report (15, 16).

The results we report show that plasma Aβ can be used as a quantitative trait for identifying novel LOAD loci. This approach is a powerful complement to other methods for identifying genetic risk factors for LOAD. It enables the evaluation of candidate genes at a mechanistic level and, because multiple generations can be analyzed in extended pedigrees grouped according to their phenotypic characteristics, the power to detect linkage and to obtain precise localization is increased. Thus, by analyzing 124 subjects in five families identified via a proband with extremely high Aβ42, we obtained highly significant linkage that was well localized to chromosome 10 with a 1-lod support interval of ~8 cM. These results fit well with those obtained in the second stage of the sibling pair study that provided our candidate regions (17). In that study, published jointly with our findings, Myers et al. analyzed 429 affected sibling pairs in 342 sibships and obtained significant linkage to the same region of chromosome 10 with a 1-lod support interval of ~16 cM. Together, the results of these two studies, performed on nonoverlapping family series, provide compelling, mutually confirmatory evidence for a novel LOAD locus on chromosome 10. From our results, it appears that this locus increases risk for AD by increasing Aβ. Because we have sought linkage to the high Aβ phenotype in only a small fraction of the human genome, it is likely that additional LOAD loci will be detected by this method as we evaluate the remainder of the genome in our collection of families.

Mutations in three genes encoding β-amyloid precursor protein (APP), presenilin 1, and presenilin 2 cause the rare, early-onset autosomal dominant form of Alzheimer’s disease (AD) (1). These mutations all affect APP metabolism such that more Aβ42 peptide is produced (2). In contrast, most AD cases have ages of onset above 65 years and exhibit no clear pattern of inheritance (late-onset Alzheimer’s disease or LOAD). The E4 allele of the apolipoprotein E (APOE) gene is the only known genetic risk factor for LOAD (3, 4). However, 50% of LOAD cases carry no APOE4 alleles, suggesting that other risk factors must exist. We performed a two-stage genome-wide screen in sibling pairs with LOAD to detect other susceptibility loci. Here we report evidence for an Alzheimer’s disease locus on chromosome 10. Our stage one multipoint lod score (logarithm of the odds ratio for linkage/no linkage) of 2.48 (266 sibling pairs) increased to 3.83 in stage 2 (429 sibling pairs) close to D10S1225 (79 centimorgans). This locus modifies risk for Alzheimer’s disease independent of APOE genotype.

The apolipoprotein E (APOE) gene is the only genetic risk factor that has so far been linked to risk for late-onset Alzheimer’s disease (LOAD). However, 50 percent of Alzheimer’s disease cases do not carry an APOE4 allele, suggesting that other risk factors must exist. We performed a two-stage genome-wide screen in sibling pairs with LOAD to detect other susceptibility loci. Here we report evidence for an Alzheimer’s disease locus on chromosome 10. Our stage one multipoint lod score (logarithm of the odds ratio for linkage/no linkage) of 2.48 (266 sibling pairs) increased to 3.83 in stage 2 (429 sibling pairs) close to D10S1225 (79 centimorgans). This locus modifies risk for Alzheimer’s disease independent of APOE genotype.

Susceptibility Locus for Alzheimer’s Disease on Chromosome 10

Amanda Myers,1 Peter Holmans,1* Helen Marshall,1
Jennifer Kwon,1 David Meyer,1 Dzanan Ramic,1 Shantia Shears,1
Jeremy Booth,1 Fabienne Wavrant DeVrieze,2 Richard Crook,2
Marian Hamshire,3 Richard Abraham,3 Nigel Tunstall,4
Francis Rice,3 Stephanie Carty,3 Sara Lillystone,3 Pat Kehoe,3
Varuni Rudrasingham,5 Lesley Jones,3 Simon Lovestone,4
Jordi Perez-Tur,5 Julie Williams,3 Michael J. Owen,3 John Hardy,2
Alison M. Goate1†

The apolipoprotein E (APOE) gene is the only genetic risk factor that has so far been linked to risk for late-onset Alzheimer’s disease (LOAD). However, 50 percent of Alzheimer’s disease cases do not carry an APOE4 allele, suggesting that other risk factors must exist. We performed a two-stage genome-wide screen in sibling pairs with LOAD to detect other susceptibility loci. Here we report evidence for an Alzheimer’s disease locus on chromosome 10. Our stage one multipoint lod score (logarithm of the odds ratio for linkage/no linkage) of 2.48 (266 sibling pairs) increased to 3.83 in stage 2 (429 sibling pairs) close to D10S1225 (79 centimorgans). This locus modifies risk for Alzheimer’s disease independent of APOE genotype.

†To whom correspondence should be addressed. E-mail: goate@icarus.wustl.edu

1Department of Psychiatry, Washington University School of Medicine, 660 S. Euclid, St. Louis, MO 63110, USA. 2Laboratory for Neurogenetics, Birdsell Building, Mayo Clinic Jacksonville, Jacksonville, FL 32224, USA. 3Department of Psychological Medicine, University of Wales College of Medicine, Cardiff, UK. 4Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK. 5Unitat de Genètica Molecular, Institut de Biomedicina de València-CSIC, E-46010 València, Spain.

*Present address: MRC Biostatistics Unit, Institute of Public Health, Cambridge CB2 2SR, UK.

†To whom correspondence should be addressed. E-mail: goate@icarus.wustl.edu
reports

the genome (5, 6). Nonparametric methods, which do not require the mode of inheritance to be specified, were used to analyze these data in the whole sample and in two subsamples stratified by APOE genotype. We observed 16 chromosomal regions with a multipoint logarithm of the odds ratio for linkage/no linkage (lod score) (MLS) ≥ 1 (6). Four of the sixteen peaks, including one on chromosome 10, met the criteria for “suggestive” linkage (7).

For stage 2, markers within the stage 1 peaks were genotyped in an additional 168 ASPs (83 newly ascertained in the United Kingdom, 80 obtained from the Indiana Alzheimer Disease Center National Cell Repository, and 5 from the National Institute of Mental Health Genetics Initiative) (8). On chromosome 10, 15 additional markers were genotyped in all 429 ASPs, reducing the average interval to 5 cM. Two-point analyses were carried out between each marker locus and the disease allele, and reflect changes in diagnoses. This lod score increased to 3.83 at 79 cM in stage 2 (between D10S1227 and D10S1225). An MLS of 3.83 would be expected to occur by chance 0.01 times per genome scan, considering the whole-sample analysis alone (or ~0.05 per genome allowing for all three analyses) (12). The stage 2 analysis of APOE4+ve ASPs gave a maximum MLS of 2.78 at D10S1225, whereas the APOE4–ve pairs gave a maximum MLS of 0.66 at 85.4 cM. However, allele sharing was similarly elevated (to 59%) in all three subgroups, indicating that stratification of the sample by APOE4 did not change the proportion of allelic sharing at the peak.

In conclusion, we have confirmed our preliminary observation of a region of suggestive linkage on chromosome 10 (6), providing strong evidence for a susceptibility locus for LOAD. This locus was robustly detected in both stages of our genome screen and shows a maximum MLS greater than that observed in the same data set on chromosome 19 around the APOE locus. This suggests that the chromosome 10 locus is a major risk factor for LOAD. Indeed, we estimate the chromosome 10 locus-specific λ’s (relative risk to siblings) to be about equivalent to that for APOE. In the accompanying report by Ertekin-Taner et al. (13), there is evidence that a quantitative trait locus for high Aβ42 levels maps to the same chromosomal region. This suggests that the AD susceptibility allele identified in our study increases risk for disease by modifying Aβ42 metabolism.

Fig. 1. Chromosome 10 multipoint map for LOAD. Multipoint linkage analyses were carried out with the program MAPMAKER/SIBS (11) on the whole sample, on pairs where both siblings had at least one APOE4 allele, and on pairs where neither sibling had an APOE4 allele (Fig. 1). These analyses use information from adjacent markers to determine the most likely location of the disease susceptibility allele. The stage 1 maximum MLS of 2.48 at 77.6 cM is slightly different from that previously reported (6) and reflects changes in diagnoses. This lod score increased to 3.83 at 79 cM in stage 2 (between D10S1227 and D10S1225).

References and Notes
5. Many data and biomaterials were collected in three projects that participated in the National Institute of Mental Health (NIMH) Alzheimer’s Disease Genetics Initiative. From 1991 to 1998, the principal investigators and coinvestigators were as follows: Massachusetts General Hospital, Boston, MA, U01 MH46260, Marilyn S. Albert and Deborah Blacker; Johns Hopkins University, Baltimore, MD, U01 MH46290, Susan Bassett, Gary A. Chase, and Marshal F. Folstein; and University of Alabama, Birmingham, AL, U01 MH46373, Rodney C. P. Go and Lindy E. Harrell.
8. See Web table 1 for sample characteristics (14).
10. See Web table 2 for two-point lod scores and allele sharing identical-by-descent (IBD) sharing (15).
12. Accurate estimates of genome-wide significance were obtained by repeating the analysis on replicate “genomes” simulated in the absence of a disease locus with the observed marker maps, allele frequencies, and typed individuals. For more details on the method, see N. M. Williams et al. [Hum. Mol. Genet. 8, 1729 (1999)].
14. Supplementary material is available at www.sciencemag.org/cgi/content/full/290/5500/2304/DC1.
15. See www.marshfieldmed.genetics/mapmarkers/maps/indexmap.html.
16. J.W., M.J.O., and S.L. are supported by the UK Medical Research Council. A.M.G. and J.H. are supported by NIH grants AG16208 and AG5681. A.M.C. was supported by the Nettie and Rebecca Brown Fund. We thank the families who participated in this study.
31 August 2000; accepted 16 November 2000