Published in final edited form as:

Neurobiol Aging. 2008 October ; 29(10): 1602–1604. doi:10.1016/j.neurobiolaging.2007.03.010.

No association of dynamin binding protein (*DNMBP*) gene SNPs and Alzheimer's disease

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Abstract

A recent scan of single nucleotide polymorphisms (SNPs) on chromosome 10q found significant association of six correlated SNPs with late-onset Alzheimer's disease (AD) among Japanese. We examined the SNP with the highest statistical significance (*rs3740058*) in a large Caucasian American case-control cohort and the remaining five SNPs in a smaller subset of cases and controls. We observed no association of statistical significance in either the total sample or the *APOE**4 non-carriers for any of the SNPs.

Keywords

Alzheimer's disease; genetics; *DNMBP*; chromosome 10

Genome-wide linkage mapping has identified chromosome 10 as harboring putative susceptibility genes for Alzheimer's disease (AD) [see 1 for review]. To date no variation in a gene on chromosome 10 has been definitively associated with risk of AD. A recent scan of 1206 single nucleotide polymorphisms (SNPs) between 60 Mb and 107 Mb on 10q in a Japanese case-control cohort identified six highly correlated SNPs associated with LOAD among non-*APOE**4 carriers [6]. Three of the six SNPs, including the most statistically significant (*rs3740058*), are located in the dynamin binding protein gene (*DNMBP*) on 10q24; the other three fall downstream of this gene. Since the reported significant SNPs are located in a single LD block, we examined the most significant SNP in a large case-control cohort and the remaining five in a subset of this cohort in an effort to replicate the association detected by Kuwano et al. [6].

All six SNPs were genotyped using TaqMan SNP Genotyping Assays (Applied Biosystems). *rs3740058* (*DNMBP*:c.3051+42C>T) was genotyped in 1,030 Caucasian Americans with LOAD and 910 healthy Caucasian Americans. To assess error rate, 10% of samples were repeated. *rs11190302* (*DNMBP*:c.*3993G>A), *rs11190305* (*DNMBP*:c.4239T>G; p.C1413W), *rs35715207* (*DNMBP*:c.3156+1767C>G), *rs3740066* (*ABCC2*:c.3972C>T; p.=)

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Disclosure statements

None of the authors has any actual or potential conflicts of interest that could inappropriately influence this work. This study was approved by the University of Pittsburgh Institutional Review Board.

and *rs911541* (*ENTPD7*:c.192–562G>A) were genotyped in 298 LOAD cases and 311 controls. The *rs429358* (*APOE*:c.388T>C; p.C130R) and *rs7412* (*APOE*:c.526C>T; p.R176C) SNPs were genotyped in all individuals as previously described [5]. Sequence variation nomenclature based on GenBank sequences NT_030059 (*DNMBP*, *ABCC2* and *ENTPD7*) and NT_011109.15 (*APOE*).

Genotype and allele frequencies were calculated using the direct counting method. Deviation from Hardy–Weinberg equilibrium was tested using Pearson’s goodness-of-fit χ^2 test. Differences in allele and genotype frequencies between cases and controls and cases and controls stratified by *APOE**4 carrier status were also tested using the χ^2 test. Calculations of statistical power were completed using PS 2.1.30 [2]. Linkage disequilibrium (LD) measures were determined using the genetics package in R 2.2.2 [8].

Genotyping efficiency for *rs3740058* was 92.7%; the estimated error rate was 0.8%. Genotyping efficiencies for the other five SNPs in the region varied ranged from 93.2% to 98.0%. Genotype frequencies did not deviate with statistical significance from those anticipated under Hardy–Weinberg equilibrium for the examined SNPs.

Genotype and allele frequencies for *rs3740058* are shown in Table 1. Differences between cases and controls in genotype and allele frequencies were not statistically significant ($p = 0.708$ and $p = 0.582$, respectively). Frequencies in cases and controls stratified by *APOE**4 carrier status were also not statistically significant ($p = 0.547$ for *APOE**4 and $p = 0.841$ for non-*APOE**4). With our sample, we had 80.5% power to detect the reported odds ratio (OR) of 1.22 in the total sample and 93.4% power to detect the reported OR of 1.38 in the non-*APOE**4 subjects.

Genotype and allele frequencies for the remaining five SNPs are shown in Table S1. There were no statistically significant differences in allele or genotype frequencies between cases and controls for any SNP. LD among the various SNPs in our sample and in Kuwano and colleagues’ sample are shown in Table S2. The differences in measures between the two samples are small.

Unfortunately, associations observed in scans of large numbers of SNPs and followed up in one or more validation populations often fail to be replicated in subsequent studies. This has certainly been the case in analyses of LOAD risk and reported associations with SNPs on chromosome 10. Another recent scan of this chromosome detected several potential SNPs, also on 10q24, associated with LOAD [3]; however, ensuing studies of the most significant SNPs failed to reproduce the same association [1,7].

Clearly, a direct comparison of association or lack thereof in Caucasian Americans and Japanese is limited because the genetic histories, and therefore the allele frequencies and LD patterns, may be different. The frequency of the minor allele of *rs3740058* in the examined Japanese sample is 0.184 but is 0.366 in our Caucasian American sample. The similar LD pattern between these six SNPs indicates that it is not variation between the cohorts within the examined block that is contributing to the disparate findings. It is possible, however, that differences in LD between the two populations allow *rs3740058* and the other nearby SNPs to be correlated with a SNP associated with LOAD in the Japanese cohort but not the Caucasian American cohort that is outside the examined linkage block. Nonetheless, we have been unable to confirm the reported associations of *DNMBP* SNPs in our Caucasian American sample.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acknowledgements

This study was supported by National Institute on Aging grants AG13672 and AG05133.

Table 1
Distribution of the rs3740058 SNP in LOAD cases and controls

	Genotype				Allele		<i>p</i> ^a		
	CC		CT		C	T			
	<i>n</i>	%	<i>n</i>	%	%	%			
Total AD Cases	347	(39.6)	401	(45.8)	128	(14.6)	62.5	37.5	0.708
Total Controls	340	(41.5)	360	(43.9)	120	(14.6)	63.4	36.6	
<i>APOE</i> *4 AD Cases	201	(40.3)	227	(45.5)	71	(14.2)	63.0	37.0	
<i>APOE</i> *4 Controls	74	(45.1)	68	(41.5)	22	(13.4)	65.9	34.1	0.355
Non- <i>APOE</i> *4 AD Cases	146	(38.7)	174	(46.2)	57	(15.1)	61.8	38.2	0.651
Non- <i>APOE</i> *4 Controls	266	(40.5)	292	(44.5)	98	(14.9)	62.8	37.2	

^aComparison between cases and controls.