American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 147B:778–783 (2008)

Does *APOE* Explain the Linkage of Alzheimer's Disease to Chromosome 19q13?

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We have studied the impact of the apolipoprotein E gene (*APOE*) on the chromosome 19 linkage peak from an analysis of sib-pairs affected by Alzheimer's disease. We genotyped 417 affected sib-pairs (ASPs) collected in Sweden and Norway (SWE), the UK and the USA for 10 microsatellite markers on chromosome 19. The highest Zlr (3.28, chromosome-wide *P*-value 0.036) from the multipoint linkage analysis was located approximately 1 Mb from *APOE*, at marker D19S178. The linkage to chromosome 19 was well explained by *APOE* in the whole sample as well as in the UK and USA subsamples, as identity by descent (IBD) increased with the number of *ε4* alleles in ASPs. There was a suggestion from the SWE subsample that linkage was higher than would be expected from *APOE* alone, although the test for this did not reach formal statistical significance. There was also a significant age at onset (aao) effect on linkage to chromosome 19q13 in the whole sample, which manifested itself as increased IBD sharing in relative pairs with lower mean aao. This effect was partially, although not completely, explained by *APOE*. The aao effect varied considerably between the different subsamples, with most of the effect coming from the UK sample. The other samples showed smaller effects in the same direction, but these were not significant.

KEY WORDS: Alzheimer's disease; *APOE*; linkage; age at onset; apolipoprotein E

Please cite this article as follows: Blom ES, Holmans P, Arepalli S, Adighibe O, Hamshere ML, Gatz M, Pedersen NL, Bergem ALM, Owen MJ, Hollingworth P, Goate A, Williams J, Lannfelt L, Hardy J, Wavrant-De Vrièze F, Glaser A. 2008. Does *APOE* explain the linkage of Alzheimer's disease to chromosome 19q13? Am J Med Genet Part B 147B:778–783.

INTRODUCTION

Apolipoprotein E (APOE) is a lipid transporting protein involved in cholesterol homeostasis [Mahley, 1988]. It is so far the only well established genetic risk factor for sporadic late onset Alzheimer's disease (AD) where it accounts for about one-third of the genetic risk [Kamboh, 2004]. The *ε4* allele of *APOE* increases the risk of developing AD and decreases the age at onset (aao) in a dose-dependent manner [Corder et al., 1993].

Results from several genome-wide linkage studies of AD have consistently demonstrated linkage to chromosome 19q13, a region which includes the *APOE* locus [Kehoe et al., 1999; Pericak-Vance et al., 2000; Myers et al., 2002; Blacker et al., 2003; Sillén et al., 2006]. Due to the strong impact of *APOE*, it is difficult to determine if additional loci within the region also contribute to AD development. In the present study we have investigated the effect of *APOE* on the chromosome 19q13 linkage peak generated from an analysis of sib-pairs from Sweden and Norway (SWE), the UK, and the USA. We have also examined the effect of aao on the linkage peak and the influence of *APOE* on the aao effect.

MATERIALS AND METHODS

Samples

The 827 samples used in this study were collected in Sweden and Norway (182 samples from a Swedish collection of familial AD, 20 samples from the Swedish twin registry [Gatz et al., 1997, 2005] and 16 samples from the Norwegian twin registry [Bergem and Lannfelt, 1997; Bergem et al., 1997]), the UK and the USA (the National Institute of Mental Health, the Alzheimer's Disease Genetics Initiative and the National Cell Repository for Alzheimer's Disease). The samples included 417 affected sib-pairs (ASPs) (121, 113, and 183, respectively), 113 of which were genotyped with another microsatellite marker set in the genome scan by Myers et al. [2002]. The ASPs were selected from families with at least two siblings diagnosed with possible, probable or

Grant sponsor: The Swedish Research Council; Grant sponsor: The Swedish Alzheimer Foundation, APOPIS; Grant number: LSHM-CT-2003-503330; Grant sponsor: NIH; Grant number: R01 AG08724; Grant sponsor: Alzheimer's Research Trust; Grant sponsor: Medical Research Council.

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Received 10 April 2007; Accepted 29 October 2007

DOI 10.1002/ajmg.b.30681

definite AD according to NINCDS-ADRDA diagnostic criteria. All available family members, both affected and healthy, were sampled and genotyped (see Table I for a summary of sample data). To reduce potential genetic heterogeneity and allelic frequency differences caused by ethnic origin, only Caucasian families were included. This study was approved by Local and National Ethics Committees.

Genotyping

Ten microsatellite markers on chromosome 19 (D19S591, D19S1034, D19S586, D19S433, D19S245, D19S178, D19S246, D19S589, D19S254, and D19S714) with an average spacing of 10 cM, were amplified by multiplex PCR and separated according to size on an ABI PRISM 3700 (Applied Biosystems, Foster City, CA). Allele calling was performed using the Genotyper software version 3.7 (Applied Biosystems). Marker order and inter marker distance were obtained from linkage reference maps (see http://research.marshfieldclinic.org/genetics/markersearch/buildmap.asp). The markers had an average completion rate of 83%. In each run, two CEPH samples (1331-01 and 1331-02) [Dausset et al., 1990] and two water samples were used for quality control.

All samples were also genotyped for two single nucleotide polymorphisms (SNPs) in the *APOE* promoter (−491/rs449647 and −219/rs405509) using the TaqMan 5′-allele discrimination assay on the Applied Biosystems 7900HT (Applied Biosystems).

Primer sequences are available upon request. All genotypes were scored blindly as to phenotype and pedigree structure.

Linkage Testing

Multipoint linkage analyses of the three subsamples (SWE/UK/USA) and the whole sample were performed using the Zlr statistic of the program ALLEGRO [Gudbjartsson et al., 2000]. Chromosome-wide significance levels were estimated by simulating 5,000 replicate datasets of identical structure to the actual data under the null hypothesis of no linkage. The equality of identity by descent (IBD) probabilities in the three subsamples was tested by expressing the IBD probabilities as a logistic regression with subsample as a covariate. Significance was assessed by randomly permuting the subsample labels among the families.

Does *APOE* Account for Linkage?

The method of Sun et al. [2002] was extended to sib-ships with arbitrary numbers of affected and unaffected sibs, arbitrary numbers of typed parents, and arbitrary numbers of alleles at the test locus (in this case, *APOE*). The larger pedigrees were broken into their constituent sib-ships. The posterior probability that each sibling inherited a particular allele of the four possible parental alleles at the test locus was calculated conditional on the observed genotypes at that locus and the allele frequencies ($\varepsilon 2$–5%, $\varepsilon 3$–80%, $\varepsilon 4$–15%). These probabilities were then used to generate replicate sets of marker data of identical structure to the actual dataset. The proportion of replicates giving a Zlr statistic larger than the observed value can be regarded as a *P*-value for a test of the hypothesis that *APOE* accounts for the observed linkage peak.

Effects of aao on Linkage

The effect of aao on the chromosome 19 linkage was tested by modeling the IBD sharing probability for each affected relative pair as a logistic regression with either the mean aao of a pair or the absolute difference in aao between the members of a pair as a covariate. The difference between the maximum lod score on the chromosome allowing for the aao covariate and the maximum lod score without the aao covariate was used as the test statistic for aao effect. Note that these two maxima need not occur at the same location (Fig. 2). Significance of the aao effect was assessed by randomly permuting the aao values among affected individuals and repeating the analysis. For a fuller description of the method, see Holmans et al. [2005].

Does *APOE* Account for aao Effects?

It is well known that *APOE* has a small but significant influence on aao of late-onset AD, with aao decreasing as the number of $\varepsilon 4$ alleles increases [Corder et al., 1993]. It is therefore possible that any effects of aao on linkage may be entirely due to increased IBD sharing in affected pairs with more $\varepsilon 4$ alleles. To test this hypothesis, the mean aao was calculated for each of the six possible *APOE* genotypes. Each individual's aao was then "corrected" by subtracting the mean aao corresponding to that individual's genotype. The resulting residuals were used as covariates in the linkage analysis, as described above. Since both aao and overall linkage evidence vary between samples, the correction of aao for *APOE* genotype effects was performed in each sample separately. This removed the possibility that the aao effect was due merely to inter-sample differences in linkage evidence and aao, without the two necessarily being related. The resulting residuals were standardized to remove any potential bias due to different variances of aao in the three samples.

RESULTS

Linkage Testing

We genotyped 296 multiplex pedigrees containing 431 AD affected relative pairs (including 417 ASPs) for 10 microsatellite markers on chromosome 19 with an average spacing of 10 cM. Multipoint linkage analysis revealed the highest Zlr (3.28, chromosome-wide $P = 0.036$) in the total sample, located 1 Mb from *APOE* at marker D19S178 (Fig. 1 and Table II). The SWE sample showed higher IBD sharing (Zlr 3.35, chromosome-wide $P = 0.007$) than the UK and USA samples (Zlr 0.88, $P = 0.6$ and Zlr 1.64, $P = 0.32$, respectively). The difference in

TABLE I. Summary Statistics of the Samples Used

	PED	IND	AIND	ASP	ASP with aao	ASP *APOE* $\varepsilon 4+$	Affected half sibs	Affected first cousins	aao ± SD
SWE	67	218	171	121	106	99	0	11	70.3 ± 6.7
UK	88	195	195	113	89	90	0	0	74.8 ± 7.6
USA	141	414	330	183	181	164	1	2	72.7 ± 6.0
ALL	296	827	696	417	376	353	1	13	72.6 ± 6.8

PED, number of pedigrees; IND, number of genotyped individuals; AIND, number of genotyped affected individuals; ASP, number of genotyped affected sib-pairs; aao, age at onset; ASP *APOE* $\varepsilon 4+$, ASPs where both siblings carried at least one *APOE* $\varepsilon 4$ allele; SD, standard deviation.

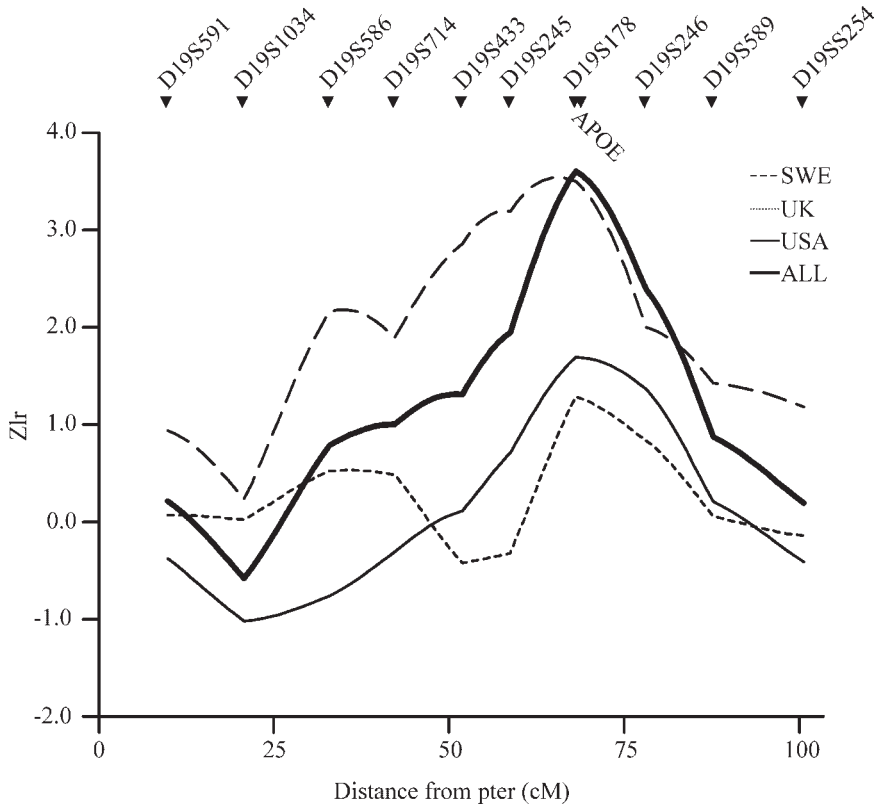

Fig. 1. Linkage analysis. Multipoint linkage analysis for chromosome 19 of the three subsamples (SWE/UK/USA) and the whole sample was performed using the Zlr statistic of the program ALLEGRO.

IBD between the SWE group and the other samples was significant (chromosome-wide $P = 0.035$). This difference can be explained at least partially by the somewhat earlier aao in the SWE group, since it was no longer significant when correcting for age (chromosome-wide $P = 0.089$).

Does *APOE* Account for Linkage?

To test whether the observed Zlr is exclusively explained by *APOE*, we used the method of Sun et al. [2002]. If *APOE* is entirely responsible for the peak, one would expect a replicate set of marker data to give similar Zlr scores to the actual data. If *APOE* is not exclusively responsible for the peak, one would expect the actual Zlr score to be higher than those from the replicates. The *APOE P*-value measures the proportion of replicates with higher Zlr than the actual data, so if *APOE* is not entirely responsible, one would expect this p-value to be small. We found that *APOE* explained the linkage peak in the UK and USA samples ($P = 0.64$ and $P = 0.29$, respectively; Table II). There was some evidence that the linkage effect in the SWE sample was not completely explained by *APOE*, but this did not reach significance ($P = 0.064$). Looking at the combined sample, there was no evidence that *APOE* does not explain the linkage peak ($P = 0.18$). Two SNPs in the promoter region of *APOE* were added to the analysis, but this did not significantly change the outcome (data not shown).

Effects of aao on Linkage

We also investigated the effect of aao on the chromosome 19 linkage peak. There were 390 genotyped affected relative pairs (including 376 ASPs) with aao information across the three sample sets, of which 380 also had *APOE* genotypes. The mean aao of the pair or the difference in aao between the members of a pair were used as covariates. A maximum lod score of 2.48 was observed in the whole sample in the absence of covariates (Table III). There was a very significant effect of mean aao, with IBD increasing as mean aao decreases (lod increase = 3.31, chromosome-wide $P = 0.002$). There was also a smaller, though

TABLE II. *APOE* Is Responsible for the Zlr Scores

	Max Zlr	*P*	cM	*APOE P*
SWE	3.35	**0.007**	65.3	0.064
UK	0.88	0.6	68.1	0.64
USA	1.64	0.32	68.1	0.29
ALL	3.28	**0.036**	68.1	0.18

Result of the linkage analysis for chromosome 19 with chromosome-wide *P*-values. "*APOE P*" is the *P*-value when testing if the observed Zlr score is entirely explained by *APOE*. "*APOE P*" is a measure of the proportion of replicates with higher Zlr than the actual data Therefore, if *APOE* is not entirely responsible, this *P*-value would be significant. Bold values denote significant *P*-values.

TABLE III. Variations of Lod Scores With Covariates

	SWE		UK		USA		ALL	
	Lod	*P*	Lod	*P*	Lod	*P*	Lod	*P*
Lod (no covariates)	2.94		0.19		0.50		2.48	
Δ Lod (mean aao)	0.86	0.12	2.53	**0.009**	0.73	0.21	3.31	**0.002**
Δ Lod (Δ aao)	0.20	0.21	0.12	0.52	0.48	0.21	0.70	**0.04**
Δ Lod (mean aao, *APOE* correction)	0.36	0.30	2.16	**0.01**	0.21	0.63	1.68	**0.03**
Δ Lod (Δ aao, *APOE* correction)	0.02	0.85	0.29	0.90	0.41	0.41	0.63	0.47

Linkage analyses for chromosome 19 with chromosome-wide *P*-values, with mean aao and difference in aao as covariates, and with correction for *APOE*. Bold values denote significant *P*-values.

still significant effect of differences in aao, so that siblings with similar aao have a higher degree of IBD sharing, (lod increase = 0.7, chromosome-wide $P = 0.039$) in the combined sample, although this was not significant in any of the individual samples. Further inspection of the results for the individual samples (Fig. 2 and Table III) revealed that a large part of the mean aao effect was coming from the UK sample (lod increase = 2.53, chromosome-wide $P = 0.009$). Smaller effects of mean aao were visible in the SWE (lod increase = 0.86, chromosome-wide $P = 0.12$) and USA (lod increase = 0.73, chromosome-wide $P = 0.21$) samples, but these were not significant.

Does *APOE* Account for aao Effects?

When the effects of *APOE* genotypes were regressed out, the effect of mean aao was still significant in the combined sample (lod increase = 1.68, chromosome-wide $P = 0.032$) and the UK sample (lod increase = 2.16, chromosome-wide $P = 0.014$),

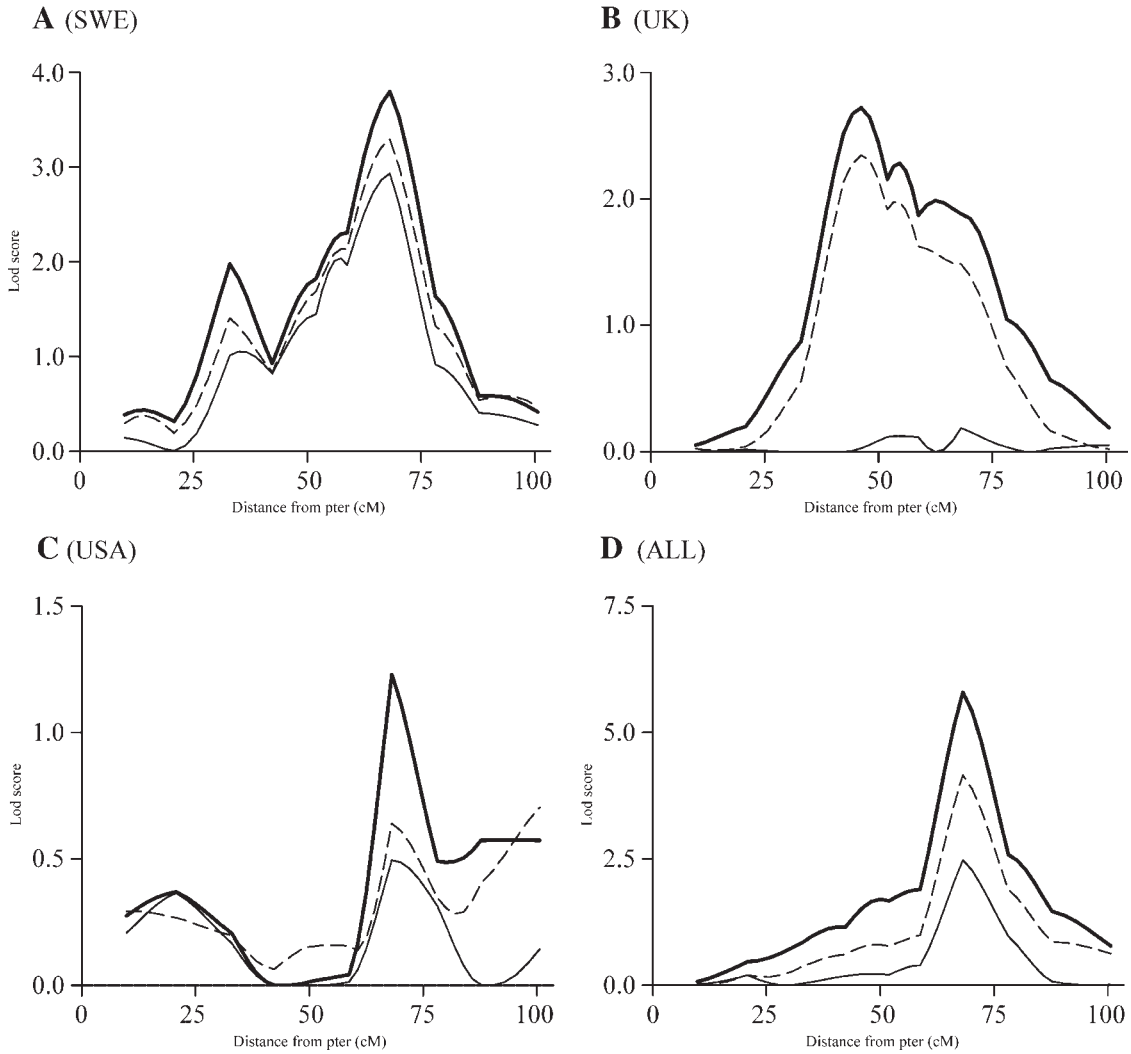

Fig. 2. Variations of lod scores with covariates. Multipoint lod score graphs of SWE (**A**), UK (**B**), USA (**C**), and ALL samples (**D**). A thin line symbolizes lod without covariates, a thick line represents lod with mean aao as a covariate, and a dashed line is lod with mean aao corrected for *APOE*.

although the size of the effect and its significance were reduced. This suggests that *APOE* explained some, but not all, of the effect of mean aao. The effect of difference in aao disappeared after allowing for *APOE* (Table III). The multipoint lod scores obtained without covariates and with mean aao, both with and without correction for *APOE*, are shown in Figure 2 for each of the three groups (SWE, UK, USA) and the combined sample.

DISCUSSION

A linkage peak at chromosome 19q13 including the *APOE* locus is generally expected when performing complete genome screens in collections of AD samples and is also consistently reported from such studies [Kehoe et al., 1999; Pericak-Vance et al., 2000; Myers et al., 2002; Blacker et al., 2003; Sillén et al., 2006]. In the present investigation we set out to study the extent to which this peak can be explained by *APOE*, reflecting the possible effects of other loci within the 19q13 peak. Linkage analysis of 417 sib-pairs affected by AD from Sweden and Norway, the UK and the USA with 10 microsatellite markers on chromosome 19 revealed a linkage peak which was explained by *APOE* in the whole sample (Fig. 1 and Table II). This data is consistent with previous results involving a subsample of the present study, where Myers et al. [2002] found a significant increase in IBD sharing at the microsatellite marker nearest the *APOE* gene in *ε4* positive compared to *ε4* negative ASPs. Within the SWE subsample there was a tendency that *APOE* did not explain the entire linkage peak, although this did not reach statistical significance. Chance variation occurs in statistical analysis and can therefore not be excluded as a possible cause of the unexplained linkage in the SWE subsample.

Additional genetic variants on chromosome 19q13 could potentially affect the linkage peak, for example, mRNA expression of the *ε4* allele has been reported to be increased in AD compared to controls [Lambert et al., 1997]. Two SNPs within the *APOE* promoter, −491/rs449647 and −219/rs405509, were included in the analysis but had little effect on the results. The *APOC1* locus has previously been reported to show allelic association with AD [Poduslo et al., 1995], but due to linkage disequilibrium (LD) with the *APOE* locus, the independent influence of the *APOC1* gene is difficult to estimate. This was recently further demonstrated by Coon et al. in a whole genome association study of AD [Coon et al., 2007]. The SNPs representing the *APOE ε2/ε3/ε4* variants were not included in the study, but SNP rs4420638 positioned just distal to both *APOE* and A*POC1* revealed the strongest association, reflecting the strong LD in this region.

APOE has been described both as a susceptibility gene for AD and to affect aao. The *ε4* allele provides its greatest risk before the age of 70 years [Blacker et al., 1997] and there are suggestions that no *ε4/4* carriers reach the age of 90 without being affected by AD [Ashford, 2004]. In the present study the mean aao effect (IBD increases as mean aao decreases) on the chromosome 19 linkage peak was significant in the whole sample and the UK subsample, but not in the SWE and USA subsamples. This effect was still significant after correcting for *APOE* genotype.

In conclusion, we cannot find significant evidence for genes other than *APOE* within the chromosome 19q13 region with linkage to AD. As expected, aao had a strong effect on this linkage peak, and *APOE* explained most but not all of the aao effect.

ACKNOWLEDGMENTS

We would like to express our appreciation to all the families who generously participated in this study and to all the people involved in the collection of the samples. The Swedish work was supported by The Swedish Research Council, The Swedish Alzheimer foundation, APOPIS (Contract No. LSHM-CT-2003-503330), and NIH grant number R01 AG08724. The UK group was supported by funding from the Alzheimer's Research Trust and the Medical Research Council. The USA samples were collected with support from the NIA/NIH intramural research program and grants numbers U01 MH46281, U01 MH46290, U01 MH46373 (NIMH), U24 AG21886 (NCRAD), and AG16208 (AG).

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