Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Description of cohorts

The study included subjects from the Adult Changes in Thought (ACT) Study[1], the National Institute on Aging (NIA) Alzheimer's Disease Centers (ADCs),[2] the University of Miami/Vanderbilt University (UM/VU),[3,4] the Mount Sinai School of Medicine (MSSM) Brain Bank,[5] the Washington Heights Inwood Columbia Aging Project (WHICAP),[6] The African American Alzheimer's Disease Genetics (AAG) Study,[7] the MIRAGE Study,[8] NIA- LOAD/NCRAD,[9] the Mayo Clinic,[10] the Rush University Alzheimer's disease Center (ROS/MAP, MARS/CORE),[11–14] the Chicago Health and Aging Project (CHAP),[15,16] the Indianapolis Ibadan Dementia Study (Indianapolis),[17] the Genetic and Environmental Risk Factors for Alzheimer's Disease Among African Americans (GenerAAtions) Study,[18] the University of Pittsburgh (UP),[19] and Washington University (WU)[20–23]. As described in the main text, the analyses were restricted to individuals of African American ancestry. All subjects were recruited under protocols approved by the appropriate Institutional Review Boards.

The Adult Changes in Thought Study (ACT): The ACT cohort[1] is an urban and suburban elderly population from a stable HMO. The original cohort of 2,581 cognitively intact participants age ≥ 65 were enrolled between 1994 and 1998; of these 4% were African American. An additional 811 participants were enrolled in 2000-2002 using the same methods except oversampling clinics with more minorities, resulting in an overall rate of 5% African Americans. More recently, a continuous enrollment strategy was initiated in which new participants are contacted, screened and enrolled to keep 2,000 active at-risk person-years accruing in each calendar year. This resulted in an overall enrollment of 4,729 participants as of June 2012, of whom 193 (4.1%) were African American. All clinical data are reviewed at a consensus conference. Dementia onset is assigned half way between the prior biennial and the exam that diagnosed dementia. Enrollment for the eMERGE Study began in 2007. A waiver of consent was obtained from the IRB to enroll deceased ACT participants, and consent for data sharing was obtained from living participants. In total, ACT/eMERGE contributed data on 32 individuals with probable or possible AD and on 65 CNEs who were included in analyses.

The African American Alzheimer's Disease Genetics (AAG) Study. Participants of the multisite AAG study[7] that contributed to this study were recruited between 2008 and 2011 from communities surrounding four locations: Columbia University in New York City, NY, North Carolina State A&T University in Greensboro, NC, University of Miami, FL, and Vanderbilt University in Nashville, TN. Participants were recruited from various sources, including naturally occurring retirement communities, churches, Black fraternal and other organizations, community centers, health fairs, physician's offices, newspaper ads, and word-of-mouth. All participants were age 60 and older and described themselves as non-Hispanic and Black. A one-time in- person evaluation included a comprehensive neuropsychological test battery, a medical and neurological examination, and assessment of memory complaints, as well as an informant interview assessing functional status and possible change in cognitional and daily activities.

These data were evaluated in a consensus conference and diagnoses were based on standard research criteria[24] and categorized according to National Alzheimer's Coordinating Center (NACC) criteria. Blood was drawn and sent to the National Cell Repository for Alzheimer's Disease (NCRAD). The current study included 624 people with AD and 161 controls from the AAG cohort. DNA was prepared by NCRAD for genotyping and sent to the genotyping site at Children's Hospital of Philadelphia.

The NIA ADC Samples (ADC): The NIA ADC cohort[13] included subjects ascertained and evaluated by the clinical and neuropathology cores of the 29 NIA-funded ADCs. Data collection is coordinated by the NACC. NACC coordinates collection of phenotype data from the 29 ADCs, cleans all data, coordinates implementation of definitions of AD cases and controls, and coordinates collection of samples. The ADC cohort consists of 228 autopsy-confirmed or clinically-confirmed African American AD cases, and 189 autopsy-confirmed or clinically-confirmed cognitively normal elders (CNEs) who were older than 60 years at death or at assessment. Based on the data collected by NACC, the

ADGC Neuropathology Core Leaders Subcommittee derived inclusion and exclusion criteria for AD and control samples. The clinical evaluation was made using the Uniform dataset (UDS) protocol. AD cases were demented according to DSM-IV criteria or Clinical Dementia Rating (CDR) ≥ 1. Neuropathologic stratification of cases followed NIA/Reagan criteria explicitly, or used a similar approach when NIA/Reagan criteria were coded as not done, missing, or unknown. Cases were intermediate or high likelihood by NIA/Reagan criteria with moderate to frequent amyloid plaques and neurofibrillary tangle (NFT) Braak stage of III-VI. Persons with Down's syndrome, non-AD tauopathies and synucleinopathies were excluded. All autopsied controls had a clinical evaluation within two years of death. Controls did not meet DSM-IV criteria for dementia, did not have a diagnosis of mild cognitive impairment (MCI), and had a CDR of 0, if performed. Controls also did not meet or were low-likelihood AD by NIA/Reagan criteria, had sparse or no amyloid plaques, and a Braak NFT stage of 0 – II. ADCs sent frozen tissue from autopsied subjects and DNA samples from some autopsied subjects and from living subjects to the ADCs to NCRAD. DNA was prepared by NCRAD for genotyping and sent to the genotyping site at Children's Hospital of Philadelphia. ADC samples were genotyped and analyzed in separate batches. The subjects included in this study were genotyped in three waves. While most neuropathologically- and clinically-characterized cases and CNEs were part of the first two waves (ADC1 and ADC2, n=62 cases and 77 CNEs), the third wave consisted of clinically-identified living cases and CNEs (ADC3, n=186 cases and 112 CNEs.

The Chicago Health and Aging Project (CHAP) is a longitudinal cohort study[15,16] of all participating residents 65-years-of-age-and older of a geographically defined biracial community located on the southwest side of Chicago. At each of six data collection cycles (every three years), all subjects have undergone brief cognitive testing and a stratified random sample of about 500-600 subjects (aggregate 2844) has undergone detailed clinical evaluation. The subjects provided for analysis were diagnosed with prevalent or incident Alzheimer's disease at these clinical evaluations.

The Genetic and Environmental Risk Factors for Alzheimer's Disease Among African Americans (GenerAAtions) Study: Participants of the GenerAAtions Study[18] were identified through the electronic claims database of the Henry Ford Health System. Community-dwelling African Americans aged 65 and older who had at least one encounter with the Henry Ford Health System in the three years prior to their recruitment and who had an available proxy informant were eligible for this study. Cases met NINCDS-ADRDA criteria for possible or probable AD, determined in a consensus conference which included a behavioral neurologist, psychiatrist, neuropsychologist, and a behavioral neurology nurse practitioner. Phenotypic and GWAS data were available for 242 AD cases and 204 cognitively normal controls. GWAS genotyping of this sample was performed using the Illumina 660 chip as previously described[18].

Indianapolis Cohort of the Indianapolis Ibadan Dementia Study, Indiana University (IU): The African American participants that were included in this study (173 cases, 1002 controls)[17] were part of the community-based longitudinal comparative epidemiological study of African Americans in Indianapolis, and Yoruba Nigerians living in the city of Ibadan. In 1992 enrollment staff employed home visits to randomly sampled residential addresses in 29 contiguous U.S. Census tracts. Entry criteria were: age $\geq$ 65, self-identified African American, and living at sampled address. At that time 2,212 participants were enrolled. In 2001 new participants were enrolled using random sampling from Medicare rolls, with entry criteria: age $\geq$ 70, and self-identified African American. At that time 1,892 participants were enrolled. Participants were evaluated every two to three years with the Community Screening Interview for Dementia (CSI- D). Based on CSI-D scores individuals were selected for a full diagnostic clinical assessment including: CERAD neuropsychological battery, physical and neurological exam, and informant interview. Diagnoses were made by a panel of clinicians using standard criteria.[17]

Mayo Clinic: Included from the Mayo Clinic were 64 cases and 195 CNEs.[10] All subjects were

diagnosed by a neurologist at the Mayo Clinic in Jacksonville, Florida or Rochester, Minnesota. The neurologist confirmed a Clinical Dementia Rating score of 0 for all controls; cases had diagnoses of possible or probable AD made according to NINCDS-ADRDA criteria.[24]

The MIRAGE Study (MIRAGE): The MIRAGE study[8] is a family-based genetic epidemiological study of AD that enrolled AD cases and unaffected sibling controls at 17 clinical centers in the United States, Canada, Germany, and Greece, and contributed 51 African American cases and 65 CNEs that were genotyped on the Illumina 300k chip and 188 African American cases and 236 CNEs that were genotyped on the Illumina 660k chip. In brief, families were ascertained through a proband meeting the NINCDS-ADRDA criteria for definite or probable AD. Unaffected sibling controls were verified as cognitively healthy based on a Modified Telephone Interview of Cognitive Status score ≥ 86.

Mount Sinai School of Medicine (MSSM): The MSSM dataset[12] contains 29 African American AD cases (all neuropathologically confirmed) and 14 CNEs (all neuropathologically confirmed), recruited to the Mount Sinai Brain Bank. Subjects had been residents of the Jewish Home and Hospital in Manhattan and The Bronx, NY and were participants in a longitudinal study of aging and dementia[12]. Brains were donated by the next of kin of deceased residents. AD diagnoses were based on clinical assessment including neuropathological assessments and subjects met CERAD criteria for definite AD or probable AD. CDR assessments, based on cognitive and functional status during the last 6 months of life, had been carried for every subject.

NIA-LOAD/NCRAD: The NIA LOAD Family Study[9] recruited families with two or more affected siblings with LOAD and unrelated, CNEs similar in age and ethnic background. A total of 35 African American familial cases and 61 unaffected individuals were recruited through the NIA- LOAD study, NCRAD, and the University of Kentucky and included for analysis. One case per family was selected

after determining the individual with the strictest diagnosis (definite> probable > possible LOAD). If there were multiple individuals with the strictest diagnosis, then the individual with the earliest age of onset was selected. The controls included only those samples that were neurologically evaluated to be normal and were not related to a study participant.

The Rush Studies (ROS/MAP/MARS/CORE): ROS/MAP are two community-based cohort studies[12–14]. The ROS has been on-going since 1993, with a rolling admission. Through July of 2010, 1,147 older nuns, priests, and brothers from across the United States initially free of dementia who agreed to annual clinical evaluation and brain donation at the time of death completed their baseline evaluation. Of these, 89 self-reported African Americans were included in the current study. The MAP has been on-going since 1997, also with a rolling admission.

Through July of 2010, 1,392 older persons from across northeastern Illinois initially free of dementia who agreed to annual clinical evaluation and organ donation at the time of death completed their baseline evaluation and 97 self-reported African Americans were included in this meta-analysis. Details of the clinical and neuropathologic evaluations have been previously reported[12–14]. A total of 130 persons passed genotyping QC. Of these, 30 met clinical criteria for AD at the time of their last clinical evaluation or time of death and met neuropathologic criteria for AD for those on whom neuropathologic data were available, and 100 were without dementia or MCI at the time of their last clinical evaluation or time of death and did not meet neuropathologic criteria for AD for those on whom neuropathologic data were available. MARS[11] is a community-based cohort study of older African Americans with a rolling admission. Through July of 2010, 356 self-reported African Americans without known dementia who agreed to annual clinical evaluation completed their baseline evaluation. CORE[11] is a community-based cohort study of older African Americans with and without dementia at baseline. Through July 2010, CORE has enrolled 218 older Africans without dementia at baseline.

University of Miami/Vanderbilt University (UM/VU): The UM/VU dataset[3,4] contains 110 African

American cases and 189 CNEs ascertained at the University of Miami and Vanderbilt University. Each affected individual met NINCDS-ADRDA criteria for probable or definite AD with age at onset greater than 60 years as determined from specific probe questions within the clinical history provided by a reliable family informant or from documentation of significant cognitive impairment in the medical record. Cognitively healthy controls were unrelated individuals from the same catchment areas and frequency matched by age and gender, and had a documented MMSE or 3MS score in the normal range.

University of Pittsburgh. The UPITT dataset[19] contains 114 African American AD cases (of which 6 were autopsy-confirmed) recruited by the University of Pittsburgh Alzheimer's Disease Research Center, and 79 African American CNEs ages 60 and older (2 were autopsy-confirmed). All AD cases met NINCDS/ADRDA criteria for probable or definite AD[24].

The Washington Heights Inwood Aging Project (WHICAP). The African American participants that were included in the present study (170 cases, 299 controls) were part of a longitudinal cohort study enrolled by a random sampling of Medicare recipients 65 years or older residing in northern Manhattan, New York[6,25]. Each participant underwent an interview of general health and function, medical history, a neurological examination, and a neuropsychological battery. Baseline data were collected from 1999 through 2001. Follow-up data were collected at sequential intervals of 18 months. Diagnosis of dementia etiology was made based on standard criteria[24], and severity of dementia was assessed using the Clinical Dementia Rating scale.

Washington University (WU): An African American LOAD case-control dataset consisting of 87 cases and 30 healthy elderly controls was used in analyses for this study[20–23]. Participants were recruited as part of a longitudinal study of healthy aging and dementia. Diagnosis of dementia etiology

was made in accordance with standard criteria and methods[24]. Severity of dementia was assessed using the Clinical Dementia Rating scale.

eMethods.

Study subjects and samples. Written informed consent was obtained from all study participants; for participants with substantial cognitive impairment, informed consent was acquired from the legal guardian. All study protocols were approved by the corresponding institutional review boards.

Diagnosis of AD and age of onset. All participants underwent rigorous phenotyping for AD, and diagnoses were made by National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria[26,27]. For most datasets, information on age at onset for affecteds and age at examination or death for unaffecteds was available. However, for some datasets, surrogate age information was available including age at diagnosis (Chicago Health and Aging Project [CHAP], Minority Aging Research Study/Clinical Minority Core [MARS/CORE]), age at ascertainment (Indiana University), or age at death (subset of autopsy-confirmed samples in the University of Miami/Vanderbilt University [UM/VU] dataset). To restrict the analyses to cases with late-onset AD, persons younger than 60 years at symptom onset, last examination or death were excluded.

Genotyping. Genome-wide genotyping arrays and methods for APOE genotyping employed in the individual datasets are summarized in the **Supplemental Material** (**Supplementary Methods** and **Supplementary Table 1**). For all data sets, samples were randomly plated to minimize potential batch effects.

APOE **genotyping.** For the Alzheimer Disease Centers, Adult Changes in Thought, National Institute in Aging–LOAD/National Cell Repository for Alzheimer Disease (NIA-LOAD/NCRAD), UM/VU, CHAP, Columbia University, and Mayo Clinic cohorts, *APOE* genotypes were based on haplotypes derived

from single-nucleotide polymorphisms (SNPs) rs7412 and rs429358. For the MIRAGE and GenerAAtions cohorts, *APOE* genotypes were determined using the Roche Diagnostics LightCycler 480 instrument (Roche Diagnostics) and LightMix Kit ApoE C112R R158 (TIB MOLBIOL); for the University of Pittsburgh, Washington Heights Columbia Aging Project, and Indianapolis cohorts, they were determined by pyrosequencing or analysis of restriction fragment length polymorphisms; for the Religious Orders Study/Rush Memory and Aging Project (ROS/MAP) and MARS/CORE they were determined by high-throughput sequencing of codons 112 and 158 in *APOE* by Agencourt Bioscience Corporation; for the Washington University samples they were determined using a taqman-based assay from Applied Biosystems.

Genotype quality control. Standard quality control for genotype and sample-level data was conducted individually for each dataset. Single-nucleotide polymorphisms with call rates less than 98% or not in Hardy-Weinberg equilibrium ($P < 10^{-6}$ in controls) were excluded. Individuals with non-African American ancestry according to principal components (PCs) analysis of ancestry informative markers were excluded, as were participants whose reported sex differed from the sex assignment determined by analysis of the X-chromosome SNPs. Latent relatedness among participants within and across the case-control datasets was identified by the estimated proportion of alleles (π) shared identical by descent (IBD). One participant from each duplicate pair ($\pi > 0.95$) or relative pair ($0.4 \leq \pi < 0.95$) was included in the sample used for association analyses, prioritizing based on nonmissing disease status and then higher SNP call rate. Relationships among individuals in the family-based cohorts (MIRAGE, NIA-LOAD/NCRAD) were confirmed by pairwise genome-wide estimates of IBD allele sharing.

Genotype imputation. After genotype quality control, all datasets were individually phased and imputed to both the 1000 Genomes Phase 3 and African Genome Resource (AGR) panel using the

Sanger Imputation server and employing EAGLE2 and PBWT (https://imputation.sanger.ac.uk/). The AGR reference panel provides information on 93,421,145 bi-allelic markers and contains 4,956 samples, ie. all of the African and non-African populations from 1000 Genomes Phase 3 and additionally ~2000 samples from Uganda (Baganda, Banyarwanda, Barundi and others) and ~100 samples from each of a set of populations from Ethiopia (Gumuz, Wolayta, Amhara, Oromo, Somali), Egypt, Namibia (Nama/Khoesan) and South Africa (Zulu). Common variants (MAF ≥ 0.01) with imputation quality score < 0.4, rare variants (MAF < 0.01) with imputation quality < 0.7, and variants present in less than 30% of AD cases and 30% of controls across all datasets were excluded from downstream analyses. Comparison of imputation quality of 1000G and AGR vs. available WES data in 800 subjects slightly highly quality in the AGR (see **Supplementary Table 2**). Therefore, this panel was used for primary analyses. The final SNP set for analysis included a total of 29,610,185 genotyped and imputed variants, more than doubling the number of variants from our previous analysis in 2013[28].

Association analysis. Restricting the analysis to variants with minor allele frequency (MAF) > 0.005 and present in >= 30% of cases and 30% controls, single variant association analysis was performed on genotype dosages employing an additive model adjusting for age, sex, PCs for population substructure (Model 1), and subsequently in addition *APOE* genotype (Model 2). For case-control datasets, we employed logistic regression using SNPTEST 2.5.2. For family-based datasets (MIRAGE, NIALOAD/NCRAD) we employed generalized estimating equations (GEE) as implemented in GWAF v2.2[29]. Within-study results were meta-analyzed using an inverse-variance based model with genomic control as implemented in METAL (version released on 2011-03-25)[30]. Variants with high heterogeneity between studies (I^2 > 75%) were removed. Genomic inflation (λ) was estimated using the GenABEL package version 1.8-0[31].

Gene-based analyses. Genome-wide gene-based analyses were conducted using MAGMA via FUMA v1.3.5b[32,33]. Adding a 15kb window to each side of the genes, gene-based testing was implemented for models adjusting (1) for PCs, age and sex, and (2) PCs, age, sex and *APOE* genotype, including all variants with minor allele frequency >0.001 and present in >= 30% of cases and 30% controls. Genome-wide significance was determined using Bonferroni correction.

Postmortem brain data from the ROS/MAP cohort

Postmortem neuropathological assessment. All postmortem brain data were generated as part of the Religious Orders Study[34] and Memory and Aging Project (ROS/MAP)[35]; two ongoing, longitudinal cohort studies of aging coordinated by the Rush Alzheimer's Disease Center (RADC) in Chicago, that also contributed samples to the genotyping (see detailed description of the ROS/MAP cohort in the eMethods). All subjects are recruited free of dementia at age 65 and older (mean age at entry 78±9 years), are administered annual cognitive and clinical assessments, and sign an Anatomical Gift Act. All study protocols were approved by the Institutional Review Board of Rush University Medical Center, and all study participants have provided informed, written consent. Data generated from ROS/MAP are available for download via the RADC Resource Sharing Hub (https://www.radc.rush.edu/). All ROS/MAP subjects were administered detailed neuropathological evaluations at autopsy by a board-certified neuropathologist who was blind to clinical data, and neuroimmunohistochemical quantifications of total amyloid and tau burden were derived[36]. Detailed descriptions of each pathological measure are readily available at the RADC website (https://www.radc.rush.edu/).

RNA sequencing and gene expression quantification. Gene expression data were generated using RNA-seq from dorsolateral prefrontal cortex (DLPFC) of 478 ROS/MAP subjects, according to previously published methods[37]. Briefly, RNA was extracted using Qiagen's miRNeasy mini kit and RNase free DNase Set. Libraries were prepared by the Broad Institute's Genomic Platform (strand specific dUTP method and poly-A selection)[38,39]. Sequencing was performed using the Illumina HiSeq platform (50 million paired-end reads, 101bp each). Alignment was performed using Trinity[40] to the GENCODE v14 transcriptome (GRCh37; https://www.gencodegenes.org/releases/). Quantification of gene counts was performed using RSEM[41], batch normalization with Combat[42], and mean-variance correction weights calculated using the edgeR[43] and voom[44] Bioconductor packages in R (v3.4.1)[45].

Association of gene expression with clinical diagnosis and neuropathological endophenotypes of AD in the ROS/MAP cohort. To detect associations between the expression of target genes and levels of postmortem neuropathology, gene counts from voom were analyzed in a robust linear model using iterative re-weighted least squares regression with amyloid and tau pathology as independent variables (implemented in the 'MASS' R package), co-varying for effects of sex, age at death (age at last visit for clinical AD diagnosis), postmortem interval, RNA integrity, *APOE ε4* status, and first three genomic principal components calculated using EIGENSTRAT. Subsequent models were further adjusted for differences in cell type composition by adding expression values of neuronal nuclear protein (NeuN) to the model. Significance was determined using Bonferroni correction per pathological outcome.

Pathway analysis. Pathway analyses were performed with MAGMA[23], which performs SNP-wise gene analysis of summary statistics with correction for LD between variants and genes to test whether sets of genes are jointly associated with a phenotype (i.e. LOAD), compared to other genes across the genome.

5,917 gene-sets from GO[89] pathways were used in the analyses. Primary analyses used a 15-kb upstream/downstream window around each gene in order to potential regulatory variants for each gene.

eTable 1. Genotyping Platforms used in the individual datasets

Dataset	Platform
ADC1/2	Human660W-Quad_v1
ADC3	HumanOmniExpress-12v1
ADC4	HumanOmniExpress-12v1
ADC5	HumanOmniExpress-12v1
ADC6	HumanOmniExpress-12v1
ADC7	HumanOmniExpressExome-8 v1.2
ADC8	HumanOmniExpressExome-8 v1.2
CHOP_2017 (ADC9)	Global Screening Array v1
ACT	Illumina 660k
CHAP	Illumina 1 M
Indianapolis	Illumina 1 M
NIA-LOAD/NCRAD	Illumina 610k and 370k
ADGC [2013]*	Illumina 1Mduo (v3)
ADGC [2018a]‡	Illumina 1Mduo (v3)
Mirage 300k	Illumina 300k
Mirage 660k	Illumina 660k
GenerAAtions	Illumina 660k
ADGC [2018b]**	Global Screening Array v1
WHICAP	Illumina MEGA and Illumina OmniExpress-24v1

* includes samples from the AAG Study, ADCs, CHAP, Mayo Clinic, MSSM, NIA-LOAD/NCRAD, ROS/MAP/MARS/CORE, UM/VU, UP, WHICAP and WU
‡ includes samples from Mayo Clinic, Kamboh, WU, WHICAP, CHAP, AAG Study
** includes samples from UM/VU, North Carolina A&T, MIRAGE, ROS/MAP/MARS/CORE

eTable 2. Comparison of imputation quality of 1000G Phase 2 and AGR reference vs. whole-exome sequencing data in 800 subjects

MAF	1000G vs. WES Kappa†	AGR vs. WES Kappa†	1000G vs. AGR Kappa†
Info > 0.4			
<0.01	0.65	0.72	0.89
0.01-0.05	0.86	0.87	0.95
>0.05	0.94	0.95	0.99
Info > 0.75			
<0.01	0.79	0.83	0.92
0.01-0.05	0.92	0.92	0.98
>0.05	0.96	0.96	0.99

†Cohen's kappa κ which takes into account the possibility of the agreement occurring by chance. Kappa's baseline is the agreement (κ = 0) that would occur by random chance, given the quantities by the marginal totals.

$$k = \frac{p_o - p_e}{1 - p_e}$$

$p_e = \frac{1}{N^2}\sum_k n_{k1} n_{k2}$, *N* = sum of all entries, n_{ki}= number of times "rater" *i* predicted category *k*.

$p_o = \frac{1}{N}\sum_k r_{k1} == r_{k2}$, the number of times both "raters" predicted the same category.

eTable 3. Demographic characteristics of datasets.

Dataset	Unaffected N (% Women)	Affected N (% Women)	Age at last evaluation (mean (SD))	APOE genotype (%)			
				-/-	-/4	4/4	Missing
ACT	65 (58.5)	32 (75.0)	80.5 (6.1)	57 (58.8)	32 (33.0)	4 (4.1)	4 (4.1)
ADC1/2	72 (80.6)	53 (58.5)	70.1 (18.9)	57 (43.5)	55 (42.0)	8 (6.1)	11 (8.4)
ADC3	104 (82.7)	150 (73.5)	76.4 (12.2)	90 (35.4)	107 (42.1)	21 (8.3)	36 (14.2)
ADC8	473 (77.4)	296 (66.6)	65.9 (25.4)	400 (52.0)	315 (41.0)	54 (7.0)	0
CHAP	430 (67.2)	113 (62.5)	78.3 (9.3)	325 (59.6)	193 (35.4)	17 (3.1)	10 (1.8)
Indianapolis	1,000 (66.2)	172 (62.2)	83.0 (5.5)	747 (63.7)	371 (31.7)	54 (4.6)	0
NIA-LOAD/NCRAD	56 (69.6)	34 (79.4)	73.9 (6.9)	43 (47.3)	37 (40.7)	11 (12.1)	0
ADGC (2013*)	1,621 (74.6)	866 (74.1)	71.8 (19.3)	1,339 (52.8)	797 (31.4)	131 (5.2)	269 (10.6)
ADGC (2018a)‡	52 (71.2)	35 (80.0)	69.4 (29.1)	55 (63.2)	26 (29.9)	5 (5.7)	1 (1.1)
Mirage 300k	51 (68.6)	65 (70.8)	69.5 (13.9)	42 (36.2)	61 (52.6)	13 (11.2)	0
Mirage 600k	236 (71.2)	188 (72.9)	70.7 (12.2)	190 (44.8)	183 (43.2)	49 (11.6)	2 (0.5)
GenerAAtions	203 (60.1)	240 (56.7)	78.4 (11.5)	204 (46.0)	174 (39.3)	32 (7.2)	33 (7.4)
ADGC (2018b)**	437 (76.2)	382 (75.9)	72.8 (13.0)	430 (52.5)	306 (37.4)	67 (8.2)	16 (2.0)
WHICAP	422 (71.1)	162 (62.3)	78.4 (7.4)	737 (63.9)	191 (32.7)	19 (3.3)	1 (0.2)
Totals	5,222 (71.7)	2,784 (69.8)	74.2 (13.6)				

* includes samples from the AAG Study, ADCs, CHAP, Mayo Clinic, MSSM, NIA-LOAD/NCRAD, ROS/MAP/MARS/CORE, UM/VU, UP, WHICAP and WU
‡ includes samples from Mayo Clinic, Kamboh, WU, WHICAP, CHAP, AAG Study
** includes samples from UM/VU, North Carolina A&T, MIRAGE, ROS/MAP/MARS/CORE

eTable 4. *APOEe4*-stratified results for top loci.

Closest Gene	Marker Chr:Position	dbSNP	A1	A2	*APOE* Negative Model							*APOE* Positive Model						
					Freq A1	Beta	SE	P-value	Direction	Het ChiSq	Het Pval	Freq A1	Beta	SE	P-value	Direction	Het ChiSq	Het Pval
Novel Common Loci																		
EDEM1	3:5302077	rs168193	G	A	0.27	-0.17	0.07	0.014	-+-------+--	8.4	0.67	0.27	-0.11	0.07	0.123	+-------++++	14.6	0.19
ALCAM	3:104409208	rs2633682	A	C	0.36	0.11	0.06	0.071	+-+++++-+--+	13.3	0.27	0.37	0.03	0.06	0.599	++++-+++--++	15.5	0.16
GPC6	13:94159800	rs9516245	C	T	0.04	0.54	0.15	0.0004	+++++--++?++	23	0.01	0.09	0.59	0.16	0.0004	?-++++++-++	18.7	0.04
Novel Rare Loci																		
SIPA1L2	1:232376163	rs115684722	T	A	0.006	1.35	0.66	0.041	???+++?+???-	4.9	0.28	0.006	1.5	0.51	0.0034	?+?++++++???	2.8	0.82
WDR70	5:37483940	rs184179037	T	C	0.005	-2.08	0.5	4.3×10^{-05}	???----+-???	10.5	0.06	0.007	-1.01	0.48	0.037	+??--?---???	2.7	0.74
API5	11:43166842	rs569584007	G	T	0.001	1.32	1.68	0.431	????+??-????	2.2	0.13	0.003	1.05	0.68	0.123	????+?-++???	2	0.56
ACER3	11:76541840	rs115816806	G	A	0.005	1.8	0.59	0.002	???+++++???+	3.3	0.64	0.008	1.91	0.49	0.0001	??++++++???+	6	0.41
PIK3C2G	12:18471546	rs75739461	A	G	0.011	-0.92	0.31	0.003	??+------??-	4	0.77	0.011	-1.18	0.33	0.0004	+?---+--???+	6.3	0.5
ARRDC4, IGF1R	15:97992685	rs570487962	A	C	0.003	0.75	1.15	0.511	???-?++-????	3.5	0.31	0.005	-2.8	0.93	0.0026	???----?????	0.36	0.94
RBFOX1	16:8288401	rs79537509	T	G	0.008	-2.05	0.41	7.5×10^{-07}	+??-----+??-	11.4	0.11	0.006	-0.62	0.45	0.174	??+----+-??+	9.1	0.23
Loci reported in Reitz et al. (JAMA 2013)																		
--	5:174014114	rs145848414	A	G	0.04	-0.69	0.18	0.0001	-+-------?+-	12.2	0.2712	0.10	-0.47	0.18	0.01	---+-----++-	7.7	0.73
ABCA7	19:1050420	rs115550680	G	A	0.14	0.27	0.12	0.028	+-+-+++++-+-	25.4	0.0078	0.15	0.33	0.13	0.013	+--++++++-++	12.6	0.31
APOE	19:45423934	rs157591	A	G	0.19	-0.01	0.29	0.968	-++---++-+?+	15.3	0.1212	0.30	-0.06	0.07	0.446	+--+-++++---	10.2	0.51

Marker Chr:Position are in hg19/GRCh37 coordinates
SE: standard error
Direction: Study-specific direction of the SNP beta-coefficient
HetChiSq: Heterogeneity test statistic
HetPVal: Heterogeneity p-value

eTable 5. Sample sizes for *APOEe4*-stratified analyses.

COHORT	APOE Negative		APOE Positive	
	Cases	Controls	Cases	Controls
ACT	15	42	16	20
ADC1/2	16	41	36	27
ADC3	33	57	87	41
ADC8	109	291	187	182
ADGC CHOP	313	1026	399	529
CHAP	65	260	46	164
CHOP REDO	24	31	11	20
IGSGSA	154	276	221	152
INDIANAPOLIS	77	670	95	330
JHU	87	117	137	69
MIR600	55	132	131	100
NIALOAD	8	35	26	22
WHICAP	104	269	58	152
TOTAL	1060	3247	1450	1808

eTable 6. Single-marker meta-analysis results for previously reported variants[46–51]. Beta results are reported with respect to the minor allele.

GENE	Marker Chr:Position:A1:A2	dbSNP	MAF	Model 1			Model 2		
				Beta	SE	P-Value	Beta	SE	P-Value
Loci previously reported in African Americans									
TREM2	6:41127972:G:A	rs7748513	0.456	0.16	0.03	**3.6×10^{-5}**	0.16	0.04	**5.4×10^{-5}**
TREM2	6:41126429:T:C	rs2234258	0.037	0.32	0.10	**0.001**	0.41	0.11	**0.0001**
TREM2	6:41126655:G:A	rs2234256	0.124	0.17	0.05	**0.002**	0.18	0.06	**0.001**
COBL	7:51578022:T:A	rs112404845	0.008	0.89	0.22	**6.8×10^{-5}**	1.05	0.23	**5.4×10^{-06}**
AKAP9	7:91709085:G:A	rs14662445	0.007	0.59	0.24	**0.01**	0.17	0.18	0.34
AKAP9	7:91732110:T:C	rs149979685	0.006	0.72	0.26	**0.006**	0.79	0.28	**0.005**
SLC10A2	13:103663945:G:C	rs16961023	0.017	0.16	0.17	0.35	0.17	0.18	0.34
Loci previously reported in non-Hispanic Whites									
CR1	1:207802552:A:C	rs4844610	0.038	-0.01	0.13	0.88	0.12	0.11	0.25
BIN1	2:127892810:T:C	rs6733839	0.396	0.11	0.04	**0.01**	0.14	0.04	**0.0009**
INPP5D	2:233981912:C:G	rs10933431	0.400	-0.02	0.05	0.57	0.01	0.04	0.79
HLA-DRB1	6:32575406:T:A	rs78738018	NP	--	--	--	--	--	--
OARD1	6:41034000:C:G	rs114812713	0.005	0.18	0.29	0.52	0.10	0.32	0.75
TREM2	6:41129252:C:T	rs75932628	NP	--	--	--	--	--	--
CD2AP	6:47431284:C:A	rs9473117	0.208	0.09	0.04	**0.03**	0.10	0.04	**0.02**
NYAP1	7:100091795:T:C	rs12539172	0.127	-0.01	0.05	0.80	-0.01	0.06	0.83
EPHA1	7:143099133:A:C	rs11762262	0.184	0.01	0.04	0.80	0.02	0.05	0.69
PTK2B	8:27219987:T:C	rs73223431	0.257	0.04	0.04	0.29	0.04	0.04	0.33
CLU	8:27467686:T:C	rs9331896	0.439	-0.02	0.03	0.57	-0.02	0.04	0.54
ECHDC3	10:11720308:G:A	rs7920721	0.165	0.07	0.05	0.17	0.07	0.05	0.18
SPI1	11:47380340:G:T	rs3740688	0.268	0.02	0.04	0.56	0.03	0.04	0.51
MS4A2	11:59936926:C:A	rs7933202	0.093	-0.01	0.06	0.81	0.005	0.07	0.93
PICALM	11:85868640:T:C	rs3851179	0.156	-0.06	0.05	0.20	-0.04	0.05	0.43
SORL1	11:121435587:C:T	rs11218343	0.083	-0.06	0.06	0.37	-0.06	0.07	0.41
FERMT2	14:53391680:G:A	rs17125924	0.067	-0.11	0.07	0.12	-0.19	0.08	**0.01**
SLC24A4	14:92932828:C:T	rs12881735	0.133	-0.03	0.05	0.58	-0.02	0.06	0.68
ADAM10	15:59045774:G:A	rs593742	0.307	0.06	0.04	0.09	0.06	0.04	0.13
IQCK	16:19808163:T:C	rs7185636	0.213	-0.02	0.04	0.59	-0.06	0.05	0.18
WWOX	16:79355857:A:G	rs62039712	0.025	-0.29	0.14	**0.04**	-0.25	0.15	0.10
ACE	17:61538148:A:G	rs138190086	0.006	0.06	0.31	0.84	0.08	0.33	0.80
CASS4	20:54997568:A:G	rs6024870	0.090	0.03	0.06	0.64	0.04	0.07	0.55
ADAMTS1	21:28156856:A:C	rs2830500	0.103	-0.05	0.06	0.35	-0.05	0.06	0.39

Marker Chr:Position are in hg19/GRCh37 coordinates
A1:A2: allele 1, allele 2 with A2 representing he minor allele
MAF: minor allele frequency from Model 1
NP: Not present

eTable 7. Gene-based results for AD genes previously identified in non-Hispanic Whites or African Americans[46–49]

GENE	CHR	START BP (hg37)	STOP BP (hg37)	N	Model 1			Model 2		
					NSNPS	ZSTAT	P-Value	NSNPS	ZSTAT	P-Value
Loci previously reported in African Americans										
COBL	7	51073909	51419515	7984	3078	1.24	1.07E-01	3060	0.40	3.44E-01
AKAP9	7	91535181	91749987	7984	1333	-0.20	5.77E-01	1316	0.33	3.70E-01
SLC10A2	13	103686350	103754196	7984	704	0.82	2.07E-01	700	0.90	1.83E-01
Loci previously reported in non-Hispanic Whites										
CR1	1	207634492	207823992	7984	1004	-0.25	6.00E-01	1221	-0.18	5.73E-01
BIN1	2	127795603	127899931	7984	890	0.81	2.10E-01	1093	1.31	9.51E-02
INPP5D	2	233889677	234126549	7984	1672	0.41	3.40E-01	2104	-1.68	9.53E-01
HLA-DRB1	6	32536546	32592625	7984	1058	0.67	2.53E-01	1057	1.24	1.07E-01
*TREM2**	6	41116244	41165924	7984	450	3.98	**3.43E-05**	444	4.27	**9.89E-06**
CD2AP	6	47410525	47604999	7984	1568	1.46	7.20E-02	1555	1.84	**3.30E-02**
NYAP1	7	100046550	100102422	7984	328	-0.66	7.44E-01	324	-1.17	8.79E-01
EPHA1	7	143077382	143140985	7984	568	-0.33	6.31E-01	568	0.02	4.91E-01
PTK2B	8	27133999	27326903	7984	1933	-1.02	8.46E-01	1917	-0.22	5.86E-01
CLU	8	27444434	27507548	7984	608	0.21	4.17E-01	597	-0.01	5.05E-01
ECHDC3	10	11749365	11816069	7984	801	-0.69	7.55E-01	799	-1.60	9.45E-01
SPI1	11	47366411	47435127	7984	553	1.33	9.19E-02	551	0.39	3.49E-01
MS4A2	11	59820734	59873444	7984	573	-0.91	8.20E-01	568	-1.51	9.35E-01
PICALM	11	85658727	85815924	7984	1476	1.09	1.38E-01	1464	0.43	3.33E-01
SORL1	11	121287912	121514402	7984	1855	-0.52	6.99E-01	1846	-0.84	8.00E-01
FERMT2	14	53313986	53454153	7984	1307	-1.34	9.10E-01	1301	-1.00	8.41E-01
SLC24A4	14	92753925	92972596	7984	2431	0.29	3.86E-01	2421	0.80	2.11E-01
ADAM10	15	58877403	59077177	7984	1869	-0.76	7.77E-01	1865	-0.76	7.75E-01
IQCK	16	19692778	19878907	7984	1523	-1.22	8.88E-01	1508	-0.75	7.75E-01
ACE	17	61519422	61609205	7984	868	-0.68	7.50E-01	859	-0.43	6.66E-01
CASS4	20	54952168	55044396	7984	943	-0.37	6.43E-01	935	-0.48	6.84E-01
ADAMTS1	21	28198066	28252728	7984	594	-0.59	7.22E-01	592	-0.21	5.84E-01

Model 1 is adjusted for PCs, age, sex
Model 2 is adjusted for PCs, age, sex, APOE genotype
*First reported in NHW, and subsequently African-Americans[47,52,53]

eTable 8. Results of top African-American (A) single variant associations, (B) gene-based associations and (C) pathways in the IGAP non-Hispanic white dataset. The top associated P-value from model 1 or 2 is presented for AA. The P-values for NHW are from a model adjusting for age, sex and PCs.

A. Single Variant Associations

Gene	Chr:Position	AA MAF	AA P-value	NHW MAF	NHW SNV P-value	NHW Gene-based P-value
SIPA1L2	1:232376163	0.01	6.3×10^{-7}	0.015	0.29	0.32
EDEM1	3:5302077	0.25	8.9×10^{-7}	0.10	0.47	0.90
ALCAM	3:104409208	0.33	9.3×10^{-7}	0.39	0.61	0.64
WDR70	5:37483940	0.006	1.8×10^{-7}	0.05	**0.05**	0.18
API5	11:43166842	0.01	8.8×10^{-8}	Not Present	-	0.98
ACER3	11:76541840	0.01	5.1×10^{-7}	Not Present	-	0.28
PIK3C2G	12:18471546	0.01	9.9×10^{-7}	Not Present	-	**0.03**
GPC6	13:941598800	0.04	4.0×10^{-7}	0.16	0.94	**0.04**
ARRDC4, IGF1R	15:97992685	0.01	1.6×10^{-9}	Not Present	-	0.25, 0.93
RBFOX1	16:8288401	0.007	5.3×10^{-7}	0.03	0.07	0.84
VRK3	19:50524332	0.10	3.5×10^{-7}	0.15	0.37	0.31

B. Gene-based Associations

Gene	Chromosome	AA P-value	NHW P-value
TRANK1	3	6.4×10^{-5}	0.91
FABP2	4	3.1×10^{-5}	0.57
LARP1B	4	1.9×10^{-5}	0.89
TSRM	7	2.7×10^{-5}	0.46
ARAP1	11	9.1×10^{-5}	0.06
STARD10	11	3.9×10^{-5}	**0.02**
SPHK1	17	9.3×10^{-5}	0.77
SERPINB13	18	7.4×10^{-5}	0.81

C. Pathway Associations

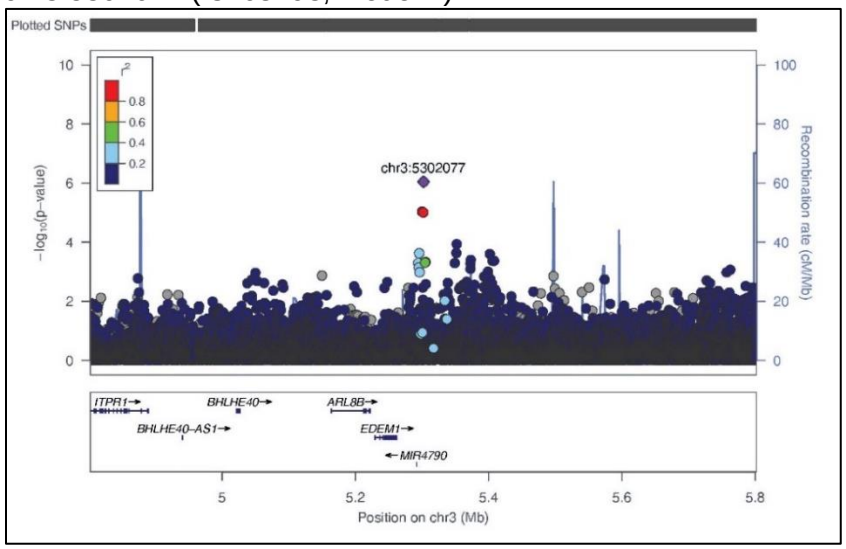
GO Term	AA P-value	NHW P-value
GO_bp:go_distal_tubule_development	1.0×10^{-4}	0.99
GO_bp:go_metanephric_epithelium_development	2.2×10^{-4}	0.85
GO_bp:go_secretory_granule_organization	3.4×10^{-4}	0.16
GO_bp:go_regulation_of_long_term_neuronal_synaptic_plasticity	3.5×10^{-4}	0.41
GO_bp:go_phospholipid_catabolic_process	4.6×10^{-4}	0.16
GO_bp:go_regulation_of_protein_targeting	5.7×10^{-4}	0.11
GO_mf:go_inositol_tetrakisphosphate_phosphatase_activity	6.5×10^{-4}	**0.02**
GO_mf:go_protein_tyrosine_kinase_binding	6.5×10^{-4}	0.07
GO_bp:go_glycerophospholipid_catabolic_process	7.3×10^{-4}	0.17
GO_bp:go_regulation_of_intracellular_transport	8.8×10^{-4}	0.11
GO_bp:go_positive_regulation_of_mitotic_nuclear_division	9.7×10^{-4}	0.08
GO_bp:go_regulation_of_rna_polymerase_ii_transcriptional_preinitiation_complex_assembly	2.0×10^{-5}	0.13
GO_bp:go_magnesium_ion_transport	3.8×10^{-4}	0.90
GO_bp:go_positive_regulation_of_nuclear_division	4.3×10^{-4}	**0.05**
GO_bp:go_dna_ligation	4.7×10^{-4}	0.42
GO_bp:go_response_to_drug	5.2×10^{-4}	0.09
GO_cc:go_main_axon	5.6×10^{-4}	0.68
GO_bp:go_macrophage_activation_involved_in_immune_response	6.6×10^{-4}	0.11

GO_bp:go_dna_ligation_involved_in_dna_repair	8.4×10^{-4}	0.64
GO_mf:go_poly_a_binding	9.3×10^{-4}	0.48

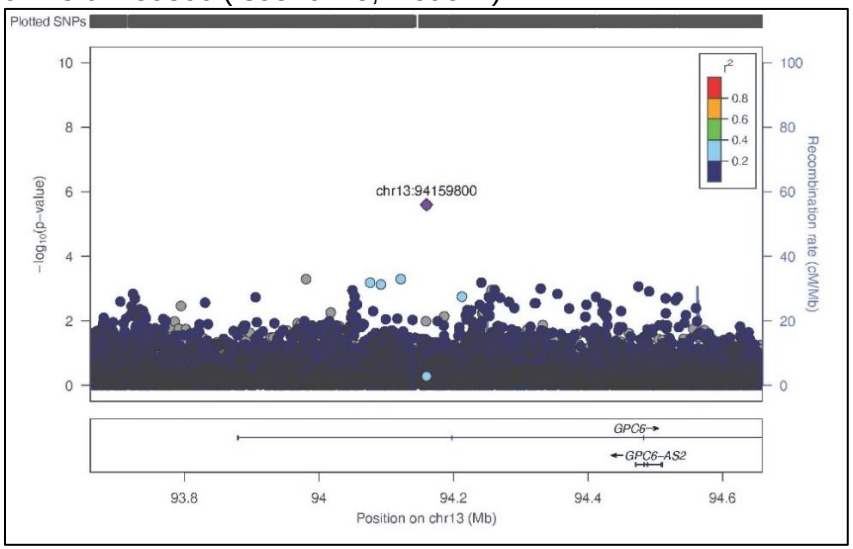
eFigure 1. Regional association plots for the (A) three novel common and (B) seven rare loci identified in single-variant meta-analysis. The SNPs labeled on each regional plot had the lowest *P* value at each locus and are represented by a purple diamond. *Each dot* represents a SNP and *dot colors* indicate LD with the labeled SNP. *Blue vertical lines* show recombination rate marked on the right-hand *y*-axis of each regional plot.

A)

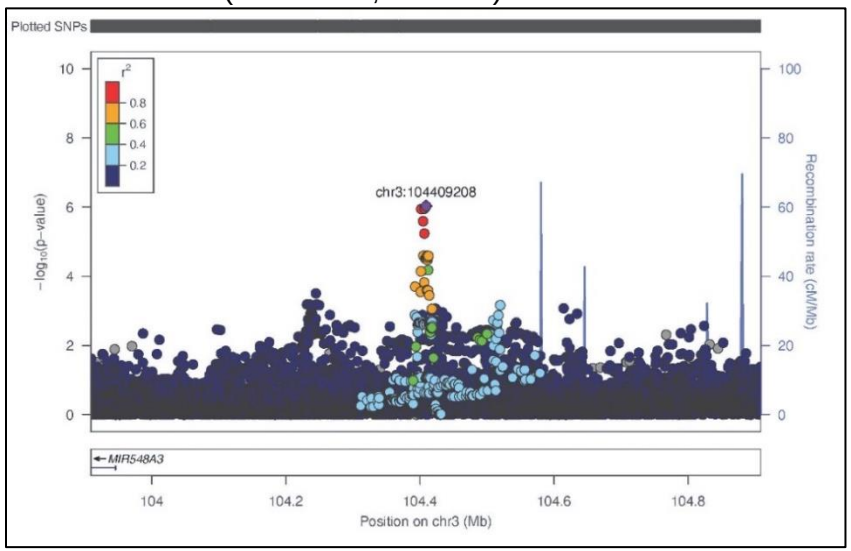
chr3:5302077 (rs168193; Model 1)



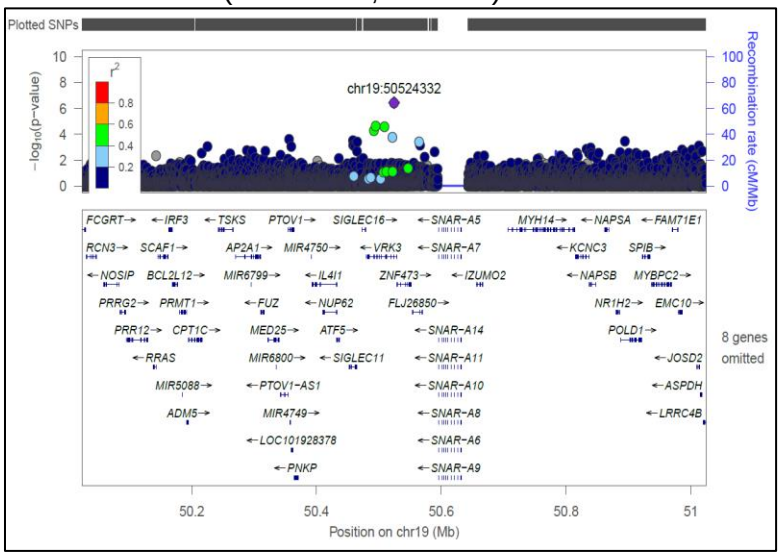
chr13:94159800 (rs9516245; Model 2)



chr3:104409208 (rs2633682; Model 1)

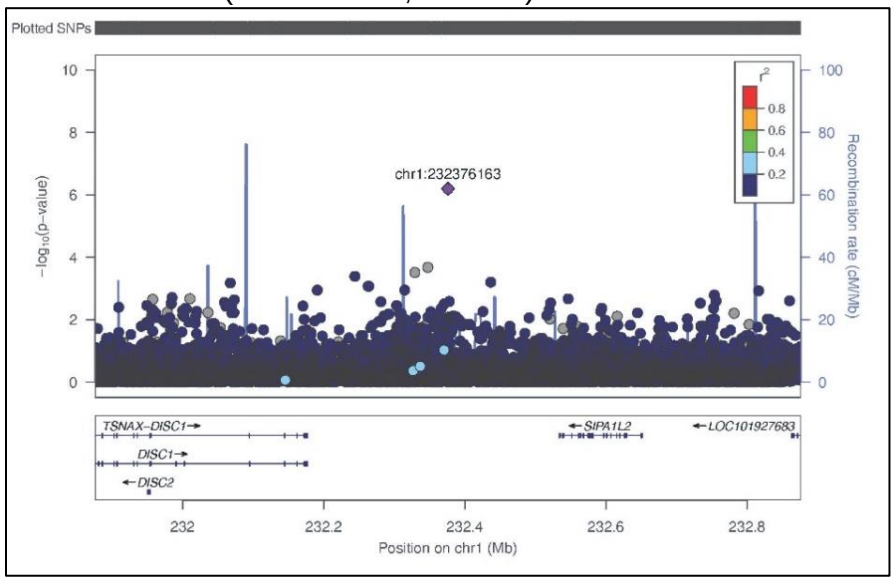


chr19:50524332 (rs3745495; Model 2)

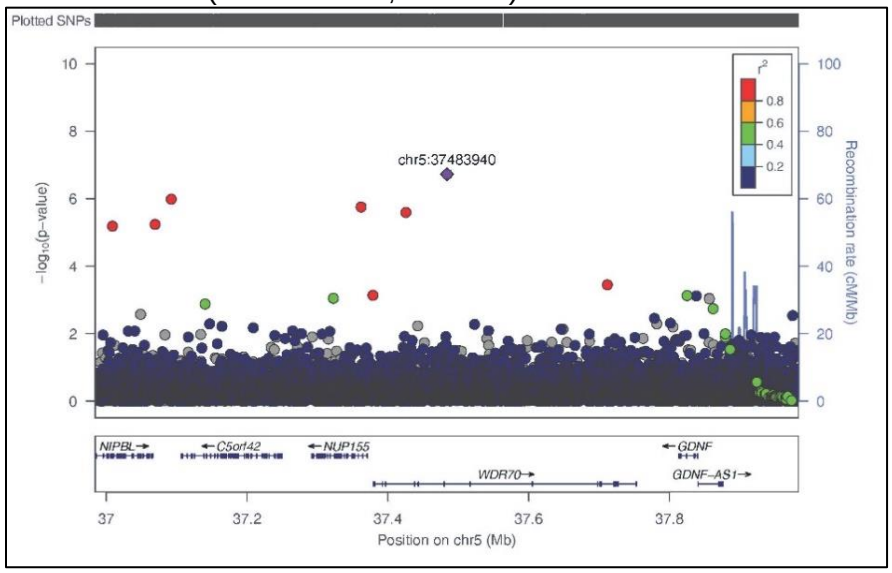


B)

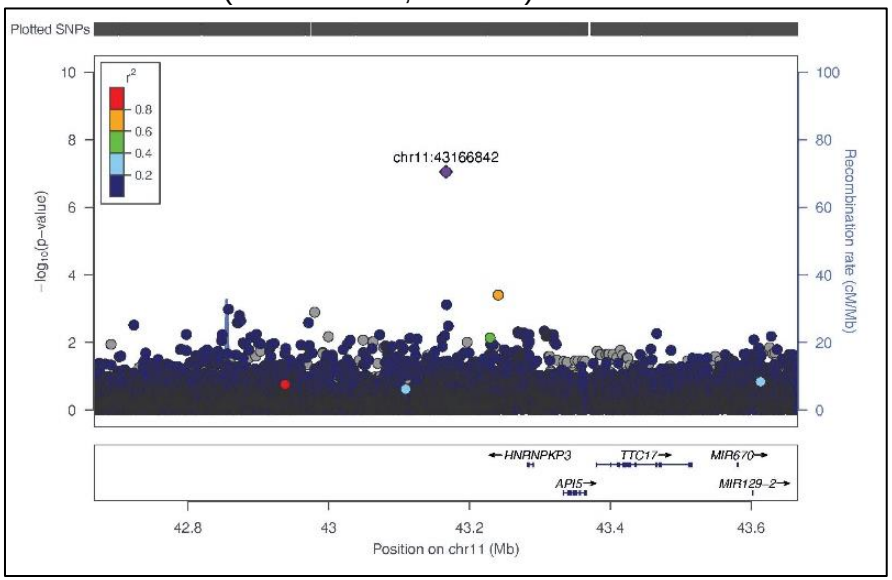
chr1:232376163 (rs115684722; Model 1)



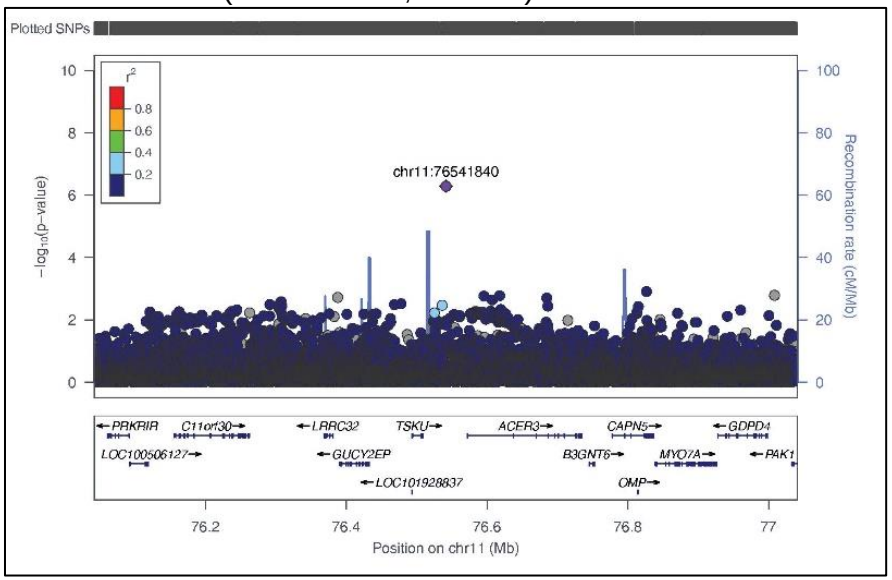
chr5:37483940 (rs184179037; Model 1)



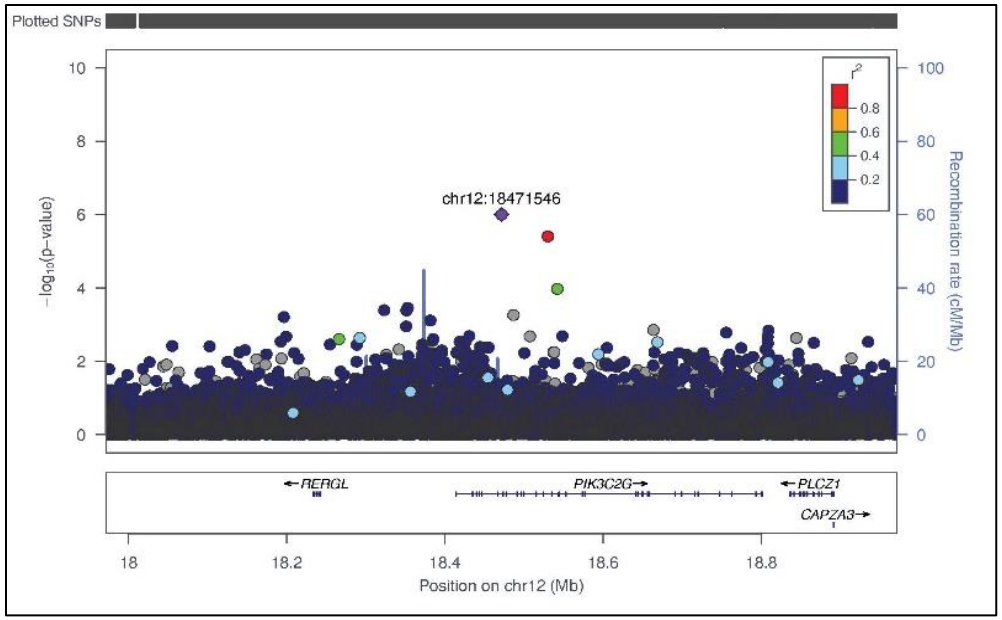
chr11:43166842 (rs569584007; Model 2)

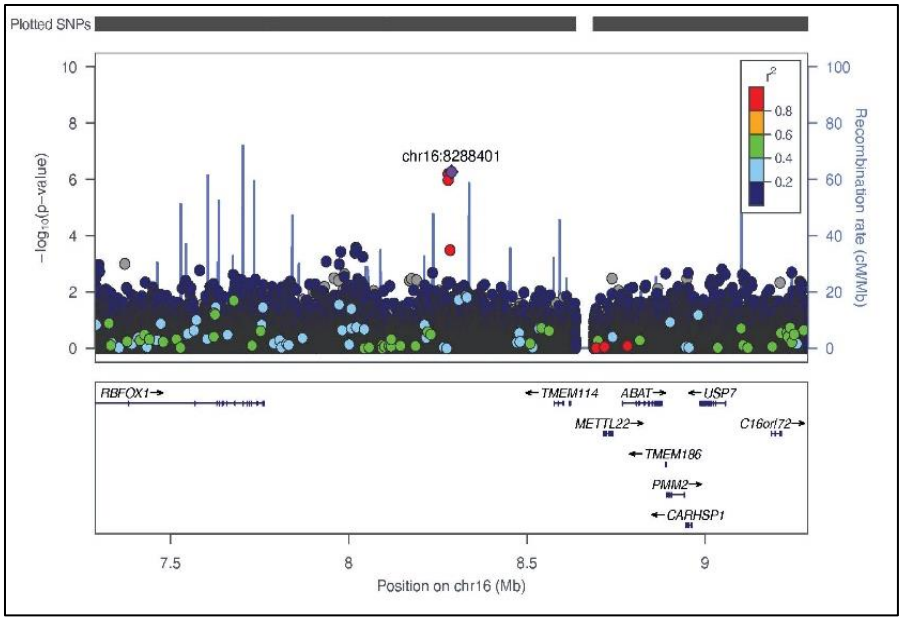


chr11:76541840 (rs115816806, Model 2)

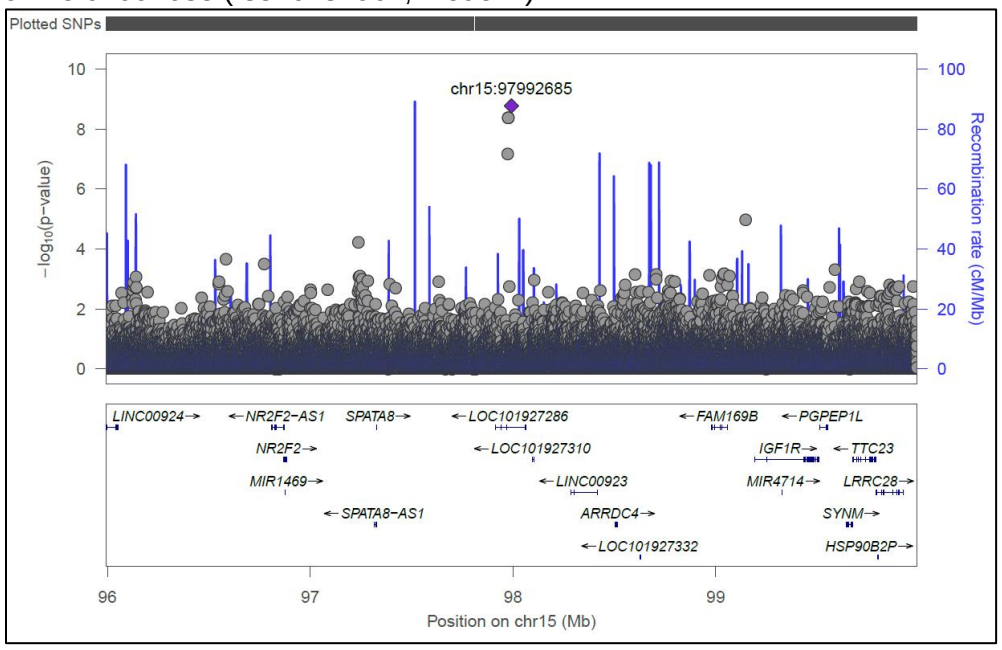


chr12:18471546 (rs75739461, Model 2)





chr15:97992685 (rs570487962; Model 2)

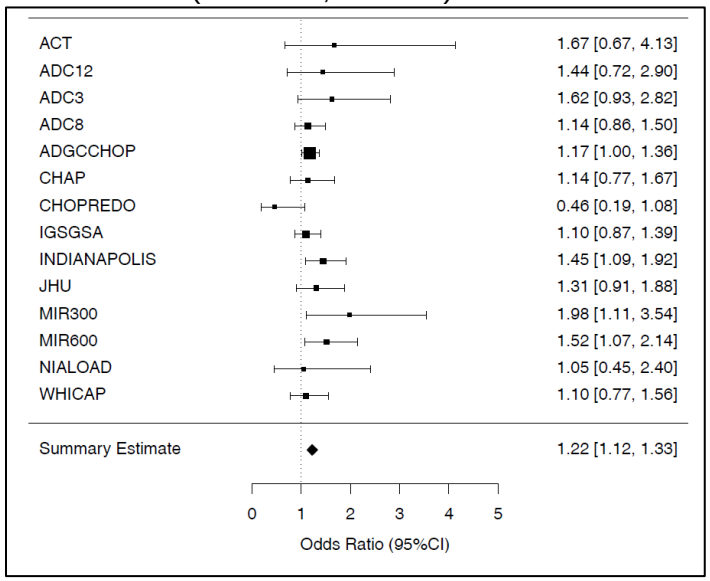


chr16:8288401 (rs79537509, Model 2)

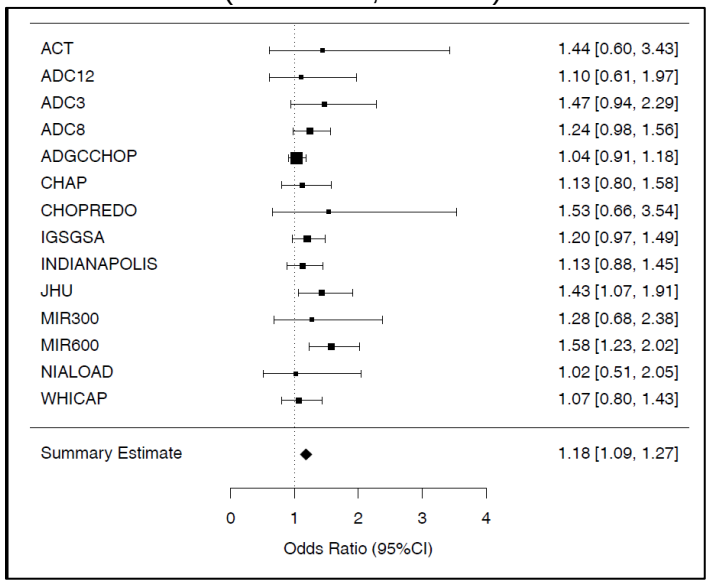
eFigure 2. Forest Plots of Odds Ratios (ORs) for the (A) three novel common and (B) seven rare loci identified in single-variant meta-analysis

A)

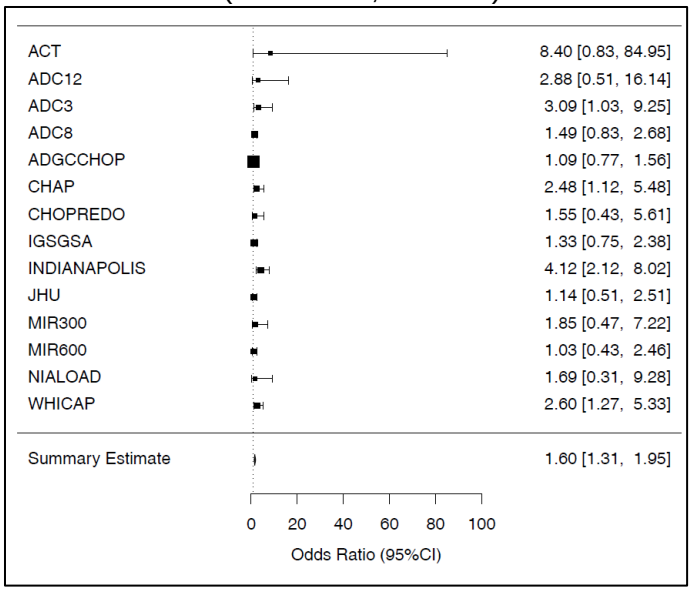
chr3:5302077 (rs168193; Model 1)



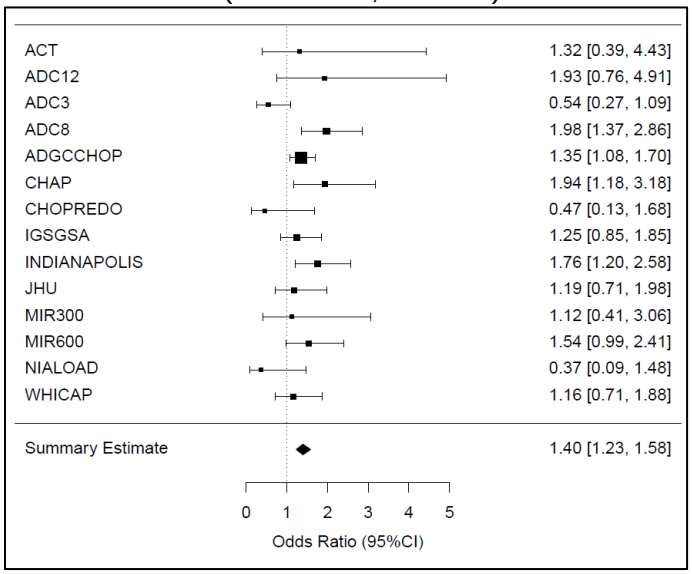
chr3:104409208 (rs2633682; Model 1)



chr13:94159800 (rs9516245; Model 2)

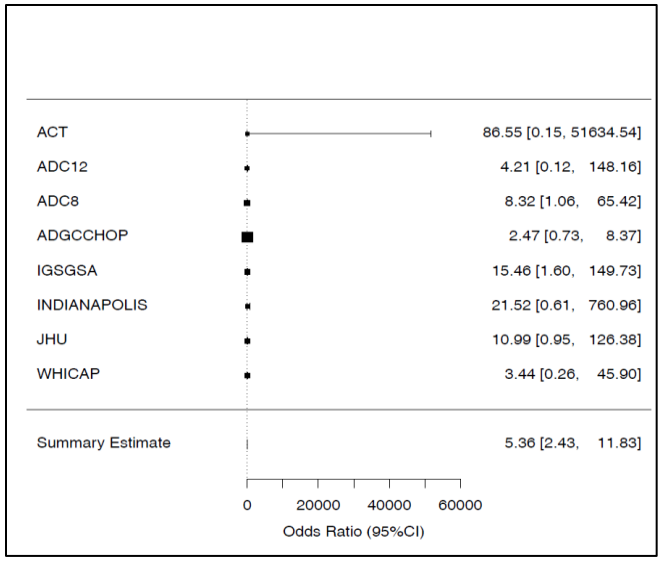


chr19:50524332 (rs3745495; Model 2)

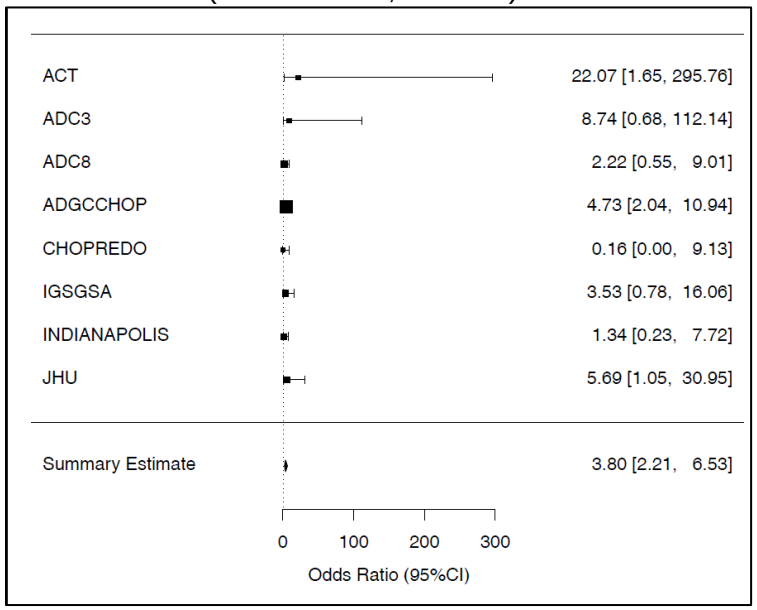


B)

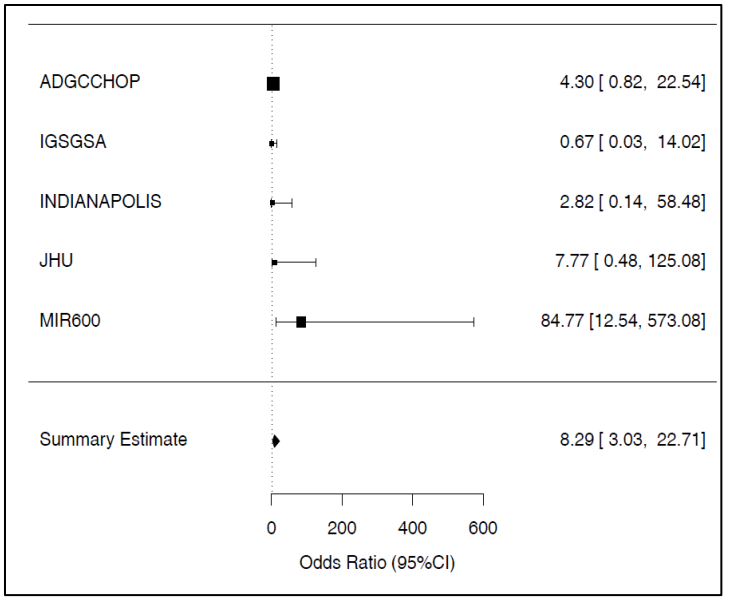
chr1:232376163 (rs115684722; Model 1)



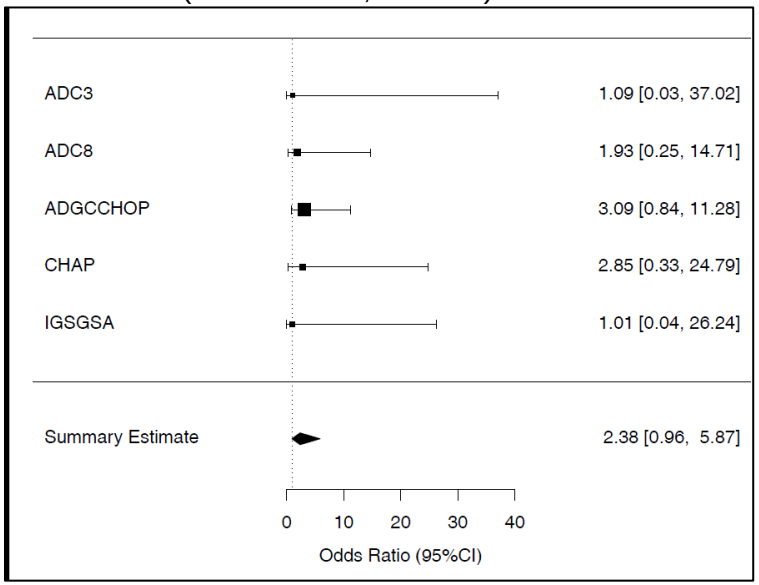
chr5:37483940 (rs184179037; Model 1)



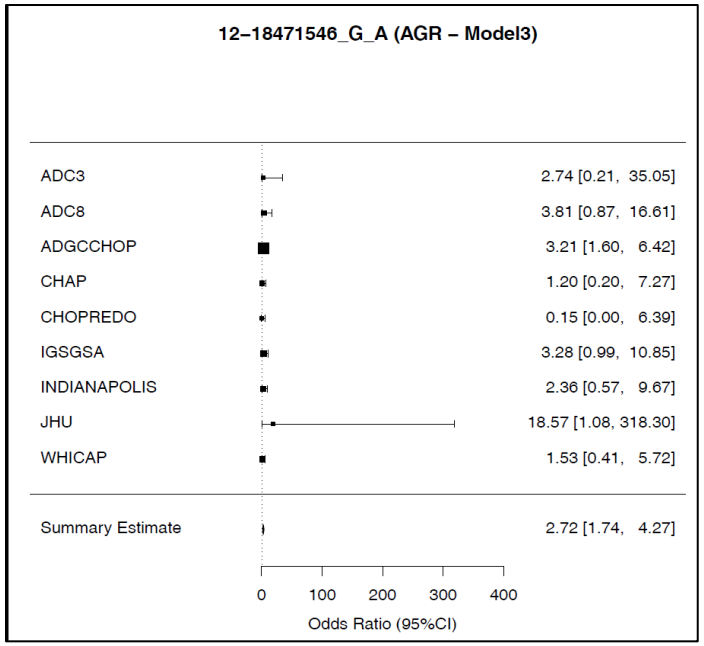
chr11:43166842 (rs569584007, Model 2)

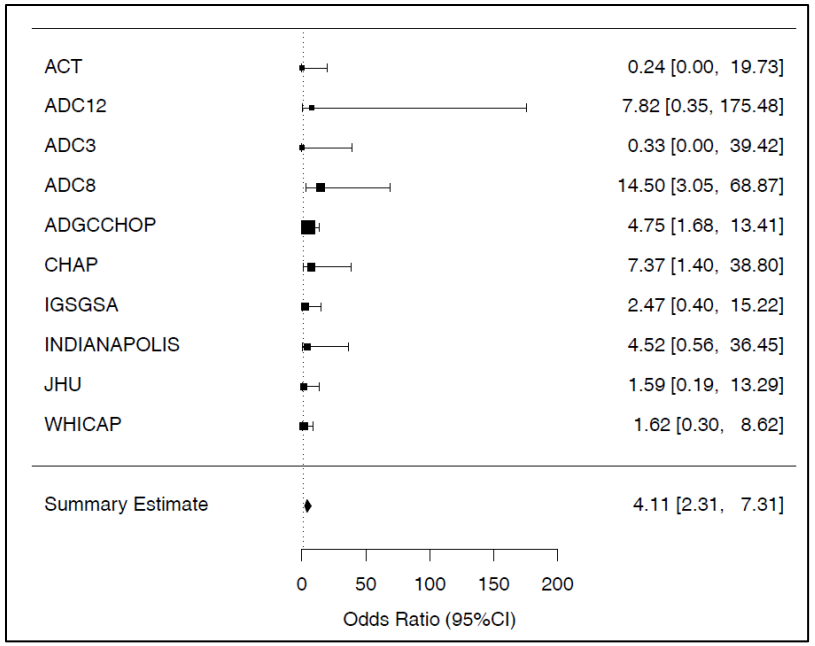


11:76541840 (rs115816806; Model 2)

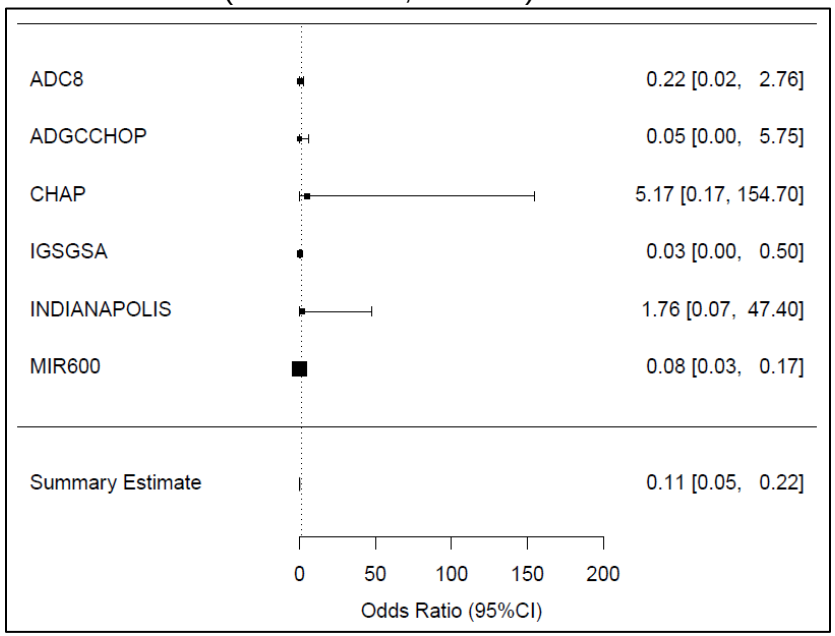


chr12:18471546 (rs75739461; Model 2)





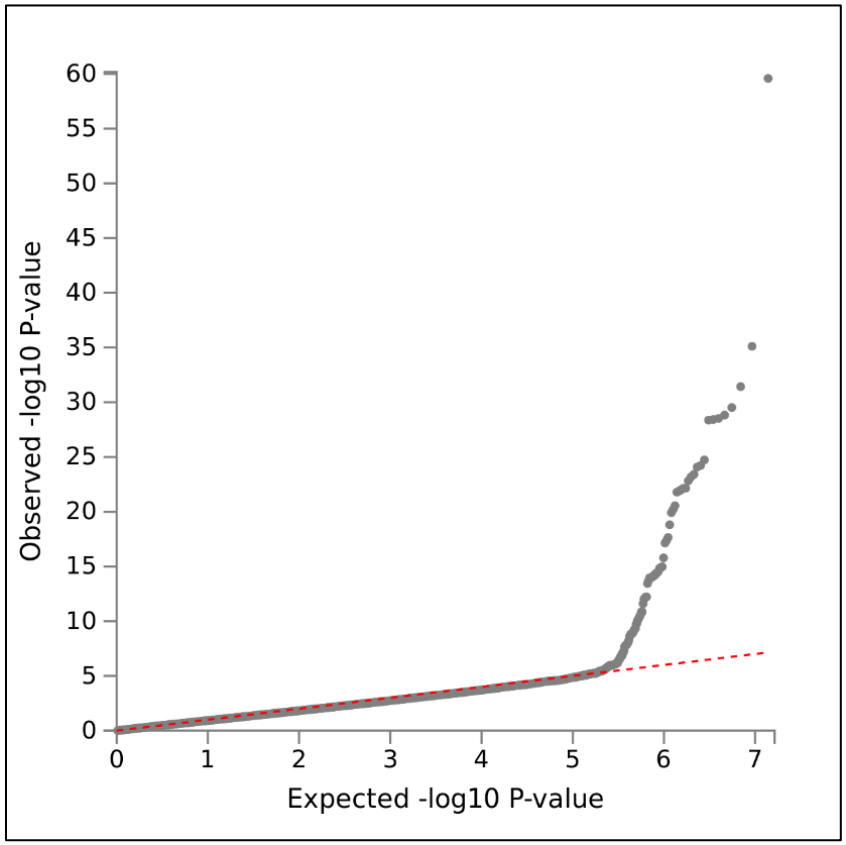
chr15:97992685 (rs570487962, Model 2)



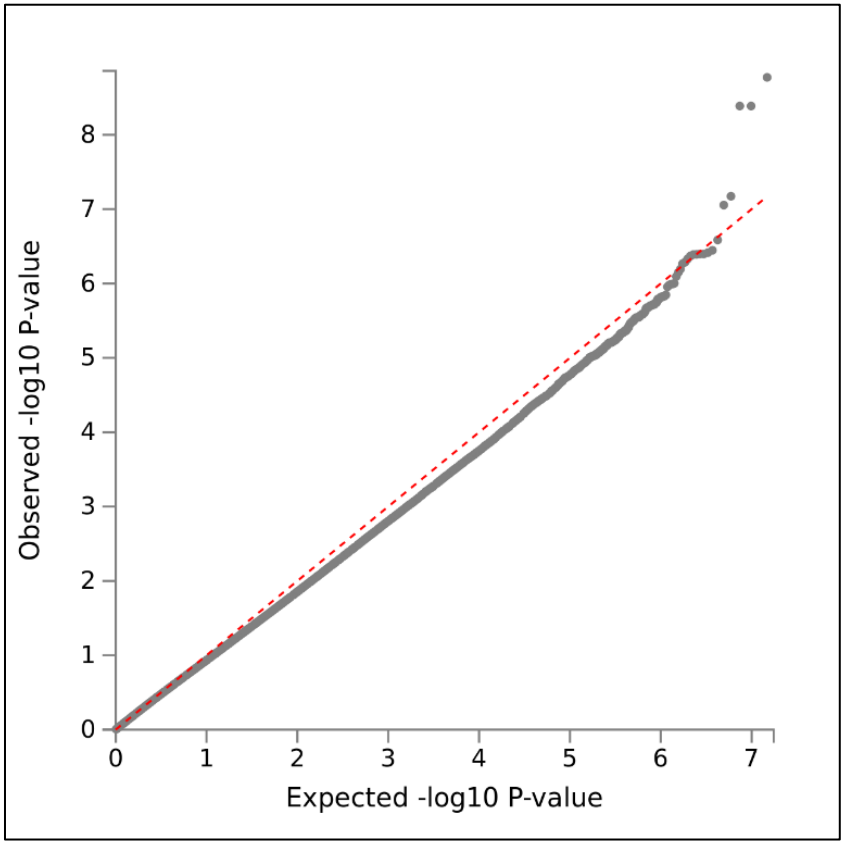
chr16:8288401 (rs79537509; Model 2)

eFigure 3. Quantile-quantile plots for single marker association analyses based (A) on the model adjusted for age, sex and population stratification and (B) age, sex, population stratification and APOE showing the deviation of observed from expected p-values

A)

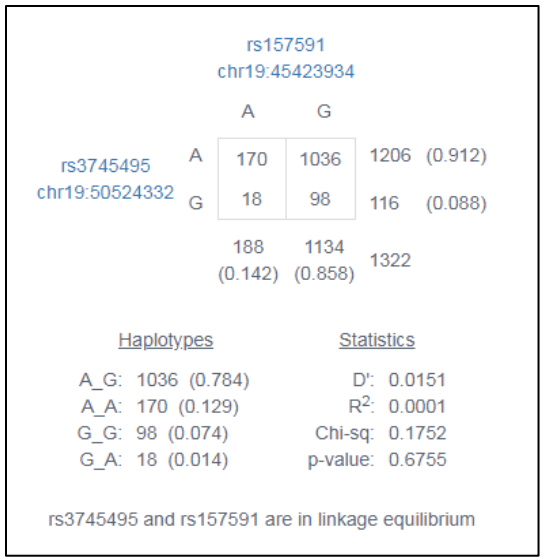


B)

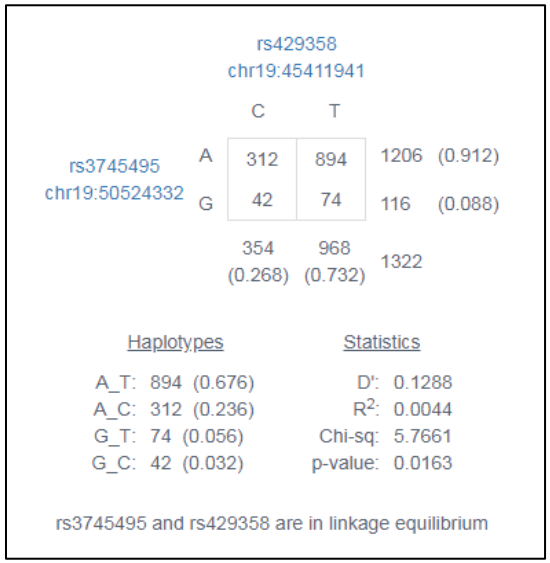


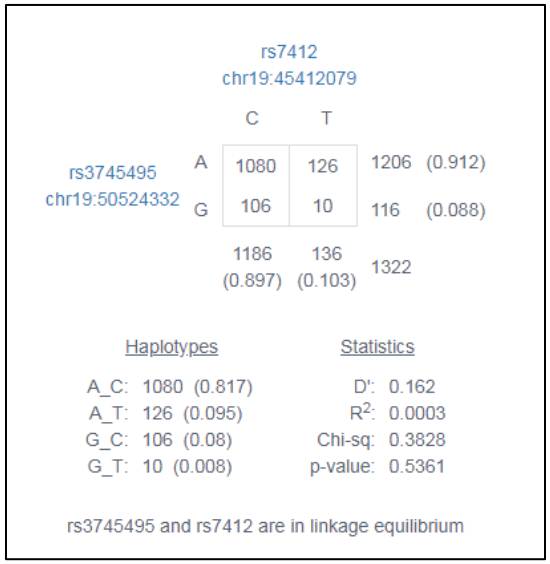
eFigure 4. Linkage disequilibrium analyses between the top associated variant in 19q13.33 (rs3745495) and three variants in APOE: A) The top associated AA variant within APOE (rs147491), and B) The two variants that define the APOE genotype (rs429358 and rs7412). Analyses were done using LDLink[54].

A.



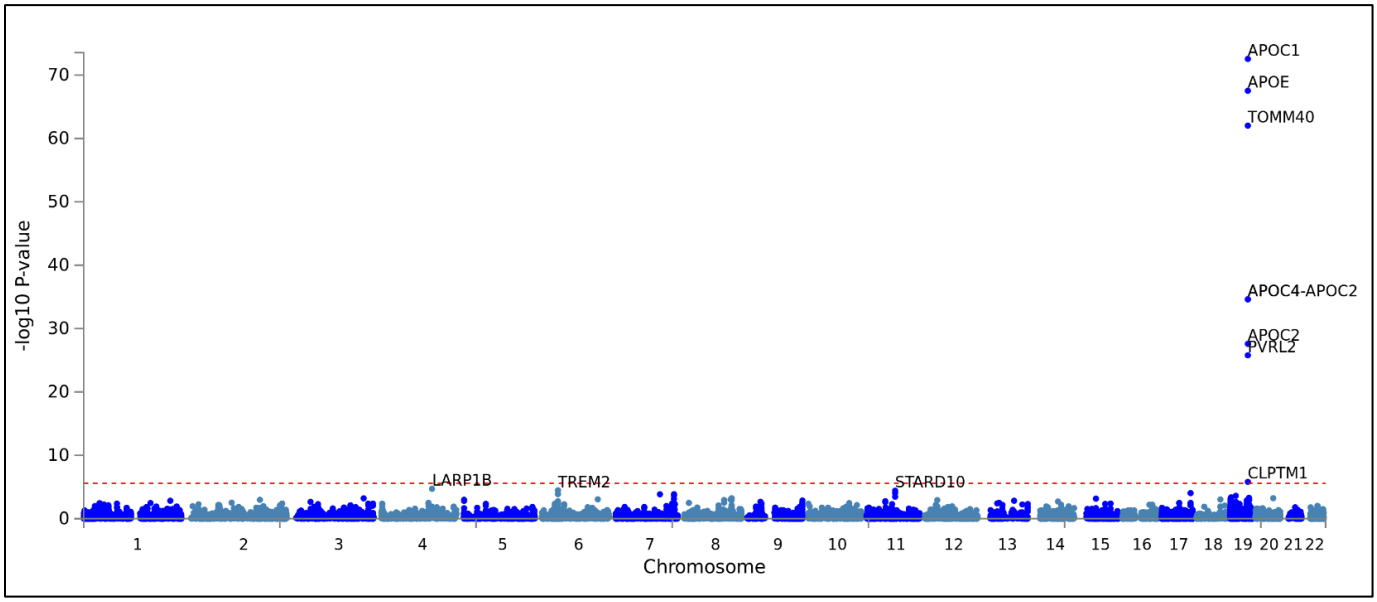
B.



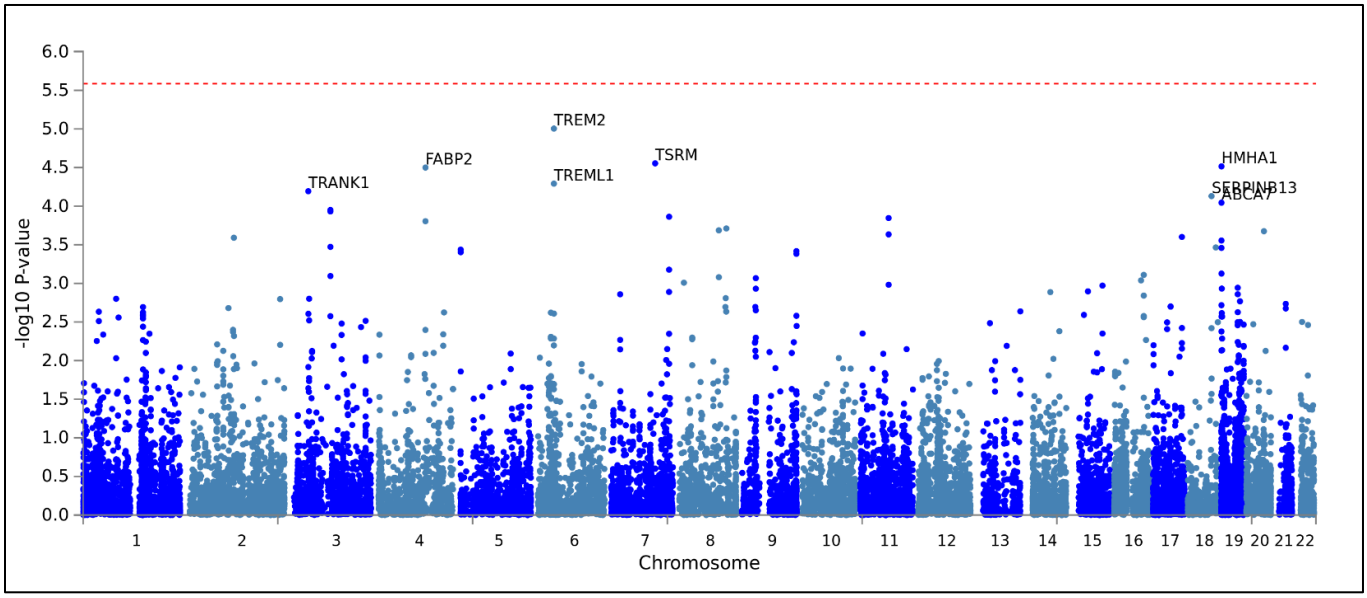


eFigure 5. Manhattan plot of gene-based analysis results. Model 1 (a) is adjusted for age, sex and population stratification; Model 2 (b) is adjusted for age, sex, population stratification and *APOE*.

a) Model 1



b) Model 2



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