Evidence For Genetic Variance in White Matter Hyperintensity Volume in Normal Elderly Male Twins

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Background and Purpose—White matter hyperintensities (WMHs), as detected by MRI, are common among the elderly and are frequently interpreted as representing a subclinical form of ischemic brain damage. We used volumetric MR techniques to investigate the contribution of genes and the environment to measures of brain morphology in a sample of community dwelling elderly male twins.

Methods—Brain MR (1.5 T) scans were obtained from 74 monozygotic (MZ) and 71 dizygotic (DZ), white, male, World War II veteran twins born in the United States and age 68 to 79 when scanned. MR quantification used a previously published semiautomated segmentation algorithm to segment brain images into total brain, cerebrospinal fluid (CSF), and WMH volumes. Twin pair covariances were computed for each measure, and structural equation genetic models were fitted to these data.

Results—Total cranial, brain parenchyma, CSF, and WMH volumes were highly correlated in MZ pairs, and correlations in MZ pairs were significantly greater than those in DZ pairs. Structural equation modeling indicated heritabilities of 91%, 92%, and 73%, respectively, for total cranial, brain parenchyma, and WMH volumes. Correction for age and head size reduced the heritability of brain parenchyma to 62% (95% confidence interval, 56% to 68%) and the heritability of WMH volume to 71% (95% confidence interval, 66% to 76%). Proband concordance rates for large amounts of WMH were 61% in MZ pairs and 38% in DZ pairs, compared with a prevalence of 15% in the entire sample.

Conclusions—This study is the first to quantify the relative contribution of genetic and individual environmental influences to measures of brain morphology in the elderly. **(*Stroke*. 1998;29:1177-1181.)**

Key Words: aging ■ genetics ■ magnetic resonance imaging ■ white matter

Cerebral WMHs are commonly identified on MR images of the elderly and are more prevalent and severe in patients with CVD and CVD risk factors.[1] Although small amounts of WMHs are thought to be the consequence of normal aging,[2] extensive amounts are recognized as pathological and have been associated with reduced cerebral metabolism, brain atrophy, Alzheimer's disease, and cognitive impairment.[3–8] The pathophysiology of WMHs remains uncertain, but the association with CVD risk factors and cardiovascular pathology suggests an ischemic pathogenesis.[9,10] Although individual differences in CVD[11] and CVD risk factors[12] are known to be under genetic control, the contribution of genetic and environmental influences to normal and abnormal amounts of WMHs is unknown.

There have been occasional reports of gross inspections of brain morphology in MZ human twins, which qualitatively examined differences and similarities in brain structures, including cortical surface area,[13] corpus callosum area,[14] hippocampal size, and ventricle volume.[15] More recently, a 3-D MRI genetic study[16] in 10 MZ and 9 DZ same-sex twin pairs estimated the heritability of brain volume to be 94% but found no consistent evidence for significant genetic variance for gyral and sulcal patterns.

In the present study, we were able to compare volumetric MRI data, including brain, CSF, and WMH volumes, for 74 MZ twin pairs and 71 DZ pairs who are a subgroup of the NHLBI Twin Study.[17] Specifically, the objective of this study was to quantify the contribution of genetic and environmental influences to individual differences in brain morphology in late life.

Subjects and Methods

Study Population

Subjects in the present study are a subgroup of the NHLBI Twin Study. The sample was drawn from a population-based registry of almost 16 000 pairs of white, male, veteran twin pairs, which was created and is maintained by the Medical Follow-Up Agency at the National Academy of Sciences-National Research Council.[18] Baseline examinations were conducted during 1969 to 1972 on 514 intact pairs, or 1 028 individuals, at 5 research facilities in the United States. Details of the

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Selected Abbreviations and Acronyms

CI = confidence interval
CSF = cerebrospinal fluid
CVD = cerebrovascular disease
df = degrees of freedom
DZ = dizygotic
MZ = monozygotic
WMH = white matter hyperintensities

study design and methods and analyses of baseline and follow-up risk factors and cardiovascular events have been published.[19] Data for the present study were collected during 1995 to 1997 as part of a fourth follow-up examination of this panel. Only a brief review of the variables relevant to this report is provided.

Cerebral MR Scans and Definition of WMH

MR (1.5-T) scanning on GE scanners was performed at 4 study sites with a conventional spin-echo, double-echo sequence in the axial orientation with a repetition time of 2000 msec, echo times of 20 and 100 msec, a 24-cm field of view, and 5-mm contiguous slices from the vertex to the foramen magnum imaged in a 256×192 matrix and interpolated to 256×256 with 1 excitation. Axial images were angled to be parallel to the anterior commissure-posterior commissure line. After acquisition of the MR scans, the digital information was transferred to a central location for processing and analysis by one of the authors (C.D.), who was blinded to zygosity and medical history of the subjects. Quantitative analysis of the MR scans was performed with a custom-written program operating on a Sun Microsystems Ultra 1 workstation. Image evaluation was based on a semiautomated segmentation analysis that involves operator-guided removal of nonbrain elements, as previously described.[20–22] For segmentation of brain parenchyma from CSF, a difference image was created by the subtraction of the second echo image from the first echo image. Image intensity nonuniformities were then removed from the difference image, and the resultant corrected image was modeled as a mixture of two gaussian probability functions. The segmentation threshold was determined at the minimum probability between the modeled CSF and brain matter intensity distributions.[20] For segmentation of WMH from brain matter, the first and second echo images were summed, and after removal of CSF and correction of image intensity nonuniformities, a lognormal distribution was fitted to the summed image data. A segmentation threshold for WMH was a priori determined as 3.5 SDs in pixel intensity above the mean of the fitted distribution of brain parenchyma. Intrarater and interrater reliabilities of this method have been published.[20]

Statistical Analyses

Subjects in the present analyses were 290 individual twins, including 74 intact MZ and 71 intact DZ pairs. Because the distribution of WMHs was skewed to the right, we used a natural logarithm transformation to minimize skewness. Prior to genetic modeling, the differences in means and variances between MZ and DZ twins for each volumetric MR measurement were tested, and pairwise Pearson correlations were calculated to determine associations between brain parenchyma, CSF, and WMH volumes, as well as their relationship with age and total brain volume.

Genetic model fitting was then carried out with the MZ and DZ variance-covariance matrices calculated for each volumetric brain measurement. A genetic model specifies the variation in phenotype to be due to genotype and environmental influences. Sources of variation considered in biometric genetic analyses are A, additive genetic variation due to the sum of effects of individual alleles at all loci; D, dominance genetic variation due to interaction of alleles at a given locus and between loci; C, shared familial environmental effects; and E, random individual environmental variation that is not shared by family members. The relative contribution of genetic and environmental influences to individual differences in brain morphology were estimated by maximum likelihood, using the computer program Mx.[23] Goodness of fit was assessed by likelihood-ratio chi-square tests, which test the agreement between the observed and predicted variance-covariance matrices in MZ and DZ twins. A large χ^2 (corresponding to a low probability) indicates a poor fit; a small χ^2 (accompanied by a high *P* value) indicates that the data are consistent with the model. Submodels were compared by hierarchical χ^2 tests, where the χ^2 for a reduced model is subtracted from that of the full model. The *df* in such tests are equal to the difference between the *df* for the full and the *df* for the reduced model.[24]

To test for twin pair similarities on white matter disease, we classified subjects into "diseased" and "nondiseased," depending on whether subjects' estimated WMH volume was >0.5% of intracranial volume or was equal to or below this value. For the present sample, this cut point corresponded to the 85th percentile of the distribution of WMHs (ie, the prevalence of white matter disease was 15% for both MZ and DZ individual twins). Twin concordance rates for white matter disease were assessed by the proband concordance method.[25] This rate measures the likelihood of disease in the cotwins of affected twins, assuming that twins were ascertained independently. To calculate this rate, the formula $2c/(2c+d)$ was used, where *c* is the number of affected concordant pairs and *d* is the number of discordant pairs. The prevalence of white matter disease was calculated by the formula $(2c+d)/2N$, where N is the total number of pairs. To test whether proband concordance rates were statistically significantly different from those expected by chance alone, we used a χ^2 statistic.

TABLE 1. Mean, SD, and Intrapair Correlation Coefficients of Brain Morphology Volumes, by Zygosity

	MZ Twins (n=74)			DZ Twins (n=71)		
Variable	Mean	SD	ICC	Mean	SD	ICC
Age, y	72.3	2.9	...	71.8	2.8	...
Head size, cm^3	1278.2	105.4	0.91	1270.6	103.4	0.54
Brain volume, cm^3	959.9	82.8	0.92	953.0	86.8	0.50
CSF, cm^3	317.2	41.3	0.68	316.7	47.9	0.35
WMH, cm^3	3.39	4.56	0.73	3.89	6.10	0.31

ICC indicates intrapair correlation coefficients.

Results

Table 1 shows means and SDs of MR volumetric measurements in MZ and DZ twins. No significant difference in the distribution of WMH volume was observed between MZ twins (3.4±4.6) and DZ twins (3.9±6.1). Mean age of the MZ twin pairs was 72.3±2.9 years, and that of DZ pairs was 71.8±2.8 years. As seen from Table 1, there was no significant difference between MZ and DZ twins in mean total cranial volume, brain parenchyma, and CSF volume. The SD, however, of brain parenchyma was significantly greater in DZ twins than in MZ twins. Age was positively and significantly correlated with WMH (r=.21, P<0.001) and CSF volume (r=.26, P<0.001) and negatively and not significantly correlated with brain volume (r=.07, P=0.15). Brain parenchyma was strongly associated with total cranial volume (r=.91, P<0.001); CSF was moderately associated (r=.59, P=0.0001) and WMH volume was significantly and positively associated with total cranial volume (r=.16, P=0.001). Also shown in Table 1 are intraclass twin correlations for total cranial volume, brain parenchyma, CSF, and log-transformed WMH volume. Both the MZ and DZ intraclass correlations are statistically significant (all P<0.01), and the MZ intraclass correlation is twice that of DZ pairs for

TABLE 2. Model Comparisons for Unadjusted Brain MR Morphology Volumes

Measure	Model	h^2	c^2	e^2	χ^2	*df*	*P*	Diff χ^2	*df*	*P*
ICV	ACE	0.73	0.18	0.09	2.89	3	0.45	...	...	...
	CE	...	0.73	0.27	46.07	4	<0.001	43.18	1	<0.001
	AE	0.91	...	0.09	3.97	4	0.40	1.08	1	NS
	E	...	...	1.00	156.0	5	<0.001	153.1	2	<0.001
Brain	ACE	0.85	0.07	0.08	4.48	3	0.30	...	...	...
	CE	...	0.70	0.30	58.47	4	<0.001	53.93	1	<0.001
	AE	0.92	...	0.08	4.63	4	0.27	0.15	1	NS
	E	...	...	1.00	155.9	5	<0.001	151.5	2	<0.001
CSF	ACE	0.72	0.00	0.28	11.23	3	0.01	...	...	...
	CE	...	0.48	0.52	26.77	4	<0.001	15.54	1	<0.001
	AE	0.72	...	0.28	11.23	4	0.03	0.00	1	NS
	E	...	...	1.00	64.89	5	<0.001	53.66	2	<0.001
WMH	ACE	0.73	0.00	0.27	1.26	3	0.60	...	...	...
	CE	...	0.52	0.48	18.71	4	<0.001	17.45	1	<0.001
	AE	0.73	...	0.27	1.26	4	0.85	0.00	1	NS
	E	...	...	1.00	63.69	5	<0.001	62.43	2	<0.001

ICV indicates intracranial volume; A, C, and E refer to additive genetic, shared environmental, and nonshared environmental influences respectively. h^2, c^2, and e^2 are estimates of the proportion of additive genetic, shared environmental, and nonshared environmental components of variance, respectively, calculated for the different structural equation models. Diff χ^2 represents the likelihood-ratio test for the difference between two goodness-of-fit χ^2 statistics, which is itself distributed as χ^2. *df* indicates degrees of freedom. Model fit is summarized by the *P* value, with higher values indicating better fit. NS, not significant.

most of the MR variables. This pattern of results suggests the presence of a significant additive genetic component of variance.

Indeed, genetic modeling of the observed variance-covariance matrices of MZ and DZ twins by maximum-likelihood methods (Table 2) established that environmental effects alone could not account for twin pair similarities (model E rejected, $P<0.01$, for all MR volumes). Inclusion of shared environmental effects was similarly inadequate (model CE rejected, $P<0.01$, for all volumes). Additive genetic effects, however, provide a reasonable explanation of within-twin pair similarities on total cranial volume (model AE not rejected, $P=0.40$), brain parenchyma (model AE not rejected, $P=0.27$), and WMH volume (model AE not rejected, $P=0.85$). Inclusion of shared environmental effects (model ACE) did not significantly improve the goodness of fit beyond that of an additive genetic model. We therefore conclude that additive genetic effects provide the best explanation for the observed twin similarities on MR volumetric measurements. Moreover, additive genetic effects explain 91% of the variability in total cranial volume; 92% and 72%, respectively, of the variability in brain parenchyma and CSF volumes, and 73% of the variability in WMH volume (Table 2).

Adjustment of WMH volume for among-pair differences in age and total cranial volume was also undertaken but did not change our previous estimates of genetic variance. Genetic model fitting to the adjusted log-transformed WMH volume established that both the E and CE models were rejected ($P<0.001$), whereas the AE model was not rejected at $P=0.90$. The resulting estimate of additive genetic variance of adjusted WMH volume was 71% (95% CI, 66% to 76%). Similar analyses established that neither environmental effects alone (model E) nor shared environmental effects (model CE) could account for the observed twin covariances of age and head size adjusted brain parenchyma and CSF volumes (both models rejected at $P<0.001$). Both the MZ and DZ intraclass correlation coefficients decreased after adjustment of brain parenchyma for age effects and twin similarities in head size. In the final model, additive genetic effects still explained 62% (95% CI, 56% to 68%) of the total variance in brain parenchyma. CIs were calculated based on the comparison of the AE versus the E model under the assumption that $C=0.0$, since estimates of C after adjustment for differences in age and head size were negative for both WMH and total cortical brain volumes.

Table 3 shows probandwise concordance rates for white matter disease (WMHs >0.5% of total cranial volume). These data indicate that 61% of MZ and 38% of DZ cotwins of twins with white matter disease were affected, compared with a prevalence of 15% in the whole cohort. In addition, both concordance rates are statistically significant, and the concordance rate for MZ pairs is significantly greater than that for DZ pairs ($P<0.05$). Even more impressive is the finding that the risk for an MZ cotwin of an affected twin is 4 times the risk in the entire sample, whereas the risk for a DZ

TABLE 3. Proband Concordance Rates for Large Amounts of WMH, by Zygosity

	No. of Pairs	Concordant Pairs	Discordant Pairs	Concordance Rate	Prevalence
MZ twins	74	7	9	0.61*	0.15
DZ twins	71	4	13	0.38*	0.15

*Significantly different than the value expected by chance alone $P<0.01$.

cotwin of an affected twin is 2.5 times that of a random individual in this sample.

Discussion

The present study is the first to quantify the contribution of genetic and environmental influences to structural brain changes detected on cranial MR scans of normal, community-dwelling elderly male subjects. Specifically, we found evidence for a substantial contribution of genetic factors to individual differences in brain, CSF, and WMH volumes regardless of differences in brain size and age effects. There are two possible explanations for these findings. First, genetic influences observed on MR measures of cerebral atrophy may reflect genetic influences that regulate neuronal cellular loss with advanced age. Second, they may overlap at least partly with hereditary risk factors such as hypertension, diabetes, and cardiac disease.[12] Since apoptosis cannot be controlled, the corollary to these findings is that by control of individual environmental factors it should be possible to decrease subjects' risk for CVD, which in turn may reduce the risk for brain atrophy. The most interesting situation arises when gene-environment interaction effects are involved whereby the combination of a certain genotype (eg, ApoE) and CVD risk factors have a synergistic effect on outcome.[26] In these situations, early therapeutic interventions in subjects who may be genetically susceptible to greater neuronal cell loss will have a far-reaching effect.

Previous epidemiological studies on WMH in the elderly have used qualitative ratings of WMHs, which are difficult to evaluate and compare across studies. An extreme example of this type of variability is evident from a comparison of the prevalence of WMHs in the Rotterdam Study,[27] which was 27% in subjects 65 to 85 years old using one definition of WMH, with the prevalence in the CHS study,[28] which was 87% for healthy volunteers of similar ages but using a different definition of WMH. The volumetric methodology used in the present study avoids such variability and allows for a uniform definition of WMHs. Moreover, our definition of severity was based on a previous study of a healthy group of individuals aged 19 to 91 years, in which we investigated age-related changes in WMH volumes and determined a threshold of approximately 10 cc as abnormal.[4] Volumes above this threshold, even in this group of healthy individuals, were associated with elevated blood pressure and structural and functional brain changes, suggestive of the presence of subclinical cerebrovascular disease.

In subjects of the NHLBI cohort, we previously found that midlife systolic blood pressure and a positive family history of hypertension and stroke were significant predictors of large amounts of WMH in late life.[29,30] Moreover, our studies of the heritability of blood pressure in this cohort found that, on average, 50% of the variability in systolic BP and hypertension throughout adult life may be due to additive genetic influences.[31,32] Concordance rates, however, for stroke in this twin registry[33] are much lower than those for large amounts of WMH, suggesting that the genetic susceptibility for white matter disease cannot be explained entirely by a genetic predisposition for cerebrovascular disease. If, however, we accept the notion that large amounts of WMHs reflect a subclinical form of disease, then the increased concordance for large WMH as opposed to that of stroke may be due to the sensitivity of WMH as an early marker for cerebrovascular pathology. If so, future follow-ups of this cohort should show an increased risk for stroke in subjects with large amounts of WMH.

Extensive WMHs have also been associated with a variety of clinical symptoms, including diminished cognitive function and unsteady gait, even after adjustment for other factors.[3,28] For this twin sample, we found both cross-sectional and longitudinal relationships between WMHs and performance on neuropsychological test exams,[34] and since the heritability for cognitive function is well within the range of the heritability of WMH, it will be of interest in the future to estimate for this sample the genetic overlap between structural and functional brain changes.[35]

Finally, we demonstrated, in the present study, that variability in brain volumes can be explained almost entirely by genetic factors, whereas individual environmental influences play little if any role. To our knowledge, only a few anatomical traits, such as dermatoglyphics[36] and EEG patterns,[37] show MZ intraclass correlation coefficients of this magnitude in elderly subjects. We also observed that adjustment of brain parenchyma for differences in head size reduced the initial heritability estimate by 30%. This reduction is not surprising, given the significant correlation between brain parenchyma and head size and the high heritability estimate for intracranial volume. In future genetic analysis of the present data, we plan to use the methods of multivariate genetic analyses[25] to determine the magnitude of genetic overlap between these different measures of brain morphology.

The strengths of the present study lie in the large sample size, the fact that twins were drawn from a population-based twin registry, and the use of a standardized methodology to quantify MRI volumes without any information on zygosity, age, and health status. Because of various selection criteria (eg, World War II veterans; selective participation in the follow-up exams; and attrition of one of the twin subjects due to death, disease, or nonparticipation), however, subjects in the present analysis may represent a somewhat select group that is healthier than the population of US males of this age. If anything, this selectivity may have underestimated the prevalence of severe WMH but should have no effect on estimates of heritability of total WMH volume. In addition, although this study concentrated on the contribution of genetic influences to brain morphology, the twin study paradigm holds considerable promise for identifying nonshared individual environmental influences on brain aging. Our next study will use the matched cotwin design to investigate the role of midlife risk factors on brain morphology in late life after removal of shared genetic and familial influences.

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