7. Myers A, Holmans P, Marshall H, Kwon J, Meyer D, Ramic D, Shears S, Booth J, DeVrieze FW, Crook R, Hamshere M, Abraham R, Tunstall N, Rice F, Carty S, Lillystone S, Kehoe P, Rudrasingham V, Jones L, Lovestone S, Perez-Tur J, Williams J, Owen MJ, Hardy J, Goate AM (2000) Susceptibility locus for Alzheimer's disease on chromosome 10. Science 290:2304–2305
8. Li Y-J, Scott WK, Hedges DJ, Zhang F, Gaskell PC, Nance MA, Watts RL, et al (2002) Age at onset in two common neurodegenerative diseases is genetically controlled. Am J Hum Genet 70:985–993
9. Lee JH, Mayeux R, Mayo D, Mo J, Santana V, Williamson J, Flaquer A, Ciappa A, Rondon H, Estevez P, Lantigua R, Kawarai T, Toulina A, Medrano M, Torres M, Stern Y, Tycko B, Rogaeva E, St George-Hyslop P, Knowles JA (2004) Fine mapping of 10q and 18q for familial Alzheimer's disease in Caribbean Hispanics. Mol Psychiatry 9:1042–1051
10. Bertram L, Tanzi RE (2004) Alzheimer's disease: one disorder, too many genes? Hum Mol Genet Spec No 1 13:R135–R141
11. Hoggart CJ, Parra EJ, Shriver MD, Bonilla C, Kittles RA, Clayton DG, McKeigue PM (2003) Control of confounding of genetic associations in stratified populations. Am J Hum Genet 72:1492–1504
12. Lange C, DeMeo D, Silverman EK, Weiss ST, Laird NM (2004) PBAT: tools for family-based association studies. Am J Hum Genet 74:367–369

From the Genetics and Aging Research Unit, MassGeneral Institute for Neurodegenerative Diseases, Department of Neurology (L.B.; M.H.; R.E.T.), and Gerontology Research Unit, Department of Psychiatry (D.B.), Massachusetts General Hospital, Harvard Medical School, Charlestown, MA; and Departments of Biostatistics (C.L.) and Epidemiology (D.B.), Harvard School of Public Health, Boston

Address for correspondence and reprints: Dr. Lars Bertram, Genetics and Aging Research Unit, MGH-East, MassGeneral Institute for Neurodegenerative Diseases, 114 16th Street, Charlestown, MA 02129. E-mail: bertram@helix.mgh.harvard.edu

Am. J. Hum. Genet. 2006;79:180–183.

0002-9297/2006/7901-0022$15.00

Reply to Bertram et al.

To the Editor: The study by Bertram and colleagues (in this issue)[1] failed to replicate, in two family-based sample sets, the association of *rs498055* with Alzheimer disease (AD [MIM 104300]) that we observed in four large, well-characterized case-control sample sets.[2] Although the result is disappointing, there are several differences between the studies that may have contributed to these discrepant findings. First, there are significant differences in the study designs. Bertram et al. used two family-based sample sets that included subjects with both early- and late-onset AD (e.g., 320 families with late-onset AD and 117 families with early/mixed-onset in the National Institute of Mental Health [NIMH] sample set) of different ethnicities (94% white; 6% others),[3] which resulted in 147 informative families with late-onset AD for both sample sets combined. The characterization of their unaffected controls was based on self-assessment or a telephone interview, a procedure sufficient when "unaffecteds" are used solely to determine phase in linkage studies, but likely to significantly impact power in association studies, especially when familial loading is high, as it is in the sample of Bertram et al. Indeed, the authors acknowledge this in one of their previous publications by pointing out that the characterization of controls "may miss some mild cases of dementia" and lead "to a decrease in power."[3] In contrast, our study included only clinically evaluated, late-onset cases and nondemented controls of white origin. Second, the use of a family-based sample that was ascertained on the basis of multiple affected relatives is likely to particularly adversely impact power to detect a risk allele of relatively high frequency and small effect size, such as *rs498055*. Under these circumstances, the allele frequency in unaffected relatives also increases,[4] with consequent loss of power in comparison with case-control studies such as our own. To investigate this more fully, we compared the allele frequencies for a known genetic risk factor for AD, apolipoprotein E (*APOE* [MIM 107741]), and for the putative risk factor under debate, *rs498055,* in our combined case-control series and in the NIMH linkage families used by us in the study described by Myers et al.[5] In this context, it is worth noting that 355 of 372 individuals from the linkage sample–derived cases in our recent publication overlap with affected individuals in the NIMH family sample set described by Bertram et al. For the comparison, we identified the subgroup of NIMH families with genotypes for at least one unaffected and one affected individual and then selected at random one unaffected and one affected individual from each of these families. Table 1 illustrates clearly that the frequency of the *APOE4* allele is substantially higher in unaffected individuals from the linkage families than in unaffected individuals from the case-control series (30.4% vs. 12.5%) and that, although the *APOE4* allele frequency is highest in the linkage cases, the difference between the unrelated cases and controls is much greater than that between familial cases and related controls (35.6% vs. 12.5% compared with 42.8% vs. 30.4%). As a result, the odds ratio (OR) for the *APOE4* allele in the case-control series is 3.8, compared with only 1.7

Table 1. Frequency of AD Risk Alleles Is Higher in Unaffected Individuals from Multiply Affected Families Than in Unrelated Controls

	No. (%) of Subjects			
	Cases		Controls	
Locus and Allele	Linkage	CC	Linkage	CC
APOE:				
2	7 (2.3)	80 (4.2)	16 (5.2)	181 (8.5)
3	169 (54.9)	1,144 (60.2)	197 (64.4)	1,691 (79)
4 (Risk allele)	132 (42.8)	676 (35.6)	93 (30.4)	268 (12.5)
rs498055:				
A	133 (46.2)	915 (47.9)	140 (46.4)	1,174 (54.4)
G (Risk allele)	155 (53.8)	995 (52.1)	162 (53.6)	984 (45.6)

NOTE.—CC = case-control study.

for the family-based samples. Similarly for *rs498055,* the difference in frequencies between the cases and controls is greater for the unrelated samples than for the linkage families (table 1). Thus, the failure of Bertram et al. to replicate our results does not necessarily indicate that the original association was a false-positive result. We concur with Bertram et al. that the significant association of *rs498055* in four of six samples "may be unlikely to occur by chance"[1(p181)] (in this issue). However, it is possible that our initial study provided an overestimate of the allelic OR for *rs498055*. If this were true and the OR were <1.3, then the study by Bertram et al. would clearly be underpowered. Further replication in well-characterized sample sets is required to assess whether the association is genuine. Ideally, this should be done with large case-control sample sets, to achieve maximum power. For this particular marker, we estimate that 360 cases and 360 controls are needed to achieve 80% power in a replication study (one-sided $\alpha = .05$), assuming an allelic OR of 1.3 and a risk-allele frequency of 45.6%. A meta-analysis of all studies should then be performed to determine whether *rs498055* is associated with late-onset AD. In addition, it might be interesting to test the other reported significant markers from this region in additional sample sets.

Andrew Grupe, Yonghong Li, Charles Rowland, Tony Hinrichs, Peter Holmans, John Hardy, Michael O'Donovan, Michael J. Owen, Julie Williams, and Alison Goate

Acknowledgments

Funding for this work was partly provided by National Institutes of Health grant RO1 AG16208 (to A. Goate), the Medical Research Council, UK (to J.W., M.J.O., and M.O.), and the Alzheimer's Research Trust (to J.W. and M.J.O). J.H. is supported by the National Institutes of Health intramural program and by the VERUM Foundation (DIADEM project).

Web Resource

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for AD and *APOE*)

References

1. Bertram L, Hsiao M, Lange C, Blacker D, Tanzi RE (2006) Single-nucleotide polymorphism *rs498055* on chromosome 10q24 is not associated with Alzheimer disease in two independent family samples. Am J Hum Genet 79:180–183 (in this issue)
2. Grupe A, Li Y, Rowland C, Nowotny P, Hinrichs AL, Smemo S, Kauwe JSK, et al (2006) A scan of chromosome 10 identifies a novel locus showing strong association with late-onset Alzheimer disease. Am J Hum Genet 78:78–88
3. Bertram L, Hiltunen M, Parkinson M, Ingelsson M, Lange C, Ramasamy K, Mullin K, Menon R, Sampson AJ, Hsiao MY, Elliott KJ, Velicelebi G, Moscarillo T, Hyman BT, Wagner SL, Becker KD, Blacker D, Tanzi RE (2005) Family-based association between Alzheimer's disease and variants in UBQLN1. N Engl J Med 352:884–894
4. Risch N, Teng J (1998) The relative power of family-based and case-control designs for linkage disequilibrium studies of complex human diseases I: DNA pooling. Genome Res 8:1273–1288
5. Myers A, Wavrant De Frieze F, Holmans P, Hamshere M, Crook R, Compton D, Marshall H, et al (2002) A full genome screen for Alzheimer's disease: stage two analysis. Neuropsychiatric Genetics 114:235–244

From Celera Diagnostics, Alameda, CA (A. Grupe; Y.L.; C.R.); Departments of Psychiatry, Neurology, and Genetics, Washington University, St. Louis (T.H.; A. Goate); Biostatistics and Bioinformatics Unit and Department of Psychological Medicine, Wales College of Medicine, Cardiff University, Cardiff (P.H.; M.O.; M.J.O.; J.W.); and National Institute on Aging, Bethesda (J.H.)

Address for correspondence and reprints: Dr. Alison Goate, Department of Psychiatry, B8134, Washington University School of Medicine, 660 S. Euclid Avenue, St. Louis, MO 63110. E-mail: goate@icarus.wustl.edu

Am. J. Hum. Genet. 2006;79:183–184.

0002-9297/2006/7901-0023$15.00

The *SERPINE2* Gene and Chronic Obstructive Pulmonary Disease

To the Editor: In the February 2006 issue of the *Journal,* DeMeo et al.[1] identified *SERPINE2* as a positional candidate gene for susceptibility to chronic obstructive pulmonary disease (COPD [MIM 606963]) and reported on the association of polymorphic variants of this gene with early-onset disease in a family-based study and with severe disease in a case-control study. With early prior information provided by the authors, we have independently tested for an association of the *SERPINE2* gene with COPD in the largest case-control study reported to date. Our study consists of 1,018 COPD cases and 911 controls prospectively recruited from six European centers. We have provided details about the patients elsewhere.[2] The study population was screened for genotypes at the Medical Research Council (United Kingdom) Gene Services Unit for five SNPs (table 1) in the *SERPINE2* gene. All the SNPs evaluated were reported in the study by DeMeo et al. as associated with disease, with three of the five associated with disease in both the family and case-control study cohorts they assessed.

Table 1. LD between *SERPINE2* SNPs Expressed as r^2

	r^2 for SNP			
SNP	*rs1438831*	*rs920251*	*rs6747096*[a]	*rs3795879*
rs920251	.952 (1.0)	…	…	…
rs6747096[a]	.140	.148	…	…
rs3795879[a]	.140 (.145)	.145 (.145)	.964	…
ss49785625[a]	.020	.023	.054	.055

NOTE.—The r^2 values in parentheses are values obtained from HapMap and compared with our own data in controls. *ss49785625* and *rs6747096* are not in HapMap.

[a] SNP reported by DeMeo et al.[1] to be associated with disease in both family and case-control cohorts.