that 78.7 and

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14.9% of the genes were of Swedish and Finnish origin, respectively, whereas the remaining 6.3% were distributed throughout ten European countries. The control subjects (34 men and 23 women) were free from current or previous psychiatric morbidity. The age range was 29–55 years (mean age 38.6 years). Genealogical data indicated that 88.8% of the genes were of Swedish origin, 6.1% of Finnish origin and the remaining 5.0% were distributed throughout six European countries.

Venous blood was taken from all individuals and put into EDTA-containing tubes. DNA was isolated according to Luthman and Datta (Geijer et al. 1994). APOE genotypes were determined by Affigene ApoE (Sangtec Medical AB, Bromma, Sweden). Genotypes were examined blindly to the clinical status of the subjects.

Calculations were performed with the χ^2-test. Analysis of variance (ANOVA) was used to test continuous variables (age). For 2×2 contingency tables continuity correction was applied. More than 200 different calculations were performed. To correct for chance significances, Boniferroni's correction was used. The overall level of significance was set to 0.05, leading to a probability significance level of less than 0.00025 for each comparison to be regarded as significant.

Results

After Boniferroni correction, no significant differences were found when schizophrenic patients were compared with control subjects (Table 1); nor were there any significant findings when the schizophrenic patients were divided into the following different clinical subgroups: geographical origin, age at first hospitalisation, four DSM-III-R subdiagnoses of schizophrenia, family history of psychosis in first- or second-degree relatives, abuse of alcohol, solvents or drugs, previous suicide attempts, positive response to neuroleptic drug treatment, extrapyramidal side effects and treatment with anticholinergic drugs (data not shown). When no adjustment was made for multiple testing, there was a trend for a different allele distribution in schizophrenic patients who had attempted suicide as compared with those who had not, with higher ε2 and lower ε4 allele frequencies in the former group ($\chi^2 = 0.52$, $df = 2$, $p = 0.052$). When another 13 patients treated for schizophrenic symptoms but not fulfilling DSM-III-R criteria for schizophrenia, but instead mainly schizophrenia spectrum disorders (Kendler et al. 1995); and 21 control subjects with DSM-III-R disorders, mainly alcohol or anxiety diagnoses (Geijer et al. 1995), were added to the schizophrenic and control samples, respectively, the relationship to suicide attempt was somewhat strengthened ($\chi^2 = 6.95$, $df = 2$, $p = 0.031$). However, when schizophrenic patients who had attempted suicide were compared with control subjects, there was no difference ($\chi^2 = 1.11$, $df = 2$, $p = 0.574$), whereas there was a trend for schizophrenic patients who had not commited suicide to display a lower ε2 frequency ($\chi^2 = 5.17$, $df = 2$, $p = 0.076$). Schizophrenic patients who had not received anticholinergic medication ($n = 9$) had a higher ε4 allele frequency than patients who had been on medication ($n = 78$; 0.39 vs 0.16; $\chi^2 = 4.2$, $df = 1$, $p = 0.040$). However, when the patient and control samples were expanded as described above, there was no longer any significant difference between patients who had not and who had been prescribed anticholinergic drugs ($\chi^2 = 2.38$, $df = 1$, $p = 0.123$); nor was there any difference when schizophrenic patients were divided with regard to anticholinergic medication and compared with controls ($\chi^2 = 2.43$, $df = 1$, $p = 0.119$ and $\chi^2 = 0.30$, $df = 1$, $p = 0.591$, respectively).

Table 1 Apolipoprotein E allele and genotype frequencies (percent) and counts (in parentheses) in schizophrenic patients ($n = 87$) and control subjects ($n = 57$)

Allele	Schizophrenic patients	Control subjects
ε2	5.2 (9)	9.6 (11)
ε3	76.4 (133)	71.1 (81)
ε4	18.4 (32)	19.3 (22)
Genotype		
ε2ε3	9.2 (8)	15.8 (9)
ε2ε4	1.1 (1)	3.5 (2)
ε3ε3	56.3 (49)	47.4 (27)
ε3ε4	31.0 (27)	31.6 (18)
ε4ε4	2.3 (2)	1.8 (1)

Discussion

No association was found between APOE alleles or genotypes and schizophrenia. This is in accordance with Joober et al. (1995) who did not find any differences in ε4 allele frequencies in 58 Canadian caucasian schizophrenic patients and 38 controls. The present trend of a difference in ε2 and ε4 allele frequencies between patients who had attempted suicide and patients who had not did not reach statistical significance. Most likely, this is a chance finding, because even without correction for multiple testing, there was no statistically significant difference when patients who had attempted suicide were compared with control subjects. Similarly, the higher ε4 frequency in patients who had not received anticholinergic medication when compared with patients who had received these drugs also probably reflects a type-I error. Thus, the results are in agreement with most previous studies failing to find similar genetic, neuropathological, or neuropsychological changes in schizophrenic and Alzheimer's disease patients indicating different aetiopathologies in the two disorders (Mant et al. 1992; Heaton et al. 1994; Davidson and Haroutunian 1995; Jönsson et al. 1995). We conclude that the APOE gene variants are of not major importance in the pathophysiology or genesis of schizophrenia in the Swedish caucasian sample investigated.

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