Heritability of Magnetic Resonance Imaging (MRI) Traits in Alzheimer Disease Cases and Their Siblings in the MIRAGE Study

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Abstract: Magnetic resonance imaging (MRI) traits can serve as more specific measures of degenerative or cerebrovascular brain injury than can be ascertained through personal history, risk factors, clinical signs, or symptoms. They are potentially useful intermediate phenotypes for genetic studies of Alzheimer disease (AD). Recent studies have estimated heritability of white matter hyperintensity (WMH) among cognitively normal family members to be between 0.55 and 0.73. Persons discordant for AD are expected to have substantially different MRI phenotype distributions; our goal was to determine whether MRI traits in siblings discordant for AD are heritable. We measured cerebral atrophy, medial temporal atrophy (MTA), WMH, and a rating of cerebrovascular disease (CVR) via MRI in 815 participants from 424 families of the Multi-Institutional Research in Alzheimer's Genetic Epidemiology Study. Residual heritability after adjustment for covariates ranged from 0.17 ($P = 0.009$) for MTA to 0.57 ($P = 10^{-7}$) for CVR. The number of APOE-ε4 alleles was significantly associated with WMH ($P = 0.01$) and CVR ($P = 0.005$) but not cerebral atrophy ($P = 0.25$) or MTA ($P = 0.83$). Heritability remained significant and high after adjusting for APOE genotype, suggesting that a substantial proportion of the additive genetic variation in these MRI traits is explained by other genes. In the Multi-Institutional Research in Alzheimer's Genetic Epidemiology Study of AD-discordant siblings, MRI traits are heritable and are potential endophenotypes for genetic association studies.

Key Words: Alzheimer disease, magnetic resonance imaging, heritability, APOE

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Genetic studies focusing on the complex phenotype of Alzheimer disease (AD) have shown that the APOE-ε4 allele is a major AD risk factor in most populations,[1] accounting for 40% to 60% of the genetic susceptibility.[2,3] Numerous other genes have been reported to be associated with AD, however, none have been widely accepted.[4] There are several explanations for lack of consistent genetic association findings including genetic heterogeneity, population admixture, and clinical heterogeneity.

Magnetic resonance imaging (MRI) measures are associated with the anatomic brain changes that accompany the AD process. For example, hippocampal atrophy occurs early in the disease[5–8] and correlates with impairments in memory function[9] and AD postmortem pathology.[10,11] In addition, cross-sectional and longitudinal measures of cerebral atrophy (CA) also differ between AD patients and age-matched controls[7,12–17] and are associated with the rate of cognitive deterioration.[18–20]

Clinically silent cerebrovascular disease (CVD) is also quite common to the elderly[21] and epidemiologic studies reveal a high prevalence of silent vascular brain injury among the elderly.[21–24] In addition, there are strong associations between vascular risk factors, cognitive impairment, and dementia,[25–34] suggesting that CVD may interact with the pathophysiology of AD to increase the likelihood of expressed dementia.[35–37] MRI measures such as abnormalities of cerebral white matter and cerebral infarction are 2 common MRI abnormalities thought to represent clinically silent CVD.[33,34,38]

Recognition that MRI measures can serve as a biologic marker of the AD and CVD processes that offers the possibility for MRI measures to serve as an endophenotype for genetic studies of dementing diseases. One goal of the Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) Study is to identify genes influencing susceptibility to AD and differences in MRI measures in a multiethnic group of sibships comprising affected and unaffected members. MRI endophenotypes might facilitate a better understanding of the genetic basis of a complex disease by decomposing the disease into measurable phenotypes that are more directly related to the genetic components of the

disease process. However, to be useful, the endophenotypes must be heritable and associated with disease in the population and within families.[39] Previously, we described methods and group differences in brain structure derived from MRI data obtained as part of the MIRAGE Study and examined the effect of multiple potential confounding variables on these group differences.[40] Here, we establish the heritability of the MRI measures within these sibships. The heritability of some of the measures have been previously reported.[41–47] However, this is the first study examining semiquantitative measures using a sibpair design. It is critical to establish that heritability is significant when families are ascertained using the AD-discordant sibship design before attempting to establish genetic associations between these traits and various genetic polymorphisms.

METHODS

Subjects and Data Collection

The MIRAGE Study is a multicenter, family-based study of genetic and environmental risk factors for AD. Details of data collection procedures, protocols for obtaining family histories, and reports of validity of study questionnaires have been published elsewhere.[48–50] MIRAGE probands (AD cases) were ascertained at sites in the United States, Canada, Germany, and Greece through research registries or specialized memory clinics between February 1998 and November 2006. All AD cases were living individuals diagnosed with probable AD in accordance with the NINCDS/ADRDA criteria.[51] Medical history and risk factor information and blood samples were obtained from AD patients and their available siblings after obtaining informed consent from the nondemented subjects and a combination of consent or assent along with informed consent by proxy on living demented subjects. Cognitive status of individuals identified as nondemented was confirmed by administration of the modified Telephone Interview of Cognitive Status.[52] Ethnicity of subjects was determined by self-report.

MRI Methods

MRI acquisition and analysis protocols for this group of individuals have been described previously.[40] In brief, each individual received a double spin echo, fluid-attenuated inversion recovery, and high resolution T1 images for analysis. CA was rated from the second echo images of the double echo sequence. White matter hyperintensities (WMH) were rated from fluid-attenuated inversion recovery images. Medial temporal atrophy (MTA) was rated from the high resolution T1 images. Finally, the presence or absence of MRI infarction was determined according to a standard protocol previously described using information from all available images.[24]

Semiquantitative estimates of CA and the severity of WMH were each rated on 100-mm analog scales where 0 denoted no atrophy or no WMH and 100 denoted the most severe atrophy and the most extensive WMH. This process included examples of quantified abnormalities as tie-points for the rating process.

MTA was rated using a previously described method[53–55] that discriminates well between AD and cognitively normal individuals and has a high degree of interrater reliability. The presence of MRI infarction was determined from the size, location, and imaging characteristics of the lesion as previously described.[24] Interrater reliabilities for this method vary between 0.73 and 0.90. Using the combined WMH and infarction data, we created an overall rating of cerebrovascular disease (CVR) to describe the additive effects of both WMH and MRI infarction. CVR is the summed severity of WMH and MRI infarction. For example, CVR in the absence of MRI infarction is equal to WMH severity. If there is accompanying MRI infarction, the rating is additive (eg, 20 WMH + 20 infarct = 40 CVR).

All images were rated by a single observer (C.D.) who was blind to family id, subject sex, age, APOE genotype, and affectation status.

Statistical Methods

The sample consisted of AD-affected individuals and their unaffected siblings. Categorical variable distributions for affected and unaffected sibs were compared using the Cochran-Mantel-Haenszel general association test implemented in SAS software,[43] stratifying on sibship. Differences between affected and unaffected individuals for continuous traits were tested for significance using a generalized estimating equation approach as implemented in SAS software,[43] accounting for the correlated sibling data. WMH and CVR were log-transformed to reduce skewness and kurtosis. Pearson correlations were computed between each pair of the 4 MRI traits within cases and unaffected sibs, using a randomly chosen single affected sib or unaffected sib from each family so that all observations within these subgroups were independent.

The 4 MRI traits CA, MTA, log(WMH), and log(CVR) were examined for heritability. The presence of MRI infarcts was rated for each individual, but the dichotomous nature of this variable (present or absent) does not allow for estimation of heritability, which measures the proportion of variance of a continuous trait that may be due to genetic factors.

We adjusted for covariates and estimated residual heritability using the variance components approach implemented in SOLAR (Sequential Oligogenic Linkage Analysis Routines v2.1.4[56]). The SOLAR method applies a mixed effect model to account for the fixed effects of covariates, random additive genetic effects, and individual error. The sibships were not ascertained on the basis of any of the MRI measures. However, as case status has a very strong effect on these measures, we applied an ascertainment correction by conditioning on the probands, as described by Almasy and Blangero.[56]

For each MRI trait, we considered the covariates sex, age at MRI, ethnicity, AD affection status, and duration of disease measured in years (0 for unaffected).

We tested each covariate for significance in the model as a fixed effect, using a likelihood ratio test comparing the full model with all covariates to a reduced model with the covariate removed. We included all fixed effect covariates that were significant at the 0.10 level in the model. After removing variation in the MRI traits attributable to the significant covariates, SOLAR estimates the heritability as the proportion of the remaining variance due to additive genetic factors.

After establishing heritability, we tested for association between APOE genotype and each trait by including either the number of APOE-ε4 alleles (0, 1, or 2) carried by each individual or whether or not they carried any APOE-ε4 alleles (0 or 1 for no, yes) as an additional fixed effect covariate in the model. Ethnicity was also included in the APOE models, to help avoid spurious association due to stratification. As for other covariates, the significance of the APOE genotype was tested using a likelihood ratio test. When APOE genotype was significant, the differences in the proportion of variance explained by the covariates with and without the APOE genotype in the model were compared, to determine the proportion of variance in the phenotype explained by the APOE genotype.

All P values presented in the text and tables are nominal P values.

RESULTS

Sample

Tables 1 and 2 present the number of AD cases and unaffected siblings and also the ethnicity of the sibships. MRI data were available on a total of 815 individuals from 424 families, including 113 singletons (52 affected, 61 unaffected) for whom the sib's data were not yet available, and 311 sibships with 2 or more individuals. Approximately 65% of the sibships and individuals self-identified as white/non-Hispanic; the remaining sibships were white/Hispanic (11.3%), African American (14.4%), and Japanese American (9. 4%) (Table 2).

There were 366 AD cases, including 347 probands and 19 affected siblings, and 449 unaffected sibling controls. Table 3 presents demographic and clinical characteristics of the sample for AD affected and unaffected sibs. As expected, the AD patients had significantly more APOE-ε4 alleles than their unaffected siblings ($P = 1.6 \times 10^{-9}$). At the time that the MRI scans were performed, the AD cases were on average 4.2 years older than their unaffected siblings, and had been diagnosed with AD 5.7 years prior on average.

TABLE 1. Sibship Counts by Number of AD Cases and Unaffected Cases

	No. AD Unaffected						
No. AD Affected	0	1	2	3	4	5	Total
0	0	61	12	3	0	0	76
1	52	238	28	9	3	0	330
2	8	4	3	1	1	1	18
Total	60	303	43	13	4	1	424

TABLE 2. Sample Characteristics: Ethnicity

Ethnicity	No. Sibships	Percent	No. Individuals	Percent
White/Hispanic	48	11.32	89	10.92
White/non-Hispanic	275	64.86	522	64.05
African American	61	14.39	127	15.58
Japanese American	40	9.43	77	9.45
Total	424	100.00	815	100.00

MRI Trait Heritability

The means and standard deviations of the 5 MRI traits are presented in Table 3 by AD case status. WMH and CVR were log-transformed to reduce high skewness and kurtosis (Table 3). AD cases had significantly higher scores on MRI measures of CA, MTA, WMH, and CVD. AD patients had more observable infarcts on MRI than their unaffected sibs ($P = 0.0003$).

Pearson correlations among the traits for cases and controls are shown in Table 4. As described in the Methods section, CVR is an estimate of the combined effects of WMH plus any infarcts seen on MRI; thus log(CVR) and log(WMH) are highly correlated ($r = 0.93$ among unaffected sibs, $r = 0.95$ among cases). The cerebral and MTA measures are more correlated with each other than with the white matter and CVR measures. All correlations are highly significant.

All 4 MRI traits are significantly heritable (Table 5). Log(CVR) and log(WMH) have the highest heritability (0.57, $P = 1.0 \times 10^{-7}$ and 0.49, $P = 1.7 \times 10^{-6}$). Although CVR seems to have the higher heritability of the 2 measures, the 95% confidence bounds for the heritability of the 2 measures overlap considerably [log(CVR) 95% confidence interval: (0.37, 0.76); log(WMH) 95% confidence interval: (0.29, 0.68)]. There is no evidence that the 2 measures differ significantly in heritability. The atrophy measures have lower, but still significant, heritability. The heritability estimate for CA (0.35, $P = 5.9 \times 10^{-5}$) is 2 times greater than the estimate for MTA (0.17, $P = 0.009$). Age at MRI was the most significant predictor of all 4 MRI traits. Disease duration was significantly associated with all traits except MTA. AD status was significantly associated with MTA ($P = 5.1 \times 10^{-8}$) instead of disease duration. Sex was a significant covariate for CA only ($P = 0.01$). Ethnicity was not a significant predictor of any of the MRI traits. The proportion of total variance in MRI traits explained by the significant covariates ranged from 0.18 for log(CVR) to 0.30 for MTA.

Heritability was estimated using the full set of 815 individuals. While the 113 singletons did not contribute to the estimate of the additive genetic variance, they did contribute to the analysis of fixed effects (covariates) and estimates of total variance. Including these individuals in the analysis yields more precise parameter estimates, and therefore increases power. To confirm that these 113

TABLE 3. Sample Characteristics by AD Affection Status

	AD Affected		AD Unaffected	
	Probands	Siblings	Siblings	*P*
(a) Qualitative Trait Distribution				
N	347	19	449	
Female (%)	57.9		60.8	0.16
APOE-ε4 genotypes:				
0 ε4 alleles (%)	36.7		58.2	
1 ε4 allele (%)	49.6		37.5	
2 ε4 alleles (%)	13.7		4.4	1.6×10^{-9}
MRI infarcts present (%)	21.9		12.5	0.0003

	AD Affected				AD Unaffected			
	Mean	SD	Skewness	Kurtosis	Mean	SD	Skewness	Kurtosis
(b) Quantitative Traits Distribution								
Age at MRI	75.0	8.9	−0.4	−0.3	70.8	9.1	−0.1	−0.4
Duration of AD in y	5.7	4.6	3.0	14.4				
CA	61.4	12.8	−0.03	0.02	47.9	12.9	-0.1	0.2
MTA	2.5	1.2	−0.4	−0.9	0.8	1.0	1.2	0.8
WMH	19.3	22.1	1.5	1.3	9.2	15.1	2.9	8.5
CVR	21.7	24.0	1.3	0.5	10.6	16.7	2.5	6.4
Log(WMH)	2.3	1.2	−0.1	−0.6	1.4	1.3	0.1	0.6
Log(CVR)	2.4	1.3	−0.04	−1.1	1.5	1.3	0.1	0.3

individuals did not bias our estimates of residual heritability, we also estimated heritability using only sibships with at least 2 individuals and found that the estimates of heritability were identical when rounded to 2 decimal places and the same covariates were included in the models (results not shown).

The number of APOE-ε4 alleles was significantly associated with log(WMH) ($P = 0.0099$) and log(CVR) ($P = 0.0050$) but not with CA or MTA ($P = 0.25$, 0.83). The proportion of total variance explained by the number of APOE-ε4 alleles that an individual carried was small: 0.009 for log(WMH) and 0.008 for log(CVR). Recoding APOE genotype to indicate whether or not an individual carried any APOE-ε4 alleles (ie, a dominant model) produced slightly smaller *P* values and slightly greater proportion of variance explained [log(WMH): proportion of variance 0.01, $P = 0.0068$; log(CVR) proportion of variance 0.01, $P = 0.0033$]. Residual heritability did not change substantively after including either the number of APOE-ε4 alleles or an indicator for ε4 carrier status as a fixed effect in the model.

Subsequent regression analysis of AD cases and unaffected sibs as separate subgroups, using generalized estimating equation models to account for sibling correlations and adjusting for age, ethnicity, sex (and disease duration in AD affected), revealed that carrying an APOE-ε4 allele was marginally associated with increased log(WMH) and log(CVR) in the unaffected sibs [$\beta = 0.25$ $P = 0.03$ for log(WMH), $\beta = 0.26$ $P = 0.03$ for log(CVR)], and not associated with either in the affected sibs ($P = 0.24$, 0.18).

TABLE 4. Pearson Correlation Between MRI traits*

	CA	MTA	Log(WMH)	Log(CVR)
CA		0.46	0.34	0.31
MTA	0.47		0.35	0.30
Log (WMH)	0.28	0.28		0.93
Log (CVR)	0.28	0.29	0.96	

*All correlations are significant with $P < 1 \times 10^{-6}$.
Upper triangle indicates unaffected sibs; lower triangle, cases.

DISCUSSION

Our study yielded estimates of heritability for semiquantitative MRI measures among siblings discordant for AD which are consistent with estimates from numerous previous reports on the basis of a variety of study designs.[41–47] Moreover, our analyses indicate that the heritability is not explained by APOE genotype. Given that the unaffected siblings in this study are at increased risk for future AD,[50,57] these findings suggest that MRI traits may prove to be valuable endophenotypes in studies aimed at identifying genetic factors that influence risk and natural history of AD.

Our findings of substantial heritability for both atrophy and MRI measures of cerebrovascular brain injury also offer additional opportunities to refine genetic associations. Some evidence suggests that cerebrovascular and AD pathologies may work additively or synergistically to produce the dementia syndrome,[35] which could confound genetic associations on the basis of solely clinical measures. Thus, study designs using MRI traits as endophenotypes independent of clinical status or as external criteria to reduce heterogeneity (by stratifying patients or families) could enhance the search for genetic risk factors for late life cognitive impairment.

Our results are in general agreement with previous studies of MRI heritability,[41–47] although there are

TABLE 5. Proportion of Variance in MRI Traits Explained by Covariates, and Proportion of Residual Variance Explained by Additive Genetic Effects (Heritability)

	P value for Likelihood Ratio Test of Covariate					Proportion of Variance Explained by Covariates	Residual Heritability		
Trait	AD Affection Status	Disease Duration	Age at MRI	Ethnicity	Sex		h^2	(SE)	*P*
CA	0.06	0.0086	3.5×10^{-23}	0.98	0.01	0.25	0.35	(0.09)	5.9×10^{-5}
MTA	5.1×10^{-8}	0.55	1.7×10^{-25}	0.14	0.64	0.30	0.17	(0.08)	0.009
Log(WMH)	0.62	0.0027	9.8×10^{-19}	0.52	0.76	0.19	0.49	(0.10)	1.7×10^{-6}
Log(CVR)	0.25	8.8×10^{-5}	2.7×10^{-18}	0.31	0.64	0.18	0.57	(0.10)	1.0×10^{-7}

several reasons why our heritability estimates were smaller. First, unlike previous studies, we used semiquantitative MRI measures. This approach, although less precise, has good measurement characteristics, excellent reliability, and shows significant group differences between AD patients and their unaffected siblings.[40] Second, our discordant sibling pair design, by definition, introduced significant differences in our MRI measures owing to the presence of AD in the affected sibling, and the absence of AD in the unaffected sibling. To account for these differences, we adjusted our analyses for several covariates including age, sex, and disease duration. As disease duration is often difficult to estimate in AD, we may not have accounted for all of the variance owing to true disease duration, and this could have reduced the strength of our estimates.

In addition to the significant heritability estimates, we also found an association between the number and presence of APOE-ε4 alleles and measures of cerebrovascular brain injury [log(WMH) and log(CVR)] after adjusting for age at MRI and duration of disease, defined as 0 for unaffected siblings, and number of years affected for AD-affected cases. AD status was not a significant covariate in this model. As AD is associated with both ε4 and WMH independently, it is interesting that the association between ε4 and WMH persists after adjusting for disease duration. Further examination of this association within the unaffected sibling controls revealed that the number of ε4 alleles was marginally associated with log(WMH) and log(CVR) ($P = 0.03$ for both), and not associated with either trait within the cases. These results are consistent with some previous studies in dementia[58,59] and at least one study of cognitively normal older individuals,[60] although not others.[61] This result suggests that APOE genotype may be a genetic risk factor for brain evidence of cerebrovascular injury among cognitively normal older individuals, but unrelated to CVD when specifically examining individuals with AD type dementia. The results in AD patients are somewhat surprising given that cerebral amyloid angiopathy is common to AD and associated with increased WMH. We remain cautious in our interpretation of these results because the associations we have observed with APOE genotype are modest and will revisit these analyses as our dataset of available individuals increases in size.

At first glance, it may seem surprising that ε4 was not associated with the 2 measures of brain atrophy in our study, but was associated with the 2 measures of CVD. However, this result is consistent with previous work indicating that ε4 is associated with age of onset of AD,[62] but not with disease course or regional atrophy.[63]

In conclusion, we have established that the 4 semiquantitative measures of atrophy and CVD are significantly heritable in AD cases and their unaffected siblings. In addition, our preliminary data revealing the APOE association with cerebrovascular MRI phenotypes support the hypothesis that genetic factors may have pleiotropic effects on brain structure and cognition. We hope that future investigations will identify the genetic factors responsible for the genetic variance of these traits, and that the traits will prove to be useful for refinement of the clinical AD phenotype, furthering our understanding of the AD disease process.

ADDITIONAL INVESTIGATORS

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