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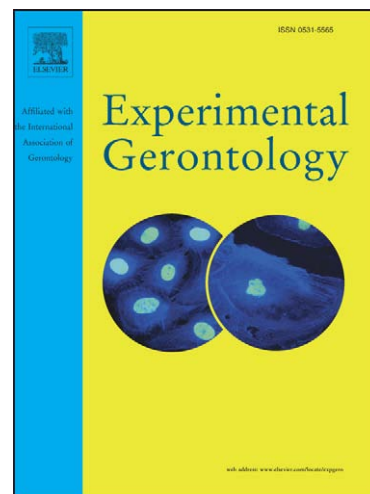
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APOE polymorphism affects episodic memory among non demented elderly subjects.

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Abstract

The *APOE* ϵ 4 allele has been associated with a number of neurodegenerative disorders e.g. Alzheimer's disease. Inconsistent results have been obtained for cognitive decline in 'normal' aging. We investigated whether specific aspects of cognitive decline were associated with *APOE* ϵ 4 among 620 'healthy' elderly subjects living in Calabria, southern Italy. MMSE scores ranged from 11 to 30. A lower MMSE score was unrelated to *APOE* polymorphism, i.e. a global measure of cognition. However, poorer episodic memory was associated with *APOE* ϵ 4, both registration ($p=0.01$) and recall ($p=0.01$). Temporal and spatial orientation, attention and calculation, language, and constructive function were not affected. We conclude that episodic memory, specifically, is adversely affected by *APOE* ϵ 4 and urge evaluation of precise phenotypes in genetic association studies of cognitive decline in order to avoid inconsistent results due to phenotypic heterogeneity.

Introduction

The polymorphism of Apolipoprotein E leading to E2, E3, E4 isoforms (Utermann et al. 1979; Weisgraber et al. 1981; Rall et al. 1982) has attracted the interest of many scientists due to its involvement in Alzheimer's disease (AD) and in a number of complex diseases (Saunders et al. 1993; Corder et al. 1993; Srinivasan et al. 2006; Bernardi et al. 2006). In addition, many studies have focused on the possible correlation between *APOE* polymorphism and cognitive performances in non demented subjects. Among the most important results it is worth mentioning that Deary et al. (2002) found that *APOE* variability is not correlated with differences in mental ability in youth, but the allele $\epsilon 4$ is significantly associated with decreased mental ability at old age. In agreement, Wilson et al. (2002) found that the $\epsilon 4$ allele is associated with a more rapid decline in cognitive functions in the elderly, particularly episodic memory which allows the recollection of events and episodes of the recent past. A prominent effect of *APOE* variability on episodic memory has recently been confirmed by a study on a Swedish population (the Betula Study, Nilsson et al. 2006). However, the studies on the correlation between *APOE* and cognitive performances in the elderly have also shown some contrasting results (for a review see Savitz et al. 2006). Many reasons may explain the incoherence of the data so far obtained on the effects of *APOE* polymorphism in non demented old subjects. Among the others is the fact that the studies have been carried out in different populations, with different genetic backgrounds and different environments. In addition, in some cases different cognitive functions have not been tested separately but within inclusive tests. Indeed, recent analyses have highlighted the importance of disentangling the different items included in inclusive tests, as the crude computation of overall scores may be not fully representative of important phenotypic differences (Antonelli Incalzi et al. 2005, 2008)

In the last few years coordinated international surveys are showing that the quality of aging is quite different across Europe. Indeed, specific markers of the quality of aging showed that the age related physical decline is faster in southern than in northern Europeans (Jeune et al. 2006). This phenomenon may be due to different historic and demographic reasons (differences in childhood growth, lifestyle and public health care for old people). However biological reasons cannot be excluded. This clearly poses interesting questions to the researchers who are dealing with the effect of polymorphisms on age related phenotypes. In fact, genetic variants and environmental factors may interact in a population specific way in modulating some specific age-related phenotypes (De Benedictis and Franceschi 2006).

In order to further explore the effect of *APOE* variability on the age related cognitive decline we analysed *APOE* genotypes and cognitive performances in non demented subjects aged 65-85 years, that is in the age range where there is a dramatic increase of cognitive impairment (De Ronchi et al. 2005). The study was carried out on a population sample from Calabria, a southern Italian region where previous surveys have highlighted that the aging decline, including the cognitive decline, is faster than in other European regions (Jeune et al. 2006).

Materials and Methods

Samples

The sample we analyzed included 65-85 years old healthy subjects (N=620; 287 males and 333 females; median ages 72 years in both cases). The sample has been recruited in the frame of different recruitment campaigns focused on the monitoring of the quality of aging in Calabria, which have been carried out by our research group between 2002 and 2007. All the subjects were considered healthy after a thorough clinical assessment

with detailed clinical history, including MMSE, ADL, IADL, Physical tests, GDS and a set of the most common clinical haematological tests. Subjects with dementia and/or neurologic disorders were not included. The blood for DNA extraction was obtained at the same time of the medical visit, when also blood for clinical exams was extracted.

All the subjects were born in Calabria and their ancestry in the region had been ascertained up to the grandparents generation. The vital status of subjects recruited is ascertained by our research group every 18 months. The questionnaire used for the interviews are available at the following web address: http://biologia.unical.it/echa/documents/minute/First_Steering/QUEST_G2.pdf . Before the interview each subject consented to her/his phenotypic and genetic data to be used anonymously for genetic studies on aging (informed consent).

Cognitive functions

Cognitive functions were assessed by Mini Mental State Examination (MMSE) test a 30-item questionnaire that assesses orientation, episodic memory, attention, language, and construction functions (Folstein et al. 1975). Since the test is affected by age and educational status, the MMSE scores were normalized for these variables according to a standardised procedure (Grigoletto et al. 1999). A score of 23 was considered as a cut-off for recognizing impaired or conserved cognitive functioning (Rait et al. 2005; Anderson et al. 2007).

Episodic memory was evaluated by two tests of immediate and delayed recall of a 12-word list (McGue and Christensen 2001; Nilsson et al. 2006). The interviewer read 12 words to the subject. Then, the subject was invited to repeat all the words he/she caught (*Recognition and Registration test*). After a few minutes where the subject was distracted with other questions, the interviewer asked the subject to repeat all the words she/he could remember of the 12-word list (*Delayed Recall test*). As the scores varied

according to age and education ($p < 0.05$ in both cases) we adjusted the scores with respect to these variables by using the standardized residuals of a linear regression model where the scores were used as dependent variable and age and education as independent variables. It is worth mentioning that these two tests have been introduced in the questionnaire not from the beginning but after some time, in order to replicate preliminary observations on episodic memory. For this reason data for these tests were available for 271 subjects out of 620.

DNA Analysis

DNA was prepared from blood buffy-coats according to standard procedures and stored at -20°C until use. *APOE* genotyping (alleles $\epsilon 2$, $\epsilon 3$, $\epsilon 4$) was carried out according to the protocol described in Carrieri et al. 2001.

Statistical analysis

Testing for independence in 2 by 2 table (Table 2) has been carried out by using Fisher's exact test. For larger than 2 by 2 tables (Tables 3 and 4), because of the sparseness of the observed data, testing for independence has been performed by a Monte Carlo approximation to Fisher's exact test (Agresti et al. 1979). Statistical analyses were performed by using SPSS 15.0 (SPSS Inc., Chicago, IL). A significance level of $\alpha = 0.05$ was chosen in all the tests.

Results

In order to explore the influence of the *APOE* polymorphism on the preservation of cognitive functioning, we analyzed the association between *APOE* genotypes and MMSE scores.

The frequency of *APOE* genotypes and alleles are reported in Table 1. The frequencies observed in the present study are in agreement with those previously reported for the Calabrian population (Carrieri et al. 2001).

MMSE scores, adjusted for age and education, > 23 or ≤ 23, was essentially the same for *APOE* ε4 carriers and *APOE* ε4 non carriers (Table 2; p=0.619).

We then determined whether any of the component cognitive domains were associated with *APOE* ε4 (Table 3). Both tests of episodic memory, registration (p=0.01) and recall (p=0.01) indicated poorer function among *APOE* ε4 carriers. None of the other cognitive domains (orientation, attention, language, and construction functions) was associated with *APOE* status. We did not correct for multiple comparisons because of previous studies indicating worse episodic memory for *APOE* ε4 subjects and because we then went on to replicate the finding.

In fact, in order to have an independent evidence of our findings we analyzed data for two tests specifically testing episodic memory: *Recognition-and-registration test* and *Delayed recall test*. In order to verify if allele ε4 affects episodic memory, the sample was partitioned into four groups according to the quartiles of the scores obtained for each test (Quartile 1 represented the group with the lowest score). This allowed us to replicate the finding of poorer episodic memory among *APOE* ε4 subjects for both registration (p=0.05) and recall (p=0.0046) (Table 4).

Discussion

APOE polymorphisms are certainly among the most studied human genetic variations, due to their role in individual risk for age related diseases, primarily for AD. A significant share of literature has also been dealing with the effects of *APOE*

polymorphisms on the age related cognitive decline. Aim of the present study was to explore the relationship between *APOE* variation and age related cognitive decline in a southern European population characterized by a poor quality of aging (Jeune et al. 2006).

We found that *APOE* variation is not correlated to the overall cognitive performance as evaluated by the MMSE test (Table 2). However, we found that the performances at different tests which specifically evaluate episodic memory were able to show a significant higher frequency of $\epsilon 4$ carriers among the subjects with the lowest performances (Tables 3 and 4). These observations are in line with the results obtained by Nilsson et al. (2006) in a population from Sweden and highlight the specific effect of *APOE* $\epsilon 4$ on episodic memory. This is particularly interesting if we consider the different environmental, social and biological backgrounds of the two populations examined. On the other hand, if we consider the importance of memory in the cognitive decline and, consequently, in the quality of aging, it is not surprising that $\epsilon 4$ may, as a side effect, lead to a proneness to frailty, as reported in other papers (Passarino et al. 2007; Packard et al. 2007).

The observations reported, might be possibly connected to the age-related reduction of hippocampal volume which has been found to be more pronounced in $\epsilon 4$ carriers (Cohen et al. 2001; Lind et al. 2006). Indeed, a reduction of hippocampus is associated to cognitive failures without objective cognitive impairment and to Mild Cognitive Impairment (van Norden et al. 2008, Martin et al. 2008). On turn, this phenomenon may be possibly derived from the decreased antioxidant activity of $\epsilon 4$ (Myiata and Smith 1996) or from the altered use of the nutrients observed in $\epsilon 4$ carriers (Reiman et al. 2004). In any case, our data have confirmed that *APOE* $\epsilon 4$ allele has specific deleterious effects on episodic memory and that, unlike other polymorphisms, its

effects on the quality of aging is mostly independent from population specificity. In addition our findings urge for a clear definition of the studied phenotype to untangle the genetic component of complex traits.

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Table 1. Genotypic and allelic frequencies of *APOE* polymorphism in the sample analyzed (N= 620).

Genotype	Absolute frequency (Relative Frequency)
ε2-ε2	3 (0.5)
ε2-ε3	82 (13.2)
ε2-ε4	10 (1.6)
ε3-ε3	443 (71.5)
ε3-ε4	81 (13.1)
ε4-ε4	1 (0.2)

Allele	Absolute frequency (Relative Frequency)
ε2	98 (7.9)
ε3	1049 (84.6)
ε4	93 (7.5)

HWE $\chi^2 = 3.01$ gdl = 3 p=0.390

Table 2. Distribution of *APOE* $\epsilon 4$ carriers and non carriers across the two groups defined on the basis of the MMSE scores.

	$\epsilon 4$ carriers	$\epsilon 4$ non carriers
MMSE ≤ 23	26 (31.7%)	188 (34.9%)
MMSE > 23	56 (68.3%)	350 (65.1%)
<i>p-value</i>	0.619	

p-value refers to a Fisher's exact test.

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Table 3. Distribution of *APOE* ε4 carriers and *APOE* ε4 non carriers across the groups defined by the scores obtained for each item included in the MMSE test.

MMSE items	Scores	ε4 carriers	ε4 non carriers
<i>Temporal Orientation</i>	0 correct answers	0 (0.0%)	3 (0.6%)
	1 correct answers	0 (0.0%)	5 (0.9%)
	2 correct answers	6 (7.3%)	13 (2.4%)
	3 correct answers	0 (0.0%)	37 (6.9%)
	4 correct answers	14 (17.1%)	110 (20.4%)
	5 correct answers	62 (75.6%)	370 (68.8%)
	<i>p-value</i>	0.376	
<i>Spatial Orientation</i>	0 correct answers	0 (0.0%)	0 (0.0%)
	1 correct answers	1 (1.2%)	1 (0.2%)
	2 correct answers	3 (3.7%)	14 (2.6%)
	3 correct answers	9 (11.0%)	36 (6.7%)
	4 correct answers	18 (22.0%)	135 (25.1%)
	5 correct answers	51 (62.2%)	352 (65.4%)
	<i>p-value</i>	0.224	
<i>Registration</i>	0 correct answers	0 (0.0%)	1 (0.2%)
	1 correct answers	2 (2.4%)	2 (0.4%)
	2 correct answers	4 (4.9%)	7 (1.3%)
	3 correct answers	76 (92.7%)	528 (98.1%)
	<i>p-value</i>	0.009	
<i>Attention and Calculation</i>	0 correct answers	12 (14.6%)	87 (16.2%)
	1 correct answers	7 (8.5%)	74 (13.8%)
	2 correct answers	8 (9.8%)	55 (10.2%)
	3 correct answers	11 (13.4%)	66 (12.3%)
	4 correct answers	11 (13.4%)	60 (11.2%)
	5 correct answers	33 (40.2%)	196 (36.4%)
	<i>p-value</i>	0.295	
<i>Recall</i>	0 correct answers	18 (22.0%)	63 (11.7%)
	1 correct answers	9 (11.0%)	47 (8.7%)
	2 correct answers	23 (28.0%)	189 (35.1%)
	3 correct answers	32 (39.0%)	239 (44.4%)
	<i>p-value</i>	0.006	
<i>Language</i>	2 correct answers	0 (0.0%)	1 (0.2%)
	3 correct answers	0 (0.0%)	4 (0.7%)
	4 correct answers	3 (3.7%)	19 (3.5%)
	5 correct answers	16 (19.5%)	130 (24.2%)
	6 correct answers	63 (76.8%)	384 (71.4%)
		<i>p-value</i>	0.311
<i>Constructive function</i>	0 correct answers	17 (20.7%)	102 (19.0%)
	1 correct answers	14 (17.1%)	84 (15.6%)
	2 correct answers	22 (26.8%)	144 (26.8%)
	3 correct answers	29 (35.4%)	208 (38.7%)
	<i>p-value</i>	0.526	

p-values refer to 2-sided Montecarlo approximation to Fisher's exact test.

Table 4. Distribution of *APOE* $\epsilon 4$ carriers and non carriers across the four quartiles defined on the basis of the scores obtained to the *Recognition and Registration test* and to the *Delayed Recall test*.

Memory test	Quartiles of scores	$\epsilon 4$ carriers	$\epsilon 4$ non carriers
<i>Recognition and Registration test</i>	1 st Quartile	10 (33.3%)	58 (24.1%)
	2 nd Quartile	9 (30.0%)	59 (24.5%)
	3 rd Quartile	7 (23.3%)	61 (25.3%)
	4 th Quartile	4 (13.3%)	63 (26.1%)
	<i>p-value</i>	0.0501	
<i>Delayed Recall test</i>	1 st Quartile	14 (46.7%)	54 (22.4%)
	2 nd Quartile	6 (20.0%)	62 (25.7%)
	3 rd Quartile	5 (16.7%)	63 (26.1%)
	4 th Quartile	5 (16.7%)	62 (25.7%)
	<i>p-value</i>	0.0046	

p-values refer to 2-sided Montecarlo approximation to Fisher's exact test.