(unpublished observation: AK and AS). These SNPs may either directly influence the binding of DISC1 and *Citron* proteins, or they may be markers of polymorphism(s) responsible for modulating binding. Alternately, we found the SNPs to have an association with BP in the study may reflect causal genetic variation in an adjacent gene. It is conceivable that *Citron* is one of a cluster of susceptibility genes for BP in the chromosomal region of 12q23–24. Together, our studies warrant further study of *Citron* and adjacent genes in larger samples and in other ethnic groups in the investigation of a possible etiology for major mood disorders.

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The *BDNF* val66met polymorphism is not associated with late onset Alzheimer's disease in three case–control samples

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SIR—Brain-derived neurotrophic factor (BDNF) has been implicated in hippocampal anatomy and plasticity, learning and memory. *BDNF*, located on chromosome 11p13, contains a common, functional single nucleotide polymorphism (SNP), rs6265, at codon 66 (val66met) of the pro-region of the protein, which appears to exert an effect on intracellular trafficking and activity-dependent secretion of BDNF.[1] Individuals carrying the methionine allele have impaired hippocampal function and volume and poor episodic memory.[1] Memory deterioration and hippocampal pathology are prominent features of late-onset Alzheimer's disease (LOAD), and this has prompted several groups to seek association between *BDNF* polymorphisms and Alzheimer's disease (AD). Association between the val66met polymorphism in *BDNF* and LOAD was claimed,[2] and positive associations of the 270C/T polymorphism, in the 5′-noncoding region of the *BDNF* gene have also been reported in two different sample sets.[3,4] Other studies have not found evidence for association of either the val66met SNP [5–8] or the 5′-noncoding 270C/T SNP with AD.[8,9] The studies with lack of association were based on samples of very different ethnic backgrounds including sample sets from Brazil, China, Italy, and Spain. This and the fact that samples of relatively small size were employed in these studies make it difficult to definitively assess the potential association of the *BDNF* SNPs with LOAD. As a result of its suggested functional significance in AD and other psychiatric disorders such as schizophrenia, bipolar disorder, and anxiety, we chose to genotype the val66met SNP in three independently collected LOAD case control series of Caucasian decent, totaling 2041 individuals (935 cases *vs* 1106 controls) and examined whether the SNP is associated with LOAD.

The three case–control series were the WU series, collected through the Washington University Alzheimer's Disease Research Center (ADRC) patient registry, the UK series, collected as part of the MRC LOAD Genetic Resource by Cardiff University, Wales College of Medicine and King's College London, and the UCSD series, collected through the ADRC of the University of California, San Diego. Cases in these series have a clinical diagnosis of dementia of the Alzheimer's type according to NINCDS-ADRDA or similar criteria with a minimum age of onset of 65 years. Nondemented controls have a full neuropsychological and clinical

Table 1 Allelic tests of *BDNF* val66met SNP with LOAD

Sample	*Stratum*	*Case*[a]						*Control*						*P-value*[b]
		11[c]	*12*	*22*	*Sum*	*MAF*	*HWE P-value*[d]	*11*	*12*	*22*	*SUM*	*MAF*	*HWE P-value*	
UK	All	15	105	239	359	0.188	0.39	13	114	269	396	0.177	0.86	0.59
UK	APOE4−	5	40	95	140	0.179	0.77	10	92	199	301	0.186	1.00	0.85
UK	APOE4+	10	65	144	219	0.194	0.52	3	22	70	95	0.147	0.42	0.18
UCSD	All	6	73	109	188	0.226	0.21	16	110	235	361	0.197	0.51	0.27
UCSD	APOE4−	1	29	37	67	0.231	0.16	10	86	181	277	0.191	1.00	0.34
UCSD	APOE4+	5	43	70	118	0.225	0.79	6	23	53	82	0.213	0.18	0.81
WU	All	11	126	251	388	0.191	0.41	7	105	237	349	0.171	0.34	0.34
WU	APOE4−	3	51	108	162	0.176	0.42	7	75	187	269	0.165	1.00	0.71
WU	APOE4+	8	75	143	226	0.201	0.84	0	30	50	80	0.188	0.06	0.82
All	All	32	304	599	935	0.197	0.47	36	329	741	1106	0.181	1.00	0.21
All	APOE4−	9	120	240	369	0.187	0.23	27	253	567	847	0.181	0.91	0.73
All	APOE4+	23	183	357	563	0.203	1.00	9	75	173	257	0.181	0.83	0.32

[a]Counts of genotypes 11, 12, and 22 and minor allele frequency (MAF) are presented.
[b]Allelic *P*-value (exact test).
[c]Genotypes 11, 12, and 22 correspond to met/met, met/val, and val/val, respectively.
[d]Hardy–Weinberg equilibrium *P*-value.

interview and are assessed in the same manner as the cases. These samples all show an expected age- and *APOE4*-genotype distribution and do not appear to have any evidence of population stratification; more detailed information about these samples can be found in our recent publication.[10]

We carried out the SNP genotyping by allele-specific real-time PCR for individual samples.[10] Cases and controls were always run on the same plate in a blinded fashion. Overall, our genotyping accuracy is expected to be better than 99% as determined by internal and across group comparisons. The distributions of the three genotypes, 11, 12 or 22, corresponding to met/met, met/val and val/val, respectively, are provided in Table 1. An exact test showed that the observed genotype frequency conformed to Hardy–Weinberg equilibrium in cases and controls of all three sample sets. Exact tests and χ^2 tests were then used to assess allelic and genotypic associations, respectively. We found no significant association of the *BDNF* val66met SNP with LOAD in any of the three case control series, either individually or in a meta-analysis. Riemenschneider *et al*[4] reported that the *BDNF* 270C/T polymorphism was significantly associated with LOAD and the effect was stronger in *APOE4* negative individuals. We did not find a significant association between the val66met polymorphism and LOAD in our sample sets after stratifying for *APOE4* presence or absence. Thus, the *BDNF* val66met polymorphism is unlikely to be a risk factor in the etiology of LOAD.

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