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Negative results

Lack of association of hepatic lipase polymorphisms with late-onset Alzheimer's disease

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Abstract

Several polymorphisms in hepatic lipase (LIPC) are similar to apoE4 because they associate with cholesterol concentrations and, for rs6084, coronary artery disease (CAD). Since apoE4 is also a primary genetic risk factor for late-onset Alzheimer's disease (LOAD), LIPC single nucleotide polymorphisms (SNP)s represent excellent candidates for LOAD association studies. Because this issue has not been addressed previously, we evaluated LIPC SNP association with LOAD. In a population from the Religious Orders Study (ROS), rs6084 was nominally associated with LOAD odds ($p = 0.015$ by χ^2 test). However, this association was not confirmed in two subsequent series based at the University of Kentucky (UKY, $p = 0.15$) or the Mayo Clinic in Jacksonville (MCJ, $p = 0.97$). Hence, rs6084 is not consistently associated with LOAD.

Keywords: Alzheimer's disease; Genetics; Hepatic lipase; Apolipoprotein E

We selected three LIPC SNPs, rs6083, rs6084 and rs6074, for association with LOAD because of their prior association with cholesterol and CAD (Baroni et al., 2003; Knoblauch et al., 2004). These SNPs were genotyped by using a TaqMan approach in two LOAD series, which included: (i) the ROS series with 86 LOAD individuals (37 male and 49 female, average age at diagnosis was 85 ± 7 (mean $\pm$ S.D.)) and 69 non-LOAD individuals (36 male and 33 female, average age at last evaluation was 82 ± 7) and (ii) the UKY series with 132 LOAD individuals (38 male and 94 female, average age at diagnosis was 76 ± 6) and 147 non-LOAD individuals (60 male and 87 female, average age at last evaluation of 81 ± 7). Rs6084, implicated in the first two series, was tested further in the MCJ series, which included 415 LOAD individuals (261 male and 154 female, average age at diagnosis was 78 ± 5) and 404 non-LOAD individuals (253 male and 151 female, average age at last evaluation was 77 ± 6). AD in all three series was clinically diagnosed following National Institute of Neurologic and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS/ADRDA) criteria.

Among the three SNPs evaluated in the ROS series, only rs6084 was nominally associated with LOAD, i.e., the minor allele was found more often in LOAD individuals (Table 1 and supplementary data). A similar trend was observed in the UKY series, although rs6084 association with LOAD did not achieve significance (Table 1 and supplementary data). Significant associations were not identified in haplotype analyses in the ROS or UKY series (supplementary data). Since the minor allele of rs6084 was similar to apoE4 in that both are enriched in LOAD as well as CAD (Baroni et al., 2003), we tested this SNP further in the MCJ series. However, rs6084 was not associated with LOAD in the MCJ series (Table 1). To evaluate rs6084 association with LOAD in the overall population, we performed a logistic regression

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Table 1
rs6084 genotypic and allelic frequencies in ROS, UKY and MCJ series

	AD, *n* (%)	Non-AD, *n* (%)	χ^2 test, *p* value
ROS			
Genotype	81 (100)	65 (100)	0.035
C/C	12 (15)	20 (31)	
C/g	45 (56)	34 (52)	
g/g	24 (30)	11 (17)	
Allele	162 (100)	130 (100)	0.015
C	69 (43)	74 (57)	
g	93 (57)	56 (43)	
UKY			
Genotype	121 (100)	145 (100.0)	0.33
C/C	32 (26)	50 (34)	
C/g	61 (50)	68 (47)	
g/g	28 (23)	27 (19)	
Allele	242 (100)	290 (100)	0.15
C	125 (52)	168 (58)	
g	117 (48)	122 (42)	
MCJ			
Genotype	415 (100)	404 (100)	0.993
C/C	106 (25.5)	102 (25.2)	
C/g	212 (51.1)	208 (51.5)	
g/g	97 (23.4)	94 (23.3)	
Allele	830 (100)	808 (100)	0.970
C	424 (51.1)	412 (51.0)	
g	406 (48.9)	396 (49.0)	

The lower case nucleotide refers to the minor allele.

analysis by using age and apoE as covariates; rs6084 was not significantly associated with LOAD odds ($p = 0.132$). In summary, the minor allele of rs6084, which has been associated with decreased HDL, increased triglycerides and CAD odds (Baroni et al., 2003), is not associated significantly with LOAD.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2006.11.015.

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