The Number of Trait Loci in Late-Onset Alzheimer Disease

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Summary

Although it is clear that apoE plays an important role in the genetics of late-onset Alzheimer disease (AD), evidence exists that additional genes may play a role in AD, and estimates of the total contribution of apoE to the variance in onset of AD vary widely. Unfortunately, little information is available on the number and contribution of additional genes. We estimated the number of additional quantitative-trait loci and their contribution to the variance in age at onset of AD, as well as the contribution of apoE and sex, in an oligogenic segregation analysis of 75 families (742 individuals) ascertained for members with late-onset AD. We found evidence that four additional loci make a contribution to the variance in age at onset of late-onset AD that is similar to or greater in magnitude than that made by apoE, with one locus making a contribution several times greater than that of apoE. Additionally, we confirmed previous findings of a dose effect for the apoE ε4 allele, a protective effect for the ε2 allele, evidence for allelic interactions at the apoE locus, and a small protective effect for males. Furthermore, although we estimate that the apoE genotype can make a difference of ≤17 years in age at onset of AD, our estimate of the contribution of apoE (7%–9%) to total variation in onset of AD is somewhat smaller than that which has previously been reported. Our results suggest that several genes that have not yet been localized may play a larger role than does apoE in late-onset AD.

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Introduction

The search for novel genetic loci affecting liability for Alzheimer disease (AD [MIM 104300]) is proceeding, but there is little information on how many AD loci there may be. To date, four such genes have been conclusively identified. Three of these—APP, PS1, and PS2—have been linked to rare, autosomal dominant forms of AD that generally have an early onset (Goate et al. 1991; Schellenberg et al. 1992; Levy-Lahad et al. 1995a, 1995b; Sherrington et al. 1995). Only one, apoE, has been associated, in multiple studies, with common late-onset AD (Pericak-Vance et al. 1991; Saunders et al. 1993). The apoE gene has three alleles—ε2, ε3, and ε4—with the ε3 allele being most common. The ε4 allele has been associated with high risk for AD, relative to the ε3 allele, in a large number of studies (e.g., Corder et al. 1993; Jarvik et al. 1995; Levy-Lahad et al. 1998), whereas a smaller number of studies have reported evidence indicating that the less-common ε2 allele may have a protective effect (Corder et al. 1994; Jarvik et al. 1995). A number of other studies have not estimated an effect for the ε2 allele, since their sample sizes for this allele were small. Indeed, the protective effect for ε2 was confirmed in a reanalysis that combined a large number of individuals from multiple studies (Farrer et al. 1997).

Although most studies agree that genetic factors other than apoE play a role in late-onset AD, estimates of the relative contribution, to AD risk, of apoE versus these other factors vary widely. One study estimates that apoE accounts for 50% of the “predicted total genetic effect” (Roses et al. 1995), whereas others estimate that apoE accounts for 10%–15% of the total variance in age at onset (Bennett et al. 1995; Slooter et al. 1998). These different estimates may, in fact, be slightly closer together than they appear: the genetic variance (VC) is only a component of the total variance (VT). In a twin study, Bergem et al. (1997) estimated the heritability (narrow sense: VC/VT), where VC is the additive genetic variance) for AD to be 0.6. It is also possible to estimate, by use...
of the data of Bergem et al. (1997), that the fraction of the total genetic variance (broad sense: $V_G / V_T$) has a range of 0.76–0.83. However, since Bergem et al. (1997) do not allow for any censoring and since only a few years have passed since diagnosis of the discordant MZ twin pairs (Bergem and Lannfelt 1997), the broad-sense heritability could well be larger. These results indicate that $\geq 30\%$ of the total variance in AD—and possibly $\geq 70\%$—is explained by unidentified genetic loci.

Clearly, $30\%–70\%$ is a large fraction of the total variance, but our ability to localize genes contributing to this variance will be determined by the number of such genes and by the contribution of each. If there is a single gene accounting for this variance, that gene should be fairly easy to localize. In fact, it would be surprising if such a single gene existed, since several complete genome screens (Pericak-Vance et al. 1998; Kehoe et al. 1999) have failed to produce any LOD scores $\geq 3$ for such a gene. On the other hand, if there are many genes of small effect, localization of these genes may prove to be intractable. An estimate of the number of additional genes can give us an indication of how fruitful the search for additional AD genes will be.

In the present study, we estimated the number and effects of additional genes on age at onset of AD, by performing a Monte Carlo Markov chain (MCMC) oligogenic segregation analysis on a collection of families with late-onset AD. This study makes complete use of the available family data. The number of additional quantitative-trait loci (QTLs) involved in age at onset of AD and the relative contributions of each QTL to the variance in age at onset of AD were estimated, while both controlling for and estimating the effects of apoE and sex. Thus, the current analysis also provides a new estimate of the effects of apoE genotype, while controlling for the effects of the other genes and, at the same time, making complete use of the family data. Previously, most estimates of the effects of apoE have been from case-control studies or from family studies treated as case-control studies (Corder et al. 1993; Jarvik et al. 1995; Slooter et al. 1998). In such studies, it is impossible to account for the effects of other genes, since the individuals studied are unrelated (or are assumed to be so) and since other genes involved in late-onset AD have not been conclusively identified. Although our estimates of the effects of apoE have some similarities to previous estimates, we estimate that there are four QTLs, in addition to apoE, that have effects that are as large as or larger than those of apoE.

### Subjects and Methods

#### Sample

Individuals in 75 families (including two Volga German families) with no known PS1, PS2, APP, or TAU mutations were evaluated either by the University of Washington Alzheimer’s Disease Research Center, the Oregon Health Sciences University Alzheimer’s Disease Center, or the University of Minnesota Alzheimer disease research group. Informed consent was obtained from all subjects. The families contained a total of 742 individuals, with a family-size range of 4–53 individuals. apoE genotypes were available for 419 individuals. Of these individuals, 203 had an age at onset of AD (affected), 201 had a censoring age at which they were last known to be free of AD (unaffected), and 15 had missing phenotype information. Individuals were considered to be missing phenotype data for this analysis if information on either age (age at onset of AD or censoring age) or affection status was unavailable. Phenotypic data were available for 600 individuals, of whom 282 were affected and 318 were unaffected. Living affected individuals without autopsies and for five families who were referred from outside our centers and who were not examined by our personnel, the diagnosis of probable AD was established on the basis of detailed medical records that often included consultations by neurologists, neuropsychological testing, computed tomography (CT) or magnetic-resonance imaging (MRI) of the brain, and laboratory testing excluding other causes of dementia. For the sample used here, the mean age at onset was $70.6 \pm 7.9$ years, with an individual-onset range of 40–89 years. The range of mean onset within each individual family was 63–82 years, and 66 of the 75 families had at least one member with a case of AD confirmed at autopsy, with a total of 132 autopsies conducted in the families. Neuropathologic confirmation of the diagnosis met the criteria published by The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD; Mirra et al. 1991) and The Ronald and Nancy Reagan Research Institute of the Alzheimer’s Association/National Institute on Aging Working Group (1998). apoE genotypes were determined by use of methods described elsewhere (Hixson and Vernier 1990).

#### Statistical Methods

To estimate the number of trait loci and the effects of each such locus, the effects of each apoE genotype, and the effect of sex on age at onset of AD, we applied the MCMC methods described elsewhere (Heath 1997; Daw et al. 1999). With the use of these methods, age at onset is modeled as a censored quantitative trait while an oligogenic segregation analysis is performed. Effectively, this is a survival analysis in which the failure curves for each covariate and genotypic group are cumulative normal distributions with the same variance. By using the term “covariate and genotypic group,” we mean to de-
scribe all individuals who share a particular multilocus genotype at all QTLs and who share a common value for each covariate. Such groups may also include individuals for whom the apoE genotype and other genetic data are probabilistically inferred from data on other family members. This inference effectively increases our sample size beyond the 419 individuals for whom apoE genotype is available. With use of this model, age at onset is given by: \( y = M + X \beta + \sum_{i=1}^{q} Q_i \alpha_i + e \), where \( M \) is the “baseline” age at onset, \( X \) is the incidence matrix for covariate effects (i.e., a matrix indicating the values at all the covariates; the entries for discrete covariates will be 0’s or 1’s), \( \beta \) is the vector of covariate effects, \( Q_i \) is the incidence matrix for the effects of QTL \( i \), \( \alpha_i \) is the vector of effects for QTL \( i \), \( e \) is the normally distributed residual effect, and \( k \) is the number of QTLs currently estimated. All these parameters, with the exception of the elements of \( X \) determined by the data, are estimated by use of an MCMC process, as detailed elsewhere (Heath 1997; Daw et al. 1999). In brief, this process samples configurations of model parameters randomly but in such a way that these configurations are sampled with a frequency that is proportional to their posterior probability. Thus, after many iterations of this sampling process, the sampled model configurations provide an estimate of the posterior probability distribution over the space of possible parameter configurations. In the analyses presented here, this process was run for 500,000 iterations, and values from every 5th iteration were retained for estimation of posterior distributions.

Covariates of age at onset can be continuous (e.g., weight, height, and blood pressure) or discrete (e.g., sex, ethnic group, and country of birth), and they can include genotype at known genes or candidate genes. Such “genetic covariates” are useful because they allow the known mutation status to be used in the estimation of genotypic effects for a loci. Also, whereas the basic QTL model assumes that a locus is diallelic, a QTL modeled as a covariate can have any number of alleles. Furthermore, since the effect of each genotype at a genetic covariate is estimated independently, no restrictive assumptions are made with respect to allelic interactions at a genetic covariate locus. For example, the estimates of the effects of the apoE \( \epsilon 3/\epsilon 3 \) and apoE \( \epsilon 4/\epsilon 4 \) genotypes do not impose restrictions either on each other or on the estimate of the effect of the apoE \( \epsilon 3/\epsilon 4 \) genotype.

We also considered sex to be a covariate. An additive effect was estimated for males, with the female effect estimated as the baseline. In contrast to the apoE covariate, sex is a relatively simple covariate, with only two values and no missing data. As with the other effects, the sex effect was estimated to be an additive effect—that is, the years’ difference between the average onset in males and that in females, after controlling for all other estimated effects.

In addition to providing estimates of the effects of sex and apoE, use of this MCMC method allows us to model the effects of additional genes that may contribute to AD. This not only gives us an estimate of the number of additional genes involved in late-onset AD, but it also gives us estimates of the effects of apoE while controlling for the additive effects of other genes and sex. All four possible models defined by sex and additional QTLs were considered: the effects of apoE genotypes on age at onset were estimated both with and without sex as a covariate and both with and without modeling of additional QTLs. In the analyses where additional QTLs were allowed, we estimated the variance attributed to each of these QTLs as well as the number of such QTLs. We then compared the variances of these QTLs to the variance estimated for apoE, to examine the effect sizes (i.e., the attributable phenotypic variance) for other putative late-onset AD genes and to examine the overall contribution of apoE to the variance of late-onset AD.

For purposes of comparison and for evaluation of our methods, a Kaplan-Meier survival analysis was done. Separate survival curves were computed for each apoE genotype. We were then able to compare these results both with the results that we obtained using the MCMC methods and with those obtained by other researchers using Kaplan-Meier survival analysis.

Results

Number of QTLs

Our MCMC analysis of the 75 available families with late-onset AD found evidence for a number of genes, in addition to apoE, affecting age at onset of AD (table 1). The number of additional genes was estimated to be in the range of four to seven (fig. 1), with four of the QTLs generally having a variance that was as large as or larger than that of apoE. Of these four additional QTLs, one was substantially larger than the rest, accounting for \( >50\% \) of the total genetic variance (fig. 2 and table 1). This largest QTL was estimated to be an overdominant locus—that is, the effect of the heterozygote genotype was estimated to be the most detrimental. The frequency of the common allele at this locus was estimated to be \( .60 (.07 \text{ SD}) \), and, with the common homozygote fixed as baseline (zero effect), the heterozygote had an estimated effect of \( -7.8 \) years (3.0 SD) and the less-frequent homozygote had an estimated effect of \( +28.8 \) years (12.3 SD). The next three QTLs all had highly overlapping distributions, and they accounted for \( \sim 13\% < 8\% \), and \( \sim 5\% \) of the genetic variance (square-root variance \( \sim 3.5–6 \) years). apoE accounted for \( 7\%–9\% \) of the ge-
Table 1

Partitioning of Variance of Age at Onset of AD

<table>
<thead>
<tr>
<th>Source of Variance</th>
<th>apoE, Sex, and Other QTLs</th>
<th>apoE and Other QTLs</th>
<th>apoE and Sex</th>
<th>apoE Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environment/residual</td>
<td>1.5% (1.8 years)</td>
<td>2.5% (2.5 years)</td>
<td>84.7% (10.9 years)</td>
<td>85.5% (10.9 years)</td>
</tr>
<tr>
<td>Sex</td>
<td>.7% (1.2 years)</td>
<td>.5% (.9 years)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Total genetic variance</td>
<td>97.9% (14.8 years)</td>
<td>97.5% (15.8 years)</td>
<td>14.7% (4.5 years)</td>
<td>14.5% (4.5 years)</td>
</tr>
<tr>
<td>apoE</td>
<td>9.2% (4.5 years)</td>
<td>6.6% (4.1 years)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Total variance, other QTLs</td>
<td>88.7% (14.1 years)</td>
<td>90.9% (15.3 years)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>QTL 1st</td>
<td>57.1% (11.3 years)</td>
<td>64.0% (12.7 years)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>QTL 2d</td>
<td>13.5% (5.4 years)</td>
<td>13.4% (5.8 years)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>QTL 3d</td>
<td>8.1% (4.2 years)</td>
<td>7.6% (4.4 years)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>QTL 4th</td>
<td>5.7% (3.5 years)</td>
<td>5.1% (3.6 years)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>QTL 5th</td>
<td>3.1% (2.6 years)</td>
<td>2.1% (2.3 years)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>QTL 6th</td>
<td>1.4% (1.8 years)</td>
<td>.7% (1.4 years)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>QTL 7th</td>
<td>.4% (1.0 years)</td>
<td>.2% (.7 years)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Smaller QTLs</td>
<td>&lt;.1% (.2 years)</td>
<td>&lt;.1% (.3 years)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Total variance</td>
<td>224.4</td>
<td>256.6</td>
<td>140.1</td>
<td>138.5</td>
</tr>
</tbody>
</table>

* Average total effect of all QTLs other than apoE.

* Average effect of each QTL (other than apoE) ranked by effect size.

apoE Effects

In addition to providing evidence for multiple QTLs, our analysis provides new estimates for the effects of each apoE genotype. These new estimates clearly confirm that apoE genotype affects age at onset of AD. The extreme genotypes—e4/e4 and e2/e3—differ in mean age at onset by ~17 years (no individuals with the apoE e2/e2 genotypes were available in our data set) (table 2 and fig. 3). The apoE e3 and e4 alleles appear to act approximately additively, with the e3/e4 genotype falling approximately midway between the e3/e3 and e4/e4 genotypes. The e2/e3 genotype is clearly protective, relative to the other genotypes, with mean onset occurring 6–8 years later than that for the genotype e3/e3, which has the next oldest onset. The e2/e3 estimate has a large SD (4–5 years) as a result of the small number of such individuals in our sample. The SD for the e2/e4 genotypic effect is also large as a result of the small sample size. This latter distribution spans those for the e4/e4, e3/e4, and e3/e3 genotypes, although its mean is consistently placed between the e3/e4 and e3/e3 genotypic means. To which of these means the e2/e4 genotypic mean is nearest depends on whether the effects of additional QTLs are allowed: when no other genes are modeled, the e2/e4 genotype mean is estimated to be closer to the e3/e3 genotypic mean; when other genes are modeled, the e2/e4 genotype mean is estimated to be closer to the e3/e4 genotypic mean.

Comparison of the results of our MCMC analysis of the effects of apoE on age at onset of AD (table 2) with results that we obtained from Kaplan-Meier survival
analysis (table 3) showed that the two methods produced remarkably similar results. The years effect estimated by survival analysis was within one standard error of the effects estimated by use of MCMC methods for each genotype. The difference between the $e4/e4$ and $e2/e3$ genotypes was very slightly greater in the Kaplan-Meier analysis than in the MCMC analyses (18.2 years vs. 15.9–17.6 years). Although the results of the two methods of estimation of the effects of apoE are quite similar, the MCMC methods use all family data, can estimate many effects in addition to those of apoE, and can also be used to localize genes when marker data are available.

**Sex Effect**

Sex also appears to affect age at onset of AD. The mean onset for males was estimated to be 1–2 years later than that for females, after accounting for other additive effects. Although this effect is small, the posterior probability that this effect is positive is 95%. The only discernible effect of the inclusion of sex was an increase in the difference between the $e3/e3$ and $e4/e4$ genotypes in the models allowing for the effects of other QTLs (table 2), suggesting an interaction between sex and apoE effects.

The estimated apoE effects were consistent across three MCMC-analysis runs of the same model. With use of a stochastic analysis method, such as the one used in the present study, an important issue is the stability of the results under different starting conditions. Table 4 shows the stability of the estimates of the effects of apoE in separate analysis runs of 500,000 iterations each, in which the effects of apoE genotype and other QTLs are modeled. The range of values between these runs is smaller for each effect than is the range between models shown in table 2. In particular, this indicates that the larger differences in apoE-genotype effects among models seen in table 2 are likely to reflect the different models, rather than the stochastic process (i.e., Monte Carlo error), although all the differences seen between models are within 1 SD of each other.

The estimate of the number of QTLs appears to be more variable (fig. 1), but the estimates of the effect sizes for the largest four QTLs were consistent in iterations with ≳4 QTLs present. The remaining QTLs all tended to have a smaller effect than did apoE and, in some cases, the effect was very small. In iterations with seven QTLs, for example, the effects attributed to the two smallest QTLs modeled are probably too small to be detectable in linkage analyses of this data. Some of these smaller QTLs may be artifacts of the MCMC analysis process. In any case, in all runs, the posterior probability of the presence of four to seven additional QTLs was greater than the posterior probability of the presence of any other number of QTLs.

**Discussion**

Our analysis of familial late-onset AD data provides novel evidence that four additional genes make a contribution to age-at-onset variation that is as large as or

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Means and SDs for Estimated Covariate Effects</strong></td>
</tr>
<tr>
<td><strong>Mean (SD) Estimated Covariate Effect</strong>&lt;sup&gt;a&lt;/sup&gt; (years)</td>
</tr>
<tr>
<td>apoE Genotype</td>
</tr>
<tr>
<td>Effects Modeled</td>
</tr>
<tr>
<td>apoE, sex, other QTLs</td>
</tr>
<tr>
<td>apoE, other QTLs</td>
</tr>
<tr>
<td>apoE, sex</td>
</tr>
<tr>
<td>apoE</td>
</tr>
</tbody>
</table>

<sup>a</sup> Of posterior distribution of effects, relative to sample mean.
larger than that of apoE. This analysis also provides new estimates of the effects of sex and each apoE genotype. Our estimates of the relative direction of the effects of apoE genotypes and sex confirm previous findings and thus support the use of MCMC methods. However, our estimate of the proportion of the total variance attributed to apoE appears to be slightly smaller than previously reported estimates and places new emphasis on the role that additional genes may play in late-onset AD.

The results from our oligogenic model suggest that $\geq 4$ additional QTLs may each account for at least as much of the variability in age at onset of AD as does apoE. The true number of genes cannot be precisely estimated: multiple genes with similar effects segregating in different families can produce evidence for a single gene with a larger effect; some other effects, such as transmissible environment effects, could potentially mimic genes. Also, an astute reader will have noticed that, in table 1, the total variance estimated is different, depending on whether additional QTLs are modeled. This difference is caused in part by underestimation of the total phenotypic variance, under the data-censoring model, when additional QTLs are not modeled. Underestimation occurs because, when additional QTLs are not modeled, the trait values for censored individuals are constrained to be near those of uncensored individuals, by the assumption of normality in the residual variance. The difference in total variance seen in the two cases is similar to the difference that one would see between estimation of total variance in a sample including only cases and estimation of total variance in a mixed sample that is more representative of the whole population. In addition, the residual variance in the oligogenic analyses may be underestimated. In data collection, only families with multiple affected individuals were ascertained, which could bias the estimate of the environmental variance downward.

The overdominance estimated in the largest QTL could result from a number of factors. The QTL could, in fact, be overdominant. If this were the case, caution would be suggested in the use of methods that have high power only for modes of inheritance in which the heterozygote falls between the two homozygotes. Another possibility is that gene-gene interactions might result in estimation of an overdominant effect. The degree to which this is a problem for gene localization will depend on the degree of the interaction. An additional genetic reason for estimation of overdominance could be the presence of multiple alleles at the trait locus. The model used here allowed for only two alleles at a QTL, so if the actual trait locus has three or more alleles with different effects, as is the case for apoE, the diallelic model could cause an overdominant trait to be estimated. Finally, the results of a previous study (Daw et al. 1999), showed some overdominance as a result of trait-model overfitting. This overfitting was not detrimental to localization of genes.

It might seem surprising that a QTL with the effect of the largest QTL found here has not already been localized. If this QTL does in fact exist, there could be a number of reasons why it has not yet been found. For a simple overdominant trait—that is, a monogenic diallelic trait where the heterozygotes are affected but the homozygotes are not affected—with a 60% frequency for the common allele, the expected identity-by-descent allele sharing at the disease locus between affected siblings is $\sim 1.3$. We believe that the trait is far more complex than this simple overdominant model, and complications such as the presence of multiple alleles at the trait locus, the interactions between those alleles, the presence of other trait loci, and the nongenetic influences on the trait would all tend to reduce this already modest identity-by-descent sharing. Thus, to detect such a locus, marker-allele sharing methods may require a sample far larger than any that have been collected to date. Alternatively, LOD-score methods depend on a model for the disease locus and are known to perform poorly when the model is wrong. Overdominant models are not gen-

### Table 3

<table>
<thead>
<tr>
<th>Kaplan-Meier Survival Analysis</th>
<th>apoE Genotype</th>
<th>$e4/e4$</th>
<th>$e3/e4$</th>
<th>$e2/e4$</th>
<th>$e3/e3$</th>
<th>$e2/e3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at onset</td>
<td></td>
<td>71.2</td>
<td>75.2</td>
<td>77.3</td>
<td>81.2</td>
<td>89.4</td>
</tr>
<tr>
<td>Effect$^a$</td>
<td></td>
<td>$-6.4$</td>
<td>$-2.4$</td>
<td>$-.3$</td>
<td>$3.6$</td>
<td>$11.8$</td>
</tr>
<tr>
<td>Standard error</td>
<td></td>
<td>(1.3)</td>
<td>(0.7)</td>
<td>(2.8)</td>
<td>(1.3)</td>
<td>(4.8)</td>
</tr>
</tbody>
</table>

$^a$ Data represent deviation from overall mean.
ever, the mean of the posterior distribution for the
H9255
/ the generally accepted findings of a dose effect for the
analysis with these methods.

The analysis with use of these MCMC methods can also be
expected to be smaller or the
H255
/ and
H9255
/ alleles is suggested by the results of the present study. How-

Unfortunately, we could not estimate the effects of the
H255
/ genotype, since there were neither any sampled
individuals with the
H255
/ genotype nor any individuals
in whom this genotype could be clearly inferred. However,
the placement of the
H255
/ and
H255
/ effects, relative to the placement of other effects, suggests that
H255
/ allele does not interact additively with both the
H3
/ and
H4
/ alleles. In a strictly additive system, one would
expect either the protective effect of the
H255
/ genotype to be smaller or the
H255
/ genotype to have a larger
mean than the
H3
/ genotype. Since these results suggest
allelic interaction, in the search for additional AD genes,
it may be important to account for apoE genotype, as
is done here, rather than use a model based on the simple
presence or absence of each of the alleles.

While some previous discussion has focused on
whether apoE is a causative locus or a modifier locus
for AD, this distinction may be semantic and is irrelevant
under the model used here. Our model assumes that
everyone will eventually get AD if they live long enough
and that the QTLs simply shift the mean age at on-
set—that is, a highly protective genotype would be mod-
eled as shifting the mean age at onset to a much later
age. The ramifications and limitations of this model are
discussed elsewhere (Daw et al. 1999). With a disease
that occurs as late in life as does late-onset AD, there
is no question that the difference of 16–17 years found
between the
H4
/ genotype and
H255
/ genotypes represents an
important factor in AD liability. Delaying the onset by
even as much as a few years would greatly reduce the
number of clinical AD cases.

Finally, we confirmed evidence for a protective effect
for AD in males. Such a protective effect is consistent
with findings from previous studies (Payami et al. 1994; Gao et al. 1998). Although this effect was relatively small (1–2 years), sex could interact with other risk factors, thereby making it more significant in some situations than in others. The precision of the estimates of covariate effects (sex and apolipoprotein E in the present study) is affected by the number sampled in each covariate group, and the estimates of these effects, relative to the mean, are also affected by the number in each group. However, different numbers in each group do not bias the estimates of the effect of each covariate group relative to each other. For example, the estimate of the male effect versus the female effect is not biased by different numbers of male and female family members sampled. In addition, the estimates are not biased on the basis of whether family members are unaffected or have observed ages of onset, since the censored-data model used (Daw et al. 1999) accounts for this. The differences seen in the estimates of the apoE effects, in a comparison of the model including apoE, sex, and other QTLs with the model including just apoE and other QTLs, suggest an interaction between apoE genotype and sex. This finding is consistent with previously reported results for the risk of Alzheimer’s disease in a case-control study (Jarvik et al. 1995).

Although these results clearly confirm the important role of apoE in late-onset familial Alzheimer’s disease, they also suggest that apoE represents only 7%–9% of the total variance in age at onset of familial Alzheimer’s disease and that it is but one of several important genes. There appear to be ≥4 additional QTLs that have an effect, at least on a par with that of apoE, on age at onset of familial Alzheimer’s disease. One of these QTLs appears to have a much greater effect. These results indicate that MCMC methods should be able to localize several novel late-onset Alzheimer’s disease loci, once a full-genome screen is completed on this data set.

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Electronic-Database Information

Accession number and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for AD [MIM 104300])

References


pices of Department of Health and Human Services Task Force on Alzheimer’s Disease. Neurology 34:939–944