

Apolipoprotein E Genotype and Odor Identification in Schizophrenia

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The authors examined Apolipoprotein E (ApoE) genotype frequencies and unirhinal odor identification in 28 schizophrenia patients and 26 healthy comparison subjects. No significant associations between ApoE status and olfaction were observed in either diagnostic group. The authors concluded that olfactory deficits in schizophrenia do not appear to be mediated by the ApoE allele.

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Olfactory dysfunction in patients with schizophrenia has been well described in the literature, with deficits in odor identification, detection threshold sensitivity, discrimination, memory, and hedonics being reported.^{1–3} A genetic influence regarding this deficit has also been reported, with deficits in odor identification observed in non-ill family members⁴ and in unaffected twins.⁵ Recent studies have suggested a link between the presence of the Apolipoprotein E (ApoE) $\epsilon 4$ allele and odor identification deficits in healthy elderly subjects^{6,7} and in patients with Alzheimer's disease.⁸ While a number of studies have examined the frequency of the ApoE genotype in schizophrenia, no study has yet examined whether the $\epsilon 4$ allele modulates the olfactory deficits seen in this disorder. The objective of our study was to examine the association of ApoE allele status to odor identification skills in patients with schizophrenia and healthy comparison subjects.

METHOD

Participants

Twenty-eight patients with a DSM-IV⁹ diagnosis of schizophrenia (14 men, 14 women) and 26 healthy volunteers (15 men, 11 women) were recruited from the Schizophrenia Research Center at the University of Pennsylvania Medical Center. Subjects were matched for sex ($\chi^2=0.32$, $df=1$, $p=0.57$) and race ($\chi^2=2.7$, $df=1$, $p=0.10$). Patients were older than healthy comparison subjects (mean ages of 36.6 [SD=9.1] years and 29.4 [SD=11.2] years, respectively; $t=26$, $df=52$, $p=0.01$). Age was subsequently used as a covariate in all analyses. Due to the fact that schizophrenia adversely affects educational attainment, it was expected that patients attained fewer years of formal education than healthy comparison subjects ($t=-2.0$, $df=52$, $p=0.04$). However, parental education, a more appropriate indicator of preillness educational expectation, revealed no significant difference between groups (Wilks' λ (2, 51)=0.96, $p=0.38$). Patients tended to smoke more than comparison subjects (mean pack-years: patients = 7.7 [SD=11.2]; comparison subjects = 2.4 [SD=7.4]; t (49) = 1.9, $p<0.053$). All patients met DSM-IV criteria for schizophrenia, with no other concurrent diagnoses. Healthy subjects were free of any Axis I diagnosis, Axis II Cluster A (i.e., schizotypal, schizoid, or paranoid) personality disorder, and family history of psychiatric illness.

Subjects were excluded if they had a history of neurological disorder, including head trauma with loss of consciousness; a history of substance abuse or dependence (as assessed by history, record review, and serum toxicology); a history of any medical condition that might alter cerebral functioning; or a recent respiratory

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infection or any other condition that could affect olfactory functioning (e.g., common cold or allergies). Written informed consent was obtained after the procedures had been fully explained.

ApoE Genotyping

Apolipoprotein E (ApoE) genotyping was performed on blood using polymerase chain reaction-based methods.¹⁰ ApoE genotypes for each subject were scored independently by two observers who were blind to diagnostic status, and allele frequencies were calculated for each group.

Olfactory Assessment

Odor identification skills were assessed with the University of Pennsylvania Smell Identification Test (UPSIT).¹¹ The UPSIT was administered unilaterally (each nostril separately), with the contralateral naris occluded using a piece of Durapore™ tape (3M Corporation, Minneapolis, MN) fitted tightly over the edges of the nostril. This procedure effectively isolated the nostril being examined and prevented retronasal airflow. Two booklets of the test were administered to the left nostril, and two to the right nostril, with the booklets systematically counterbalanced among subjects.

Statistical Methods

The relationship between ApoE genotype and UPSIT performance was probed in two ways. First, each group was divided into two subgroups based on the presence or absence of at least one $\epsilon 4$ allele. These $\epsilon 4$ -positive and $\epsilon 4$ -negative subgroups were then contrasted with regard to UPSIT performance using multivariate analysis of covariance (MANCOVA) with age as a covariate. Second, in order to gauge any potential "dose-effect" relationships, each subject's ApoE genotype was graded on a 5-point scale with the ApoE $\epsilon 2/2$ genotype representing the lowest point and ApoE $\epsilon 4/4$ the highest point. Employing such a scale incorporated all combinations of the three alleles: 1) the possible protective effects of the $\epsilon 2$ allele, 2) presumed neutral effect of the $\epsilon 3$ allele, and 3) the putative negative effect of the $\epsilon 4$ allele. These relationships were examined using Spearman correlations.

RESULTS

Consistent with prior studies, there were no significant differences between diagnostic groups for ApoE gene frequencies ($\chi^2 = 0.77$, $df = 1$, $p = 0.38$) (Table 1).

Results revealed no significant difference in UPSIT performance for either nostril between $\epsilon 4$ -positive and $\epsilon 4$ -negative subgroups in the patient group ($F(1, 26) = 0.08$, $p = 0.78$) or in the healthy subjects group ($F(1, 24) = 0.37$, $p = 0.54$). Spearman correlations of ApoE grade and UPSIT performance did not reveal any significant relationship in patients ($p > 0.28$) or in healthy subjects ($p > 0.08$) across nostrils. No significant main effects of sex, diagnosis by sex interactions, or sex-specific correlations with APOE status or olfactory measures were observed.

DISCUSSION

Data reported in this study do not support an effect of ApoE allele status on the expression of odor identification deficits in patients with schizophrenia. By and large, prior investigations of the $\epsilon 4$ allele in schizophrenia have not supported a greater prevalence of this allele in patients but have suggested that genetic status may influence expression of the disease (i.e., younger age of onset).^{10,12,13} In older patients, the $\epsilon 4$ allele has been associated with coexistent dementia as well as more neurofibrillary pathology on postmortem.¹⁰ While there appears to be a genetic contribution to olfactory processing deficits in patients with schizophrenia, these deficits do not appear to be mediated at the level of the ApoE allele. Thus, they are likely to have an etiology that is distinct from the olfactory processing deficits observed in Alzheimer's disease.

There are several limitations to this study. First, the sample size was relatively small, perhaps limiting the distribution of genotypes in each group. It is notable, however, that the current ApoE genotype distribution described is generally consistent with other studies in the literature.^{10,14} Second, only odor identification abilities were examined. Future studies might determine whether the findings in our study could be applied to other olfactory domains.

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TABLE 1. Frequency of ApoE Genotypes in Schizophrenia Patients and Healthy Comparison Subjects

Genotypes	$\epsilon 2/2$	$\epsilon 2/4$	$\epsilon 3/3$	$\epsilon 3/4$	$\epsilon 4/4$	Total
Comparison	5	0	17	3	1	26
Patients	7	4	14	3	0	28

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