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The *FAS* gene, brain volume and disease progression in Alzheimer's disease

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Abstract

OBJECTIVE—To identify single nucleotide polymorphisms (SNPs) that are associated with Alzheimer's disease (AD) progression and brain volume.

METHODS—Ninety-seven SNPs were genotyped in 243 subjects from a longitudinal study of healthy aging. Subjects who carried a diagnosis of cognitive impairment (CI) at any study visit (prior to their last visit) and had DNA in the study DNA bank were included. AD progression was defined as the duration from onset of CI to diagnosis of AD. Association of each of the 97 SNPs with AD progression was tested via Cox model. SNPs meeting a nominal significance criterion ($p < 0.05$) for association with AD progression were reassessed to account for multiple testing by repeating the marker selection process in 10,000 random permutations. Next, the association between the one SNP that survived the multiple-testing adjustment and brain volume was determined by multiple regression analysis in a subgroup of subjects for whom MRI derived brain volume data were available. Brain volumes were adjusted for age at MRI, gender and time from MRI to onset of CI.

RESULTS—The minor allele of rs1468063 in *FAS*, member 6 of the tumor necrosis factor receptor superfamily, was significantly associated with faster AD progression after adjustment for multiple testing ($P_{\text{permutation}}=0.049$). The same allele in rs1468063 was associated with smaller brain, and larger ventricular volumes ($p = 0.02$ and 0.04 respectively)

CONCLUSION—*FAS*, which plays a role in apoptosis, may be associated with AD by modulating apoptosis and neuronal loss secondary to AD neuropathology.

Keywords

Alzheimer's disease; MRI; brain volume; genetics; *FAS*

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder resulting from a complex interaction between genetic and environmental factors. While mutations in three genes (*PSN1*, *PSN2*, *APP*) have been established as a cause of autosomal dominant early-onset AD¹⁻³ only the *APOE* $\epsilon 4$ allele has been robustly established as a risk factor for late-onset AD.⁴

With the availability of large genome-wide scans, the list of candidate SNPs reported to be associated with AD is increasing^{3, 5-9}. Most of these loci await replication in independent cohorts and functional and neuropathological studies to understand the pathophysiology underlying such associations.

Brain volume represents a disease endophenotype, which is related to the underlying progression of disease and neuropathology of AD.¹⁰ Previous studies suggest that faster disease progression in AD is associated with smaller brain volumes.¹¹ The association with both disease progression and brain volume provides more compelling evidence that associations are based on biological mechanisms. This study investigates the associations of 97 candidate SNPs with AD progression and brain volume.^{6, 12-15}

2. Methods

2.1 Description of Cohorts

Subjects were selected from the longitudinal cohort studies conducted at the NIA-OHSU Layton Aging and Alzheimer's Disease Center. Recruitment, exclusion and inclusion criteria for these studies and subject evaluations have been described previously.¹⁶ Briefly, elderly volunteers with no cognitive impairment are recruited from the community. Subjects with cognitive impairment (CI) or AD are recruited from the Oregon Health & Science University Memory clinics. All subjects are followed semi-annually with standardized clinical examinations. Some subjects receive annual MRI evaluations as described previously^{16, 17}. Cognitive and functional assessments are made using the Clinical Dementia Rating Scale (CDR) score¹⁸, Mini-Mental State Examination (MMSE)¹⁹, Neurobehavioral Cognitive Status Examination (NCSE)²⁰, and a psychometric test battery covering key domains²¹.

A CDR score was assigned to each subject by a neurologist at each semiannual visit that was based on cognitive and functional exams and collateral history. For subjects enrolled before onset of CI and with a CDR of 0 at enrollment, onset of CI was defined as the first CDR score of 0.5 and not meeting diagnostic criteria for dementia as determined by the examining neurologist. For subjects who already had a CDR of 0.5 at enrollment and did not meet diagnostic criteria for dementia, onset of CI was defined as the first time when subjects or family members noted cognitive decline. Cognitively normal was defined as a CDR=0. Diagnosis of AD was based on established diagnostic criteria.²²

2.2 Subject Selection

From the longitudinal studies at the Layton Aging and Alzheimer's Disease Center, all subjects who had DNA available, had clinical evaluation data for at least two visits, carried a diagnosis of CI during any study visit prior to their last visit and were of European ancestry were included (n = 243). Of these, 71 had onset of CI before they enrolled in the study and 172 subjects after they enrolled. Selected subjects had been followed for a mean of 5.79 (± 3.6) years (range 0.5–17.2).

2.3. SNP selection and genotyping

All of the 97 SNPs genotyped in this study were previously tested in AD related case-control studies.^{6, 12–15} The majority of these SNPs had originally been selected to represent putative functional variants or because of their location in linkage regions. They are either missense variations, or are variations located in exonic splicing silencer regions, transcription factor binding sites, or in 3' or 5' untranslated regions. This increases the likelihood that the disease-associated SNPs may alter gene or protein function. While 24 of the 97 SNPs showed strong evidence of association with AD in previous studies, the remaining 73 SNPs represented markers that had not met the same level of significance as the reported 24 SNPs.^{6, 12–15} Genotyping has been described previously.¹² Briefly, genotypes were assigned after allele-specific real-time PCR with primers designed and validated at Celera. Genotyping accuracy on this platform has generally been found to be greater than 99%.

2.4 MRI methods

A subset of subjects (n=65) had annual magnetic resonance imaging (MRI) scans measuring intracranial, total brain, ventricular and hippocampal volumes. Only subjects that had an MRI scan *before* the onset of CI were included in the MRI analysis (n=56). Clinicians evaluating study subjects were blinded to MRI scans obtained before symptom onset. Scan protocols and analysis methods for MRI volumes have been described previously¹⁷. Briefly, MRI images were acquired with a 1.5-T magnet. The protocol consisted of continuous-slice, multiecho, multiplanar image acquisition, with 4-mm-thick coronal slices and a 24-cm² field of view using a 256 × 256 acquisition matrix with two excitations. The brain was visualized using the following sequences: multiecho coronal sequence; repetition time, 3,000 msec; echo time, 30 and 80 msec. T1-weighted sagittal images centered in the midsagittal plane were used to orient the coronal plane. Analysis of the MR images was performed using the computer program REGION, developed by our research group¹⁷. Inter-rater reliability for volume measurements for all regions assessed by intra-class correlation coefficient was ≥0.9.

There is evidence that rate of brain atrophy, significantly accelerates a couple of years before onset of CI.²³ The time from MRI scan to onset of CI in the study subjects ranged from 0.4 to 14.7 years (mean 4.37 (±3.69) years). Therefore we decided to include time from MRI to onset of symptoms as a variable in the analyses since it may affect the outcome of brain volume. Time from MRI to onset of CI was calculated by subtracting age at MRI from age at onset of CI. Because the relationship between brain volume and time from MRI to onset of CI is not linear, this effect was included in the analysis as a categorical variable: time from MRI to onset < 5 years versus > 5 years. The cut-off was empirically determined by examining the current data. Since the ventricular volume distribution was skewed, a variance-stabilizing transformation (Box-Cox transformation with $\lambda = -0.2$) was applied to the ventricular volumes before the model was fitted. Hippocampal, total brain and ventricular volumes were measured as proportion of intracranial volume.

2.5 Statistical analysis

Analysis to test for association between genotype and disease progression—

Disease progression was defined as the duration from onset of CI to diagnosis of AD, measured as the difference between age at first AD diagnosis and age at onset of CI. Survival analysis was employed to test for association between disease progression and genotype. The survival analysis took into account left and right censoring to reduce estimation bias. Left-truncation occurs to subjects who had onset of CI prior to enrollment. Right-censored subjects were diagnosed with onset of CI during the study but did not progress to AD while enrolled in the study. Thus, the duration from onset of CI to AD is

partially known. The estimation procedure was conducted using the SAS Phreg procedure with counting process style input, where exact and incomplete (censored and truncated) survival periods were included.

Association between each of the 97 SNPs and AD progression was tested using four genetic models: genotypic and dominant, recessive, and additive with respect to the minor allele. The genotypic inheritance model treats genotype as nominal value (two degrees of freedom). The association was assessed using a Cox proportional hazards model. For robustness, significance in each inheritance model was measured by the maximum p-value (least significant) of three global test statistics: likelihood ratio, Wald, and score. The marker's significance is reported for the most significant inheritance model (minimum of the four p-values). Nine significant SNPs emerged after this step as candidates for further analysis. (Figure 1)

Next we re-assessed the significance of these nine markers by adjusting for multiple testing through permutation. We randomly permuted disease progression measures of the 243 patients 10,000 times. Each permutation simulates the null condition of no association. The permutation-adjusted p-value for the candidate marker was the average proportion of times that its p-value was less than the p-values under the 10,000 simulated null conditions.

MRI Genotype association—Next, an association between the genotype that survived the multiple-testing adjustment and brain volumes was tested in a subgroup of 56 subjects. Multiple regression analysis was used to test for association between total cranial, ventricular, and hippocampal volume proportions and genotype, adjusting for sex, age at MRI, and time from MRI to onset of CI. Genotype was coded based on a dominant model with respect to the minor allele.

Comparison of group characteristics—Chi-square or Fisher's Exact Test was used to compare categorical variables and t-test to compare continuous variables between the groups with different genotypes. Statistical analysis was conducted using SAS 9.13 and JMP 5.0.1a (SAS Institute, Cary, NC, US). Significance was set at $p < 0.05$.

3. Results

3.1 Genotype-disease progression

From the 97 SNPs that were selected for genotyping, we identified 9 SNPs that met our initial criteria for significance. One SNP, rs1468063, which is located in the member 6 of the tumor necrosis factor (TNF) receptor superfamily gene (*FAS*) remained significant after applying the stringent permutation-based experimentwise error correction. Presence of the minor allele was associated with a faster disease progression rate (Figure 2) ($P_{\text{permutation}}=0.049$).

One subject had the TT genotype, 192 subjects had CC and 50 subjects were CT heterozygotes. T-allele carriers were more likely to progress faster to probable AD than CC homozygotes after being diagnosed with CI. (Table 1)

The T-allele carrier and non-carrier groups were not significantly different in age, gender, socioeconomic status, education, family history of AD and presence of *APOE* $\epsilon 4$. (Table 2) The distribution of T-allele carriers and non-carriers was not significantly different between subjects with onset of CI before enrollment and those with onset after enrollment. (Table 2)

3.2 MRI analysis

Based on the dominant inheritance model, we hypothesized that carriers of the rs1468063 risk allele (T) (CT and TT genotypes) who have a faster disease progression will have smaller total cranial and hippocampal volumes and larger ventricular volumes than CC-homozygotes. This hypothesis was based on previous observations that faster disease progression in AD is associated with smaller brain volumes.¹¹ Therefore a one-sided p-value was used to reject the null hypothesis. The T allele (in this case the CT genotype since none of the subjects in the MRI subgroup carried the TT genotype) was associated with smaller total brain and larger ventricular volumes (one-tailed p-value=0.02 and 0.04, respectively) after adjusting for age at MRI, sex, and time from MRI to onset of CI. Genotype did not show a significant association with hippocampal volume (one-sided p-value=0.06) although there was a trend towards a smaller hippocampal volume in T allele carriers. (Table 3)

4. Discussion

Our results suggest that a polymorphism in the *FAS* gene is associated with progression of AD and with presymptomatic total brain volumes. The *FAS* gene located on 10q24 is in a region implicated in AD by several linkage studies^{24–26}. It is a member of the TNF receptor superfamily²⁷ and has been shown to play a role in cell-mediated apoptosis. Since apoptosis is considered one of the main causes for the cell loss accompanying neurodegenerative diseases, *FAS*-mediated apoptosis has been implicated in AD^{28–32}.

Several studies have specifically investigated the role of *FAS* in AD-related neurodegeneration. It is suggested that amyloid-beta (A β) can directly induce neuronal death via mechanisms of apoptosis²⁸. One study demonstrated that neurons in the AD brain and A β -treated cell cultures exhibited *FAS* ligand (*FASLG*) upregulation and changes in immunoreactivity for *FAS*³¹. *FASLG* expression was particularly elevated in senile plaques and neurofilament-positive dystrophic neuritis. Transgenic mice overexpressing the wild-type human amyloid precursor protein have been shown to display a much higher expression of *FAS*³³. Hyperexpression of *FAS* mRNA and surface receptors in peripheral T-lymphocytes in AD patients³⁴, upregulation of *FAS* mRNA expression in brains of AD patients³⁵, and significantly higher levels of *FAS* in the cerebrospinal fluid from AD patients compared to controls³⁶ all support the notion that *FAS* plays a role in AD related neurodegeneration.

Several association studies have shown a significant association between polymorphisms in *FAS* and AD risk, whereas others did not. The most widely studied *FAS* polymorphism is the G/A polymorphism at –670 (rs1800682). One study reported an association between this polymorphism and non-familial early onset AD in a Scottish population³⁷. A follow up study showed an association with cognitive status and this polymorphism in early onset AD in subjects from Scotland and Sweden³⁸. In both studies, the strongest signal was in carriers of the APOE ϵ 4 alleles. However, three other studies in Han Chinese³⁹, Jewish⁴⁰, and Dutch⁴¹ populations failed to show an association between the –670 (rs1800682) polymorphism and risk of AD. Another study in subjects from Italy reported an association between an *FAS* polymorphism at position –1377 (rs2234767) and risk of late onset sporadic AD and rate of cognitive decline (measured as change in MMSE scores) in AD subjects⁴². However, the same study did not show an association with either AD or rate of cognitive decline and the –670 (rs1800682) polymorphism in *FAS*. Population stratification may be one of the reasons for the lack of consistent replication. The polymorphism in *FAS* tested in our study, rs1468063, is a 3'UTR SNP. While we speculated that it may cause functional changes in the mRNA structure or its stability, we do not have experimental data that confirm a functional effect of this SNP.

It is also possible that another loci in linkage disequilibrium (LD) with this SNP is responsible for the observed association. The promoter polymorphism -670 (rs1800682) previously genotyped in other studies showed weak LD with rs1468063 (r^2 : 0.158) in the CEU population from HapMap. The promoter polymorphism -1377 (rs2234767) was not genotyped in the HapMap CEU population.

To our knowledge this is the first study to investigate an association between brain volume and *FAS* genotype. *FAS* has been linked to apoptosis and neuronal cell loss³¹ and therefore represents a strong candidate gene for the observed brain volume loss in AD patients, which can be observed even prior to onset of clinical symptoms. In our study, the CT genotype of rs1468063 was significantly associated with more rapid disease progression, smaller total brain and larger ventricular volumes. This suggests that the CT genotype may increase neuronal apoptosis, resulting in increased neuronal loss and brain atrophy. While this polymorphism may not be a direct risk factor for AD, it may modulate response to Alzheimer's pathology by controlling apoptosis.

The lack of confirmation of the 96 other tested SNPs might be related to the difference in phenotype between this and the prior studies; i.e. disease progression instead of disease status. Differences in the association of the *APOE* ϵ 4 allele have been reported for these two phenotypes. While *APOE* ϵ 4 is unequivocally associated with age at onset of AD as well as risk of AD^{4, 43}, the relationship between *APOE* genotype and disease progression is not as well established. There are numerous studies with conflicting results^{44–50}. In our study, the two *APOE* SNPs (rs429358 and rs7412), which code for the *APOE* ϵ 2, 3, 4 alleles, were genotyped. Neither the ϵ 4 allele nor the ϵ 2 allele showed significant association with disease progression in this study (p-value of 0.086 and 0.80, respectively), and were therefore excluded from further analyses. Another possible reason for lack of confirmation of some of the other 96 SNPs is that our study may not have had the power to detect relatively small effect sizes.

This study has several limitations. First, only a small subgroup of subjects had MRI data for brain volume measures. Therefore, the findings from this study will require replication in larger cohorts that have both brain volume measures and genotype data available. Second, some of our subjects had onset of CI before they enrolled in the study while others did not progress from CI to AD during the follow up period. We accounted for this statistically by adjusting for left truncated and right censored survival periods. Third, this study only included individuals of European descent to reduce population stratification. Thus, we cannot make a firm conclusion about the role of this polymorphism for AD progression in populations from different ancestries. In summary, this study presents corroborating evidence for a potential role of rs1468063 in AD through its association with both disease progression and brain volume measures in our dataset. Further replication of these findings in additional cohorts with longitudinal data and MRI data are required to elucidate the full impact of this association on brain aging.

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[illegible]

Figure 1. p-values from the four inheritance models for the nine markers. SNP: single nucleotide polymorphism, lr: likelihood ratio, s: score, w: Wald, dom: dominant inheritance model, rec: recessive inheritance model, add: additive inheritance model, 2DF: 2 degrees of freedom-genotypic inheritance model.

Figure 2.

Kaplan-Meier plots showing the rate of disease progression from onset of cognitive impairment to diagnosis of Alzheimer's disease in the FAS genotype based on a dominant inheritance model (CC versus T-allele carriers). Rate of disease progression is significantly *faster* in the group with the CT/TT genotype compared to the CC genotype group.

Table 1

Percent of subjects with CC or CT/TT genotype at rs1468063 who have a diagnosis of Alzheimer's disease 1, 3, 5 and 7 years after onset of cognitive impairment.

	1 year	3 year	5 year	7 year
CC	8%	26%	38%	63%
CT/TT	13%	47%	70%	83%

Table 2Group Characteristics for the *FAS* CC and CT or TT genotype groups.

	<i>FAS</i> CC N =192	<i>FAS</i> CT or TT N = 50	p-value
SES	43.70 (12.34)	44.46 (12.15)	0.69
Education	13.47 (3.09)	13.49 (3.31)	0.97
Women	55.21%	66.6%	0.13
Age at onset of cognitive impairment	86.30 (7.15)	84.92 (7.90)	0.23
Age at AD diagnosis	87.89 (7.97)	86.81(7.09)	0.52
At least one <i>APOE</i> ε4	29.32%	31.27%	0.77
Onset of cognitive impairment after enrollment	72.40%	64.71%	0.28

Numbers are mean (standard deviation) or percent

Table 3

Multiple regression analyses for brain volume proportions.

	Brain/ICV		Ventricular/ICV		Hippocampal/ICV	
	Coefficient (ste)	p-value	Coefficient (ste)	p-value	Coefficient (ste)	p-value
Sex (female, n=34) (reference: male, n=22)	0.97 (0.56)	0.09	-0.42 (0.19)	0.04	0.006 (0.003)	0.02
Time from MRI to onset of CI (<5 yrs, n=39) (reference: ≥ 5 yrs, n=17)	-0.21 (0.67)	0.76	0.86 (0.24)	0.0006	-0.009 (0.003)	0.004
<i>FAS</i> genotype (CT, n=13) (reference CC genotype, n= 43)	-1.39 (0.60)	0.02 *	0.39 (0.21)	0.04 *	-0.004 (0.003)	0.06 *
Age at MRI	-0.27 (0.11)	0.01	0.008 (0.04)	0.83	-0.0008 (0.0005)	0.1

ICV: intracranial volume, CI: cognitive impairment

* one-sided p-values