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No association of *DAPK1* and *ABCA2* SNPs on chromosome 9 with Alzheimer's disease

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Abstract

Recently genetic variation in the *DAPK1* and *ABCA2* genes has been reported to be associated with late-onset and early-onset Alzheimer's disease (AD), respectively. We examined the most significant two single-nucleotide polymorphisms (SNPs) in *DAPK1* in a large case-control cohort of late-onset subjects and matched controls and one of the most significant SNPs in *ABCA2* in a small set of early-onset subjects as well. We did not detect associations with AD for any variation.

Keywords

Alzheimer's disease; genetics; *DAPK1*; *ABCA2*; chromosome 9

Alzheimer's disease (AD) is a devastating neurodegenerative disorder with complex environmental and genetic etiology. Variation in four genes has been consistently associated with risk of AD: *APP*, *PSEN1* and *PSEN2* with early-onset AD (EOAD) and *APOE* with late-onset AD (LOAD) (Kamboh, 2004). Linkage studies have identified regions on several chromosomes, including chromosome 9 (Kamboh, 2004). Recently, variation in two genes on chromosome 9q34, *DAPK1* (death-associated protein kinase 1) (Li et al., 2006) and *ABCA2* (ATP-binding cassette, sub-family A, member 2) (Macé et al., 2005; Wollmer et al., 2006) has been associated with AD.

Li et al. (2006) reported an association between *DAPK1/rs4878104* (c.63–26878C>T) and *rs4877365* (c.62+41638G>A) and LOAD. Two other groups (Macé et al., 2005; Wollmer et al., 2006) reported associations between *ABCA2/rs908832* (c.2037T>C) and EOAD.

Here we examined three single-nucleotide polymorphisms (SNPs) in a large case-control population of LOAD subjects and age-matched controls and a small series of EOAD cases for *ABCA2/rs908832*, in an effort to replicate those findings. (See Supplementary Material for case-control description and genotyping methodology.)

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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.

Genotype and allele frequencies for the three markers are presented in Table 1. Both *DAPK1* SNPs were in significant linkage disequilibrium ($D' = 0.946$, $r^2 = 0.633$). Differences between frequencies in cases and controls did not differ significantly for either *DAPK1/rs4878104* (genotype $p = 0.224$; allele $p = 0.383$) or *DAPK1/rs4877365* (genotype $p = 0.993$; allele $p = 0.928$). Our power to detect Li and colleagues' (2006) odds-ratio of 0.87 for *rs4878104* and 0.80 for *rs4877365* in their combined sample was 43.2% and 91.6%, respectively. *DAPK1* is located 3.9 Mb away from the ubiquitin 1 gene (*UBQLN1*); because *UBQLN1* has also been associated with AD risk, we performed a *post hoc* analysis of interactions between these two genes and found no interactions (see Supplementary Material).

For *ABCA2*, there were no statistically significant differences between LOAD and controls (genotypes, $p = 0.315$; alleles, $p = 0.409$), EOAD and controls (genotypes, $p = 0.184$; alleles, $p = 0.184$), or EOAD and LOAD (genotypes, $p = 0.132$; alleles, $p = 0.372$). Our study had 99.4% power to detect the odds-ratio of 3.82 reported by Macé et al. (2005) and 92.4% power to detect the odds-ratio of 6.82 reported by Wollmer et al. (2006).

The statistically significant results that Macé et al. (2005) found with the *ABCA2/rs908832* SNP in their hypothesis-testing and total samples appears to be due solely to the EOAD subgroup ($p = 5 \times 10^{-5}$ in EOAD versus $p = 0.65$ in LOAD). Wollmer and colleagues (2006) examined three groups for this *ABCA2* SNP: Swiss, Greeks and Japanese. In each group they found contrastive results. In the Swiss, they observed a significant association between EOAD and *rs908832* ($p = 0.008$); in the Greeks, no significance ($p = 0.4$); and in the Japanese, the variation was monomorphic. In our Caucasian American sample, we observed no significant association either with EOAD or LOAD.

In summary, the *DAPK1* and *ABCA2* SNPs examined showed no significant association in our AD cohort. The genetics of Alzheimer's disease, especially LOAD, has proven to be complicated, with many apparently spurious results. Pinning down causal variants, or variation correlated with such variants, under AD linkage peaks has been difficult for several chromosomes, and chromosome 9 has been no exception.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Table 1
Allele and genotype frequencies for *DAPK1/rs4878104*, *DAPK1/rs4877365* and *ABCA2/rs908832*

<i>DAPK1</i> <i>rs4878104</i>	LOAD	Controls
CC	315	271
CT	309	323
TT	117	106
	741	700
		1,000
C	939	865
T	543	535
<i>DAPK1</i> <i>rs4877365</i>	LOAD	Controls
GG	488	484
GA	415	412
AA	92	93
	995	989
		1,000
G	1391	1380
A	599	598
<i>ABCA2</i> <i>rs908832</i>	LOAD	EOAD
CC	1032	128
CT	59	8
TT	0	1
	1091	137
		1,000
C	2123	264
T	59	10
		1965
		47
		0.977
		0.023