

Analyses of the National Institute on Aging Late-Onset Alzheimer's Disease Family Study

Implication of Additional Loci

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Objective: To identify putative genetic loci related to the risk of late-onset Alzheimer disease (LOAD).

Design: Linkage analysis and family-based and case-control association analyses from a genomewide scan using approximately 6000 single-nucleotide polymorphic markers at an average intermarker distance of 0.65 cM.

Setting: The National Institute on Aging Genetics Initiative for Late-Onset Alzheimer's Disease (NIA-LOAD) was created to expand the resources for studies to identify additional genes contributing to the risk for LOAD.

Participants: We investigated 1902 individuals from 328 families with LOAD and 236 unrelated control subjects.

Main Outcome Measures: Clinical diagnosis of LOAD.

Results: The strongest overall finding was at chromosome 19q13.32, confirming the effect of the apolipoprotein E gene on LOAD risk in the family-based and case-control analyses. However, single-nucleotide polymorphisms at the following loci were also statistically significant in 1 or more of the analyses performed: 7p22.2, 7p21.3, and 16q21 in the linkage analyses; 17q21.31 and 22q11.21 in the family-based association analysis; and 7q31.1 and 22q12.3 in the case-control analysis. Positive associations at 7q31.1 and 20q13.33 were also significant in the meta-analysis results in a publicly available database.

Conclusions: Several additional loci may harbor genetic variants associated with LOAD. This data set provides a wealth of phenotypic and genotypic information for use as a resource in discovery and confirmatory research.

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Group Information: Investigators from the Consortium of Alzheimer's Disease Centers in the National Institute on Aging Late-Onset Alzheimer's Disease Family Study Group are listed at the end of this article.

ALTHOUGH THE APOLIPOPROTEIN E $\epsilon 4$ allele (APOE $\epsilon 4$) (OMIM 107741) is the most consistently replicated genetic variant influencing the risk of late-onset Alzheimer disease (LOAD),¹ it explains only 20% of the attributable genetic risk.² Daw et al³ reported that there may be 4 additional genes influencing LOAD risk. Although a number of susceptibility genes have been reported (<http://www.alzgene.org/>), the number of genes that have been replicated across multiple studies remains small. Whereas some genes (eg, sortilin-related receptor 1 [SORL1]⁴ and angiotensin-converting enzyme [ACE]⁵) are strongly supported by several studies across multiple ethnic groups, other genes need further evaluation (eg, low-density lipoprotein receptor-related protein 6 [LRP6],⁶ GRB-2-associated binding protein [GAB2],⁷ and cholesterol 25-hydroxylase [CH25H]⁸).

In early 2007, 968 association studies of 398 candidate genes were compiled by AlzGene (<http://www.alzgene.org/>), but

most have not been replicated. Ertekin-Taner⁹ has described several reasons for the lack of replication, but progress in identifying and confirming genetic variants related to LOAD may also be limited because of the paucity of data sets and samples available to the scientific community. In 2002, the National Institute on Aging (NIA) launched the NIA Genetics Initiative for Late-Onset Alzheimer's Disease (NIA-LOAD) to expand resources needed to identify the remaining genes contributing to the risk for LOAD. The NIA-LOAD Family Study, a major component of the initiative, has as its goals to identify and recruit families with 2 or more affected siblings with LOAD and unrelated, nondemented control subjects similar in age and ethnic background. The clinical data, DNA, genotyping results, and preliminary analyses will be made available to investigators worldwide. Herein we describe the families and the results of linkage, family-based association, and case-control analyses from a genomewide scan using approximately 6000 single-nucleotide polymorphic (SNP) markers.

SUBJECTS AND SETTING

Recruitment took place throughout the United States at 18 participating AD centers (ADCs), each of which had received approval by their institutional review board. A collaborative effort by each ADC, the NIA, the Alzheimer's Disease Education and Referral Center, and the Alzheimer's Association led to national media coverage, which facilitated recruitment. A toll-free number at the National Cell Repository for Alzheimer's Disease (<http://ncrad.iu.edu>) was made available. When qualifying families contacted the National Cell Repository, research staff referred the family to the geographically closest participating ADC for evaluation.

RECRUITMENT

The recruitment criteria included a family with multiple members affected with LOAD that could provide clinical information and a biological sample for DNA extraction. The proband had to have a diagnosis of definite or probable LOAD¹⁰ with onset after 60 years of age and a full sibling with definite, probable, or possible LOAD with onset after 60 years of age. A third biologically related family member was required, who could have been a first-, second-, or third-degree relative of the affected sibling pairs and 60 years or older if unaffected or 50 years or older if diagnosed as having LOAD or mild cognitive impairment.¹¹ Unaffected persons were required to have had documented cognitive testing and clinical examination results to verify the clinical designation.

CLINICAL ASSESSMENT

A minimal data set included demographic variables, diagnosis, age at onset, method of diagnosis, Clinical Dementia Rating Scale score,¹² and the presence of other relevant health problems. Each ADC was required to use standard research criteria for the diagnosis of LOAD.¹⁰ Participants with advanced disease or those living in a remote location who could not complete a detailed in-person evaluation contributed blood samples, and the site investigator conducted a detailed review of medical records to document the presence or absence of LOAD.

The age at onset for patients with LOAD was the age at which the family first observed memory problems, but, if this information was not available, the age at first examination was used. For controls, we used their age at the time of their examination confirming the absence of dementia. For 137 deceased family members who had undergone a postmortem brain evaluation, neuropathologic results were used to document the diagnosis. The clinical diagnosis of LOAD agreed with the autopsy diagnosis for 95% of the case patients who had both diagnoses.

FAMILY RELATIONSHIP AND HARDY-WEINBERG EQUILIBRIUM CHECKS

Before SNP genotyping, we verified the reported family relationships using 9 microsatellite markers (7 autosome markers and 1 X and 1 Y chromosome marker). Subsequently, we used 3 sets of more than 570 SNPs by selecting every 10th SNP to evaluate relationships among family members with the Pedigree Relationship Statistical Test.^{13,14} Based on the results, we corrected family relationships in 40 families (detailed information is available from the authors upon request), and we ex-

cluded individuals who were not biologically related to any family ($n=3$ individuals). Four families were excluded because problems with reported relationships could not be resolved adequately, and we excluded 1 family with a presenilin 1 gene (*PSEN1*) mutation. We then checked for inconsistencies in mendelian transmission using PedCheck¹⁵ and corrected them. We considered erroneous genotypes from these individuals as missing.

We assessed Hardy-Weinberg equilibrium using the Haploview software (<http://www.broad.mit.edu/mpg/haploview/>)¹⁶ and excluded SNPs that deviated from Hardy-Weinberg equilibrium with a P value of less than .001. To identify regions with high linkage disequilibrium (LD) we computed pairwise LD coefficients and created 95% confidence bounds on D' to define SNP pairs in strong LD.¹⁷ For multipoint linkage analysis, we used 1 SNP from each haplotype block to ensure that the D' between adjacent markers remained low; as a result, we dropped 255 SNPs that were in strong LD with adjacent SNPs.

GENOTYPING

Single-nucleotide polymorphisms were genotyped at the Center for Inherited Disease Research using a marker panel (Illumina Linkage-IVb Marker Panel; <http://www.cidr.jhmi.edu>). From this panel, 5954 SNP markers were originally genotyped. After eliminating SNP genotypes with uncertain calls, excess missing data, or mendelian errors, a total of 5616 SNPs were available for statistical analysis at an intermarker distance of 0.65 cM (519 kilobase [kb]); the average marker heterozygosity was 0.43. Missing data rate among the released genotype data was 0.21% (32 581 of 15 450 676 total genotypes).

Genotyping of *APOE* polymorphisms (based on SNPs rs7412 and rs429358) was performed at PreventionGenetics (<http://www.preventiongenetics.com>). Genotyping was performed in array tape using allele-specific polymerase chain reaction analysis with universal molecular beacons. The DNA sequencing of positive control DNA samples was completed to ensure correct assignment of alleles.

STATISTICAL ANALYSIS

Unless stated otherwise, analyses were conducted using the following definitions of LOAD based on standard research criteria: (1) broad, which included definite, probable, or possible LOAD and (2) narrow, which included as affected only those individuals who met criteria for definite or probable LOAD. We classified the affection status of family members with other forms of dementia or with mild cognitive impairment as unknown for the purposes of genetic analyses. For the linkage and family-based analyses using the narrow definition, we also classified patients with possible LOAD as unknown.

LINKAGE ANALYSIS

Single-point and multipoint nonparametric linkage analyses based on the algorithm of Kong and Cox¹⁸ were implemented using a multipoint engine for rapid likelihood inference (MERLIN),^{19,20} and we calculated nonparametric logarithm of odds (LOD) scores based on an established algorithm.²¹ We computed allele frequencies using all genotyped subjects. Given the important role of *APOE* $\epsilon 4$ in LOAD, we performed a conditional linkage analysis to test for a 2-locus model in which a polymorphism or variant at a given locus has an influence on LOAD only in the presence of the *APOE* $\epsilon 4$ allele.

Table 1. Characteristics of Families With LOAD Included in the Genomewide Scan

	Family-Based Analyses		Case-Control Analyses	
	Individuals or Families (n=1902 Individuals or 328 Families)		Patients ^a (n=328)	Controls (n=236)
Alzheimer disease, No. (%) ^b or No.				
Broad definition ^c	776 (40.8)	320	NA	
Narrow definition ^d	665 (34.9)	319	NA	
Unaffected	873 (45.9)	NA	237	
Unknown	253 (13.3)	NA	NA	
Mean (SD) age at onset, y ^e	73.9 (7.5)	73.3 (7.1)	78.1 (9.1)	
Mean (SD) No. of patients per family	2.4 (0.68)	NA	NA	
Affected persons per family, No. (%) ^f				
≥5	6 (1.8)	NA	NA	
4	16 (4.9)	NA	NA	
3	69 (21)	NA	NA	
2	237 (72.3)	NA	NA	
Women, No. (%)	1183 (62.2) ^b	203 (61.9)	138 (58.5)	
<i>APOE</i> allele frequency, %				
ε4	30.9	43.1	9.5	
ε3	65.5	53.7	80.7	
ε2	3.5	3.2	9.8	

Abbreviations: *APOE*, apolipoprotein E gene; LOAD, late-onset Alzheimer disease; NA, not applicable.

^a One patient from each family was chosen as the case for the case-control analysis. In most instances, this was the proband.

^b Based on a total of 1902 individuals.

^c Includes possible, probable, and definite LOAD.

^d For linkage analyses including the narrow definition of affected (ie, probable and definite LOAD), individuals with possible LOAD were reclassified as unknown.

^e For the case-control data set, age at the last evaluation is presented.

^f Based on a total of 328 families.

FAMILY-BASED AND CASE-CONTROL ASSOCIATIONS

We conducted single-point family-based association test (FBAT) analysis as implemented in version 1.7.3 of the FBAT software.^{22,23} We tested the hypothesis of no linkage and no association under an additive model, rather than the hypothesis of no association in the presence of linkage, because the primary goal of the analysis was to identify a novel candidate region rather than to fine map previously identified loci from the linkage analysis. We estimated allele frequencies for FBAT using parental genotype data, which we estimated from the offspring genotype database using the expectation-maximization algorithm. We also used the FBAT software to confirm the relation between *APOE* and LOAD. For the case-control data set, we first performed the χ^2 test to assess the allelic association between LOAD and SNPs.

For the case-control analysis, we selected 1 affected individual from each family with definite or probable LOAD. The unrelated, unaffected individuals served as controls. For the case-control analysis, we used the χ^2 test to assess the allelic association between LOAD and SNPs. We assessed population stratification using the Structure program, version 2.2 (<http://pritch.bsd.uchicago.edu/structure.html>),^{24,25} by using 103 unlinked SNPs to measure population substructure. We chose 103 SNPs that were present in both the Illumina-IVb linkage panel and the HapMap data set (<http://www.hapmap.org>). This was necessary because the present study participants were predominantly white and we lacked genotype data for nonwhite subjects. Thus we used the genotype data from the NIA-LOAD samples for white subjects and used the genotype data from the HapMap data set for nonwhite subjects. The allele frequencies for white subjects with LOAD in the NIA-LOAD data set were similar to those for white subjects in the HapMap data set. The results from the Structure analysis were used in an association analysis implemented in the STRAT program, version 1.0.^{24,25}

To determine the consistency of our findings, we examined allelic associations in an independent, publicly available data set from the Translational Genomics Research Institute (TGen) that included 859 patients and 552 controls, for a total of 1411 individuals (<http://www.tgen.org/neurogenomics/data>).⁷ We restricted our evaluation of the TGen data to SNPs that were only significant in the case-control analysis discussed in the "Results" section at $P < .005$. However, the TGen data set was genotyped using a microarray platform (Affymetrix platform; Affymetrix, Inc, Santa Clara, California) that included approximately 500 000 SNPs. Because SNPs were not identical, we included 5 SNPs on either side of the candidate SNP location derived from the current analysis. Imputation was not possible owing to the sparse genotyping in the NIA-LOAD families. Single-point allelic association was performed using Haploview software.¹⁶ Haplotype analysis was not performed.

RESULTS

CHARACTERISTICS OF THE FAMILY DATA SET

The linkage and association analyses were restricted to 328 white families (1902 individuals) because more than 90% of the cohort were of European or North American ancestry (**Table 1**). The mean (SD) age at onset of symptoms for affected individuals was 73.9 (7.5) years, and the mean (SD) age at diagnosis was 77.2 (7.5) years. Of the 1902 individuals, 40.8% were affected and 45.9% were considered unaffected. The remaining 13.3% had other forms of dementia or mild cognitive impairment. All data, including pedigree structure, affection status, and genotype data used in the analysis, are available at the Web

Table 2. Single-Point LOD Scores for 2 Definitions of LOAD

Chr No.	SNP	Physical Position, bp ^a	Distance, cM	Broad Definition ^b		Narrow Definition ^c	
				LOD	P Value	LOD	P Value
1	rs7528979	10 027 723	16.70	1.69	.003	2.97	.00011
1	rs2361364	242 585 416	270.69	1.08	.013	2.37	.0005
3	rs714697	116 840 845	122.99	2.44	.0004	1.49	.004
4	rs230490	103 744 598	107.43	2.06	.001	1.59	.003
6	rs767022	9 084 652	21.68	1.11	.012	2.26	.0006
6	rs2036256	119 879 621	119.71	2.30	.0006	0.32	.11
7	rs798485	2 576 751	6.30	3.77	.00002	2.67	.0002
7	rs719423	7 128 355	13.58	2.89	.00013	3.58	.00002
8	rs388047	26 496 146	45.69	2.06	.001	1.60	.003
8	rs985942	57 984 794	69.22	2.80	.0002	0.84	.02
9	rs1143025	14 602 188	30.90	0.80	.03	2.23	.0007
9	rs720974	21 509 904	42.25	2.10	.0009	1.34	.006
10	rs1537626	7 693 130	21.81	2.35	.0005	1.17	.01
11	rs526572	56 918 458	64.12	1.97	.0013	2.82	.0002
12	rs2058290	125 600 027	149.59	1.62	.003	2.50	.0003
16	rs889551	31 167 923	56.80	1.93	.0014	2.99	.0001
16	rs1510986	47 722 142	58.69	1.56	.004	2.17	.0008
16	rs2063099	50 018 372	62.70	0.92	.02	2.07	.001
16	rs837529	54 043 795	70.70	2.52	.0003	1.61	.003
16	rs735144	55 441 425	72.69	2.58	.0003	3.50	.00003
16	rs1982395	56 226 257	74.24	2.04	.0011	2.88	.00014
16	rs37358	56 752 427	75.21	1.62	.003	2.12	.0009
16	rs1482258	58 068 592	76.94	3.32	.00005	3.98	.00001
16	rs768462	58 627 349	78.28	1.86	.002	2.27	.0006
16	rs244415	68 224 184	85.91	1.90	.002	2.35	.0005
18	rs972900	33 589 644	59.09	2.24	.0007	1.03	.015
19	rs2341000	52 774 852	75.77	2.49	.0004	1.12	.012
22	rs7286586	48 122 970	70.43	1.13	.011	2.08	.001

Abbreviations: bp, base pair; Chr, chromosome; LOAD, late-onset Alzheimer disease; LOD, logarithm of odds; SNP, single-nucleotide polymorphism.

^aThis study used the SNPs from the Illumina Linkage IVb SNP panel. The physical positions are based on the Human Genome Build 35, and the genetic locations are the interpolated position from the deCODE genetic map.²⁶

^bIncludes definite, probable, and possible LOAD.

^cIncludes definite and probable LOAD.

site at the NIA Genetics of Alzheimer Disease Data Storage Site (<http://www.niageneticsdata.org>).

For the case-control analysis, we studied 328 patients and 236 unrelated controls. The mean age at onset of dementia was 73.3 (range, 60-92) years, and the mean age of the last evaluation for controls was 78.1 (range, 60-99) years. Women constituted 61.9% of the participating family members and 58.5% of the controls. The *APOE* ε4 allele was present in 43.1% of the cases and 9.5% of the controls.

SINGLE-POINT LINKAGE ANALYSIS

Using the broad definition of LOAD, 15 SNPs had LOD scores exceeding 2, including the following 2 SNPs with LOD scores of greater than 3: rs798485 (7p22.2; LOD score, 3.77) and rs1482258 (16q21; LOD score, 3.32) (**Table 2**). The SNP rs1482258 and 3 adjacent markers within a 6-cM region showed strong support for linkage with LOD scores exceeding 2. In addition, rs719423 (7p21.3) showed evidence of suggestive linkage (LOD score, 2.89). At 19q13.32, SNP rs2341000 similarly showed a strong support for linkage (LOD score, 2.49), most likely due to its proximity to *APOE*. Three markers with evidence of suggestive linkage, rs2036256 (6q22.31), rs720974 (9p21.3), and rs1537626 (10p14),

have been previously reported as statistically significant in other studies (<http://www.alzgene.org>).

Using the narrow definition, the following 3 SNPs achieved LOD scores of 3.0 or greater: rs719423 at 7p21.3 (7.28 cM from rs798485 at 7p22.2), rs735144 at 16q13 (4.25 cM from rs1482258 at 16q21), and rs1482258 at 16q21. For the 3 most significant SNPs under the broad definition, LOD scores for rs1482258 at 16q21 and rs719423 at 7p21.3 increased under the narrow definition, whereas the LOD score for rs798485 at 7p22.2 decreased slightly. At or near 16q21 within a 27-cM region, a total of 9 SNPs had LOD scores exceeding 2.

MULTIPOINT LINKAGE ANALYSIS

Using the broad definition, the strongest evidence of linkage in the multipoint analysis was for 2 SNPs near *APOE* at 19q13.31-2 (LOD scores, 3.10 and 3.19) (**Figure 1A**). In fact, 23 SNPs within a 14.8-cM region near *APOE* had LOD scores greater than 2.0 in the region extending from 19q13.12 to 19q13.32. Three additional SNP clusters at chromosomes 7p22.1, 8p21.3, and 18q12.2 also had LOD scores of 2.0 or greater. The LOD scores decreased slightly using the narrow definition of LOAD in the multipoint analysis for the SNPs clustering at 19q13.31-32 (**Figure 1B**). Findings for 7 SNPs near 7p22.1-3, 2 SNPs

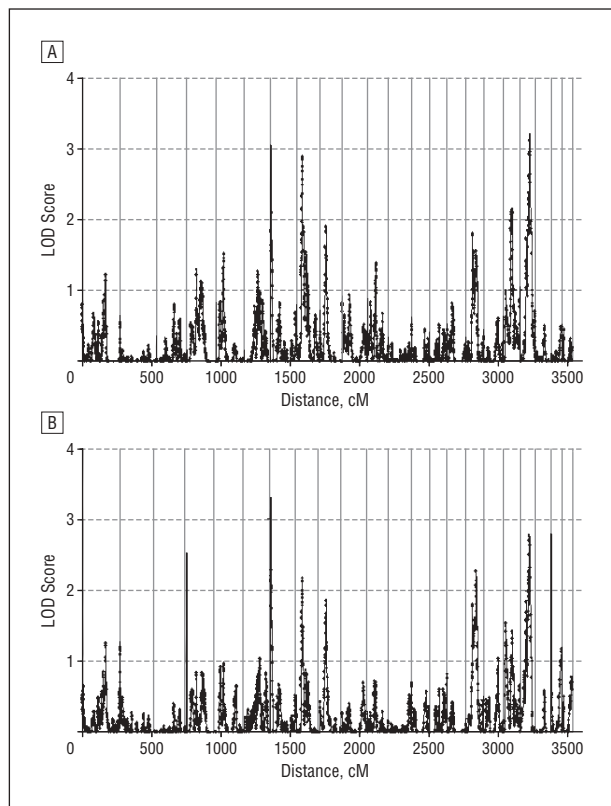


Figure 1. Multipoint logarithm of odds (LOD) scores for late-onset Alzheimer disease (LOAD). A, Multipoint LOD scores for a broad definition of LOAD (ie, definite, probable, and possible). Results for all 22 chromosomes are shown on a single graph. Single-nucleotide polymorphisms (SNPs) near the gene for apolipoprotein E (*APOE*) at 19q13.31-2 had the highest LOD scores. Additional SNP clusters at 7p22.1, 8p21.3, 6q21, and 18q12.2 also had LOD scores of 2.0 or greater in 1 of the analyses. B, Multipoint LOD scores for a narrow definition of LOAD (ie, definite and probable). Results for all 22 chromosomes are shown on a single graph.

at 8p21.3, and 4 SNPs in a 1.5-cM region around 16q21 remained suggestive of linkage.

FAMILY-BASED ASSOCIATION

Using the broad definition, 6 SNPs showed association with LOAD, with P values of less than .001 (range, .000063 to $<.000968$). The SNP rs174345 at 22q11.21 showed the strongest association ($P=.000063$). Of interest, rs744281 proximal to 17q21.31 was also strongly associated with LOAD, a marker near the gene encoding tau at 17q21.1. The SNPs at 2p14, 3q13.31, 8p21.3, and 11p14.3 were also associated with LOAD. Under the narrow definition, 9 SNPs had P values of less than .001 (range, .000174 to $<.000815$). At 8p21.3, SNP rs4427168 showed the most significant association with LOAD ($P=.000174$). This SNP, along with rs174345 at 22q11.21, was associated with LOAD under both disease definitions. These associations are illustrated in **Figure 2**.

CASE-CONTROL ASSOCIATION ANALYSIS

In addition to the 2 coding SNPs for *APOE*, the most significant association was observed with rs762883 at 22q12.3 ($P=.000069$) (**Table 3**). We found that other loci showed evidence of association (defined as $-\log [P] > 2.5$) in-

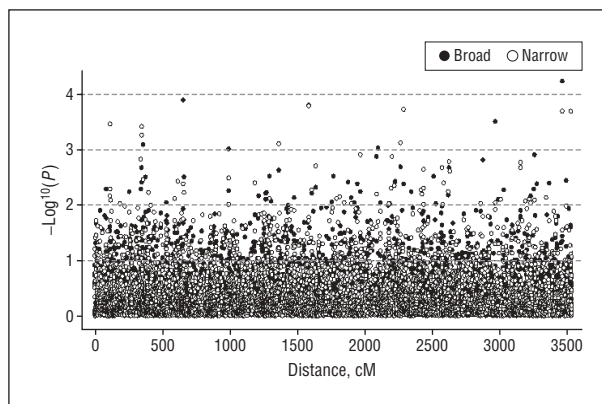


Figure 2. Family-based association test (FBAT) analysis using broad (ie, definite, probable, and possible) and narrow (ie, definite and probable) definitions of late-onset Alzheimer disease (LOAD). The $-\log_{10}(P)$ represents logarithm-transformed P values for the Z scores from the FBAT analysis. The single-nucleotide polymorphisms (SNPs) at 22q11.21 showed the strongest association ($P=.000063$). An SNP proximal to 17q21.31 was also strongly associated with LOAD, a marker near the gene encoding tau at 17q21.1. Under the narrow definition, 9 SNPs had P values less than .001. At 8p21.3, SNP rs4427168 showed the most significant association with LOAD ($P=.000174$). This SNP and rs174345 at 22q11.21 were associated with LOAD under both disease definitions.

cluded SNPs at 1p34.3, 1q41, 2p21, 2q24.3, 3q26.1, 7q21.3, 7q31.1, 8q23.3, 11q24.3, 14q13.1, 15q15.1, 20q13.33, and 22q12.3. All SNPs that were significant in the χ^2 analysis remained significant in the STRAT analysis.^{24,25}

Using the TGen LOAD data set,⁷ we found concordance with allelic associations at $P < .05$ for 3 SNPs that were significant in this case-control analysis (results available from the authors upon request). Single-nucleotide polymorphism A-2236481 (rs41377151) (located 10.9 kb away from rs7412, 1 of the coding SNPs for *APOE*) was significantly associated with LOAD ($P=3.29 \times 10^{-36}$) in the TGen data set. In addition, SNP A-1968867 (rs6027452) on chromosome 20 (located 4.5 kb away from the candidate SNP rs1381100 [20q13.33; $P=.04$]) and SNP A-4212589 (rs728273) on chromosome 7 (located 14.2 kb away from rs43077 [7q31.1; $P=.047$]) were also associated with LOAD in the TGen data set. The candidate SNPs identified from the TGen study were in strong LD with those from the NIA-LOAD study (D' range, 0.97-1.00). (Details are available from the authors upon request.)

APOE ANALYSIS AND *APOE* CONDITIONAL LINKAGE AND FBAT ANALYSES

The FBAT analysis indicated that the 2 SNPs within *APOE* designating the $\epsilon 4$ allele were significantly associated with Alzheimer disease ($Z=8.68$; $P=1.98 \times 10^{-18}$; data not shown), as did the case-control analysis ($\chi^2=150.46$; $P=1.4 \times 10^{-34}$). In the *APOE* conditional linkage analysis, many loci that were significant in the unadjusted analysis remained significant; however, some loci were significant only in the presence of the *APOE* $\epsilon 4$ allele. Five SNPs within a 5-cM region surrounding *APOE* provided LOD scores ranging from 3.06 to 4.84. Outside the *APOE* region, rs1482258 (located at 16q21), rs798485 (7p22.3), and rs985942 (8q12.1) had LOD scores suggestive of linkage. Some SNPs were found to be significant in the *APOE* $\epsilon 4$ conditional linkage analysis only, including rs2034222 (located at 5p; 31.31cM), rs1349710 (6q;

Table 3. Results of Case-Control Association Analysis Using the Broad Definition of LOAD^a

Chr No.	SNP	Cytogenetic Location	Physical Position, bp	Distance, cM	Allele	Associated Allele	Case:Control	χ ² Test	P Value
1	rs999918	1p34.3	39 141 147	62.12	G/C	C	0.431:0.3411	9.231	.0024
1	rs1846224	1q41	213 112 610	221.28	T/C	T	0.761:0.676	9.816	.0017
2	rs726548	2p21	41 968 203	66.04	T/G	T	0.482:0.393	8.740	.0031
2	rs1517342	2q24.3	168 841 180	173.07	T/C	C	0.540:0.448	9.065	.0026
2	rs1517343	2q24.3	168 841 482	173.07	A/C	C	0.540:0.448	9.052	.0026
3	rs1899169	3q26.1	167 377 570	168.06	A/G	A	0.593:0.474	15.538	.00008
7	rs1013719	7p21.3	10 327 990	21.09	T/C	T	0.791:0.706	10.703	.0011
7	rs961262	7q21.3	94 376 205	105.77	G/C	C	0.535:0.433	11.249	.0008
7	rs43077	7q31.1	111 837 265	120.57	C/G	C	0.526:0.429	10.244	.0014
8	rs2166842	8p23.3	507 596	0.00	T/G	G	0.165:0.099	9.999	.0016
11	rs1027323	11q24.3	128 729 876	139.46	T/G	T	0.559:0.470	8.746	.0031
14	rs2027338	14q13.1	33 656 414	36.49	T/C	T	0.591:0.496	10.101	.0015
15	rs1565863	15q15.1	38 225 412	42.50	A/G	A	0.735:0.639	11.670	.0006
19	rs429358 ^b	19q13.32	50 103 781	71.71	T/C	C	0.446:0.095	161.617	5.02 × 10 ⁻³⁷
19	rs7412 ^b	19q13.32	50 103 919	71.71	C/T	C	0.969:0.901	22.129	.000003
20	rs1381100	20q13.33	58 273 271	101.90	A/G	A	0.261:0.170	13.070	.0003
22	rs762883	22q12.3	31 460 264	36.94	C/G	C	0.485:0.365	15.950	.000065

Abbreviations: Chr, chromosome; LOAD, late-onset Alzheimer disease; SNP, single-nucleotide polymorphism.

^aThis study used the SNPs from the Illumina Linkage IVb SNP panel. The physical positions are based on the Human Genome Build 35, and the genetic locations are the interpolated position from the deCODE genetic map. The broad definition includes definite, probable, and possible AD.

^bUsed to determine the apolipoprotein E genotype. Individuals with the C allele at both SNPs had an ε4 allele; those with the T allele at both SNPs had an ε2 allele; and those with the T allele at rs429358 and the C allele at rs7412 had an ε3 allele. This SNP was flanked by rs11671074 (70.94 cM) and rs1603 (72.49 cM) from the linkage panel set.

Table 4. Comparison of P Values From the Linkage, FBAT, and Case-Control Association Analyses Using 2 Definitions of Affection Status^a

Locus	SNP	Distance, cM	P Value							
			Single-Point Analysis		Multipoint Analysis		FBAT Analysis		Case-Control Analysis	
			Broad	Narrow	Broad	Narrow	Broad	Narrow	Broad	Narrow
3q26.1	rs1899169	168.1	.2	.4	.07	.2	.89	.9	.00008	.000074
7p22.2	rs798485	6.3	.00002	.0002	.003	.002	.06	.06	.6057	.6137
7p21.3	rs719423	13.6	.00013	.00002	.005	.01	.7	.6	.0942	.0994
7q21.3	rs961262	105.8	.4	.3	.14	.2	.84	.98	.0008	.0007
7q31.1	rs43077	120.6	.12	.06	.4	.4	.04	.05	.0014	.0019
8p21.3	rs4427168	38.3	.012	.013	.0002	.0012	.0002	.0002	.1826	.1815
16q13	rs735144	72.7	.0003	.00003	.008	.004	.05	.06	.2473	.2976
16q21	rs1482258	76.9	.00005	.00001	.007	.002	.5	.9	.2551	.2514
19q13.32	rs2341000	75.8	.0004	.012	.0003	.0008	.2	.5	.7216	.7629
20q13.33	rs1381100	101.9	.9	>.99	.7	.9	.2	.1	.0003	.0002
22q11.21	rs174345	3.6	.3	.13	.5	.5	.00006	.0002	.9747	.9362
22q12.3	rs762883	36.9	.6	.6	.9	.9	.4	.9	.000065	.000084

Abbreviations: FBAT, family-based association test; SNP, single-nucleotide polymorphism.

^aBroad definition includes definite, probable, and possible Alzheimer disease (AD); narrow definition, definite and probable AD.

144.87 cM), rs189811 (7q; 185.95 cM), and rs337663 (12q; 101.97 cM); 19q13.32 showed the strongest multipoint LOD score (11.5). (Additional figures are available from the authors upon request.)

COMMENT

Using the NIA-LOAD family data set, we identified loci that may contain genetic variants related to the risk of LOAD. Not surprisingly, the APOE locus was identified and remains the most consistently replicated genetic risk factor for LOAD. Multiple candidate loci were identified from linkage and association analyses, but the re-

sults obtained from the family-based linkage and association analyses shared little overlap with the results from the case-control analysis (Table 4). The sample size for the case-control set provided 68% power to detect an allelic association at a significance level of .001, assuming an allele frequency of 0.3, risk ratio of 1.5, and genotyping error of 0.1%. Thus, it is possible that reduced power was a factor contributing to the observed differences.

Linkage analysis tests the cosegregation of the disease and genetic markers within families, without reference to a specific allele, and this method is powerful in diseases that conform to mendelian inheritance. In contrast, association analysis determines the excess transmission of a spe-

Table 5. Examination of Several Previously Identified Candidate Genes

Gene ^a	SNP	Location	FBAT Analysis		Case-Control Analysis	
			Z Score	P Value	χ ² Test	P Value
<i>MTHFR</i>	rs6685318	1p36.22	0.422	.67	1.988	.16
	rs6671723		1.538	.12	1.364	.24
<i>NCSTN</i>	rs10594	1q23.2	-0.767	.44	2.293	.13
	rs570901	1q23.3	-1.057	.29	0.005	.95
<i>TF</i>	rs2370409	3q22.1	-0.31	.76	0.3	.58
	rs12595		0.178	.86	0.033	.86
	rs1984630		-0.962	.34	0.158	.69
<i>TNF</i>	rs169679	6p22.1	-0.386	.69	0.009	.92
	rs11908	6p21.32	0.747	.45	1.734	.19
<i>ESR1</i>	rs10002	6q25.1	-0.407	.68	0.473	.49
	rs718527		0.221	.82	0.014	.91
<i>UBQLN1</i>	rs1359168	9q21.32	1.388	.17	0.019	.89
	rs944947		0.814	.42	1.204	.27
	rs918223		-1.547	.12	0.695	.40
<i>TFAM</i>	rs1338799	10q21.1	0.1	.92	0.021	.88
	rs1904764		0.531	.59	1.197	.27
	rs1427209		-0.371	.71	0.042	.84
<i>PLAU</i>	rs2227551	10q22.2	0.012	.99	1.38	.24
	rs4065		-0.255	.79	0.073	.79
<i>IDE</i>	rs1329656	10q23.33	-1.492	.14	0.768	.38
	rs1111875		-0.75	.45	0.016	.90
<i>CALHM1</i>	rs6580	10q24.33	-0.481	.63	1.393	.24
	rs276219	10q25.1	-1.151	.25	1.947	.16
<i>GAB2</i>	rs1945085	11q14.1	-0.719	.47	0.094	.76
	rs1945465		0.346	.73	1.419	.23
<i>SORL1</i>	rs596437	11q23.3	-1.613	.11	0.552	.46
	rs617847		2.146	.03	0.017	.90
	rs676943		-1.103	.27	1.446	.23
<i>GAPDH</i>	rs740839	12p13.31	-1.878	.06	0.03	.86
	rs2365567		0.854	.39	1.217	.27
<i>LRP6</i>	rs732868	12p13.2	1.689	.09	7.888	.005
	rs4763797		0.545	.56	0.228	.63
	rs7155380	14q24.2	2.568	.01	0.026	.87
<i>PSEN1</i>	rs977357	14q24.3	-0.149	.88	0.448	.50
	rs1557720	17q23.2	0.712	.48	0.906	.34
<i>ACE</i>	rs4353	17q23.3	-1.952	.05	0.004	.95
	rs1043127	17q23.3	-0.101	.92	0.057	.81
<i>APOC</i>	rs11671074	19q13.31	-0.063	.95	0.017	.90
	rs1603		-1.593	.11	0.722	.40
	rs2041975		0.402	.69	0.006	.94
<i>PRNP</i>	rs241605	20p13	-0.717	.47	2.335	.13
	rs1535382		-0.682	.49	1.984	.16
	rs1131382		-1.45	.15	0.197	.66
<i>GST3</i>	rs970177	20p11.22	-0.766	.44	0.091	.76
	rs7988	20p11.21	0.571	.57	0.173	.68
	rs958075	20p11.21	-1.519	.13	0.098	.75

Abbreviations: FBAT, family-based association test; SNP, single-nucleotide polymorphism.

^aEach row represents the results for a single SNP within the named gene. Available SNPs within the candidate genes were examined. Modestly significant associations were found for *SORL1*, *LRP6-1*, *PSEN1-1*, and *ACE1*.

cific allele to affected individuals within families or co-occurrence of the specific allele among cases compared with unrelated individuals without disease.²⁷ It is possible to observe an allelic association in the absence of linkage when the allele frequency is high. Without dense SNP coverage, it is possible to miss allelic associations, even in the presence of linkage. Gene identification for common diseases is difficult when a single method is applied²⁸⁻³⁰; thus, it is optimal to apply linkage as well as association analyses when the data are available.

There continues to be support for linkage for LOAD at 6p, 9q, 10q, 12p, and 19q, but it has been extraordi-

narily difficult to identify the specific genes at each locus (see Kamboh³¹ for review). Moreover, there is little concordance between case-control and family-based linkage or association studies suggesting clinical and genetic heterogeneity. For example, variants in the alpha-2-macroglobulin gene (*A2M*); catenin alpha 3 gene (*CTNNA3*); plasminogen activator, urokinase gene (*PLAU*); insulin-degrading enzyme gene (*IDE*); glutathione S-transferase omega 1 and 2 genes (*GSTO1* and *GSTO2*); and glyceraldehyde-3-phosphate dehydrogenase gene (*GAPDH*) have been identified in family-based or case-control studies but lack consistent repli-

cation. Loci in a broad region of 12p11 to 12q13 may contain genetic variants for LOAD, including *GAPDH*³² and *LRP6* at 12p13.31,⁶ but both remain unconfirmed. In addition, several other genetic variants surrounding a locus at 10q24 have been related to LOAD.³³⁻³⁶ Linkage to LOAD and plasma amyloid β at 10q24 were reported.³⁷⁻³⁹ Li et al^{40,41} found support for an association with *GSTO1* and *GSTO2* at 10q25.1 with LOAD, but neither finding has been confirmed,⁴² and a new variant in the ribosomal protein S3A gene (*RPS3A*; located at 4q31.3) has been reported.⁴³ The locus on 9p21-22 has also eluded identification, but an association between LOAD and variants in the ubiquitin 1 gene (*UBQLN1*) at 9q22 have been described^{44,45} and confirmed in at least one study.⁴⁶ However, other studies do not support this finding.^{47,48}

Putative loci in our report overlap with some of those compiled by Bertram and colleagues⁴⁹ (<http://www.alzgene.org>), but many will remain unconfirmed. For independent confirmation without performing additional genotyping, we compared the findings from the publicly available LOAD data set from TGen against the findings from the present study. We found similar associations proximal to 7q31.1 and 20q13.33 in the NIA-LOAD data set. Second, we investigated candidate genes associated with LOAD using SNPs that were near or within these genes. As recommended, markers from previously implicated regions were treated differently from markers for which there was no prior evidence of an association.⁵⁰ We investigated 18 such candidates and found that at least 1 SNP at 12p13.2 (*LRP6*), 11q23.3 (*SORL1*), 17q23.2 (*ACE*), and 14q24.2 (*PSEN1*) was modestly associated with AD, with *P* values ranging from .004 to more than .05 (**Table 5**). Although none of these findings would survive a conservative correction for multiple testing, this exercise demonstrates the consistency in our findings and the value of this well-characterized data set for discovery or confirmation of genetic variants predisposing to LOAD.

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