Rate of Progression of Alzheimer's Disease Is Associated With Genetic Risk

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Objective: To determine whether differences in genetic origin affect the clinical course of Alzheimer's disease (AD). The limited number of cases of AD linked to a known genetic abnormality is a major obstacle in determining whether the disorder is expressed differently in patients with familial AD and those with sporadic AD.

Design: Cross-sectional study.

Setting: Memory Disorders Unit of the Alzheimer's Disease Research Center at Massachusetts General Hospital, Boston.

Participants: A total of 186 patients who had a clinical diagnosis of probable AD, family history information available for all first-degree relatives, and three or more outpatient visits were identified from a consecutive case series.

Main Outcome Measure: Rate of decline on the Blessed Dementia Scale and the Activities of Daily Living Scale.

Results: We calculated the probability that an individual patient has a major genetic locus for AD (MGAD) using an algorithm that incorporates information from a genetic model and the individual's family. We measured cognitive and functional changes by the average annual rate of increase (slope) in scores for the Blessed Dementia Scale and Activities of Daily Living Scale, respectively. Multivariate analysis adjusted for age at onset, duration of illness at entry into the study, and education level indicated that scores on the Activities of Daily Living Scale worsened significantly faster in men with MGAD than in men with non-MGAD. No differences in Activities of Daily Living Scale slopes were observed among women with MGAD and non-MGAD. The slopes for Blessed Dementia Scale scores were similar in men and women regardless of the MGAD probability.

Conclusions: Genetic factors may account for heterogeneity in rates of functional decline in AD. This study also illustrates the practical application of a probabilistic method that characterizes the genetic status of AD in an individual patient.

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DIFFERENCES IN the clinical features of Alzheimer's disease (AD) sparked the hypothesis that subgroups of AD differ from one another in biologically meaningful ways. Some of these distinct features include age at onset of symptoms,[1,2] the nature of the initial or predominant symptoms,[3] the presence of specific signs on neurologic examination,[4,5] and the rate of deterioration.[6] Are these differences simply due to variation in the AD phenotype, or do they reflect different origins? To answer this question, it is necessary first to establish a biologically relevant independent basis for defining subgroups of AD.

Underlying genetic differences are the most obvious and accessible basis for subgrouping AD. A small number of families with familial AD (FAD) have point mutations in the amyloid precursor protein gene on chromosome 21.[7] A different group of FAD cases are linked to a genetic abnormality located on chromosome 14.[8-11] Although study of these families has potential importance for understanding the cause of AD, the number of such cases is too small to support large-scale studies comparing FAD with sporadic AD or even comparing FAD cases linked to chromosome 14 with those linked to chromosome 21. Both groups of cases display an autosomal dominant mode of inheritance with an early age at onset. Finding a third gene locus (chromosome 19) linked to families with late-onset FAD[12] led to the discovery of disequilibrium in allelic frequencies of apo-

SUBJECTS AND METHODS

SUBJECTS

Subjects were ascertained from a consecutive series of patients attending the Memory Disorder Unit of the Massachusetts General Hospital, Boston, between June 1983 and February 1993. The three criteria for inclusion in the study were as follows: a clinical diagnosis of probable AD,[22-24] family history information available for all first-degree relatives, and three or more outpatient visits with recorded Blessed Dementia Scale (BDS) and Activities of Daily Living Scale (ADL) scores. Of the 415 subjects with complete family histories, 186 (72 men and 114 women) had undergone at least three outpatient examinations (average, 4.8 visits; range, three to 14 visits) and were followed up for an average of 33 months. Although these criteria excluded 55% of the potentially eligible patients with AD, no significant differences were noted in distributions of age, sex, and cognitive or functional level at baseline. Patient selection was completed before the MGAD probability was estimated.

MGAD PROBABILITY CALCULATION

We applied the method of Farrer and Cupples,[21] which computes a Bayesian probability that a patient has MGAD. This method uses pertinent parameter estimates from the best-fitting genetic model for the disorder,[25] data on the cumulative incidence of AD in the general population, and genealogic and clinical information. Specifically, the autosomal dominant mode of transmission as well as gene frequency, penetrance, and cumulative incidence quantities are incorporated into the prior probability that a given patient has MGAD. This probability is common to all subjects and is estimated to be .36.[21] Infor-

mation from family members (including affection status and age at onset or age at last known report) was then used to modify this prior probability to produce a posterior probability that the subject has MGAD given the subject's affection status and information from the family members. This posterior probability, unique to each subject, also allows for the possibility that some relatives may acquire the disease through nongenetic means and adjusts for the familial tendency for age at onset and sex differences in risk of disease. Resultant scores ranging on a scale from 0 (definitely not MGAD) to 1 (definitely MGAD) were determined for each subject (**Figure 1**). Although these estimates are sensitive to assumptions of gene frequency and cumulative incidence of AD in the general population, the ranking of individuals is robust regardless of the assumptions used.[21] These statistical procedures make no assumptions about the nature of the genetic abnormality or its chromosomal location; the data are independent of any molecular genetic studies.

MEASUREMENT OF RATE OF PROGRESSION

The rate of progression was measured in two ways: (1) the average annual rate of increase (slope) on the information, memory, and concentration subtest of the BDS[26] and (2) the average annual rate of increase (slope) on our modification of the ADL.[27] The Information, Memory, and Concentration subtest of the BDS measures intellectual and cognitive abilities and is based on direct examination of the patient. The ADL gauges level of function in normal daily tasks and is based on reports from the patient's caregiver. The modified ADL contains 31 questions grouped in seven general areas: self-care activities, household care, employment and recreation, shopping and money, travel, com-

lipoprotein E (ApoE) in late-onset AD.[13-17] It is now known that the risk and age at onset of illness is related to the number of ApoE type 4 alleles a person has.[18,19] In contrast to the autosomal dominant inheritance of AD in cases linked to chromosomes 14 and 21, having the ApoE type 4 allele is apparently not sufficient to cause AD but rather is considered a risk factor for FAD and sporadic AD. Although ApoE type 4 is disproportionately prevalent in AD cases, more than one third of patients with AD do not carry this allele. Also, among ApoE type 4 carriers, family history of dementia is independently associated with a statistically significant risk of AD, suggesting that additional genetic factors play an important role even in those who have an ApoE type 4 allele.[20]

We developed an algorithm to estimate the probability that a proband has a major genetic AD locus (MGAD).[21] This probability is based on genetic models of AD transmission and the estimated gene frequency of AD in the general population, combined with clinical and genealogic data from the proband. The method aims to distinguish sporadic AD and FAD cases based on statistical probability, independent of any molecular genetic information. To illustrate how likelihood estimates of MGAD can be used in clinical research, we applied our algorithm to 186 individuals with a clinical diagnosis of AD. We examined whether there are differences in the rates of cognitive and functional decline in patients
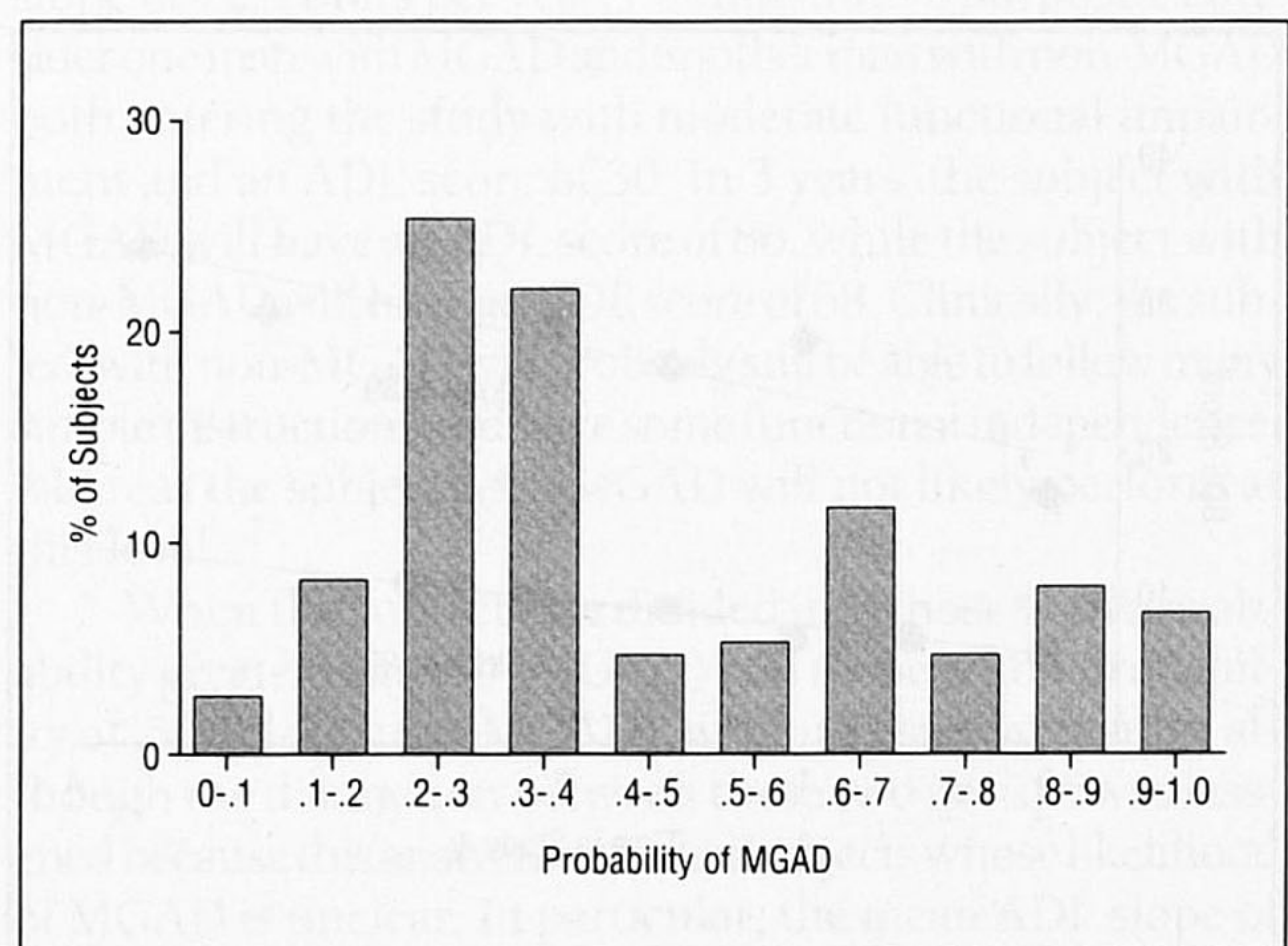

Figure 1. *Frequency distribution of probabilities of a major genetic locus for Alzheimer's disease (MGAD) for 186 patients with Alzheimer's disease.*

with AD caused by a major gene compared with those with sporadic AD.

RESULTS

For the 186 subjects, the mean±SD age at onset was 66.6±8.1 years (range, 46 to 83 years) and the average

munication, and social relationships. Independence in each item is rated ranging from 0 (normal) to 3 (fully dependent). If the individual never performed a particular activity (eg, cooking at home and working outside the home), the question about that activity was excluded from the calculation of the ADL score. Test scores range from 0 to 37 on the BDS and from 0 to 100 on the ADL; higher values on both scales are associated with greater impairment. Rate of progression scores were calculated for each subject by fitting a regression line to their BDS or ADL scores over time. **Figure 2** shows the changes in BDS score over time in two patients. Given that the subjects entered the study relatively early in the course of their illness, with BDS and ADL scores averaging 13.5 and 33.6, respectively, the straight-line assumption in the progression of disease seemed appropriate for these data. However, we examined whether a straight-line measure provided a good fit to the data and found that the average R^2 for the BDS and the ADL were 0.72 and 0.73, respectively. Nonlinearity of slopes was further investigated by adding a quadratic term for time to the model for each measure. The average coefficients for the quadratic term were 0.05 units per year (BDS model) and 0.03 units per year (ADL model), suggesting that a straight line provides a reasonable measure of the rate of progression in these subjects with AD.

ANALYSIS

An inherent assumption of our hypothesis (ie, the rate of progression is associated with the probability of MGAD) is that there exist at least two distinct groups of patients who differ by rate of progression (ie, fast progressors and slow progressors). Commingling analysis was used to evaluate whether the slopes for the BDS and the ADL exhibited a mixture of distributions. Potential confounding effects

of age at onset and duration of illness were removed by obtaining standardized residuals for the BDS slope and the ADL slope from multiple linear regression analyses.[28] The method used to assess multimodality described by MacLean et al[29] uses a maximum likelihood procedure to fit mixtures of two or three normal distributions to observed data and compares the fit with that obtained with use of a single distribution. This procedure was performed with the computer program SKUMIX.[29] Solutions for one and two distribution models were compared by a likelihood ratio test.

Comparisons between men and women were evaluated by Student's t test.[30] The association between the rate of progression variables (BDS slope and ADL slope) and the probability of MGAD, adjusting for sex, age at onset, and duration of illness at entry into the study, was evaluated with use of multiple linear regression techniques. We adjusted for age at onset and duration of illness because individuals may differ in rate of progression by these measures. In a second statistical approach, we included only subjects at the tails of the MGAD probability distribution, ie, subjects in whom the disease was most likely caused by a major gene and subjects in whom the disease was most likely not caused by a major gene. Subjects were classified as MGAD (1) or non-MGAD (0) according to the MGAD probability score, to focus the analysis on patients whose genetic status was relatively certain, by excluding subjects whose probability scores fell in the middle third of the range (ie, probability between .33 and .67). This procedure reduced the sample size from 186 to 131 subjects. In this statistical approach, differences in rates of progression (adjusted for sex, age at onset, duration, and years of education) between subjects with MGAD and non-MGAD were assessed by analysis of covariance.[28]
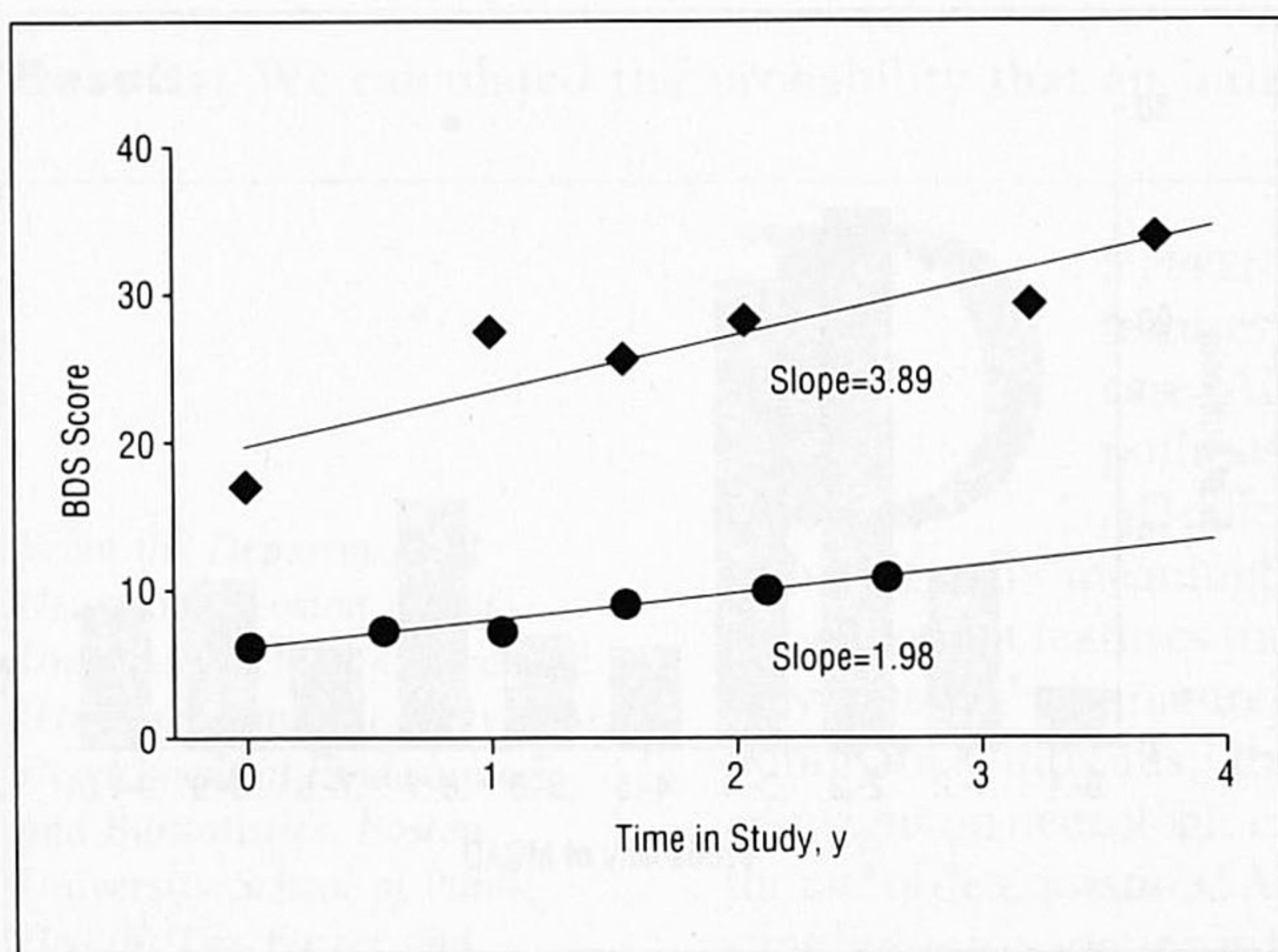

Figure 2. *Change in Blessed Dementia Scale (BDS) score over time in two patients with Alzheimer's disease. The slope of the fitted line (ie, rate of change) is greater for subject 2 (diamonds) than for subject 1 (circles), indicating that the rate of cognitive decline is faster in subject 2.*

number of visits was 4.8; the mean interval between visits was 6 to 7 months. **Table 1** shows the mean BDS and ADL test scores for the 186 subjects at the time of the initial visit. Men and women did not differ significantly in their initial BDS scores ($P=.34$) or ADL scores ($P=.24$),

with an average BDS score of 13.5 and an average ADL score of 33.6. Slopes for BDS could not be computed for 19 subjects (six men and 13 women) because fewer than three test scores were available, although they had at least three visits during which ADL scores were determined. Another eight subjects (four men and four women) were excluded from the ADL slope computation because of missing data, but all had three or more BDS scores. On average, patients worsened by 4.2±3.1 units per year on the BDS scale and 13.4±9.5 units per year on the ADL scale. The rate of progression did not differ between men and women on the BDS ($P=.33$) or the ADL ($P=.31$).

Figure 1 shows that the sample includes subjects whose probability of MGAD is relatively certain (ie, probability close to 0 or 1) as well as those whose genetic status is uncertain (ie, probability close to .5). The distribution of probabilities is similar to that in the larger sample of 415 subjects.[21] The minimum and maximum MGAD probability values were .04 and 1.0, respectively. No sex-specific differences were evident (Table 1).

Commingling analysis revealed evidence for two normal distributions of ADL slopes in the total group of subjects ($\chi^2=11.57, P<.005$; **Figure 3**). These distributions are apparently not indicative of a sex difference because two distributions were evident in male subjects ($\chi^2=9.55, P=.009$)

Table 1. Descriptive Statistics of Subjects With Probable Alzheimer's Disease Having Three or More Outpatient Visits*

	No. of Cases	Age at Onset, y	Status at First Visit		Rate of Progression†		Probability of MGAD
			BDS Score	ADL Score	BDS Score	ADL Score	
Men	72	67.1±7.6	12.9±7.2	31.5±17.3	4.5±2.9	14.3±8.5	.48±.27
Women	114	66.3±8.4	13.9±7.0	34.9±19.5	4.0±3.2	12.8±10.1	.44±.25
Total	186	66.6±8.1	13.5±7.1	33.6±18.7	4.2±3.1	13.4±9.5	.45±.26

*BDS indicates Blessed Dementia Scale; ADL, Activities of Daily Living; and MGAD, major genetic locus for Alzheimer's disease. Values are mean± SD.
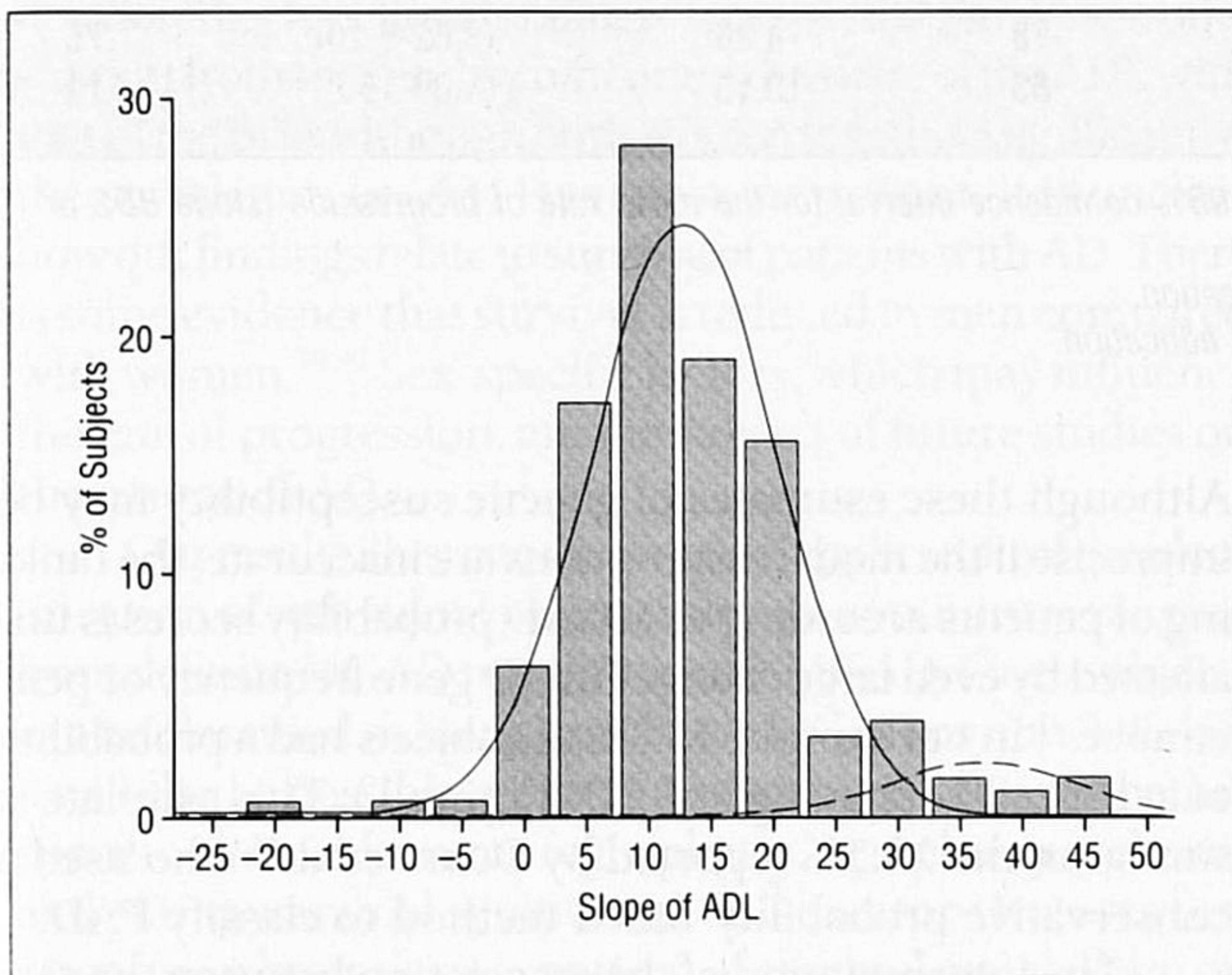†Rate of change per year (slope).

Figure 3. Frequency distribution for slope of Activities of Daily Living Scale (ADL). Slope is measured as the change in ADL units per year. Commingling analysis revealed evidence for a bimodal distribution of slopes (ie, "slow progressors" and "fast progressors") indicated by the fitted curves. The distribution of slopes for slow progressors (left curve) has a mean±SD of 13.4±7.2 units per year and accounts for 91.6% of the subjects. The distribution of slopes for fast progressors (right curve) has a mean of 36.0±7.2 units per year and accounts for 8.4% of the subjects.

Table 2. Linear Regression Analysis of Rate of Progression on the Probability of Major Genetic Locus for Alzheimer's Disease*

Rate of Progression (Dependent) Variable	No.	Regression Coefficient†	P
Men‡			
Slope BDS	62	.0145	.32
Slope ADL	66	.0813	.05
Women‡			
Slope BDS	97	−.0080	.52
Slope ADL	106	.0035	.93
Total§			
Slope BDS	159	−.0016	.86
Slope ADL	172	.0305	.28

*BDS indicates Blessed Dementia Scale; ADL, Activities for Daily Living.
†Predicted rate of change in the rate of progression for each percentage point increase in the probability of major genetic locus for Alzheimer's disease (see text for example).
‡Adjusted for age at onset, duration of illness, BDS/ADL score at entry, and education.
§Adjusted for sex, age at onset, duration of illness, BDS/ADL score at entry, and education.

and possibly in female subjects (χ^2=5.25, P=.08). Lack of evidence for skewness in a single distribution (χ^2=1.34, P=.34) further supports the conclusion of two normal distributions. There was marginally significant evidence for two distributions of BDS slopes (χ^2=5.46, P=.07), but a single distribution adequately fits the data in male and female subjects analyzed separately.

In men, the probability of MGAD was found to predict the ADL slope after adjusting for age at onset, duration of illness, ADL score at entry into the study, and education level (**Table 2**). The positive value for the regression coefficient implies that men with a higher probability of MGAD decline faster than men with a lower probability. The estimate of .081 suggests that for each percent increase in the probability, the slope increases by 0.081 units. For example, a man who has a probability that is 20% greater than another man will decline 1.6 units per year faster. No such effect was evident in women. The analogous model for BDS slope was not significant in patients of either sex.

Analysis of covariance demonstrated that men who are most likely to be MGAD (ie, persons having a probability of MGAD greater than .67) had significantly greater ADL slopes than men who are unlikely to be MGAD (ie, persons having a probability of MGAD less than .33). **Table 3** shows that men with MGAD have an adjusted average ADL slope

of 18.7 while men with non-MGAD have an average adjusted slope of 12.5 units per year. For illustrative purposes, consider one man with MGAD and another man with non-MGAD both entering the study with moderate functional impairment and an ADL score of 30. In 3 years, the subject with MGAD will have an ADL score of 86, while the subject with non-MGAD will have an ADL score of 68. Clinically, the subject with non-MGAD will probably still be able to follow many simple instructions and have some functional independence, whereas the subject with MGAD will not likely perform at this level.

When the subjects are divided into those with a probability greater than .50 (MGAD) and those with a probability of .50 or less (non-MGAD), we found similar results, although the distinction between these two groups was lessened because this analysis included subjects whose likelihood of MGAD is unclear. In particular, the mean ADL slope of 16.0 in men with MGAD was lower but not significantly different from the mean ADL slope of 13.0 in men with non-MGAD (P=.18). When using a more conservative criterion for selecting subjects with MGAD (probability, >.75) and those with non-MGAD (probability, <.25), the difference between the two groups was more stark, although the number of subjects in this analysis is small. In this case, the mean ADL slope of 21.5 in 14 men with MGAD was significantly greater than the mean ADL slope of 8.2 in 13 men with non-MGAD (P=.0006).

Table 3. Adjusted Mean Slopes for Rate of Progression Among Subjects With and Those Without a Major Genetic Locus for Alzheimer's Disease (MGAD)*

Dependent Variable	MGAD (Probability>.67)			Non-MGAD (Probability<.33)			P
	No.	Mean	95% CI	No.	Mean	95% CI	
Men†							
Slope BDS	16	4.89	(3.26-6.52)	31	4.34	(3.18-8.52)	.59
Slope ADL	17	18.72	(14.52-22.92)	31	12.46	(9.40-15.52)	.024
Women†							
Slope BDS	20	3.74	(2.30-5.18)	47	4.29	(3.35-5.23)	.53
Slope ADL	22	14.48	(10.26-18.70)	52	13.36	(10.62-16.10)	.66
Total‡							
Slope BDS	**36**	4.15	(3.07-5.23)	**78**	4.36	(3.62-5.10)	.75
Slope ADL	**39**	16.07	(13.06-19.08)	**83**	13.15	(11.09-15.21)	.11

*BDS indicates Blessed Dementia Scale; ADL, Activities of Daily Living; 95% CI, 95% confidence interval for the mean rate of progression (slope BDS or ADL) per year.
†Adjusted for age at onset, duration of illness, BDS/ADL score at entry, and education.
‡Adjusted for sex, age at onset, duration of illness, BDS/ADL score at entry, and education.

COMMENT

Our results indicate that, in men, progression of AD measured on the behavioral ADL was faster for subjects with MGAD than for those with non-MGAD. No significant association between MGAD and change in ADL score was found in women. In contrast to the behavioral scale, we found that the presence or absence of MGAD did not influence the rate of cognitive deterioration in AD, as judged by the BDS score. The BDS score declined by approximately 4 points per year, which is similar to reports of several published studies using this test.[31-35] Our data show that our population of patients with AD was similar to AD populations studied in other parts of the country. We also did not find an association between rate of functional decline, as measured by the ADL score, and probability of MGAD, when pooling the data for men and women. Using very different definitions of genetic risk and disease progression measured by the ADL, Drachman et al[36] also did not find an association between the two variables in a sample of 52 men and women combined.

The patients with AD in our study were selected from a subspeciality memory disorders clinic and may not be representative of all patients with AD. First, our population consisted entirely of white, educated, middle-class subjects. Second, patients in our study were in the mild to moderate stages of dementia. All subjects were living at home with a spouse, child, or other care provider; at entry into the study, no subject was institutionalized. These factors may be related to AD progression, but to distort the association between MGAD and progression, these factors should also be related to the MGAD probability. At present, there is no evidence that genetic factors are associated with any of these population characteristics. All subjects met research criteria for the diagnosis of probable AD and displayed a clinical course characteristic of AD during the years of follow-up visits. This sample is therefore valid for addressing the scientific goal of our research, which was to determine whether progression of dementia was influenced by genetic factors.

Computation of the probability of MGAD incorporates aspects of the genetic model, including mode of inheritance and frequency and penetrance of the major gene, and prevalence of the disorder in the general population. Although these estimates of genetic susceptibility may be imprecise if the model assumptions are inaccurate, the ranking of patients according to MGAD probability scores is unaffected by even large changes in AD gene frequency or penetrance.[21] In our sample, 15.1% of subjects had a probability of at least .80 of having MGAD (Figure 1). This estimate is similar to the 13.5% reported by Duara et al,[37] who used a conservative probability-based method to classify FAD.

The interpretation of the association between the rate of decline on the ADL and likelihood of genetic disease in men but not women is uncertain, although there are several possibilities. The first possibility is that the finding is a statistical artifact owing to small subgroup sizes in the sex-specific analysis. This explanation is unlikely because there was no difference in the distribution of MGAD between men and women. Furthermore, men and women did not differ in terms of age at disease onset or duration of illness at entry into the study. The fact that the BDS and ADL slopes were the same in men and women, a finding in agreement with the study of Henderson and Buckwalter,[38] who used a cognitive test modified from the BDS, argues further for a specific effect on the ADL slope in MGAD men.

The second possible explanation is that the ADL questionnaire is weighted for the detection of functional problems in men more than women. This explanation is unlikely because the ADL is not slanted toward masculine behaviors. The ADL form has 22 sex-neutral questions (eg, eating, dressing, and bathing), six questions about activities that are commonly viewed as pertaining to women (eg, shopping for food, meal preparation, housekeeping, and laundry), and only three that could be considered principally performed by men (home repairs, employment, and managing finances). Also, the sex of the person completing the questionnaire could influence the outcome. Specifically, women who care for men might be more acute observers of behavioral impairments than men who care for women. We cannot answer this question definitively. For men, there were 63 female caregivers and 11 male caregivers; for women, there were 62 female caregivers and 49 male caregivers. Overall, most of the ADL questionnaires were completed by women. The principal arguments against sex bias in the ADL or caregiver reports accounting for an association with MGAD probability in

men and not women are as follows: (1) There was no sex difference in the distribution of either MGAD probabilities or rate of decline on the ADL. (2) The primary finding of an association between MGAD probability and ADL slope is *within* one sex, ie, men.

The third possibility is that a major gene causing autosomal dominant AD may truly affect functional behavior in men more than women and that this impairment is out of proportion to cognitive deficits. This hypothesis derives support from the commingling analysis, which suggests subgroups for ADL score but not for BDS score in both sexes and implies that cognitive decline in AD is separable from deteriorating functional abilities. This speculation draws some support from the results comparing the slope of the ADL with that of the BDS: although both worsen together significantly, the correlation ($r=.43$) is modest. At present, it is unclear how our findings relate to survival of patients with AD. There is some evidence that survival is reduced in men compared with women.[39-41] Sex-specific factors, which may influence the rate of progression, are the subject of future studies on the course of AD.

Our results illustrate the practical application of the identification of individual patients along a continuum ranging from definite MGAD to definite non-MGAD. Once subjects can be classified as having probable MGAD or non-MGAD, it will also be possible to determine with confidence whether specific clinical features (eg, aphasia, agraphia, psychosis, and extrapyramidal symptoms) or laboratory features (eg, atrophy on brain scan or pattern of cerebral metabolism on positron emmision tomographic scan) are characteristic of MGAD or non-MGAD. Furthermore, security in diagnosing MGAD or non-MGAD is crucial to determine the influence of risk factors (eg, the extent to which ApoE behaves as a major genetic factor for AD). Application of our algorithm for computing the probability of MGAD will allow these issues to be reinvestigated with greater assurance than in previous studies.

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