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Autosomal Recessive Causes Likely in Early-Onset Alzheimer Disease

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Objectives: To determine the genetic contribution to non–autosomal dominant early-onset Alzheimer disease (EOAD) (onset age ≤60 years) cases and identify the likely mechanism of inheritance in those cases.

Design: A liability threshold model of disease was used to estimate heritability of EOAD and late-onset Alzheimer disease (AD) using concordance for AD among parent-offspring pairs.

Setting: The Uniform Data Set, whose participants were collected from 32 US Alzheimer's Disease Centers, maintained by the National Alzheimer's Coordinating Center.

Participants: Individuals with probable AD and detailed parental history (n=5370).

Main Outcome Measures: The concordance among relatives and heritability of EOAD and late-onset AD.

Results: For late-onset AD (n=4302), we found sex-specific parent-offspring concordance that ranged from approximately 10% to 30%, resulting in a heritability of 69.8% (95% confidence interval, 64.6%-75.0%), and equal heritability for both sexes regardless of parental sex. For EOAD (n=702), we found that the parent-offspring concordance was 10% or less and concordance among siblings was 21.6%. Early-onset AD heritability was 92% to 100% for all likely values of EOAD prevalence.

Conclusions: We confirm late-onset AD is a highly polygenic disease. By contrast, the data for EOAD suggest it is an almost entirely genetically based disease, and the patterns of observed concordance for parent-offspring pairs and among siblings lead us to reject the hypotheses that EOAD is a purely dominant, mitochondrial, X-linked, or polygenic disorder. The most likely explanation of the data is that approximately 90% of EOAD cases are due to autosomal recessive causes.

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ALZHEIMER DISEASE (AD) IS the most common of the neurodegenerative diseases and the leading cause of dementia. Prevalence estimates range from 29 to 125 per 1000 among those older than 65 years[1-4] and 0.17 to 0.41 per 1000 for those 60 years or younger.[5-8] Although the major risk factor for AD is age, genetic factors like apolipoprotein E ε4 (*APOE4*) also play an important role in the disease. Individuals with AD are typically divided into 2 groups based on the arbitrary criterion of age at onset, with symptoms appearing at or before age 60 years for early-onset AD (EOAD) and at or after age 65 years for late-onset AD (LOAD).[9,10] Studies of families with autosomal dominant transmission of EOAD led to the identification of important AD-causing mutations, including amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*).[11] These mutations increase β-amyloid production, and their study has profoundly influenced our understanding of AD pathogenesis.[12]

The discovery of highly penetrant dominant AD-causing mutations has led to the common perception that all EOAD is due to dominant alleles.[13] Yet, this belief is inconsistent with epidemiologic data that found apparent autosomal dominant transmission in approximately 10% of all EOAD cases, leaving the majority of EOAD unexplained.[6] The apparent failure to identify new AD-causing autosomal dominant alleles in EOAD may mean that all responsible genes have been identified or that other genetic mechanisms are at work.

Herein, we sought to test the hypothesis that all forms of EOAD are due to dominant alleles in the Uniform Data Set (UDS), whose participants were col-

lected from 32 Alzheimer's Disease Centers (ADCs). To do so, we determined the genetic contribution to EOAD and likely mechanism of inheritance by examining the concordance among parents and offspring. Using established quantitative genetic models, we found that EOAD is almost entirely due to genetic factors. However, our data lead us to reject a purely dominant, polygenic, mitochondrial, or sex-linked mode of inheritance. The simplest and surprising interpretation is that EOAD is likely autosomal recessive in most cases, with dominant causes accounting for a minority (≤10%) of cases. The data could also be explained by alleles that have a very low (≤20%) average heterozygote penetrance making them usually autosomal recessive but not invariably so. Indeed, a combination of these 2 explanations is possible. In either case, we find strong evidence for new genetic causes of EOAD that should be systematically evaluated.

METHODS

PROBANDS ASCERTAINED FROM THE UDS

Probands were ascertained from 32 US ADCs through the UDS maintained by the National Alzheimer's Coordinating Center.[14] Individuals recruited from September 1, 2005, to March 11, 2010, were eligible for inclusion. All individuals in this data set complete a standardized clinical examination, have family history obtained by interviewing a knowledgeable informant, undergo neuropsychiatric testing, and are diagnosed based on criteria established by the National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Work Group for probable AD.[15-18] Inclusion criteria for our study were individuals with dementia primarily due to probable AD who had at least 1 parent whose dementia status was known. Exclusion criteria were the presence of Down syndrome and, when twins were recruited from a single family, only the first recruited twin was included. A small replication data set was also analyzed consisting of probands recruited at the Emory ADC who underwent a similar evaluation, including systematic evaluation of parental history of dementia, but did not participate in the UDS. Further details on the subjects are provided in the supplementary "Methods" section (http://userwww.service.emory.edu/~twingo/).

CONCORDANCE CRITERIA

Enrollees in the UDS reported whether their parents or siblings had "dementia," not specifically whether AD was present. Since AD is the most common cause of dementia, we defined parent-offspring concordance as parents with dementia and offspring with probable AD.[19] For probands with unknown age at onset, we used age at diagnosis as a surrogate. For LOAD concordance, we required concordant pairs to have an onset at or after age 65 years; subjects whose parents died before age 65 years were counted as missing for the LOAD analysis. For EOAD concordance, we required concordant pairs to have onset at or before age 60 years; parents who died at or before age 60 years without developing dementia were counted as missing. For probands with EOAD, we defined the sibling as concordant if the sibling was known to have dementia at or before 60 years of age. Discordant siblings occurred when the sibling developed dementia after age 60 years or was alive after age 60 years without dementia.

STATISTICAL ANALYSIS

Sex-specific concordant and discordant parent-offspring pairs were determined for the entire cohort (all AD), as well as EOAD and LOAD separately. To calculate AD heritability, we followed Falconer[20] and assumed the existence of a normally distributed latent liability to AD in the general population. *Liability* herein refers to all possible genetic and environmental influences on AD development. In this model, individuals who are beyond a certain liability threshold develop disease, ie, AD. We used AD prevalence estimates to set the thresholds of the model. Since the prevalence of LOAD and EOAD are not known precisely in the population from which the ADC registry was drawn, we used a range of likely prevalence estimates in the United States. For LOAD, we chose a range that corresponded to the 95% confidence interval (CI) of AD prevalence in the Cache County cohort (men: 3.74%-5.70% and women: 6.75%-8.71%).[3] This cohort was chosen because it provided sex-specific AD prevalence estimates and has demographics similar to the ADC registry participants. A point estimate of LOAD heritability in the United States was calculated using point-prevalence estimates of 4.72% for men and 7.73% for women. For EOAD, we chose to examine all prevalence values less than 1 per 1000, which represents a plausible upper limit of EOAD prevalence.[5-8] To calculate a conservative point estimate of EOAD heritability, we used prevalence estimates of 0.239 per 1000 for men and 0.577 per 1000 for women, based on a large French population-based study with the highest reported prevalence of EOAD in the literature.[6] Heritability was calculated for each combination of parent and offspring sexes independently and the details are provided in the supplementary "Methods" section (http://userwww.service.emory.edu/~twingo/). Mean heritability was calculated weighted by the reciprocal of the sampling variance for each parent-offspring pair. For participants with AD, the heritability of age at onset was estimated by regressing normalized parent age at onset on that of the child for all 4 sex-specific parent-child pairs. Normalization of age at onset was done using a Box-Cox transformation.

RESULTS

DEMOGRAPHICS AND CONCORDANCE OF AD

A total of 5370 individuals met our inclusion criteria in the ADC registry, and their demographics are presented in **Table 1**. Sex-specific parent-offspring concordance is presented in **Table 2** for the entire cohort (all AD), LOAD, and EOAD. Demographics and concordance for EOAD in the Emory data set (n=36) are presented in eTable 1 and eTable 2 (http://www.archneurol.com). In general, missing data were relatively consistent for both parents, with only 1.8% (n=95) having missing data from the mother but not the father and 4.7% (n=252) missing data from the father but not the mother. The concordance pattern among all AD and LOAD was higher when the affected proband (offspring) was male and the relative (parent) was female, which is the expected pattern of inheritance if LOAD is a polygenic disease and AD is more prevalent in women than men.[11] No such pattern was seen for EOAD, suggesting it is not a polygenic disease. As expected, the concordance for individuals with EOAD and a known autosomal dominant mutation approached 50% (eTable 3), albeit based on a small sample size. Finally, we found that among probands with EOAD

Table 1. Demographics

	No. (%)		
	All AD (n=5370)	LOAD (n=4302)	EOAD (n=702)
Male	2283 (42.5)	1781 (41.4)	323 (46.0)
Female	3087 (57.5)	2521 (58.6)	379 (54.0)
APOE4 positive	3449 (64.2)	2784 (64.7)	434 (61.8)
APOE4 negative	1921 (35.8)	1518 (35.3)	268 (38.2)
Years of formal education, median (range)	14 (0-27)	14 (0-26)	16 (0-25)
Race[a]			
White	4375 (81.5)	3464 (80.5)	604 (86.0)
Black	669 (12.5)	587 (13.6)	47 (6.7)
American Indian or Alaska Native	29 (0.5)	26 (0.6)	1 (0.1)
Native Hawaiian or other Pacific Islander	3 (0.1)	3 (0.1)	0
Asian	89 (1.7)	76 (1.8)	11 (1.6)
Other	194 (3.6)	139 (3.2)	35 (5.0)

Abbreviations: AD, Alzheimer disease; *APOE4*, apolipoprotein E ε4 allele; EOAD, early-onset AD (onset age ≤ 60 years); LOAD, late-onset AD (onset age ≥ 65 years).

[a] Does not sum to 100% because of missing racial data (<1%).

there was 21.5% concordance among siblings for dementia occurring at or before age 60 years. This does not significantly differ from the expected concordance of 25% for an autosomal recessively inherited trait (χ^2=0.5617; P=.4536) but does differ significantly from the 50% expected concordance for an autosomal dominant illness (χ^2=38.65; $P=5.079\times10^{-10}$).

GENETIC CONTRIBUTION TO AD

To estimate the inherited genetic contribution to a disease, or its heritability, information about both the concordance of disease among relatives and the prevalence of the disease in the population are necessary. Since we cannot directly estimate the prevalence of EOAD or LOAD in the UDS, because it is not a population-based sample, we estimated the heritability over a likely range of EOAD and LOAD prevalence values. The heritability of EOAD was more than 92% for any prevalence less than 1 per 1000. Using the point estimates from a French EOAD prevalence study of 0.239 per 1000 for men and 0.577 per 1000 for women, the weighted mean EOAD heritability was 100.0% (95% CI, 93.8%-100.0%).[6] For LOAD, we found the heritability ranged from approximately 62% to 81% for all values of AD prevalence based on the 95% CI of the Cache County cohort (men: 3.74%-5.70% and women: 6.75%-8.71%).[3] These results are graphically displayed in supplementary Figure 1 (http://userwww.service.emory.edu/~twingo/). Using point-prevalence estimates found in the Cache County cohort (male prevalence of 4.72% and female prevalence of 7.73%), the weighted mean heritability of LOAD was 69.8% (95% CI, 64.6%-75.0%). For other estimates of LOAD prevalence, we found that LOAD heritability was between 45% and 73%; however, these results should be viewed as rough estimates since sex-specific prevalence estimates are not given for these cohorts, and the cohorts are not well matched to the ADC registry participants' demographics.[1,4] We also found that the precise age at AD onset was a highly heritable trait, with heritability estimates between 66.9% and 86.8% (supplementary Table 1, http://userwww.service.emory.edu/~twingo/).

The polygenic nature of LOAD suggested by the pattern of concordance predicts that heritability estimates should be independent of sex and that *APOE4*, a known genetic risk factor with large effect size, should account for a relatively small proportion of the total contribution to genetic LOAD risk. To address the first prediction, we looked at all combinations of proband and relative sexes and found that heritability was approximately equal whenever female prevalence of AD was approximately 2.5 times male prevalence of AD, regardless of the underlying male prevalence (supplementary Figure 2, http://userwww.service.emory.edu/~twingo/). Interestingly, a similar prevalence ratio was seen in the Framingham cohort of approximately 2.6 but the ratio was lower (approximately 1.6) in the Cache County cohort.[2,3] This analysis also suggests that LOAD heritability is approximately 60% to 80% for likely values of AD prevalence. To address the second prediction, we stratified LOAD probands by the presence or absence of an *APOE4* allele and found the heritability among *APOE4* carriers was 71.2% (95% CI, 66.6%-8.0%) and among noncarriers was 67.3% (95% CI, 60.5%-74.2%) assuming equal LOAD prevalence for both groups. This finding suggests that the *APOE4* allele accounts for about 4% of the variance in LOAD prevalence.

COMMENT

Herein, we analyzed a large data set of probable AD cases ascertained by 32 US ADCs over 5 years to investigate the genetic basis of EOAD. To our knowledge, our analysis represents the first EOAD heritability study and the largest LOAD heritability study to date and shows that EOAD and LOAD have distinct genetic disease mechanisms.

Our results for EOAD argue against it being a polygenic disease, but they do indicate that EOAD is substantially or even entirely genetically based (heritability 92%-100%). If EOAD were most often autosomal dominant with full penetrance, as with known AD-causing mutations, we would expect a concordance of about 50% between parent and offspring, which was found for known mutation carriers (eTable 3). However, we found an overall concordance of less than 10%. If, on the other hand, EOAD were caused by a single autosomal recessive allele, and given that the prevalence of EOAD is less than 1 in 1000, we would expect parent-offspring concordance to be less than 2.5%. The reason for this is that if EOAD were due only to 1 autosomal recessive locus, then both parents of an affected child would each have to carry at least 1 copy of the disease allele. The chance of either parent carrying a second copy is the frequency of the disease allele. For an autosomal recessive disease, the frequency of the disease allele must be less than or equal to the square root of the prevalence of the disease, which is about 2.5%. Thus, the simplest explanation for the concordance we see is that approximately 10% of EOAD is

Table 2. Parent-Offspring Concordance

	No. (%)					
	All AD[a]		LOAD[b]		EOAD[c]	
	Concordant	Discordant	Concordant	Discordant	Concordant	Discordant
Father-son	374 (17.1)	1814	248 (15.1)	1390	13 (4.3)	290
Father-daughter	358 (12.2)	2572	239 (10.3)	2082	17 (4.8)	338
Mother-son	738 (32.9)	1501	516 (30.4)	1182	23 (7.4)	287
Mother-daughter	870 (28.7)	2166	636 (26.5)	1765	30 (8.1)	341

Abbreviations: AD, Alzheimer disease; *APOE4*, apolipoprotein E ε4 allele; EOAD, early-onset AD (onset age ≤ 60 years); LOAD, late-onset AD (onset age ≥ 65 years).
[a] Concordant pairs with any age at onset.
[b] Concordant pairs who both have onset at or after age 65 years.
[c] Concordant pairs who both have onset at or before age 60 years.

due to known autosomal dominant causes and the bulk of cases, the remaining approximately 90%, are either due to recessive alleles at 1 locus or a relatively small number of separate loci that are fully penetrant in women but have reduced (about 50%) penetrance in men, explaining the overall sex prevalence difference. Lending further support to the conclusion EOAD is due to autosomal recessive causes is the concordance for EOAD among siblings of 21.6%, which is consistent ($P = .46$) with the expected concordance of 25% among siblings for an autosomal recessive disease but not with the 50% expected for autosomal dominant inheritance ($P = 5.079 \times 10^{-10}$). Alternatively, incompletely penetrant dominant mutations may still give rise to the concordance patterns we observe. However, such mutations must be largely recessive, having an average heterozygous penetrance of 20% or less (for the total parent-offspring concordance to be less than 10%), but they need not be completely recessive. Other genetic mechanisms are less likely. If mitochondria were largely responsible, then we would see much higher concordance between mothers and their offspring but not fathers, and if X-linked causes were significant, we would see high concordance between mothers and their male offspring but not fathers and their male offspring. In principle, there could be very different genetic mechanisms for EOAD in men than in women, but we have no evidence to support this view. Taken together, our data, the known autosomal dominant causes, and the effect of *APOE4* allele on AD argue that a mixture of autosomal recessive, dominant, and potentially other strong genetic risk factors influence the occurrence of EOAD.[21] Finally, a recently identified autosomal recessive mutation in a proband with EOAD showed that autosomal recessive causes of AD are indeed possible.[22]

In contrast to EOAD, there are many lines of evidence in our data pointing to LOAD as a polygenic disease with a substantial genetic basis. First, the pattern of concordance is highest whenever the proband is the least affected sex (ie, male) and the relative is the most affected sex (ie, female). This pattern of observed concordance is considered de facto proof of a highly polygenic mechanism of inheritance, since no other genetic cause can easily produce such a pattern.[20] Furthermore, we found that LOAD heritability is independent of sex and that the strongest and best-validated genetic risk factor for AD, *APOE4*, explains just a relatively small proportion of the overall genetic basis of the disease.[23] This implies there are many more loci that likely influence LOAD, and several new loci have been confirmed in a recent large genome-wide study.[24,25] Our findings are also in line with other AD heritability studies, which also find LOAD to be polygenic, with heritability between approximately 60% and 80%.[26-30] We also find that AD age at onset is a substantially heritable trait and that with increasing age at onset the heritability of AD declines, implying increased environmental contribution to AD at older ages.

In our analysis, we define EOAD as AD at age 60 years or before and LOAD as AD at age 65 years or after. Both definitions are traditional but arbitrary.[9,10] Interestingly, raising the maximum age to qualify for EOAD leads to increased EOAD prevalence, decreased EOAD concordance, and an EOAD concordance pattern that begins to suggest polygenic inheritance, ie, higher concordance from the less affected sex. Conversely, as we lower the age at onset defining EOAD, we find it looks more autosomal dominant. In fact, defining EOAD as AD prior to age 40 years we find a nearly 50% concordance, which is the expected concordance for an autosomal dominant disorder. However, this conclusion is based on fewer than 10 probands.

One of the chief problems with studying any age-dependent illness is that concordance among living relatives may change with time. Our solution was to look only at individuals who were known to have AD and ask whether their parents were similarly affected. Because the vast majority of parents are now deceased, concordance estimates we found are unlikely to change with time. Although we were fortunate to have a large number of probands and recruitment centers for this study, making our results resistant to the influences of recruitment strategies at individual ADCs, we are still potentially limited, since parents were not assessed in the same way as probands. For parents, we had to infer that a history of dementia indicated the presence of AD; however, considering that AD is the most common cause of dementia and underlying AD pathology is found in approximately 84% of individuals with dementia, this inference seems reasonable.[19] Additionally, potential selection bias in the UDS for AD cases who have a family history will cause an overestimate of AD heritability. However, this concern is some-

what mitigated since our estimates of LOAD heritability are consistent with those found by population-based twin studies. To address the limitation that arises from not knowing the true prevalence of AD in the population from which this sample was drawn, we calculated AD heritability over the range of all likely AD prevalences. Another concern is that the use of an ethnically mixed cohort (Table 1) could be problematic if there were vastly different causes of AD within different ethnic groups, but available evidence does not support this.[31-33] Moreover, we assessed this directly by analyzing the data for white individuals alone; in fact, there were no significant differences in the patterns of concordance by sex or heritability (EOAD heritability, 100% [95% CI, 94.0%-100%] and LOAD heritability, 73.1% [95% CI, 67.7%-78.6%]). Also, since we cannot discern if multiple members of a particular family are included in the National Alzheimer's Coordinating Center cohort (other than twins), it is possible that more siblings are included. However, less than 10% of probands share the same race and parental diagnosis (age at onset, age at diagnosis) with any other proband. This suggests that at most 10% of samples are siblings. Of course, random unrelated individuals with AD are likely to share the same race and parental AD status, so this figure likely represents a generous overestimate of the true number of related probands.

Our results for LOAD are consistent with established heritability estimates. By contrast, our results for EOAD differ from prior studies that only found support for autosomal dominant transmission.[34,35] This is due to several key study design differences. First, the current study contains more than 3 times as many EOAD probands as any previous work. Second, the current study focuses on even earlier-onset cases (a maximum age at onset of 60 years vs an average age at onset of 62.5 years), and finally, the current study is the first, to our knowledge, to formally consider the possibility that EOAD might be caused by a mixture of dominant and recessive causes.

In conclusion, our results give us new insight into the genetic basis of EOAD through the simple but surprising conclusion that EOAD likely has autosomal recessive causes.

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