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Genetic overlap between Alzheimer's disease and Parkinson's disease at the *MAPT* locus

Rahul S. Desikan, MD, PhD[1,#], **Andrew J. Schork, MS**[2], **Yunpeng Wang, PhD**[3,5], **Aree Witoelar, PhD**[5], **Manu Sharma, PhD**[6,7], **Linda K. McEvoy, PhD**[1], **Dominic Holland, PhD**[3], **James B. Brewer, MD, PhD**[1,3], **Chi-Hua Chen, PhD**[1,4], **Wesley K. Thompson, PhD**[4], **Denise Harold, PhD**[8], **Julie Williams, PhD**[8], **Michael J. Owen, FRCPsych PhD**[8], **Michael C. O'Donovan, FRCPsych, PhD**[8], **Margaret A. Pericak-Vance, PhD**[9], **Richard Mayeux, MD**[10], **Jonathan L. Haines, PhD**[11], **Lindsay A. Farrer, PhD**[12], **Gerard D. Schellenberg, PhD**[13], **Peter Heutink, PhD**[14], **Andrew B. Singleton, PhD**[15], **Alexis Brice, MD**[16], **Nicolas W. Wood, MD, PhD**[17], **John Hardy, PhD**[18], **Maria Martinez, PhD**[19], **Seung Hoi Choi, MS**[20], **Anita DeStefano, PhD**[20,27], **M. Arfan Ikram, MD, PhD**[21], **Joshua C. Bis, PhD**[22], **Albert Smith, PhD**[23], **Annette L. Fitzpatrick, PhD**[24], **Lenore Launer, PhD**[25], **Cornelia van Duijn, PhD**[21], **Sudha Seshadri, MD**[26,27], **Ingun Dina Ulstein, MD, PhD**[28], **Dag Aarsland, MD, PhD**[29], **Tormod Fladby, MD, PhD**[30], **Srdjan Djurovic, PhD**[5], **Bradley T. Hyman, MD, PhD**[31], **Jon Snaedal, MD**[32], **Hreinn Stefansson, PhD**[33], **Kari Stefansson, MD, PhD**[33,34], **Thomas Gasser, MD, PhD**[6], **Ole A. Andreassen, MD, PhD**[4,5,#], **Anders M. Dale, PhD**[1,2,3,4,#], and **for the ADNI*, ADGC, GERAD, CHARGE and IPDGC Investigators ,****

[1]Department of Radiology, University of California, San Diego, La Jolla, CA, USA [2]Department of Cognitive Science, University of California, San Diego, La Jolla, CA, USA [3]Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA [4]Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA [5]NORMENT; Institute of Clinical Medicine, University of Oslo and Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway [6]Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research

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[#]Correspondence should be addressed to: Drs. Rahul S. Desikan and Anders M. Dale, Department of Radiology, University of California, San Diego, 8950 Villa La Jolla Drive, Suite C101, La Jolla, CA, USA 92037-0841, ; Email: rdesikan@ucsd.edu, ; Email: amdale@ucsd.edu, Phone: (858)-822-6671, Fax: (858)-534-1078, Dr. Ole A. Andreassen: KG Jebsen Centre for Psychosis Research, Building 49, Oslo University Hospital, Ullevål, Kirkeveien 166, PO Box 4956 Nydalen, 0424 Oslo, Norway, ; Email: o.a.andreassen@medisin.uio.no, Ph: +47 23 02 73 50 (22 11 78 43 dir), Fax: +47 23 02 73 33

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[**]Full list of investigators included in the Supplemental materials.

DISCLOSURES

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University of Tubingen, Germany [7]Institute for Clinical Epidemiology and Applied Biometry, University of Tübingen, Germany [8]Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Wales [9]The John P. Hussman Institute for Human Genomics, University of Miami, Miami, Florida, USA [10]Department of Neurology, Taub Institute on Alzheimer's Disease and the Aging Brain, and Gertrude H. Sergievsky Center, Columbia University, New York, New York, USA [11]Department of Molecular Physiology and Biophysics, Vanderbilt Center for Human Genetics Research, Vanderbilt University, Nashville, Tennessee, USA [12]Departments of Medicine (Biomedical Genetics), Neurology, Ophthalmology, Biostatistics, and Epidemiology, Boston University Schools of Medicine and Public Health, Boston, Massachusetts, USA [13]Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA [14]German Center for Neurodegenerative Diseases (DZNE)-Tübingen, Paul-Ehrlich-Straße 15, 72076 Tübingen, Germany [15]Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA [16]Sorbonne Université, UPMC Univ Paris 06, UM 75, ICM; Inserm, U 1127, ICM; Cnrs, UMR 7225, ICM; ICM, Paris, F-75013 Paris, France [17]UCL Genetics Institute; and Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK [18]Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK [19]INSERM UMR1043, CPTP, CHU Purpan, Toulouse, France [20]Department of Biostatistics, School of Public Health, Boston University, Boston, MA, USA [21]Deparment of Epidemiology, Erasmus MC University Medical Center, Rotterdam, Netherlands [22]Deparment of Internal Medicine, University of Washington, Seattle, WA, USA [23]Icelandic Heart Association, Kopavogur, Iceland [24]Department of Epidemiology, University of Washington, Seattle, WA, USA [25]Laboratory of Epidemiology, Demography and Biometry, Intramural Research Program, National Institute on Aging, Washington, DC, USA [26]Department of Neurology, Boston University School of Medicine, Boston, MA [27]The National Heart Lung and Blood Institute's Framingham Heart Study, Framingham, MA [28]Norwegian Centre for Dementia Research, Department of Old Age Psychiatry, Oslo University Hospital, Oslo, Norway [29]Alzheimer's Disease Research Centre, Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Stockholm, Sweden; Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway; Department of Geriatric Psychiatry, Akershus University Hospital, Oslo, Norway [30]Institute of Clinical Medicine, University of Oslo, Oslo, Norway; Department of Neurology, Akershus University Hospital, Norway [31]Department of Neurology, Massachusetts General Hospital, Boston, MA, USA [32]Department of Geriatric Medicine, University Hospital Reykjavik, Iceland [33]deCODE Genetics/Amgen, Reykjavik, Iceland [34]Faculty of Medicine, University of Iceland, Reykjavik, Iceland

Abstract

We investigated genetic overlap between Alzheimer's disease (AD) and Parkinson's disease (PD). Using summary statistics (p-values) from large recent genomewide association studies (GWAS) (total n = 89,904 individuals), we sought to identify single nucleotide polymorphisms (SNPs) associating with both AD and PD. We found and replicated association of both AD and PD with the A allele of rs393152 within the extended *MAPT* region on chromosome 17 (meta analysis p-value across 5 independent AD cohorts = 1.65×10^{-7}). In independent datasets, we found a dose-dependent effect of the A allele of rs393152 on intra-cerebral *MAPT* transcript levels and volume loss within the entorhinal cortex and hippocampus. Our findings identify the tau-associated *MAPT* locus as a site of genetic overlap between AD and PD and extending prior work, we show that the *MAPT* region increases risk of Alzheimer's neurodegeneration.

INTRODUCTION

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative disorders. Neuropathologically, AD is characterized by the presence of extracellular amyloid-β (Aβ) plaques and intracellular tau-associated neurofibrillary tangles whereas PD involves deposition of α-synuclein containing Lewy bodies.[1] Though AD and PD are considered distinct neurodegenerative entities, there is evidence for Lewy body pathology in AD [2] and Alzheimer's-type pathology in PD [3] suggesting overlap between these two disorders. Importantly, although tau-associated pathology is considered a hallmark of AD, genome-wide association studies (GWAS) in PD have identified several polymorphisms in and around the tau encoding microtubule-associated protein gene (*MAPT*) [4,5] indicating that similar biochemical perturbations may contribute to both AD and PD. [6] Furthermore, prior reports investigating the genetic relationship between *MAPT* and AD risk have been conflicting, with some studies finding a positive association [7–8] and other studies showing no association [8–9], indicating that the role of the *MAPT* gene in influencing Alzheimer's neurodegeneration is still largely unknown.

Combining GWAS from two disorders provides insights into genetic pleiotropy (defined as a single gene or variant being associated with more than one distinct phenotype) and could elucidate shared pathobiology. Here, using summary statistics (p-values and minor allele frequencies) from large genetic studies [11–15], we sought single nucleotide polymorphisms (SNPs) associating with both AD and PD.

METHODS

Participant Samples

We obtained complete GWAS results in the form of summary statistics from the PD International Parkinson's Disease Genetics Consortium (IPDGC) and AD Alzheimer's Disease Genetics Consortium (ADGC). The PD GWAS summary statistic results from IPDGC consisted of 5,333 cases and 12,019 controls obtained from 5 studies with genotyped and imputed data at 7,689,524 SNPs (Table 1a, for additional details see reference [11]). The AD GWAS summary statistic data from ADGC consisted of 11,840 cases and 10,931 controls obtained from 15 studies with genotyped and imputed data at 2,324,889 SNPs (Table 1a, for additional details see reference [12]). The ADGC GWAS summary statistic data were co-varied for age, sex and number of *APOE* alleles. There was no overlap between the ADGC and the IPDGC cases/controls.

To test for replication, we also assessed the p-values of the PD genome-wide significant SNPs in four separate AD cohorts, namely the Genetic and Environmental Risk in Alzheimer's Disease (GERAD) sample, a cohort of AD cases and controls drawn from the population of Iceland (deCODE cohort), a small cohort of mild cognitive impairment or AD cases and controls drawn from the population of Norway (Oslo), and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. The AD GWAS summary statistic results from the GERAD consortium were obtained from 13 studies and consisted of 3,941 cases (62.7% female) and 7,848 controls (55.6 % female) with genotyped data at 529,205 SNPs (for additional details see reference [13]). A total of 5571 controls from the PD IPDGC GWA were also present in the AD GERAD GWA. The AD GWAS summary statistic data drawn from the Icelandic population (deCODE) included 3,759 AD cases (65.8 % female) and 8,888 older controls (57.8% females) greater than 85 years of age (for additional details see references [14] and [15]). The AD GWAS summary statistic data from the CHARGE consortium were obtained from 4 studies and included 1,315 AD cases (62.1% female) and 21,766 controls (56.9 % female) (for additional details see reference [27]). The AD GWAS summary statistic data drawn from the Norwegian population (Oslo) included 434 individuals classified as AD or mild cognitive impairment (57% female) and 1,830 controls (49% female) (for additional details please see Supplemental Information).

These studies addressed potential concerns of population stratification by limiting analysis to individuals of European descent, including principal components of genetic variation in the regression tests and controlling *post-hoc* for genomic inflation with genomic control (for additional details see references [11–15,27]).

For the gene expression analyses, we used publicly available, genotyping (performed on the Affymetrix GeneChip Human Mapping 500K Array Set platform) and RNA expression data (performed on the Illumina HumanRefseq-8 Expression BeadChip system) from neuropathologically confirmed 176 late-onset AD cases (mean age = 83.4 years, standard deviation = 6.6) and 188 controls (mean age = 81.2 years, standard deviation = 9.1) from the Gene Expression Omnibus (GEO) data set GSE15222. [16] We additionally evaluated genotype and imaging data obtained from 620 older participants (174 healthy older controls, 311 individuals with mild cognitive impairment (MCI) and 135 individuals with probable AD) from the Alzheimer's Disease Neuroimaging Initiative (ADNI – see Table 1b and Supplemental Methods). We restricted our analyses to those participants with available genotype and quality-assured baseline and follow-up MRI scans (6 months to 3.5 years, mean of 2.02 years, standard deviation 0.80 years) available as of April 2011. We assessed longitudinal sub-regional change in gray matter volume (atrophy) on serial 2471 T_1-weighted MRI scans using a modified version of the FreeSurfer software package (for additional details see Supplemental Methods).

Statistical analyses

We used stepwise gatekeeper hypothesis testing [17] to identify SNPs associating with both PD and AD. We restricted our analyses to only those SNPs assayed in both GWASs from the IPDGC and the ADGC Consortia. First, we identified 'pruned' SNPs (removing all SNPs with $r^2 > 0.2$, within 1 Mb of a given SNP) that were significant at a genome-wide level ($p < 5 \times 10^{-8}$) within PD. Next, we evaluated the p-values of these PD genome-wide significant SNPs within the AD ADGC GWAS (Apolipoprotein E (*APOE*), age and sex co-varied summary statistic p-values) and applied a Bonferroni correction to control for multiple comparisons. Note that since the SNPs were *a priori* selected independently of the p-values from AD ADGC the proper Bonferroni correction is in terms of the number of PD genome-wide significant SNPs. Therefore, the p-value threshold for detecting significant ADGC loci controls for the number of PD genome-wide significant SNPs rather than $p < 5 \times 10^{-8}$. It is important to note that this stepwise gatekeeper hypothesis testing approach implies a strict control for family-wise error rate in a multiple testing framework.[17]

RESULTS

Genetic overlap between AD and PD at the A allele of rs393152

We found 8 SNPs on 4 chromosomes that were genome-wide significant in PD, thus requiring a Bonferroni corrected p-value significance threshold of 0.00625 (Table 2). Across all 8 SNPs, we found that the A allele of rs393152, within the *CRHR1* region on chromosome 17 (within the extended *MAPT* locus) and with a minor allele frequency of 23.1%, significantly increased AD risk in the ADGC cohort (p-value = 1.17×10^{-4}, odds ratio (OR) for the minor allele = 0.90, 95% confidence interval (CI) = 0.86–0.95) (Table 2) (Figure 1). In a replication analysis, we found that the A allele of rs393152 also significantly increased AD risk within the GERAD (one-tailed p-value = 0.0048, OR for the minor allele = 0.92, 95% CI = 0.86–0.98), deCODE (one-tailed p-value = 0.017, OR for the minor allele = 0.92, 95% CI = 0.85–0.99) and Oslo cohorts (one-tailed p-value = 0.047, OR for the minor allele = 0.85, 95% CI = 0.71–1.02). We replicated directionality of effect for the A allele of rs393152 within the CHARGE cohort (one-tailed p-value = 0.318, OR for the minor allele = 0.97, 95% CI = 0.85–1.10). We conducted an inverse variance weighted meta-analysis[18] and found a two-tailed meta-analysis p-value of 1.65×10^{-7} (meta analysis OR = 0.91, 95% CI = 0.88–0.94) (Figure 1).

We evaluated the statistical power for detecting an association of rs393152 with AD across the discovery (ADGC) and the combined, meta-analysis AD cohorts (ADGC + GERAD + deCODE + Oslo + CHARGE). Using a GWAS threshold of $p < 5 \times 10^{-8}$ the power within ADGC was 0.028 and within the meta-analysis cohort was 0.36, demonstrating that even the combined cohort consisting of 21,289 AD cases and 51,263 controls was underpowered to detect an association between AD and rs393152 using a standard GWAS approach. However, leveraging PD such that power is computed conditional on discovery in the PD sample (stepwise gatekeeper hypothesis testing), by using $p < 0.00625$ (where Bonferroni corrected $p = 0.05$/number of genome-wide significant SNPs in PD), the power within ADGC was 0.854 and within the meta-analysis cohort was 0.998 indicating that restricting evaluation to only PD-significant SNPs results in considerable increase in statistical power for AD gene discovery. We also calculated the sample size needed to detect rs393152 (($C^{-1} \Theta^{-1}(5 \times 10^{-8})^2 / \Theta^{-1}(0.00625)^2$), where Θ^{-1} is the inverse standard normal cumulative distribution function) and found that in comparison to our discovery cohort, 4.5 times as many subjects would be needed to detect rs393152 using a standard GWAS approach at the same alpha /Type I error.

Based on the 1000 Genomes Project LD structure, we found that rs393152 was in r^2 LD > 0.8 with a number of variants within the *MAPT* gene on chromosome 17 (Figure 2a). Fine mapping showed that rs1981997 constituted the peak of the AD association signal within

MAPT (r^2 = 1.0 with rs393152 in HapMap 2; Figure 2b). Across the ADGC (risk allele = A, two tailed p-value = = 9.54×10^{-5}, OR = 0.90, 95% CI = 0.85–0.95), GERAD (one tailed p-value = 0.006, OR = 0.92, 95% CI = 0.86–0.98, deCODE (one tailed p-value = 0.018, OR = 0.92, 95% CI = 0.84–0.99), Oslo (one tailed p-value = 0.047, OR = 0.85, 95% CI = 0.71–1.03) and CHARGE (one-tailed p-value = 0.0327, OR = 0.96, 95% CI = 0.84–1.08) cohorts, the leading SNP in the *MAPT* region, rs1981997, demonstrated a similar meta-analysis p-value to rs393152 (two-tailed meta-analysis p-value of 1.29×10^{-7}, see Supplemental Figure 4) providing further evidence that our AD/PD pleiotropic variant was tagging the *MAPT* gene and not a false positive result. We also note that rs393152 has been previously shown to tag the H1 haplotype at the *MAPT* locus (r^2 = 0.761). [5] Because of the extensive LD structure in this region, we cannot exclude the possibility that other genes, besides *MAPT*, are the pathologically relevant genes. However, *MAPT* is biologically the most plausible candidate.

Non-polygenic pleiotropy between AD and PD

We further investigated whether the observed genetic overlap between AD and PD was polygenic and generalizable across a number of loci or non-polygenic and driven by the *MAPT* locus alone. Using recently developed statistical methods to evaluate pleiotropic effects [19_22], we investigated relative ‘enrichment’ of pleiotropic SNPs in AD (*APOE*, age and sex co-varied summary statistic p-values from ADGC) as a function of significance in PD (summary statistic p-values from IPDGC) (for additional details see Supplemental Methods). Removing the *MAPT*-associated genetic signal, consisting of all SNPs in $r^2 > 0.2$ (based on 1000 Genomes Project LD structure) within 1 Mb of *MAPT* variants, resulted in considerable attenuation of genetic enrichment (Supplemental Figured 1a–d) indicating that the observed pleiotropy between AD and PD was non-polygenic and likely confined to the *MAPT* region. Similarly, after ‘pruning’ (removing SNPs in $r^2 > 0.2$) all available ADGC SNPs, we found a single pleiotropic locus on chromosome 17 between AD and PD that was in r^2 = 1.0 with *MAPT*. Though some genetic enrichment was still present after removing the *MAPT*-associated SNPs, we found a similar pattern in PD SNP enrichment conditioned on AD (Supplementary Figure 2).

AD-PD pleiotropic locus correlates with MAPT transcript levels

We assessed the relationship between the AD-PD pleiotropic locus on chromosome 17 and *MAPT* transcript levels within the brain (target id = GI_8400714-A and reference sequence = NM_016841. 1 in GSE15222, for additional details see references [16] and [32]). Since rs393152 was not available in the GEO dataset, we focused on rs422112 within the *CRHR1* locus on chromosome 17, the best available proxy (closest distance and $r^2 > 0.98$) for rs393152. We used an additive model with minor allele (T) counts coded as 0, 1, and 2. Given the allele frequencies and near complete LD between rs393152 and rs422112, the ‘A’ allele of rs393152 tags the ‘C’ allele of rs422112 and the ‘G’ allele of rs393152 tags the ‘T’ allele of rs422112. Using linear regression, co-varying for the effects of age at death, *APOE* ε4 carrier status, diagnosis (AD cases vs. controls), brain tissue region (frontal, parietal, temporal, or cerebellar), postmortem interval, institute source of sample, and hybridization date, we evaluated the relationship between rs422112 and *MAPT* transcript expression levels. Across all cases and controls, we found a strong association between the T allele of rs422112 and decreased *MAPT* transcript expression levels (standardized β-coefficient = −0.27, t-statistic = −6.61, p-value = 1.45×10^{-10}) which corresponds to presence of the A allele of rs393152 and increased *MAPT* transcript expression (Figure 3). Subgroup analyses demonstrated similar results within the AD cases and controls (see Supplemental Results). We further assessed the specificity of our findings by evaluating the relationship between the AD-PD pleiotropic locus and transcript levels of synaptophysin (*SYP*), a neuronal protein, and synuclein (*SNCA*), a neural protein associated with tau and PD. In contrast to *MAPT* transcript levels, we found no relationship between rs422112 and transcript levels of either *SYP* or *SNCA* (see Supplemental Results and Figure 3). We additionally performed a 'locus wide association study' testing all SNPs in the *MAPT* region for association with *MAPT* transcript expression levels. SNPs in $r^2 = 1.0$ with rs393152 constituted the peak of the association signal ($p < 1.0 \times 10^{-8}$) with *MAPT* transcript expression levels (Figure 4). We also evaluated the relationship between SNPs in LD with rs393152 and transcript levels of other chromosome 17 genes within the larger *MAPT* region that were available within GSE15222. [16] As illustrated in Supplemental Figures 3a–f, SNPs in LD with rs393152 did not demonstrate significant association with transcript levels of other genes within the *MAPT* region further illustrating the specificity of our *MAPT* findings.

AD-PD pleiotropic locus correlates with longitudinal brain atrophy

Using linear mixed effects models, we assessed the relationship of rs393152 with longitudinal brain atrophy specifically within the entorhinal cortex and hippocampus, two medial temporal lobe regions selectively affected in the earliest stages of AD. [23] These models co-varied for the effects of baseline age, sex, education, group status (healthy older control vs. MCI vs. AD), disease severity (Clinical Dementia Rating-Sum of Box score), and *APOE* ε4 carrier status. We used an additive model with major allele (A) counts coded as 0,1 2. Across all available ADNI participants, we found that the A allele of rs393152 was significantly associated with increased atrophy rates (volume loss) of the entorhinal cortex (standardized β-coefficient = −0.003, SE = 0.001, p-value = 0.0071) and hippocampus (standardized β-coefficient = −0.003, SE = 0.001, p-value = 0.0031).

AD-PD pleiotropic locus demonstrates larger effect among APOE ε4 non-carriers

We further assessed the relationship between rs393152, *MAPT* transcript expression levels, and medial temporal lobe atrophy separately among *APOE* ε4 carriers (presence of at least one ε4 allele) and non-carriers (absence of at least one ε4 allele). Using the linear mixed effects model framework described above, we found a stronger effect between rs393152 and *MAPT* transcript expression levels among *APOE* ε4 non-carriers (standardized β-coefficient = −0.22, SE = 0.04, p-value = 1.1×10^{-6}) than the *APOE* ε4 carriers (standardized β-coefficient = −0.14, SE = 0.04, p-value = 0.001). Similarly, we found a stronger effect between rs393152 and medial temporal lobe atrophy among *APOE* ε4 non-carriers (entorhinal cortex: standardized β-coefficient = −0.002, SE = 0.001, p-value = 0.04; hippocampus: standardized β-coefficient = −0.003, SE = 0.001, p-value = 0.01) than among *APOE* ε4 carriers (entorhinal cortex: standardized β-coefficient = −0.003, SE = 0.002, p-value = 0.07; hippocampus: standardized β-coefficient = −0.003, SE = 0.002, p-value = 0.07) (Figure 5).

DISCUSSION

In this study, we leveraged gene variants associating with PD to search for variants that associate with AD. We found a gene variant that was in strong LD with markers in the *MAPT* gene on chromosome 17 and that was previously associated with PD. This SNP was significantly associated with longitudinal atrophy of the entorhinal cortex and hippocampus and demonstrated a strong association with *MAPT* transcript levels within the brain. Considered together, our findings point to the tau-associated *MAPT* locus as a site genetic overlap between AD and PD.

These results indicate that leveraging the genetic signal in one phenotype may improve statistical power for gene discovery in a second, related phenotype. Rather than evaluating all possible AD susceptibility loci, we restricted our analyses to only those 8 SNPs that were below genome-wide threshold in PD. As such, detection of AD susceptibility loci only among genome-wide significant PD susceptibility loci obviates the need for applying a $p < 5 \times 10^{-8}$ threshold and constitutes stepwise gatekeeper hypothesis testing. [17] This two-stage stepwise gatekeeper framework is conceptually similar to the 'proxy-phenotype' method, which has recently been utilized to identify common variants associated with cognitive performance. [24] It is important to note that this approach does not lower the statistical 'bar' for gene discovery and maintains a constant Type I error rate. By exploiting statistical power from PD, we were able to identify one SNP within the *CRHR1* locus on chromosome 17 (meta-analysis p-value = 1.65×10^{-7}, OR = 0.91, 95% CI = 0.88–0.94) that was significantly associated with increased AD risk. Importantly, use of this stepwise, pleiotropic approach, where power is computed conditional on discovery in the PD sample, resulted in considerable improvement in statistical power for AD gene detection. In contrast, using a standard GWAS approach, neither the discovery ADGC cohort nor the combined meta-analysis cohort were sufficiently powered to detect rs393152. Given the comparable sample sizes with our current study, it is likely that the original AD GWASs [12_13, 25_26] and even the recent meta-analysis (stage 1) [27] were underpowered to detect *MAPT*-associated signal in AD.

There are several indications that the detected pleiotropy within chromosome 17 represents biological signal and not analysis artifacts or type 1 error. First, the use of *APOE* co-varied SNPs from the ADGC minimizes concerns that the detected SNPs represent spurious association resulting from the known large effect of *APOE* on AD risk (for an example of this, see reference [28]). Importantly, our findings indicate the presence of genetic signal independent of the chromosome 19 *APOE* cluster. Second, rs393152 was significantly associated with AD risk in three independent AD replication cohorts and demonstrated equivalent effect sizes in all five AD cohorts. Third, the identified pleiotropic locus was in r^2 LD > 0.8 with a number of variants within the tau-encoding *MAPT* gene on 17q21 indicating that the detected signal was specific to the *MAPT* region. Fourth, the leading AD-associated SNP in the *MAPT* region (rs1981997, r^2 LD = 1.0 with rs393152 in the HapMap 2) demonstrated a similar meta-analysis p-value to rs393152 providing further evidence that our AD/PD pleotropic SNP was not a false positive result. Finally, the A allele of rs393152 showed a dose-dependent effect specifically with *MAPT* transcript levels within the brain and was significantly associated with longitudinal medial temporal lobe atrophy, an established endophenotype of Alzheimer's neurodegeneration.

These single locus results point to shared pathobiology between AD and PD. Although we cannot exclude the possibility that other genes at this chromosome 17 locus are the pathologically relevant genes, our data are biologically plausible and consistent with prior experimental evidence establishing the role of *MAPT* in neurodegenerative diseases. [29] The pleiotropic variant we found, rs393152, tags the H1 haplotype at the *MAPT* locus[5], which has been associated with a number of tauopathies including corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and PD. [5,30] Furthermore, broadly consistent with a prior study [31], our results suggest non-extensive, non-polygenic pleiotropy between AD and PD localized to the *MAPT* cluster on chromosome 17.

Despite a number of prior studies [7–10], the role of *MAPT* in AD is still unclear. Extending prior work suggesting a significant relationship between the *MAPT* H1 [7] (within the GERAD cohort) and H2 [8] (within the ADGC cohort) haplotypes and AD risk, our findings indicate that the A allele of rs393152, which tags the H1 haplotype at the *MAPT* locus [5], increases risk for AD. Building on prior research demonstrating a robust association between a variant in the H2 haplotype and reduced MAPT brain expression levels [8], we found a dose-dependent effect of the A allele of rs393152 (Figure 3) on intracranial *MAPT* gene expression. In contrast, we found no association between rs393152 and transcript levels of either synaptophysin or synuclein indicating the specificity of the relationship between the identified AD-PD pleiotropic locus and *MAPT* transcript expression. Our gene expression findings are consistent with prior work demonstrating a significant relationship between the H1 haplotype and MAPT levels. [32–33] However, a previous study [34] of exon levels from multiple human brain regions found no association between the H1c subhaplotype and *MAPT* expression indicating that additional work using large samples is needed to systematically investigate the H1/H2 sub-haplotypes and MAPT brain expression levels. Additionally, building on prior work detecting smaller gray matter volumes within cognitively normal [35] and cognitively impaired [36] *MAPT* carriers, we found a significant relationship between the A allele of rs393152 and longitudinal atrophy of the entorhinal cortex and hippocampus, two medial temporal lobe regions selectively affected with tau-associated neurofibrillary pathology in the earliest stages of AD. Considered together, this suggests that the PD-associated *MAPT* cluster influences Alzheimer's neurodegeneration likely via tau-related mechanisms.

From an AD perspective, these results highlight the importance of considering tau. Recent evidence indicates that dominantly inherited mutations in *MAPT* cause forms of frontotemporal dementia with parkinsonism [29], a rare *MAPT* variant (p.A152T) increases risk for AD and frontotemporal dementia syndromes [37] and tau modulates Aβ-associated Alzheimer's neurodegeneration. [38] Consistent with this work, our present results indicate that tau-associated polymorphisms impact *MAPT* transcript levels and affect medial temporal lobe volume loss. When considered together with prior CSF [39–41], and imaging research [42–43], our findings suggest that data from GWAS, expression quantitative trait loci, and structural imaging measures may better elucidate underlying pathobiology than any of these markers by themselves. These results also demonstrate the utility of using entorhinal cortex and hippocampal atrophy rates as endophenotypes to identify and confirm AD risk variants.

In this study the diagnosis of AD and PD was based on clinical evaluations, without histopathological confirmation. Post-mortem evidence indicates the co-occurrence of α-synuclein, tangle and amyloid pathology.[44] Therefore, one concern is that concomitant Parkinson's pathology may have contributed to our *MAPT* associated effect in AD. In a small cohort of autopsy confirmed AD cases and controls, we replicated the directionality and magnitude of the A allele of rs393152 (Supplemental Figure 5) indicating that our AD-associated findings are not due to concomitant PD pathology. Furthermore, building on prior genetic work[45], among *APOE* ε4 non-carriers, we found a stronger relationship between rs393152 and both gene expression levels and medial temporal lobe atrophy (Figure 5) suggesting that *MAPT* may predominantly influence Alzheimer's neurodegeneration in a smaller subset of individuals who do not possess *APOE* ε4 alleles. As a caveat, we note that since we primarily evaluated summary statistics from the discovery and replication cohorts, additional work with raw genotype data is needed to determine whether the AD-associated *MAPT* effect varies based on *APOE* ε4 carrier status. Another concern is the potential 'contamination' of PD samples with other tauopathies (such as PSP and CBD) strongly associated with *MAPT*. Using neuropathologically confirmed PD cases, a recent study[46] found a significant association between rs393152 and idiopathic PD indicating that our current findings are unlikely due to contamination with unrecognized cases of PSP or CBD.

From a translational perspective, this work illustrates that data from large GWAS and a pleiotropic framework can provide important insights into the relationships between various diseases. Complementary to recently developed polygenic pleiotropic methods[19–22], the analytic framework used in this manuscript is useful for detecting non-polygenic pleiotropy and can be integrated with other biomarkers to test biologically driven hypotheses. The combination of genetic, molecular, and neuroimaging measures may be additionally helpful for detecting and quantifying the biochemical effects of therapeutic interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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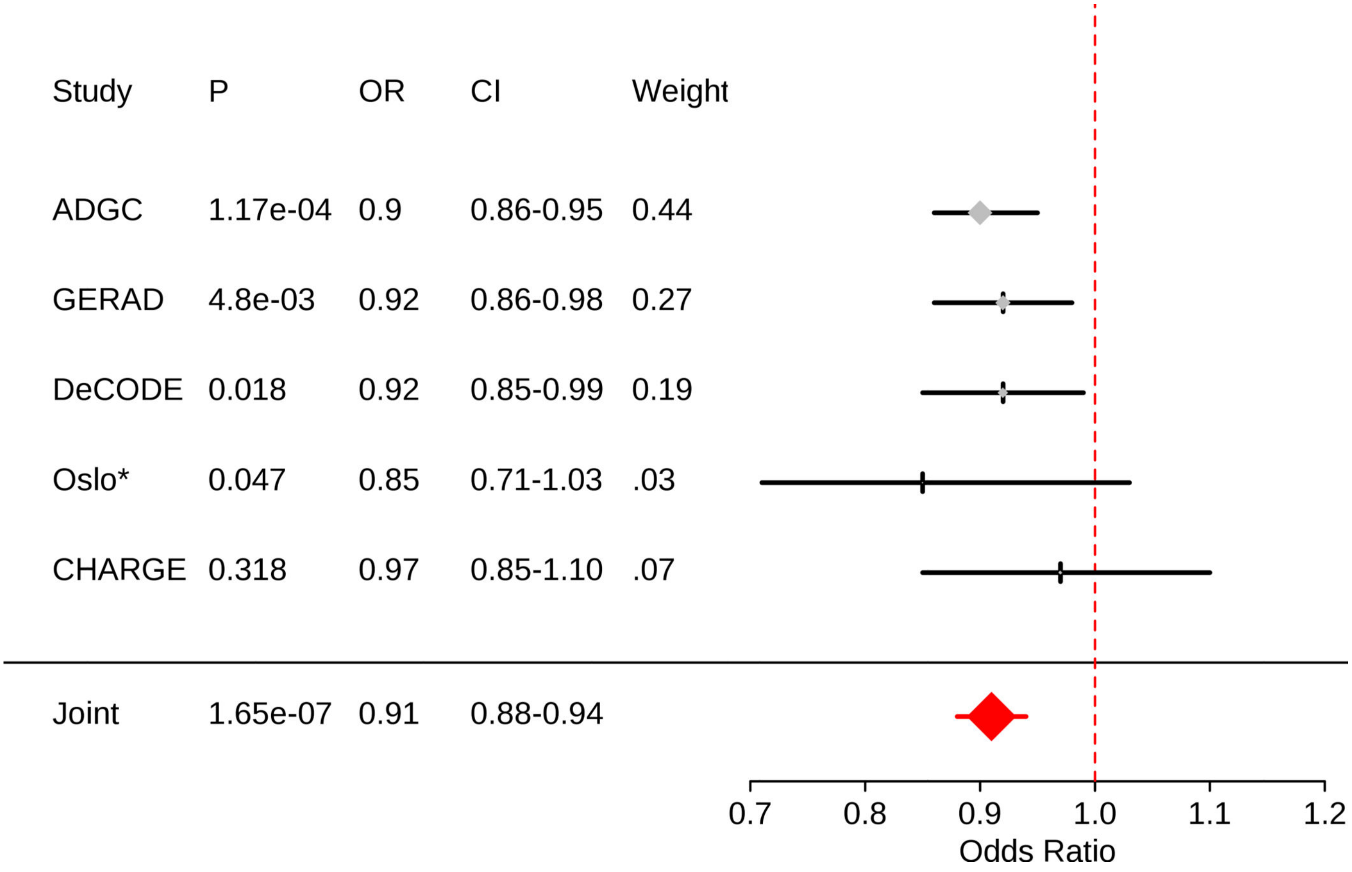
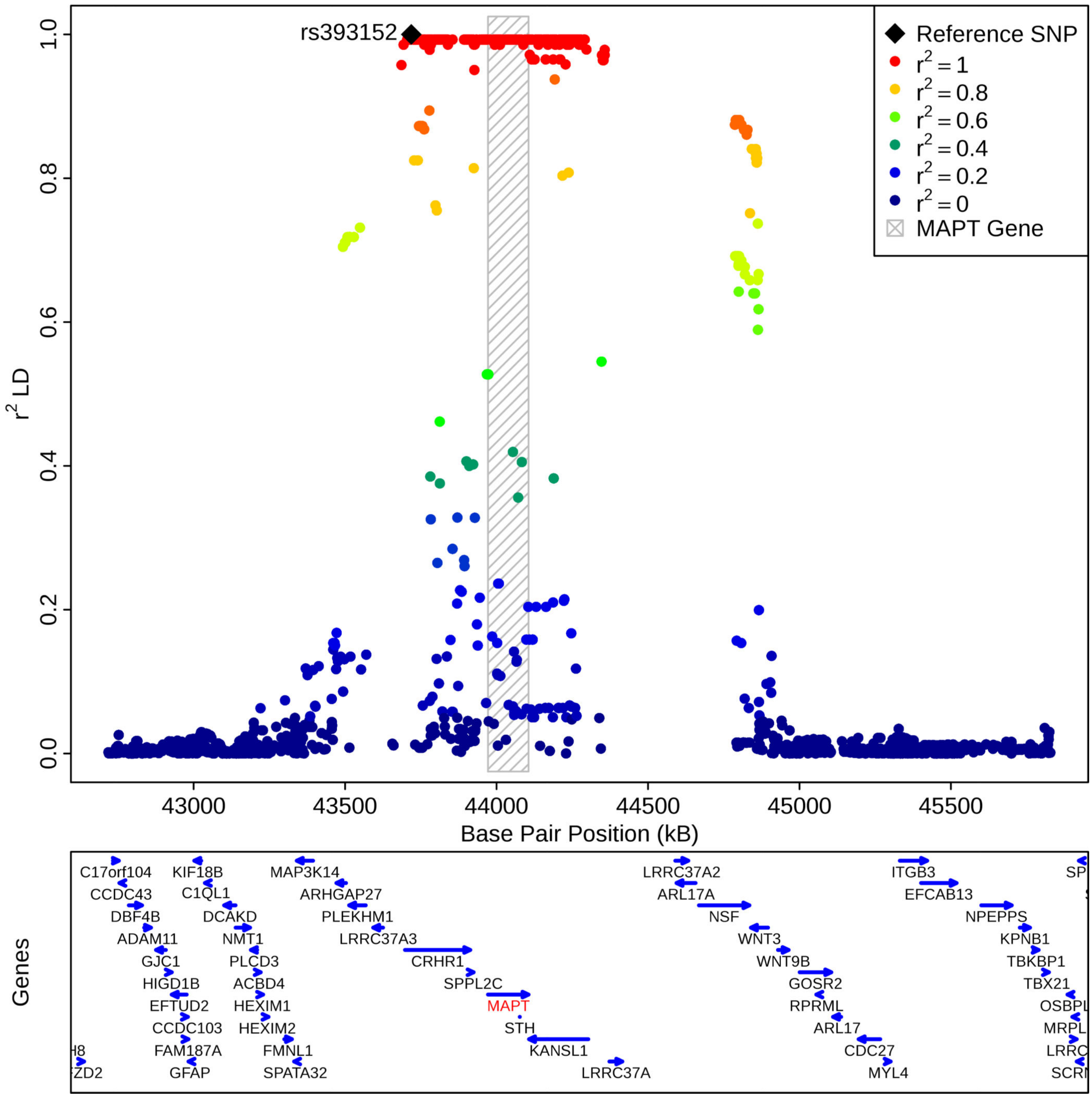


Study	P	OR	CI	Weight
ADGC	1.17e-04	0.9	0.86-0.95	0.44
GERAD	4.8e-03	0.92	0.86-0.98	0.27
DeCODE	0.018	0.92	0.85-0.99	0.19
Oslo*	0.047	0.85	0.71-1.03	.03
CHARGE	0.318	0.97	0.85-1.10	.07
Joint	1.65e-07	0.91	0.88-0.94	

Figure 1.

Forest plot for rs393152. Since rs393152 was not available within the Oslo cohort (*), we used a proxy SNP (rs17690703; r^2 = .765, D'=1 in Hapmap2).


rs393152
◆ Reference SNP
● $r^2 = 1$
● $r^2 = 0.8$
● $r^2 = 0.6$
● $r^2 = 0.4$
● $r^2 = 0.2$
● $r^2 = 0$
☒ MAPT Gene
r^2 LD
0.0
0.2
0.4
0.6
0.8
1.0
43000
43500
44000
44500
45000
45500
Base Pair Position (kB)
Genes
C17orf104
CCDC43
DBF4B
ADAM11
GJC1
HIGD1B
EFTUD2
CCDC103
FAM187A
GFAP
H8
ZD2
KIF18B
C1QL1
DCAKD
NMT1
PLCD3
ACBD4
HEXIM1
HEXIM2
FMNL1
SPATA32
MAP3K14
ARHGAP27
PLEKHM1
LRRC37A3
CRHR1
SPPL2C
MAPT
STH
KANSL1
LRRC37A
LRRC37A2
ARL17A
NSF
WNT3
WNT9B
GOSR2
RPRML
ARL17
CDC27
MYL4
ITGB3
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NPEPPS
KPNB1
TBKBP1
TBX21
OSBPL
MRPL
LRRC
SCRI
SP

Figure 2a

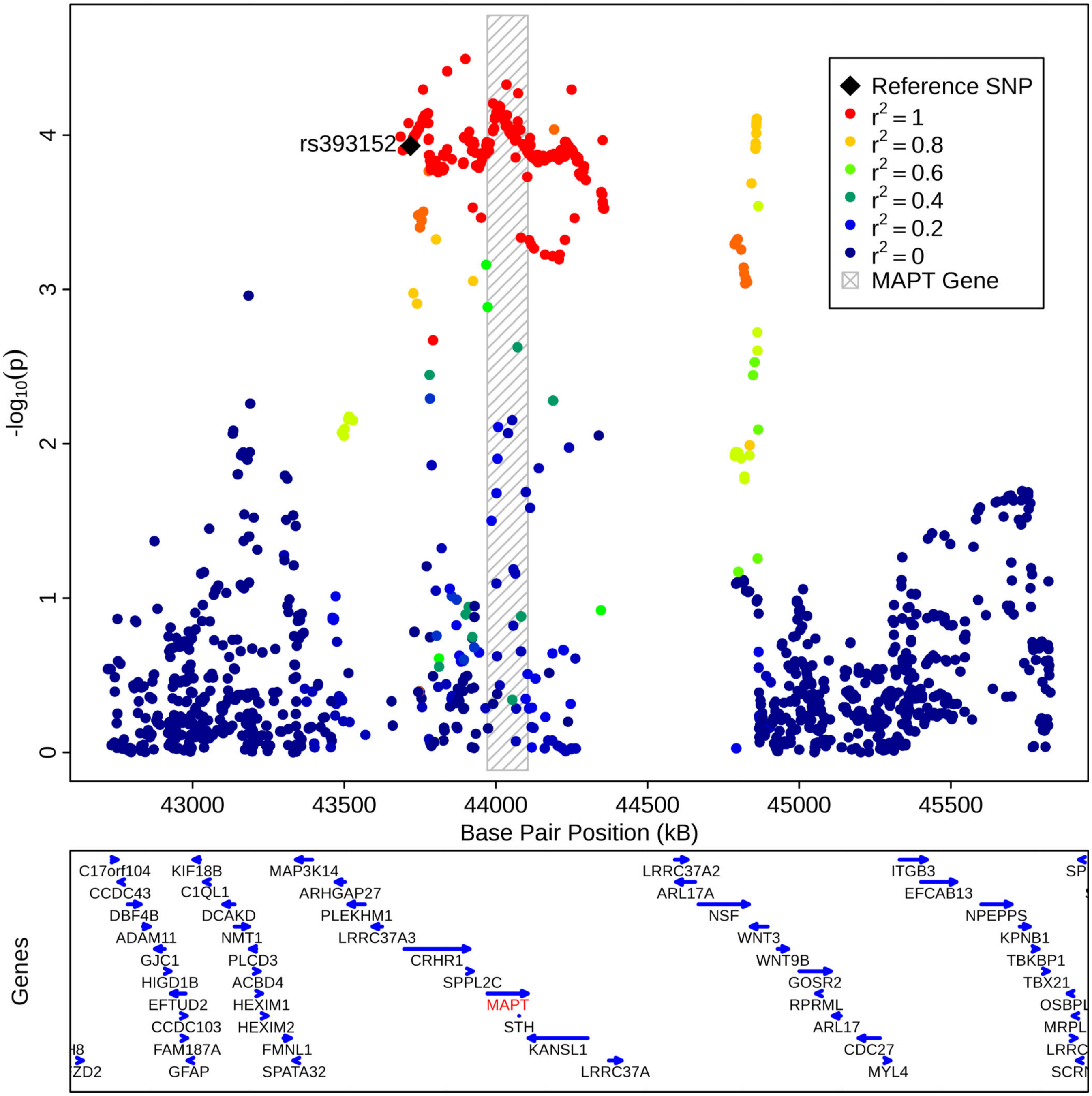

Figure 2b

Figure 2.

(a) Regional linkage disequilibrium (LD) plot demonstrating the relationship between rs393152 on chromosome 17 and loci greater than and less than 1 MB. The bottom panel indicates the location of genes in the region. Linkage Disequilibrium measured in the 1000 genomes European Populations using plink v1.07.

(b) Regional association plot illustrating the association signal within the *MAPT* region on chromosome 17. The bottom panel indicates the location of genes in the region. Linkage Disequilibrium measured in the 1000 genomes European Populations using plink v1.07.

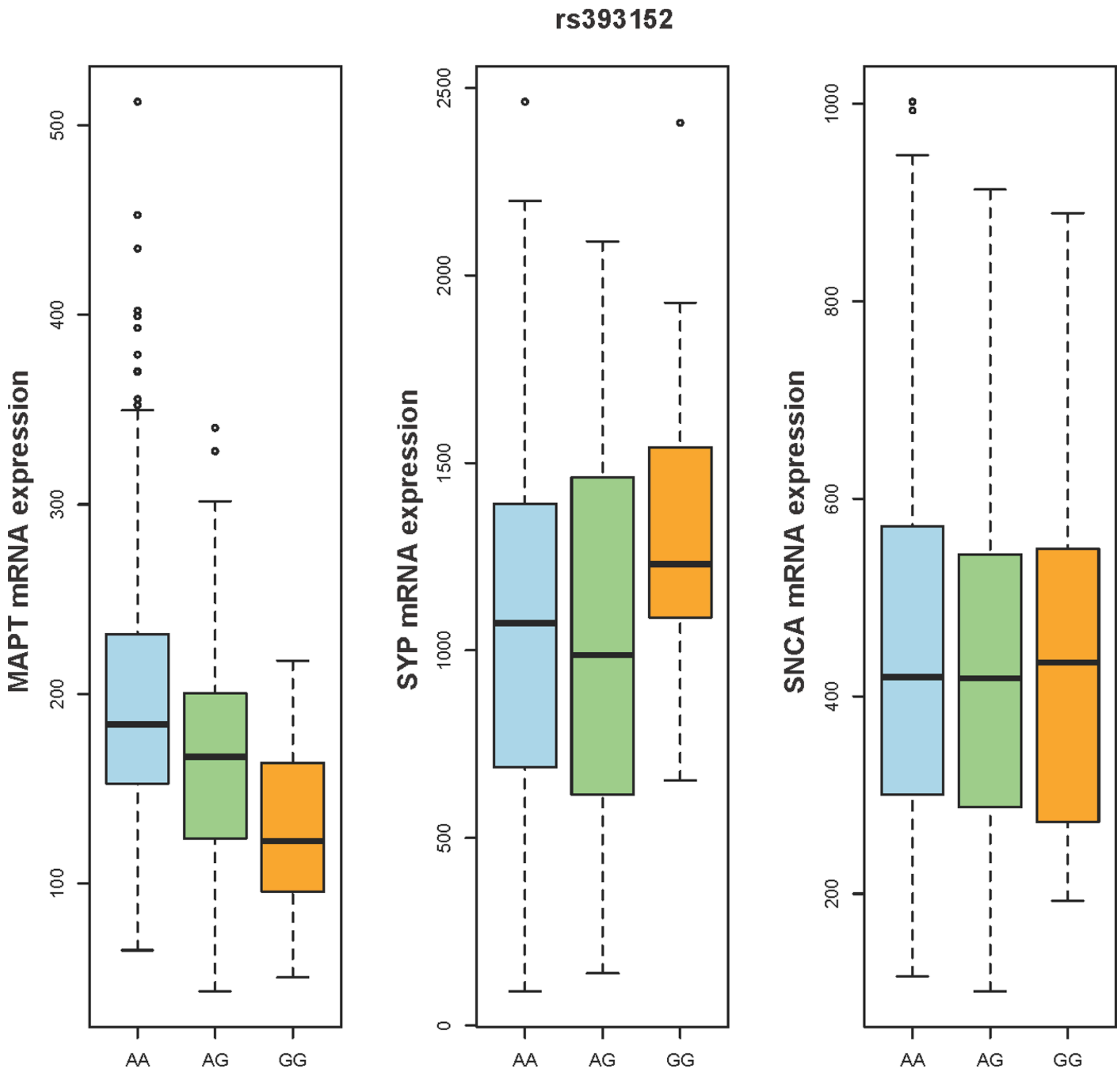

Figure 3.

Box plots illustrating the relationship between rs393152 alleles (x-axis) and gene expression levels of *MAPT*, *SYP*, and *SNCA* (y-axis). For each plot, thick black lines show the median value. Regions above and below the black line show the upper and lower quartiles, respectively. The dashed lines extend to the minimum and maximum values with outliers shown as open circles. For *MAPT*, a proxy SNP was used (please see Results for additional details). As illustrated, the A allele of rs393152 demonstrated a selective dose-dependent effect on the level of intracranial *MAPT* transcript.

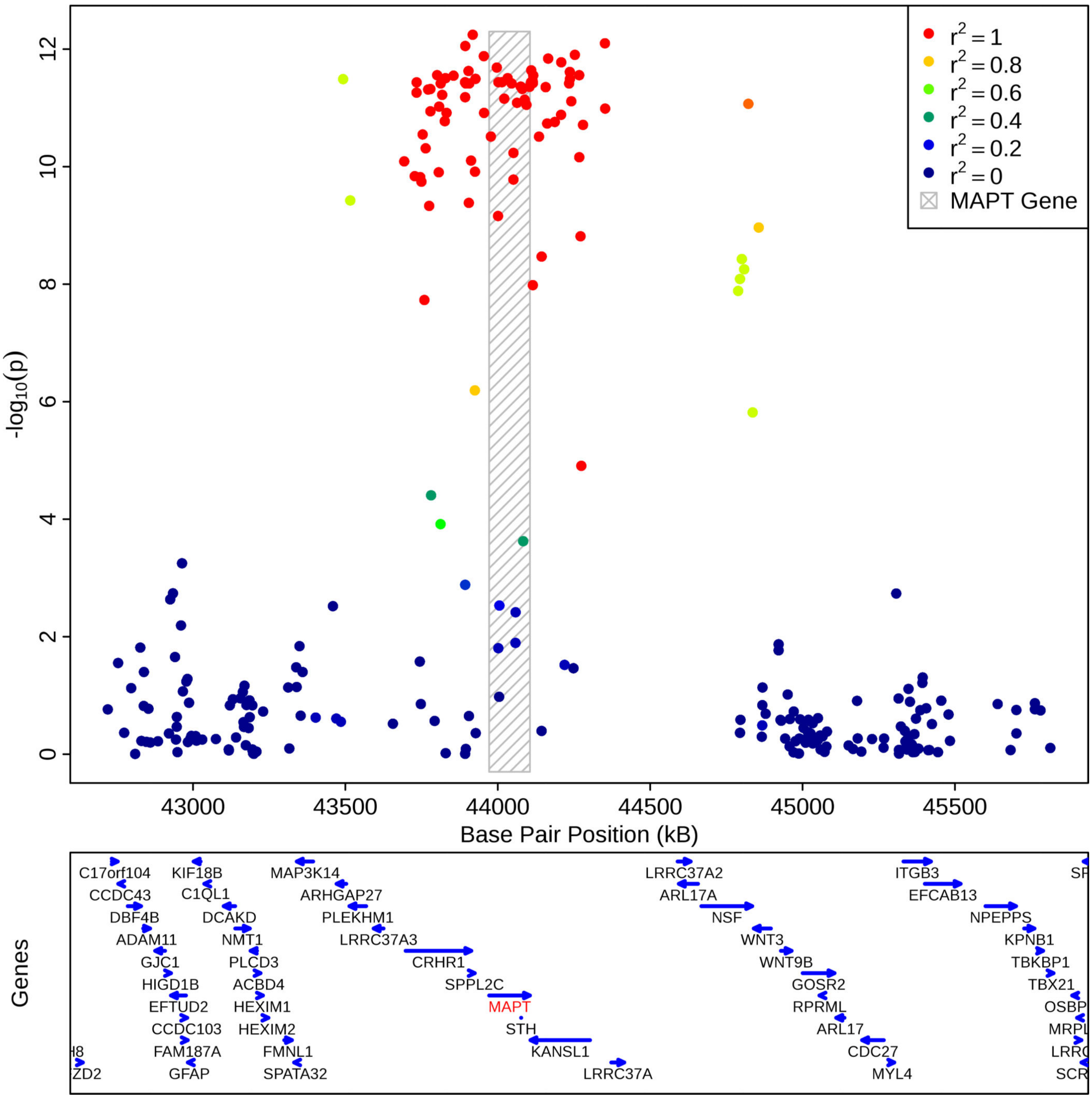

Figure 4.

Regional association plot demonstrating the relationship between *MAPT* transcript expression levels (y-axis) and SNPs in LD with rs393152 on chromosome 17. The bottom panel indicates the location of genes in the region. Linkage Disequilibrium measured in the 1000 genomes European Populations using plink v1.07. As illustrated, SNPs in r^2 LD =1 with rs393152 constituted the peak of the association signal with *MAPT* transcript expression levels.

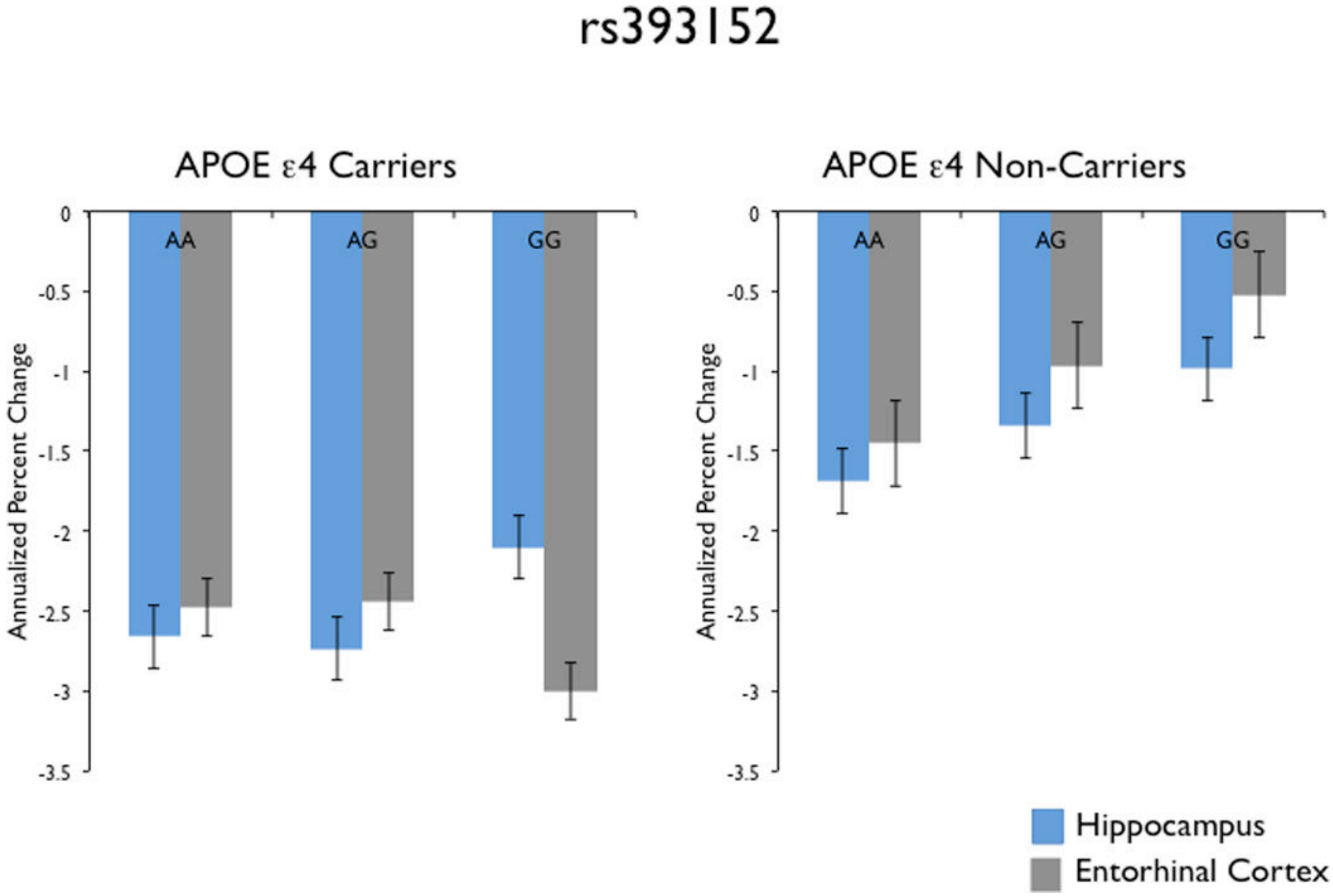

Figure 5.

Bar plots demonstrating the relationship between rs393152 alleles (x-axis) and volume loss (annualized percent change – y-axis) of the hippocampus (blue) and entorhinal cortex (gray) among *APOE* ε4 carriers (left panel) and *APOE* ε4 non-carriers (right panel). As illustrated, the A allele of rs393152 demonstrated a selective dose-dependent relationship with medial temporal lobe atrophy only among *APOE* ε4 non-carriers.

Table 1

a: Characteristics of Parkinson's disease (IPDGC) and primary Alzheimer's disease (ADGC) genome-wide association studies evaluated in this manuscript.

	IPDGC		**ADGC**	
	Cases	**Controls**	**Cases**	**Controls**
N	5333	12019	11840	10931
Age at assessment (mean)	57.6	67.8	80.6	76.7
% Women	41	48.7	61	58.5
% ***APOE*** **ε4 carriers**	N/A	N/A	51.6	26.7

b: Demographic, clinical, and imaging data for all ADNI participants evaluated in this study. AD = Alzheimer's disease, MCI = mild cognitive impairment, HC = cognitively normal older adults, MMSE = Mini-mental status exam, CDR-SB = Clinical Dementia Rating-Sum of Boxes score

	HC (n = 174)	**MCI (n = 311)**	**AD (n = 135)**
Age, Mean (SD)	76.3 (5.1)	75.0 (7.3)	75.4 (7.7)
Female, %	48	36	48
Education Years, Mean (SD)	16.1 (2.7)	15.7 (2.9)	14.9 (2.9)
CDR-SB, Mean (SE)	0.03 (0.11)	1.6 (0.9)	4.2 (1.5)
APOE ε4 carriers (%)	25	57	69
Entorhinal cortex APC, Mean (SD)	−0.57 (2.5)	−2.10 (1.6)	−2.92 (1.7)
Hippocampus APC, Mean (SD)	−0.90 (1.1)	−2.19 (1.7)	−3.45 (1.9)

Table 2

Summary of evaluated loci.

SNP	Chr	Nearest Gene	Minor Allele Frequency	Risk Allele for PD	PD p-value	Risk Allele for AD	ADGC p-value	Other genes in genomic region defined by LD
rs9917256	2	*STK39*	0.1365	A	1.62×10^{-9}	A	0.79	
rs11248051	4	*GAK*	0.1299	T	3.50×10^{-8}	T	0.19	*DGKQ, TMEM175*
rs4698412	4	*BST1*	0.4344	A	2.03×10^{-8}	G	0.031	
rs356220	4	*SNCA*	0.4869	T	1.47×10^{-25}	C	0.014	*CR605611*
rs3857059	4	*SNCA*	0.0684	G	1.66×10^{-14}	A	0.78	*AK123890, MMRN1*
rs2197120	4	*SNCA*	0.1995	G	6.29×10^{-10}	G	0.99	*AK123890*
rs12603319	17	*FBXW10*	0.2192	T	1.144×10^{-8}	T	0.39	
rs393152	17	*CRHR1*	0.231	A	2.22×10^{-18}	A	1.17×10^{-4}	*ARHGAP27, KANSL1, LOC100128977, LOC5132, LOC644172, MAPT, MGC57346, PLEKHM1*