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Genome Wide Association Study of the Rate of Cognitive Decline in Alzheimer's Disease

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Abstract

Background—Substantial inter-individual variability exists in the disease trajectories of Alzheimer's disease (AD) patients. Some decline rapidly while others decline slowly and there are no known explanations for this variability. We describe the first genome wide association study to examine rate of cognitive decline in a sample of AD patients with longitudinal measures of cognition.

Methods—The discovery sample was 303 AD cases recruited in the AD Neuroimaging Initiative and the replication sample was 323 AD cases from the Religious Orders Study and Rush Memory and Aging Project. In the discovery sample, Alzheimer's Disease Assessment Scale-cognitive subscale responses were tested for association with genome-wide SNP data using linear regression. We tested the 65 most significant SNPs from the discovery sample for association in the replication sample.

Results—We identified SNPs in the gene *SPONI* whose minor alleles were significantly associated with a more rapid rate of decline (rs11023139, $P = 7.0 \times 10^{-11}$) in the discovery sample. A *SPONI* SNP 5.5 KB upstream was associated with decline in the replication sample (rs11606345, $P=0.002$).

Conclusion—*SPONI* has not been previously associated with AD risk, but it is plausibly related since the gene product binds to the amyloid precursor protein and inhibits its cleavage by β -secretase. These data suggest that *SPONI* may be associated with the differential rate of cognitive decline in AD.

Keywords

Alzheimer's disease; GWAS; cognitive decline

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Introduction

Alzheimer's disease (AD) is a common form of dementia with an enormous public health impact and for which there are no treatments yet available that can slow progression. Through the efforts of large consortia that pool data from many genome wide association studies (GWAS) of late onset AD, a number of risk genes have been identified and robustly replicated.¹⁻⁵ Only with samples in excess of 10,000 AD cases and similar numbers of controls, has consensus been reached on the veracity of these risk variants, and with the exception of the APOE ϵ 4 allele, these variants exert very modest effects on overall disease risk, generally with odds ratios less than 1.2. Although these findings have provided valuable insights into AD pathogenesis, the individual predictive value of these small-effect variants is limited.

Although AD is characterized by progressive cognitive deterioration over time, substantial variability exists in the cognitive trajectories of affected individuals. There have been a number of previous studies of factors reported to be associated with cognitive decline in AD patients that have not examined genetic factors. One suggests that the pathological findings such as neurofibrillary tangles, cerebral infarction, and Lewy bodies that mediate normal and pathological age-related cognitive decline also mediate more rapid cognitive decline in some AD patients.⁶ Other reports have postulated superimposed medical factors to be associated with rate of decline in AD, including diabetes⁷ and other vascular risk factors,⁸ kidney function,⁹ and muscle strength.¹⁰ Two recent candidate gene studies^{11, 12} tested a limited number of candidate SNPs for association with rate of decline and identified some promising associations.

In this report, we present the first genome wide association analysis of cognitive decline in a sample of AD cases with longitudinal measures of cognition. By limiting the analysis to AD cases, we hoped to identify novel variants specific to rate of decline. While identifying variants explaining the heterogeneity in rate of decline is important for understanding AD pathogenesis, it may also produce novel therapeutic targets that are distinct from those associated with the presence or absence of AD.

Methods

Discovery Sample

Data used in the discovery sample were obtained from the AD Neuroimaging Initiative (ADNI) database.¹³ ADNI was launched in 2003 with the primary goal of testing whether longitudinal magnetic resonance imaging (MRI), positron emission tomography (PET), and other serum or CSF biomarkers could serve as proxy markers for the progression of mild cognitive impairment (MCI) and early AD. After several waves of recruitment, ADNI has enrolled over 1000 individuals with AD, MCI or who are normal controls. Detailed protocols for subject recruitment and biomarker accrual are available at the ADNI website <http://www.adni-info.org/>. Briefly, subjects were recruited from over 50 sites across the U.S. and Canada and were measured longitudinally for changes in the brain measured through neuroimaging, biomarkers, and cognitive tests. At the time we accessed the ADNI database, there were 243 normal, 235 MCI and 340 AD subjects in total. The subset of ADNI subjects analyzed for the discovery sample included 303 individuals of European descent who either had AD at baseline or converted to AD during follow-up and had cognitive data. Baseline data was defined as data from the examination with the first clinical diagnosis of AD. Seventeen individuals with age at onset < 60 years (indicative of familial AD) were excluded.

Replication Sample

We selected the 65 most promising SNPs from the discovery sample based upon association with the outcome measure (see below) and biological relevance to AD pathology. These SNPs were evaluated for replication in an independent sample of 323 AD cases combined from the Religious Orders Study (ROS, 174 participants) and the Rush Memory and Aging Project (MAP, 149 participants). The ROS and MAP cohorts were developed and are managed by the same group of investigators at the Rush University Medical Center, and information about study design and data collection in these studies has been previously published.^{14, 15} Briefly, subjects free of dementia were enrolled and followed annually for cognitive testing that is the same in both studies. We limited our analyses to subjects of European descent with a clinical diagnosis of AD after the age of 60.

Phenotypic Measures

In ADNI, AD was defined as a participant meeting NINCDS/ADRDA criteria for probable AD.¹⁶ Data were collected from participants with MCI at baseline and then at 6-month intervals up to 24 months, followed by a visit at 36 and at 48 months. Data were collected from participants with AD at baseline and then at 6, 12, and 24 months (no visit at 18 months or after 24 months, by design). Cognitive decline was measured based on longitudinally collected Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) items. The ADAS-cog consists of 11 tasks measuring the disturbances of memory, language, praxis, attention and other cognitive abilities, which are often referred to as the core symptoms of AD. ADAS-cog scores range from 0 to 70, with 0 indicating little or no cognitive impairment and 70 indicating severe cognitive impairment.¹⁷

In the replication sample, we analyzed an independent composite measure of global cognition (GCOG)¹⁸ based on 17 tests of cognition including immediate and delayed recall of the East Boston Story and Logical Memory II; immediate and delayed recall and recognition of a 10-item word list; a 15-item Boston Naming Test; verbal fluency; 20-item form of the National Adult Reading Test; digit Span Forward and Backward; Digit Ordering; Number Comparison; the oral form of the Symbol Digit Modalities Test; judgment of line orientation; and Raven's Standard Progressive Matrices. Total scores of each of these tests were transformed into Z-scores and GCOG was the average of those 17 Z-scores.

Genotyping and Quality Control

ADNI participants contributed blood samples from which DNA was extracted and were genotyped using the Illumina Human Genome 610 Quad BeadChips. In the entire ADNI sample (both cases and controls) 67 individuals were excluded due to a genotyped SNP call rate < 98% and 17 individuals were excluded because the onset of their AD began with age < 60 years. For analysis, we imputed the genotypes for all 1000 Genomes¹⁹ SNPs using the Markov chain haplotyping software (MACH)²⁰ and retained those with pairwise linkage disequilibrium ($r^2 > 0.80$) for further analysis. Imputed genotypes were analyzed as allele dosages adjusted by the quality of the imputation. SNPs were not analyzed if they had minor allele frequencies (MAF) of less than 4%. EIGENSTRAT²¹ was used to measure principal components of ancestry (continuous measures summarizing genetic variation that were used to adjust for potential admixture in the sample).

For the ROS/MAP replication cohort, DNA was extracted from blood samples or frozen postmortem brain tissue and genotyped on the Affymetrix Genechip 6.0 platform as previously described.²² Only self-declared non-Hispanic Caucasians were genotyped to minimize population heterogeneity. We applied standard quality control measures for subjects (genotype success rate >95%, genotype-derived gender concordant with reported

gender, excess inter/intra-heterozygosity) and for SNPs (HWE $p > 0.001$; MAF > 0.01 , genotype call rate > 0.95 ; misshap test $> 1 \times 10^{-9}$) to these data. In all, 13 individuals were removed due to low SNP call rate. Subsequently, EIGENSTRAT²¹ was used to identify and remove population outliers using default parameters. SNP genotypes were imputed using MACH software (version 1.0.16a)²³ and the 1000 Genomes reference panel. At the conclusion of the QC pipeline and imputation, 203 ROS and 171 MAP subjects with AD diagnosis, longitudinal cognitive data (2 or greater evaluations), and quality-controlled genotyping were available for the replication analysis.

Statistical Analysis

We used linear regression models in the discovery cohort to test for genetic association with ADAS-cog. We included every available post-diagnosis cognitive score in these models. The parameters of interest were the β coefficient and P -values from an interaction term between the minor allele dosage at each SNP and the time in months since AD diagnosis. Conceptually, this interaction term tests whether SNP genotype is associated with a different effect of time on cognitive score. We used R version 2.10.0 to evaluate these models with generalized estimating equations to account for the intra-individual correlation in cognitive performance and genotype. Covariates such as APOE $\epsilon 4$ allele count, education, age, gender, and pre-baseline disease duration (for those who already had AD at baseline) were considered and retained in the final models if significant at $P < 0.05$. We also included the first three principal components of ancestry in our final models. To limit the number of tests performed in the replication sample, we created a list of the 65 most promising SNPs based on the strength of statistical evidence for association, including supporting evidence from flanking SNPs.

In the replication sample, we used general linear mixed models to model global cognition (GCOG) decline over time, adjusted for age at AD diagnosis ($P = 0.02$), years of education ($P < 0.0001$), and sex ($P = 0.0004$). From these models, we obtained estimated random slopes for each individual with at least two recorded measures of global cognition. Using these random slope estimates as outcomes, we then fit linear regression models using PLINK. Only post-diagnosis GCOG scores were used to compute the slopes.

Finally, we meta-analyzed the results from the discovery and replication samples using sample size-weighted P -values and the direction of the effect using METAL.²⁵ Associations were considered significant if P values were less than 5×10^{-8} .

Results

The discovery sample contained 303 AD cases, including 137 who converted during the study period from MCI to AD. The 166 individuals who were diagnosed with AD prior to the first study visit had a mean pre-baseline disease duration of 3.3 years (SD = 2.6). Table 1 shows the baseline characteristics of the discovery and replication samples. The replication sample contained a higher percentage of females, had an older mean age at AD onset, and a lower frequency of APOE $\epsilon 4$ alleles. Only sex and pre-baseline disease duration were associated with rate of decline in ADAS-cog ($P < 0.05$) and were retained as covariates, with males showing a slower rate of decline and individuals who had AD for a longer period prior to baseline showing more rapid decline. Figure 1 shows Manhattan and QQ plots for ADAS-cog in the discovery cohort. There was a significant genomic inflation factor ($\lambda = 1.079$) for the interaction tests for rate of decline, thus all P -values presented were adjusted accordingly. The strongest associations were with relatively rare (MAF = 3%) SNPs in and near the alpha mannosidase gene (*MAN2A1*) on chromosome 5 (109,230,839 BP, $P = 1.0 \times 10^{-20}$). There were also associated variants in the spondin 1 (*SPON1*) gene on chromosome 11 (rs11023139, $P = 7.0 \times 10^{-11}$), with minor alleles associated with more rapid progression

(3.8 points per year in ADAS-cog). Figure 2 shows the mean ADAS-cog scores throughout the follow-up period for minor allele carriers vs. non-carriers. We subsequently tested this SNP for association in the discovery sample with the rate of decline in other cognitive measures (the Rey Auditory Verbal Learning Test (RAVLT) and the Mini-Mental State Examination (MMSE)) and also with the rate of amyloid β -40 ($A\beta$ -40) and $A\beta$ -42 accumulation in cerebrospinal fluid (CSF).

The AD cases in the replication sample were followed for a mean of 2.5 years post-diagnosis ($SD = 2.6$ years). We compiled a list of 65 of the top SNP associations in ADNI of rate of decline among people with AD. Table 2 shows the results for these SNPs in the discovery sample. None of the 65 SNPs identified in the discovery sample trended towards association with rate of decline in GCOG in the replication sample at $P = 0.05$ with the same effect direction. Although rs11023139 in *SPON1* was not significantly associated with a change in GCOG slope in ROS/MAP, a different SNP located 5.5 KB upstream did show evidence for association with the same effect direction (rs11606345, $P = 0.002$). Although these SNPs are in complete LD, the correlation between them is minimal ($r^2 = 0.002$).

Finally, we evaluated whether or not there was an association with cognitive decline for all SNPs identified as significantly associated with AD at $P < 10^{-4}$ (supplementary Table 5 in Naj et al.)⁴ in the recently published results from the Alzheimer Disease Genetics Consortium (ADGC) study that contains more than 19,490 AD cases and 36,770 controls. Five of the 447 AD-associated SNPs selected in this manner were associated with rate of decline in ADAS-cog at a significance level of $P < 0.05$ in the discovery sample. The minor alleles for a SNP in *PVRL2* (rs440277, $P = 0.003$) was associated with a lower risk of developing AD and a slower rate of decline, as was a SNP in *CD33* (rs1354106, $P = 0.04$). In the replication sample, however, there were three SNPs near the gene gap junction protein, beta 5 (*GJB5*) that were associated with GCOG. The strongest effect was from rs12048230 ($P = 1.9 \times 10^{-7}$) and was associated with a slower rate of decline and lower risk of AD in the ADGC samples.

Discussion

This study is the first to search for and discover unbiased associations between genome-wide genetic variants and rate of cognitive decline in AD cases and despite the small sample size, a number of intriguing candidate genes were identified. The most interesting candidate gene we identified is *SPON1*, both because variants were significantly associated in both discovery and replication cohort, and because of its biological plausibility. The protein SPON1 binds the central terminal domain of the amyloid precursor protein (APP) and inhibits its cleavage by the β -secretase complex (BACE).²⁶ Although all the common ($MAF > 3\%$) associated SNPs in *SPON1* are all intronic, there is a rare ($MAF = 1\%$) missense mutation that is strongly associated with rate of decline. The most significant associated SNP in the gene was also associated (much less significantly) with more rapid rate of decline in the RAVLT ($P = 0.008$) and the MMSE ($P = 0.003$), and the same SNP was associated with a slower rate of $A\beta$ -40 (but not $A\beta$ -42) accumulation in cerebrospinal fluid (CSF) ($P = 0.001$). Although the directions of the effects on cognition and $A\beta$ -40 accumulation appear to be opposite, it has previously been suggested that slower accumulation of $A\beta$ in CSF is indicative of more accumulation in the brain²⁷.

Several of the other significant association results are in genes with functions relevant to neuronal maintenance and neurotransmission (*EXOC4*, *GABRG3*, *VAT1L*), with many involved in Ca^{2+} signaling and homeostasis (*CAMK4*, *CYCS*, *NCSI*, *CACNA1G*). Other notable candidates for association with variable rate of decline in AD patients are involved

in neuronal apoptosis signaling (*ELMO1*, *CYCS*), while two are involved in lipid homeostasis (*LIPC*²⁸, *OSBPL7*).

Our results require confirmation in larger datasets, but support the intriguing possibility that previously unknown genetic variants may influence the rate of decline in AD. Larger cohorts with longitudinal data, providing improved statistical power, are being collected to provide more definitive replication.

The strengths of this analysis were the unbiased nature of the GWAS, a discovery and a replication sample, and a statistical model that allowed us to specifically measure test for a differential *rate* of decline (rather than cognitive function in general) while maximizing the information content of the data (use of repeated measures). Our study was limited by small sample sizes in both datasets, and by the fact that the phenotype of cognitive decline was measured and analyzed differently in the discovery and replication cohorts. A full description of these differences is beyond the scope of this paper, but there is face validity to the assumption that both represent a general measure of overall cognitive ability, since both the ADAS-Cog, and the GCOG incorporate measures on a variety of cognitive domains. Our experience with the ADNI data indicates that the genetic association tests for decline are highly sensitive to the assessment scale used.

One of the previous candidate gene studies of rate of decline in AD cases identified SNP rs1868402 in a gene that encodes the regulatory sub-unit of protein phosphatase B (*PPP3R1*) that was not associated with risk for AD or age at onset, but was associated with rate of decline as measured by the clinical dementia rating sum of boxes (CDR-SB) and also tau phosphorylated at threonine 181 (ptau₁₈₁) levels measured in CSF, a known biomarker for AD.¹² The other candidate gene study found two SNPs (rs3746319, rs8192708) associated with global cognition, one the zinc finger protein 224 gene (*ZNF224*) and one in the gene encoding phosphoenolpyruvate carboxykinase (*PCK1*).¹¹ Examining these 3 SNPs, we found a trend towards association with ADAS-cog for rs1868402 ($P = 0.14$) in the same direction as the previous report.¹² The significant results in that study were generated under a dominant model and only in individuals with low levels of A β ₄₂ in CSF. Given the different phenotypes, subsets of the ADNI data, and statistical and genetic models used for analysis across these studies, the trend towards replication in this analysis substantially increases the evidence that *PPP3R1* variants may mediate AD progression through pathways related to ptau₁₈₁. In the present study, there was also a trend towards association with rs3746319 ($P = 0.08$) but not rs8192708 with change in ADAS-cog.

In summary, we utilized a discovery sample and a replication sample to perform the first genome wide study to assess genetic variants associated with cognitive rate of decline in people with AD. We identified several SNPs with statistical evidence in genes that have not been previously associated with AD risk, most notably *SPONI* which may contain variants whose minor alleles slow disease progression by lowering the amount of extracellular A β -40. A different, nearby SNP was associated with decline in an independent sample using a different measure of cognition. Novel genetic associations with rate of decline in AD may provide new insights into the pathophysiology of AD and new targets for therapeutic development.

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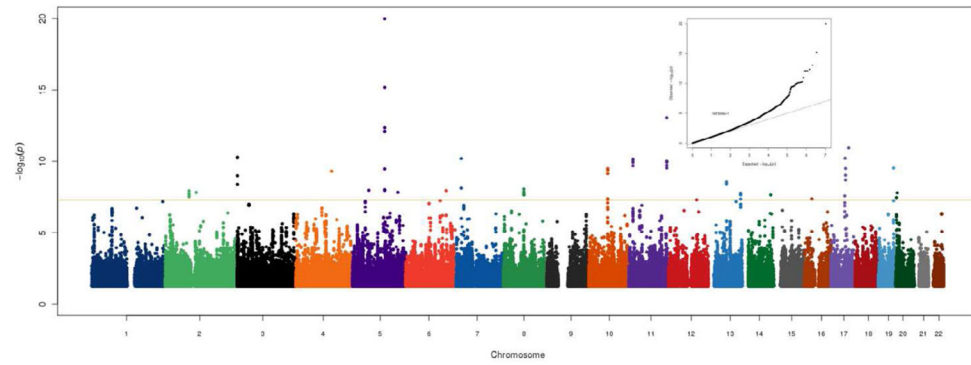


Figure 1. Genome wide association results for cognitive decline measured with ADAS-cog in the discovery sample

The Y-axis shows the P-values (on the $-\log_{10}$ scale) for each association test. The X-axis is the chromosomal position of each SNP. The gold horizontal line at 5×10^{-8} indicates genome-wide significance. The inset shows the Q-Q plot for the adjusted P-values.

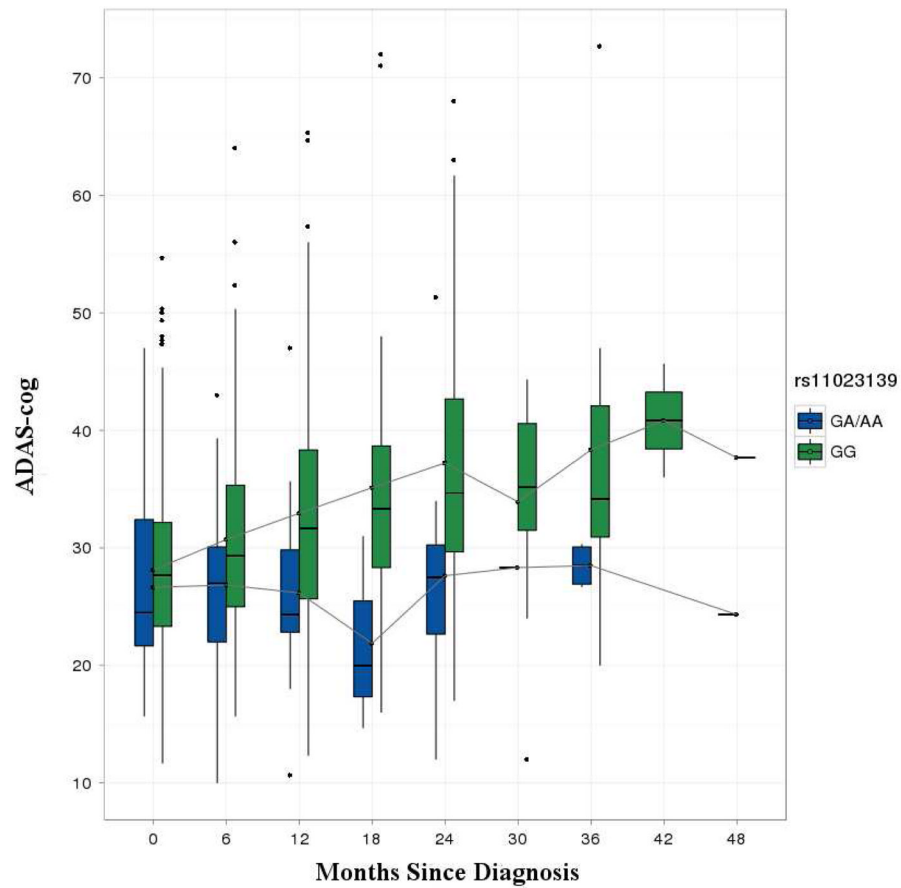


Figure 2. Boxplots of ADAS-cog scores in rs11023139 minor allele carriers vs. non-carriers
 The line in each box represents the mean ADAS-cog score at each time point. The box heights indicate the interquartile range, and the whiskers extend to the most extreme data point which is no more than 1.5 times the interquartile range

Table 1

Baseline characteristics of the discovery and replication samples

Variable	Percent or Mean ADNI	Percent or Mean ROS/MAP
Female	44%	70%
Age at onset (SD)	72.8 (7.6)	85.0 (6.4)
APOE ε4 positive (1 or 2 copies)	67%	39%
Years education (SD)	15.2 (3.0)	16.4 (3.6)

Table 2

Association results for ADAS-cog in ADNI

Chr	BP	SNP	MAF	SNP Type	Gene	Beta	P
1	171557600	rs2421847	0.04	missense	PRRC2C	0.26	8.71E-07
1	240605052	rs12091371	0.07	intron	FMN2	0.17	6.70E-08
2	14987571	NA	0.03	NA	NA	-0.49	5.67E-07
2	16965493	NA	0.06	NA	NA	0.28	1.29E-06
2	80281173	rs6738962	0.04	intron	CTNNA2	0.18	1.17E-08
2	128396167	rs78022502	0.06	3' UTR	LIMS2	0.23	1.69E-06
3	39513278	rs538867	0.03	intron	MOBP	0.26	1.01E-07
3	51095028	rs9857727	0.1	intron	DOCK3	0.18	9.70E-06
3	165493136	rs2668205	0.03	intron	BCHE	0.27	9.63E-06
4	5237153	rs78647349	0.04	intron	STK32B	0.3	5.24E-07
4	87931404	rs340635	0.03	intron	AFF1	0.23	2.18E-07
5	55510656	rs4700060	0.1	intron	ANKRD55	0.21	1.07E-08
5	109111327	rs113689198	0.03	intron	MAN2A1	0.3	9.65E-09
5	109221026	rs112724034	0.03	NA	PGAM5P1	0.31	8.51E-13
5	109230839	NA	0.03	NA	NA	0.38	1.03E-20
5	110719187	rs77636885	0.03	intron	CAMK4	0.3	1.80E-06
5	118435127	rs116348108	0.04	intron	DMXL1	0.28	8.91E-07
5	126729450	rs143954261	0.04	intron	MEGF10	0.29	8.11E-07
5	127382302	rs146579248	0.04	NA	FLJ33630	0.21	4.30E-07
5	153837106	rs148763909	0.03	3' UTR	SAP30L	0.15	1.49E-08
6	78357637	NA	0.05	NA	NA	0.29	8.97E-08
6	116056915	NA	0.04	NA	NA	0.3	5.71E-08
6	124326227	rs117780815	0.03	intron	NKAIN2	0.31	6.28E-07
6	136288895	rs9494429	0.03	intron	PDE7B	0.23	5.97E-07
6	136368005	rs11154851	0.03	intron	PDE7B	0.25	1.14E-08
6	151102830	rs75253868	0.04	intron	PLEKHG1	0.26	2.24E-06
7	16707861	rs58370486	0.03	intron	BZW2	0.36	6.37E-11

Chr	BP	SNP	MAF	SNP Type	Gene	Beta	P
7	16811139	rs73071801	0.04	intron	TSPAN13	0.33	9.97E-07
7	251161602	rs1861525	0.03	3' UTR	CYCS	0.25	1.67E-07
7	37365196	rs2392492	0.04	intron	ELMO1	0.32	1.15E-06
7	43377276	rs17172199	0.08	intron	HECW1	0.28	1.09E-06
7	133747946	rs11770757	0.04	intron	EXOC4	0.16	4.76E-07
8	3088173	rs73660619	0.06	intron	CSMD1	0.26	7.45E-07
8	53214265	rs7009219	0.06	intron	ST18	0.16	5.12E-07
8	68761014	NA	0.05	NA	NA	0.28	8.81E-09
9	132939792	rs4836694	0.11	intron	NCS1	0.21	7.15E-07
10	64635265	NA	0.04	NA	NA	0.26	3.90E-10
10	122279476	rs118048115	0.04	intron	PPAPDC1A	0.34	6.41E-07
11	14224346	rs11023139	0.05	intron	SPO11	0.31	7.00E-11
11	14338703	rs61883963	0.06	intron	RRAS2	0.26	5.19E-07
11	14556220	rs34162548	0.05	intron	PSMA1	0.27	1.14E-06
11	37033930	NA	0.06	NA	NA	0.16	8.22E-07
11	110499253	rs326946	0.17	intron	ARHGAP20	0.16	6.81E-07
11	128185570	NA	0.03	NA	NA	0.31	8.92E-14
12	51878760	rs147845115	0.03	intron	SLC4A8	0.29	2.84E-07
12	94235165	rs61144803	0.04	intron	CRADD	0.16	5.02E-08
12	101221239	rs1399439	0.04	intron	ANO4	0.2	3.51E-07
13	61617648	NA	0.07	NA	NA	0.24	2.83E-09
13	93945858	rs143258881	0.03	intron	GPC6	0.29	6.73E-08
13	109473946	rs17393344	0.06	intron	MYO16	0.26	1.69E-08
14	95764564	rs115102486	0.03	intron	CLMN	0.31	2.28E-08
15	27712644	rs74006954	0.03	intron	GABRG3	0.28	2.74E-07
15	58730639	rs17301739	0.07	intron	LIPC	0.28	1.45E-06
16	24675589	rs8045064	0.05	NA	FLJ45256	0.21	4.27E-08
16	77876763	rs9934540	0.03	intron	VAT1L	0.25	3.55E-07
17	45888374	rs62076103	0.07	intron	OSBPL7	0.26	3.32E-07

Chr	BP	SNP	MAF	SNP Type	Gene	Beta	P
17	45905622	rs62076130	0.06	intron	MRPL10	0.26	7.82E-07
17	45930539	rs4794202	0.08	intron	SP6	0.19	7.99E-08
17	47134762	NA	0.03	NA	NA	0.3	6.07E-11
17	48692082	rs117964204	0.04	intron	CACNA1G	0.28	9.44E-10
17	59292436	rs72832584	0.05	intron	BCAS3	0.3	1.14E-11
19	51422877	NA	0.05	NA	NA	0.34	3.00E-10
19	51430596	rs7245858	0.04	missense	LOC390956	0.28	2.03E-06
20	2384972	rs34972666	0.11	intron	TGM6	0.23	3.46E-08
22	44526105	rs75617873	0.03	intron	PARVB	0.17	5.01E-07

Type = type of SNP

BP = base pair location in release 19, build 135 of the human genome in the dbSNP database

SNPs in bold were genotyped

MAF = minor allele frequency in ADNI

Beta = Change in ADAS-cog per copy of the minor allele per month with AD, positive numbers indicate slower decline and negative numbers indicate more rapid decline

P = P-value after correction for a genomic inflation factor of 1.079