

Abstract

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Genome-wide association study of the rate of cognitive decline in Alzheimer's disease

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Background: Substantial interindividual variability exists in the disease trajectories of Alzheimer's disease (AD) patients. Some decline rapidly whereas 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 Alzheimer's Disease 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 single-nucleotide polymorphism (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 spondin 1 gene (*SPON1*), the minor alleles of which were significantly associated with a slower rate of decline (rs11023139, $P = 7.0 \times 10^{-11}$) in the discovery sample. A *SPON1* SNP 5.5 kb upstream was associated with decline in the replication sample (rs11606345, P = .002). **Conclusion:** *SPON1* has not been previously associated with AD risk, but is plausibly related be-

cause the gene product binds to the amyloid precursor protein and inhibits its cleavage by β -secretase. These data suggest that *SPON1* may be associated with the differential rate of cognitive decline in AD. © 2014 The Alzheimer's Association. All rights reserved.

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1. Introduction

Alzheimer's disease (AD) is a common form of dementia with an enormous public health impact and for which

1552-5260/\$ - see front matter \odot 2014 The Alzheimer's Association. All rights reserved. http://dx.doi.org/10.1016/j.jalz.2013.01.008 there are no treatments yet available to slow progression. Through the efforts of large consortia that pool data from many genome-wide association studies (GWAS) of lateonset AD, several 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 several 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 diabetes [7] 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 single-nucleotide polymorphisms (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. Although 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.

2. Methods

2.1. Discovery sample

Data used in the discovery sample were obtained from the Alzheimer's Disease 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 cerebrospinal fluid (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 with normal cognitive function. Detailed protocols for subject recruitment and biomarker accrual are available at the ADNI website (http://www.adni-info.org/). In brief, subjects were recruited from over 50 sites across the United States 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 cognitively 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 were defined as data from the examination with the first clinical diagnosis of AD. Seventeen individuals with age at onset younger than 60 years (indicative of familial AD) were excluded.

2.2. Replication sample

We selected the 65 most promising SNPs from the discovery sample on the basis of association with the outcome measure (see *Phenotypic measures*). 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]. In brief, 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.

2.3. Phenotypic measures

In ADNI, AD was defined as a participant meeting National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association 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; 20item 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.

2.4. Genotyping and quality control

ADNI participants contributed blood samples from which DNA was extracted and genotyped using the Illumina Human Genome 610 Quad BeadChips. In the entire ADNI sample (cases and controls), 67 individuals were excluded because of a genotyped SNP call rate less than 98% and 17 individuals were excluded because the onset of their AD began at an age younger than 60 years. For analysis, we imputed the genotypes for all 1000 Genomes [19] SNPs using the Markov chain haplotyping software (MACH) [20] and retained those with pairwise linkage disequilibrium $(r^2 > .80)$ 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 3%. EIGENSTRAT [21] 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 call rate >95%, genotype-derived gender concordant with reported gender, excess inter/intraheterozygosity) and for SNPs (Hardy-Weinberg equilibrium P > .001; MAF > 0.01, genotype call rate > 0.95; misshap test >1 \times 10⁻⁹) to these data. In all, 13 individuals were removed because of low SNP call rate. EIGENSTRAT [21] was subsequently 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 (December 2010 release) reference panel. At the conclusion of the quality control pipeline and imputation, 203 ROS and 171 MAP subjects with AD diagnosis, longitudinal cognitive data (≥ 2 evaluations), and qualitycontrolled genotyping were available for the replication analysis.

2.5. Statistical analysis

We used linear regression models in the discovery cohort to test for genetic association with ADAS-cog. We included every available postdiagnosis 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 intraindividual correlation in cognitive performance and genotype. Covariates such as APOE £4 allele count, education, age, gender, and prebaseline disease duration (for those who already had AD at baseline) were considered and retained in the final models if significant at a P value less than .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 on the basis of strength of statistical evidence for association, including supporting evidence from flanking SNPs.

In the replication sample, we used general linear mixed models to model GCOG decline over time, adjusted for age at AD diagnosis (P = .02), years of education (P < .0001), and sex (P = .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 postdiagnosis 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 [24]. Associations were considered significant if *P* values were less than 5×10^{-8} .

3. 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 before the first study visit had a mean prebaseline 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 had a lower frequency of *APOE* ε 4 alleles.

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)		



Fig. 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 QQ plot for the adjusted *P* values.

Only sex and prebaseline disease duration were associated with rate of decline in ADAS-cog (P < .05) and were retained as covariates, with males showing a slower rate of decline and individuals who had AD for a longer period before 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; all *P* values presented were adjusted



Fig. 2. Boxplots of ADAS-cog scores in rs11023139 minor allele carriers vs noncarriers. 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 datapoint, which is no more than 1.5 times the interquartile range.

accordingly. The strongest associations were with relatively rare (MAF = 3%) SNPs in and near the α -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 slower 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 versus noncarriers. 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 with the rate of amyloid β -40 (A β -40) and A β -42 accumulation in CSF.

The AD cases in the replication sample were followed for a mean of 2.5 years postdiagnosis (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 toward association with rate of decline in GCOG in the replication sample at *P* values of .05 or less 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 = .002). Although these SNPs are in complete linkage disequilibrium, the correlation between them is minimal ($r^2 = .002$).

Finally, we evaluated whether or not there was an association with cognitive decline for all SNPs identified as significantly associated with AD at P values less than 10^{-4} (Supplementary Table 5 in Naj et al [4]) in the recently published results from the Alzheimer Disease

Table 2Association results for ADAS-cog in ADNI

	Chromosome	BP*	SNP	MAF^\dagger	SNP type [‡]	Gene	β [§]	P¶
1 20005052 rst2001571 0.07 Intron FMN2 0.17 6.705 6.705 2 14963591 NA 0.06 NA NA 0.49 5.705 0.77 2 16955493 NA 0.06 NA NA 0.49 5.705 0.77 3 3505520 0.05 3'UTR LIMS2 0.23 1.695 0.65 3 1656913.6 r5386727 0.1 Intron DOCK3 0.18 9.705 0.65 4 5351145 r526900 0.04 Intron BCRE 0.27 0.03 Lister 0.8 5 109011327 r413850198 0.03 Intron AFK32B 0.33 Lister 0.8 9.655 0.031 Intron DMAL21 0.33 BSDE 5 1092100 1.81272404 0.03 NA NA NA 0.34 BSDE 5 1092100 1.812851 1.814507 0.31 BSDE 5 1193187 1.91580 0.31 Intron DMAL14	1	171557600	rs2421847	0.04	Missense	PRRC2C	-0.26	8.71E-07
2 14987571 NA 0.03 NA NA NA 0.04 NA NA 0.05 5.07L07 2 180281173 ref.7399022 0.04 Inron C7NN12 0.18 1.17E-06 3 39513278 ref.7892022 0.03 Intron MOBP 0.26 1.01E-07 3 51095012 ref.87737 0.1 Intron DOCK3 0.18 0.70E-06 3 1659913-0 ref.876749 0.03 Intron ACHE 0.23 2.18E-07 4 3297153 ref.179600 0.1 Intron ANROST 0.21 1.07E-08 5 10011127 ref.112869198 0.03 Intron ANROST 0.21 1.07E-08 5 10021005 ref.12784010 0.03 Intron CAML4 4.03 8.05E-0 5 1129724050 ref.149679202 0.04 Intron CAML4 4.03 8.01E-10 5 112972450 ref.149763990	1	240605052	rs12091371	0.07	Intron	FMN2	-0.17	6.70E-08
2 16055903 NA 0.06 NA NA NA 2.8 1.2986 2 128396167 rs73822502 0.06 3' UTR LMN22 -0.23 1.6994.05 3 51095028 rs538867 0.0 Intron MCK14 -0.26 1.011-07 3 15095028 rs5388727 0.1 Intron MCK14 -0.26 1.011-07 4 55731066 rs7400630 0.03 Intron AFK12 -0.23 1.2816-07 5 100211327 ril 1689198 0.03 Intron AFK225 -0.21 1.071-08 5 10021020 ril 1274034 0.03 NA PCAMF71 -0.31 S.181-07 5 10021039 NA 0.03 NA PCAMF71 -0.31 S.181-07 5 113732420 ril 4595309 0.03 2'UTR DAF20L -0.21 4.389-110 5 113837166 ril 4595309 0.03 3'UTR DAF20L	2	14987571	NA	0.03	NA	NA	0.49	5.67E-07
2 80281173 rs78023902 0.04 Intron C/NNA2 0.18 1.1750.8 3 33951378 rs7802392 0.06 3' UTR LIMS2 0.23 1.069406 3 35913278 rs7867372 0.1 Intron MOBP 0.26 1.018-07 4 5297153 rs7867329 0.03 Intron AFFI 0.3 2.188-07 5 5510656 rs700600 0.1 Intron AAX2L1 0.3 9.658-05 5 10011127 rs113680198 0.03 Intron AAX2L1 0.3 9.658-05 5 10021064 rs112724018 0.03 No CAM44 0.3 8.518-15 5 10021064 rs112748108 0.04 Intron CAM44 0.3 8.518-15 5 112673450 rs143954261 0.04 Intron CAM44 0.38 8.916-07 5 12673450 rs14596399 0.03 NTP 0.25 1.1490-08	2	16965493	NA	0.06	NA	NA	-0.28	1.29E-06
2 128396167 pr5822502 0.06 3' UTR LMS2 -0.23 1.69E-06 3 35095028 pr5825727 0.1 Intron DOCK3 0.18 9.70E-06 3 16549313 pr58677349 0.04 Intron BCKE 0.2 9.63E-06 4 \$53510656 pr37667349 0.04 Intron AFK21E 0.3 \$24E-07 5 \$5510656 pr3706055 0.03 Intron AFK21E 0.21 1.07E-08 5 10921089 NA 0.03 NA PCAMSPI 0.3 8.51E-13 5 109230899 NA 0.03 NA NA 0.3 1.80E-06 5 110719187 pr7856858 0.03 Intron CAMK4 0.3 8.891E-07 5 12378230 pr44875049 0.03 NTR SAP90. 0.15 4.3062-06 6 112353010 pr44875049 0.03 Intron MK471. 0.31 S2256-0	2	80281173	rs6738962	0.04	Intron	CTNNA2	-0.18	1.17E-08
3 39313278 rs53867 0.03 Intron MOBP -0.26 1.011-07 3 151095028 rs6867727 0.1 Intron BCIE 0.27 9.681-06 4 87331404 rs34635 0.03 Intron AFK2B 0.3 2.3181-07 5 55510666 rs470060 0.1 Intron AFK1D 0.3 9.665.00 5 10911027 rs113689198 0.03 Intron AFK2D 0.3 8.51E-13 5 109221026 rs1172404 0.03 NA PCAMKPI 0.31 1.805-05 5 110719187 rs77636855 0.03 Intron DMK1/L 0.32 8.91F-07 5 128783202 rs14367560 0.03 3'UTR S/P20L 0.11 1.3967 6 12452027 rs14786300 0.03 3'UTR S/P20L 0.31 6.2324561 6 12452027 rs1778045 0.03 Intron MAK1/L 0.32	2	128396167	rs78022502	0.06	3' UTR	LIMS2	-0.23	1.69E-06
3 51099028 ps85727 0.1 Intron DCK3 0.18 9.702-06 3 165493130 rp2647349 0.04 Intron RTK22H 0.03 5.244.07 4 R3731404 rs340635 0.03 Intron AVKRD55 0.21 1.077.08 5 10921127 rs11369198 0.03 Intron AVKRD55 0.21 1.077.08 5 109230839 NA 0.03 NA PCAMSPI 0.03 8.516.13 5 109230839 NA 0.03 NA NA 0.03 1.087.07 5 110719187 ps7636885 0.03 Intron CAMK41 0.03 1.085.09 5 122729450 rs14354180 0.04 Intron MKL1 -0.28 8.91E.07 5 153837106 rs148763090 0.03 3'UTR SAF366 0.03 5.71E.08 6 116365015 NA 0.04 NA 0.02 S.97E.07	3	39513278	rs538867	0.03	Intron	MOBP	-0.26	1.01E-07
3 16549136 rs268205 0.03 Intron BCILE 0.27 9.63L-65 4 87331404 rs340535 0.03 Intron AFFI 0.23 2.188-07 5 55511065 rs113689198 0.03 Intron AFFI 0.23 2.188-07 5 109212026 rs11324044 0.03 NA PGAMSP1 0.31 8.51E-13 5 109221026 rs11724044 0.03 NA PGAMSP1 0.31 8.51E-13 5 110719187 rs71363685 0.03 Intron CAMK4 0.3 1.80E-06 5 12328202 rs146592461 0.04 Intron MAK14 0.3 1.80E-06 6 12452627 rs14756090 0.03 3'UTR SAP00 0.11 1.495630 0.21 4.30E-07 6 12452627 rs117760815 0.03 Intron NALAV2 0.31 6.224E-07 6 126688005 rs1194851 0.03 Intr	3	51095028	rs9857727	0.1	Intron	DOCK3	-0.18	9.70E-06
4 5237153 m;78647349 0.044 Intron STK32B 0.23 2181-07 5 35510656 m;77066619 0.01 Intron AVRRDS 0.21 1.0771-08 5 10021026 m;112724034 0.03 NA NA 0.31 8.511E-13 5 100220089 NA 0.03 NA NA 0.33 I.0381-03 5 110719187 m;77656885 0.03 Intron CAMKA -0.3 1.801E-05 5 12373202 m;143954261 0.04 Intron MECF10 -0.29 8.911E-07 5 12373202 m;143752428 0.04 NA MA -0.29 8.971E-08 6 116056915 NA 0.04 NA NA 0.03 5.71E-08 -0.23 5.71E-08 6 11303600 r;11780815 0.03 Intron PDE78 -0.23 5.97E-07 7 16811130 r;73071801 0.04 Intron P	3	165493136	rs2668205	0.03	Intron	BCHE	-0.27	9.63E-06
4 8/981404 rs/40055 0.03 Intron APP1 -0.23 2.188-00 5 109111227 rs/13689198 0.03 Intron MAR2D55 -0.21 1.077E-08 5 109221026 rs/1272044 0.03 NA PGAMSPI -0.31 8.51E-13 5 110719187 rs/7565885 0.03 Intron CAMK4 -0.3 1.80E-06 5 1123729450 rs/140579248 0.04 Intron DMXL1 -0.28 8.91E-07 5 123739450 rs/140579248 0.04 Intron DMXL1 -0.28 8.91E-07 6 11605615 NA 0.04 NA NA -0.31 5.71E-08 6 116056015 NA 0.04 NA NA -0.23 5.97E-07 6 13628895 rs/94429 0.03 Intron PKA/1/82 -0.31 6.2385 075E-02 6 151102830 rs/97E-07 1.070780 0.04 Intron PK	4	5237153	rs78647349	0.04	Intron	STK32B	-0.3	5.24E-07
5 10911127 rs170000 0.1 Intron AV&RD23 0.21 1072-03 5 10921026 rs112724034 0.03 NA PGAMSP1 0.31 \$\$ 5 10922083 NA 0.03 NA NA 0.38 \$\$ 5 110719187 rs77636885 0.03 Intron CAMKA 0.33 \$\$ 5 11273217 rs116348108 0.04 Intron MECF10 -0.28 \$\$ \$\$ 5 12378202 rs14879248 0.04 NA \$\$ \$	4	87931404	rs340635	0.03	Intron	AFFI	-0.23	2.18E-07
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3 109/21020 N11/2/20/3 0.03 NA PCAMP/1 -0.31 Solt=10 5 110719187 n.77656885 0.03 Intron CAMK -0.33 1.808-00 5 118(435127 n.161648108 0.04 Intron DMXL1 -0.28 8.916-07 5 127382302 n.146759248 0.04 Intron MEG/10 -0.29 8.116-07 6 78357637 NA 0.05 NA NA -0.21 4.306-07 6 116056915 NA 0.04 NA NA -0.23 5.71E-08 6 1163568005 n.11770815 0.03 Intron NCAMV2 -0.31 6.23E-07 7 16661186 n.575235868 0.04 Intron PDE7B -0.25 1.67E-07 7 16511189 n.752535868 0.04 Intron PDE7B -0.25 1.67E-07 7 1561602 rs1807355 0.03 intron TDEM/13 -0.38	5	109111327	rs113689198	0.03	Intron	MAN2A1	-0.3	9.65E-09
3 10220039 NA 0.03 NA NA 0.03 NA 0.04 Intron CAMK4 0.03 1.00E-06 5 116719187 rs16548108 0.04 Intron DAMK4 -0.38 8.91E-07 5 126729407 rs149595201 0.04 Intron DAMK4 -0.29 8.11E-07 5 135387100 rs146579248 0.04 NA <i>FLJS1630</i> -0.21 4.30E-07 6 135387300 rs14756309 0.03 3'UTR SAP304 -0.15 1.39E-08 6 114050915 NA 0.04 NA NA -0.3 5.97E-07 6 136288895 rs11154851 0.03 Intron PDE7B -0.23 5.97E-07 6 15110280 rs7323868 0.04 Intron PDE7B -0.23 5.97E-07 7 16707861 rs53370486 0.03 J'UTR -0.25 1.67E-07 7 1373745196 rs2392492	5	109221026	rs112/24054	0.03	INA NA	PGAMSPI	-0.31	8.51E-15
J 110 Long Lon	5	109230839	INA *077626885	0.03	INA		-0.38	1.05E-20 1.80E-06
J 11034012 1103402 0.04 Intron DATL 40.25 571E-07 5 126729450 rs146579248 0.04 NA FLJ356300 40.21 4.30E-07 5 125382302 rs146579248 0.04 NA FLJ356300 40.21 4.30E-07 6 13638706 rs14753090 0.03 3'UTR SAP200 40.15 1.30E-08 6 13628895 rs9494429 0.03 Intron PDETB 40.23 5.71E-07 6 13628895 rs9494429 0.03 Intron PDETB 40.23 5.71E-07 7 16707861 rs53370486 0.03 Intron PDETB 40.23 1.51E-07 7 25161602 rs1861525 0.03 3'UTR CPCS 40.25 1.16E-07 7 37365196 rs2392492 0.04 Intron ELCVI 40.23 1.15E-06 7 37365196 rs2392492 0.04 Intron ELCVI <td< td=""><td>5</td><td>110/1910/</td><td>ro116248108</td><td>0.03</td><td>Intron</td><td>DMVL1</td><td>-0.3</td><td>1.80E-00 8.01E-07</td></td<>	5	110/1910/	ro116248108	0.03	Intron	DMVL1	-0.3	1.80E-00 8.01E-07
5 12382302 114557831 0.04 NA <i>FLJ33630</i> 0.12 0.12 0.12 5 133837106 rs14876309 0.03 3' UTR SAP30L 0.15 1.43064 6 116056915 NA 0.04 NA NA 0.3 5.71160 6 112432627 rs117780815 0.03 Intron <i>NKAIN2</i> 0.31 6.2288 6 1136368005 rs114780815 0.03 Intron <i>PDE7B</i> -0.23 5.97167 6 1136368005 rs11454851 0.03 Intron <i>PDE7B</i> -0.26 2.24160 7 16811139 rs73071801 0.04 Intron <i>BZW2</i> -0.36 6.3717-147 7 373071801 0.04 Intron <i>BZW2</i> -0.25 1.671-07 7 37350466 rs292492 0.04 Intron <i>ELMO1</i> -0.26 7.45107 8 308173 rs73660019 0.06 Intron <i>SMD1</i> -0.26 </td <td>5</td> <td>126729450</td> <td>rs1/395/261</td> <td>0.04</td> <td>Intron</td> <td>DMALI MEGE10</td> <td>-0.28</td> <td>8.91E-07</td>	5	126729450	rs1/395/261	0.04	Intron	DMALI MEGE10	-0.28	8.91E-07
5 1236212 134012 134012 134012 13411 134003 5 133837166 rs148753009 0.03 3' UTR SAP302 0.13 1342603 6 116055915 NA 0.04 NA NA 0.33 5.71E-08 6 124326227 rs117780815 0.03 Intron PDC7B -0.23 5.97E-07 6 136368005 rs1154851 0.03 Intron PDC7B -0.23 1.14E-08 6 151102830 rs7523868 0.04 Intron PDC7B -0.23 1.14E-08 7 16707861 rs58370486 0.03 Intron BZW2 -0.36 6.37E-11 7 25161602 rs1861525 0.03 3' UTR CYCS -0.23 1.15E-06 7 43372726 rs1177077 0.04 Intron EXO74 -0.16 4.76E-07 8 63761014 NA 0.05 NA NA -0.28 8.81E-09	5	127382302	rs1/65702/8	0.04	NA	FL 133630	-0.2)	4 30E-07
5 1000000000000000000000000000000000000	5	153837106	rs1/8763000	0.03	3' LITR	SAP301	-0.21	1.49E-08
0 10050015 NA 0.04 NA NA NA 0.02 5.7116.08 6 110050015 NA 0.03 Intron NA NA 0.02 5.7116.08 6 132028895 rs9494429 0.03 Intron PDE7B 0.23 5.751-07 6 15102830 rs75253868 0.04 Intron PDE7B 0.25 1.145.08 6 15110280 rs75253868 0.03 Intron PLEKHGT 0.26 2.248-06 7 16707861 rs8370486 0.03 Intron PLEKHGT 0.22 1.561-07 7 25161602 rs1861525 0.03 3'UTR CYCS 0.22 1.67E-07 7 37365196 rs2392492 0.04 Intron ELCVI 0.28 1.15E-06 7 43377276 rs170777 0.04 Intron CYCA 0.16 3.425E-07 8 53214265 rs7009219 0.06 Intron ST18	6	78357637	NA	0.05	NA	NA	-0.29	8.97E-08
6 124326227 rsi 17780815 0.03 Intron NKAIN2 0.03 6.28E.07 6 13636805 rsi 17780815 0.03 Intron PDE7B -0.23 5.57E-07 6 13636805 rsi 1154851 0.03 Intron PDE7B -0.23 5.57E-07 7 16707861 rs53370486 0.04 Intron PDE7N -0.33 9.97E-07 7 25161602 rs3071801 0.04 Intron TSPAN13 -0.33 9.97E-07 7 37365196 rs2392492 0.04 Intron ELMO1 -0.32 1.15E-06 7 43377276 rs17172199 0.08 Intron EXOC4 -0.16 4.76E-07 8 53214265 rs73660619 0.06 Intron CSMD1 -0.25 7.45E-07 8 68761014 NA 0.05 NA NA -0.26 3.90E-10 10 122279476 rs18048115 0.04 Intron PSPDC1A	6	116056915	NA	0.05	NA	NA	-0.3	5.71E-08
6 136288895 rs9494429 0.03 Intron PDE7B -0.23 5.97E-07 6 136368005 rs11154851 0.03 Intron PDE7B -0.25 1.144-08 6 15110230 rs75253868 0.04 Intron PLEKHG1 0.26 2.24E-06 7 16811139 rs73071801 0.03 Intron PLEKHG1 0.25 2.57E-07 7 25161602 rs1861525 0.03 3' UTR CYCS -0.25 1.67E-07 7 37365196 rs2392492 0.04 Intron HECW1 0.28 1.09E-06 7 43377276 rs1177077 0.04 Intron EXCC4 -0.16 5.12E-07 8 53214265 rs7009219 0.06 Intron ST18 -0.16 5.12E-07 8 63701014 NA 0.04 NA NA -0.24 6.81E-07 11 14224346 rs11023139 0.05 Intron SCM21 -0.12 <td>6</td> <td>124326227</td> <td>rs117780815</td> <td>0.03</td> <td>Intron</td> <td>NKAIN2</td> <td>-0.31</td> <td>6.28E-07</td>	6	124326227	rs117780815	0.03	Intron	NKAIN2	-0.31	6.28E-07
6 136388005 rs1154851 0.03 Intron PDE7B -0.25 1.14E-08 6 151102830 rs7223868 0.04 Intron <i>PLEKHG1</i> -0.26 2.24E-06 7 16707861 rs5370486 0.03 Intron <i>BZW2</i> -0.36 6.3TE-11 7 1681139 rs73071801 0.04 Intron <i>BZW1</i> -0.33 9.9TE-07 7 37365196 rs2392492 0.04 Intron <i>ELMO1</i> -0.32 1.15E-06 7 43377276 rs17172199 0.08 Intron <i>ELMO1</i> -0.28 1.09E-06 7 133747946 rs11700757 0.04 Intron <i>EXOC4</i> -0.16 4.76E-07 8 53214265 rs7000219 0.06 Intron <i>STM1</i> -0.26 7.45E-07 10 64633265 NA 0.04 NA NA -0.26 5.99E-01 11 142367 rs18048115 0.04 Intron <i>RAAS2</i>	6	136288895	rs9494429	0.03	Intron	PDE7B	-0.23	5.97E-07
6 151102830 rs75253868 0.04 Intron PLEKHG1 -0.26 2.24E-06 7 16707861 rs58370486 0.03 Intron <i>JZW2</i> -0.36 6.37E-11 7 1661139 rs53701801 0.04 Intron <i>JZW13</i> -0.33 9.97E-07 7 25161602 rs1861525 0.03 3' UTR CVCS -0.25 1.67E-07 7 43377276 rs17170757 0.04 Intron <i>EXOC4</i> -0.16 4.76E-07 8 3038173 rs73660619 0.06 Intron <i>CSNC4</i> -0.16 5.12E-07 8 68761014 NA 0.05 NA NA -0.26 3.90E-10 10 64035265 NA 0.04 NA NA -0.26 3.90E-10 10 12229746 rs110048115 0.04 Intron <i>PSPOX1</i> -0.31 7.00E-11 11 1423360 rs6183963 0.06 Intron <i>PRA2C1</i> -0.25 </td <td>6</td> <td>136368005</td> <td>rs11154851</td> <td>0.03</td> <td>Intron</td> <td>PDE7B</td> <td>-0.25</td> <td>1.14E-08</td>	6	136368005	rs11154851	0.03	Intron	PDE7B	-0.25	1.14E-08
7 16707861 rsS8370486 0.03 Intron BZW2 -0.36 6.37E-11 7 16811139 rs73071801 0.04 Intron TSPAN13 -0.33 9.97E-07 7 25161602 rs186152 0.03 3' UTR CYCS -0.25 1.67E-07 7 43377276 rs17172199 0.04 Intron EXOC4 -0.16 4.76E-07 8 3088173 rs73606019 0.06 Intron ST18 -0.16 5.12E-07 8 53214265 rs7009219 0.06 Intron ST18 -0.16 5.12E-07 8 53214265 rs7009219 0.06 Intron ST18 -0.16 5.12E-07 10 64635265 NA 0.04 NA NA -0.26 3.90E-10 11 142279476 rs11023139 0.05 Intron SPAN22 -0.26 5.19E-07 11 14338703 rs61883963 0.06 Intron SPAN22 -0.26 <td>6</td> <td>151102830</td> <td>rs75253868</td> <td>0.04</td> <td>Intron</td> <td>PLEKHG1</td> <td>-0.26</td> <td>2.24E-06</td>	6	151102830	rs75253868	0.04	Intron	PLEKHG1	-0.26	2.24E-06
7 16811139 rs73071801 0.04 Intron TSPAN13 -0.33 9.97E-07 7 25161602 rs1861525 0.03 3' UTR CYCS -0.25 1.67E-07 7 43377276 rs1717219 0.08 Intron <i>HEWO</i> -0.28 1.09E-06 7 133747946 rs1717077 0.04 Intron <i>EXOC4</i> -0.16 5.12E-07 8 3088173 rs73660619 0.06 Intron <i>CSMD1</i> -0.26 7.45E-07 8 68761014 NA 0.05 NA NA -0.21 7.15E-07 10 64635265 NA 0.04 NA NA -0.23 3.9961-01 11 14224346 rs118048115 0.04 Intron <i>PRAPDC1A</i> -0.34 6.41E-07 11 14328703 rs5183963 0.06 Intron <i>PRAPDC1A</i> -0.34 6.21E-07 111 14328703 rs5183963 0.06 Intron <i>PRAPDC1A</i> <t< td=""><td>7</td><td>16707861</td><td>rs58370486</td><td>0.03</td><td>Intron</td><td>BZW2</td><td>-0.36</td><td>6.37E-11</td></t<>	7	16707861	rs58370486	0.03	Intron	BZW2	-0.36	6.37E-11
7 25161602 rs1891525 0.03 3' UTR CYCS -0.25 1.67E-07 7 37365196 rs2392492 0.04 Intron <i>ELMOI</i> -0.32 1.15E-06 7 133747946 rs11712199 0.04 Intron <i>EXOC4</i> -0.16 4.76E-07 8 308173 rs73660619 0.06 Intron <i>STU1</i> -0.16 5.12E-07 8 68761014 NA 0.05 NA NA -0.26 7.45E-07 9 13293792 rs4836694 0.11 Intron <i>NCS1</i> -0.21 7.15E-07 10 64635265 NA 0.04 Intron <i>PAPDCIA</i> -0.34 6.41E-07 11 14224346 rs11023139 0.05 Intron <i>PAPDCIA</i> -0.34 6.41E-07 11 14358703 rs61883963 0.06 Intron <i>PRADI</i> -0.27 1.14E-06 11 11456220 rs34162548 0.05 Intron <i>ARAGP20</i>	7	16811139	rs73071801	0.04	Intron	TSPAN13	-0.33	9.97E-07
7 37365196 rs2329292 0.04 Intron <i>ELMOI</i> -0.32 1.15E-06 7 43377276 rs17172199 0.08 Intron <i>HECWI</i> -0.28 1.09E-06 8 3088173 rs7360619 0.06 Intron <i>CSMDI</i> -0.26 7.45E-07 8 53214265 rs7009219 0.06 Intron <i>STIB</i> -0.16 5.12E-07 8 68761014 NA 0.05 NA NA -0.28 8.81E-09 9 132930792 rs4336694 0.11 Intron <i>NCSI</i> -0.21 7.15E-07 10 64635265 NA 0.04 Intron <i>PAPDCIA</i> -0.34 641E-07 11 14338703 rs61883963 0.06 Intron <i>RAS2</i> -0.26 5.19E-07 11 14338703 rs61883963 0.05 Intron <i>RAS2</i> -0.26 5.19E-07 11 14338703 rs142548 0.03 Intron <i>RALGP20</i> <td< td=""><td>7</td><td>25161602</td><td>rs1861525</td><td>0.03</td><td>3' UTR</td><td>CYCS</td><td>-0.25</td><td>1.67E-07</td></td<>	7	25161602	rs1861525	0.03	3' UTR	CYCS	-0.25	1.67E-07
7 43377276 rs1172199 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 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 11 14224346 rs118048115 0.04 Intron PAPDC1A -0.31 6.01E-07 11 14328703 rs61883963 0.06 Intron PRAS2 -0.26 5.19E-07 11 14358703 rs61462548 0.05 Intron PSMAI -0.27 1.14E-06 11 12818570 NA 0.06 NA NA -0.16 6.81E-07 11 12848570 rs61444803 0.04 Intron ARHG	7	37365196	rs2392492	0.04	Intron	ELMO1	-0.32	1.15E-06
7 133747946 rs170757 0.04 Intron EXOC4 -0.16 4.76E-07 8 33214265 rs7060219 0.06 Intron CSMD1 -0.26 7.45E-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 5.90E-10 11 14328703 rs6183963 0.06 Intron PAPDCIA -0.34 6.41E-07 11 14338703 rs6183963 0.06 Intron PRAJ2 -0.26 5.90E-11 11 14338703 rs6183963 0.06 Intron PMAI -0.27 1.14E-06 11 1435620 rs3162548 0.05 Intron ARGAP20 -0.16 6.81E-07 11 10499253 rs326946 0.17 Intron ARGAP20 -0.16 6.81E-07 12 94235165 rs61144803 0.04 Intron	7	43377276	rs17172199	0.08	Intron	HECW1	-0.28	1.09E-06
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 11 14224346 rs118048115 0.04 Intron <i>PPADC1A</i> -0.34 6.41E-07 11 14338703 rs61883963 0.06 Intron <i>PRAS2</i> -0.26 5.19E-07 11 14556220 rs34162548 0.05 Intron <i>PSMA1</i> -0.27 114E-06 12 51878760 rs147845115 0.03 Intron <i>SLC4A8</i> -0.29 2.84E-07 11 128185570 NA 0.04 Intron <i>RAHGAP20</i> -0.16 <td>7</td> <td>133747946</td> <td>rs11770757</td> <td>0.04</td> <td>Intron</td> <td>EXOC4</td> <td>-0.16</td> <td>4.76E-07</td>	7	133747946	rs11770757	0.04	Intron	EXOC4	-0.16	4.76E-07
8 53214265 rs7009219 0.06 Intron ST18 -0.16 S.12-07 8 68761014 NA 0.05 NA NA -0.28 8.81E-09 9 132393792 rs483664 0.11 Intron NCSJ -0.21 7.15E-07 10 64635265 NA 0.04 Intron PPAPDCIA -0.34 6.41E-07 11 14224346 rs118048115 0.04 Intron SPONI -0.31 7.00E-11 11 14338703 rs61883963 0.05 Intron SPMAI -0.26 S.19E-07 11 143556220 rs34162548 0.05 Intron SPMAI -0.26 S.19E-07 11 110499253 rs326946 0.17 Intron ARHGAP20 -0.16 6.81E-07 11 12818570 NA 0.03 Intron SLC4A8 -0.29 2.84E-07 12 94235165 rs6114803 0.04 Intron ANO4 -0.2	8	3088173	rs73660619	0.06	Intron	CSMD1	-0.26	7.45E-07
8 68761014 NA 0.05 NA 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 -0.34 6.41E-07 11 14224346 rs118048115 0.04 Intron PPAPDCIA -0.34 6.41E-07 11 14238703 rs61883963 0.05 Intron SPON1 -0.31 7.00E-11 11 1435620 rs34162548 0.05 Intron RAS2 -0.26 5.19E-07 11 1455620 rs326946 0.17 Intron RAR22 -0.16 6.81E-07 11 128185570 NA 0.03 Intron RRAP20 -0.16 6.81E-07 12 94235165 rs147845115 0.03 Intron RRAP20 -0.16 5.02E-08 12 01221239 rs1399439 0.04 Intron CRADD	8	53214265	rs7009219	0.06	Intron	ST18	-0.16	5.12E-07
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 PAPDC1A -0.31 6.41E-07 11 14224346 rs11023139 0.05 Intron <i>RRAS2</i> -0.26 5.19E-07 11 14556220 rs34162548 0.05 Intron <i>RRAS2</i> -0.26 5.19E-07 11 110499253 rs326946 0.17 Intron <i>RRAS2</i> -0.16 6.81E-07 11 110499253 rs326946 0.17 Intron <i>ARIGAP20</i> -0.16 6.81E-07 11 128185570 NA 0.03 NA NA -0.31 8.92E-14 12 94235165 rs61144803 0.04 Intron <i>CRADD</i> -0.16 5.02E-08 12 101221239 rs1399439 0.04 Intron <i>ANO4</i>	8	68761014	NA	0.05	NA	NA	-0.28	8.81E-09
10 64635265 NA 0.04 NA NA NA -0.26 3.90E-10 10 122279476 rs118048115 0.04 Intron PPAPDCIA -0.34 6.41E-07 11 14224346 rs11023139 0.05 Intron PPAND -0.31 7.00E-11 11 14338703 rs61883963 0.06 Intron PSMA1 -0.27 1.14E-06 11 37033930 NA 0.06 NA NA -0.16 6.81E-07 11 10499253 rs326946 0.17 Intron ARHGAP20 -0.16 6.81E-07 11 128185570 NA 0.03 NA NA -0.31 8.92E-14 12 94235165 rs61144803 0.04 Intron CRADD -0.16 5.02E-08 12 101221239 rs1399439 0.04 Intron CRADD -0.24 2.83E-07 13 03945858 rs1393344 0.06 Intron MO4 -0	9	132939792	rs4836694	0.11	Intron	NCS1	-0.21	7.15E-07
10 12279476 rsl18048115 0.04 Intron PPAPCIA -0.34 6.41E-07 11 14224346 rsl1023139 0.05 Intron SPON1 -0.31 7.00E-11 11 14338703 rs01883963 0.06 Intron RRA52 -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-17 11 12185570 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	10	64635265	NA	0.04	NA	NA	-0.26	3.90E-10
11 14224346 rs11023139 0.05 Intron SPONI -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 -0.29 2.84E-07 12 51878760 rs147845115 0.03 Intron SLC4A8 -0.29 2.84E-07 12 101221239 rs1399439 0.04 Intron CRADD -0.16 5.02E-08 13 09473946 rs1393344 0.06 Intron MO4 -0.2 3.51E-07 14 95764564 rs115102486 0.03 Intron GPC6 -0.29 6.73E-08 15 27712644 rs74006954 0.03 Intron	10	122279476	rs118048115	0.04	Intron	PPAPDC1A	-0.34	6.41E-07
11 14338703 rs61883963 0.06 Intron <i>RAS2</i> -0.26 5.19E-07 11 14556220 rs34162548 0.05 Intron <i>PSMA1</i> -0.27 1.14E-06 11 37033930 NA 0.06 NA NA -0.66 8.22E-07 11 110499253 rs326946 0.17 Intron <i>ARHGAP20</i> -0.16 6.81E-07 11 128185570 NA 0.03 NA NA -0.29 2.84E-07 12 94235165 rs61144803 0.04 Intron <i>SIC4A8</i> -0.29 2.84E-07 13 0101221239 rs1399439 0.04 Intron <i>ANO4</i> -0.2 3.51E-07 13 0147548 NA 0.07 NA NA -0.24 2.83E-09 13 019473946 rs17393344 0.06 Intron <i>MYO16</i> -0.26 1.69E-08 14 95764564 rs115102486 0.03 Intron <i>CLMN</i> -0.31 2.28E-08 15 27712644 rs74006954 0.03 Intr	11	14224346	rs11023139	0.05	Intron	SPON1	-0.31	7.00E-11
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 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 14 95764564 rs115102486 0.03 Intron MYO16 -0.31 2.28E-08 15 27712644 rs74006954 0.03 Intron CLMN -0.31 2.28E-08 16 77876763 rs9934540 0.03 Intron <t< td=""><td>11</td><td>14338703</td><td>rs61883963</td><td>0.06</td><td>Intron</td><td>RRAS2</td><td>-0.26</td><td>5.19E-07</td></t<>	11	14338703	rs61883963	0.06	Intron	RRAS2	-0.26	5.19E-07
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19 51422877 NA 0.05 NA NA -0.34 3.00E-10 (Continued	17	59292436	rs72832584	0.05	Intron	BCAS3	-0.3	1.14E-11
(Continued	19	51422877	NA	0.05	NA	NA	-0.34	3.00E-10
(Commuted)								(Continued)

Chromosome	BP*	SNP	MAF^\dagger	SNP type [‡]	Gene	β [§]	P¶
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

Association results for ADAS-cog in ADNI (*Continued*)

Abbreviations: NA, not available; UTR, untranslated region.

NOTE: SNPs in bold were genotyped.

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

[†]Minor allele frequency in ADNI.

[‡]Type of SNP.

[§]Change in ADAS-cog per copy of the minor allele per month with AD, in which positive numbers indicate more rapid decline and negative numbers indicate slower decline.

[¶]*P* value after correction for a genomic inflation factor of 1.079.

Genetics Consortium (ADGC) study, which 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 *P* value less than .05 in the discovery sample. The minor alleles for a SNP in the poliovirus receptor-related 2 gene (*PVLR2*) (rs440277, *P* = .003) were associated with a lower risk of developing AD and a slower rate of decline, as was a SNP in the CD33 antigen gene (*CD33*) (rs1354106, *P* = 0.04). However, in the replication sample, there were three SNPs near the gene gap junction protein, beta 5 (*GJB5*), which were associated with GCOG. The strongest effect was from rs12048230 (*P* = 1.9×10^{-7}) and was associated with a slower rate of decline and lower risk of AD in the ADGC samples.

4. 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. Although the sample size was small, several intriguing candidate genes were identified. The most interesting candidate gene we identified is SPON1, because variants were significantly associated in the 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) [25] Although all of the common (MAF > 3%) associated SNPs in SPON1 are intronic, there is a rare (MAF = 1%) missense mutation that is strongly associated with rate of decline. The most significantly associated SNP in the gene was also associated (much less significantly) with slower rate of decline in the RAVLT (P = .008) and the MMSE (P = .003), and the same SNP was associated with a slower rate of A β -40 (but not A β -42) accumulation in CSF (P = .001).

Several of the other significant association results are in genes with functions relevant to neuronal maintenance and neurotransmission, including exocyst complex component 4 (*EXOC4*), gamma-aminobutyric acid receptor gamma-3 (*GABRG3*), and vesicle amine transport protein 1 homolog (*VAT1L*), and many involved in calcium signaling and

homeostasis, including calcium/calmodulin-dependent protein kinase IV (*CAMK4*), neuronal calcium sensor 1 (*NCS1*), and voltage-dependent calcium channel alpha 1G subunit (*CACNA1G*). Other notable candidates for association with variable rate of decline in AD patients are involved in neuronal apoptosis signaling, including engulfment and cell motility protein 1 (*ELMO1*) and somatic cytochrome C (*CYCS*), whereas hepatic lipase (*LIPC*) [26] and oxysterol binding protein-like 7 (*OSBPL7*) are involved in lipid homeostasis [26].

Our results require confirmation in larger datasets, but they 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 because the ADAS-Cog and the GCOG incorporate measures on various 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 subunit of protein phosphatase B (*PPP3R1*) that was not associated with risk for AD or age at onset, but it was associated with rate of decline as measured by the Clinical Dementia Rating Sum of Boxes (CDR-SB) and 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,

Table 2

one the zinc finger protein 224 gene (*ZNF224*) and one in the gene encoding phosphoenolpyruvate carboxykinase (*PCK1*) [11]. Examining these three SNPs, we found a trend toward association with ADAS-cog for rs1868402 (P = .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 Aβ-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 toward replication in this analysis substantially increases the evidence that *PPP3R1* variants may mediate AD progression through pathways related to ptau₁₈₁. In the study presented here, there was also a trend toward association with rs3746319 (P = .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 *SPON1*, which may contain variants of which minor alleles slow disease progression by lowering the amount of extracellular Aβ-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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RESEARCH IN CONTEXT

- 1. Systematic review: The authors have directly participated in several studies and consortia dealing with the cognitive decline associated with AD and normal aging. As such, they have direct knowledge of and participation in much of the previous body of research on cognitive change. They also conducted a thorough literature search to identify other projects with similar goals.
- 2. Interpretation: This research represents the first GWAS to search for genetic variants affecting disease trajectory in AD cases. Previous efforts have included a mixture of cognitively normal participants, AD cases, and individuals with non-AD dementias. As such, this research has provided the first evidence that novel genetic variants (not variants previously associated with AD risk in general) contribute to the variability in disease trajectory.
- 3. Future directions: This project was done in a relatively small sample of AD cases; thus, the results must be considered as preliminary. However, we have learned valuable lessons about cognitive testing and the genetic architecture of AD-associated decline, and efforts are currently underway to conduct these analyses in much larger samples and to better harmonize the various cognitive tests used across datasets. In the future, we hope to identify novel biological pathways involved in AD progression and potential treatment targets within those pathways.

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