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No Association or Linkage Between an Intronic Polymorphism of Presenilin-1 and Sporadic or Late-Onset Familial Alzheimer Disease

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Recent reports have shown an association between an intronic polymorphism of the presenilin-1 (PSEN1) gene and late-onset (age at onset > 65) familial and sporadic (no family history) Alzheimer disease (AD). The reported association was independent of the effect of the only previously identified gene associated with late-onset AD, APOE. Blood samples were obtained from members of 122 multiplex AD families, 42 unrelated cases of AD with positive family histories of dementia, 456 sporadic cases of AD, and 317 controls of similar ages at examination to the cases. These samples were genotyped for an intronic polymorphism of the PSEN1 gene, located 3′ to exon 8, and the data analyzed for evidence

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of association or linkage. The samples were also genotyped for APOE and the data analyzed to see if the association or linkage changed when controlling for APOE genotype. There was no statistically significant increase (at $\alpha = .01$) in allele 1 (199 bp) or genotype 1/1 in the sporadic AD cases, or in a random sample of one affected from each multiplex family, compared to controls. When examining the effect of the PSEN1 polymorphism while controlling for APOE genotype, APOE genotype was strongly associated with AD, but the PSEN1 polymorphism genotype was not. Model-trait dependent (lod score) and independent (SimIBD) methods detected no evidence of linkage between PSEN1 and AD. In this independent dataset, the previously reported association between the intronic PSEN1 polymorphism and AD cannot be confirmed, and the conclusion that PSEN1 is a major susceptibility gene for late-onset AD is not supported. Genet. Epidemiol. 14:307–315, 1997.

Key words: dementia; genetics; linkage analysis; PSEN1; APOE

INTRODUCTION

Alzheimer disease (AD) is a common neurological disease occurring late in life. The leading cause of dementia in older adults, AD is often clinically stratified into early- (age ≤ 65) and late- (age > 65) onset forms, and is genetically complex. Mutations in three different genes have been linked to the early-onset form: amyloid precursor protein (APP) on chromosome 21 [Goate et al., 1991], presenilin-1 (PSEN1) on chromosome 14 [Sherrington et al., 1995], and presenilin-2 (PSEN2) on chromosome 1 [Levy-Lahad et al., 1995; Rogaev et al., 1995]. Mutations in the PSEN1 gene are the most common identified cause of this early-onset, autosomal dominantly inherited form of AD [Sherrington et al., 1995].

Only one gene has been associated with the more prevalent late-onset form of familial AD: apolipoprotein E (APOE), located on chromosome 19. This gene is strongly associated with AD in both late-onset familial [Corder et al., 1993; Strittmatter et al., 1993], late-onset sporadic [Saunders et al., 1993], and early-onset sporadic [van Duijn et al., 1994] cases. Risk of AD is increased in a dose-dependent fashion by the APOE-4 allele [Corder et al., 1993], an effect replicated many times in independent datasets [Pericak-Vance and Haines, 1995]. Despite the well-established association between APOE and AD, it explains only 45–55% of the genetic risk of AD [Roses et al., 1995]. Therefore, additional genes must exist that influence the risk of late-onset familial and sporadic AD.

The identification of PSEN1 as a causative gene in early-onset familial AD made it a potential susceptibility gene for late-onset AD. Recently, it was reported that an intronic polymorphism in the PSEN1 gene, located in the intron 3′ to exon 8, was associated with late-onset AD [Higuchi et al., 1996; Kehoe et al., 1996; Wragg et al., 1996]. We examined the relationship of this polymorphism to AD in our own data, a well-established longitudinal study of the genetics of AD with a large series of sporadic AD cases and multiplex families with late-onset AD.

MATERIALS AND METHODS

Genotyping

Blood samples were obtained with informed consent, from all subjects, and DNA was extracted from whole blood or transformed lymphocytes using standard proce-

dures. The PSEN1 intronic polymorphism was genotyped using the primers as reported [Wragg et al., 1996]. Genotyping at Duke used a semiautomated fluorescence scanning system (Molecular Dynamics SI) [Vance et al., 1996] and genotyping at MGH used silver staining [Bassam et al., 1991]. Allele 1 is 199 bp, and allele 2 is cleaved by BamHI into fragments of 181 bp and 18 bp [Wragg et al., 1996]. APOE genotypes were determined as previously reported [Saunders et al., 1993]. All genotyping was carried out by individuals blinded to the affection status of individuals in the dataset.

Patients and Controls

The 122 multiplex late-onset AD families were obtained from the Joseph and Kathleen Bryan Alzheimer's Disease Research Center (ADRC) at Duke University, the Indiana Alzheimer Disease Center National Cell Repository, the UCLA Neuropsychiatric Institute, the UCLA ADRC, and the ADRC of the Massachusetts General Hospital for a longitudinal study of the genetics of AD. The 122 families used in this study contained 241 affected individuals and 333 unaffected, at-risk individuals genotyped for the PSEN1 polymorphism. The mean age at examination for the affected family members (39% male) was 78.0 years, standard deviation (SD) 8.8 years (mean age at onset 70.5, SD 7.9).

As well, 42 unrelated AD cases with a reported family history of dementia in a first degree relative were collected from the Massachusetts General Hospital ADRC or the Alzheimer Disease Clinic at Boston University. The mean age at examination for these patients (30% male) was 78.6 years, SD 6.7 years (mean age at onset 73.4, SD 7.7).

These 42 cases were combined with a random sample of one affected individual (when available) from each family described above for the association study. This combined sample contained 151 individuals (35% male) and had a mean age at examination of 75.1 years, SD 8.20 years (mean age at onset 70.4, SD 9.3).

An additional 458 patients (38% male) with no reported family history of AD or dementia (sporadic cases) were identified at the Joseph and Kathleen Bryan ADRC, the Massachusetts General Hospital ADRC, or the ADC at Boston University. The mean age at examination was 73.6 years, SD 8.1 years (mean age at onset 68.9, SD 8.5).

All cases selected for this study were diagnosed with AD by using the standard clinic criteria [McKhann et al., 1984].

The 317 unrelated controls, (47% male) were aged 50 or older at examination, were free of clinical signs of dementia, and were ascertained at the sites above. A large proportion of these controls were spouses of clinic patients. The mean age at examination was 79.6 years, SD 8.8 years.

Data Analysis

Allele and genotype frequencies were generated for cases and controls, and differences detected using the χ^2 test of association. Cases were also stratified by family history of AD and age at onset, and compared to appropriate control groups stratified by age at examination. These subsets of controls were formed by selecting controls with ages of examination falling within the range of ages of examination in each case group. Therefore, cases with age at onset at or before 65 years were compared to controls aged 50–82 years at examination, and cases with age at onset after

age 65 were compared to controls aged older than 65 at examination. Logistic regression models were used to assess the effect of the 1/1 genotype of the PSEN1 polymorphism on risk of AD while controlling for APOE genotype and age at examination. Models were first constructed comparing all cases to controls: two models were considered, one containing main effects, and another testing interaction between the PSEN1 and APOE loci. The likelihood ratio test was used to test for statistically significant interaction. The logistic regression analysis was repeated in subsets of the full dataset, stratified by age at onset and family history as described above. In all, 18 models were constructed.

To adjust for multiple comparisons in the same dataset, a critical value of $\alpha = .01$ was used to evaluate statistical significance. This significance level is more conservative than $\alpha = .05$, but less conservative than adjustment using the Bonferroni method. This adjustment is reflected in all discussions of statistical significance, although only 95% confidence intervals are presented with the logistic regression model results. Given an exposure rate of 30% in controls (the genotype frequency for the PSEN1 polymorphism 1/1 genotype), the required significance level of $\alpha = .01$, and power of $(1 - \beta) = .80$, this sample can detect an odds ratio (OR) greater than 1.6. At $\alpha = .05$, the sample can detect an OR greater than 1.5. All association analyses were performed using SAS version 6.09 for the Sun OS system.

For the family data, linkage was examined using both model-trait-dependent and -independent methods. Lod scores were calculated using the Fastlink 2.2 version of the LINKAGE software package [Lathrop et al., 1984], assuming autosomal dominant inheritance, age-dependent penetrance calculated as previously described [Pericak-Vance et al., 1991], and an allele frequency of 0.001 for the AD susceptibility allele. Age-dependent penetrances ranged from 0.4% at age 40 to 99% after age 90. The analysis was repeated assuming low penetrance (affecteds-only analysis), where information on disease phenotype was included for affected individuals only, and genotypic information was included on all sampled family members. To determine if the presence of the APOE4 allele modified the lod score, the families were stratified by APOE genotype and summed lod scores calculated within each stratum. The model-independent SimIBD method [Davis et al., 1996] was also used to analyze marker data in these families, using the $f(p) = 1/\mathrm{sqrt}(p)$ weighting function. This method examines allele sharing among relative pairs and is capable of detecting either linkage or association between a marker and a disease trait.

RESULTS

The distribution of the PSEN1 polymorphism genotype and allele frequencies was consistent in the Duke and MGH cases and controls when analyzed separately (data not shown), so the data were pooled for the analysis presented here. The allele and genotype frequencies, stratified by age at onset and family history of AD, are presented in Table I. Comparing sporadic AD and familial AD to all controls, separately or combined, there is no significant increase in the frequency of allele 1. When stratifying the dataset by age at onset and family history, late-onset (age at onset > 65) sporadic or familial cases did not have a significant increase in allele 1 when compared to controls. However, early-onset (age at onset ≤ 65) sporadic cases had a slightly increased frequency of allele 1 when compared to controls (0.64 vs. 0.56;

TABLE I. PSEN1 Polymorphism Allele and Genotype Frequencies, by Age at Onset and Family History of AD[†]

		Allele		Genotype			
		1	2	1/1	1/2	2/2	1/2 or2/2
	N	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Overall							
Familial AD	151	184 (0.61)	118 (0.39)	54 (0.36)	76 (0.50)	21 (0.14	97 (0.64)
Sporadic AD	458	530 (0.58)	386 (0.42)	155 (0.34)	220 (0.48)	83 (0.18)	303 (0.66)
Combined AD	609	714 (0.59)	504 (0.41)	209 (0.34)	296 (0.49)	104 (0.17)	400 (0.66)
Controls	317	355 (0.56)	279 (0.44)	97 (0.30)	161 (0.51)	59 (0.19)	220 (0.70)
Age ≤ 65[a]							
Familial AD	36	45 (0.62)	27 (0.38)	12 (0.33)	21 (0.58)	3 (0.09)	24 (0.67)
Sporadic AD	144	183 (0.64)	105 (0.36)*	55 (0.38)	73 (0.51)	16 (0.11)	89 (0.62)
Combined AD	180	228 (0.63)	132 (0.37)**	67 (0.37)	94 (0.52)	19 (0.11)	113 (0.63)
Controls	295	331 (0.56)	259 (0.44)	91 (0.31)	149 (0.50)	55 (0.19)	204 (0.69)
Age > 65[b]							
Familial AD	112	224 (0.61)	88 (0.39)	42 (0.38)	52 (0.46)	18 (0.16)	70 (0.62)
Sporadic AD	298	334 (0.56)	262 (0.44)	97 (0.33)	140 (0.47)	61 (0.20)	201 (0.67)
Combined AD	410	470 (0.57)	350 (0.43)	139 (0.34)	192 (0.47)	79 (0.19)	271 (0.66)
Controls	220	245 (0.56)	195 (0.44)	65 (0.30)	115 (0.52)	40 (0.18)	155 (0.70)

[†]Age at onset categories do not sum to total due to missing ages at onset.
*χ^2 test, cases vs. controls, $P = 0.036$; χ^2 test, early-onset cases vs. late-onset sporadic cases, $P = 0.034$.
**χ^2 test, cases vs. controls, $P = 0.028$.
[a]Age at onset ≤ 65 for AD cases, age at examination < 83 for controls.
[b]Age at onset > 65 for AD cases, age at examinations > 65 for controls.

$P = 0.036$) or to late-onset sporadic cases (0.64 vs. 0.56; $P = .034$). These results are not statistically significant when using a significance level of $\alpha = .01$ to correct for multiple comparisons in the same dataset. No statistically significant differences in genotypes were detected between cases and controls, either when using genotype 2/2 as the referent or when using a combined 1/2 and 2/2 group as the referent. All genotypes were in Hardy-Weinberg equilibrium.

A total of 18 logistic regression models were constructed: the 9 main effects models presented in Table II, and 9 models containing the interaction between the PSEN1 genotype and APOE genotype. Comparing the 9 interaction models with the 9 main effects models, there was no statistically significant evidence of interaction between PSEN1 and APOE in any model (data not shown). In addition, an examination of the main effects models showed no statistically significant increase (at $\alpha = .05$ or $\alpha = .01$) in the odds of the 1/1 genotype in people with AD, controlling for APOE genotype, age at examination, and sex.

The results of the linkage analysis of the 122 families with late-onset AD are presented in Table III. Using a lod score of 3.0 as the criterion for significant evidence of linkage, both models (age-dependent penetrance and low penetrance) fail to show evidence of linkage between the PSEN1 polymorphism and AD. Using a lod score of –2.0 as the criterion for exclusion, the exclusion region assuming autosomal dominant inheritance and age-dependent penetrance is 15 cM on either side of the PSEN1 polymorphism; assuming low penetrance, the exclusion region is 10 cM on either side. When stratifying families by APOE genotype of affected individuals and calculating summary lod scores, there is still no evidence for linkage in any of the

TABLE II. Odds of Genotype PSEN1 1/1, APOE 4/4, and APOE 4/X in AD Patients, by Age at Onset and Family History[†]

	PSEN1 genotype		APOE genotype		
Model	1/1 OR (95% CI)	1/2 & 2/2 OR[a]	4/4 OR (95% CI)	4/X OR (95% CI)	X/X OR[a]
Overall					
Familial AD	1.05 (0.63, 1.79)	1.0	37.18 (13.54, 102.13)	6.29 (3.68, 10.75)	1.0
Sporadic AD	1.21 (0.85, 1.71)	1.0	18.58 (8.14, 42.45)	3.96 (2.82, 5.57)	1.0
Combined AD	1.21 (0.87, 1.70)	1.0	20.60 (9.15, 46.35)	4.27 (3.08, 5.92)	1.0
Age ≤ 65[b]					
Familial AD	0.80 (0.32, 2.03)	1.0	66.92 (17.48, 256.27)	6.47 (2.38, 19.08)	1.0
Sporadic AD	1.47 (0.92, 2.34)	1.0	17.40 (7.11, 42.56)	2.74 (1.73, 4.35)	1.0
Combined AD	1.37 (0.88, 2.14)	1.0	22.01 (9.25, 52.35)	3.18 (2.05, 4.93)	1.0
Age > 65[c]					
Familial AD	1.19 (0.65, 2.20)	1.0	30.34 (8.07, 114.06)	6.80 (3.61, 12.80)	1.0
Sporadic AD	1.01 (0.64, 1.60)	1.0	22.62 (7.62, 67.14)	5.83 (3.73, 9.11)	1.0
Combined AD	1.08 (0.71, 1.66)	1.0	25.44 (8.66, 74.72)	6.24 (4.08, 9.56)	1.0

[†]The logistic model results are adjusted for age of examination and sex. X, APOE2 or APOE3; OR, odds ratio; CI, confidence interval.
[a]Referent categories.
[b]Age at onset ≤ 65 for AD cases, age at examination < 83 for controls.
[c]Age at onset > 65 for AD cases, age at examination > 65 for controls.

three subgroups. Using the model-trait independent SimIBD method in all 122 families, the test statistic, using the 1/sqrt(*p*) weighting function, had a *P*-value of .56, further indicating the lack of linkage or association of this candidate locus to AD.

DISCUSSION

The results of this study do not confirm the original report of an association between the intronic polymorphism of PSEN1 and sporadic or late-onset familial AD. In fact, the data are rather strong in suggesting that there is neither association nor linkage between the PSEN1 polymorphism and AD. We observed an overall

TABLE III. Lod Scores for PSEN1 Polymorphism in Late-Onset AD Families, by APOE Genotype[*]

		Recombination fraction (θ)						
Model, penetrance	*N*	0.00	0.05	0.10	0.15	0.20	0.30	0.40
Dominant, age-dependent								
Overall	122	–15.39	–6.59	–4.12	–2.60	–1.58	–0.48	–0.08
APOE X/X	20	–1.99	–1.31	–0.93	–0.66	–0.45	–0.18	–0.04
APOE 4/X	70	–7.49	–2.72	–1.64	–0.97	–0.54	–0.11	–0.00
APOE 4/4	32	–5.75	–2.44	–1.46	–0.90	–0.54	–0.17	–0.03
Dominant, low (affecteds only)								
Overall	122	–11.13	–4.44	–2.52	–1.46	–0.83	–0.22	–0.03
APOE X/X	20	–0.98	–0.60	–0.39	–0.26	–0.17	–0.06	–0.01
APOE 4/X	70	–7.28	–2.85	–1.69	–1.03	–0.62	–0.19	–0.04
APOE 4/4	32	–2.68	–0.83	–0.32	–0.08	0.03	0.07	0.02

[*]*N*, number of families; X, APOE2 or APOE3.

odds ratio (OR) of 1.2 (95% CI: 0.87, 1.70) for the PSEN1 1/1 genotype, in contrast to the OR of 2.0 (95% CI: 1.29, 3.00) reported by Wragg and coworkers [1996]. Power calculations indicate that we should have been able to detect the effect, even if the OR was as low as 1.5. Unlike a previously published confirmation of the association in Caucasians [Kehoe et al., 1996], our dataset is completely independent of the dataset used in the initial report [Wragg et al., 1996], and contains data collected independently from multiple research centers. As we have noted previously [Scott et al., 1996a], Kehoe and associates [1996] used controls from the original study and is therefore not an independent confirmation. Higuchi and colleagues [1996] examined 79 Japanese people with late-onset AD and compared them to 186 controls. Although this independent dataset found an increase in allele 1 and genotype 1/1 in the AD cases, the associations were of borderline statistical significance, particularly if correcting for multiple comparisons in the same dataset. Replication of this finding in larger samples of Japanese AD patients would strengthen the claim of confirmation of an association between PSEN1 and late-onset AD. A brief report from an independent sample of French Caucasians [Pérez-Tur et al., 1996] also failed to replicate the original association, strengthening the evidence against linkage or association.

The difference in results between our data and the initial report could be due to several factors. Because association studies are sensitive to variations in allele frequencies, using case and control groups that are not drawn from the same underlying population may bias results. However, the control allele frequencies for the studies of PSEN1 and late-onset AD conducted in outbred Caucasian populations are relatively similar, discounting the possibility that somehow the control samples are biased. The difference in results may therefore be attributed to the differences in case sample allele frequencies. These differences could reflect heterogeneity of the PSEN1 effect on late-onset AD in Caucasians. More likely, the results reflect differing amounts of bias in the case samples. Although Wragg and colleagues [1996] correctly state that since their results are highly statistically significant they are not likely due to random statistical variation, this does not rule out an erroneous, yet statistically significant result due to a biased case sample.

It is clear that AD is a complex, multifactorial disease in which several genes act, independently or in concert, to cause similar pathological changes in the brain. Several genes, such as AACT [Kamboh et al., 1995], and VLDL-R [Okuizumi et al., 1995] have been proposed as potential susceptibility factors for AD, yet the original effects have not been confirmed upon further examination in our independent datasets [Haines et al., 1996; Pritchard et al., 1996]. Given the genetic complexity of AD, it is important that each report of a genetic association be scrutinized and independently replicated before it can be added to the causal web underlying AD. Thomson [1994] proposed that associations between candidate genes and complex traits that meet nominal significance criteria ($P < .05$) in three independent datasets need to be followed up in more detail. To this end, we have extensively examined the relationship between PSEN1 and late-onset familial and sporadic AD and have found no compelling evidence of association or linkage. These data support our original report [Scott et al., 1996b] that PSEN1 is not responsible for a significant proportion of the genetic risk of late-onset AD. Thus, while additional genetic factors exist, further studies are necessary in order to tease out these remaining genetic effects in AD.

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REFERENCES

Bassam BJ, Caetano-Anolles G, Gresshoff PM (1991): Fast and sensitive silver staining of DNA in polyacrylamide gels. Anal Biochem 196:80–83.

Corder EH, Saunders AM, Strittmatter WJ, Schmechel D, Gaskell P, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1993): Apolipoprotein E4 gene dose and the risk of Alzheimer disease in late onset families. Science 261:921–923.

Davis S, Schroeder M, Goldin LR, Weeks DE (1996): Nonparametric simulation-based statistics for detecting linkage in general pedigrees. Am J Hum Genet 58:867–880.

Goate AM, Chartier-Harlin MC, Mullan MC, Brown J, Crawford F, Fidani L, Guiffra L, Haynes A, Irving N, James L, Mant R, Newton P, Rooke K, Roques P, Talbot C, Pericak-Vance M, Roses A, Williamson R, Rossor M, Owen M, Hardy J (1991): Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 349:704–706.

Haines JL, Pritchard ML, Saunders AM, Schildkraut JM, Growdon JH, Gaskell PC, Farrer LA, Auerbach SA, Gusella JF, Locke PA, Rosi BL, Yamaoka L, Small GW, Conneally PM, Roses AD, Pericak-Vance MA (1996): No genetic effect of α 1-antichymotrypsin in Alzheimer disease. Genomics 33:53–56.

Higuchi S, Muramatsu T, Matsushita S, Arai H, Sasaki H (1996): Presenilin-1 polymorphism and Alzheimer's disease. Lancet 347:1186.

Kamboh MI, Sanghera DK, Ferrell RE, DeKosky ST (1995): APOE-4-associated Alzheimer's disease risk is modified by α 1-antichymotrypsin polymorphism. Nat Genet 10:486–488.

Kehoe P, Williams J, Lovestone S, Wilcock G, Owen MJ, Holmans P, Liddell M, Holmes C, Powall J, Neal J (1996): Presenilin-1 polymorphism and Alzheimer's disease. Lancet 347:1185.

Lathrop GM, Lalouel J-M, Julier C, Ott J (1984): Strategies for multilocus linkage analysis in humans. Proc Natl Acad Sci USA 81:3443–3446.

Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, Yu CE, Jondro PD, Schmidt SD, Wang K., Crowley AC, Fu Y-H, Guenette SY, Galas D, Nemens E, Wijsman EM, Bird TD, Schellenberg GD, Tanzi RE (1995): Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science 269:973–977.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984): Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34:939–944.

Okuizumi K, Onodera O, Namba Y, Ikeda K, Yamamoto T, Seki K, Ueki A, Nanko S, Tanaka H, Takahashi H, Oyangi K, Mizusawa H, Kanazawa I, Tsuji S (1995): Genetic association of very low density lipoprotein (VLDL) receptor gene locus with sporadic Alzheimer's disease. Nat Genet 11:207–209.

Pérez-Tur J, Wavrant-De Vrieze F, Lambert JC, Chartier-Harlin MC, Alzheimer's Study Group (1996): Presenilin-1 polymorphism and Alzheimer's disease. Lancet 347:1560–1561.

Pericak-Vance MA, Haines JL (1995): Genetic susceptibility to Alzheimer's disease. Trends Gen 11:504–508.

Pericak-Vance MA, Bebout JL, Gaskell PC, Yamaoka LH, Hung W-Y, Alberts MJ, Walker AP,

Bartlett RJ, Haynes CA, Welsh KA, Earl NL, Heyman A, Clark CM, Roses AD (1991): Linkage studies in familial Alzheimer disease: Evidence for chromosome 19 linkage. Am J Hum Genet 48:1034–1050.

Pritchard ML, Saunders AM, Gaskell PC, Small GW, Conneally PM, Rosi B, Yamaoka LH, Roses AD, Haines JL, Pericak-Vance MA (1996): No association between very low density lipoprotein receptor (VLDL-R) and Alzheimer disease in American Caucasians. Neurosci Lett 209:105–108.

Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, Chi H, Lin C, Holman K, Tsuda T, Mar L, Sorbi S, Nacmias B, Placentini S, Amaducci L, Chumakov I, Cohen D, Lannfelt L, Fraser PE, Rommens JM, St. George-Hyslop PH (1995): Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. Nature 376:775–778.

Roses AD, Devlin B, Conneally PM, Small GW, Saunders AM, Pritchard M, Locke PA, Haines JL, Pericak-Vance MA, Risch N (1995): Measuring the genetic contribution of APOE in late-onset Alzheimer disease (AD). Am J Hum Gen 57:A202.

Saunders AM, Strittmatter WJ, Schmechel D, St. George-Hyslop PH, Pericak-Vance MA, Joo SJ, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ, Hulette C, Crain B, Goldgaber D, Roses AD (1993): Association of apolipoprotein E allele ε4 with late-onset familial and sporadic Alzheimer's disease. Neurology 43:1467–1472.

Scott WK, Roses AD, Haines JL, Pericak-Vance MA (1996a): Presenilin-1 polymorphism and Alzheimer's disease. Lancet 347:1560.

Scott WK, Growdon JH, Roses AD, Haines JL, Pericak-Vance MA (1996b): Presenilin-1 polymorphism and Alzheimer's disease. Lancet 347:1186–1187.

Sherrington R, Rogaev E, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K, Tsuda T, Mar L, Foncin J-F, Bruni AC, Montesi MP, Sorbi S, Rainero I, Pinessi L, Nee L, Chumakov I, Pollen D, Brookes A, Sanseau P, Polinski RJ, Wasco W, DaSilva HAR, Haines JL, Pericak-Vance MA, Tanzi RE, Roses AD, Fraser PE, Rommens JM, St. George-Hyslop PH (1995): Cloning of a novel gene bearing mis-sense mutations in early familial Alzheimer's disease. Nature 375:754–760.

Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance MA, Enghild J, Salvesen GS, Roses AD (1993): Apolipoprotein E: High avidity binding to β-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer's disease. Proc Natl Acad Sci USA 90:1977–1981.

Thomson G (1994): Identifying complex disease genes: Progress and paradigms. Nat Genet 8:108–110.

Vance JM, Jonasson F, Lennon F, Sarrica J, Damji KF, Stauffer J, Pericak-Vance MA, and Klintworth GK (1996): Linkage of a gene for macular corneal dystrophy to chromosome 16. Am J Hum Genet 58:757–762.

van Duijn CM, deKnijff P, Cruts M, Wehnert A, Havekes LM, Hofman A, Van Broeckhoven C (1994): Apolipoprotein E4 allele in a population-based study of early-onset Alzheimer's disease. Nat Genet 7:74–78.

Wragg M, Hutton M, Talbot C, and the Alzheimer's Disease Collaborative Group (1996): Genetic association between intronic polymorphism in presenilin-1 gene and late-onset Alzheimer's disease. Lancet 347:509–512.