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Effect of Alzheimer Disease Risk Genes on Trajectories of Cognitive Function in the Cardiovascular Health Study

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Abstract

Objective—Patients with late onset Alzheimer disease (AD) vary widely in their trajectory of cognitive decline. Genetic variations in *CLU*, *PICALM*, and *CRI* are associated with AD, but it is unknown if they exert their effects via altering cognitive trajectory in elderly subjects at risk for AD.

Methods—We developed a Bayesian model to fit cognitive trajectories in a cohort of elderly subjects and test for genetic effects. We first validated the model's ability to detect the previously established effects of APOE epsilon 4 alleles on age at cognitive decline and of psychosis on the rate of cognitive decline in 802 subjects from the Cardiovascular Health Study Cognition Study who were without dementia at study entry and developed incident dementia during follow-up. We then evaluated the effects of *CLU*, *PICALM*, and *CRI* on age and rate of decline in 1831 subjects without dementia at study entry, including those who did, or did not develop incident dementia at study's end.

Results—Our model generated robust fits to the observed cognitive trajectory data. Validation analysis supported the utility of the model. *CLU* and *CRI* were associated with more rapid cognitive decline. *PICALM* was associated with an earlier age at midpoint of cognitive decline. Associations remained after accounting for the effects of *APOE* and demographic factors.

Conclusions—Evaluation of cognitive trajectories provides a powerful approach to dissecting genetic effects on the processes leading to cognitive deterioration and AD.

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Keywords

Alzheimer's disease; MCI (mild cognitive impairment); genetic; cognitive decline; endophenotype

Introduction

Some progress has been made in determining the genetic architecture of late onset Alzheimer disease (AD). The association of late onset AD with the $\epsilon 4$ variant of apolipoprotein E (*APOE*) is well established (1). More recently, replicated genome-wide associations (GWA) of late onset Alzheimer disease with genetic variation in *CLU*, *CR1*, and *PICALM*, have been reported (2;3). Ultimately, these detected associations must be related to specific neurobiologic processes leading to AD in order for them to translate into meaningful clinical predictors or therapies. Current understanding of the neurobiology of AD suggests that disease causation is dependent on a sustained period of pathologic accumulation of amyloid β protein ($A\beta$) [reviewed in(4)]. The initial accumulation of $A\beta$ occurs prior to clinically detectable cognitive impairment, setting off downstream events including generation of hyperphosphorylated tau, gray matter volume reductions, and synapse loss (5;6). It is measures of these downstream effectors that appear to change most rapidly during phases of disease characterized by more rapid cognitive decline (4).

Conceptually, genetic variation may thus be linked to cognitive change in AD in one of several ways. Genetic variations which increase the production of pathologic $A\beta$ protein, including mutations and duplications of the $A\beta$ precursor protein gene (*APP*), and mutations in presenilin 1 and 2 (*PSEN1* and *PSEN2*), all lead to an earlier age of disease presentation (7). Similarly, apolipoprotein E (*APOE*) $\epsilon 4$ alleles, which reduce $A\beta$ clearance (8), are associated with earlier age of disease presentation (9). Alternatively, one might postulate that genetic variation whose primary role is to interact with the generated or accumulated $A\beta$ so as to modify its downstream effects would influence the rate of overt cognitive decline. Currently, no such genetic variations have been definitively identified. However, psychotic symptoms in AD subjects define a genetically determined behavioral phenotype (10) that is strongly associated with a more rapid rate of cognitive decline (11–13).

It would therefore be useful for interpreting the nature of a genetic variation's relationship to AD risk to be able to measure cognitive trajectories in a way that would allow testing of genetic associations with both age and rate of cognitive decline. Intuitively, it can be seen that an individual traversing the complete course of AD will have a period prior to disease onset of relatively stable cognitive test performance, followed by a period of declining performance, until reaching a period of scores asymptotically approaching a minimum score. Such a trajectory is readily approximated by a 4-parameter logistic curve, however, several obstacles exist in practice. These include the fact that few longitudinal data sets gather complete information on all stages of the cognitive trajectory for individual AD subjects, although the picture may be complete for the group as a whole. Additionally, it is not uncommon for elderly individuals to have poor cognitive test performance in a given session due to factors unrelated to AD, such as concomitant illness, poor sleep, or medication effects. Trajectory modeling must not be overly sensitive to these outlier values.

To address these issues, we developed a novel Bayesian implementation of a hierarchical non-linear model using a 4-parameter logistic curve. Bayesian hierarchical models have the characteristics of borrowing strength and appropriately modeling multiple sources of error. This means that subjects with fewer data points automatically contribute less to the analysis, that prediction for each subject is based on a combination of whatever information is available for that subject weighted with information from other similar subjects, and that the

degree of uncertainty about parameters is not underestimated [as occurs in two-stage methods that treat the parameters fitted to individual subject curves as having no uncertainty (14)]. We evaluated our model's ability to fit trajectories reflecting cognitive deterioration and validated its ability to detect the previously established effects of *APOE* genotype on age of cognitive decline and of psychosis on rate of cognitive decline. We then implemented our approach to examine the effects of SNPs in *CLU*, *CR1*, and *PICALM* on the age at midpoint and the rate of cognitive decline in a large cohort of elderly subjects.

Methods

Subjects (Table 1)

Information on the CHS and CHS Cognition Study methods have been published previously (15–17). For the validation cohort, we analyzed data from subjects who by the end of the main study in 1998–9 developed AD (with or without comorbid Vascular Dementia) or had Mild Cognitive Impairment (MCI) and who had at least four Modified Mini-Mental Status Examination (3MS) or Digit Symbol Substitution Test (DSST) measurements and were thus suitable for trajectory modeling. For the implementation cohort, we analyzed data from Caucasian subjects who had either progressed to AD (with or without comorbid Vascular Dementia), had MCI, or were without a cognitive disorder diagnosis at study endpoint, had at least four 3MS or DSST measurements, and were successfully genotyped for at least one of the SNPs in our genes of interest (18;19). All participants provided written informed consent to participate in the study. Genetic analyses in this paper utilize data only from participants who provided consent for their samples to be used in research on disorders other than cardiovascular diseases.

Assessments

Cognition—The 3MS (20), a measure of global cognition, and the DSST, a measure of attention (21), were administered to participants annually.

Psychosis—The Neuropsychiatric Inventory (NPI) was completed in 1998–9 in a subset of validation cohort subjects (22). Classification as Ever or Never Psychotic was as previously described (16).

Statistical Analysis

We fit data to a four parameter logistic curve in the form:

$$E(Y_{it}) = A_i + \frac{B_i - A_i}{1 + \exp\left(\frac{t - M_i}{R_i}\right)}$$

where t is the time (age) of measurement, $E(Y_{it})$ is the mean outcome at time t for subject i , A_i is the asymptotic outcome value for subject i at small ages, B_i is the asymptotic outcome value for subject i at large ages, M_i is the age at midpoint of cognitive decline, that is the age at which the trajectory for subject i is half-way between A_i and B_i , i.e. the age at which the fit cognitive score is halfway between the fit maximum and the fit minimum value for that subject. R_i is a measure of the rate of change from A_i to B_i . R_i can be interpreted as follows: for any given individual the total change in outcome is $A_i - B_i$, and the time period over which the middle half of that change occurs, i.e., the time from $\frac{1}{4}$ to $\frac{3}{4}$ of the total change, is $2.20(R_i)$. We explicitly modeled the effects of covariates on M and R by replacing the simple mean parameter with a linear combination of an intercept and the products of covariates with corresponding slope parameters. For A and B , we did not model covariate

effects, but allowed for differences between subjects by modeling the random effects. Effects of covariates are reported as the posterior properties of the difference in the mean of each parameter for a change in level of the covariate. Finally, it should be noted that summaries of the posterior distributions in Bayesian analysis take the place of the p-values and confidence intervals of classical statistics. Assuming that we are using an appropriate model and prior distributions, the probability that a parameter is inside its credible interval is 95%.

We tested the effects of *APOE* $\epsilon 4$ status, psychosis status (Ever versus Never Psychotic), and individual SNPs which have been associated with AD risk: *CLU* (rs11136000), *CR1* (rs3818361), and *PICALM* (rs3851179, rs541458) (2;3) on *M* and *R*. For *APOE* $\epsilon 4$ we coded the presence or absence of at least one $\epsilon 4$ allele. SNPs were tested individually, examining additive effects of the allele identified as the risk allele in the GWA studies. Analysis of *APOE* $\epsilon 4$ included demographic factors as covariates. Analyses of the effects of psychosis status and of individual SNPs included *APOE* $\epsilon 4$ and demographic factors as covariates.

For additional methodologic details, see supplementary text.

Results

Validation Cohort

The basic model, including the effects of demographics on 3MS and DSST trajectories (Supplemental Table 1), was fit to the data from subjects in the validation cohort. Several 3MS trajectories are shown in Figure 1 along with the 95% credible (curvewise) intervals (CI). Examples of fitted trajectories for the DSST, and in the face of occasional outlier test scores, are shown in Supplemental Fig 1.

After adjusting for demographic covariates, the presence of an *APOE* $\epsilon 4$ allele was associated with a mean [95% CI] $-3.36 [-4.58, -2.16]$ year change in age at midpoint for the 3MS and a $-2.26 [-3.41, -0.92]$ year change in age at midpoint of the DSST, both in the predicted directions. In contrast, *APOE* $\epsilon 4$ carriers showed no change in rate of decline of the 3MS ($-0.14 [-0.46, 0.16]$) or the DSST ($-0.14 [-0.77, 0.47]$). Analysis of the effect of Psychosis similarly revealed changes in the predicted directions, with a more rapid rate of decline for the 3MS ($-0.42 [-0.83, -0.03]$) and for the DSST ($-1.06 [-1.98, -0.20]$). The effect of Psychosis results in the middle 50% of decline taking on average 1.83 fewer years (3MS) or 2.33 fewer years (DSST). In addition, analysis of Psychosis revealed a change in age at midpoint for the 3MS ($-3.74 [-5.51, -2.03]$), but not the DSST ($-1.70 [-3.67, 0.42]$).

Implementation Cohort

We next undertook to examine the effects of SNPs in *CLU*, *CR1*, and *PICALM* on cognitive trajectory in the larger group of subjects, including individuals with and without incident cognitive impairment (Table 2 and Figure 2). *CLU* SNP rs11136000 was associated with more rapid cognitive decline on the 3MS, and nearly reached significance for the DSST. *CR1* SNP rs3818361 was associated with more rapid cognitive decline on the DSST. *PICALM* SNP rs3851179 was not associated with change in either parameter for the 3MS or the DSST. *PICALM* SNP rs541458 was associated with earlier age at midpoint of decline of the 3MS, but not with rate of decline, and was not associated with either parameter for the DSST. The associations of *CLU* SNP rs11136000 and *CR1* SNP rs3818361 with rate of decline for the DSST did not differ between individuals who did or did not carry an *APOE* $\epsilon 4$ allele (Mean [95% CI] difference in R between *APOE* $\epsilon 4$ positive and negative subjects for *CLU* SNP rs11136000: $0.07 [-0.66, 0.88]$ for *CR1* SNP rs3818361: $0.37 [-0.57, 1.40]$). The association of *PICALM* SNP rs541458 with midpoint time for the 3MS did not differ

between individuals who did or did not carry an *APOE* $\epsilon 4$ allele (Mean [95% CI] difference between *APOE* $\epsilon 4$ positive and negative subjects for *PICALM* SNP rs541458: $-1.32 [-3.36, 0.86]$). The mean trajectories for *CR1*, *CLU*, and *PICALM* risk allele carriers are shown in Figure 3.

To address whether one or more of the associations of the four AD risk SNPs (rs11136000, rs3818361, rs3851179, and rs541458) might be a false positive due to multiple testing, we evaluated these SNPs concurrently in additive models for 3MS and for DSST trajectory. We again included *APOE* genotype, age, sex, and education in the models. The approach of evaluating all SNPs concurrently is to widen the 95% credible intervals, creating a more conservative estimate of significance. We found that the significant association of *CR1* SNP rs3818361 with DSST rate of decline persists [Mean (95% CI) $-0.61 (-1.11, -0.12)$], and the nearly significant association of *CLU* SNP rs11136000 with DSST rate of decline now reaches significance [Mean (95% CI) $-0.50 (-0.86, -0.03)$]. These observed effects are strong, equal to $0.83 - 1.0$ of the standard deviation of the random effect for the subject-to-subject variation in DSST rate in our additive model (estimated at 0.60). Significant associations with 3MS did not persist. It should be noted that evaluating the associations with *M* and *R* for a given measure can represent a single 2-dimensional test, not two tests, of association with trajectory. We therefore confirmed that the $M=0, R=0$ origin is not within the 95% posterior ellipsoid for DSST for *CR1* SNP rs3818361 and *CLU* SNP rs11136000.

Discussion

We found that a non-linear model, implemented with a Bayesian hierarchical analytic approach, generated robust fits to the observed cognitive trajectories of elderly subjects. Validating our approach, *APOE* $\epsilon 4$ alleles were associated with reduced age at midpoint of cognitive decline and psychosis was associated with increased rate of cognitive decline. We then implemented our model to test whether SNPs associated with an increased risk for late onset AD alter cognitive trajectory after accounting for the effects of *APOE* and demographic factors. We found that rs11136000 in *CLU* and rs3818361 in *CR1* were associated with more rapid cognitive decline. rs541458 in *PICALM* was associated with an earlier age at midpoint of cognitive decline, although this latter association did not persist in an additive model designed to correct, in part, for multiple testing. For all SNPs except *CLU* SNP rs11136000 the allele conferring an adverse cognitive trajectory was the same as that associated with AD in prior GWA studies.

We utilized a non-linear model that allowed for censoring at the maximum and minimum values. This choice was based on a common property of cognitive tests, which often have defined maximum and minimum scores. As a result, prior to disease onset individuals may sustain maximal scores, while in end-stage disease sustained minimal scores may be present. Such observations cannot be fit adequately with a trajectory derived from a linear or quadratic model, although multiple linear fits (e.g. as applied in changepoint models), may be used to approximate subsets of points within a longitudinal cognitive trajectory (23). Other psychometric properties of cognitive tests also contribute to non-linearity. Many tests are admixtures of easier, moderately difficult, and difficult questions, not necessarily in equal proportion. As a consequence, scores may change little during a given phase of cognitive decline, e.g. during early illness if there are few difficult questions. Alternatively, scores may show greater change during another phase, such as moderate disease, if there are proportionally more questions of moderate difficulty. Many global cognitive tests, including the 3MS, follow just such a pattern (24). In contrast, the DSST requires repeating the same cognitive function, and is scored based on how many times it is successfully completed within a timed interval. However, the overall difficulty of the task results in non-linearity in moderate to severely impaired individuals, supporting the use of a non-linear model to fit

this data (25). Whether there may be a relative advantage to the use of cognitive measurements that demonstrate more consistent linear measurement properties across levels of disease severity for detection of SNP effects on cognitive decline would benefit from testing using additional measures that differ with regard to these properties.

We found rs11136000 in *CLU* was associated with more rapid cognitive decline, however, the risk for more rapid decline was conferred by the allele opposite to that previously associated with AD (2;3;18;26). Although rate of cognitive decline and presence of AD are not identical, it seems unlikely that a causal allele would confer different directions of risk for these two outcomes. Several authors have argued that significant allelic association in opposing directions is statistically unlikely (27;28), and probably reflects true association via one of several underlying mechanisms (27–30). *CLU* encodes the protein clusterin, which is expressed at increased levels in the brains of individuals with AD, can serve to prevent fibrillization of A β , and inhibit complement activation (31). In individuals with MCI and AD, elevated plasma clusterin correlated with more rapid cognitive decline, though plasma clusterin concentrations were not associated with genetic variants in *CLU*, including rs11136000 (32).

We found that rs3818361 in *CRI* was associated with more rapid cognitive decline. *CRI* is a complement receptor expressed in cerebral cortex. There is emerging evidence that the complement cascade contributes to targeting synapses for elimination during development and in neurodegeneration via astrocyte-mediated opsonization with the complement component 3 fragment, C3b (33). *CRI* supports clearance of opsonized targets due to its high affinity for C3b (34). Recent evidence indicates that the reported associations of genetic variation in *CRI* with AD may arise from linkage disequilibrium between these variants and a low copy repeat which codes for a *CRI* isoform with an additional C3b binding site (35). It is not currently known if *CRI* contributes to synapse elimination in AD.

Finally, we found that rs541458 in *PICALM* was associated with an earlier age at midpoint of cognitive decline, although it should be noted that this association did not persist in our additive model. *PICALM* encodes the phosphatidylinositol-binding clathrin assembly (Picalm) protein, an essential factor in clathrin-mediated endocytosis (36). Recent evidence indicates that Picalm is primarily expressed in vascular endothelial cells in human brain (37), where it may affect the clearance of A β from brain. For example, rs541458 in *PICALM* is significantly associated with cerebrospinal fluid levels of A β 42 (38). This interpretation would be congruent with a mechanism by which variants that result in overproduction or over-accumulation of A β most strongly impact age of cognitive decline.

The above associations of *CLU*, *CRI*, and *PICALM* were detected in models that accounted for demographic variables and the effect of *APOE* ϵ 4. This finding stands in contrast to a recent analysis of several cohorts, including the CHS, which found that rs11136000 in *CLU* and rs3851179 in *PICALM* did not add to the prediction of AD onset beyond demographic and *APOE* effects (18). This may indicate there is increased power available in using a cognitive trajectory, rather than a dichotomous diagnosis, to identify SNP associations with longitudinal outcome in subjects at risk for AD. Of interest, we found that genetic variation in *PICALM* was associated with lower age at midpoint of decline in models that included *APOE*. This is somewhat surprising given recent evidence that *APOE* and *PICALM* genotypes are correlated, resulting in substantial reduction in the association of *PICALM* SNPs with AD risk after accounting for *APOE* status (26). Unlike *PICALM*, *CLU* and *CRI* associations with AD risk did not display confounding with *APOE* genotype (26), thus it is not surprising they demonstrated detectable effects after controlling for *APOE* ϵ 4 alleles.

We used a Bayesian approach to fit cognitive trajectories. The principal advantage of Bayesian methods over classical (e.g. mixed model) analyses is that calculation of posterior distributions is typically straightforward even for complex models. However, Bayesian methods are often computer intensive, creating a potential limitation of our approach; it may not be practical for sequential screening of large numbers of SNPs. Another potential limitation in any model fitting is inadequate model convergence. In Bayesian hierarchical models, completely uninformative prior distributions may result in invalid (improper) posterior distributions. The standard solution to this is to incorporate a small amount of prior information to create “weakly informative” prior distributions. In clinical settings like the ones we modeled, this is simple and effective, because we can put reasonable limits on parameters, e.g., we know that for our subjects the age at midpoint of cognitive decline is between 30 and 130 years. The utility of these weak prior distributions can be seen in the fidelity of our trajectory fits to the observed data. Finally, an important modification to our Bayesian implementation was the use of a t-distribution, rather than a normal distribution, to model deviations of measurements from trajectory means. This approach substantially reduced the effects of occasional outlier values, a not uncommon occurrence in our observed data (Supplemental Fig 1).

Other possible limitations to our findings should be considered. We selected for testing a limited number of SNPs based on replicated evidence of genome wide significant association in GWA studies. Other SNPs in these genes, which did not themselves reach genome wide significant association with AD risk, may nevertheless associate with trajectory of cognitive decline. The same may be true for genetic variation in other genes, including a number of SNPs since identified as demonstrating genome wide significant association in GWA studies of AD. Determining a trajectory requires a minimum number of observed measurements. We chose as inclusion criteria the presence of four measurements on the 3MS and DSST tests. This may have by necessity excluded some individuals with more rapid decline, who thus did not complete four tests. Similarly, the individuals who participated in the CHS Cognition Study and were thus available for this analysis were a non-random subset of all CHS participants, healthier and younger than the parent cohort. As such, our findings may not fully generalize to the elderly population.

In summary, we developed a Bayesian approach to addresses several goals for the analysis of cognitive trajectories in aging subjects, including the ability to: fit individual as well as group cognitive trajectories, make meaningful descriptive statements about the pattern of change and the variability in that pattern across subjects, develop credible regions for the resultant curves which include appropriate prediction limits, and evaluate the specific effects of covariates, including genetic covariates, by estimating their impact on the trajectory parameters. We validated this approach with two established predictors of different cognitive trajectory parameters, the presence of *APOE* ϵ 4 alleles and the development of psychosis. We then used our approach to detect effects of recently identified AD risk alleles on cognitive trajectories. Replication of this approach using other data sets is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Examples of four parameter non-linear fits of individual 3MS trajectories

Each panel shows the trajectory of the observed Modified Mini-Mental Status Examination (3MS) over time for a particular subject (open circles). The dashed lines are the median posterior curves, and there is a 95% probability that the whole curve would fit inside the dotted lines. (A) and (B) show individuals with similar age at mid-decline, M , but with different rates of decline, R . (C) shows an example with earlier age for M . (D) shows an example with both earlier age for M and more rapid decline. In all cases it can be seen that in the presence of numerous observations, e.g. in the falling middle portion of the trajectory, fits estimate the trajectory with good accuracy. In portions of trajectories with less information available (e.g. early and late phases in (B)) limits on the trajectories are set by

the constrained maximum and minimum values, but the 95% credible intervals are appropriately wider.

Figure 2. Effect of genetic variation on Age at Midpoint (M) of Cognitive Decline and Rate of Cognitive Decline (R)

Diamonds represent mean estimates for change in each parameter associated with the genetic variant. Horizontal lines are 95% credible intervals. Values shown are the Posterior Mean [95% Credible Interval] for the change in parameters for the presence of each additional copy of the SNP risk allele. All analyses include demographic factors in the model, and for the individual SNPs analyses also include *APOE* ε4 genotype in the model. Boldface values are significant. Variants for which the horizontal line does not touch the vertical dashed no change line are significantly associated. The large effect on Age at Midpoint of *APOE* ε4 is evident for both cognitive measures (A, C). A smaller effect of *PICALM* SNP rs541458 seen for the 3MS (A). Effects on Rate of Decline are present for variants in *CLU* on the 3MS and DSST (B, D) and for *CR1* on the DSST (D).

Figure 3. Cognitive trajectories in individuals with, or without, *CR1*, *CLU*, and *PICALM* risk alleles

Each panel shows the mean trajectory for individuals carrying 0 (–) or two (+) copies of the risk allele.

Table 1

Demographic and clinical characteristics of the Validation and Implementation Cohorts.

Validation Cohort (N=802)	
Variable	N (%) or Mean (SD)
Age at Baseline	73.8 (5.2)
Range	65–95
Sex	
Male	314 (39.2)
Female	488 (60.8)
Race	
Caucasian	593 (73.9)
Non-Caucasian	209 (26.1)
Education	
No College	562 (70.1)
Some College	240 (29.9)
Baseline 3MS	88.6 (7.1)
Range	57–100
Baseline DSST	34.81 (12.2)
Range	0–83
Psychosis Status*	
Never	388 (81.7)
Ever	87 (18.3)
APOE ε4 Carrier Status	
Absent	559 (69.7)
Present	243 (30.3)

Implementation Cohort (N=1831)	
Variable	N (%) or Mean (SD)
Age at Baseline	71.7 (4.7)
Range	65.0 – 92.9
Sex	
Male	687 (37.5)
Female	1144 (62.5)
Race	
Caucasian	1831 (100)
Non-Caucasian	0 (0.0)
Education	
No College	1100 (60.1)
Some College	731 (39.9)
Baseline 3MS	92.9 (5.6)

Implementation Cohort (N=1831)	
Variable	N (%) or Mean (SD)
Range	45 – 100
Baseline DSST	42.6 (11.4)
Range	3 – 83
<i>APOE</i> ε4 Carrier Status	
Absent	1407 (76.8)
Present	424 (23.2)

3MS: Modified Mini-Mental Status Examination; DSST: Digits Symbol Substitution Test; *APOE* Apolipoprotein E;

* of the 802 subjects, 327 were not assessed for psychosis

Table 2
Effects of genotype on the 3MS and DSST age at midpoint of cognitive decline (*M*) and rate of cognitive decline (*R*) parameters in the Implementation Cohort

Values shown are the Posterior Mean [95% Credible Interval] for the change in parameters for the presence of each additional copy of the SNP risk allele. All analyses include *APOE* ε4 genotype and demographic factors in the model. Boldface values are significant.

Gene	SNP	Minor Allele (Frequency)	Observed Risk Allele	GWAS Risk Allele	3MS		DSST	
					<i>M</i>	<i>R</i>	<i>M</i>	<i>R</i>
<i>CLU</i>	rs11136000	T (40.4%)	T	C	-0.19 [-1.17, 0.78]	-0.16 [-0.29, -0.01]	-0.07 [-1.00, 0.90]	-0.42 [-0.89, 0.00]
<i>CRI</i>	rs3818361	T (19.1%)	T	T	-0.44 [-1.59, 0.71]	-0.13 [-0.36, 0.11]	-0.11 [-1.13, 0.83]	-0.64 [-1.09, -0.15]
<i>PICALM</i>	rs3851179	A (37.5%)	G	G	-0.49 [-1.45, 0.52]	-0.01 [-0.22, 0.18]	-0.77 [-1.62, 0.13]	-0.07 [-0.50, 0.38]
<i>PICALM</i>	rs541458	C (32.1%)	T	T	-1.15 [-2.33, -0.13]	-0.18 [-0.46, 0.09]	-0.73 [-1.61, 0.11]	0.00 [-0.51, 0.42]

3MS: Modified Mini-Mental Status Examination; DSST: Digits Symbol Substitution Test