APOE stratified genome-wide association studies provide novel insights into the genetic etiology of Alzheimers's disease.

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Among the more than 90 identified genetic risk loci for late-onset Alzheimer's disease (AD) and related dementias, the apolipoprotein E gene (*APOE*) ε2/ε3/ε4 polymorphism remains the longstanding benchmark for genetic disease risk with a consistently large effect across studies[1-10]. Despite this massive signal, the exact mechanisms for how ε4 increases and for how ε2 decreases dementia risk is not well-understood. Importantly, recent trials of anti-amyloid therapies suggest less efficacy and higher risks of severe side effects in ε4 carriers[11-13], hampering the treatment of those with the highest unmet need. To improve our understanding of the genetic architecture of AD in the context of its main genetic driver, we performed genome-wide association studies (GWASs) stratified by ε4 and ε2 carrier status. Such insights may help to understand and overcome side effects, to impact clinical trial enrolment strategies, and to create the scientific basis for targeted mechanism-driven therapies in neurodegenerative diseases.

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The present work is the largest meta-analysis GWAS attempt to provide the most informative overview of the genetics of AD according to *APOE* ε2/ε3/ε4 stratification, bringing together European, Asian, Asian-American, African-American, and admixed American ancestry cohorts based on clinically diagnosed AD. The analysis strategy and included consortia and cohorts are described in Figure 1. Individuals were grouped in ε22+ε32, ε33 and ε44+ε43 strata to maximize statistical power and individuals with the ε42 genotype were excluded (Supplementary Tables 1-2). In the ε22+ε32 stratum, the meta-analysis was based on 2,734 AD cases, 71,167 controls and 13,570,193 variants (Supplementary Table 3, Supplementary Figure 1), and no signals reached a genome-wide significance level of $<5x10^{-8}$ (Supplementary Figure 2). In the ε33 stratum, the meta-analysis was based on 24,033 AD cases, 363,161 controls and 17,127,662 variants (Supplementary Table 4, Supplementary Figure 1). Finally, in the ε44+ε43 stratum, the meta-analysis was based on 29,122 AD cases, 164,206 controls and 14,672,059 variants (Supplementary Table 5, Supplementary Figure 1; Supplementary Tables 6-7 and Supplementary Figure 3 for substrata ε43 and ε44).

In total, 28 loci reached a genome-wide significance level in strata ε33 or ε44+ε33 only or in both (Figure 2, Table 1, Supplementary Figures 4-28). For the ten loci found in both strata, they are well known genetic risk loci associated with AD: *CR1*, *BIN1*, *HLA*, *TREM2*, *PILRA*, *CLU*, *MS4A64*, *PICALM*, *APH1B*, *ABCA7*. Nine loci were exclusively observed in the ε44+ε43 stratum, 5 are known AD loci: *SORL1*, *ADAM10*, *ACE*, *LILRA5*, *CASS4* and 4 loci are novel AD loci: *HP1BP3*, *PTPRC*, *FAT4, DDHD1*. Notably, *DDHD1* is close to the *FERMT2* locus, which is recognized as a genetic risk factor for AD. However, using conditional testing, we found that the *DDHD1* signal is independent of *FERMT2* (Figure 2, Supplementary Table 8). Finally, among the 9 loci only reaching genome wide significance level in the ε33 stratum, 6 are known as AD risk loci: *TMEM106B, SHARPIN, SPI1, GRN, MAPT, RBCK1*, and 3 loci are novel: *SCL50A1, NPAS3,*

CHST9. Of note, we also performed a meta-analysis restricted to the ε44 carriers. Only one well-established locus (*BIN1*) was observed in the ε44 stratum including 5,814 AD cases, 14,415 controls and 9,723,486 variants (Supplementary Table 7, Supplementary Figure 3). Forest plots across cohorts and strata are shown in Supplementary Figures 29-60. In addition, we applied clumping procedures and conditional testing to define potential independent signals within each locus detected in the ε33 and ε44+ε43 strata. This approach detected 5 loci presenting two independent signals (*HLA-DRA*, *TREM2*, *PILRA*, *CLU*, *APH1B*, Supplementary Table 8), details are specified in legend to Table 1.

The present meta-analyses do not allow us to fully determine whether there is a significant difference between the signals observed in the ε33 and ε44+ε43 strata due to sample and statistical power variations. To address this issue, we performed both an additive and a dominant test of interaction between autosomal variants and the *APOE* strata using summary statistics from the different *APOE* strata (Table 2). When testing for a dominant *APOE* ε4 interaction (meta-analysis of differences between ε33 and ε44+ε43 in each cohort) we found 6 significant interactions, 3 signals where the effect sizes were attenuated with the presence of an ε4 allele (*SLC50A1*, *TMEM106B*, *NPAS3*) (Table 2, Figure 3) and 3 signals where the effect sizes were augmented with the presence of an ε4 allele (*HLA-DRA -1*, *CLU*, *DDHD1*) (Table 2, Figure 4). Forrest plots of the effect differences across cohorts are shown in Supplementary Figures 61-62. In an additive mixed-effect model we additionally identified *SHARPIN* as interacting with *APOE* ε4, where the effect size was attenuated with an increasing number of ε4 alleles (Table 2, Figure 3). Interaction sensitivity analyses are shown in Supplementary Table 9.

We evaluated the 33 regions of interest in additional cohorts of East Asian (EAS) ancestry, representing Japanese (JADNI, CL, NP; EAS-JPN), Chinese (HKS; EAS-CHN), and Korean (GARD; EAS-KOR) populations, as well as in Asian American (ADSP-AAC), African American

(ADSP-AFR), and in admixed American (ADSP-AMR) multi-ancestry populations (Supplementary Table 10). Despite several limitations, i.e. difference in linkage structure between cohorts of different ancestries, limitation in statistical power and lead variants being different from the causal variants, similar signals could be observed for several variants (Supplementary Figures 63-93). The meta-analyzed results for *HLA-DRA-1* and *DDHD1* were similar in the East Asian cohorts compared with the European cohorts (Figure 5).

For lead variant rs10131116 in *DDHD1* a significant eQTL associated with decreased *DDHD1* expression was observed in the ROSMAP dorsolateral prefrontal cortex (β=-0.098, eQTL $p=1.67\times10^{-5}$, n=560)[6] and in the GTEx (v10) brain-putamen (basal-ganglia) (β=-0.23, eQTL $p=3.6\times10^{-5}$, n=253)[14]. We tested whether rs10131116 was associated with lower *DDHD1* expression according to *APOE* strata, and nominal p-values were 9×10^{-4} for ε33 and 7×10^{-3} for ε44+ε43 (Supplementary Table 11, Supplementary Figure 94). Further, a gene-based analysis confirmed several of the significant loci from the main stratified GWAS analysis (Figure 6). Also, in the ε44+ε43 stratum the known AD genes *EPHA1*, *TCPN1* and *BLNK* and in the ε33 stratum the *SLC24A4*, *INPP5D* and *SH2B2* (novel but close to the known loci *SPDYE3/PILRA/TMEM225B*) reached significance. *ACE* and *SNX1* were significant in both the ε44+ε43 and ε33 strata, whereas *PRAMEF1* was significant in the ε44 stratum and *GFRA1* in the ε22 stratum (Figure 6, Supplementary Tables 12-15). Next, we performed a pathway enrichment analysis on the *APOE* stratified GWAS results from the eight European studies (Supplementary Tables 16 and 17). After correction for multiple testing in each stratum ($q<0.05$), 12 and 33 pathways reached statistical significance for the *APOE* ε33 and ε44+ε43 strata, respectively. Overall, pathways related to the complement and immune systems were overrepresented in the *APOE* ε44+ε44 stratum compared to the ε33 stratum, whereas amyloid and neurofibrillary tangle biology was highlighted in both strata. No pathway analysis reached statistical significance for the ε22+ε32 nor for the ε43 stratum. Lastly,

we performed a Summary-data-based Mendelian Randomization to test for potential effects of expression on AD that are shared by a causal variant for both *APOE* ε4 carriers (ε44+ε43) and non-carriers (ε33). Four genes passed our significance threshold: *STAG3* (*PILRA* locus) in the ε44+ε43 stratum (Cortex) and *LRRC37A*, *ARL17B* and *LRRC37A2* (*MAPT* locus) in the ε33 stratum (multiple brain regions) (Supplementary Table 18).

Discussion

By conducting a comprehensive series of *APOE* stratified GWAS analyses, we identified a number of biologically plausible genomic signals that modify the effect of the strongest genetic AD risk variant to date - the *APOE* ε4 allele. Our findings may have substantial impact on how we use genetics in designing randomized clinical trials of future AD medicines and may fuel the development of novel targeted mechanism-driven therapies in neurodegenerative diseases.

New genetic signals

HP1BP3, *SLC50A1*, *PTPRC*, *FAT4*, *NPAS3*, *DDHD1*, and *CHST9* from the variant based GWAS analysis and *PRAMEF1* and *GFRA1* from the gene-based analysis are novel genomic signals for AD risk, only appearing when stratified by *APOE* carrier status, and supported by significant interaction tests for *SLC50A1*, *NPASS*, and *DDHD1*, discussed in detail in paragraphs below. *HP1BP3* encodes heterochromatin protein 1 binding protein 3 and is a regulator of cell cycle progression[15]. *PTPRC* encodes protein tyrosine phosphatase receptor type C also known as CD45 that increasingly is understood to play a role in the innate immune system[16,17]. *FAT4* encodes FAT atypical cadherin 4 and is a member of the cadherin superfamily, which represents a major group of cell-cell adhesion receptors, contributing to embryonic neuronal morphogenesis[18]. C*HST9* encodes carbohydrate sulfotransferase 9, an enzyme that transfers sulphate to the 4-position of GalNAc. GalNAc4ST-1 and -2 transcripts are highly expressed in the pituitary gland and trachea[19,20]. *PRAMEF1* encodes a protein PRAME family member 1 and has been associated with cancer[21]. *GFRA1* encodes for GDNF family receptor alpha-1 which is a receptor for both Glial cell line-derived neurotrophic factor (GDNF) and neurturin (NTN); both potent neurotrophic factors and key regulators of neuron survival and differentiation[22]. GDNF family receptor alpha-1 has been linked to the restoration of AD neuron survival[23].

Genetic variants interacting significantly with APOE carrier status with attenuated effect size in ε4 carriers

SLC50A1 is a novel AD signal that only emerges in the *APOE* ε33 stratum, and encodes solute carrier family 50 member 1, which is a sugar transporter for intercellular exchange and nutrition of pathogens[24]. The previously identified signal, *TMEM106B* [6] encodes the lysosomal type II transmembrane protein 106B, and residues of the protein have recently been shown to be amyloidogenic in an age dependent manner and in several neurodegenerative diseases including AD [25]. The presently identified lead hit is in the regulatory 3'UTR part of the gene and is in full LD (r^2 =0.99) with the previously reported rs1990622 variant – a variant that is associated with reduced expression of *TMEM106B*[26,27] and with earlier age-at-onset of frontotemporal lobar degeneration in *GRN* mutation carriers. Both the *TMEM106B* and *GRN* signals are sufficiently strong to reach genome-wide significance level in our previous overall GWAS[6], however the present *APOE* stratified analyses illustrate that these signals only manifest in the *APOE* ε33 context, although only *TMEM106B* reached statistical significance in the interaction test. Interestingly, *TMEM106B* and *GRN* were recently associated only with non-AD pathology in a comprehensive GWAS of multiple neuropathology endophenotypes of dementia[28]. Further aspects of pathophysiology are discussed in the Supplementary Note. *NPAS3* encodes a neuronal transcription factor implicated in several neuropsychiatric conditions[29] and is reported to have a regulatory function on the expression of reelin[30]. In adults, reelin binds to the ApoE-Receptor2 (apoER2) and the very low-density lipoprotein receptor (VLDLR) modulating AMPA and NMDA activity in the post-synaptic region, affecting APP processing and tau hyperphosphorylation, and competes with apoE in receptor binding[31]. Further, *SHARPIN* variants have been shown to affect NF-kB signalling in the nervous system, a central mediator of inflammatory and immune responses, and apoE is suggested to

interact with NF-kB signalling[32,33]. Additionally, we observed consistent directionality in all European cohorts, even though the interaction test did not reach statistical significance, suggesting that the effect of *MAPT* is attenuated in an ε4 context in agreement with a previous report[34]. Finally, Forrest plots of the effect differences for the significant interactions show similar directionality across cohorts.

Genetic variants interacting significantly with APOE carrier status with augmented effect size in ε4 carriers

The *HLA* region on chromosome 6 is highly complex. The present data add an extra layer to this complexity since we observed that one *HLA* locus associates with increased risk of AD in ε4 carriers, but not in ε3 carriers, while another independent *HLA* locus associates with increased risk of AD in both strata. Further, in the present study we confirmed *CLU* as one of the strongest genomic signals for AD, and documented for the first time that this signal was substantially stronger in *APOE* ε4 carriers compared to ε33 carriers. We also identified a new independent signal within the *FERMT2* locus, where the nearest gene is *DDHD1* (distance 241,028 bp) which encodes a member of the Phospholipase A1 family important in lipid and phospholipid metabolism[22]. The fact that the rs10131116 *DDHD1* variant in the present GWAS was associated with a decreased risk of AD specifically in *APOE* ε4 carriers together with the recent identification of the rs10131116 as an eQTL associated with decreased *DDHD1* gene expression[6,35], highlights *DDHD1* as an interesting focus for drug discovery. *DDHD1* is also in the same biological pathway as a genome-wide significant known signal (*PLCG2*)[6]. Importantly, the *HLA* and *DDHD1* signals were similar in European and Asian cohorts, despite differences in statistical power. Finally, Forest plots of the effect differences also here show similar directionality across cohorts.

Conclusion

By performing the to date largest *APOE* stratified GWAS, we have identified novel as well as well-established AD loci, where the effect is manifested specifically in an *APOE* ε4 carrier or in an ε33 genotype context. These findings are supported by pathway analysis, highlighting distinct *APOE* carrier status dependent biological mechanisms. These insights have the potential to change our current understanding of the pathogenesis of AD and may have substantial impact on how we use genetics in designing future randomized clinical trials of emerging AD medicines.

(Main text wordcount: 2000 (max 2000))

Methods

Populations

We used the following European ancestry consortia/biobanks: European Alzheimer's Disease & Dementia BioBank (EADB), FinnGen, European Alzheimer's Disease Initiative (EADI), Bonn, Genome Research at Fundacio ACE (Gr@CE), Genetic and Environmental Risk in Alzheimer's Disease (GERAD), Alzheimer's Disease Sequencing Project (ADSP), and UK Biobank (UKB). Additionally, we evaluated 33 regions of interest in cohorts of East Asian (EAS) ancestry, representing Japanese (JADNI, CL, NP; EAS-JPN), Chinese (HKS; EAS-CHN), and Korean (GARD; EAS-KOR) populations, as well as in Asian American (ADSP-AAC), African American (ADSP-AFR), and in native admixed American (ADSP-AMR) multi-ancestry populations. *APOE* genotype was determined by the imputed data using rs7412 and rs429358. Where directly genotyped data was available, samples with a mismatch between the imputed and genotyped *APOE* genotype were excluded. FinnGen R11 was used, excluding samples from the ADGEN study as they are embedded in the EADB. AD cases were defined by diagnosis or by use of AD medication (ATC code: N06D). Individuals diagnosed with other forms of dementia were excluded from the controls. In UKB only those defined as white British were included, and AD was defined as being diagnosed with AD from electronic medical records (EMR). No information regarding proxies was used in the AD definition or as exclusion criteria. In all datasets, controls younger than 60 years were excluded to better balance the age distributions in the cases and controls and to avoid the inclusion of young controls. All cases were kept. Written informed consent was obtained from study participants or, for those with substantial cognitive impairment, a caregiver, legal guardian, or other proxy. Study protocols for all cohorts were reviewed and approved by the appropriate institutional review boards.

Quality control and imputation

A standard quality control was performed on the samples and variants in all datasets. The samples were imputed using the TOPMed except for ADSP and FinnGen (Supplementary Table 2). FinnGen was imputed with a Finnish whole-genome sequencing (WGS) reference panel (SiSu v4). Ancestry estimates and QC for UKB and ADSP were done using GenoTools[36]

GWAS analysis

Test of the association between clinical AD status and autosomal genetic variants were conducted separately in each cohort by means of logistic regression or mixed models using an additive genetic model. Three software implementations were used, SNPTEST 2.5.6[37], PLINK2[38] and REGENIE[39] and adjusted for sex, age, PCs and genotyping centers/batches when necessary (Supplementary Table 2). Sensitivity analyses were carried out in some datasets to check that adjusting for age did not introduce spurious findings. In SNPTEST we analyzed the genotype probabilities using the newml method. In PLINK2 and REGENIE dosages were used combined with the glm regression (Firth regression if failed convergence) in PLINK2 and Firth regression in REGENIE. For each dataset we filtered out variants with (a) missing data on the effect size, standard error or p-value, (b) an absolute effect above 5, (c) an imputation quality below 0.3, and (d) variants not fulfilling $2\times\min(N_{cases},N_{controls})\times MAF\times info > 5$ (an unbalanced MAC-info score), where info is imputation quality. A fixed-effect meta-analysis using an inverse-variance weighted as implemented in METAL v2020-05-05 was performed combining the results from each dataset. Variants were excluded if a heterogeneity p-value was below 5×10^{-8} or if variants did not pass quality control in at least two of the three major datasets (EADB-TOPMed, FinnGen, UKB). The genomic inflation factor was computed with a median approach after exclusion of the *APOE* region (44-46 Mb on

chromosome 19 in GRCh38) both for variants with MAF>1% and in the entire dataset. Manhattan plots were made using topr package[40] (v.2.0.2) in R (v. 4.3.3).

Definition of loci

Around each variant with a p-value below 5×10^{-8}, a region of ±500kb was defined per fixed-effect meta-analysis. We assumed the individual stratified GWASs as separate families of analyses when setting the p-value threshold. Most of the variants will be highly correlated across the strata except for those variants that interact with the *APOE* genotype which is expected to be a small minority of the total tested variants. Hence, if one was to consider all GWAS tests as belonging to the same family it would lead to a large increase in risk of Type II errors without much gain in controlling for Type I errors. We used the PLINK2 clumping procedure to define independent hits in each region. This procedure is iterative, starting with the variant with the lowest p-value in the respective region (the lead SNP). All variants within loci and in linkage disequilibrium (LD) with the lead variant (r^2 higher that 0.01) are assigned to the clump belonging to the lead SNP. If any variant with a p-value below $5x10^{-8}$ is unassigned to a clump in the respective region, the variant with the lowest p-value is found among the remaining variants and the clumping is repeated until all variants have been assigned a clump. LD in the EADB TOPMed imputed dataset was computed using high quality imputed dosages (imputation info>0.8). The clumping procedure was run in both the ε44+ε43 and ε33 GWAS results and the results for the respective loci were compared. Loci plots were generated using locuszoomr (v. 0.3.5) in R (v. 4.3.3). Forest plots of variant effects across *APOE* strata were generated using forestplotter (v. 1.1.2) in R (v. 4.3.3). The independence of several signals within a locus was tested by SNPTEST conditional analysis in the EADB TOPMed dataset.

Interaction tests in *APOE* strata

Two different tests of interaction between autosomal variants and the *APOE* strata were performed using summary statistics results from the different *APOE* strata. P-value threshold for significance was determined using a Bonferroni correction for 33 regions of interest (including the 10 loci in common in both strata, the 9 loci found in each stratum and the 5 additional signals found in 5 of the 28 loci; p<0.05/33 regions of interest=0.0015). The first test analysed the effect difference between the ε44+ε43 and ε33 *APOE* strata. The effect difference was calculated in each cohort separately ($\Delta\beta_i = \beta_{i,\varepsilon44+\varepsilon43} - \beta_{i,\varepsilon33}$, i is the cohort, β is the autosomal effect estimated in the stratified GWASs), with the SE of the effect difference calculated as the square root of sum of squares of SE for the effects ($SE_{\Delta\beta_i} = \sqrt{SE^2_{i,\varepsilon44+\varepsilon43} + SE^2_{i,\varepsilon33}}$). The effect differences were combined across studies in a fixed effect meta-analysis with an inverse-variance weighted approach (METAL v2020-05-05 software). The test was referred to as the dominant test because it tests if the presence of an ε4-allele changes the effect of the autosomal variant (independent of number of ε4-alleles). Forest plots for the calculated effect difference in each cohort was provided to access the robustness of the interaction across the cohorts. The second test was a fixed effect model estimating the effect from the number of ε4 alleles: $\beta_{ij} = \gamma_0 + \gamma_{\varepsilon4}x_{ij} + \gamma_{cohort}C_{ij} + \varepsilon_{ij}$, where i is the cohort, j is the strata (ε33, ε43, ε44), β_{ij} is the autosomal effect, x_{ij} is the number of ε4-alleles (0,1,2), C_{ij} is the cohort, γ_0 is the intercept, $\gamma_{\varepsilon4}$ is the effect of one ε4 allele, γ_{cohort} is the cohort effect and ε_{ij} the error term. The second model was referred to as the additive model and was estimated using R (v.4.3.3) and Metafor package (v4.6.0).

We performed mixed effect sensitivity interaction models to test if the interaction results were prone to between-strata relatedness bias, which could be a potential bias in the FinnGen cohort. The models were specified as following. Dominant mixed effect model: $\beta_{ik} = \gamma_0 + \gamma_k x_{ik} + u_i + \varepsilon_{ik}$, where i is the cohort, k is the strata (ε33, ε44+ε43) x_{ik} is the strata (ε33, ε44+ε43, categorical), γ_k is the strata effect ($\gamma_{\varepsilon43+\varepsilon44}$ is the reference) and u_i is the random effect**.** Additive

mixed model: $\beta_{ij} = \gamma_0 + \gamma_{\varepsilon 4} x_{ij} + u_i + \varepsilon_{ij}$, with the same notation as above. For the calculation of effect difference both the ε33 and ε44+ε43 effects should be available for a cohort to be included in the analysis. In the other models we included all available data, e.g. the ε44 GWAS in the Bonn cohort was not performed due to power, but the data from the Bonn ε33, ε43 and ε44+ε43 GWASs were included if the SNPs passed QC.

Pathway analysis

Pathway analyses were performed on each meta-analysis stratum result separately using FUMA v1.6.1[41]. As requested by FUMA, all variants were annotated with an rsID using VEP release 112 and then lifted to the GRCh37 assembly using Picard LiftoverVcf tool (v3.1.1)[42]. Variants having no rsID or failing the lift to the GRCh37 assembly were removed from the analysis. Remaining variants were then uploaded to FUMA and the pathway analysis was performed by MAGMA v1.08 [43] using two different windows to assign a variant to a gene: 0kb (main analysis) and a window of 35kb upstream and 10kb downstream (second analysis). To account for multiple testing, we computed a false discovery rate (FDR, Benjamini-Hochberg) based on the number of genes included in the analysis. Pathways having a q-value<0.05 in either of the two windows were considered significant.

eQTL analysis

We performed an *APOE* stratified cis-eQTL mapping analysis (*APOE* ε33 (n=342) and *APOE* ε44+ε43 (n=130)) in the ROSMAP dorsolateral prefrontal cortex (DLPFC; n=560) cohort to investigate association of the lead variant in the *DDHD1* locus (*rs10131116*) with the RNA expression of nearby genes in a 1 Mb window around the variant, following the methodology described as before[6]. For the *APOE* stratified cis-eQTL mapping, the genetic principal components

(gPCs) and the gene expression Probabilistic Estimation of Expression Residuals (PEER) factors were calculated within the respective strata separately; and sex, first 3 gPCs, and PEER factors (first 45 for *APOE* ε33 and first 15 for *APOE* ε44+ε43) were included as covariates.

Summary data-based Mendelian Randomization

Summary data-based Mendelian Randomization (SMR) was performed using the SMR software developed and maintained by the Yang Lab, with default parameters[44,45]. We used cis-eQTL data from 5 of the 7 regions in the MetaBrain Consortium dataset (cerebellum, cortex, basal ganglia, hippocampus, and spinal cord)[46]. We applied a significance threshold of pSMR_multi <6.12E-06, which corresponds to the Bonferroni-corrected value at $\alpha = 0.05$ for 8,166 unique genes tested across all regions. Additionally, we filtered at a HEIDI p-value threshold of pHEIDI >0.01 to remove associations with inferred pleiotropy and only kept results where the number of SNPs included in the HEIDI tests was greater than 3 (nsnp_HEIDI >3).

Data availability

Summary statistics will be made available upon publication through the European Bioinformatics Institute GWAS Catalog (https://www.ebi.ac.uk/gwas/).

Code availability

We used publicly available software for all analyses, referenced in the Methods section.

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Competing interests

C van Duijn is currently the Research Director Brain Health of the Health Data Research UK (HDR UK) and the UK Dementia Research Institute (UK DRI), working in partnership with Dementias Platform UK (DPUK). Some authors' participation in this project was part of a competitive contract awarded to DataTecnica LLC by the National Institutes of Health to support open science research. M Nalls also owns stock in Character Bio Inc. and Neuron23 Inc.

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Table 1

								APOE ε33				*APOE* ε44+ε43		
topmed_id [a]	**Chromosome**	**Position [b]**	**Ref**	**Eff**	**Rsid [c]**	**Loci [d]**	**Gene [d]**	**EAF [e]**	**OR (95% CI) [f]**	**P-value g**	**I^2 [h]**	**EAF [e]**	**OR (95% CI) [f]**	**P-value [g]**	**I^2 [h]**
chr1:20745474:C:T	1	20745474	C	T	rs2274119	HP1BP3	HP1BP3	0.072	1.02 (0.97-1.07)	0.402	0	0.072	1.15 (1.10-1.21)	1.33e-08	0
chr1:155135691:G:A	1	155135691	G	A	rs12726330	SLC50A1	SLC50A1	0.038	1.23 (1.14-1.31)	1.09e-08	0	0.038	1.00 (0.93-1.07)	0.937	10.3
chr1:198710886:G:A	1	198710886	G	A	rs12733073	PTPRC	PTPRC	0.010	1.15 (1.02-1.30)	0.0272	0	0.010	1.46 (1.29-1.65)	1.63e-09	38.1
chr1:207577223:T:C	1	207577223	T	C	rs679515	CR1	CR1	0.77	0.90 (0.88-0.93)	1.98e-11	42.0	0.70	0.87 (0.84-0.90)	1.44e-19	55.2
chr2:127135234:C:T	2	127135234	C	T	rs6733839	BIN1	BIN1	0.38	1.14 (1.11-1.16)	1.22e-24	69.6	0.38	1.20 (1.17-1.23)	9.88e-46	58.3
chr4:125059887:G:A	4	125059887	G	A	rs182938476	FAT4	FAT4	0.0021	1.34 (0.91-1.98)	0.136	0	0.0017	2.54 (1.83-3.54)	3.24e-08	10.9
chr6:32411770:C:T	6	32411770	C	T	rs17208902	HLA-DRA [i]	HLA-DRA -1	0.25	1.03 (1.00-1.06)	0.0409	0	0.26	1.11 (1.08-1.14)	4.82e-13	10.2
chr6:32464090:G:T	6	32464090	G	T	rs9268888	HLA-DRA [i]	HLA-DRA -2	0.54	0.93 (0.91-0.96)	4.57e-09	0	0.54	0.94 (0.92-0.96)	7.60e-07	54.3
chr6:41161469:C:T	6	41161469	C	T	rs143332484	TREM2 [i]	TREM2 -1	0.011	1.29 (1.16-1.44)	3.27e-06	15.9	0.011	1.43 (1.27-1.62)	9.11e-09	7.4
chr6:41161514:C:T	6	41161514	C	T	rs75932628	TREM2 [i]	TREM2 -2	0.0029	2.78 (2.12-3.66)	2.37e-13	0	0.0032	2.18 (1.66-2.85)	1.30e-08	42.2
chr7:12242825:T:C	7	12242825	T	C	rs7805419	TMEM106B	TMEM106B	0.38	0.91 (0.89-0.93)	4.14e-15	22.7	0.37	0.97 (0.94-0.99)	0.00898	46.4
chr7:99590966:A:T	7	99590966	A	T	rs10257273	PILRA [j]	TMEM225B	0.19	1.04 (1.01-1.07)	0.00549	18.3	0.19	1.09 (1.06-1.12)	4.99e-08	34.2
chr7:100374211:A:G	7	100374211	A	G	rs1859788	PILRA [j]	PILRA	0.65	1.07 (1.05-1.10)	3.00e-08	0	0.65	1.08 (1.06-1.11)	2.23e-09	39.2
chr7:100386466:T:C	7	100386466	T	C	rs2906657	PILRA [j]	PILRA	0.30	0.94 (0.91-0.96)	4.71e-07	0	0.30	0.92 (0.89-0.94)	3.39e-10	44.1
chr8:27362470:C:T	8	27362470	C	T	rs73223431	CLU [k]	PTK2B	0.37	1.06 (1.04-1.09)	7.41e-07	43.8	0.37	1.10 (1.07-1.13)	4.30e-14	0
chr8:27610986:C:A	8	27610986	C	A	rs867230	CLU [k]	CLU	0.57	1.08 (1.06-1.11)	5.32e-11	21.9	0.57	1.15 (1.12-1.18)	6.21e-27	0
chr8:144103704:G:A	8	144103704	G	A	rs34173062	SHARPIN	SHARPIN	0.075	1.19 (1.14-1.25)	7.77e-14	4.7	0.070	1.08 (1.02-1.14)	0.00462	20.2

								APOE ε33				*APOE* ε44+ε43		
topmed_id [a]	**Chromosome**	**Position [b]**	**Ref**	**Eff**	**Rsid [c]**	**Loci [d]**	**Gene [d]**	**EAF [e]**	**OR (95% CI) [f]**	**P-value g**	**I^{2} [h]**	**EAF [e]**	**OR (95% CI) [f]**	**P-value [g]**	**I^{2} [h]**
chr11:47358789:G:T	11	47358789	G	T	rs3740688	SPI1	SPI1	0.53	1.07 (1.04-1.09)	4.83e-08	0	0.53	1.04 (1.02-1.07)	0.00152	39.1
chr11:60173126:T:A	11	60173126	T	A	rs7232	MS4A6A	MS4A6A	0.34	0.91 (0.89-0.93)	7.67e-14	0	0.33	0.89 (0.86-0.91)	2.62e-19	44.9
chr11:86113817:A:G	11	86113817	A	G	rs659023	PICALM	PICALM	0.60	1.07 (1.04-1.10)	4.03e-08	43.8	0.58	1.11 (1.09-1.14)	2.27e-16	11.6
chr11:121564878:T:C	11	121564878	T	C	rs11218343	SORL1	SORL1	0.034	0.89 (0.83-0.95)	0.000247	49.6	0.032	0.81 (0.75-0.87)	5.60e-09	0
chr14:33428905:G:C	14	33428905	G	C	rs187023552	NPAS3	NPAS3	0.016	1.42 (1.26-1.61)	1.04e-08	0	0.015	0.98 (0.86-1.11)	0.722	82.6
chr14:53394351:T:C	14	53394351	T	C	rs10131116	FERMT2	DDHD1	0.37	1.02 (1.00-1.05)	0.0416	43.0	0.37	0.93 (0.90-0.95)	6.61e-09	0
chr15:58790588:T:G	15	58790588	T	G	rs347116	ADAM10	ADAM10	0.39	0.96 (0.94-0.98)	0.000904	0	0.40	0.93 (0.90-0.95)	1.11e-08	0
chr15:63279621:C:T	15	63279621	C	T	rs75763893	APH1B [k]	APH1B	0.13	1.12 (1.08-1.15)	2.22e-10	40.5	0.13	1.14 (1.10-1.18)	3.87e-12	32.6
chr15:63407216:C:T	15	63407216	C	T	rs181364771	APH1B [k]	LINC02568	0.028	1.27 (1.18-1.37)	1.34e-09	30	0.029	1.18 (1.09-1.28)	7.69e-05	21.8
chr17:44352876:C:T	17	44352876	C	T	rs5848	GRN	GRN	0.32	1.09 (1.07-1.12)	1.74e-12	0	0.32	1.05 (1.03-1.08)	0.000124	0
chr17:46111701:A:G	17	46111701	A	G	rs7225002	MAPT	MAPT H2	0.38	0.93 (0.91-0.95)	4.88e-10	36.4	0.39	0.97 (0.95-1.00)	0.0320	31.1
chr17:63470201:G:A	17	63470201	G	A	rs8077276	ACE	ACE	0.58	1.05 (1.03-1.08)	1.10e-05	0	0.58	1.09 (1.07-1.12)	3.45e-12	14.7
chr18:27352028:C:A	18	27352028	C	A	rs544488330	CHST9	CHST9	0.0025	2.21 (1.70-2.88)	3.69e-09	70.1	0.0019	1.32 (0.85-2.06)	0.220	4.8
chr19:1050875:A:G	19	1050875	A	G	rs12151021	ABCA7	ABCA7	0.64	0.91 (0.89-0.94)	1.47e-12	70.7	0.63	0.91 (0.89-0.94)	6.75e-11	16.6
chr19:54304006:C:T	19	54304006	C	T	rs1761453	LILRA5	LILRA5	0.45	0.97 (0.95-0.99)	0.00965	48.8	0.45	0.93 (0.91-0.95)	8.53e-09	0
chr20:413334:A:G	20	413334	A	G	rs1358782	RBCK1	RBCK1	0.70	1.08 (1.05-1.11)	4.73e-08	0	0.69	1.04 (1.01-1.07)	0.0101	0
chr20:56449045:G:A	20	56449045	G	A	rs113221226	CASS4	CASS4	0.069	0.91 (0.87-0.96)	0.000188	37.8	0.063	0.84 (0.79-0.89)	4.34e-10	0

Table 1: Genome wide significant hits

[a)] Topmed R2 identifier [b)] GRCh38 assembly. [c)] Reference single-nucleotide polymorphism (SNP) (rs) numbers, according to dbSNP build 156 [d)] Nearest protein-coding or long intergenic non-protein coding RNA according to Ensembl release 111. [e)] Effect allele frequency [f)] Odds ratio (OR) and 95% confidence intervals (CI) calculated with respect to the effect allele. [g)] Two-sided raw P-values derived from a fixed-effect meta-analysis. [h)] Heterogeneity I^2 statistics. [i)] In the *HLA-DRA* and *TREM2* loci different independent variants reached genome wide significance level in the two strata. [j)] In the *PILRA* locus two different variants in the two strata reached genome wide significance and had the lowest p-value in the locus. However, the two variants were in linkage disequilibrium (r^2>0.4). A third variant (rs10257273) also reached genome wide significance in the *APOE* ε44+ε43 strata and was independent from the lead variant (rs2906657). [k)] In the *CLU* and *APH1B* loci a second independent variant reached genome wide significance in one of the strata.

Table 2

				Dominant interaction – effect difference					Additive interaction – per ε4-allele				
topmed_id [a]	**rsid** [b]	**Loci**	**Gene** [c]	**ΔBeta** [d]	**SE**	**P-value** [e]	**I²** [f]	**Het p-value** [g]	**Beta** [h]	**SE**	**P-value**	**I²** [f]	**Het p-value** [g]
chr1:20745474:C:T	rs2274119	HP1BP3	HP1BP3 -1	0.10	0.037	0.0070	0	0.96	0.069	0.028	0.014	22	0.19
chr1:155135691:G:A	**rs12726330**	**SLC50A1**	**SLC50A1**	-0.19	0.053	**0.00029**	0	0.69	-0.13	0.040	**0.0013**	40	0.070
chr1:198710886:G:A	rs12733073	PTPRC	PTPRC	0.26	0.098	0.0093	9.8	0.35	0.16	0.075	0.036	0	0.63
chr1:207577223:T:C	rs679515	CR1	CR1	-0.034	0.023	0.14	45	0.092	-0.019	0.018	0.28	54	0.0030
chr2:127135234:C:T	**rs6733839**	**BIN1**	**BIN1**	0.058	0.019	0.0024	0	0.74	0.045	0.014	0.0020	60	**0.00040**
chr4:125059887:G:A	rs182938476	FAT4	FAT4 -1	0.44	0.32	0.16	0	0.69	0.47	0.28	0.093	0	0.63
chr6:32411770:C:T	**rs17208902**	**HLA-DRA**	**HLA-DRA -1**	0.078	0.020	**0.00011**	0	0.59	0.057	0.016	**0.00036**	0	0.60
chr6:32464090:G:T	rs9268888	HLA-DRA	HLA-DRA -2	0.0089	0.018	0.61	0	0.55	-0.0027	0.014	0.85	24	0.16
chr6:41161469:C:T	rs143332484	TREM2	TREM2 -1	0.098	0.085	0.25	0	0.74	0.087	0.070	0.22	7.5	0.37
chr6:41161514:C:T	rs75932628	TREM2	TREM2 -2	-0.29	0.20	0.16	8.3	0.36	-0.14	0.22	0.51	0	0.53
chr7:12242825:T:C	**rs7805419**	**TMEM106B**	**TMEM106B**	0.065	0.018	**0.00031**	27	0.21	0.046	0.014	**0.0011**	49	0.0079
chr7:99590966:A:T	rs10257273	PILRA	TMEM225B	0.040	0.022	0.073	48	0.064	0.042	0.017	0.017	9.7	0.33
chr7:100386466:T:C	rs2906657	PILRA	PILRA	-0.015	0.019	0.43	0	0.88	-0.014	0.015	0.34	40	0.036
chr8:27362470:C:T	rs73223431	CLU	PTK2B	0.036	0.018	0.042	0	0.58	0.041	0.014	0.0042	0.17	0.46
chr8:27610986:C:A	**rs867230**	**CLU**	**CLU**	0.060	0.018	**0.00080**	0	0.99	0.051	0.014	**0.00028**	0	0.49
chr8:144103704:G:A	**rs34173062**	**SHARPIN**	**SHARPIN**	-0.10	0.037	0.0049	47	0.080	-0.098	0.029	**0.00078**	15	0.29
chr11:47358789:G:T	rs3740688	SPI1	SPI1	-0.020	0.017	0.26	0	0.77	-0.021	0.014	0.12	0	0.58
chr11:60173126:T:A	rs7232	MS4A6A	MS4A6A	-0.030	0.019	0.11	44	0.087	-0.027	0.015	0.071	6.7	0.37
chr11:86113817:A:G	rs659023	PICALM	PICALM	0.045	0.018	0.015	13.	0.33	0.039	0.015	0.0071	46	0.020
chr11:121564878:T:C	rs11218343	SORL1	SORL1	-0.079	0.050	0.12	33.	0.16	-0.096	0.041	0.019	18	0.25
chr14:33428905:G:C	**rs187023552**	**NPAS3**	**NPAS3**	-0.37	0.091	**4.2e-05**	46	0.17	-0.26	0.073	**0.00032**	65	0.034

				Dominant interaction – effect difference					Additive interaction – per ε4-allele				
topmed_id [a)]	**rsid** [b)]	**Loci**	**Gene** [c)]	**ΔBeta** [d)]	**SE**	**P-value** [e)]	**I^2** [f)]	**Het p-value** [g)]	**Beta** [h)]	**SE**	**P-value**	**I^2** [f)]	**Het p-value** [g)]
chr14:53394351:T:C	**rs10131116**	**FERMT2**	**DDHD1**	-0.10	0.018	**1.1e-08**	18.	0.29	-0.069	0.014	**1.2e-06**	32	0.088
chr15:58790588:T:G	rs347116	ADAM10	ADAM10	-0.034	0.018	0.068	0	0.74	-0.023	0.015	0.11	0	0.62
chr15:63279621:C:T	rs75763893	APH1B	APH1B	0.017	0.026	0.51	0	0.64	0.017	0.021	0.41	12	0.30
chr15:63407216:C:T	rs181364771	APH1B	LINC02568	-0.082	0.058	0.16	21	0.27	-0.067	0.047	0.15	30.	0.12
chr17:44352876:C:T	rs5848	GRN	GRN	-0.041	0.019	0.030	0	0.86	-0.034	0.015	0.021	0	0.98
chr17:46111701:A:G	rs7225002	MAPT	MAPT H2	0.045	0.018	0.012	64	0.0075	0.032	0.014	0.025	34	0.066
chr17:63470201:G:A	rs8077276	ACE	ACE	0.031	0.018	0.088	0	0.82	0.028	0.014	0.048	0	0.82
chr19:1050875:A:G	rs12151021	ABCA7	ABCA7	-0.012	0.019	0.52	0	0.89	0.012	0.015	0.43	55	0.0016
chr19:54304006:C:T	rs1761453	LILRA5	LILRA5	-0.036	0.018	0.046	0	0.61	-0.032	0.014	0.023	0	0.62
chr20:413334:A:G	rs1358782	RBCK1	RBCK1	-0.038	0.022	0.084	19	0.28	-0.029	0.017	0.095	0	0.79
chr20:56449045:G:A	rs113221226	CASS4	CASS4	-0.098	0.039	0.011	3.7	0.40	-0.058	0.031	0.061	2.9	0.42

Table 2: Interaction testing results

Results of interaction testing with a dominant and an additive fixed effect model on the summary data of the individual cohorts. The dominant model was a difference of effect analysis while the additive model included the number of ε4-allelles. Significant interactions (p-value < 0.0015) are in bold with the significant p-values underlined. [a)] Topmed R2 identifier [b)] Reference single-nucleotide polymorphism (SNP) (rs) numbers, according to dbSNP build 156 [c)] Nearest protein-coding or long intereneric non-coding RNA according to Ensembl release 111. [d)] ΔBeta is calculated as β_{43+44}- β_{33}. [e)] Two-sided raw P- values were derived from a fixed-effect meta-analysis. [f)] I^2: I-statistics, residual heterogeneity of the unaccounted variability [g)] Het P-value: Test for residual heterogeneity. [h)] effect per one ε4-allele.

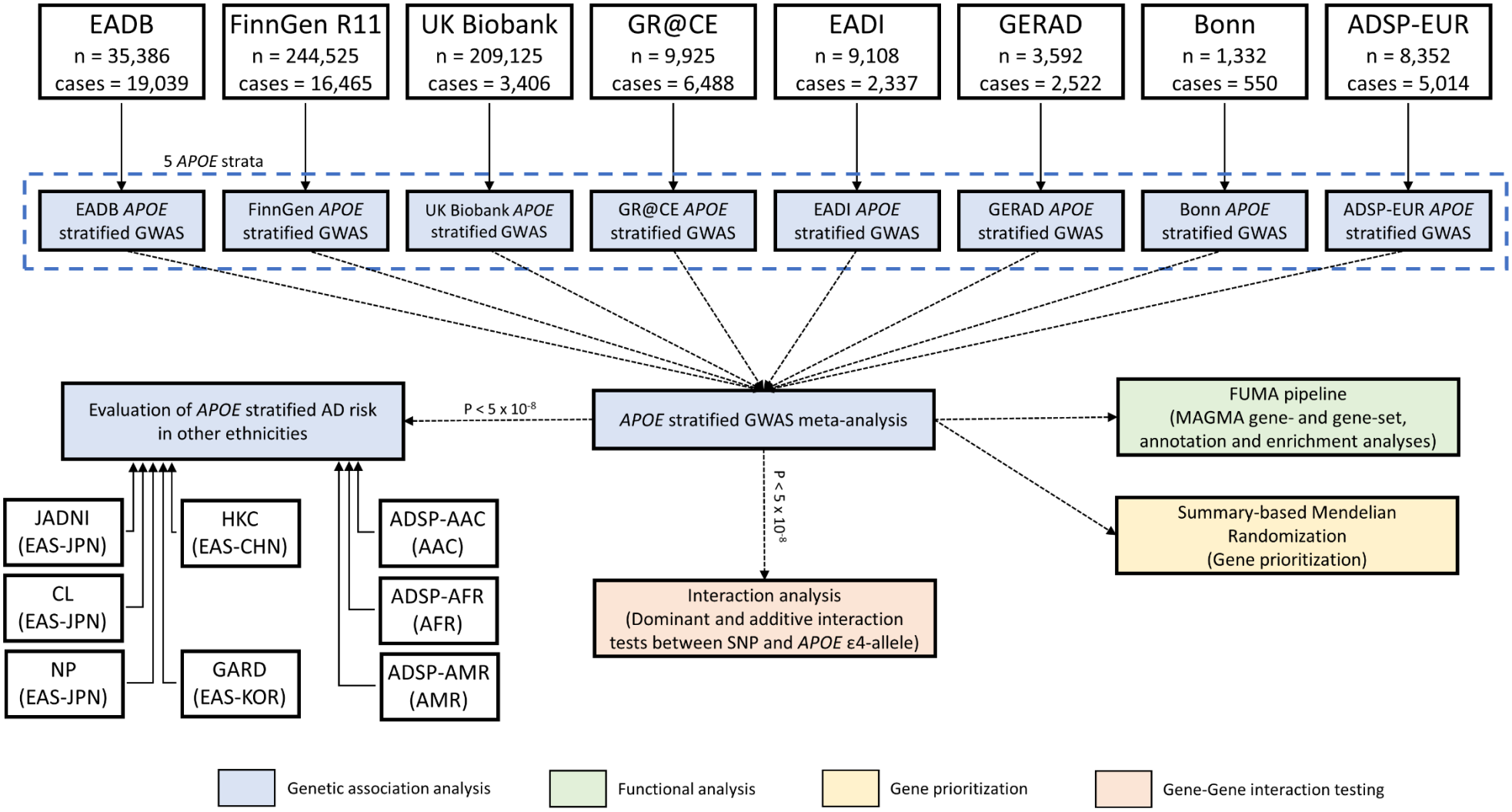

Figure 1: Flow chart of study

Flow chart illustrating the included multi-ancestry cohorts and analysis strategies.

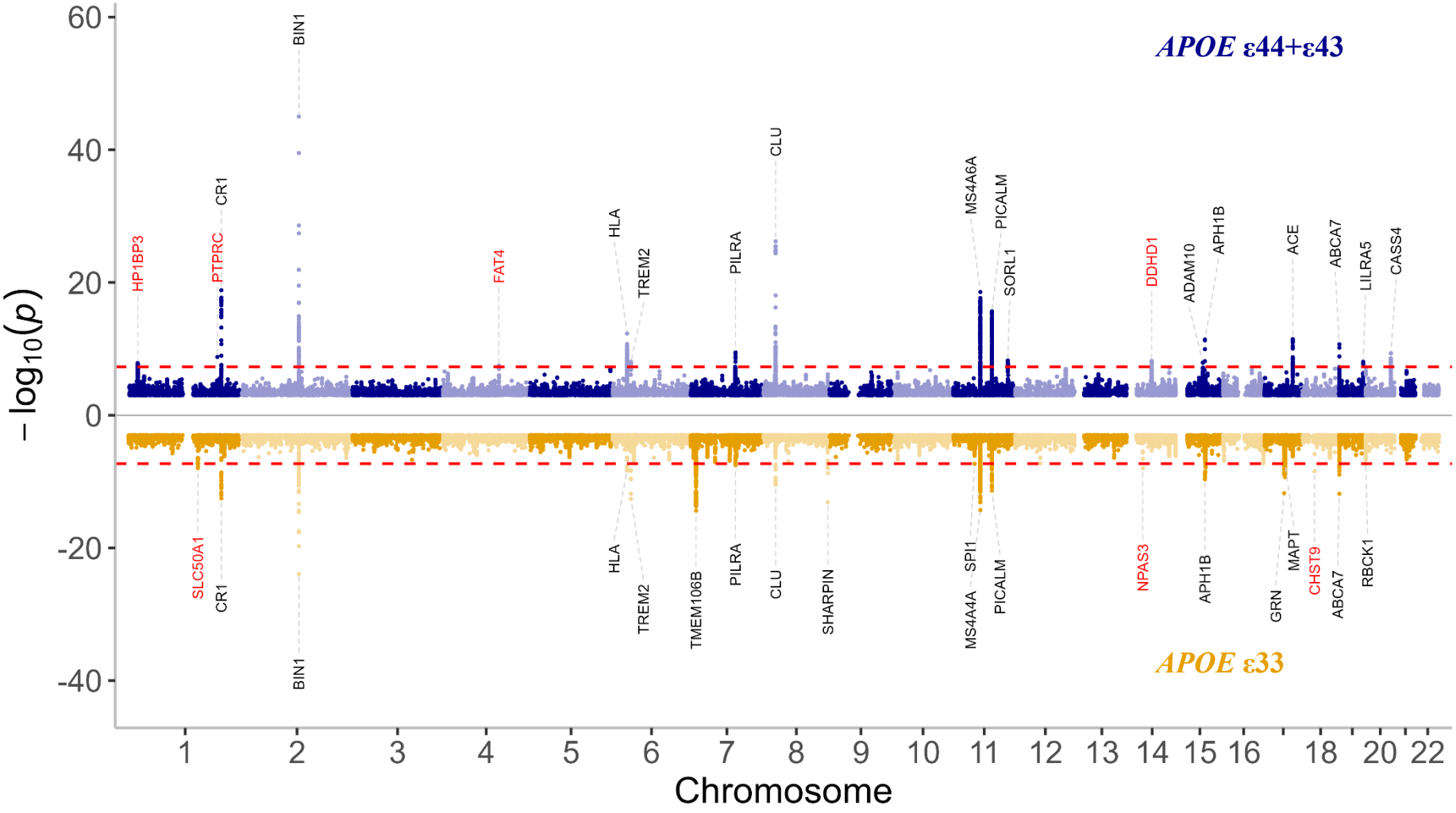

Figure 2: Miami plot of the *APOE* ε33 and ε44+ε43 strata.

The Manhattan plot for the *APOE* ε44+ε43 strata is shown in blue in the upper part of the figure and for the *APOE* ε33 strata in orange in the lower part of the figure. Genome wide significant loci are annotated with the nearest gene (known loci in black and new in red). Two-sided raw P-values were derived from a fixed-effect meta-analysis. The red dashed lines show the genome-wide significant level ($P=5\times10^{-8}$). *APOE*: Apolipoprotein E gene.

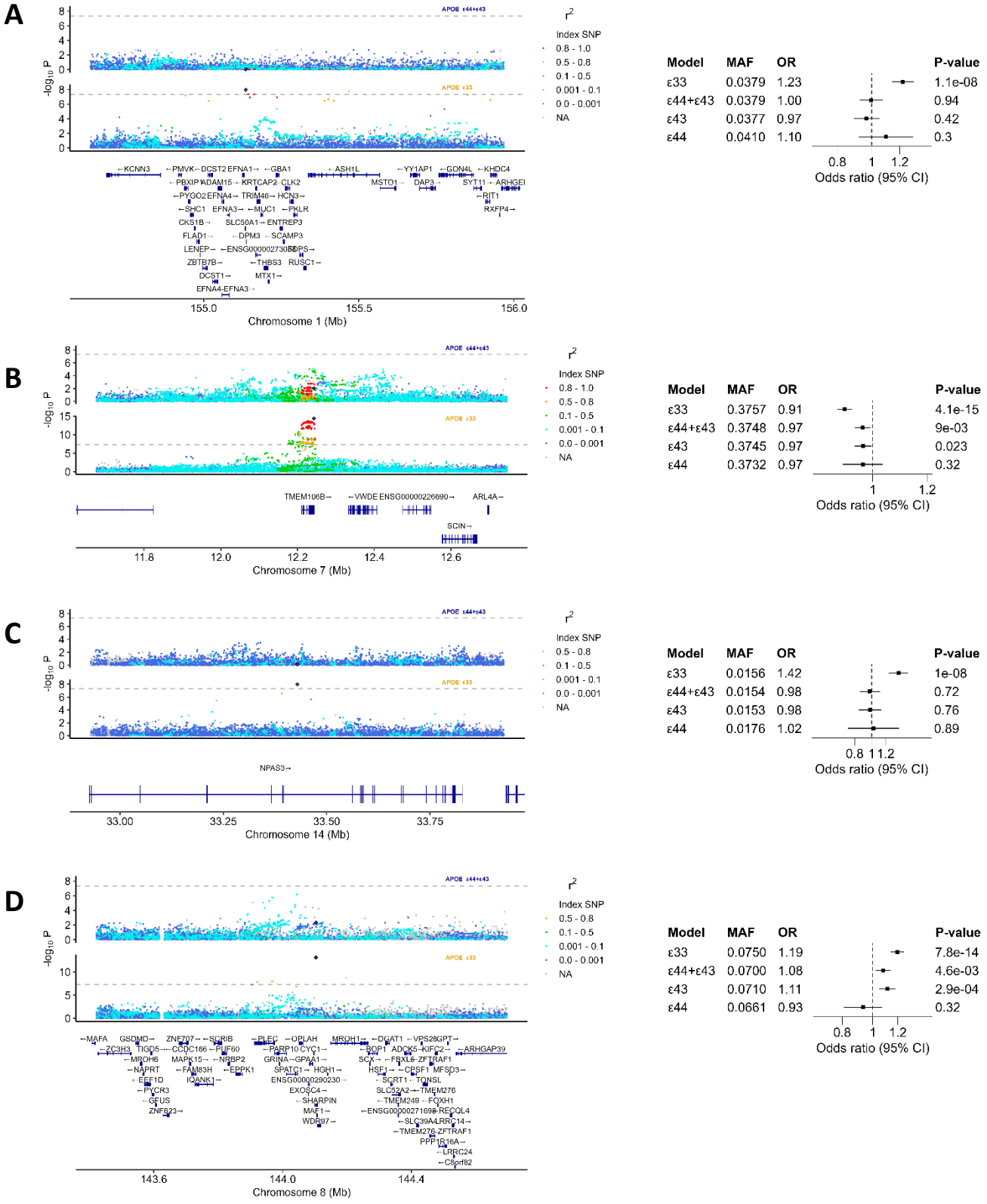

Figure 3: Loci and forest plots for *SLC50A1*, *TMEM106B*, *NPAS3*, and *SHARPIN* where the effect attenuates with the *APOE* ε4 allele.

Loci plots for *SLC50A1* (A), *TMEM106B* (B), *NPAS3* (C), *SHARPIN* (D) in *APOE* ε33 and *APOE* ε44+ε43 strata. Forest plots for the lead SNPs in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

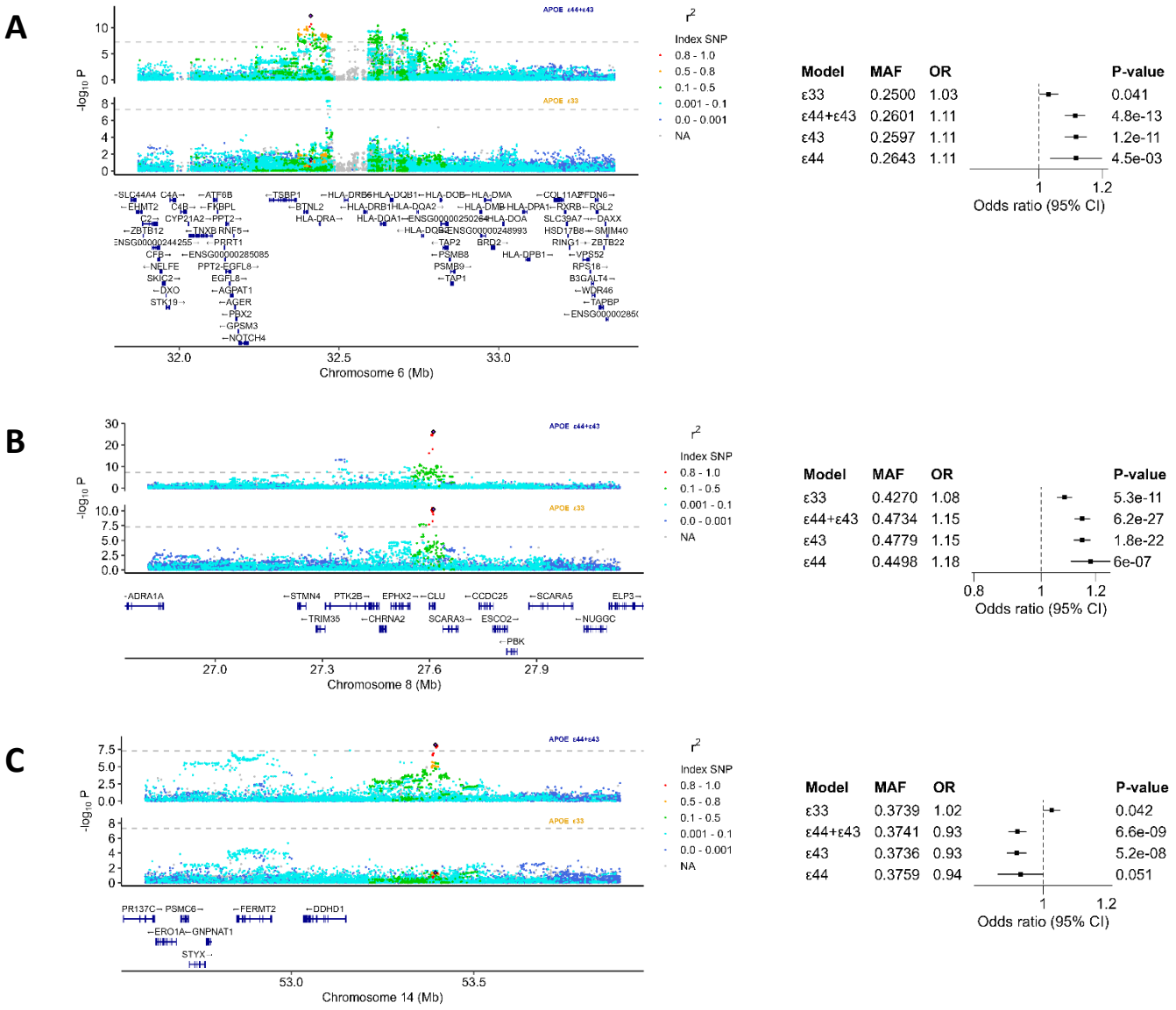

Figure 4: Loci and forest plots for the three loci (*HLA-DRA -1*, *CLU*, *DDHD1)* where the effect is augmented with the *APOE* ε4 allele.

Loci plots for *HLA-DRA -1 (A)*, *CLU (B)*, *DDHD1 (C)* in *APOE* ε33 and *APOE* ε44+ε43 strata. Forest plots for the lead SNPs in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

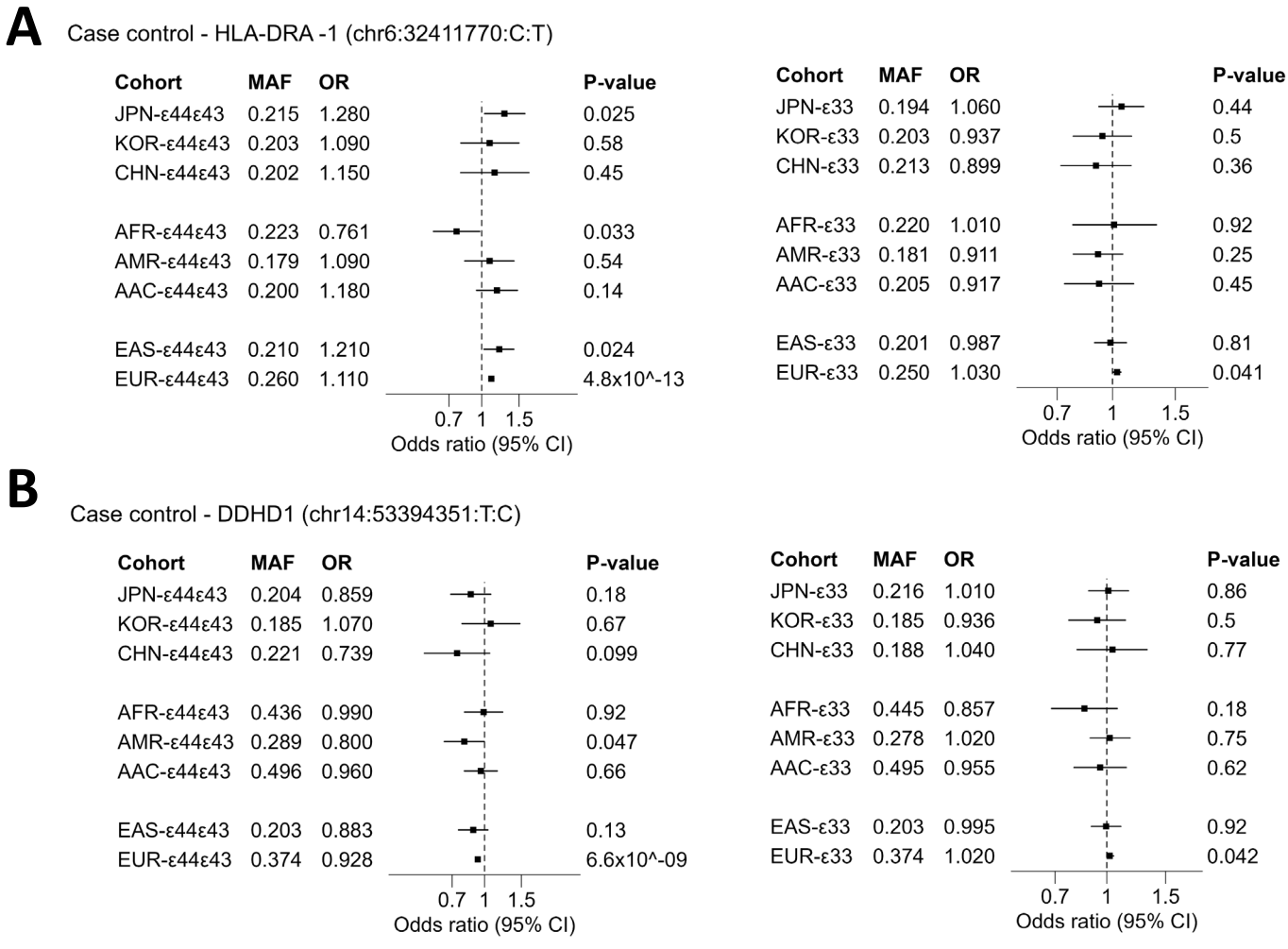

Figure 5: Multi-ancestry evaluation

A: Multi-ancestry results for lead variant in *HLA-DRA* locus. B: Multi-ancestry results for lead variant in *DDHD1* locus. AAC: Asian American, AFR: African American, AMR: Admixed American, CHN: Hong-Kong Chinese, JPN: Japanese, KOR: Korean, EAS: East Asian ancestry meta-analysis, EUR: European ancestry meta-analysis.

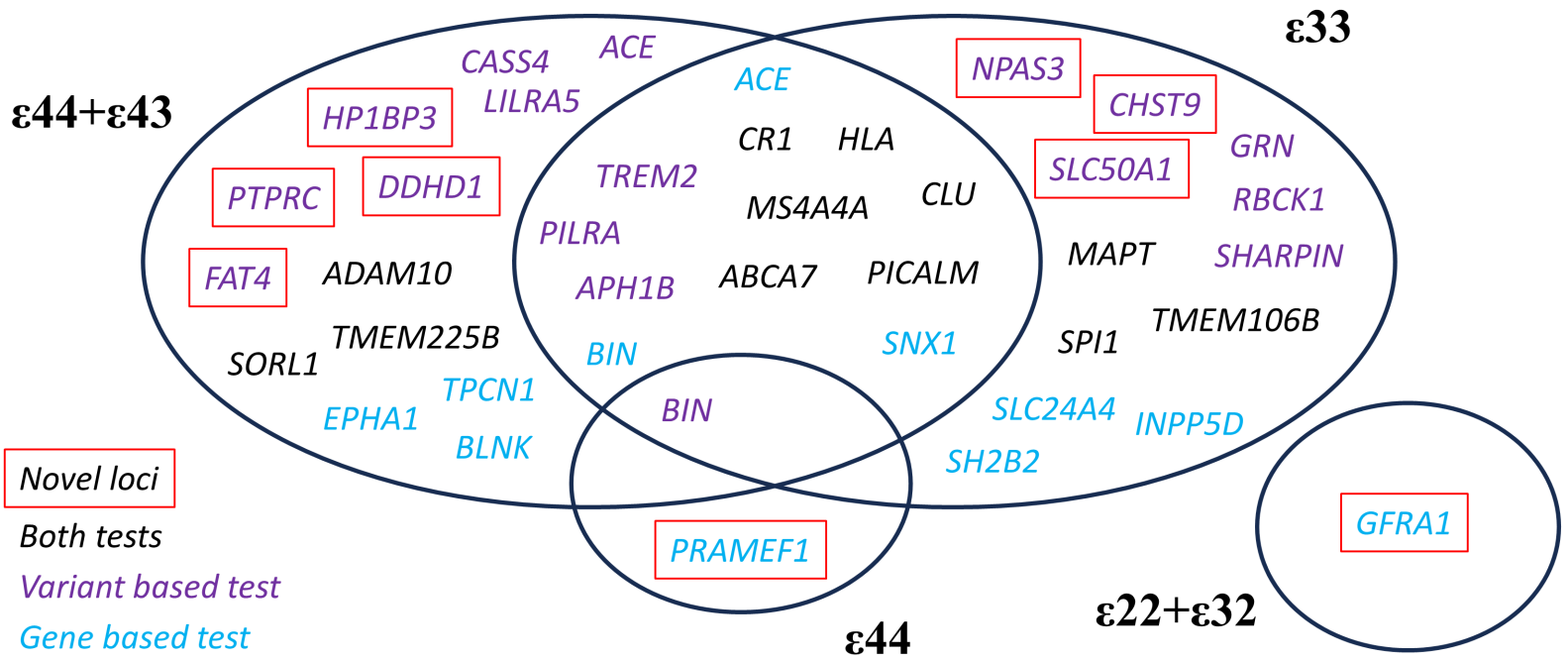

Figure 6: Variant and gene-based significant loci
Venn-diagram of the genome-wide significant loci associated with AD, showing the overlap between *APOE*-strata and between variant based testing (main GWAS) and gene-based testing (MAGMA).