An Exploration of the Relationship Between Genetic Variants Associated with Alzheimer's Disease and Measurements of Cognitive Processes Over Time

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Abstract

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Late-onset Alzheimer's Disease (LOAD) has been associated with more than twenty genetic susceptibility loci, to date. The present analysis builds on the work of the Alzheimer's Disease Genetics Consortium (ADGC), the Alzheimer's Disease Research Centers (ADRCs), and the National Alzheimer's Coordinating Center (NACC) by attempting to determine whether two of those loci, *MS4A6A* and *BIN1*, are associated with rate of symptom progression. Participants who had visited the clinic at least five times and who were classified as either cases or as having mild cognitive impairment (MCI) were stratified by the presence or absence of *APOE* E4 alleles and by their cognitive status at their initial clinic visit. Six clinical outcomes, including 1) rate of change from visit to visit of the sum of boxes of the CDR® Dementia Staging Instrument, 2) rate of change from visit to visit of scores on the Mini-Mental State Examination (MMSE), 3) mode

of onset of behavioral symptoms, 4) mode of onset of cognitive symptoms, 5) mode of onset of motor symptoms, and 6) overall course of decline were regressed on genetic variants within *MS4A6A* and *BIN1*, using genetic data stored in the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS). Four of the five variants within *MS4A6A* were significantly associated with rate of change of MMSE score for individuals with normal initial cognition and no *APOE* E4 alleles. Although a few other models did achieve significance at an alpha level of 0.05, the number of significant results is no higher than what would be expected simply from random chance. Therefore, it can be tentatively concluded that there is a relationship between *MS4A6A* and rate of change in MMSE scores.

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Background

Discovery

In the earliest part of the 20th century, Dr. Alois Alzheimer treated a female patient who was experiencing memory loss, difficulties with language, and unpredictable behavior. Upon her death, Dr. Alzheimer performed an autopsy that revealed the hallmark amyloid plaques and neurofibrillary tangles that are associated with what is now known as Alzheimer's Disease (AD; National Institute on Aging [NIA], 2019).

Basic Statistics

According to the Centers for Disease Control and Prevention (CDC), approximately 5 million Americans had been diagnosed with AD in 2014. In 2060, this number is projected to be as high as 14 million. AD is the 6th leading cause of death for U.S. adults and the 5th leading cause of death for U.S. adults aged 65 or older. Age is the best known risk factor for AD, and symptoms typically begin with memory loss (Centers for Disease Control and Prevention [CDC], 2019).

AD Neuropathological Changes and Measurement

AD is characterized by three neuropathological changes: amyloid beta (Aβ) deposits, neurofibrillary tangles (NFTs), and neuritic plaques. Aβ is formed when amyloid precursor protein (APP) is cleaved first by β-site APP-cleaving enzyme 1 (BACE1 or β-secretase) and then by γ-secretase. Aβ can exist as different species of varying lengths, depending on where it is cleaved, and it is the version of Aβ that has been cleaved at position 42, Aβ42, that is prone to aggregation. In 2012, the National Institute on Aging-Alzheimer's Association (NIA-AA) put forth standardized guidelines for the evaluation of AD neuropathological changes. They recommend the use of the "ABC score." The "A" of the ABC score is an evaluation of Aβ

plaques through a modified version of the Thal et al. (2002) phasing method (Hyman et al., 2012; Montine et al., 2012).

The Thal et al. (2002) method breaks down Aβ pathology into five phases. In phase one, deposits can only be found in the neocortex. In phase two, in addition to the neocortex, deposits can be found in the allocortical regions. In phase three, deposits can also be found in the putamen, caudate nucleus, substantia innominate, magnocellular cholinergic nuclei of the basal forebrain, and diencephalic nuclei. In phase four, deposits can also be found in brainstem nuclei. In phase five, deposits can also be found in the cerebellum (Thal et al., 2002). In the modified version of this phasing method, the absence of Aβ/amyloid plaques is scored as A0, while Thal phases 1 and 2 are scored as A1, Thal phase 3 is scored as A2, and Thal phases 4 and 5 are scored as A3.. The preferred method for Aβ plaque measurement is immunohistochemistry for Aβ (Hyman et al., 2012; Montine et al., 2012; Thal et al., 2002).

NFTs are intraneuronal deposits of hyperphosphorylated tau (Hyman et al., 2012; Montine et al., 2012). Tau is an axonal protein that contributes to the stability of microtubules by attaching to microtubule-binding domains (Blennow, de Leon, & Zetterberg, 2006). The “B” of the ABC score is an evaluation of NFTs through a modified version of the Braak and Braak (1991) staging method (Hyman et al., 2012; Montine et al., 2012).

The Braak and Braak (1991) method breaks down NFTs into six stages. In stages one and two (transentorhinal stages), patients have either mild or severe changes of the transentorhinal layer. In stages three and four (limbic stages), both the transentorhinal region and entorhinal cortex are affected. Stages five and six (isocortical stages) are characterized by isocortical destruction (Braak and Braak, 1991). In the modified version of this staging method, the absence of NFTs is scored as B0, while Braak stages 1 and 2 are scored as B1, Braak stages 3 and 4 are

scored as B2, and Braak stages 5 and 6 are scored as B3. The preferred method for NFTs is immunohistochemistry for either tau or phospho-tau (Braak and Braak, 1991; Hyman et al., 2012; Montine et al., 2012).

Neuritic plaques are mature Aβ plaques. They often have phospho-tau immunoreactivity and are thought to be indicative of neuronal injury (Hyman et al., 2012; Montine et al., 2012). The "C" of the ABC score is an evaluation of neuritic plaques through a modified version of the Consortium to Establish a Registry for Alzheimer's disease (CERAD) scoring method. The modified version of this scoring method uses only the step that involves characterizing the "frequency" of the plaques. An absence of neuritic plaques is scored as C0, sparse plaques are scored as C1, moderate plaques are scored as C2, and frequent plaques are scored as C3. The preferred method for neuritic plaque measurement is thioflavin S or modified Bielschowky (Hyman et al., 2012; Mirra et al., 1991; Montine et al., 2012).

Each sample is assigned an A, B, and C score that ranges from 0 to 3. These scores are then used to produce a level of AD neuropathological change -- either not, low, intermediate, or high. It is impossible for a patient's level of AD neuropathological change to be anything other than "not" without the presence of Aβ pathology. In the presence of Aβ pathology but the absence of tau pathology, their level can be no higher than "low." In patients who were experiencing dementia, intermediate and high levels are sufficient to attribute their dementia to their neuropathological changes (Hyman et al., 2012; Montine et al., 2012).

Biomarkers for AD Neuropathological Changes

The ABC scoring method is intended for use in tissue samples, which means that it is often used during autopsy (Hyman et al., 2012; Montine et al., 2012). In 2018, the NIA-AA published standardized guidelines on the use of biomarkers as proxies for AD neuropathological

changes through the use of the "AT(N)" classification system. The "A" of the AT(N) system is an evaluation of Aβ plaques, which can be measured either through cortical amyloid positron emission tomography (PET) ligand binding or through the measurement of Aβ42 (or the ratio of Aβ42 to Aβ40) in the cerebrospinal fluid (CSF; Jack et al., 2018).

The "T" of the AT(N) system is an evaluation of NFTs, which can be measured either through cortical tau PET ligand binding or through the measurement of phosphorylated tau in CSF (Jack et al., 2018).

The "N" of the AT(N) system is meant to evaluate neurodegeneration or neuronal injury, which can be measured through CSF total tau, fluorodeoxyglucose (FDG) PET hypometabolism, or atrophy as measured by magnetic resonance imaging (MRI). Neurodegeneration/neuronal injury are not specific to AD but may add important predictive information about cognitive decline (Jack et al., 2018).

Cognitive Staging

The NIA-AA's 2018 guidelines also laid out two cognitive staging methods: numeric and syndromal. Syndromal staging can be used regardless of the person's AT(N) biomarker profile, but numeric staging is meant only for those individuals determined by their biomarkers to be on the "Alzheimer's continuum." Syndromal cognitive staging classifies a person as either cognitively unimpaired, as having mild cognitive impairment (MCI), or as having dementia (which is then rated as either mild, moderate, or severe). A cognitively unimpaired person's cognitive performance falls within the expected range for that person. A person with MCI displays cognitive performance below the expected range for that person, and they must also display a decline in cognitive performance from their baseline. They are expected to still be able to perform daily tasks without assistance but may require assistance for more complex tasks. A

person with dementia displays a significant cognitive decline as well as deficits in social/occupational functioning and must have assistance with activities of daily living (Jack et al., 2018).

The numeric cognitive staging system contains six stages. Stage 1 represents no cognitive impairment and no cognitive decline. Individuals in stage 2 should have a decline from baseline cognitive function but will still perform within the expected range on cognitive tests. Their decline should have no impact on their daily tasks. Stage 3 is characterized by a decline in cognitive function from baseline and cognitive test results below the expected range. Individuals in stage 3 should be able to perform daily tasks without assistance but may need help with more complex activities. Stage 4 is the equivalent of mild dementia and is characterized by significant, progressive cognitive decline and the need for some assistance with daily tasks. Stage 5 is the equivalent of moderate dementia and is characterized by significant, progressive cognitive decline and the need for frequent assistance with daily tasks. Stage 6 is the equivalent of severe dementia and is characterized by significant, progressive cognitive decline and the need for assistance with all tasks, including self-care (Jack et al., 2018).

Biomarker Profiles with Cognitive Staging

The combination of a person's AT(N) biomarker profile and their cognitive staging can help to determine their diagnosis. A person must have Aβ pathology to be on the Alzheimer's continuum. If they have Aβ pathology without tau pathology, they are said to have an Alzheimer's pathologic change. A cognitively unimpaired person would be considered "preclinical" if they have Aβ pathology with or without tau pathology. However, if they have Aβ pathology without tau pathology but also have biomarkers indicative of neurodegeneration or neuronal injury, they are said to have both an Alzheimer's pathologic change and a suspected

non-Alzheimer's pathologic change with either dementia, MCI, or no cognitive impairment. A person with both Aβ pathology and tau pathology can be said to have AD with either no cognitive impairment, MCI, or dementia (Jack et al., 2018).

Blood Biomarkers

It can be difficult and expensive to measure a patient's AD neuropathological changes with CSF sampling and PET scanning. The ability to measure AD neuropathological changes through blood sampling would increase accessibility and decrease cost considerably. Recent findings have illustrated that the plasma Aβ42/40 ratio, when measured by immunoprecipitation mass spectrometry or ultrasensitive enzyme-linked immunosorbent assays, mirrors the Aβ in the brain (Zetterberg & Bendlin, 2020). However, because the Aβ42/40 ratio is only reduced by around 14-20% in plasma (compared to 50% in CSF), it could be difficult to make use of this test in clinical laboratory practice. Fortunately, there is also evidence that plasma P-tau could actually be used as a screening blood test in the primary care setting and that plasma P-tau181 is sensitive to both Aβ and tau pathology. This means that it also has the potential to be used in treatment research (Zetterberg & Blennow, 2020). Neurofilament light, an axonal protein, has also shown promise in research on plasma biomarkers, but it is not specific to AD and is rather a general measure of neurodegeneration (Blennow & Zetterberg, 2018). The downside to the use of blood biomarkers is the inability to get information about anatomy, which means that blood biomarkers will likely not replace CSF sampling and PET scanning entirely but will rather be used as a screening tool and in the research setting (Zetterberg & Blennow, 2020).

Other Neurological Conditions

AD neuropathological changes can exist on their own but commonly occur alongside and may "interact" with or be additive to neuropathological changes associated with other diseases

such as cerebrovascular disease (CVD), vascular brain injury (VBI), hippocampal sclerosis (HS), frontotemporal lobar degeneration (FTLD), and Lewy Body Disease (LBD), a group of diseases that includes Parkinson's disease and dementia with Lewy Bodies (DLB; Hyman et al., 2012; Montine et al., 2012). Some researchers have recommended that vascular dysfunction be added to the AT(N) biomarker system, due to its common occurrence alongside AD (Sweeney et al., 2019).

Subtypes of Alzheimer's Disease

AD can be divided into two subtypes: familial (early-onset) and sporadic (late-onset). Familial AD (FAD) has been shown to be associated with autosomal dominant variants in genes *APP*, *PSEN1*, and *PSEN2*. These variants are essentially 100% penetrant. FAD makes up only around 10% of all AD cases. Most AD patients are sporadic cases, with symptoms beginning in their mid-60s (Jack et al., 2018; NIA, 2019). A considerable amount of work is also being done in the realm of FAD though. The Dominantly Inherited Alzheimer Network (DIAN) Observational Study has been supported by the NIA since 2008 and is meant to become a database on the subject so as to learn more about relevant biomarkers that may eventually help lead to treatment research (Dominantly Inherited Alzheimer Network, n.d.).

Late-Onset Alzheimer's Disease and APOE

It has been well-established that late-onset AD (LOAD) is associated with the *APOE* gene. There are three alleles possible: *APOE* E2, E3, and E4. The most common genotype is comprised of two copies of the E3 allele, which is thought to be neutral for AD risk and is therefore the reference allele for comparison purposes. Each additional copy of the *APOE* E4 allele is associated with higher risk of LOAD and younger age of onset (Reiman et al., 2020).

Treatment Attempts

There are medications on the market that are meant to treat some of the symptoms of AD, but none of them yet are disease modifying (i.e., affecting amyloid, tau, or neurodegeneration). Clinical trials often target Aβ plaques but have been largely unsuccessful at improving cognitive symptoms. There are a few reasons why this might be the case including the thoughts that failed clinical trials have enrolled patients whose disease has already progressed to too advanced a stage or that they have enrolled patients whose diagnosis was based solely on clinical criteria. Because of this, it is possible that participants categorized as controls may actually have Aβ or tau deposits and that participants categorized as cases may actually be showing symptoms due to a different neurological condition. This kind of misclassification could dramatically influence results of clinical trials. Additionally, it could also be true that the success in preclinical trials with mice simply doesn't translate to humans, since, for example, transgenic mice make "human" amyloid, which is foreign to the mouse itself and may not be an accurate representation of the disease (NIA, 2019; Blennow et al., 2015).

Recent Genetic Research on AD

Relevant Organizations

There are several important organizations that aim to build upon what is known about AD. The National Alzheimer's Coordinating Center (NACC) was established by the National Institute on Aging (NIA) in 1999 and coordinates the work of the Alzheimer's Disease Research Centers (ADRCs). The ADRCs were established in 1984 and are responsible for conducting annual clinic visits. The NACC also partners with the Alzheimer's Disease Genetics Consortium (ADGC), which has a five-year $18.3 million grant from the NIA for LOAD genome-wide

association study (GWAS) research (Alzheimer's Disease Genetics Consortium [ADGC], n.d.; NIA, n.d.-a; NIA, n.d.-b).

Relevant Studies

GWAS 1. One such publication to come out of the ADGC is a GWAS from 2011. Researchers used a three-stage design, an additive model, and adjusted for population substructure, age, sex, and number of *APOE* E4 alleles. Stages one and two used both meta-analysis and joint analysis methods, and stage three used meta-analysis methods only. The researchers were able to confirm four previous associations, *BIN1*, *CR1*, *CLU*, and *PICALM*. They also found significant associations with the *MS4A* gene cluster, *CD2AP*, *EPHA1*, and *CD33*. The researchers noted what they referred to as "suggestive evidence" of an association at *ABCA7*. Including *APOE*, this brought the total number of LOAD susceptibility loci to ten. The researchers posited that there were likely still many undetected risk alleles with small effect sizes for LOAD. They also noted that their work did not account for any interaction between the loci and that their results may not be generalizable as they did not use population-based samples (Naj et al., 2011).

GWAS 2. Another even more recent study to come out of the ADGC is a meta-analysis from 2019. Kunkle et al. (2019) also used a three-stage design with meta-analysis methods. The researchers were able to confirm twenty previous associations including *CR1*, *BIN1*, *INPP5D*, *HLA-DRB1*, *TREM2*, *CD2AP*, *NYAP1*, *EPHA1*, *PTK2B*, *CLU*, *ECHDC3*, *SPI1*, *MS4A2*, *PICALM*, *SORL1*, *FERMT2*, *SLC24A4*, *ABCA7*, *APOE*, and *CASS4*. They also discovered associations with five new loci including *IQCK*, *ACE*, *ADAM10*, *ADAMTS1*, and *WWOX* (Kunkle et al., 2019).

Kunkle et al. (2019) also followed up on their results by doing functional analysis, expression analysis, and pathway analysis. They considered all protein-coding genes within plus or minus 500 kb of the sentinel variants' linkage disequilibrium regions, which gave them a sample of 400 genes. They scored these genes based on a number of criteria related to their functional, expression, and pathway analyses (e.g., LOAD tissue expression).

Their pathway analysis led to four significant functional clusters for common variants including 1) APP metabolism/Aβ formation, 2) tau protein binding, 3) lipid metabolism, and 4) immune response. The pathway analysis also led to two nominally significant function clusters for rare variants including 1) APP metabolism/AB formation and 2) lipid metabolism. They noted that common and rare variants were highly significantly correlated. This was an especially interesting finding because it demonstrated that APP metabolism is not just associated with FAD (Kunkle et al., 2019).

Limitations of GWASs

There are many potential limitations and potential issues that may arise when conducting a GWAS, including undetected population substructure and the inability to detect both common and rare variants in any given study. Additionally, signals that are detected during a GWAS typically fall within an intergenic region and then are attributed to the nearest gene. GWASs are more successful when they focus on a well-described phenotype. It could be argued that this is difficult with AD, given how common it is to see Alzheimer's neuropathological changes alongside neuropathological changes associated with other neurological conditions. Also, most GWASs to date have enrolled subjects only of European ancestry, which is problematic and leads to a lack of generalizability. If no follow-up is conducted on variants identified through a GWAS, the GWAS can only be viewed as a hypothesis-generating tool (Kunkle et al., 2019;

Marchini et al., 2004; Naj et al., 2011; Patterson et al., 2006; Rosenberg et al., 2010; Young 2019).

Present Analysis

Research Question

The goal of the present analysis was to explore whether any of the genetic variants that had previously been identified as associated with AD at a level of genome-wide significance are associated with rate of symptom progression. This analysis was conducted through the use of clinical data from the NACC and genetic data from the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS). The analysis plan was reviewed by the University of Washington IRB.

Clinical Outcomes

BEMODE. "BEMODE" refers to the mode of onset of behavioral symptoms, as judged by a clinician. Potential answers include 0 (no behavioral symptoms), 1 (gradual), 2 (subacute), 3 (abrupt), 4 (other), and 99 (unknown). In the present analysis, only participants with scores of 0-3 were included, and the value from their fifth clinic visit was utilized (Beekly et al., 2007; Besser et al., 2018).

COGMODE. "COGMODE" refers to the mode of onset of cognitive symptoms, as judged by a clinician. Potential answers include 0 (no impairment in cognition), 1 (gradual), 2 (subacute), 3 (abrupt), 4 (other), and 99 (unknown). In the present analysis, only participants with scores of 0-3 were included, and the value from their fifth clinic visit was utilized (Beekly et al., 2007; Besser et al., 2018).

MOMODE. "MOMODE" refers to the mode of onset of motor symptoms, as judged by a clinician. Potential answers include 0 (no motor symptoms), 1 (gradual), 2 (subacute), 3

(abrupt), 4 (other), and 99 (unknown). In the present analysis, only participants with scores of 0-3 were included, and the value from their fifth clinic visit was utilized (Beekly et al., 2007; Besser et al., 2018).

COURSE. "COURSE" refers to the overall course of a participant's decline, including cognitive, behavioral, and motor symptoms. Potential answers include 1 (gradually progressive), 2 (stepwise), 3 (static), 4 (fluctuating), 5 (improved), 8 (not applicable), and 9 (unknown). In the present analysis, only participants with scores of 1-5 were included, and the value from their fifth clinic visit was utilized (Beekly et al., 2007; Besser et al., 2018).

CDRSUM. "CDRSUM" refers to the sum of boxes from the CDR® Dementia Staging Instrument. This sum includes the following domains: memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. Each domain has possible scores of 0.0 (no impairment), 0.5 (questionable impairment), 1.0 (mild impairment), 2.0 (moderate impairment), and 3.0 (severe impairment), with the exception of the personal care domain which can only be recorded as 0.0, 1.0, 2.0, or 3.0. The sum of these domains can result in scores of 0-18, increasing in increments of 0.5. Scores of 16.5 and 17.5 are not possible (Beekly et al., 2007; Besser et al., 2018). In the present analysis, CDRSUM was assessed longitudinally by utilizing an average of the difference in CDRSUM score from each visit to the next for each participant's first five visits.

NACCMMSE. "NACCMMSE" refers to the total score earned on the Mini-Mental State Examination (MMSE). Possible scores include 0-30, 88 (score not calculated; missing at least one MMSE item), 95 (physical problem), 96 (cognitive/behavior problem), 97 (other problem), 98 (verbal refusal), and -4 (not available; Beekly et al., 2007; Besser et al., 2018). In the present analysis, only scores of 0-30 were included. MMSE was assessed longitudinally by utilizing an

average of the difference in MMSE score from visit to visit using the first visit and the fifth visit for each participant. The participants' initial MMSE score was considered as a covariate so as to account for the amount of possible decline. Additionally, because the MMSE was replaced by the Montreal Cognitive Assessment (MoCA) in 2015, a converted MoCA score was used for participants who were missing a fifth visit MMSE score but had a fifth visit MoCA score. This conversion from MoCA to MMSE was calculated using the Crosswalk Study (Monsell et al., 2016).

Genetic Data

ADC 1 and 2 were both genotyped using Illumina 660, while ADC3, ADC4, ADC5, and ADC6 were genotyped using Illumina OmniExpress. ADC7 was genotyped using the Infinium HumanOmniExpressExome BeadChip (Kunkle et al., 2019; Naj et al., 2011; NIAGADS, 2018). Genes of interest were selected using the work of Kunkle et al. (2019). *MS4A6A*, a member of the *MS4A* gene cluster, and *BIN1*, a gene thought to be associated with tau pathology, were selected. An initial analysis was also conducted using *APOE* as an exercise in learning how to work with the data and run the analyses.

Covariates

Strata. Participants were divided into four strata, based on two variables, *APOE* genotype and cognitive status at initial clinic visit. For *APOE* genotype, participants were divided by the presence or absence of any *APOE* E4 alleles. For cognitive status at initial clinic visit, participants were categorized as "normal" if they had a Global CDR® score of 0 and "abnormal" if they had a Global CDR® score above 0. Possible Global CDR® scores include 0 (no impairment), 0.5 (questionable impairment), 1.0 (mild impairment), 2.0 (moderate impairment), and 3.0 (severe impairment; Beekly et al., 2007; Besser et al., 2018).

Demographics. Covariates to potentially be included in adjusted models included sex, age, race, ethnicity, and years of education.

Analysis Methods

Initial filtering. Using PLINK, the NIAGADS genotypic data was filtered so as to only include those participants who had visited the clinic at least five times. Using Microsoft Excel, the NIAGADS genotypic data was then filtered so as to only include those participants who had been identified as cases or as having MCI.

Calculation of average changes. Using Microsoft Excel, the average difference in scores from the first visit to the fifth visit for both the sum of boxes of the CDR® Dementia Staging Instrument and for MMSE was calculated. Participants with missing data were excluded from the analysis.

Identification of variants. Using Microsoft Excel, variants within each gene were selected based on positions from the University of California Santa Cruz (UCSC) Genome Browser. This resulted in eight variants within *BIN1* and five variants within *MS4A6A*.

Stratification and regression. Using R, participants were divided into one of four strata based on the presence or absence of *APOE* E4 alleles and their cognitive status at their initial clinic visit (normal or abnormal). Using the lm() function from the stats v3.6.2 package, a simple linear regression was run for each clinical outcome and each genetic variant within each stratum. Simple linear regressions which reached significance at an alpha level of 0.05 were reanalyzed as multiple linear regression models with the inclusion of potential covariates.

Adjustments. Simple linear regression models that reached significance at an alpha level of 0.05 were reanalyzed as multiple linear regression models with the inclusion of potential covariates. Potential covariates which reached significance at an alpha level of 0.05 were

included in the final models, while those that did not achieve significance were ultimately not included.

Unadjusted Results

MS4A6A. Of the 120 tests conducted for *MS4A6A*, six reached significance at an alpha level of 0.05. These included 1) a regression of BEMODE on rs4939352 for individuals with normal initial cognition and no *APOE* E4 alleles (p = 0.0342), 2) a regression of COURSE on rs4939352 for individuals with abnormal initial cognition and at least one *APOE* E4 allele (p = 0.03255), 3) a regression of MMSE on rs4939352 for individuals with normal initial cognition and no *APOE* E4 alleles (p = 0.0006355), 4) a regression of MMSE on rs4938941 for individuals with normal initial cognition and no *APOE* E4 alleles (p = 0.02436), 5) a regression of MMSE on rs7926219 for individuals with normal initial cognition and no *APOE* E4 alleles (p = 0.01589), and 6) a regression of MMSE on rs1443241 for individuals with normal initial cognition and no *APOE* E4 alleles (p = 0.001218). Full unadjusted results for *MS4A6A* can be found in Appendix A.

BIN1. Of the 192 tests conducted for *BIN1*, three reached significance at an alpha level of 0.05. These included 1) a regression of COGMODE on rs360390 for individuals with abnormal initial cognition and no *APOE* E4 alleles (p = 0.004228), 2) a regression of MOMODE on rs360263 for individuals with abnormal initial cognition and at least one *APOE* E4 allele (p = 0.04969), and 3) a regression of CDRSUM on rs360314 for individuals with abnormal initial cognition and no *APOE* E4 alleles (p = 0.02049). Full unadjusted results for *BIN1* can be found in Appendix B.

Covariate-Adjusted Models

Each simple linear regression model that reached significance in the unadjusted stage was re-run with all potential covariates, including sex, race, ethnicity, age, and years of education. Additionally, initial MMSE score was included as a potential covariate when MMSE was the outcome of interest. Covariates that reached significance at an alpha level of 0.05 were included in the final models. All of the models that reached significance in the unadjusted phase remained significant after the inclusion of covariates. Final adjusted models for *MS4A6A* and *BIN1* can be found in Appendix C and Appendix D, respectively.

Conclusions

Although a few models achieved significance for *BIN1*, the number of significant results is no higher than what would be expected simply from random chance. Because of this, there is no evidence to suggest that rate of change in the sum of boxes of the CDR® Dementia Staging Instrument scores over time, rate of change in MMSE scores over time, mode of onset of behavioral, cognitive, or motor symptoms, or overall course of decline are associated with variants within *BIN1*.

Because four of the five variants within *MS4A6A* for the stratum in which participants had normal initial cognition and no *APOE* E4 alleles were significantly associated with rate of change in MMSE scores over time, it can be tentatively concluded that there is a relationship between *MS4A6A* and rate of change in MMSE scores. Further research is needed to confirm this result.

There is no evidence to suggest that rate of change in the sum of boxes of the CDR® Dementia Staging Instrument scores over time, mode of onset of behavioral, cognitive, or motor symptoms, or overall course of decline are associated with variants within *MS4A6A*.

Limitations and Future Research

There are several relevant limitations to this analysis. First, this work builds upon GWASs, which come with their own set of limitations, as mentioned earlier. Second, it could be argued that the clinical outcomes which relied upon clinician judgment contain a certain level of subjectivity. Third, rate of change from visit to visit for any given cognitive test as a look into symptom progression and the analysis methods used here are based on the assumption that symptom progression happens linearly, which is likely an oversimplification. Future research should utilize the values from each of the first five visits to fit a linear regression in order to analyze the slope of the regression lines. Fourth, although this analysis made attempts to control for the age and initial cognitive status of the participants, there is no way to know at what point in their disease the participant joined the study. Further study may be needed to control for specific neuropathological changes. Fifth, sample sizes for some of the analyses were too small to draw meaningful conclusions, as they were likely underpowered. Lastly, because participants who did not have MMSE, MoCA, or CDR® Dementia Staging Instrument sum scores available for their first five visits were excluded, it is possible that selection bias occurred, which would obscure meaningful conclusions about those participants with missing data. Further research should also be done with other variants within the *MS4A* gene cluster to validate this result, and there is much work still to be done with the other LOAD susceptibility loci.

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Appendix A

Unadjusted Results for MS4A6A

Dataset	SNP	Chr	Position	N	Init.Cog. Stat.	APOE E4	Outcome	β	P-value
ADC3-7	rs4939352	11	60,173,107	117	Normal	Present	BEMODE	-0.05	0.4987
ADC3-7	rs4938941	11	60,173,360	117	Normal	Present	BEMODE	-0.02	0.7436
ADC3-7	rs7950677	11	60,179,489	117	Normal	Present	BEMODE	-0.15	0.2887
ADC3-7	rs7926219	11	60,180,335	117	Normal	Present	BEMODE	-0.01	0.8326
ADC3-7	rs1443241	11	60,181,627	117	Normal	Present	BEMODE	-0.02	0.7814
ADC3-7	rs4939352	11	60,173,107	419	Abnormal	Present	BEMODE	0.05	0.1451
ADC3-7	rs4938941	11	60,173,360	419	Abnormal	Present	BEMODE	0.06	0.08053
ADC3-7	rs7950677	11	60,179,489	419	Abnormal	Present	BEMODE	-0.08	0.2613
ADC3-7	rs7926219	11	60,180,335	419	Abnormal	Present	BEMODE	0.05	0.1438
ADC3-7	rs1443241	11	60,181,627	419	Abnormal	Present	BEMODE	0.05	0.1817
ADC3-7	rs4939352	11	60,173,107	245	Normal	Absent	BEMODE	0.09	0.0342
ADC3-7	rs4938941	11	60,173,360	245	Normal	Absent	BEMODE	0.06	0.1419
ADC3-7	rs7950677	11	60,179,489	245	Normal	Absent	BEMODE	-0.03	0.6567
ADC3-7	rs7926219	11	60,180,335	245	Normal	Absent	BEMODE	0.04	0.3036
ADC3-7	rs1443241	11	60,181,627	245	Normal	Absent	BEMODE	0.08	0.0635
ADC3-7	rs4939352	11	60,173,107	318	Abnormal	Absent	BEMODE	-0.01	0.8542
ADC3-7	rs4938941	11	60,173,360	318	Abnormal	Absent	BEMODE	0.02	0.6124
ADC3-7	rs7950677	11	60,179,489	318	Abnormal	Absent	BEMODE	0.17	0.05149
ADC3-7	rs7926219	11	60,180,335	318	Abnormal	Absent	BEMODE	0.04	0.375
ADC3-7	rs1443241	11	60,181,627	318	Abnormal	Absent	BEMODE	-0.02	0.6971
ADC3-7	rs4939352	11	60,173,107	116	Normal	Present	COGMODE	-0.09	0.277
ADC3-7	rs4938941	11	60,173,360	116	Normal	Present	COGMODE	-0.06	0.4092
ADC3-7	rs7950677	11	60,179,489	116	Normal	Present	COGMODE	0.04	0.7748
ADC3-7	rs7926219	11	60,180,335	116	Normal	Present	COGMODE	-0.01	0.8955
ADC3-7	rs1443241	11	60,181,627	116	Normal	Present	COGMODE	-0.05	0.5526
ADC3-7	rs4939352	11	60,173,107	426	Abnormal	Present	COGMODE	0.002	0.8839

ADC3-7	rs4938941	11	60,173,360	426	Abnormal	Present	COGMODE	0.001	0.9451
ADC3-7	rs7950677	11	60,179,489	426	Abnormal	Present	COGMODE	-0.01	0.7658
ADC3-7	rs7926219	11	60,180,335	426	Abnormal	Present	COGMODE	0.002	0.894
ADC3-7	rs1443241	11	60,181,627	426	Abnormal	Present	COGMODE	0.004	0.7721
ADC3-7	rs4939352	11	60,173,107	247	Normal	Absent	COGMODE	0.09	0.06439
ADC3-7	rs4938941	11	60,173,360	247	Normal	Absent	COGMODE	0.06	0.2004
ADC3-7	rs7950677	11	60,179,489	247	Normal	Absent	COGMODE	0.06	0.5122
ADC3-7	rs7926219	11	60,180,335	247	Normal	Absent	COGMODE	0.08	0.1141
ADC3-7	rs1443241	11	60,181,627	247	Normal	Absent	COGMODE	0.09	0.08226
ADC3-7	rs4939352	11	60,173,107	322	Abnormal	Absent	COGMODE	-0.03	0.3489
ADC3-7	rs4938941	11	60,173,360	322	Abnormal	Absent	COGMODE	-0.01	0.7754
ADC3-7	rs7950677	11	60,179,489	322	Abnormal	Absent	COGMODE	0.02	0.6991
ADC3-7	rs7926219	11	60,180,335	322	Abnormal	Absent	COGMODE	-0.01	0.6039
ADC3-7	rs1443241	11	60,181,627	322	Abnormal	Absent	COGMODE	-0.04	0.189
ADC3-7	rs4939352	11	60,173,107	115	Normal	Present	MOMODE	0.06	0.2666
ADC3-7	rs4938941	11	60,173,360	115	Normal	Present	MOMODE	0.06	0.225
ADC3-7	rs7950677	11	60,179,489	115	Normal	Present	MOMODE	-0.13	0.2485
ADC3-7	rs7926219	11	60,180,335	115	Normal	Present	MOMODE	0.05	0.2832
ADC3-7	rs1443241	11	60,181,627	115	Normal	Present	MOMODE	0.07	0.1752
ADC3-7	rs4939352	11	60,173,107	419	Abnormal	Present	MOMODE	-0.03	0.4864
ADC3-7	rs4938941	11	60,173,360	419	Abnormal	Present	MOMODE	-0.01	0.7305
ADC3-7	rs7950677	11	60,179,489	419	Abnormal	Present	MOMODE	0.1	0.1966
ADC3-7	rs7926219	11	60,180,335	419	Abnormal	Present	MOMODE	-0.02	0.5436
ADC3-7	rs1443241	11	60,181,627	419	Abnormal	Present	MOMODE	-0.03	0.5075
ADC3-7	rs4939352	11	60,173,107	247	Normal	Absent	MOMODE	0.08	0.1076
ADC3-7	rs4938941	11	60,173,360	247	Normal	Absent	MOMODE	0.03	0.4602
ADC3-7	rs7950677	11	60,179,489	247	Normal	Absent	MOMODE	0.07	0.4263

ADC3-7	rs7926219	11	60,180,335	247	Normal	Absent	MOMODE	0.04	0.4171
ADC3-7	rs1443241	11	60,181,627	247	Normal	Absent	MOMODE	0.07	0.1218
ADC3-7	rs4939352	11	60,173,107	309	Abnormal	Absent	MOMODE	-0.02	0.7582
ADC3-7	rs4938941	11	60,173,360	309	Abnormal	Absent	MOMODE	-0.03	0.6184
ADC3-7	rs7950677	11	60,179,489	309	Abnormal	Absent	MOMODE	-0.16	0.09895
ADC3-7	rs7926219	11	60,180,335	309	Abnormal	Absent	MOMODE	-0.01	0.7781
ADC3-7	rs1443241	11	60,181,627	309	Abnormal	Absent	MOMODE	-0.01	0.8033
ADC3-7	rs4939352	11	60,173,107	57	Normal	Present	COURSE	0.03	0.6791
ADC3-7	rs4938941	11	60,173,360	57	Normal	Present	COURSE	0.08	0.1893
ADC3-7	rs7950677	11	60,179,489	57	Normal	Present	COURSE	-0.04	0.6961
ADC3-7	rs7926219	11	60,180,335	57	Normal	Present	COURSE	0.06	0.2787
ADC3-7	rs1443241	11	60,181,627	57	Normal	Present	COURSE	0.02	0.7927
ADC3-7	rs4939352	11	60,173,107	411	Abnormal	Present	COURSE	0.05	0.03255
ADC3-7	rs4938941	11	60,173,360	411	Abnormal	Present	COURSE	0.05	0.0512
ADC3-7	rs7950677	11	60,179,489	411	Abnormal	Present	COURSE	-0.01	0.9084
ADC3-7	rs7926219	11	60,180,335	411	Abnormal	Present	COURSE	0.02	0.3279
ADC3-7	rs1443241	11	60,181,627	411	Abnormal	Present	COURSE	0.04	0.1356
ADC3-7	rs4939352	11	60,173,107	106	Normal	Absent	COURSE	-0.07	0.1635
ADC3-7	rs4938941	11	60,173,360	106	Normal	Absent	COURSE	-0.09	0.07674
ADC3-7	rs7950677	11	60,179,489	106	Normal	Absent	COURSE	-0.07	0.4802
ADC3-7	rs7926219	11	60,180,335	106	Normal	Absent	COURSE	-0.04	0.4167
ADC3-7	rs1443241	11	60,181,627	106	Normal	Absent	COURSE	-0.02	0.7113
ADC3-7	rs4939352	11	60,173,107	298	Abnormal	Absent	COURSE	0.03	0.2703
ADC3-7	rs4938941	11	60,173,360	298	Abnormal	Absent	COURSE	0.04	0.2222
ADC3-7	rs7950677	11	60,179,489	298	Abnormal	Absent	COURSE	0.002	0.9741
ADC3-7	rs7926219	11	60,180,335	298	Abnormal	Absent	COURSE	0.04	0.1589
ADC3-7	rs1443241	11	60,181,627	298	Abnormal	Absent	COURSE	0.05	0.1319
ADC3-7	rs4939352	11	60,173,107	118	Normal	Present	CDRSUM	0.07	0.5272
ADC3-7	rs4938941	11	60,173,360	118	Normal	Present	CDRSUM	0.05	0.5806
ADC3-7	rs7950677	11	60,179,489	118	Normal	Present	CDRSUM	-0.21	0.3064
ADC3-7	rs7926219	11	60,180,335	118	Normal	Present	CDRSUM	0.06	0.5424
ADC3-7	rs1443241	11	60,181,627	118	Normal	Present	CDRSUM	0.12	0.2721
ADC3-7	rs4939352	11	60,173,107	426	Abnormal	Present	CDRSUM	0.12	0.1326
ADC3-7	rs4938941	11	60,173,360	426	Abnormal	Present	CDRSUM	0.13	0.09477
ADC3-7	rs7950677	11	60,179,489	426	Abnormal	Present	CDRSUM	0.02	0.8873
ADC3-7	rs7926219	11	60,180,335	426	Abnormal	Present	CDRSUM	0.14	0.05532
ADC3-7	rs1443241	11	60,181,627	426	Abnormal	Present	CDRSUM	0.12	0.1265
ADC3-7	rs4939352	11	60,173,107	250	Normal	Absent	CDRSUM	0.06	0.3044
ADC3-7	rs4938941	11	60,173,360	250	Normal	Absent	CDRSUM	-0.01	0.9183

ADC3-7	rs7950677	11	60,179,489	250	Normal	Absent	CDRSUM	0.05	0.6384
ADC3-7	rs7926219	11	60,180,335	250	Normal	Absent	CDRSUM	-0.01	0.9017
ADC3-7	rs1443241	11	60,181,627	250	Normal	Absent	CDRSUM	0.05	0.3462
ADC3-7	rs4939352	11	60,173,107	323	Abnormal	Absent	CDRSUM	-0.06	0.5641
ADC3-7	rs4938941	11	60,173,360	323	Abnormal	Absent	CDRSUM	0.01	0.9241
ADC3-7	rs7950677	11	60,179,489	323	Abnormal	Absent	CDRSUM	0.3	0.1104
ADC3-7	rs7926219	11	60,180,335	323	Abnormal	Absent	CDRSUM	-0.01	0.8937
ADC3-7	rs1443241	11	60,181,627	323	Abnormal	Absent	CDRSUM	-0.05	0.6157
ADC3-7	rs4939352	11	60,173,107	95	Normal	Present	MMSE	-0.13	0.4004
ADC3-7	rs4938941	11	60,173,360	95	Normal	Present	MMSE	-0.08	0.5427
ADC3-7	rs7950677	11	60,179,489	95	Normal	Present	MMSE	0.15	0.5672
ADC3-7	rs7926219	11	60,180,335	95	Normal	Present	MMSE	0.02	0.8767
ADC3-7	rs1443241	11	60,181,627	95	Normal	Present	MMSE	0.004	0.9763
ADC3-7	rs4939352	11	60,173,107	242	Abnormal	Present	MMSE	-0.09	0.505
ADC3-7	rs4938941	11	60,173,360	242	Abnormal	Present	MMSE	-0.07	0.6263
ADC3-7	rs7950677	11	60,179,489	242	Abnormal	Present	MMSE	-0.21	0.4494
ADC3-7	rs7926219	11	60,180,335	242	Abnormal	Present	MMSE	-0.04	0.7637
ADC3-7	rs1443241	11	60,181,627	242	Abnormal	Present	MMSE	-0.1	0.4903
ADC3-7	rs4939352	11	60,173,107	193	Normal	Absent	MMSE	-0.26	0.0006355
ADC3-7	rs4938941	11	60,173,360	193	Normal	Absent	MMSE	-0.15	0.02436
ADC3-7	rs7950677	11	60,179,489	193	Normal	Absent	MMSE	0.07	0.6148
ADC3-7	rs7926219	11	60,180,335	193	Normal	Absent	MMSE	-0.17	0.01589
ADC3-7	rs1443241	11	60,181,627	193	Normal	Absent	MMSE	-0.24	0.001218
ADC3-7	rs4939352	11	60,173,107	207	Abnormal	Absent	MMSE	0.05	0.735
ADC3-7	rs4938941	11	60,173,360	207	Abnormal	Absent	MMSE	0.11	0.4472
ADC3-7	rs7950677	11	60,179,489	207	Abnormal	Absent	MMSE	-0.3	0.2639
ADC3-7	rs7926219	11	60,180,335	207	Abnormal	Absent	MMSE	0.05	0.7117
ADC3-7	rs1443241	11	60,181,627	207	Abnormal	Absent	MMSE	-0.05	0.7092

Appendix B

Unadjusted Results for BIN1

Dataset	SNP	Chr	Position	N	Init. Cog. Stat.	APOE E4	Outcome	β	P-value
ALL	rs360390	2	127048167	146	Normal	Present	BEMODE	-0.04	0.4662
ALL	rs360259	2	127056534	146	Normal	Present	BEMODE	0.03	0.6684
ALL	rs360263	2	127062366	146	Normal	Present	BEMODE	0.21	0.2328
ALL	rs360308	2	127082310	146	Normal	Present	BEMODE	-0.06	0.4842
ALL	rs360314	2	127083389	146	Normal	Present	BEMODE	-0.16	0.1679
ALL	rs360317	2	127083960	146	Normal	Present	BEMODE	-0.06	0.4842
ALL	rs360323	2	127085797	146	Normal	Present	BEMODE	-0.11	0.1349
ALL	rs359683	2	127102573	146	Normal	Present	BEMODE	-0.07	0.3405
ALL	rs360390	2	127048167	539	Abnormal	Present	BEMODE	0.004	0.8953
ALL	rs360259	2	127056534	539	Abnormal	Present	BEMODE	-0.03	0.4854
ALL	rs360263	2	127062366	539	Abnormal	Present	BEMODE	0.01	0.9668
ALL	rs360308	2	127082310	539	Abnormal	Present	BEMODE	0.01	0.8132
ALL	rs360314	2	127083389	539	Abnormal	Present	BEMODE	0.06	0.2823
ALL	rs360317	2	127083960	539	Abnormal	Present	BEMODE	0.01	0.777
ALL	rs360323	2	127085797	539	Abnormal	Present	BEMODE	0.004	0.9123
ALL	rs359683	2	127102573	539	Abnormal	Present	BEMODE	0.003	0.9354
ALL	rs360390	2	127048167	272	Normal	Absent	BEMODE	-0.01	0.7291
ALL	rs360259	2	127056534	272	Normal	Absent	BEMODE	-0.07	0.1091
ALL	rs360263	2	127062366	272	Normal	Absent	BEMODE	-0.12	0.2753
ALL	rs360308	2	127082310	272	Normal	Absent	BEMODE	-0.02	0.6746
ALL	rs360314	2	127083389	272	Normal	Absent	BEMODE	-0.01	0.82
ALL	rs360317	2	127083960	272	Normal	Absent	BEMODE	-0.02	0.6746
ALL	rs360323	2	127085797	272	Normal	Absent	BEMODE	-0.06	0.1751
ALL	rs359683	2	127102573	272	Normal	Absent	BEMODE	-0.07	0.1035
ALL	rs360390	2	127048167	417	Abnormal	Absent	BEMODE	-0.001	0.8522
ALL	rs360259	2	127056534	417	Abnormal	Absent	BEMODE	-0.02	0.5858
ALL	rs360263	2	127062366	417	Abnormal	Absent	BEMODE	0.06	0.6122
ALL	rs360308	2	127082310	417	Abnormal	Absent	BEMODE	0.04	0.4437
ALL	rs360314	2	127083389	417	Abnormal	Absent	BEMODE	0.08	0.2451
ALL	rs360317	2	127083960	417	Abnormal	Absent	BEMODE	0.04	0.4437
ALL	rs360323	2	127085797	417	Abnormal	Absent	BEMODE	0.003	0.9416

ALL	rs359683	2	127102573	417	Abnormal	Absent	BEMODE	0.01	0.8731
ALL	rs360390	2	127048167	146	Normal	Present	COGMODE	-0.07	0.3057
ALL	rs360259	2	127056534	146	Normal	Present	COGMODE	0.002	0.9774
ALL	rs360263	2	127062366	146	Normal	Present	COGMODE	-0.16	0.3568
ALL	rs360308	2	127082310	146	Normal	Present	COGMODE	-0.11	0.227
ALL	rs360314	2	127083389	146	Normal	Present	COGMODE	-0.1	0.3471
ALL	rs360317	2	127083960	146	Normal	Present	COGMODE	-0.11	0.227
ALL	rs360323	2	127085797	146	Normal	Present	COGMODE	-0.06	0.4193
ALL	rs359683	2	127102573	146	Normal	Present	COGMODE	-0.08	0.2455
ALL	rs360390	2	127048167	548	Abnormal	Present	COGMODE	0.01	0.703
ALL	rs360259	2	127056534	548	Abnormal	Present	COGMODE	0.01	0.5432
ALL	rs360263	2	127062366	548	Abnormal	Present	COGMODE	0.03	0.4741
ALL	rs360308	2	127082310	548	Abnormal	Present	COGMODE	-0.01	0.722
ALL	rs360314	2	127083389	548	Abnormal	Present	COGMODE	-0.01	0.8236
ALL	rs360317	2	127083960	548	Abnormal	Present	COGMODE	-0.01	0.7179
ALL	rs360323	2	127085797	548	Abnormal	Present	COGMODE	-2E-04	0.9882
ALL	rs359683	2	127102573	548	Abnormal	Present	COGMODE	0.003	0.8422
ALL	rs360390	2	127048167	275	Normal	Absent	COGMODE	-0.02	0.5668
ALL	rs360259	2	127056534	275	Normal	Absent	COGMODE	-0.07	0.2387
ALL	rs360263	2	127062366	275	Normal	Absent	COGMODE	-0.05	0.7314
ALL	rs360308	2	127082310	275	Normal	Absent	COGMODE	0.02	0.7012
ALL	rs360314	2	127083389	275	Normal	Absent	COGMODE	0.01	0.9228
ALL	rs360317	2	127083960	275	Normal	Absent	COGMODE	0.02	0.7012
ALL	rs360323	2	127085797	275	Normal	Absent	COGMODE	-0.02	0.7433
ALL	rs359683	2	127102573	275	Normal	Absent	COGMODE	-0.01	0.7737
ALL	rs360390	2	127048167	420	Abnormal	Absent	COGMODE	-0.06	0.004228
ALL	rs360259	2	127056534	420	Abnormal	Absent	COGMODE	-0.04	0.1393
ALL	rs360263	2	127062366	420	Abnormal	Absent	COGMODE	0.03	0.6368
ALL	rs360308	2	127082310	420	Abnormal	Absent	COGMODE	-0.02	0.5966
ALL	rs360314	2	127083389	420	Abnormal	Absent	COGMODE	-0.03	0.5298
ALL	rs360317	2	127083960	420	Abnormal	Absent	COGMODE	-0.02	0.5966
ALL	rs360323	2	127085797	420	Abnormal	Absent	COGMODE	-0.04	0.1129
ALL	rs359683	2	127102573	420	Abnormal	Absent	COGMODE	-0.04	0.1713
ALL	rs360390	2	127048167	146	Normal	Present	MOMODE	0.004	0.9171
ALL	rs360259	2	127056534	146	Normal	Present	MOMODE	0.02	0.7033
ALL	rs360263	2	127062366	146	Normal	Present	MOMODE	0.11	0.3174
ALL	rs360308	2	127082310	146	Normal	Present	MOMODE	0.03	0.6778

ALL	rs360314	2	127083389	146	Normal	Present	MOMODE	-0.002	0.9745
ALL	rs360317	2	127083960	146	Normal	Present	MOMODE	0.03	0.6778
ALL	rs360323	2	127085797	146	Normal	Present	MOMODE	-0.001	0.9869
ALL	rs359683	2	127102573	146	Normal	Present	MOMODE	0.02	0.694
ALL	rs360390	2	127048167	537	Abnormal	Present	MOMODE	0.03	0.3171
ALL	rs360259	2	127056534	537	Abnormal	Present	MOMODE	-0.01	0.8388
ALL	rs360263	2	127062366	537	Abnormal	Present	MOMODE	0.24	0.04969
ALL	rs360308	2	127082310	537	Abnormal	Present	MOMODE	0.02	0.6442
ALL	rs360314	2	127083389	537	Abnormal	Present	MOMODE	0.02	0.771
ALL	rs360317	2	127083960	537	Abnormal	Present	MOMODE	0.02	0.6273
ALL	rs360323	2	127085797	537	Abnormal	Present	MOMODE	-0.04	0.2735
ALL	rs359683	2	127102573	537	Abnormal	Present	MOMODE	-0.02	0.5887
ALL	rs360390	2	127048167	275	Normal	Absent	MOMODE	-0.07	0.09058
ALL	rs360259	2	127056534	275	Normal	Absent	MOMODE	-0.09	0.09963
ALL	rs360263	2	127062366	275	Normal	Absent	MOMODE	-0.06	0.6499
ALL	rs360308	2	127082310	275	Normal	Absent	MOMODE	-0.04	0.4986
ALL	rs360314	2	127083389	275	Normal	Absent	MOMODE	-0.06	0.4181
ALL	rs360317	2	127083960	275	Normal	Absent	MOMODE	-0.04	0.4986
ALL	rs360323	2	127085797	275	Normal	Absent	MOMODE	-0.07	0.1753
ALL	rs359683	2	127102573	275	Normal	Absent	MOMODE	-0.07	0.1639
ALL	rs360390	2	127048167	407	Abnormal	Absent	MOMODE	0.01	0.8213
ALL	rs360259	2	127056534	407	Abnormal	Absent	MOMODE	-0.01	0.8061
ALL	rs360263	2	127062366	407	Abnormal	Absent	MOMODE	-0.12	0.317
ALL	rs360308	2	127082310	407	Abnormal	Absent	MOMODE	0.04	0.4721
ALL	rs360314	2	127083389	407	Abnormal	Absent	MOMODE	0.11	0.1281
ALL	rs360317	2	127083960	407	Abnormal	Absent	MOMODE	0.04	0.4721
ALL	rs360323	2	127085797	407	Abnormal	Absent	MOMODE	0.05	0.2721
ALL	rs359683	2	127102573	407	Abnormal	Absent	MOMODE	0.04	0.437
ALL	rs360390	2	127048167	61	Normal	Present	COURSE	-0.08	0.2898
ALL	rs360259	2	127056534	61	Normal	Present	COURSE	-0.01	0.9035
ALL	rs360263	2	127062366	61	Normal	Present	COURSE	0.29	0.1106
ALL	rs360308	2	127082310	61	Normal	Present	COURSE	0.02	0.8602
ALL	rs360314	2	127083389	61	Normal	Present	COURSE	-0.06	0.5553
ALL	rs360317	2	127083960	61	Normal	Present	COURSE	0.02	0.8602
ALL	rs360323	2	127085797	61	Normal	Present	COURSE	-0.04	0.5878
ALL	rs359683	2	127102573	61	Normal	Present	COURSE	0.01	0.9452
ALL	rs360390	2	127048167	526	Abnormal	Present	COURSE	-0.02	0.3641

ALL	rs360259	2	127056534	526	Abnormal	Present	COURSE	-0.03	0.1519
ALL	rs360263	2	127062366	526	Abnormal	Present	COURSE	-0.05	0.4793
ALL	rs360308	2	127082310	526	Abnormal	Present	COURSE	0.01	0.8136
ALL	rs360314	2	127083389	526	Abnormal	Present	COURSE	0.02	0.5635
ALL	rs360317	2	127083960	526	Abnormal	Present	COURSE	0.01	0.8096
ALL	rs360323	2	127085797	526	Abnormal	Present	COURSE	-0.01	0.5637
ALL	rs359683	2	127102573	526	Abnormal	Present	COURSE	-0.02	0.4465
ALL	rs360390	2	127048167	91	Normal	Absent	COURSE	0.003	0.959
ALL	rs360259	2	127056534	91	Normal	Absent	COURSE	0.03	0.7057
ALL	rs360263	2	127062366	91	Normal	Absent	COURSE	-0.04	0.7607
ALL	rs360308	2	127082310	91	Normal	Absent	COURSE	0.03	0.4953
ALL	rs360314	2	127083389	91	Normal	Absent	COURSE	0.05	0.3767
ALL	rs360317	2	127083960	91	Normal	Absent	COURSE	0.03	0.4953
ALL	rs360323	2	127085797	91	Normal	Absent	COURSE	0.07	0.1079
ALL	rs359683	2	127102573	91	Normal	Absent	COURSE	0.06	0.1539
ALL	rs360390	2	127048167	392	Abnormal	Absent	COURSE	-0.02	0.4549
ALL	rs360259	2	127056534	392	Abnormal	Absent	COURSE	0.01	0.7876
ALL	rs360263	2	127062366	392	Abnormal	Absent	COURSE	-0.01	0.9111
ALL	rs360308	2	127082310	392	Abnormal	Absent	COURSE	-0.02	0.5219
ALL	rs360314	2	127083389	392	Abnormal	Absent	COURSE	-0.07	0.08932
ALL	rs360317	2	127083960	392	Abnormal	Absent	COURSE	-0.02	0.5219
ALL	rs360323	2	127085797	392	Abnormal	Absent	COURSE	-2E-04	0.9952
ALL	rs359683	2	127102573	392	Abnormal	Absent	COURSE	-0.002	0.9504
ALL	rs360390	2	127048167	147	Normal	Present	CDRSUM	-0.05	0.4608
ALL	rs360259	2	127056534	147	Normal	Present	CDRSUM	0.07	0.3507
ALL	rs360263	2	127062366	147	Normal	Present	CDRSUM	0.34	0.1112
ALL	rs360308	2	127082310	147	Normal	Present	CDRSUM	-0.03	0.8093
ALL	rs360314	2	127083389	147	Normal	Present	CDRSUM	-0.15	0.259
ALL	rs360317	2	127083960	147	Normal	Present	CDRSUM	-0.03	0.8093
ALL	rs360323	2	127085797	147	Normal	Present	CDRSUM	-0.06	0.4723
ALL	rs359683	2	127102573	147	Normal	Present	CDRSUM	-0.004	0.9622
ALL	rs360390	2	127048167	549	Abnormal	Present	CDRSUM	0.1	0.1464
ALL	rs360259	2	127056534	549	Abnormal	Present	CDRSUM	0.16	0.05338
ALL	rs360263	2	127062366	549	Abnormal	Present	CDRSUM	0.002	0.9947
ALL	rs360308	2	127082310	549	Abnormal	Present	CDRSUM	-0.03	0.7697
ALL	rs360314	2	127083389	549	Abnormal	Present	CDRSUM	0.13	0.2465

ALL	rs360317	2	127083960	549	Abnormal	Present	CDRSUM	-0.03	0.7934
ALL	rs360323	2	127085797	549	Abnormal	Present	CDRSUM	0.11	0.1373
ALL	rs359683	2	127102573	549	Abnormal	Present	CDRSUM	0.1	0.1854
ALL	rs360390	2	127048167	276	Normal	Absent	CDRSUM	0.03	0.5651
ALL	rs360259	2	127056534	276	Normal	Absent	CDRSUM	-0.01	0.8837
ALL	rs360263	2	127062366	276	Normal	Absent	CDRSUM	-0.06	0.7137
ALL	rs360308	2	127082310	276	Normal	Absent	CDRSUM	-0.002	0.9787
ALL	rs360314	2	127083389	276	Normal	Absent	CDRSUM	-0.01	0.8983
ALL	rs360317	2	127083960	276	Normal	Absent	CDRSUM	-0.002	0.9787
ALL	rs360323	2	127085797	276	Normal	Absent	CDRSUM	-0.003	0.9636
ALL	rs359683	2	127102573	276	Normal	Absent	CDRSUM	-0.01	0.9198
ALL	rs360390	2	127048167	424	Abnormal	Absent	CDRSUM	0.07	0.3419
ALL	rs360259	2	127056534	424	Abnormal	Absent	CDRSUM	-0.17	0.06854
ALL	rs360263	2	127062366	424	Abnormal	Absent	CDRSUM	-0.32	0.1723
ALL	rs360308	2	127082310	424	Abnormal	Absent	CDRSUM	0.13	0.2389
ALL	rs360314	2	127083389	424	Abnormal	Absent	CDRSUM	0.31	0.02049
ALL	rs360317	2	127083960	424	Abnormal	Absent	CDRSUM	0.13	0.2389
ALL	rs360323	2	127085797	424	Abnormal	Absent	CDRSUM	-0.01	0.9397
ALL	rs359683	2	127102573	424	Abnormal	Absent	CDRSUM	-0.04	0.6309
ALL	rs360390	2	127048167	139	Normal	Present	MMSE	-0.05	0.649
ALL	rs360259	2	127056534	139	Normal	Present	MMSE	-0.16	0.2222
ALL	rs360263	2	127062366	139	Normal	Present	MMSE	0.19	0.5363
ALL	rs360308	2	127082310	139	Normal	Present	MMSE	0.2	0.1929
ALL	rs360314	2	127083389	139	Normal	Present	MMSE	0.09	0.5699
ALL	rs360317	2	127083960	139	Normal	Present	MMSE	0.2	0.1929
ALL	rs360323	2	127085797	139	Normal	Present	MMSE	-0.02	0.9017
ALL	rs359683	2	127102573	139	Normal	Present	MMSE	0.02	0.8729
ALL	rs360390	2	127048167	352	Abnormal	Present	MMSE	0.41	0.2647
ALL	rs360259	2	127056534	352	Abnormal	Present	MMSE	0.73	0.1092
ALL	rs360263	2	127062366	352	Abnormal	Present	MMSE	-0.43	0.7913
ALL	rs360308	2	127082310	352	Abnormal	Present	MMSE	-0.06	0.917
ALL	rs360314	2	127083389	352	Abnormal	Present	MMSE	-0.54	0.4014
ALL	rs360317	2	127083960	352	Abnormal	Present	MMSE	-0.06	0.9156
ALL	rs360323	2	127085797	352	Abnormal	Present	MMSE	0.36	0.4103
ALL	rs359683	2	127102573	352	Abnormal	Present	MMSE	0.32	0.46
ALL	rs360390	2	127048167	262	Normal	Absent	MMSE	-0.55	0.05206

ALL	rs360259	2	127056534	262	Normal	Absent	MMSE	-0.32	0.3799
ALL	rs360263	2	127062366	262	Normal	Absent	MMSE	-0.94	0.2797
ALL	rs360308	2	127082310	262	Normal	Absent	MMSE	-0.65	0.1212
ALL	rs360314	2	127083389	262	Normal	Absent	MMSE	-0.86	0.1503
ALL	rs360317	2	127083960	262	Normal	Absent	MMSE	-0.65	0.1212
ALL	rs360323	2	127085797	262	Normal	Absent	MMSE	-0.58	0.1253
ALL	rs359683	2	127102573	262	Normal	Absent	MMSE	-0.67	0.06213
ALL	rs360390	2	127048167	285	Abnormal	Absent	MMSE	-0.15	0.7056
ALL	rs360259	2	127056534	285	Abnormal	Absent	MMSE	-0.24	0.6127
ALL	rs360263	2	127062366	285	Abnormal	Absent	MMSE	-0.41	0.6766
ALL	rs360308	2	127082310	285	Abnormal	Absent	MMSE	-0.38	0.4613
ALL	rs360314	2	127083389	285	Abnormal	Absent	MMSE	-0.1	0.8637
ALL	rs360317	2	127083960	285	Abnormal	Absent	MMSE	-0.38	0.4613
ALL	rs360323	2	127085797	285	Abnormal	Absent	MMSE	-0.6	0.1507
ALL	rs359683	2	127102573	285	Abnormal	Absent	MMSE	-0.64	0.1163

Appendix C

Final Adjusted Models for MS4A6A

Initial MMSE (β, p)	NA	NA	-0.13, 0.001284	-0.14, 0.001091	-0.13, 0.001162	-0.13, 0.001445
Age (β, p)	0.01, 0.0182	NA	-0.02, 0.000671	-0.02, 0.000476	-0.02, 0.000556	-0.02, 0.000582
Education (β, p)	NA	-0.01, 0.03601	NA	NA	NA	NA
Race (β, p)	NA	NA	NA	NA	NA	NA
Hispanic (β, p)	NA	NA	NA	NA	NA	NA
Sex (β, p)	NA	-0.09, 0.00542	NA	NA	NA	NA
Genotype (β, p)	0.09, 0.0312	0.05, 0.04595	-0.25, 0.000632	-0.16, 0.02	-0.17, 0.012225	-0.23, 0.001173
Intercept (β, p)	-0.54, 0.0681	1.34, <2e-16	5.35, 0.000223	5.53, 0.000179	5.49, 0.000191	5.35, 0.000233
Sample Size	245	411	193	193	193	193
APOE E4 Allele	Absent	Present	Absent	Absent	Absent	Absent
Init. Cog. Status	Normal	Abnormal	Normal	Normal	Normal	Normal
Outcome	BEMODE	COURSE	MMSE	MMSE	MMSE	MMSE
Nearest gene	MS4A6A	MS4A6A	MS4A6A	MS4A6A	MS4A6A	MS4A6A
Position	60,173,107	60,173,107	60,173,107	60,173,360	60,180,335	60,181,627
Chr.	11	11	11	11	11	11
Major/minor allele	G/A	G/A	G/A	G/A	T/C	G/T
SNP	rs4939352	rs4939352	rs4939352	rs4938941	rs7926219	rs1443241

Appendix D

Final Adjusted Models for BIN1

SNP	Major/minor allele	Chr.	Pos.	Outcome	Initial Cognitive Status	APOE E4 Allele	Sample Size	Intercept (β, p)	Genotype (β, p)	Sex (β, p)	Hispanic (β, p)	Race (β, p)	Education (β, p)	Age (β, p)
rs360390	C/A	2	127048167	COGMODE	Abnormal	Absent	420	1.91, <2e-16	-0.05, 0.0152	NA	NA	-0.9, 4.26e-05	NA	NA
rs360263	T/C	2	127062366	MOMODE	Abnormal	Present	537	0.39, <2e-16	0.24, 0.0497	NA	NA	NA	NA	NA
rs360314	T/G	2	127083389	CDRSUM	Abnormal	Absent	424	0.9, <2e-16	0.31, 0.0205	NA	NA	NA	NA	NA