A fast and robust strategy to remove variant level artifacts in Alzheimer's Disease Sequencing Project data

Supplementary Material

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eMethods

In the current study, we used data from a variety of cohorts and sequencing projects related to AD[1-23]. While we only present analyses on ADSP data, all available genetic/phenotic data were jointly harmonized with the purpose of performing phenotype/covariate harmonization. Details are provided below.

Phenotype Ascertainment

Cohorts and Phenotype Ascertainment

Details on phenotype ascertainment are described elsewhere[1–6]. Briefly, all individuals with a diagnosis of AD met National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable or possible late onset AD[7], or met Diagnosis and Statistical Manual of Mental Disorders IV-V (DSMIV-V) criteria[8–10], or had a clinical dementia rating (CDR® Dementia Staging Instrument[11]) > 0.5. Some cohorts verified AD diagnoses by means of neuropathology, using Braak staging[12], CERAD scoring[13], or National Institute on Aging Reagan (NIA-Reagan) 1997 criteria[14]. Cognitively normal subjects (controls) did not have AD according to the above clinical criteria for AD, did not have a diagnosis of MCI, and had a CDR of 0 and/or Mini-Mental State Examination (MMSE[15]) > 25. In the MIRAGE cohort, control status was evaluated through a Modified Telephone Interview of Cognitive Status score ≥ 86 (a telephone version of the MMSE)[16].

Further, the National Alzheimer's Coordinating Center (NACC), Rush University Religious Orders Study/Memory and Aging Project (ROSMAP), and Alzheimer's Disease Neuroimaging Initiative (ADNI), are longitudinal cohorts that provide detailed information regarding clinical status (control, MCI, demented) and presumed disease etiology at repeated examinations. Additionally, deceased subjects are assessed for neuropathology. Where possible, in NACC, a final diagnoses of MCI or possible/probable/definite AD was obtained using NIA Alzheimer's Association (NIA-AA) 2011 criteria[17,18]. In all three cohorts, AD diagnoses were verified by neuropathology as middle or high AD likelihood following NIA-Reagan 1997 criteria (moderate to frequent neuritic plaques and Braak stage III-VI)[14]. In concordance with the category "possible AD dementia with evidence of the AD pathophysiological process" from the NIA-AA 2011 criteria[17], we attributed possible AD diagnoses to subjects who met clinical criteria for non-AD dementia but also met AD neuropathological criteria. In concordance with the NIA-AA 2011/2012 framework[18,19], we also evaluated neuropathology in MCI subjects to verify presumed AD etiology (cf. page 5). Controls were not re-evaluated based on neuropathology data. Subjects that reverted from dementia to control status during longitudinal follow-up were excluded. Additional cohort-specific details are listed below.

NACC

Genotyping waves 1 through 7 from the Alzheimer's Disease Centers (ADC1-7) and a subset of the ADSP projects include subjects ascertained and evaluated by the clinical and neuropathological cores of 32 NIA-funded ADCs. NACC coordinates the collection of these phenotypes, implements diagnoses (cognitively normal, cognitively impaired but not MCI, MCI, demented; and presumed disease etiology) and then provides all data to researchers under the form of the Minimum Data Set (MDS), Uniform Data Set (UDS)[20–22], and Neuropathology data set (NP)[23]. The MDS represents an older subset of the NACC data and only contains cross-sectional data, while the more recent UDS provides longitudinal phenotypes and covariates. Since 2015, the UDS was updated to incorporate the NIA-AA 2011 criteria for MCI and AD[18,24]. In the current study, we used the UDS and NP for which data was collected between September 2005 and March 2021, to determine phenotypes for subjects in ADC1-7, ADSP WES/WGS, and ADGC Exome arrays.

Subjects that had a diagnosis of Down syndrome, central nervous system neoplasm, bipolar disorder, schizophrenia, alcohol-induced dementia, or substance-abuse-induced dementia, were excluded. Subjects carrying mutations of dominantly inherited AD or frontotemporal lobar degeneration (FTLD) were also excluded. Subjects with a final diagnosis of MCI or dementia, for which the etiology was unknown, not due to AD, or only secondary due to AD (and without AD neuropathological information), were excluded. Subjects with a final diagnosis of "cognitively impaired but not MCI", but having no other neurological disorder, were kept as controls, considering that this more consistently matched control criteria in many of the other cohorts considered in this study.

ROSMAP

In ROSMAP, subjects were diagnosed at each visit: as possible/probable AD according to NINCDS-ADRDA criteria[7]; as MCI when judged to have cognitive impairment but not meeting dementia criteria according to the clinician; or as control when there was no cognitive impairment or the subject did not meet dementia criteria[25,26]. At time of death, a final clinical diagnosis was made by an expert neurologist, followed by case conference consensus review (blinded to postmortem data)[27].

ADNI

In ADNI, subjects were diagnosed at regular visits: as possible/probable AD according to NINCDS-ADRDA criteria[7]; as MCI according to Petersen/Winblad criteria; or as control when not demented, not MCI, CDR = 0, and MMSE > 28. Neuropathology assessments followed the NACC NP framework.

Phenotype Harmonization

The available sample contained many subjects that were genotyped multiple times across different studies. This largely reflected efforts from the ADGC, ADSP, and AMP-AD, to perform next generation sequencing (NGS) on existing cohort samples for the purpose of rare variant discovery and AD gene prioritization. In other instances, participants were recruited in different studies at different times. Therefore, to handle potential duplicate discordance and phenotype heterogeneity, we implemented a cross-sample phenotype harmonization procedure aiming to standardize pathology-verified diagnoses where possible, share unique missing information across all duplicate entries of a given subject, resolve longitudinal changes in diagnosis, and flag subjects with unresolvable duplicate discordance for exclusion.

Duplicate samples were identified by determining genetic cryptic relatedness (cf. page 7-8 below), but for the purpose of sample cross-referencing did not include known identical twins in LOAD and ROSMAP samples. First, duplicate samples were flagged as discordant if their age-at-death information differed by more than 2 years or if pathology measures (Braak or neuritic plaque density) differed. Across all cohorts, where possible, AD diagnoses were verified by neuropathology as middle or high AD likelihood following NIA-Reagan 1997 criteria (moderate to frequent neuritic plaques and Braak stage III-VI)[14]. Additionally, when only either neuritic plaque or Braak information was available and in line with NIA-Reagan 1997 middle or high AD likelihood criteria, and/or the cohort/project demographics provided a diagnosis of definite AD, the subject was considered to have pathology-verified AD status. Cognitively normal (CN) subjects with evidence of AD pathology were kept as CN. Further, if at least one entry across duplicate samples indicated a diagnosis of Down syndrome, central nervous system neoplasm, bipolar disorder, schizophrenia, alcohol-induced dementia, substance-abuse-induced dementia, neurological (not including Parkinson's disease) or systemic disease despite being cognitively normal, or carrying mutations of dominantly inherited AD or frontotemporal lobar degeneration (FTLD), then all duplicate samples were marked as such and flagged for exclusion. Extending on the above, all genetic samples were checked for the presence of known pathogenic mutations on *APP, PSEN1, PSEN2* and *MAPT*, whereby carriers and their duplicate samples were flagged for exclusion.

Then, duplicate samples with differing age entries (i.e. longitudinal changes) were evaluated. Reversions from AD or dementia to MCI status, or from MCI to cognitively normal (CN) status, were permitted, but reversions from AD or non-AD dementia to CN status were flagged for exclusion. "Reversions" from AD to non-AD dementia status were permitted, unless pathology (cf. above) indicated the presence of AD pathology, thereby marking the subject as AD. Vice versa, "conversions" from non-AD

dementia to AD status were permitted, unless pathology (cf. above) indicated no presence of AD pathology, thereby marking the subject as non-AD dementia. All other types of conversions were directly permitted. Then, duplicate samples for which the diagnoses at the oldest shared age entries differed, or for which diagnoses differed but age was consistent (i.e. apparent cross-sectional discordances), were evaluated. Discordances between AD and non-AD dementia status were resolved on the basis of pathology (cf. above) or flagged as discordant if no pathology data was available. Discordances between CN and AD status, or CN and non-AD dementia status, were resolved as respectively AD or non-AD dementia when those dementia diagnoses corresponded to a unique age-at-onset (of symptoms) without other available age information (i.e. indicating that a conversion likely occurred after the subject was lost to follow-up in the cohort that last observed a CN status), or, were flagged as discordant if duplicate entries shared the same age-at-examination and age-at-last-exam. Discordances between CN and MCI status, or MCI and AD status, or MCI and non-AD dementia status, were resolved as respectively MCI, AD, or non-AD dementia (i.e. keeping the most severe diagnosis).

Finally, once all clinical diagnostic and pathological data were unified across duplicate entries, pathological criteria were applied once more to obtain the final diagnoses. Where possible, AD diagnoses were verified by neuropathology as middle or high AD likelihood following NIA-Reagan 1997 criteria (moderate to frequent neuritic plaques and Braak stage III-VI)[14]. In concordance with the category "possible AD dementia with evidence of the AD pathophysiological process" from the NIA-AA 2011 criteria[17], we attributed possible AD diagnoses to subjects who met clinical criteria for non-AD dementia but also met AD neuropathological criteria. In concordance with the NIA-AA 2011/2012 framework[18,19], we also evaluated neuropathology in MCI subjects to verify presumed AD etiology and considered subjects as cases if AD pathology, following NIA-Reagan 1997 criteria (cf. above), was present (i.e. marking high likelihood of AD etiology). Controls were not re-evaluated based on neuropathology data.

Beyond cross-referencing clinical diagnostic and pathological data across subjects, other covariates were considered for cross-referencing or sharing in case of missingness across duplicate entries. These included age-at-onset of cognitive symptoms, age-at-examination providing clinical diagnosis, at-at-last exam, age-at-death, sex, race, ethnicity, *APOE* genotype provided from demographics, *APOE* genotype provided from whole-genome sequencing, and *APOE* genotype provided from whole-exome sequencing. Duplicate entries with discordant sex or race information were flagged for exclusion.

Genetic Data Quality Control and Processing

Genetic Data Harmonization and Standard Quality Control

Genotypes were available from commercial high-density single-nucleotide polymorphism (SNP) genotyping microarrays (Illumina or Affymetrix), Exome sequencing (ES), or Genome sequencing (GS) (**eTable 1**). Genotype samples had their genetic variants lifted to hg38 using liftOver if not released in hg38[28]. Autosomal variants were extracted from the SNP array data and further processed in several stages. First, SNP array data were processed by the Genotype Harmonizer with CEU and TSI HapMap populations as the reference panel, to perform automatic strand alignment[29]. Then, multi-allelic SNPs, SNPs located on common copy number or segmental duplication regions, and duplicated or monomorphic SNPs, were removed. The list of multi-allelic SNPs or SNPs located on common copy number and segmental duplication regions was created using Tri-Typer[30]. The list of CNV and segmental duplication regions was curated from the Eichler lab (eichlerlab.gs.washington.edu/database.html)[31] and the gnomAD website (gnomad.broadinstitute.org/downloads)[32]. All respective genotype data sets were then iteratively merged with each other, applying strand flipping and variant ID updating as applicable, to ultimately obtain parsimonious data sets that could be merged for cross-sample relationship determination and principal component analyses (cf. below).

Genetic data were then further processed using Plink v1.9. The numbers of remaining samples after each quality control (QC) or processing step are listed in **eTable 3-4**. For each sample platform, subjects with autosome missingness (≥ 5%) and sex problems (discordance between genetic sex and demographic sex, or deviation of expected X-chromosome homozygosity/heterozygosity) were flagged for exclusion.

Ancestry Determination

Individual ancestries were determined using SNPweights v.2.1 with populations from the 1000 Genomes Consortium as a reference[33,34]. By applying an ancestry percentage cut-off ≥ 75%, the samples were stratified into the five super populations, South-Asians (SAS), East-Asians (EAS), Americans (AMR), Africans (AFR) and Europeans (EUR) (**eFigure 1**). Subjects with a genetic ancestry that differed from their race, as provided in cohort demographics, were flagged for exclusion. Subjects belonging to the European ancestry super population were further determined according to three major ancestries, that is, Northwestern European (NWE), Southeastern European (SEE), and Ashkenazi Jewish (AJE), using reference populations available from SNPweights v.2.1.2[33]. European subjects were stratified into the above-mentioned ethnicities by applying an ancestry percentage cut-off ≥ 50% (**eFigure 1**).

Genetic Duplicate Determination using Plink

Across all cohorts the relatedness of subjects (after QC indicated above) was evaluated through identity-by-descent (IBD) analysis (using directly genotyped non-palindromic SNPs that shared across all genetic datasets with a call rate > 95%, minor allele frequency (MAF) > 1%). This outcome was used for duplicate (IBD>0.95) tracking across samples, which in turn was used to enable phenotype harmonization.

Relationship Determination and Principal Component Analysis using GENESIS

For ADSP WGS and WES data respectively, the relatedness of subjects and principal components capturing population substructure were determined using IBD and principal component analyses (PCA) as implemented through the R package GENESIS (R v3.6.0)[35]. Specifically, this approach first uses an R-implementation of KING-robust to determine kinship coefficients that take into account ancestry divergence. The derived pairwise kinship coefficients are then used to perform a PCA in related samples (PC-AiR) providing accurate ancestry inference not confounded by family structure. The latter output is then used to estimate kinship coefficients using PC-Relate, which accounts for population structure (ancestry) among sample individuals through the use of ancestry representative principal components (PCs) to provide accurate relatedness estimates due only to recent family (pedigree) structure. For each respective data set, these analyses were performed on pruned SNPs (R^2 < 0.5, call rate > 99.9%, MAF > 1%, and excluding palindromic SNPs) in non-Hispanic white European ancestry individuals (**eFigure 2**).

APOE genotype assessment in ADSP WES/WGS

In ADSP WGS, the rs429358 and rs7412 variants showed low genotype missingness across subjects, reflecting good variant quality metrics. In ADSP WES, there was a high genotype missingness at rs7412 (32.5%). This resulted from a low read depth and genotype quality in some of the different WES capture kits that were used in the ADSP WES[2]. We therefore sought to re-call both variants in order to fill out missing *APOE* information where possible. We first inferred the variants' genotype using data called by the ADSP, which required a read depth read depth (DP) >=10 and genotype quality (GQ) >= 20. We then further inferred the variants' genotype if DP and GQ were respectively greater than or equal to 6 and 20, observing at least 20% alternate allele reads to call a heterozygote (e.g. *APOE**3/4).

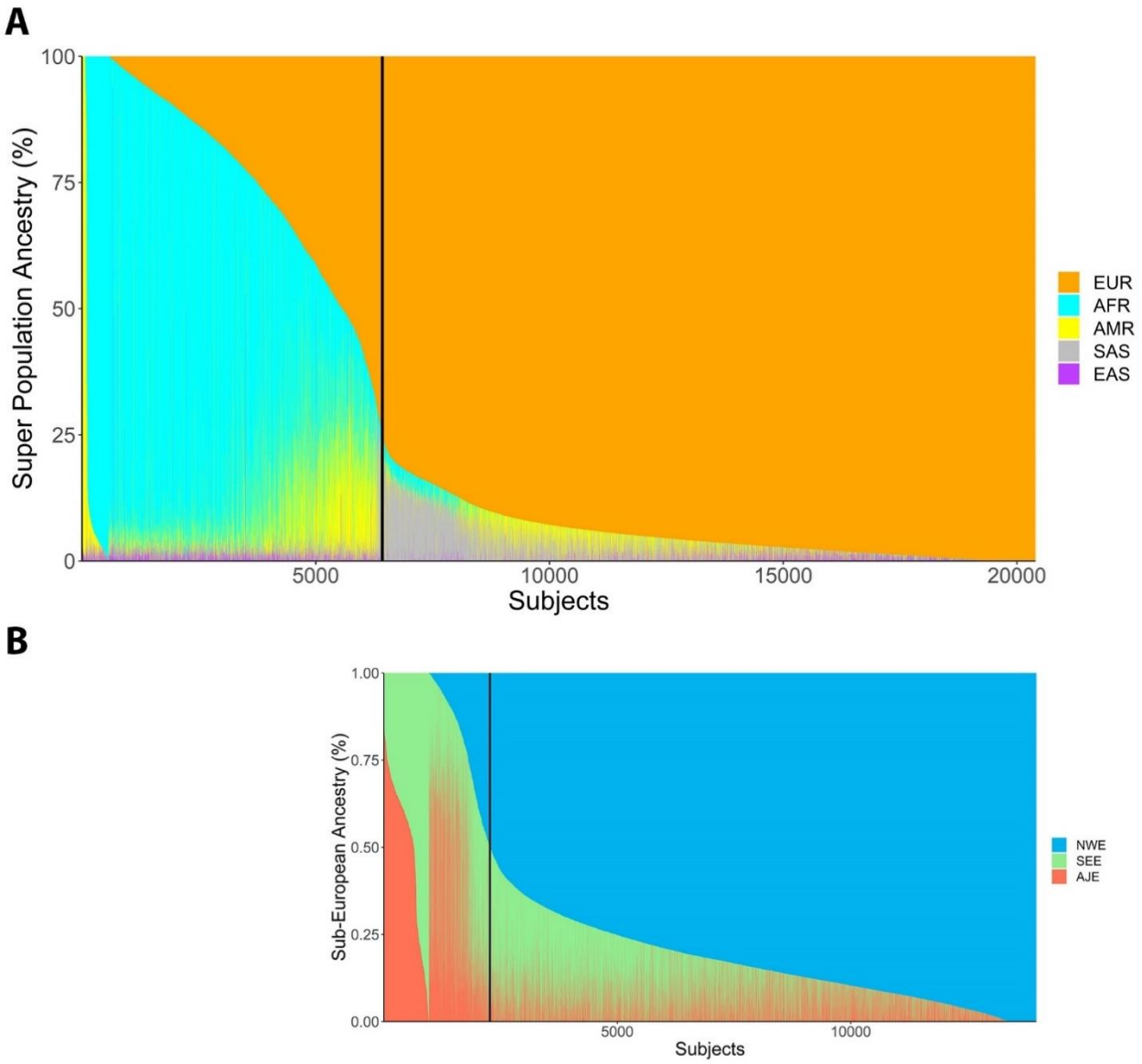
After this first round of *APOE* genotype ascertainment, some individuals still had either the rs7412 or rs429358 genotype missing (i.e., only one of the two variants could be called using the above criteria), making it impossible to infer their *APOE* genotype from the ADSP NGS data alone. Many of these

remaining individuals however had a reported *APOE* genotype in their demographics that could be used to complete the missing information in a second additional round of *APOE* genotype ascertainment. This approach was preferred over relying solely on the *APOE* genotype in the demographics, since the genotype calls on the ADSP NGS data are expected to provide higher accuracy compared to other commonly used *APOE* direct genotyping methods[36]. To illustrate, consider the example where one of these remaining individuals in the sequencing data was homozygous for the reference allele at rs429358, which would suggest the subject is *APOE**3/3, but had a missing genotype at rs7412. In this case, from the ADSP NGS data, we know that this individual is not carrying an *APOE**4 allele, but we cannot determine the presence or absence of an *APOE**2 allele. We then turned to the information from the *APOE* genotype provided in the demographics to infer the most likely *APOE* genotype. For the current example, if the individual has a provided *APOE* genotype that was 2/2, 2/3, or 3/3, then the information in the ADSP NGS data is deemed concordant with the provided *APOE* genotype (that is, rs429358 is always the reference allele for those provided *APOE* genotypes) and we used the provided *APOE* genotype. However, if the provided *APOE* genotype was 4/4 or 3/4, then we would correct it to *APOE**3/3, because the ADSP NGS information clearly indicated there was no *APOE**4 genotype call (similarly a provided *APOE**2/4 genotype would be corrected to *APOE**2/3). This can be generalized as: for remaining individuals with DP>=6 and GQ>=20 at rs429358, the ADSP NGS data at rs429358 was used to change, when discordant, the provided *APOE**3 genotype to *APOE**4, or vice-versa. One additional extension to this step was implemented for the few scenarios where the ADSP NGS data called two rs429358 alleles (i.e. *APOE**4/4) but the allelic distribution indicated that the reference allele was still observed (e.g. 1 REF allele and 7 ALT alleles). In these situations, if the provided *APOE* genotype indicated the presence of *APOE**3, then the genotype was corrected to *APOE**3/4 (reasoning there is sufficient evidence to support the presence of an *APOE**3 genotype). The extra checks described in this paragraph were also applied to subjects in the first QC round (prior paragraph), who had 6<=DP<10 and GQ>=20 for both rs429358 and rs7412.

As a quality check, using these thresholds, we did not observe any discordance in the inferred *APOE* genotype across 3,499 duplicates between the ADSP WGS and ADSP WES.

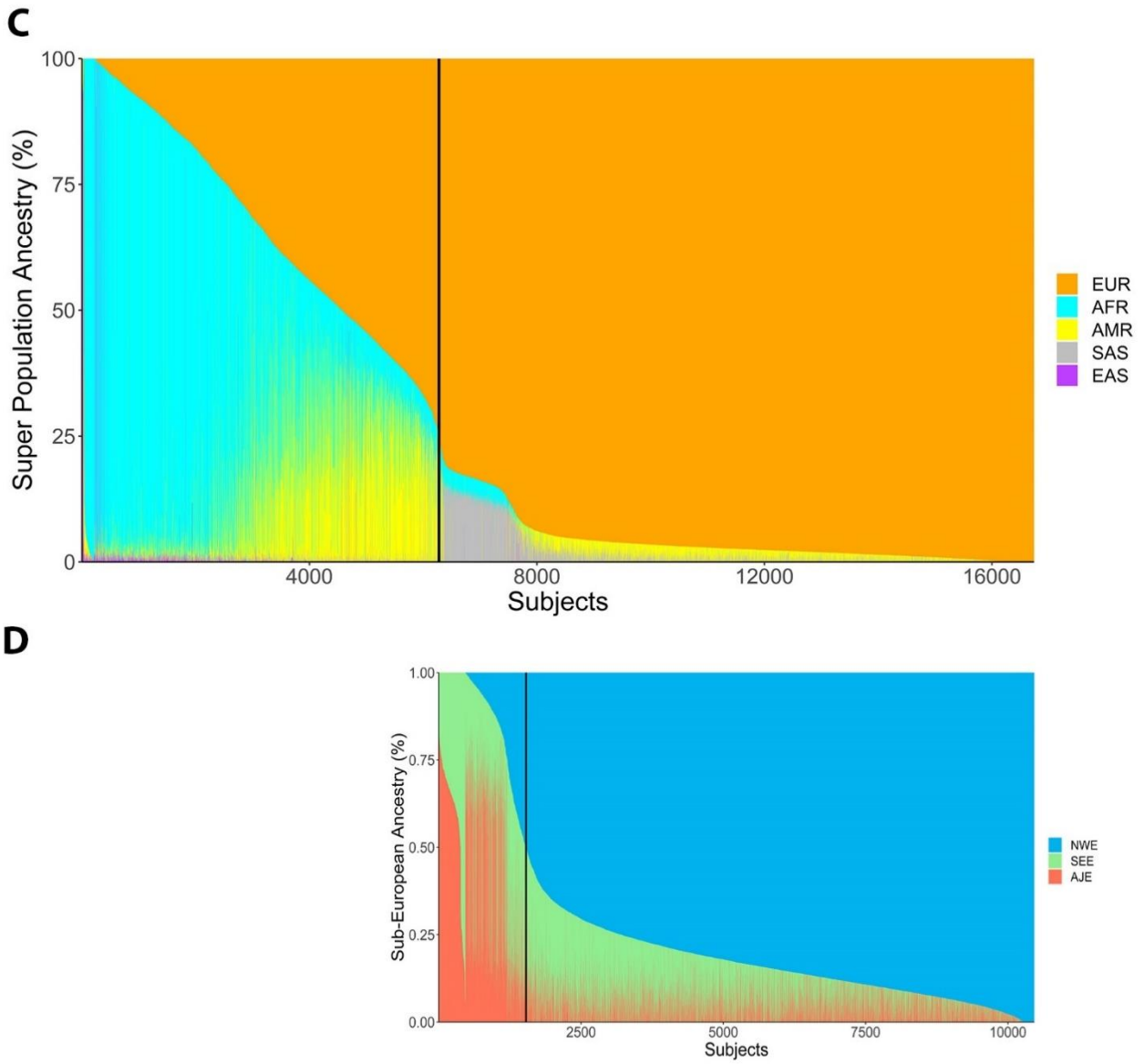
ADSP WES/WGS quality control prior to genetic association testing

After the genetic and phenotypic quality control/harmonization described in the above, the ADSP WES and WGS samples were respectively restricted to all non-Hispanic European ancestry individuals that pass filtering criteria (**eTable 3-4**). The remaining samples underwent genetic quality control as detailed in the manuscript's method section, followed by association testing and construction of the genotype filters.



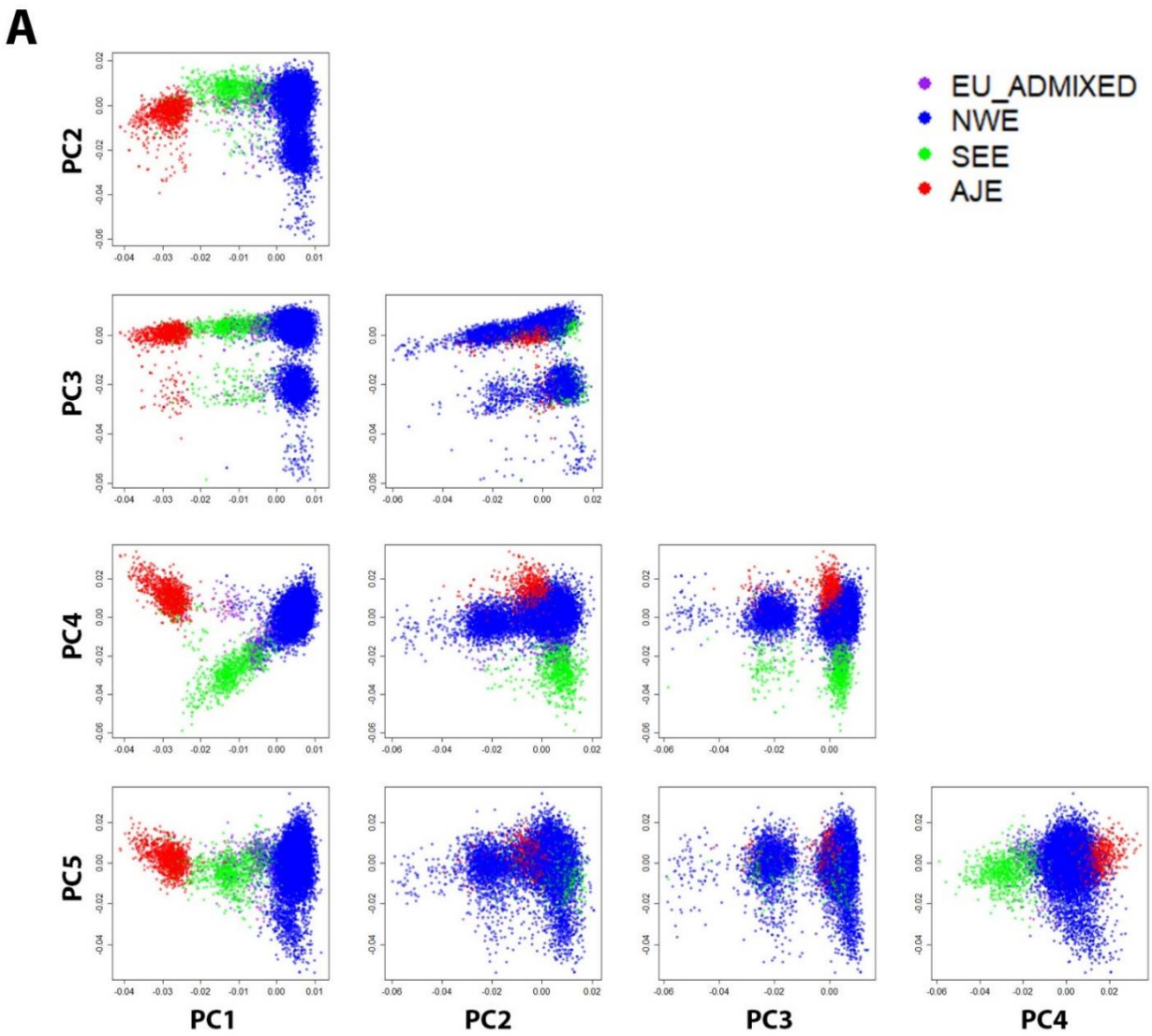
eFigure 1 (part 1). Admixture plot for the five major super populations across ADSP samples. (A-B) ADSP WES. A) Black vertical line marks the cut-off for EUR ancestry [>=75%]. **B)** Black vertical line marks the cut-off for NWE ancestry [>=50%].

Abbreviations: EUR, European; AFR, African; AMR; American; SAS, South Asian; EAS; East Asian; NWE, Northwestern European; SEE, Southeastern European; AJE, Ashkenazi Jewish.



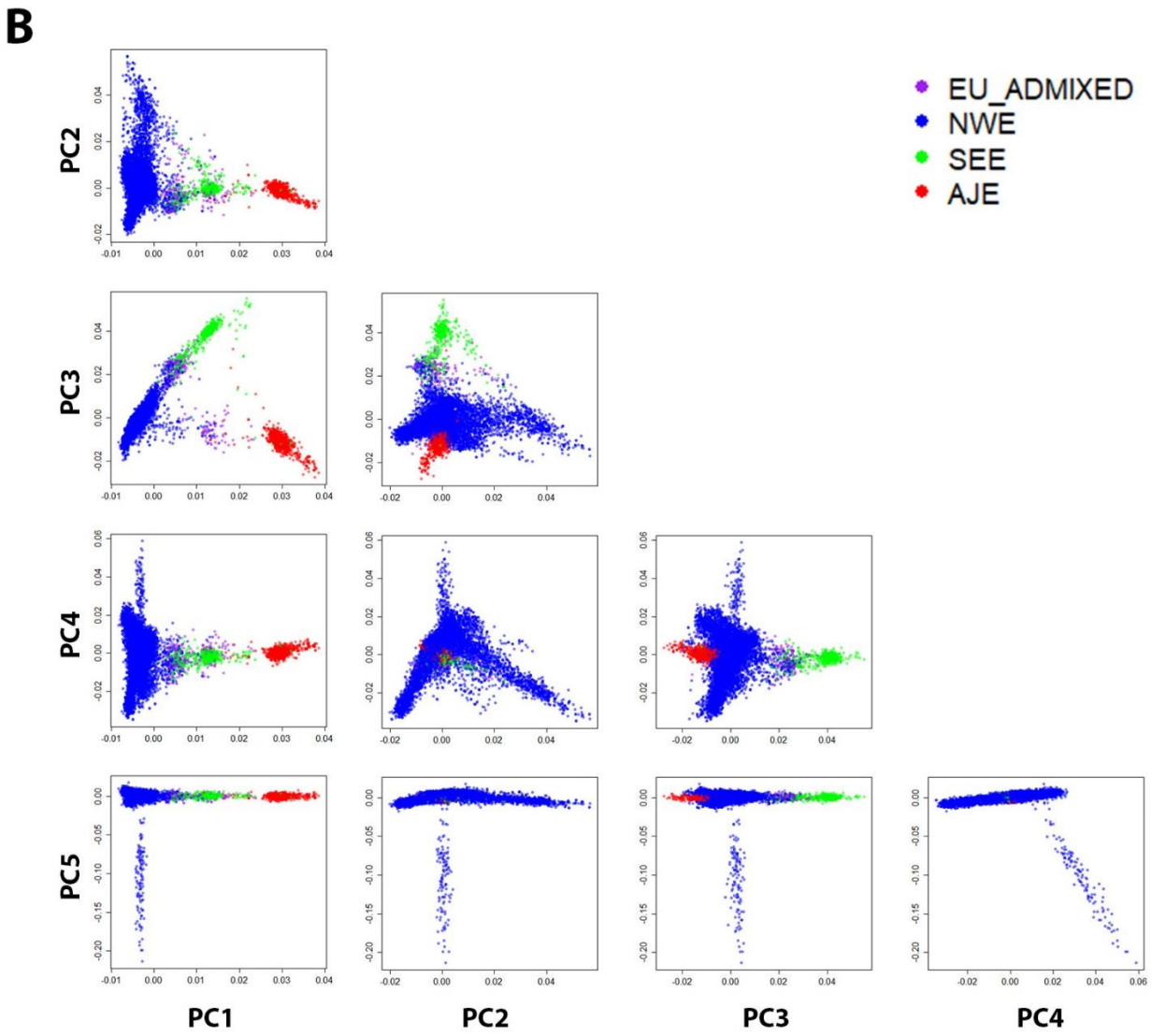
eFigure 1 (part 2). Admixture plot for the five major super populations across ADSP samples. (C-D) ADSP WGS. C) Black vertical line marks the cut-off for EUR ancestry [>=75%]. **D)** Black vertical line marks the cut-off for NWE ancestry [>=50%].

Abbreviations: EUR, European; AFR, African; AMR; American; SAS, Southern Asian; EAS; Eastern Asian; NWE, Northwestern European; SEE, Southeastern European; AJE, Ashkenazi Jewish.



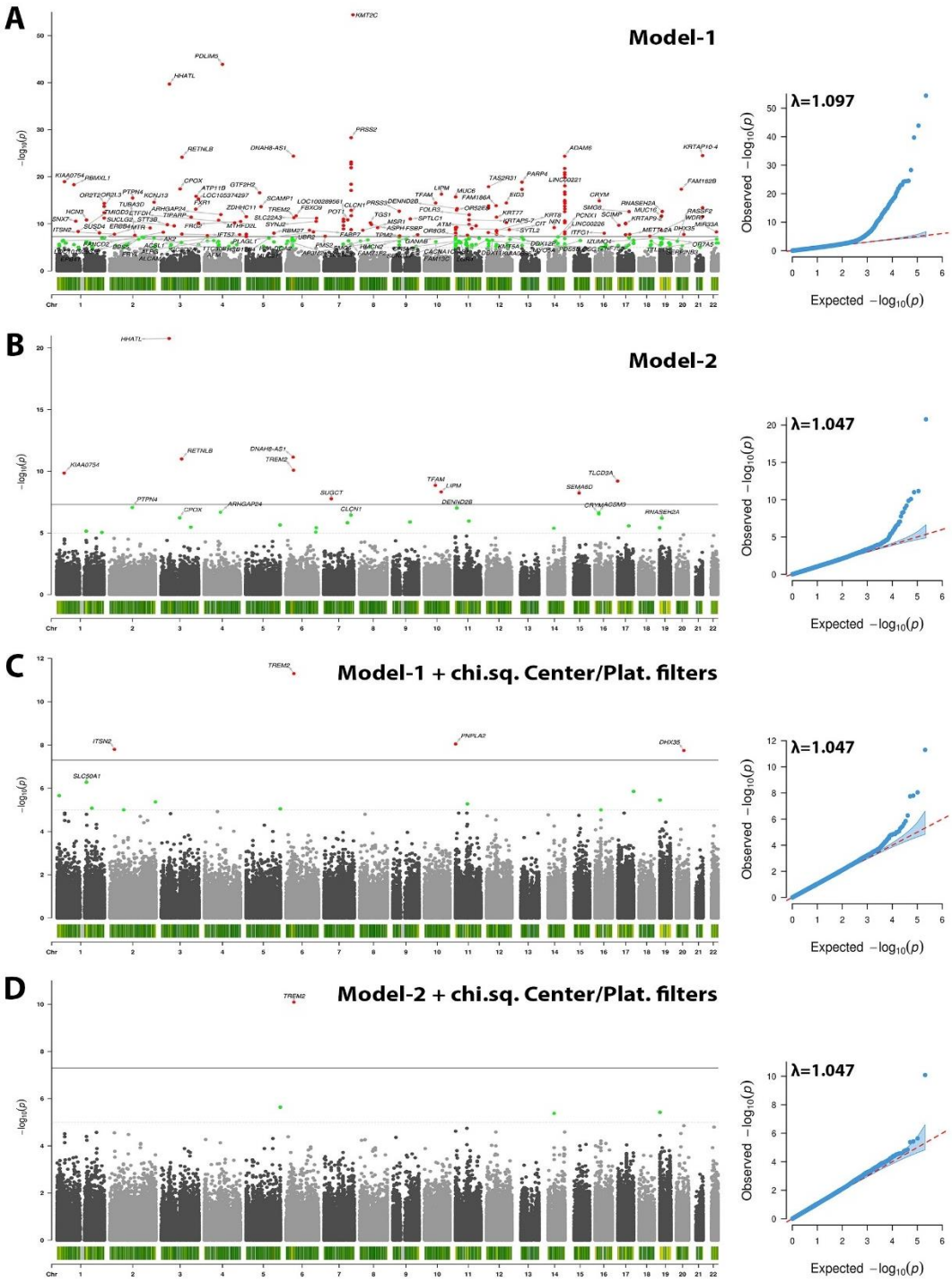
eFigure 2 (part 1). First five principal components of the genetic population structure in European subjects. (A) ADSP WES. PCs are labelled by sub-European ancestries and confirm that sub-population stratification is well captured.

Abbreviations: PC, principal component; EU, European; NWE, Northwestern European; SEE, Southeastern European; AJE, Ashkenazi Jewish.

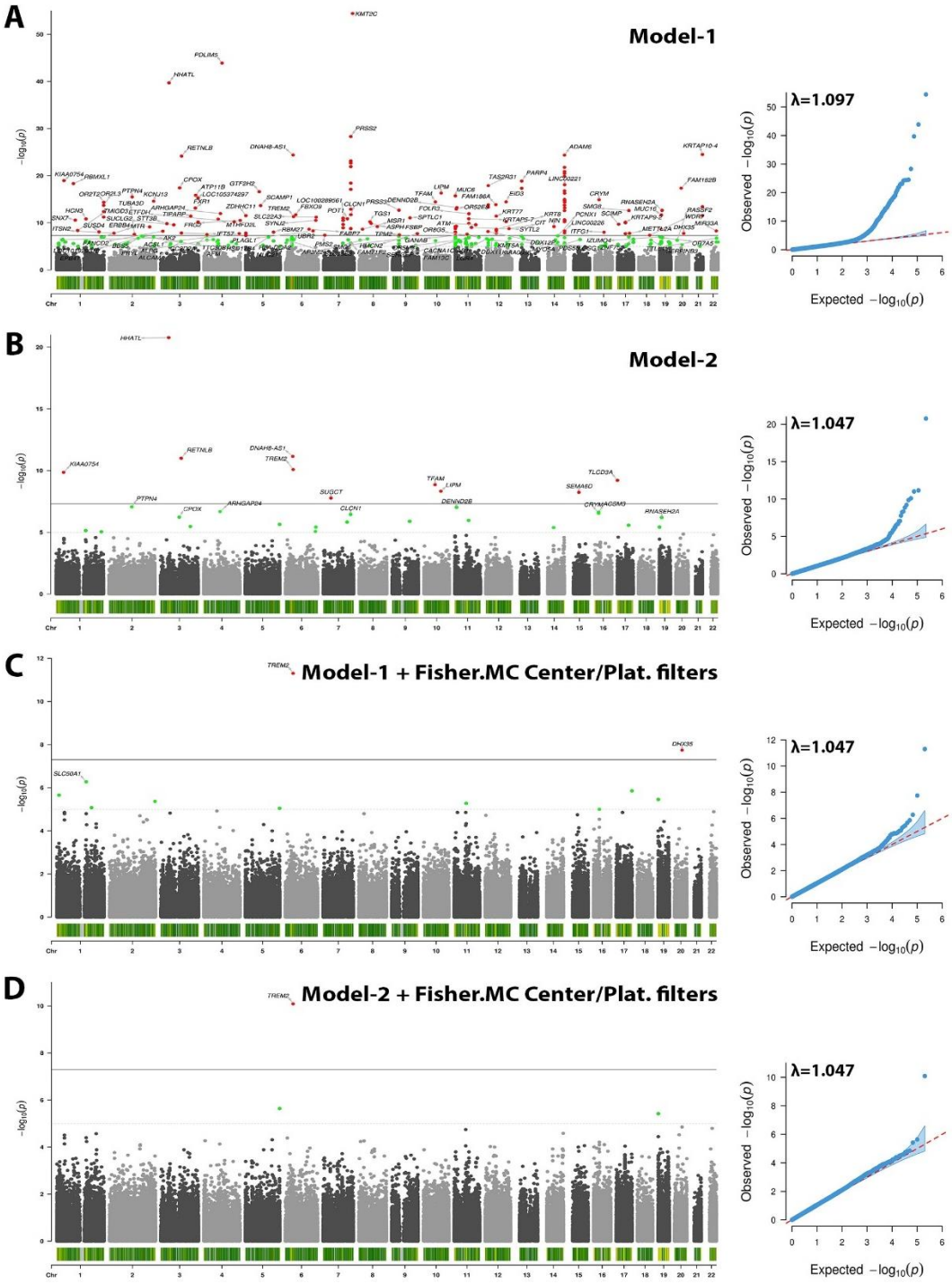


eFigure 2 (part 2). First five principal components of the genetic population structure in European subjects. (B) ADSP WGS. PCs are labelled by sub-European ancestries and confirm that sub-population stratification is well captured. The NWE outliers in ADSP WGS (B, blue) correspond to samples from the Erasmus (Rotterdam) study, indicating they presented a distinct genetic background.

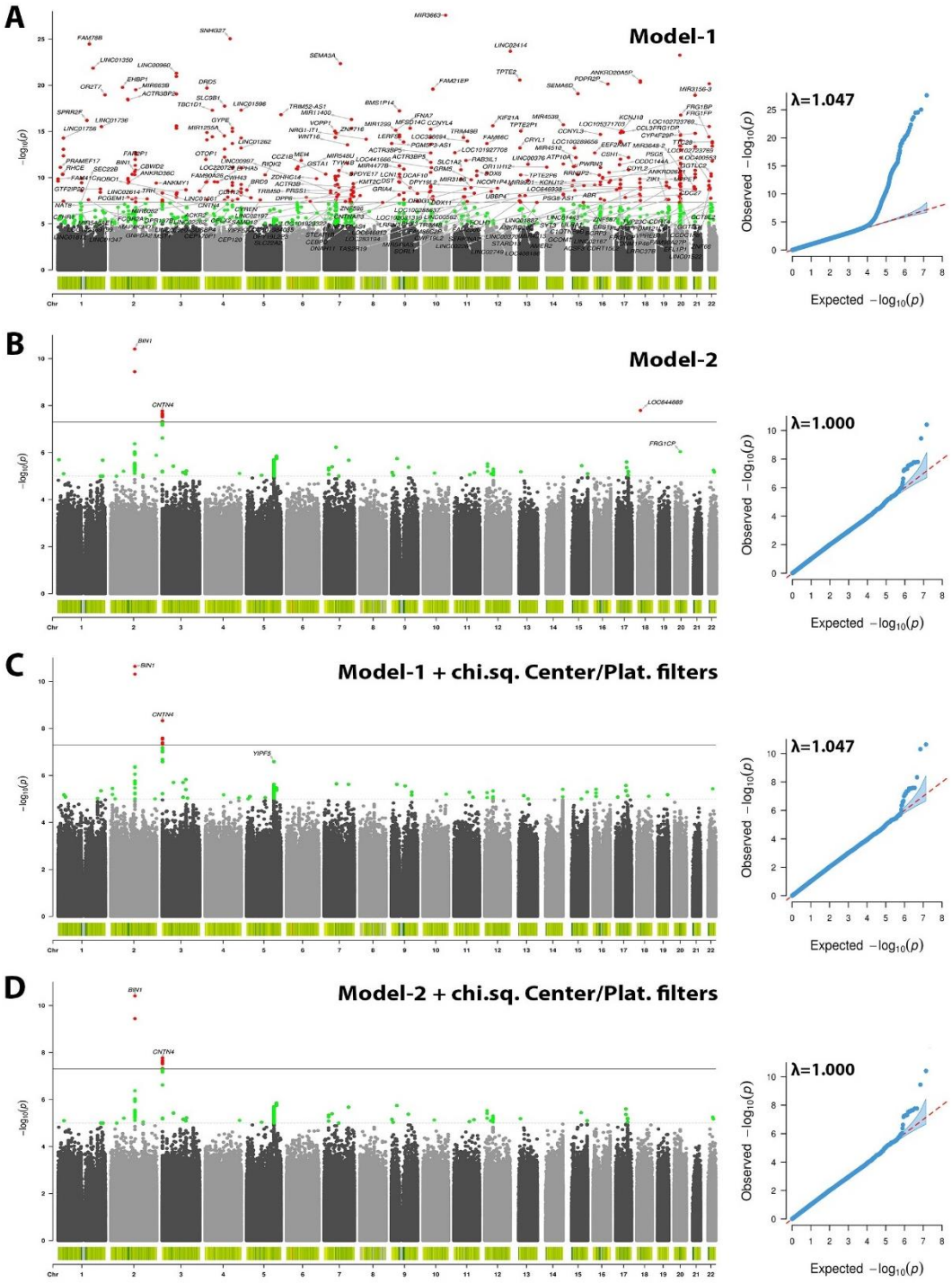
Abbreviations: PC, principal component; EU, European; NWE, Northwestern European; SEE, Southeastern European; AJE, Ashkenazi Jewish.



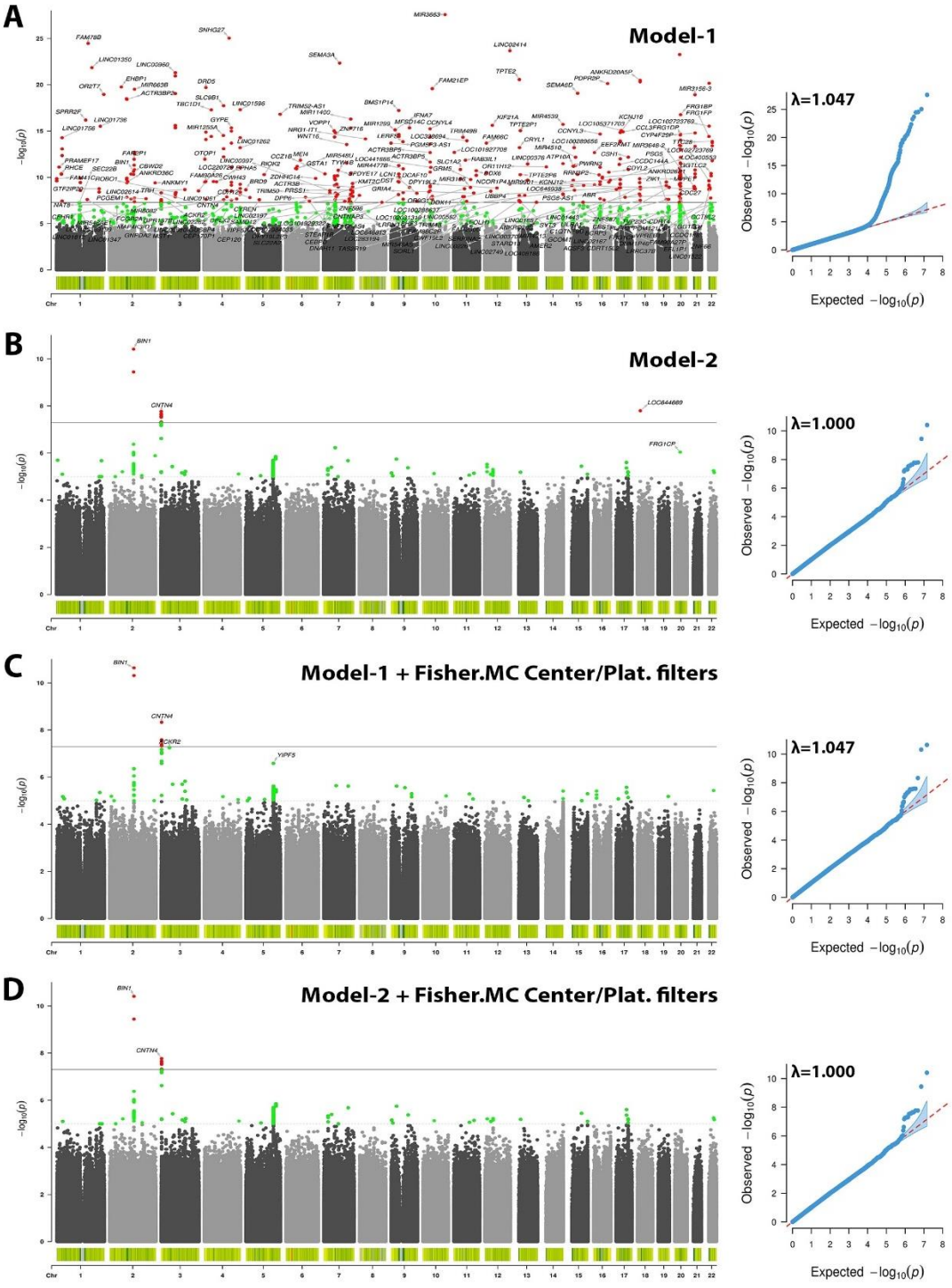
eFigure 3. The proposed center/platform-based variant filters, using chi square tests in R, remove spurious associations in ADSP WES. EFigurehows Manhattan (left) and quantile-quantile (right) plots. **A)** Model-1 indicates many spurious hits. **B)** Model-2 shows that adjustment for center/platform can reduce many, but not all, spurious hits. **C)** Filters remove most spurious hits. **D)** Further adjustment for center/platform removes few additional spurious hits.



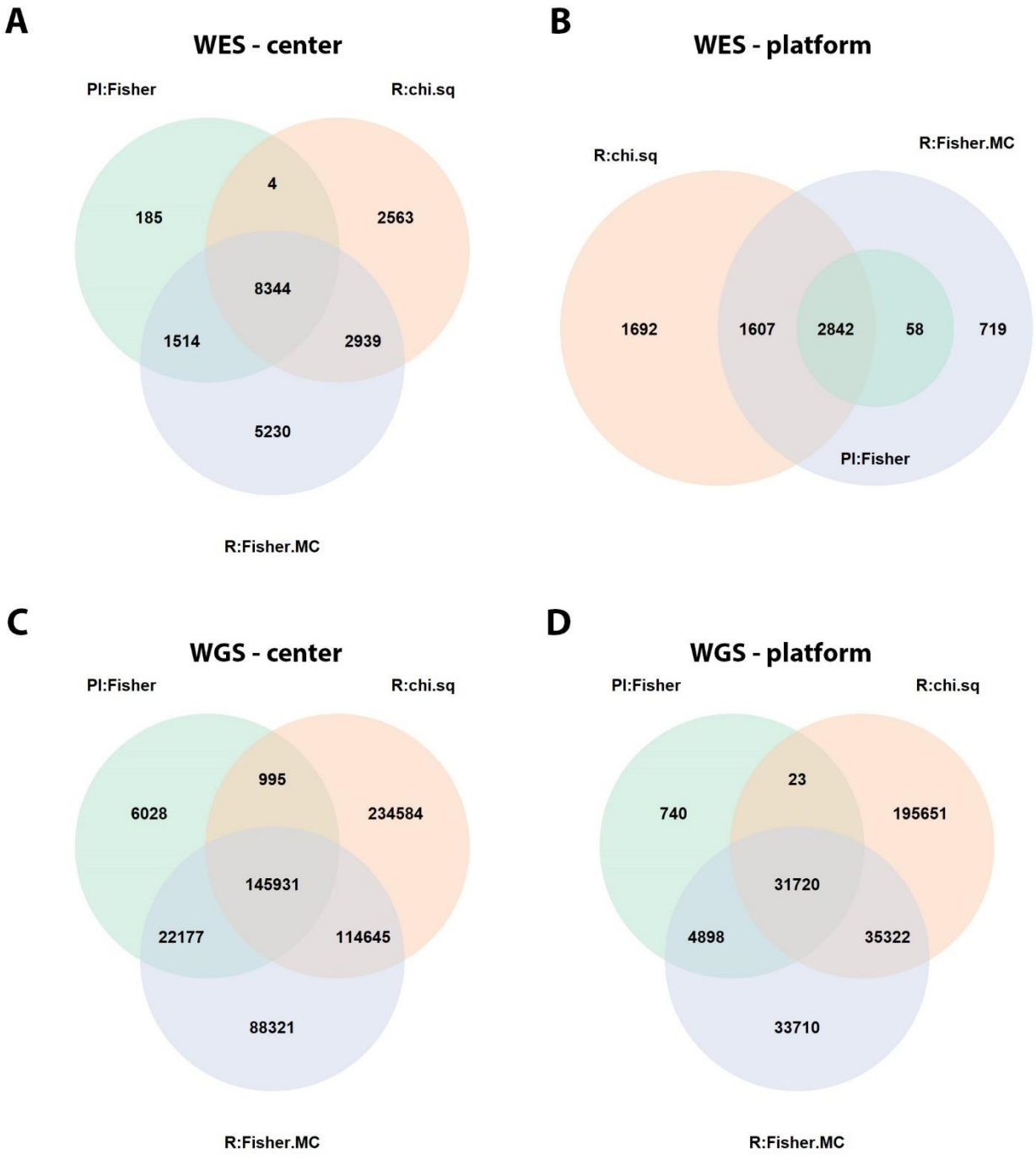
eFigure 4. The proposed center/platform-based variant filters, using Fisher exact Monte Carolo simulation tests in R, remove spurious associations in ADSP WES. EFigurehows Manhattan (left) and quantile-quantile (right) plots. **A)** Model-1 indicates many spurious hits. **B)** Model-2 shows that adjustment for center/platform can reduce many, but not all, spurious hits. **C)** Filters remove most spurious hits. **D)** Further adjustment for center/platform removes few additional spurious hits.



eFigure 5. The proposed center/platform-based variant filters, using chi square tests in R, remove spurious associations in ADSP WGS. EFigurehows Manhattan (left) and quantile-quantile (right) plots. **A)** Model-1 indicates many spurious hits. **B)** Model-2 shows that adjustment for center/platform can reduce many, but not all, spurious hits. **C)** Filters remove most spurious hits. **D)** Further adjustment for center/platform removes few additional spurious hits.

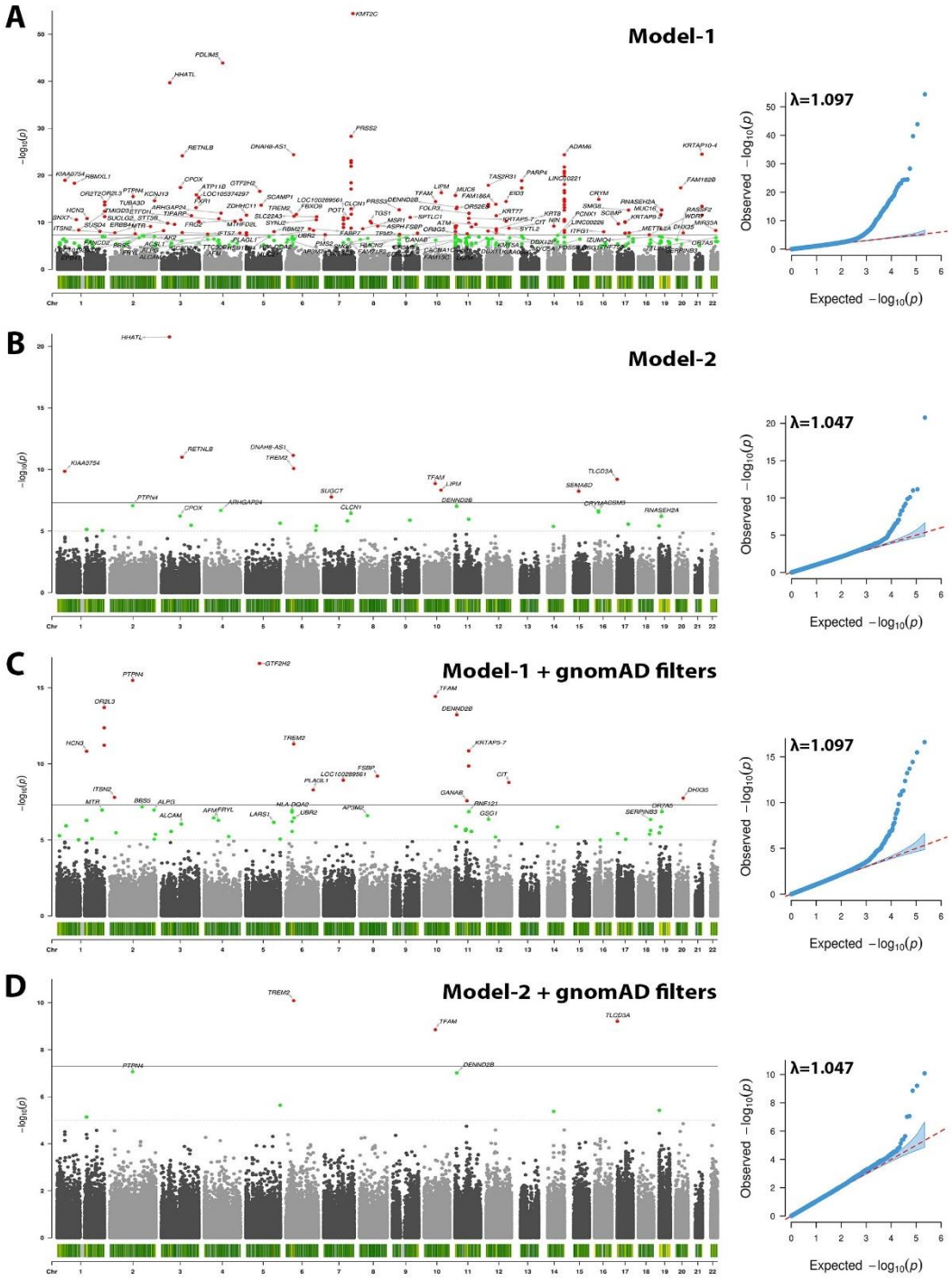


eFigure 6. The proposed center/platform-based variant filters, using Fisher exact Monte Carolo simulation tests in R, remove spurious associations in ADSP WGS. EFigurehows Manhattan (left) and quantile-quantile (right) plots. **A)** Model-1 indicates many spurious hits. **B)** Model-2 shows that adjustment for center/platform can reduce many, but not all, spurious hits. **C)** Filters remove most spurious hits. **D)** Further adjustment for center/platform removes few additional spurious hits.

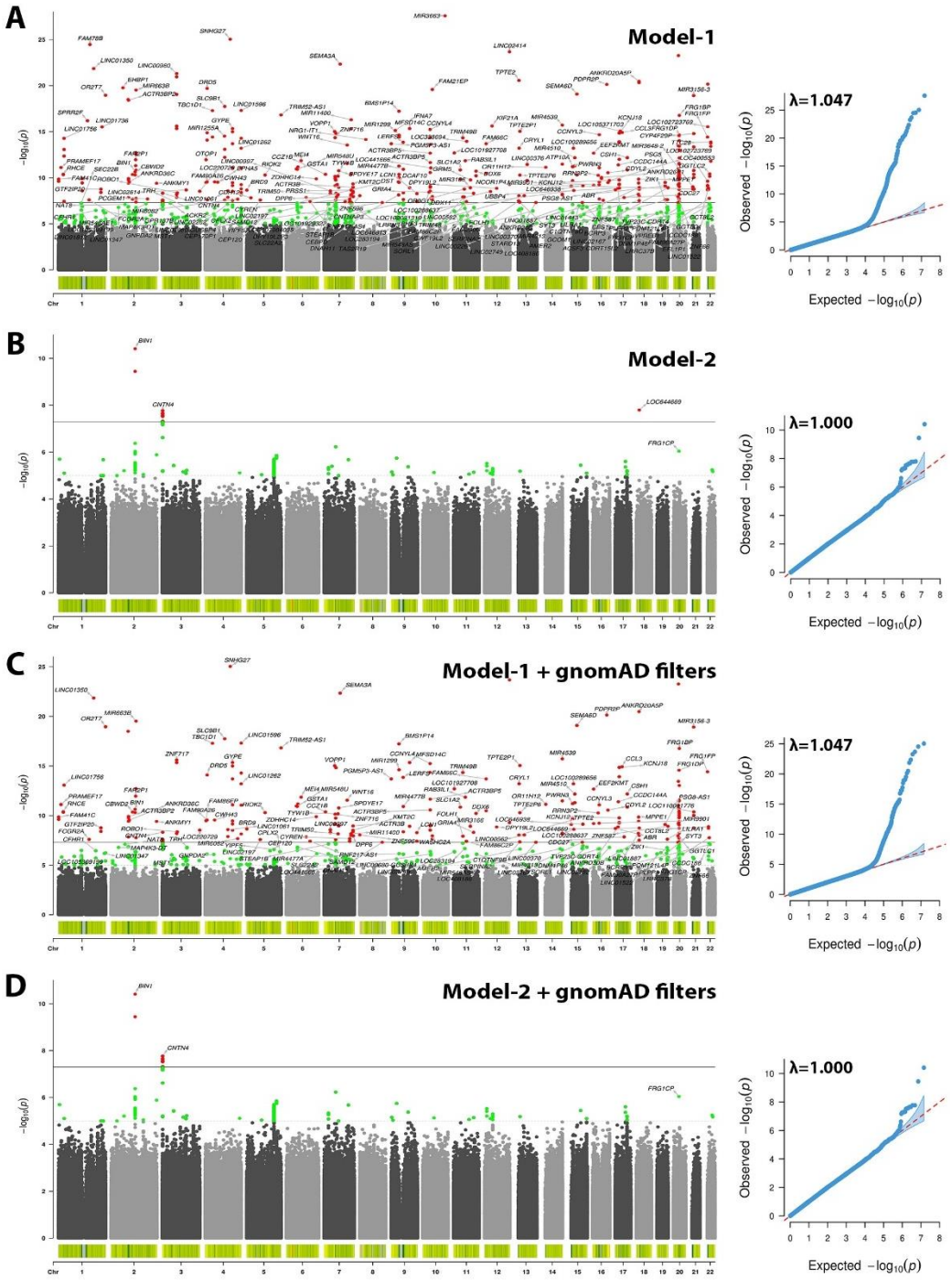


eFigure 7. Variant overlap between three types of considered sequencing center/platform-based filters. A). ADSP WES – sequencing center. **B)** ADSP WES – sequencing platform. **C)** ADSP WGS – sequencing center. **D)** ADSP WGS – sequencing platform.

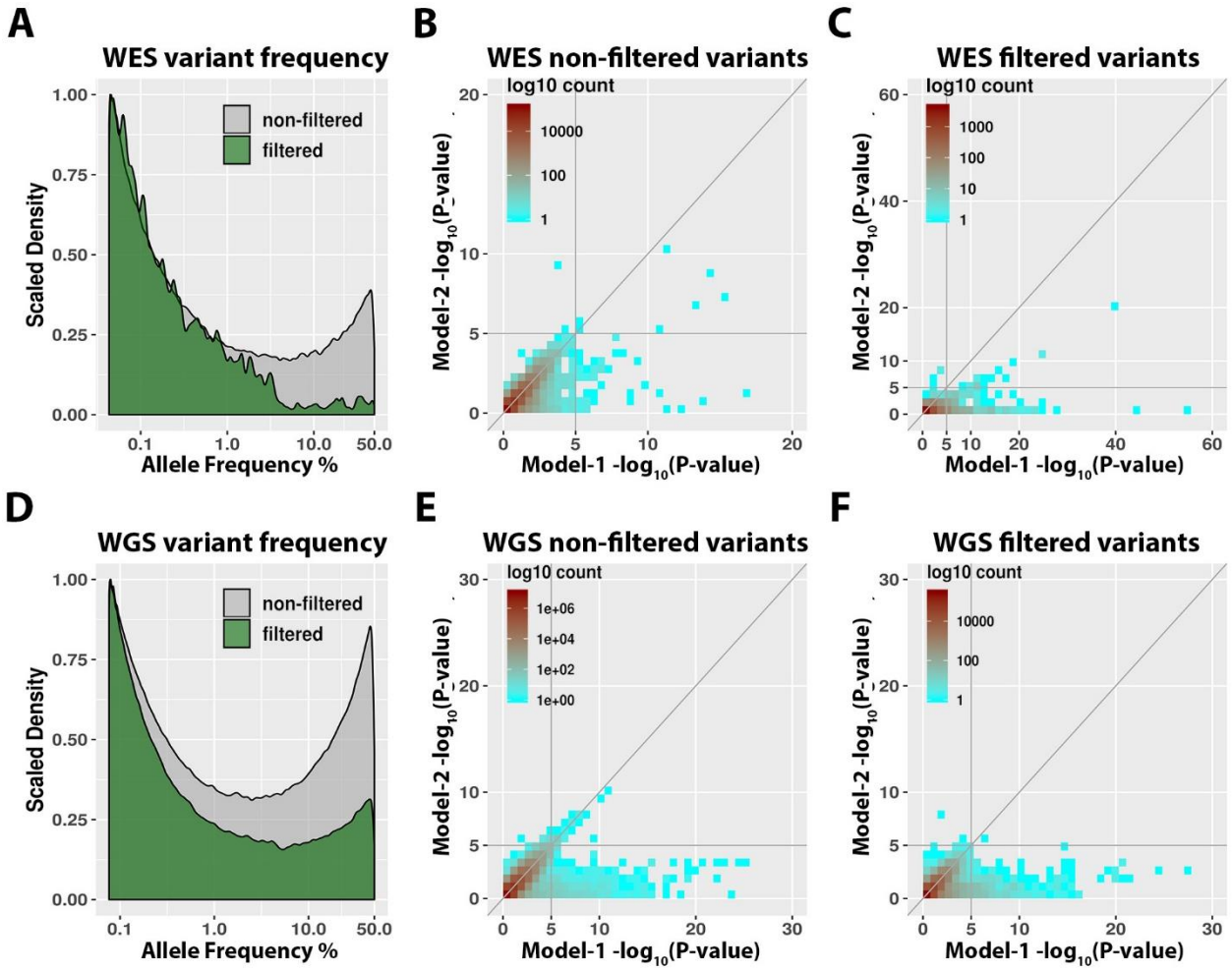
Abbrevations: Pl:Fisher, Plink-based Fisher test; R:chi.sq, R-based chi-square test; R:Fisher.MC, R-based fisher exact test with Monte Carlo simulation.



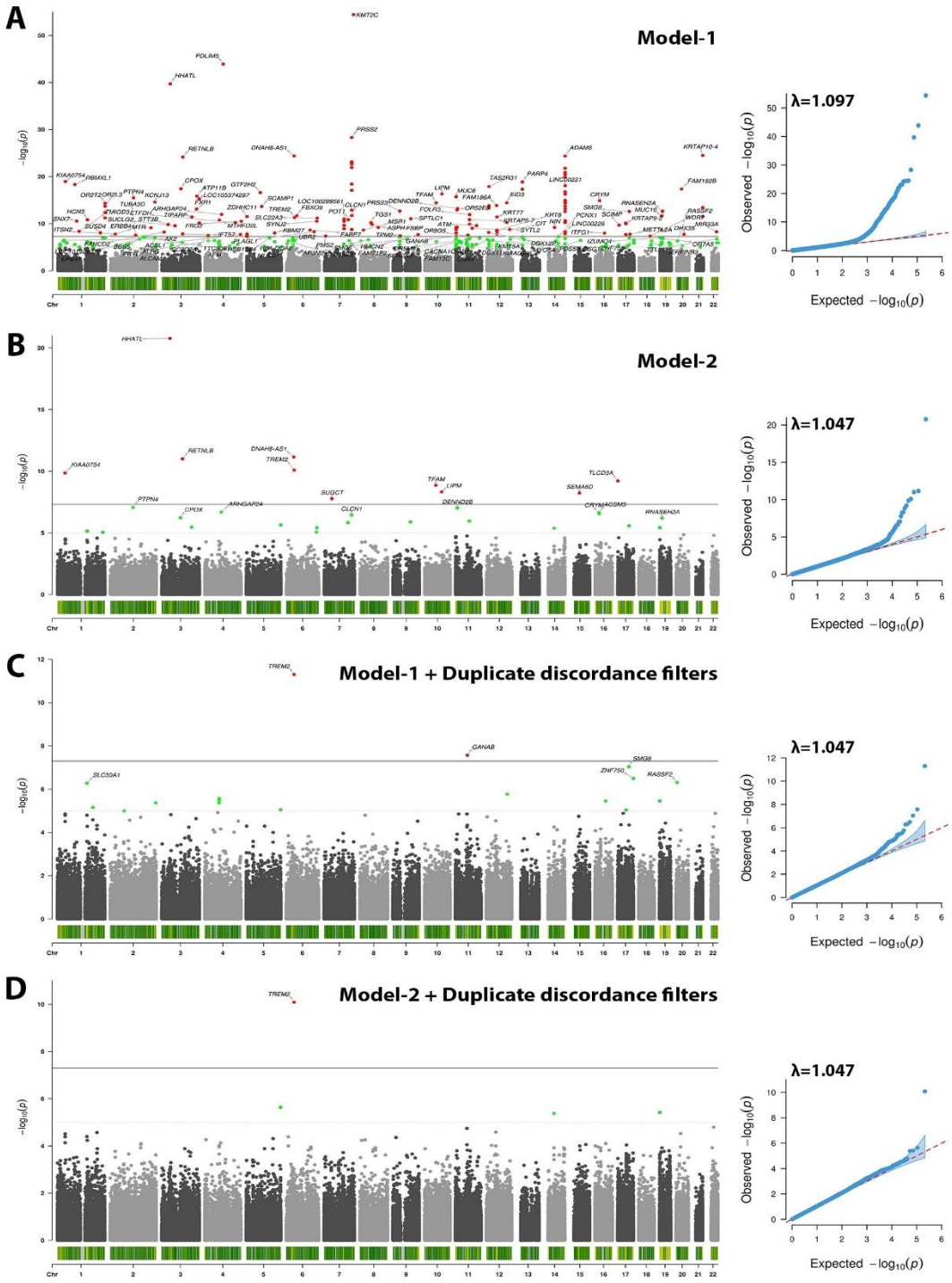
eFigure 8. The proposed gnomAD-based filters partially remove spurious associations in ADSP WES. EFigurehows Manhattan (left) and quantile-quantile (right) plots. **A)** Model-1 indicates many spurious hits. **B)** Model-2 shows that adjustment for center/platform can reduce many, but not all, spurious hits. **C)** Filters remove many spurious hits but several remain and inflation remains at the same level as in (A). **D)** Further adjustment for center/platform removes additional spurious hits but not all.



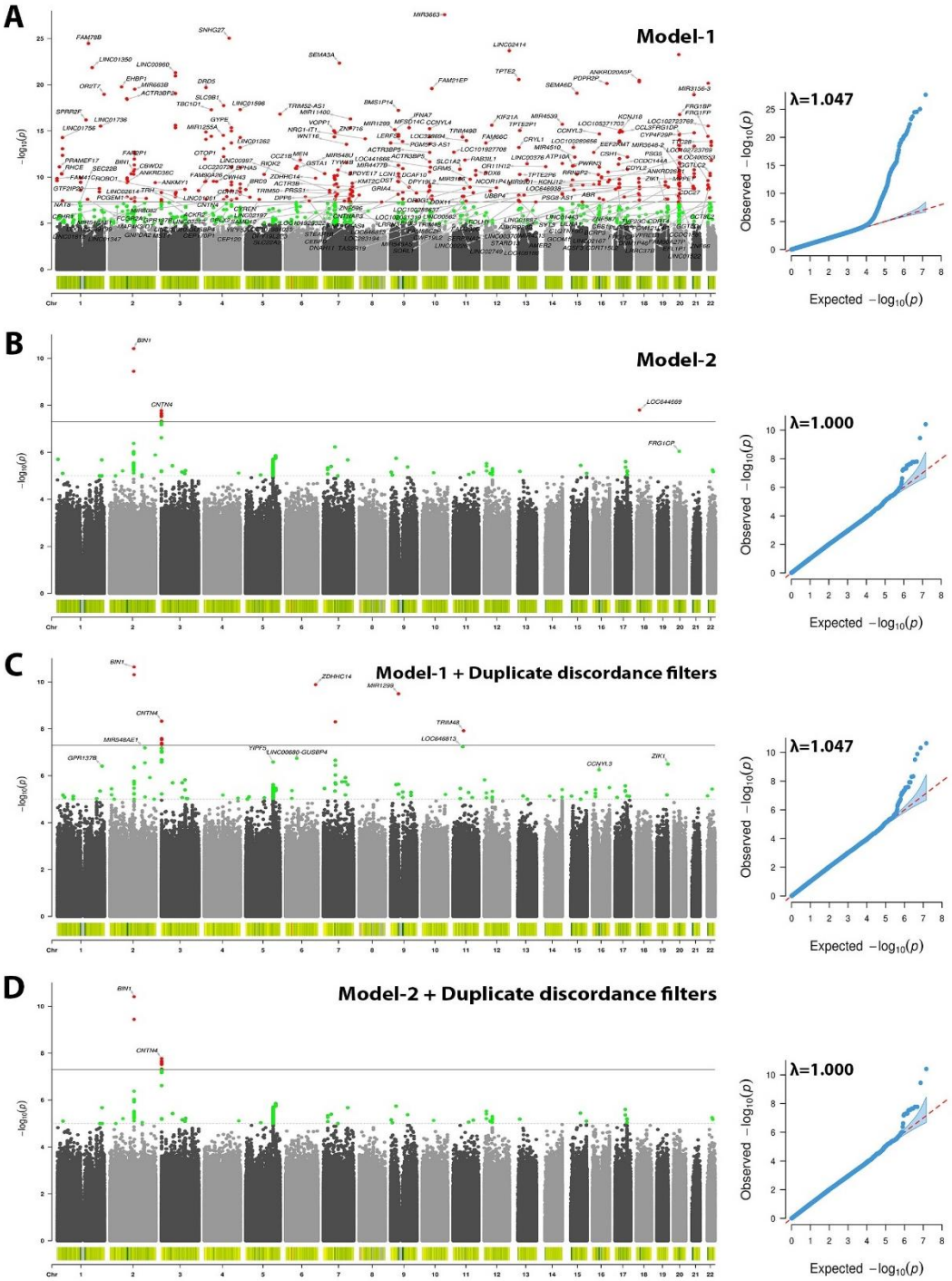
eFigure 9. The proposed gnomAD-based filters partially remove spurious associations in ADSP WGS. EFigurehows Manhattan (left) and quantile-quantile (right) plots. **A)** Model-1 indicates many spurious hits. **B)** Model-2 shows that adjustment for center/platform can reduce many, but not all, spurious hits. **C)** Filters remove many spurious hits but many remain. **D)** Further adjustment for center/platform removes most remaing spurious hits but not all as shown in Figure 3D.



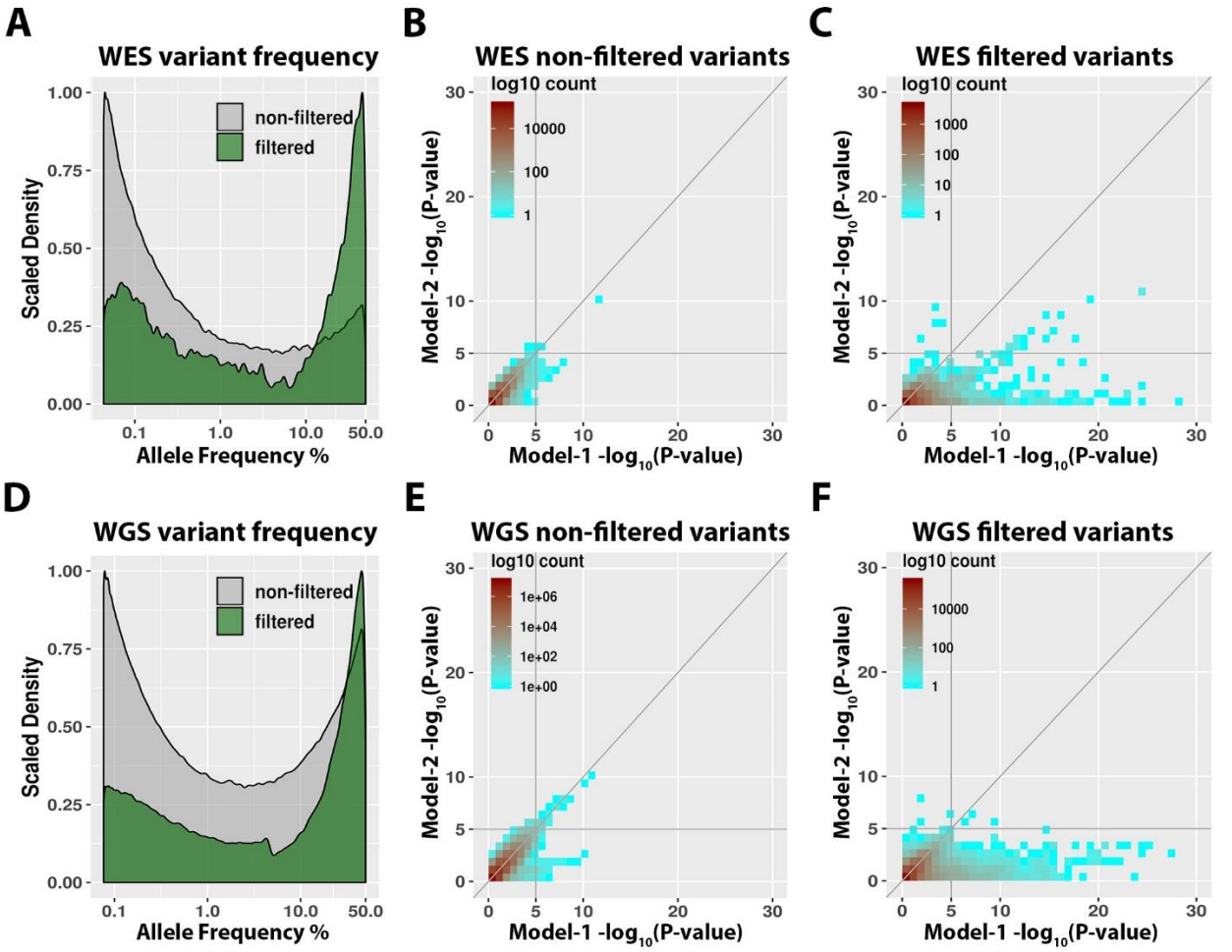
eFigure 10. Metrics of variants removed by the proposed gnomAD-based variant filters. A-C) ADSP WES. **D-F)** ADSP WGS. **A & D)** Frequency density plots, comparing variants that were filtered/removed to those that were not filtered. Note that variants were not consistently filtered across the full frequency range, with decreased density at frequencies >1% in both ADSP WES and WGS. **B & E)** Variants that passed filters showed many inconsistent P-values across model-1 and model-2. **C & F)** Variants that were removed by filters showed even more inconsistent P-values across model-1 and model-2 as compared to (B & E).



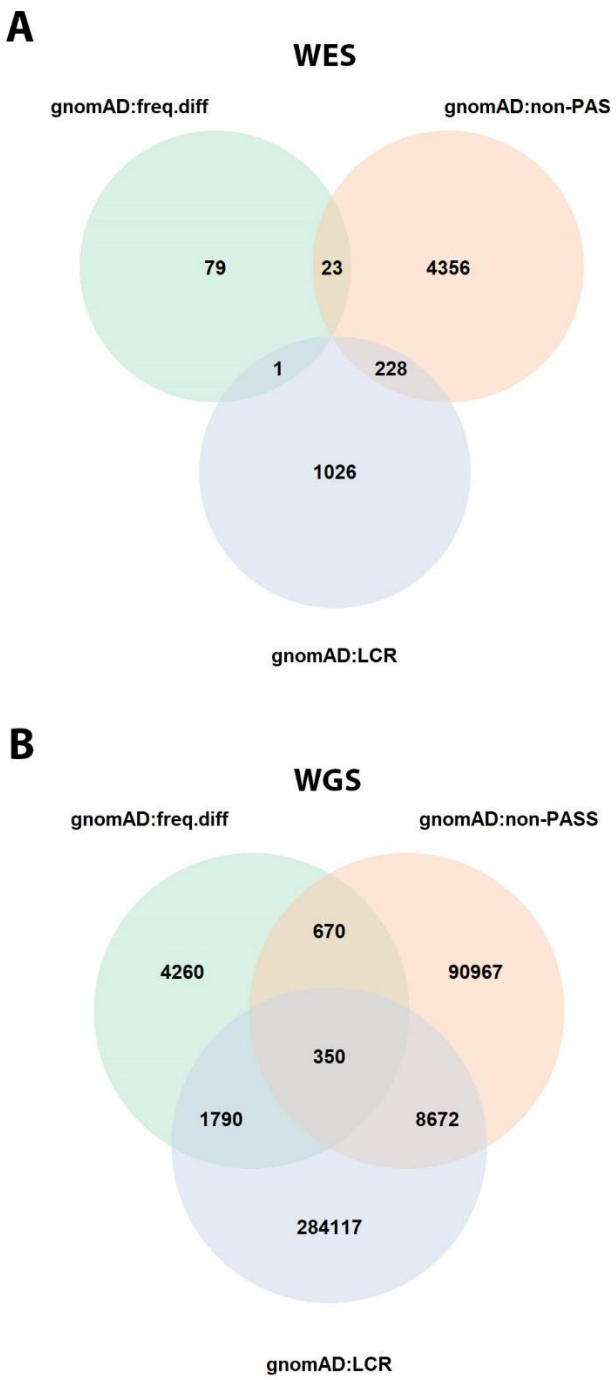
eFigure 11. The proposed duplicate discordant variant filters remove spurious associations in ADSP WES. EFigurehows Manhattan (left) and quantile-quantile (right) plots. **A)** Model-1 indicates many spurious hits. **B)** Model-2 shows that adjustment for center/platform can reduce many, but not all, spurious hits. **C)** Filter removes most spurious hits. **D)** Further adjustment for center/platform removes additional spurious hits.



eFigure 12. The proposed duplicate discordant variant filters remove spurious associations in ADSP WGS. EFigurehows Manhattan (left) and quantile-quantile (right) plots. **A)** Model-1 indicates many spurious hits. **B)** Model-2 shows that adjustment for center/platform can reduce many, but not all, spurious hits. **C)** Filter removes many spurious hits, but not all. **D)** Further adjustment for center/platform removes additional spurious hits.

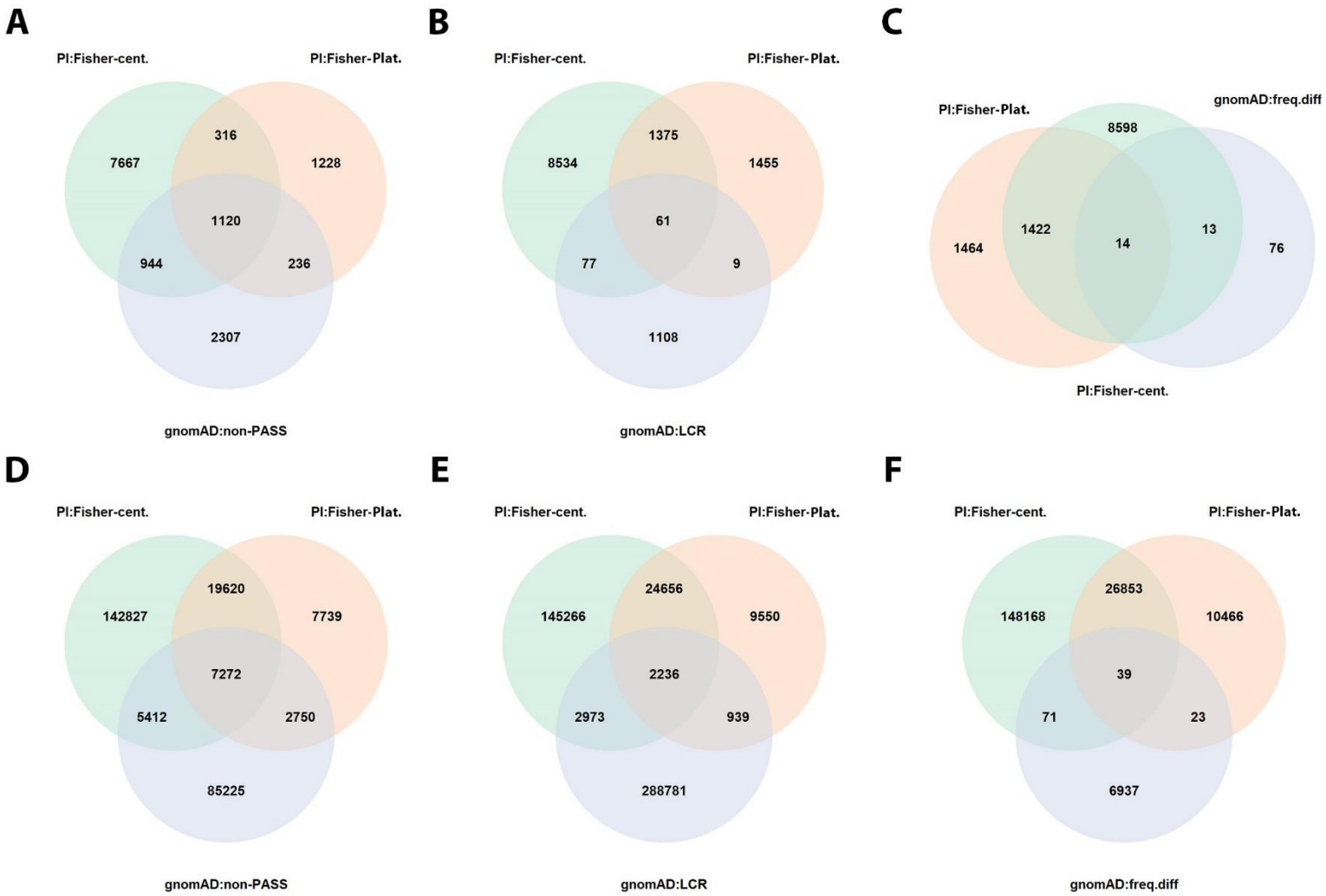


eFigure 13. Metrics of variants removed by the proposed duplicate discordance variant filters. A-C) ADSP WES. **D-F)** ADSP WGS. **A & D)** Frequency density plots, comparing variants that were filtered/removed to those that were not filtered. Note that variants were not consistently filtered across the full frequency range, with decreased density at frequencies <10% in both ADSP WES and WGS. **B & E)** Variants that passed filters showed largely consistent P-values across model-1 and model-2 case-control association analyses, but there was still a set of variants remaining that reach suggestive significance in model-1 but lose suggestive significance upon center/platform adjustment in model-2 (lower right quadrant). **C & F)** Variants that were removed by filters showed many inconsistent P-values across model-1 and model-2, indicating that the duplicate discordance filters removed many center/platform-related variant artifacts that could not fully be accounted for by model-2.



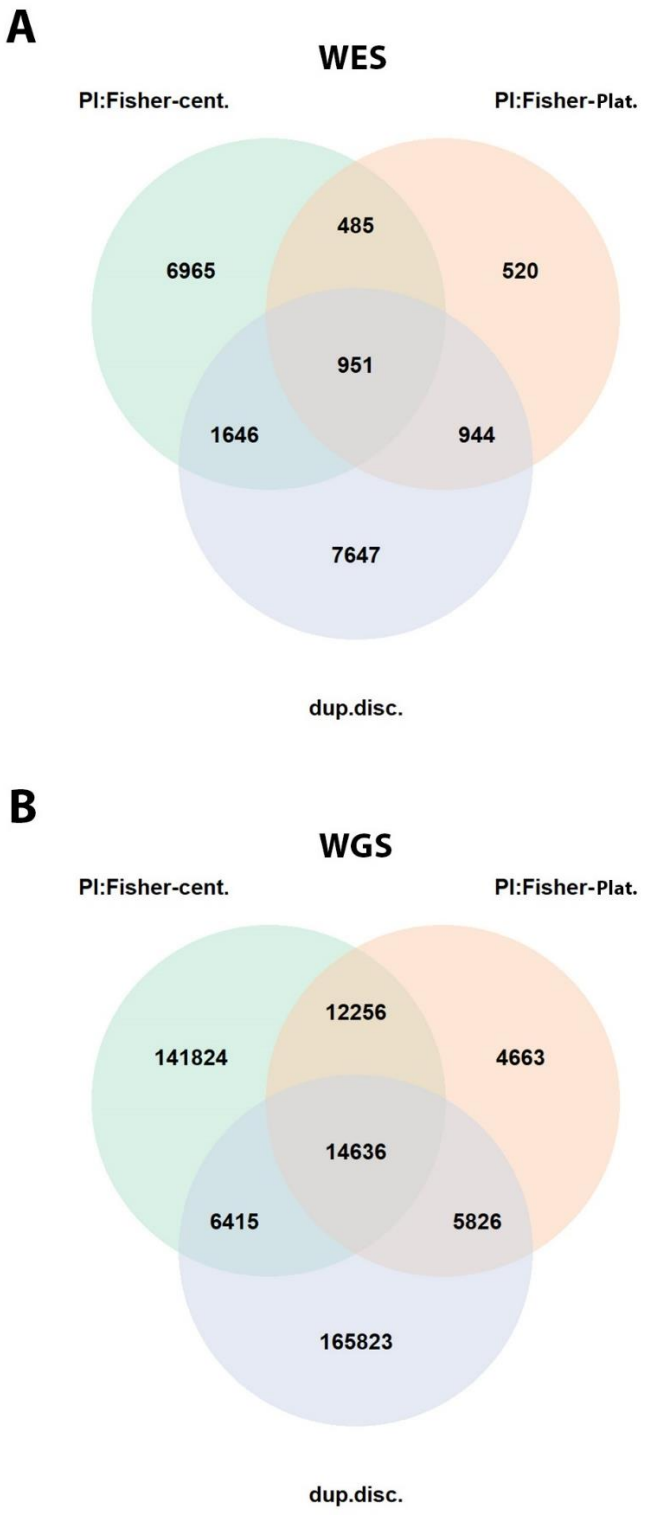
eFigure 14. Variant overlap between the three gnomAD-based filters. A) ADSP WES. **B)** ADSP WGS.

Abbrevations: gnomAD:freq.diff, 10% frequency difference between gnomAD non-Finish Euopeans and ADSP Europeans; gnomAD:non-PASS, not having a PASS flag in gnomAD; gnomAD:LCR; gnomAD tagged low complexity region.



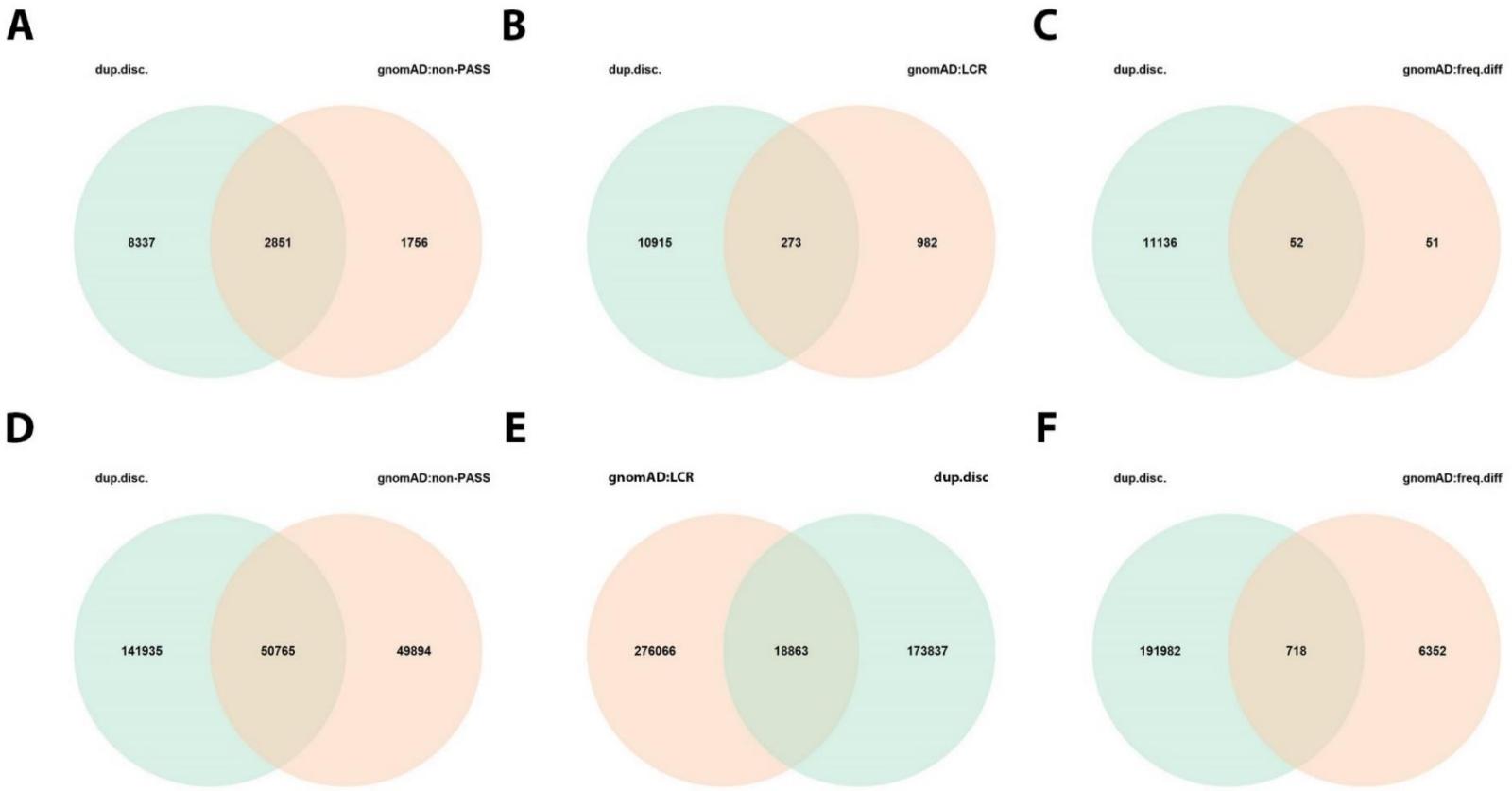
eFigure 15. Variant overlap between Plink Fisher-exact center/platform-based and gnomAD-based filters. A-C) ADSP WES. **D-F)** ADSP WGS.

Abbrevations: gnomAD:freq.diff, 10% frequency difference between gnomAD non-Finish Euopeans and ADSP Europeans; gnomAD:non-PASS, not having a PASS flag in gnomAD; gnomAD:LCR; gnomAD tagged low complexity region; Pl:Fisher, Plink-based Fisher test.



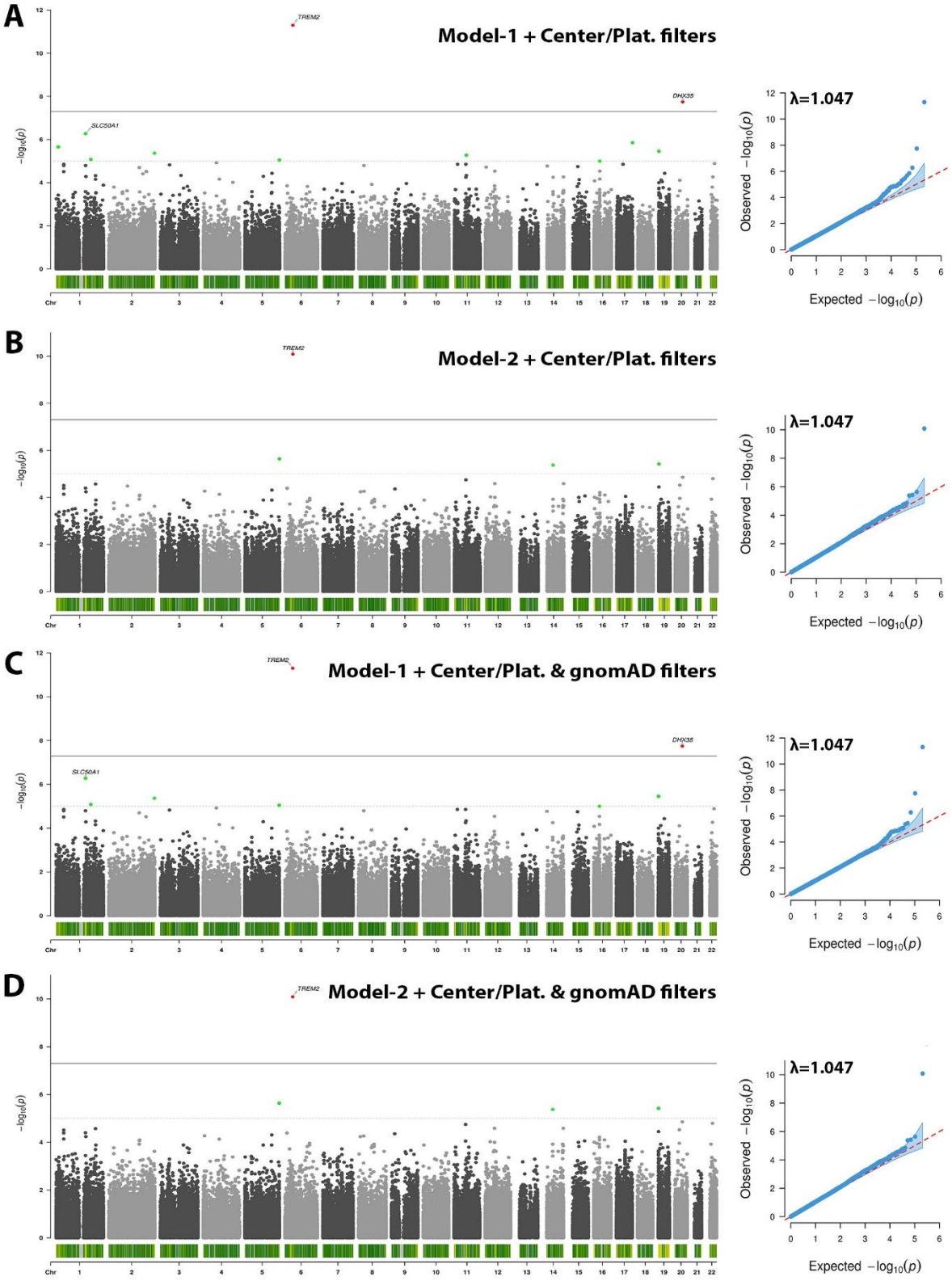
eFigure 16. Variant overlap between Plink Fisher-exact center/platform-based filters and duplicate discordant variant filters. A) ADSP WES. **B)** ADSP WGS.

Abbrevations: dup.disc, duplicate discordant variants; Pl:Fisher, Plink-based Fisher test.

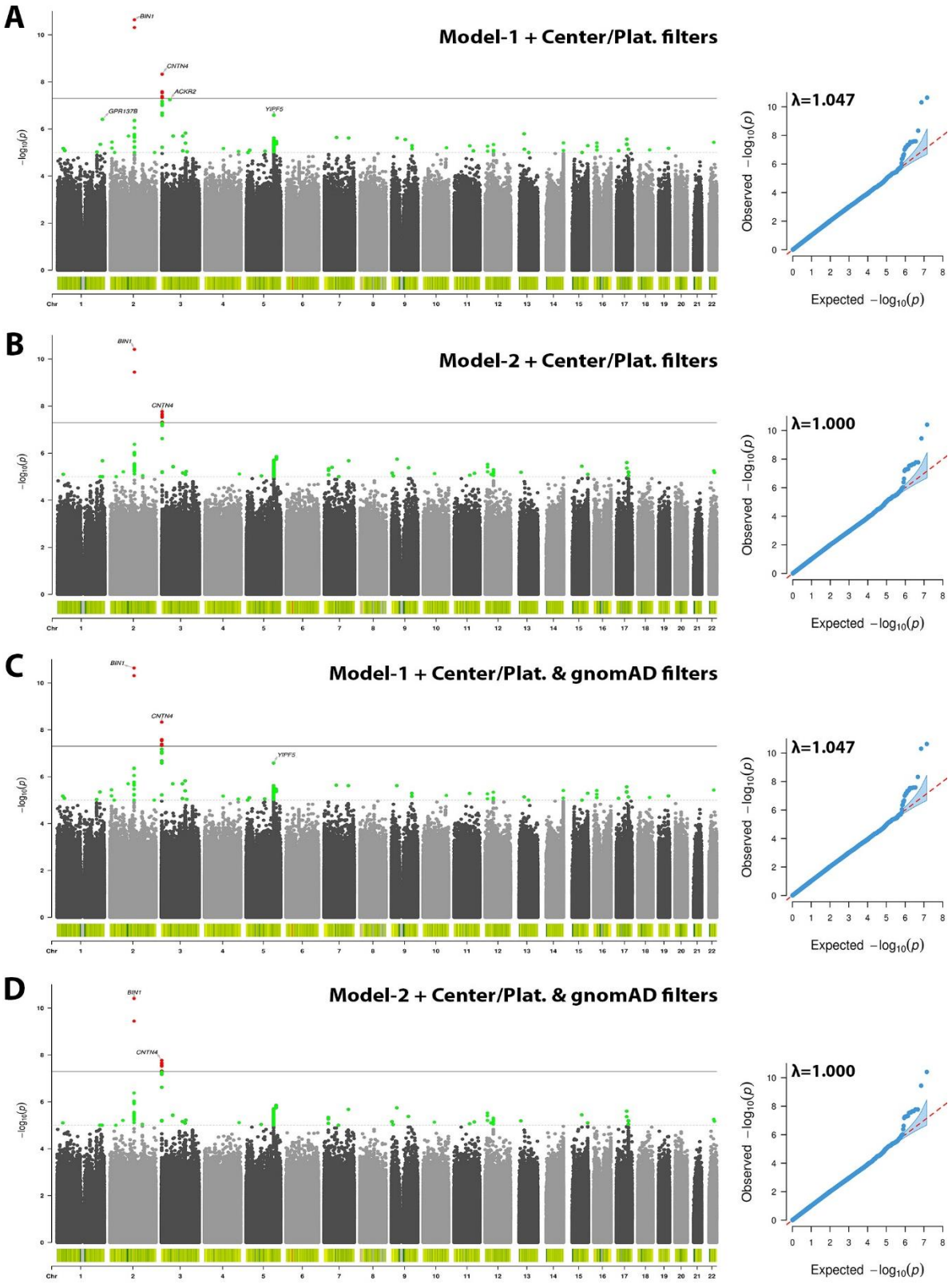


eFigure 17. Variant overlap between gnomAD-based filters and duplicate discordant variant filters. A-C) ADSP WES**. D-F)** ADSP WGS**.**

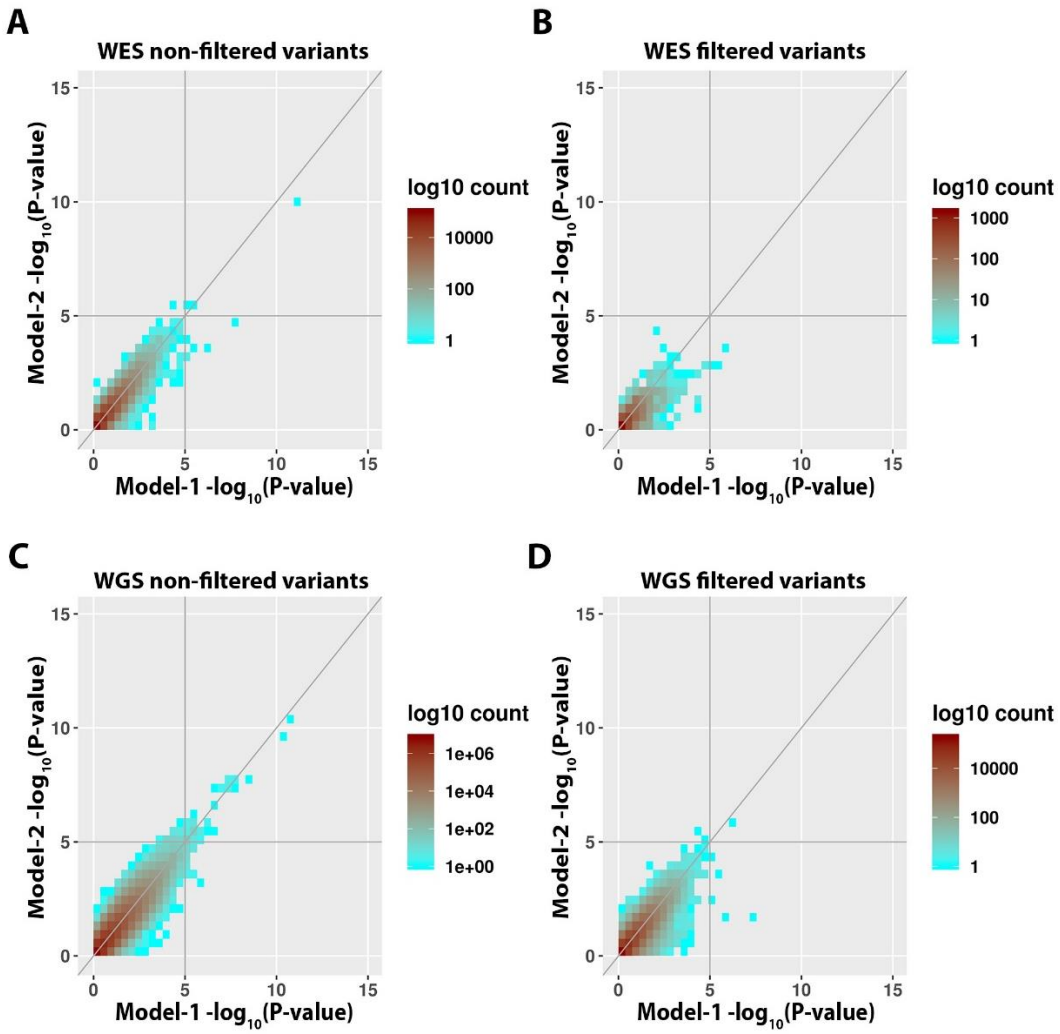
Abbrevations: dup.disc, duplicate discordant variants; gnomAD:freq.diff, 10% frequency difference between gnomAD non-Finish Euopeans and ADSP Europeans; gnomAD:non-PASS, not having a PASS flag in gnomAD; gnomAD:LCR; gnomAD tagged low complexity region.



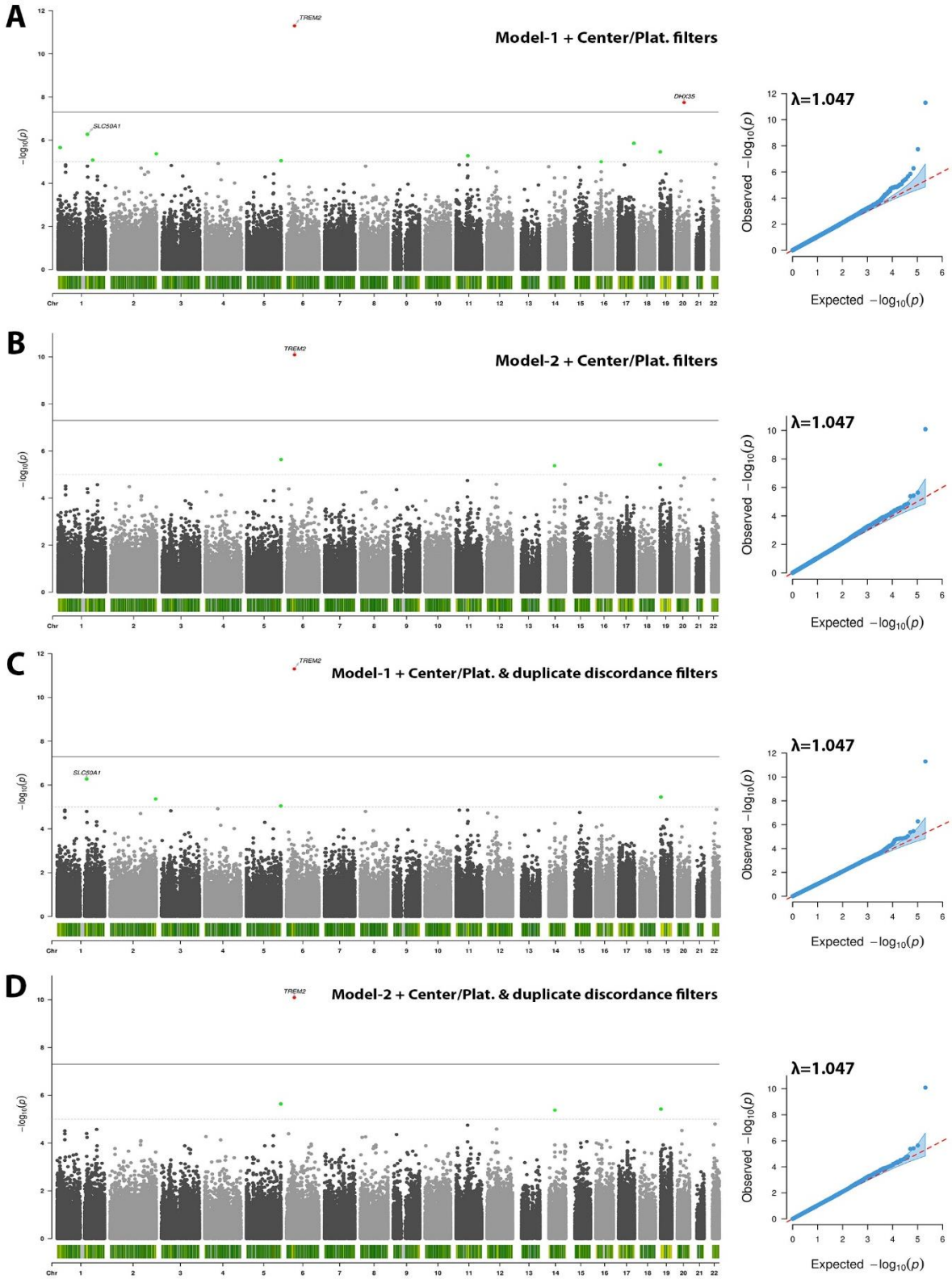
eFigure 18. GnomAD-based filters remove few additional spurious associations after applying center/platform-based variant filters in ADSP WES.



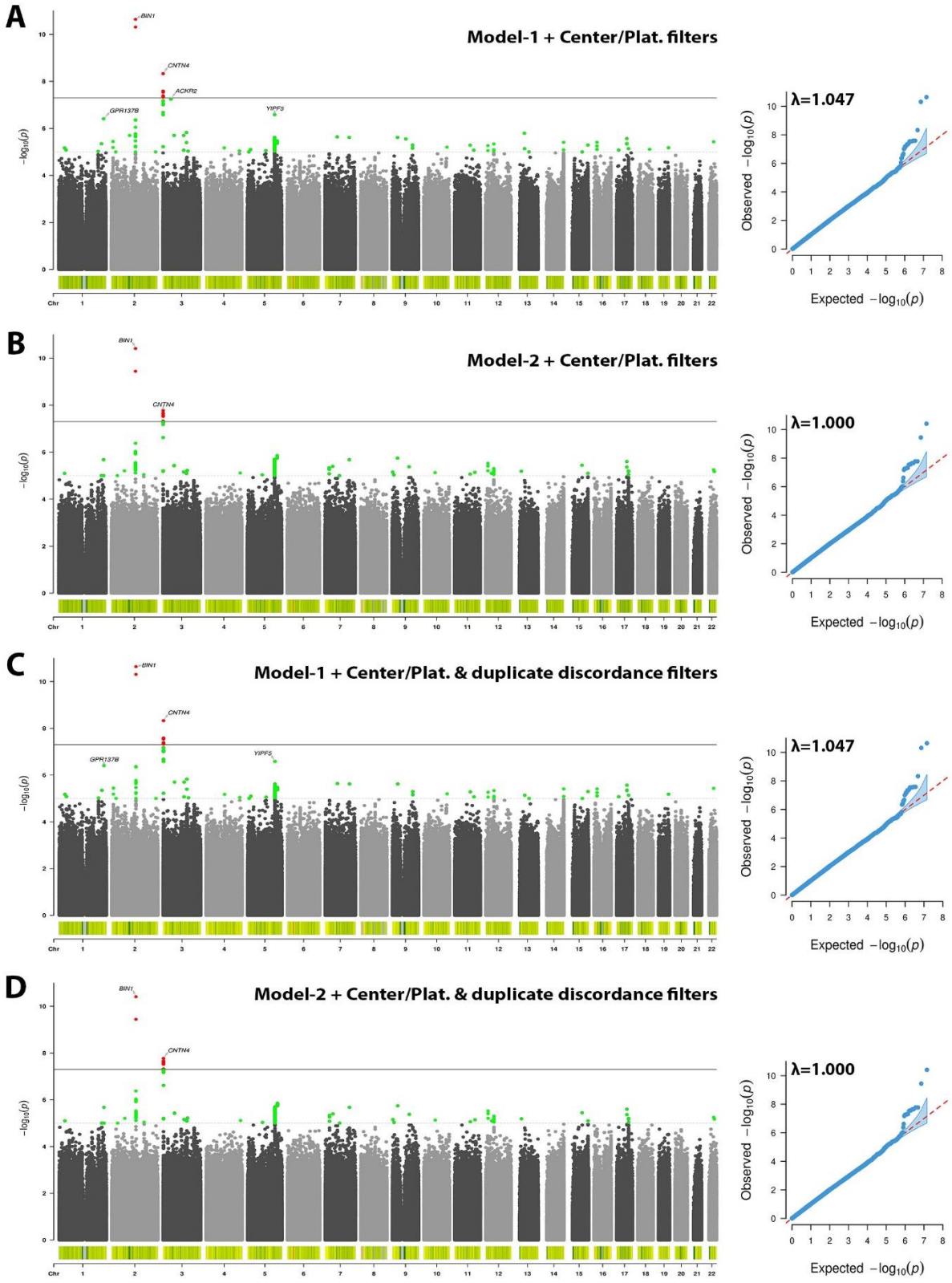
eFigure 19. GnomAD-based filters remove few additional spurious associations after applying center/platform-based variant filters in ADSP WGS.



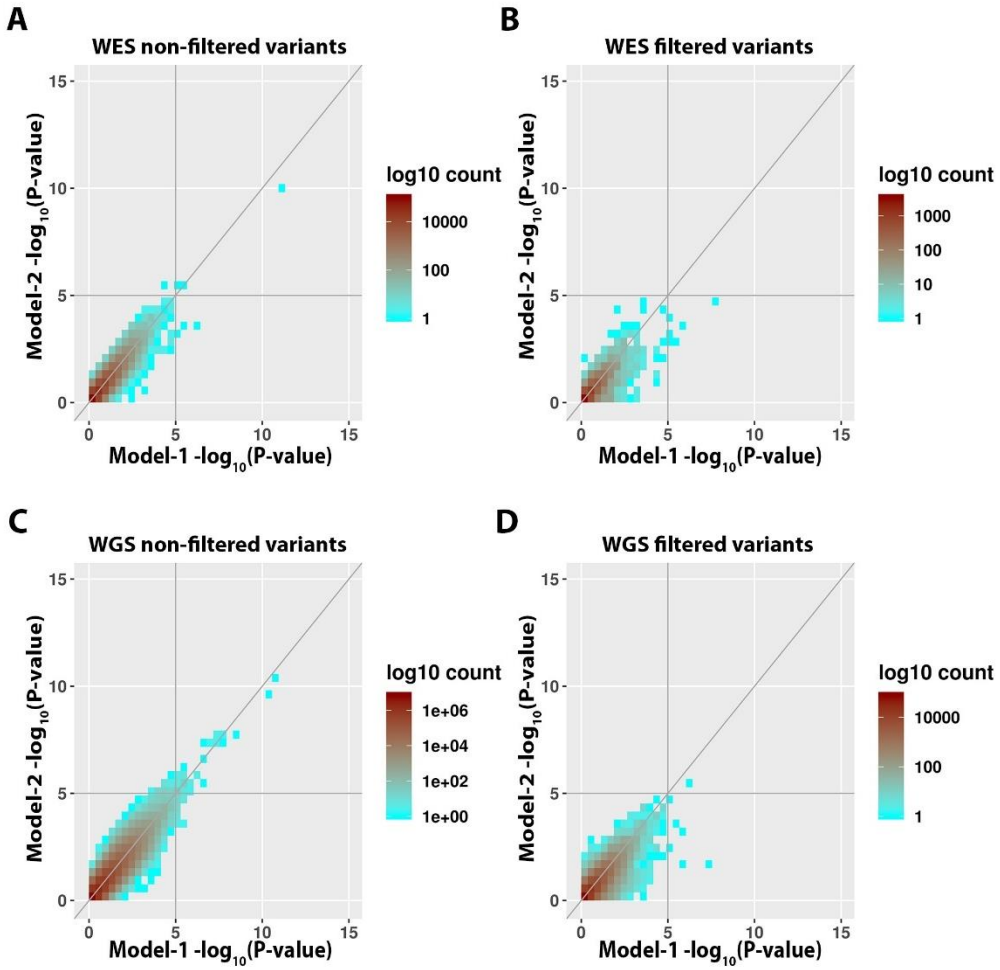
eFigure 20. Metrics of variants removed by the gnomAD-based variant filters after first applying center/platform-based variant filters. A-B) ADSP WES. **C-D)** ADSP WGS. The density distributions appear largely consistent between non-filtered (A & C) and filtered (B & D) variants. There were few additional variants that reach suggestive significance in model-1 but lose suggestive significance upon center/platform adjustment in model-2 that were filtered (lower right quadrant in (B & D)), but some of this type variants still remained (lower right quadrant in (A & C)).



eFigure 21. Duplicate discordant variant filters remove few additional spurious associations after applying center/platform-based variant filters in ADSP WES.



eFigure 22. Duplicate discordant variant filters remove few additional spurious associations after applying center/platform-based variant filters in ADSP WGS.



eFigure 23. Metrics of variants removed by the duplicate discordant variant filters after first applying center/platform-based variant filters. A-B) ADSP WES. **C-D)** ADSP WGS. The density distributions appear largely consistent between non-filtered (A & C) and filtered (B & D) variants. There were few additional variants that reach suggestive significance in model-1 but lose suggestive significance upon center/platform adjustment in model-2 that were filtered (lower right quadrant in (B & D)); very few of this type variants still remained (lower right quadrant in (A & C)).

eTable 1. Overview of genotyping platforms across all available AD-related genetic data.

Cohort/Project	Genotyping Platform	Cohort-Platform ID	Sample count	Data Repository
A4	Illumina Global Screening Array (GSA)	A4	3465	LONI A4
ACT	Illumina Human 660W-Quad	ACT	2790	NIAGADS (NG00034) / dbGaP (phs000234)
ADC1	Illumina Human 660W-Quad	ADC1	2731	NIAGADS (NG00022) / NACC
ADC2	Illumina Human 660W-Quad	ADC2	928	NIAGADS (NG00023) / NACC
ADC3	Illumina Human OmniExpress	ADC3	1526	NIAGADS (NG00024) / NACC
ADC4	Illumina Human OmniExpress	ADC4	1054	NIAGADS (NG00068) / NACC
ADC5	Illumina Human OmniExpress	ADC5	1224	NIAGADS (NG00069) / NACC
ADC6	Illumina Human OmniExpress	ADC6	1333	NIAGADS (NG00070) / NACC
ADC7	Illumina Infinium Human OmniExpressExome	ADC7	1462	NIAGADS (NG00071) / NACC
ADDNEUROMED	Illumina Human 610-Quad	ADM_Q	315	Synapse AddNeuroMed (syn4907804)
	Illumina Human OmniExpress	ADM_O	329	Synapse AddNeuroMed (syn4907804)
ADNI	Illumina Human 610-Quad	ADNI_1	757	LONI ADNI
	Illumina Human OmniExpress	ADNI_2	361	LONI ADNI
	Illumina Global Screening Array (GSA)	ADNI_3	327	LONI ADNI
	Illumina Omni 2.5	ADNI_O25	812	LONI ADNI
	Whole Genome Sequencing - Illumina	ADNI_WGS	812	LONI ADNI
ADNI-DOD	Illumina Human OmniExpress	ADNI_DOD	204	LONI ADNIDOD
ADGC Exome-Arrays	Illumina HumanExome BeadChip v1.0 - CHOP	CHOP	5180	NIAGADS (NG00081) / NACC
	Illumina HumanExome BeadChip v1.0 - Miami	MIA	1923	NIAGADS (NG00080) / NACC
	Illumina HumanExome BeadChip v1.0 - Northshore	NS	5998	NIAGADS (NG00079) / NACC
	Illumina HumanExome BeadChip v1.0 - WashU	WU	868	NIAGADS (NG00085) / NACC
ADSP WES	**Whole Exome Sequencing**	**ADSP_WES**	**20503**	**NIAGADS DSS (NG00067.v5) / NACC**
ADSP WGS	**Whole Genome Sequencing**	**ADSP_WGS**	**16906**	**NIAGADS DSS (NG00067.v5) / NACC**
Indianapolis African-American	Illumina Human 1M-Duo	IIDP_AA	1175	NIAGADS (NG00047)
Indianapolis Yoruba	Illumina Omni 2.5	IIDP_YOR	1264	dbGaP (phs000378)
CIDR	Illumina Human Omni1-Quad	CIDR	3101	NIAGADS (NG00015) / dbGAP (phs000496)
GenADA	Affymetrix 500K	GSK	1571	dbGaP (phs000219)

HBTRC	Illumina Human Hap650Y	HBTRC_ILL	338	Synapse AMP-AD (syn3159435)
	Illumina Human Hap650Y	HBTRC_PERL	402	Synapse AMP-AD (syn3159435)
LATC	Illumina Multi-Ethnic – BU	LATC	63	RADC Rush (contact:Gregory_Klein@rush.edu)
NIA-LOAD	Illumina Human 610-Quad	LOAD	5220	NIAGADS (NG00020)
MARS	Illumina Multi-Ethnic – BU	MARS	708	RADC Rush (contact:Gregory_Klein@rush.edu)
MAYO	Illumina Human Hap300	MAYO_1	2099	Synapse AMP-AD (syn5591675) / NIAGADS (NG00029)
	Whole Genome Sequencing	AMP_AD_MAYO_WGS	349	Synapse AMP-AD (syn22264775)
MAYO2	Illumina Omni 2.5	MAYO_2	314	Synapse AMP-AD (syn5550404)
	Whole Genome Sequencing	AMP_AD_MAYO_WGS	349	Synapse AMP-AD (syn22264775)
MIRAGE	Illumina Human CNV370-Duo	MIRAGE_370	397	NIAGADS (NG00031)
	Illumina Human 610-Quad	MIRAGE_610	1105	NIAGADS (NG00031)
MSBB	Whole Genome Sequencing	AMP_AD_MSBB_WGS	349	Synapse AMP-AD (syn3159438, syn22264775)
MTC	Illumina Human OmniExpress	MTC	542	NIAGADS (NG00096)
OHSU	Illumina Human CNV370-Duo	OHSU	647	NIAGADS (NG00017)
ROSMAP	Affymetrix GeneChip 6.0 - Broad Institute	ROSMAP_1B	1126	RADC Rush (contact:Gregory_Klein@rush.edu) / Synapse AMP-AD
	Affymetrix GeneChip 6.0 - TGen	ROSMAP_1T	582	RADC Rush (contact:Gregory_Klein@rush.edu) / Synapse AMP-AD
	Illumina Human OmniExpress 12 - Chop	ROSMAP_2C	382	RADC Rush (contact:Gregory_Klein@rush.edu) / Synapse AMP-AD
	Illumina Multi-Ethnic - BU	ROSMAP_3BU	494	RADC Rush (contact:Gregory_Klein@rush.edu)
	Whole Genome Sequencing	AMP_AD_ROSMAP_WGS	1196	RADC Rush (contact:Gregory_Klein@rush.edu) / Synapse AMP-AD
TARCC	Affymetrix 6.0	TARCC	625	NIAGADS (NG00097)
	Illumina Multi-Ethnic – BU	TARCC_full	2718	TARCC (contact: Bruce.Jones@UTSouthwestern.edu)
TGEN2	Affymetrix 6.0	TGEN	1599	NIAGADS (NG00028)
UPITT	Illumina Human Omni1-Quad	UPITT	2440	NIAGADS (NG00026)
UM/VU/MSSM	Illumina Human 1M-Duo, Illumina 1M	UVM_A	1153	NIAGADS (NG00042)
	Affymetrix 6.0	UVM_B	864	NIAGADS (NG00042)
	Illumina Human 550K. Illumina Human 610-Quad	UVM_C	445	NIAGADS (NG00042)
WASHU	Illumina Human 610-Quad	WASHU_1	670	NIAGADS (NG00030)
WASHU2	Illumina Human OmniExpress	WASHU_2	235	NIAGADS (NG00087)
WHICAP	Illumina Human OmniExpress	WHICAP	647	NIAGADS (NG00093)

eTable 2. Overview of ADSP studies with WES or WGS available through NIAGADS DSS (NG00067).

Study	Accession Number	Related Datasets
Accelerating Medicines Partnership- Alzheimer's Disease (AMP-AD)	sa000011	NG00067 – ADSP Umbrella
Cache County Study	sa000014	NG00067 – ADSP Umbrella
University of Pittsburgh- Kamboh WGS	sa000012	NG00067 – ADSP Umbrella
CurePSP and Tau Consortium PSP WGS	sa000016	NG00067 – ADSP Umbrella
NIH, CurePSP and Tau Consortium PSP WGS	sa000015	NG00067 – ADSP Umbrella
UCLA Progressive Supranuclear Palsy	sa000017	NG00067 – ADSP Umbrella
NACC Genentech WGS	sa000013	NG00067 – ADSP Umbrella
Alzheimer's Disease Sequencing Project (ADSP)	sa000001	NG00067 – ADSP Umbrella
Alzheimer's Disease Neuroimaging Initiative (ADNI)	sa000002	NG00067 – ADSP Umbrella
Alzheimer's Disease Genetics Consortium: African Americans (ADGC AA)	sa000003	NG00067 – ADSP Umbrella
The Familial Alzheimer Sequencing (FASe) project	sa000004	NG00067 – ADSP Umbrella
Brkanac – Family-based genome scan for AAO of LOAD	sa000005	NG00067 – ADSP Umbrella
HIHG Miami Families with AD	sa000006	NG00067 – ADSP Umbrella
Washington Heights/Inwood Columbia Aging Project (WHICAP)	sa000007	NG00067 – ADSP Umbrella
Charles F. and Joanne Knight Alzheimer's Disease Research Center (Knight ADRC)	sa000008	NG00067 – ADSP Umbrella
Corticobasal degeneration Study (CBD)	sa000009	NG00067 – ADSP Umbrella
Progressive Supranuclear Palsy Study (PSP)	sa000010	NG00067 – ADSP Umbrella

eTable 3. ADSP WES Sample sizes per center after sequential quality control and filtering steps (detailed in column titles).

Sequencing Centers	1. All genotyped subjects	2. No sex problems	3. No ancestry/race discordance	4. No duplicate discordance	5. Filter to CN/AD	6. *APOE* genotype available	7. AGE available	8. AGE 60y and up	9. European (EU)	10. Retain unique non-duplicate
ADSP_WES_Baylor	2368	2367	2364	2359	2330	2327	2327	2308	2221	2203
ADSP_WES_Broad	4584	4583	4574	4562	4259	4259	4259	4249	4228	4222
ADSP_WES_CHOP	346	345	343	341	1	1	1	1	1	1
ADSP_WES_CU_IGM	3861	3861	3823	3811	3759	3758	3731	3730	830	719
ADSP_WES_FGC	330	330	329	327	0	0	0	0	0	0
ADSP_WES_IDOM	103	103	102	102	0	0	0	0	0	0
ADSP_WES_MGI	1036	1033	1027	1020	892	892	891	806	776	747
ADSP_WES_Otogenetics	714	714	714	705	608	608	608	605	594	564
ADSP_WES_PGFI	117	117	117	117	0	0	0	0	0	0
ADSP_WES_UM_HIHG	3265	3265	3248	3244	3035	3035	3009	2945	94	84
ADSP_WES_UW_GenomeSciences	75	75	73	67	53	50	50	44	36	30
ADSP_WES_WashU	3704	3702	3687	3661	3353	3353	3352	3337	3012	3003
Total	20503	20495	20401	20316	18290	18283	18228	18025	11792	11573

eTable 4. ADSP WGS Sample sizes per center after sequential quality control and filtering steps (detailed in column titles).

Sequencing Centers	1. All genotyped subjects	2. No sex problems	3. No ancestry/race discordance	4. No duplicate discordance	5. Filter to CN/AD	6. *APOE* genotype available	7. AGE available	8. AGE 60y and up	9. European (EU)	10. Retain unique non-duplicate
ADSP_WGS_BAYLOR	1272	1272	1268	1268	1228	1228	1228	1207	119	119
ADSP_WGS_BROAD	1493	1492	1489	1482	1330	1330	1329	1277	1018	1000
ADSP_WGS_GENENTECH	55	55	52	51	49	49	48	26	26	21
ADSP_WGS_ILLUMINA	1450	1449	1418	1417	820	820	820	760	730	682
ADSP_WGS_MACROGEN	886	886	879	879	1	1	1	1	1	1
ADSP_WGS_NYGC	1646	1638	1621	1569	1192	1192	1192	1192	1160	1148
ADSP_WGS_USUHS	8777	8773	8704	8676	7240	7239	6939	6422	3474	3423
ADSP_WGS_WASHU	1327	1326	1310	1308	1242	1241	1240	1202	143	139
Total	16906	16891	16741	16650	13102	13100	12797	12087	6671	6533

eTable 5. Sample demographics for ADSP WES analyses, stratified by Sequencing Center and Platform.

ADSP WES samples		Diagnosis		Sex	Age	*APOE* status	
Name	Participants after QC (N)	Type	(N)	Female (N (%))	Age (Mean (SD))	APOE*4-pos	APOE*2-pos
All samples	11573	CN	5418	3152 (58.2 %)	85.4 (6.5)	926 (17.1 %)	1057 (19.5 %)
		AD	6155	3619 (58.8 %)	75.4 (8.6)	2938 (47.7 %)	493 (8.0 %)
Sequencing Centers							
Baylor	2203	CN	1100	597 (64.3 %)	86.2 (3.9)	435 (39.4 %)	243 (22.1 %)
		AD	1103	689 (62.5 %)	76.2 (5.8)	689 (62.5 %)	113 (10.2 %)
Broad	4222	CN	1606	995 (62.0 %)	88.1 (4.8)	1277 (48.8 %)	366 (22.8 %)
		AD	2616	1412 (54.0 %)	73.9 (8.4)	1412 (54.0 %)	203 (7.8 %)
CHOP	1	CN	0	-	-	1 (100.0 %)	-
		AD	1	0 (0.0 %)	75.0 (-)	0 (0.0 %)	0 (0.0 %)
CU_IGM	719	CN	667	395 (59.2 %)	79.8 (6.7)	159 (23.8 %)	75 (11.2 %)
		AD	52	31 (59.6 %)	83.9 (6.9)	15 (28.8 %)	9 (17.3 %)
MGI	747	CN	356	206 (57.9 %)	74.1 (7.5)	125 (35.1 %)	54 (15.2 %)
		AD	391	210 (53.7 %)	72.5 (7.3)	262 (67.0 %)	22 (5.6 %)
Otogenetics	564	CN	146	83 (56.8 %)	79.8 (7.3)	68 (46.6 %)	12 (8.2 %)
		AD	418	279 (66.7 %)	74.0 (7.0)	320 (76.6 %)	11 (2.6 %)
UM_HIHG	84	CN	17	6 (35.3 %)	76.2 (6.8)	4 (23.5 %)	1 (5.9 %)
		AD	67	46 (68.7 %)	76.2 (5.8)	38 (56.7 %)	6 (9.0 %)
UW_GenomeSciences	30	CN	0	-	-	-	-
		AD	30	19 (63.3 %)	72.9 (7.7)	19 (63.3 %)	1 (3.3 %)
WashU	3003	CN	1526	870 (57.0 %)	87.9 (4.1)	204 (13.4 %)	306 (20.5 %)
		AD	1477	933 (63.2 %)	78.4 (8.6)	571 (38.7 %)	128 (8.7 %)
Sequencing Platforms							
HiSeq_2000	11021	CN	5125	2980 (58.1 %)	86.1 (5.8)	837 (16.3 %)	1010 (19.7 %)
		AD	5896	3486 (59.1 %)	75.5 (8.6)	2791 (47.3 %)	417 (8.0 %)
HiSeq_2000/2500	84	CN	17	6 (35.3 %)	76.2 (6.8)	4 (23.5 %)	1 (5.9 %)
		AD	67	46 (68.7 %)	76.2 (5.8)	38 (56.7 %)	6 (9.0 %)
HiSeq_2500	1	CN	0	-	-	-	-
		AD	1	0 (0.0 %)	75.0 (-)	1 (100.0 %)	0 (0.0 %)
HiSeq_4000	467	CN	276	166 (60.1 %)	73.1 (7.4)	85 (30.8 %)	46 (16.7 %)
		AD	191	87 (45.5 %)	71.0 (7.4)	108 (56.5 %)	16 (8.4 %)

eTable 6. Sample demographics for ADSP WGS analyses, stratified by Sequencing Center and Platform.

ADSP WGS samples		Diagnosis		Sex	Age	*APOE* status	
Name	Participants after QC (N)	Type	(N)	Female (N (%))	Age (Mean (SD))	APOE*4-pos	APOE*2-pos
All samples	6533	CN	2949	1791 (60.7 %)	81.6 (6.6)	1075 (36.4 %)	204 (6.9 %)
		AD	3584	2051 (57.2 %)	76.7 (8.3)	2078 (58.0 %)	177 (4.9 %)
Sequencing Centers							
Baylor	119	CN	75	48 (64.0 %)	81.0 (4.5)	25 (33.3 %)	5 (6.7 %)
		AD	44	37 (84.1 %)	74.5 (6.8)	29 (65.9 %)	2 (4.5 %)
Broad	1000	CN	437	265 (60.6 %)	81.3 (6.6)	91 (20.8 %)	68 (15.6 %)
		AD	563	303 (53.8 %)	75.0 (8.8)	353 (62.7 %)	29 (5.2 %)
Genentech	21	CN	6	1 (16.7 %)	80.8 (2.9)	6 (100.0 %)	0 (0.0 %)
		AD	15	12 (80.0 %)	76.2 (6.7)	6 (40.0 %)	4 (26.7 %)
Illumina	682	CN	409	225 (55.0 %)	80.3 (5.9)	253 (61.9 %)	32 (7.8 %)
		AD	273	111 (40.7 %)	71.6 (7.8)	207 (75.8 %)	10 (3.7 %)
Macrogen	1	CN	0	-	-	-	-
		AD	1	0 (0.0 %)	64.0 (-)	0 (0 %)	0 (0 %)
NYGC	1148	CN	300	187 (62.3 %)	85.4 (7.0)	44 (14.7 %)	60 (15.6 %)
		AD	848	566 (66.7 %)	80.4 (8.6)	432 (50.9 %)	69 (8.1 %)
USHS	3423	CN	1682	1034 (61.5 %)	81.6 (6.3)	643 (38.2 %)	33 (2.0 %)
		AD	1741	961 (55.2 %)	76.4 (7.3)	1006 (57.8 %)	55 (3.2 %)
WashU	139	CN	40	31 (77.5 %)	70.8 (8.4)	13 (32.5 %)	6 (15.0 %)
		AD	99	61 (61.6 %)	76.2 (8.1)	45 (45.5 %)	8 (8.1 %)
Sequencing Platforms							
Illumina_HiSeq_2000	569	CN	210	105 (50.0 %)	79.7 (7.6)	50 (23.8 %)	34 (16.2 %)
		AD	359	193 (53.8 %)	75.0 (7.0)	223 (62.1 %)	20 (5.6 %)
Illumina_HiSeq_X_Ten	1014	CN	523	325 (62.1 %)	80.7 (6.9)	118 (22.6 %)	74 (14.1 %)
		AD	491	259 (52.7 %)	76.3 (8.5)	286 (58.2 %)	29 (5.9 %)
PCRAmplified_HiSeq2000	304	CN	218	129 (59.1 %)	80.8 (3.7)	213 (97.7 %)	0 (0.0 %)
		AD	86	39 (45.3 %)	65.7 (6.5)	77 (89.5 %)	4 (4.7 %)
PCRAmplified_HiSeq2000/2500	15	CN	12	7 (58.3 %)	67.8 (3.7)	3 (25.0 %)	2 (16.7 %)
		AD	3	0 (0.0 %)	76.7 (5.5)	2 (66.7 %)	0 (0.0 %)
PCRAmplified_HiSeqX	65	CN	8	5 (62.5 %)	86.1 (5.8)	6 (75.0 %)	1 (12.5 %)
		AD	57	33 (57.9 %)	75.5 (8.6)	53 (93.0 %)	0 (0.0 %)
PCRFree_HiSeqX	3965	CN	1777	1117 (62.9 %)	82.7 (6.4)	591 (33.3 %)	68 (3.8 %)
		AD	2188	1343 (61.4 %)	78.6 (7.8)	1190 (54.4 %)	101 (4.6 %)
PCRFree_Novaseq	601	CN	201	103 (62.9 %)	77.9 (6.3)	94 (46.8 %)	25 (12.4 %)
		AD	400	184 (46.0 %)	72.9 (7.5)	247 (61.8 %)	23 (5.8 %)

eTable 7. Illustration of a variant underlying an artifactual genome-wide significant signal in model-1 after applying duplicate discordance filters. The displayed variant (rs895262150) corresponds to the hit annotated with gene "*ZDHHC14*" in EFigure16. Note the enrichment in control carriers on the Illumina center and PCR amplified HiSeq2000 platform. Closer inspection revealed that this variant shows a considerably higher variant missingness rate in subjects sequenced using the PCR amplified HiSeq2000 platform compared to other platforms (40%). Control individuals on this platform were almost solely contributed by a single cohort (G-CCS) with a variant missingness rate of 50%, whereas cases were mainly contributed by two other cohorts (A-ADC, A-LOAD), with a variant missingness rate rate of 25%. All control variant carriers were contributed by a single cohort (G-CCS). These observations confirm the variant appears artifactual.

Sequencing Center		ADSP_WGS_BAYLOR	ADSP_WGS_BROAD	ADSP_WGS_GENENTECH	ADSP_WGS_ILLUMINA	ADSP_WGS_MACROGEN	ADSP_WGS_NYGC	ADSP_WGS_USUHS	ADSP_WGS_WASHU
AD	WT	40	561	4	239	1	846	1735	84
	HET	0	0	0	3	0	2	5	0
	HOM	0	0	0	0	0	0	0	0
CN	WT	75	435	0	257	0	300	1672	37
	HET	0	2	0	35	0	0	10	0
	HOM	0	0	0	0	0	0	0	0

Sequencing Platform		Illumina_HiSeq_2000	Illumina_HiSeq_X_Ten	PCRAmplified_HiSeq2000	PCRAmplified_HiSeq2000/2500	PCRAmplified_HiSeqX	PCRFree_HiSeqX	PCRFree_Novaseq
AD	WT	315	491	64	3	57	2180	354
	HET	2	0	1	0	0	7	0
	HOM	0	0	0	0	0	0	0
CN	WT	183	521	84	12	8	1769	46
	HET	2	2	33	0	0	8	1
	HOM	0	0	0	0	0	0	0

eTable 8. Overview of the number of variants and suggestive significance variants after applying the different types of presented filters.

No. Variants after applying filters respectively (non-sequentially)								
	ADSP WES				ADSP WGS			
	Model-1		Model-2		Model-1		Model-2	
	P <= 1	P <= 10^{-5}	P <= 1	P <= 10^{-5}	P <= 1	P <= 10^{-5}	P <= 1	P <= 10^{-5}
No filter	224270	296	224270	30	14772936	873	14772936	166
Center/Platform filters	212759	11	212759	4	14587316	144	14587316	161
Gnomad PASS filter	219663	62	219663	9	14672277	555	14672277	165
Gnomad LCR filter	223015	290	223015	29	14478007	844	14478007	163
Gnomad MAF filter	224167	282	224167	30	14765866	872	14765866	166
Duplicate filter	213082	17	213082	4	14580236	178	14580236	160
No. Variants after applying filters sequentially								
	ADSP WES				ADSP WGS			
	Model-1		Model-2		Model-1		Model-2	
	P <= 1	P <= 10^{-5}	P <= 1	P <= 10^{-5}	P <= 1	P <= 10^{-5}	P <= 1	P <= 10^{-5}
No filter	224270	296	224270	30	14772936	873	14772936	166
Center/Platform filters	212759	11	212759	4	14587316	144	14587316	161
Gnomad PASS filter	210452	8	210452	4	14502091	142	14502091	161
Gnomad LCR filter	209467	8	209467	4	14220833	139	14220833	158
Gnomad MAF filter	209396	8	209396	4	14216639	139	14216639	158
Duplicate filter	203064	5	203064	4	14102841	136	14102841	157

eTable 9 (part 1). ADSP WGS variants passing suggestive significance after applying centers/platform-based filters. Note that many variants that lose suggestive significance after center/platform adjustment in model-2 have fairly small P-values (but above threshold) in the center/platform Fisher tests and/or are present in the gnomAD-based or duplicate discordance variant filters.

Variant info							Model 1				Model 2				Filters			
GENE	CHR	BP	dbSNP153 ID	effect allele	other allele	effect allele frq.	OR	95% CI (lb)	95% CI (ub)	P	OR	95% CI (lb)	95% CI (ub)	P	Center Fisher P	Plat. Fisher P	gnomAD filter	Duplicate check
LINC01648	1	30307706	rs147201606	T	C	1.11%	0.48	0.35	0.66	**6.7E-06**	0.50	0.37	0.68	**7.9E-06**	0.98	0.98	PASS	ok
LINC01343	1	38312264	rs140123944	A	G	1.22%	0.51	0.38	0.68	**8.3E-06**	0.54	0.40	0.72	2.3E-05	0.93	0.97	PASS	ok
CR1	1	207510847	rs12037841	T	G	19.96%	1.21	1.11	1.32	**9.5E-06**	1.19	1.10	1.29	1.8E-05	0.03	0.94	PASS	ok
CNIH3	1	224768842	rs193214846	T	C	0.68%	0.40	0.27	0.61	1.4E-05	0.42	0.28	0.61	**1.0E-05**	0.97	0.96	PASS	ok
DNAH14	1	225331510	rs41303992	A	G	0.34%	0.26	0.15	0.46	**4.5E-06**	0.29	0.17	0.51	**1.0E-05**	0.98	0.96	PASS	ok
GPR137B	1	236155980	rs187878039	T	C	0.19%	0.14	0.06	0.30	**3.9E-07**	0.17	0.08	0.35	**2.1E-06**	0.99	0.89	LCR	ok
LINC01814	2	8511225	-	G	GAA	70.11%	1.19	1.10	1.28	**3.6E-06**	1.14	1.07	1.22	1.7E-04	0.08	1.2E-04	PASS	ok
LINC01884	2	22439246	rs115335046	G	A	0.25%	0.22	0.11	0.43	**1.0E-05**	0.24	0.13	0.46	1.8E-05	0.98	0.98	PASS	ok
GALNT14	2	31129922	rs11676188	G	C	20.69%	0.84	0.77	0.91	3.2E-05	0.84	0.77	0.91	**1.0E-05**	0.66	0.19	PASS	ok
PLEK	2	68419120	rs149490106	T	C	0.76%	0.44	0.30	0.64	2.1E-05	0.43	0.30	0.62	**6.2E-06**	0.98	0.93	PASS	ok
FAHD2CP	2	96008264	rs138643748	C	G	1.06%	0.45	0.33	0.63	**2.0E-06**	0.58	0.42	0.79	6.4E-04	1.4E-03	5.3E-04	PASS	discordant
BIN1	2	127135234	rs6733839	T	C	40.39%	1.26	1.18	1.35	**2.3E-11**	1.25	1.17	1.33	**3.9E-11**	0.62	0.02	PASS	ok
MYO3B-AS1	2	170490308	rs111867349	A	G	1.87%	0.59	0.47	0.76	3.1E-05	0.59	0.47	0.74	**9.0E-06**	0.41	0.46	PASS	ok
INPP5D	2	233073186	rs72982255	A	G	13.02%	0.80	0.72	0.88	**1.0E-05**	0.81	0.74	0.89	1.3E-05	0.90	4.8E-04	PASS	ok
CNTN4	3	1780132	rs113207766	TTAAA	T	49.63%	0.82	0.77	0.87	**4.7E-09**	0.83	0.78	0.89	**1.7E-08**	0.08	0.15	PASS	ok
ACKR2	3	42837221	rs879898582	GT	G	0.49%	3.83	2.36	6.21	**5.7E-08**	1.81	1.09	3.03	0.02	0.97	0.88	non-PASS	discordant
FHIT	3	59786111	rs374541147	C	A	1.63%	0.52	0.40	0.68	**2.0E-06**	0.55	0.42	0.71	**3.7E-06**	0.96	0.96	PASS	ok
-	3	110419318	rs115395207	T	G	1.38%	0.50	0.37	0.66	**2.0E-06**	0.53	0.40	0.70	**6.9E-06**	0.96	0.96	PASS	ok
ITGB5	3	124876108	rs1948696	T	C	37.20%	1.19	1.11	1.27	**1.5E-06**	1.16	1.09	1.24	**8.1E-06**	0.65	0.50	PASS	ok
LINC01565	3	128575196	rs532515415	A	G	0.25%	0.26	0.14	0.51	8.1E-05	0.23	0.12	0.44	**6.0E-06**	0.98	0.95	PASS	ok
BFSP2	3	133401263	rs138196830	A	T	0.14%	0.13	0.05	0.32	**9.3E-06**	0.16	0.07	0.37	2.6E-05	0.98	0.96	PASS	ok
STPG2-AS1	4	97428849	rs866286162	C	G	0.47%	0.32	0.19	0.52	**6.7E-06**	0.39	0.25	0.63	1.1E-04	0.98	0.98	PASS	ok
NEIL3	4	177342041	rs34539659	C	A	0.30%	0.25	0.13	0.46	**9.0E-06**	0.32	0.18	0.58	1.6E-04	0.98	0.89	PASS	ok
LINC02500	4	181486820	rs17071607	A	G	2.00%	1.67	1.31	2.12	2.6E-05	1.69	1.34	2.12	**7.7E-06**	0.98	0.96	PASS	ok
MTRR	5	7931168	rs6883636	A	T	7.05%	1.34	1.18	1.53	**1.0E-05**	1.28	1.13	1.45	9.0E-05	0.50	0.98	PASS	ok
MYO10	5	16924467	rs112418255	T	C	0.35%	0.28	0.16	0.49	**7.9E-06**	0.35	0.20	0.59	1.1E-04	0.97	0.02	PASS	ok
ARSB	5	78811930	rs75497745	C	T	2.50%	0.63	0.51	0.79	3.2E-05	0.63	0.51	0.77	**9.2E-06**	0.98	0.96	PASS	ok
LINC01340	5	97649168	rs145076322	T	A	0.26%	0.22	0.11	0.43	**8.8E-06**	0.26	0.14	0.49	3.1E-05	0.95	0.98	PASS	ok
YIPF5	5	144039218	rs113589858	AT	A	9.88%	1.35	1.20	1.51	**2.6E-07**	1.30	1.16	1.45	**2.2E-06**	0.03	0.02	PASS	ok
YIPF5	5	144078830	rs7708467	C	T	25.16%	1.18	1.09	1.28	2.1E-05	1.20	1.11	1.29	**2.0E-06**	0.91	0.96	PASS	ok
CYFIP2	5	157393949	rs6555992	G	A	18.42%	0.81	0.75	0.89	**3.4E-06**	0.82	0.75	0.89	**1.4E-06**	0.96	0.93	PASS	ok
LOC401312	7	22662017	rs10265117	A	G	12.66%	0.80	0.72	0.88	1.3E-05	0.80	0.73	0.88	**4.6E-06**	0.65	0.18	PASS	ok
SUGCT	7	40867131	rs146711196	T	TATA	32.26%	0.86	0.80	0.93	5.0E-05	0.85	0.79	0.91	**4.0E-06**	0.19	0.95	LCR	ok
YWHAEP1	7	64472092	rs143068421	A	C	0.73%	0.39	0.26	0.57	**2.3E-06**	0.43	0.30	0.63	1.3E-05	1.7E-03	0.96	PASS	ok
STYXL1	7	76006286	rs182846177	G	C	0.32%	0.30	0.16	0.53	5.0E-05	0.28	0.16	0.49	**1.0E-05**	0.98	0.93	PASS	ok

eTable 9 (part 2). ADSP WGS variants passing suggestive significance after applying centers/platform-based filters. Note that many variants that lose suggestive significance after center/platform adjustment in model-2 have fairly small P-values (but above threshold) in the center/platform Fisher tests and/or are present in the gnomAD-based or duplicate discordance variant filters.

Variant info							Model 1				Model 2				Filters			
GENE	CHR	BP	dbSNP153 ID	effect allele	other allele	effect allele frq.	OR	95% CI (lb)	95% CI (ub)	P	OR	95% CI (lb)	95% CI (ub)	P	Center Fisher P	Plat. Fisher P	gnomAD filter	Duplicate check
LRRC4	7	128041888	rs76593352	T	G	0.77%	0.40	0.27	0.58	**2.4E-06**	0.41	0.29	0.59	**2.1E-06**	0.90	0.30	PASS	ok
KCNV2	9	2751431	rs543363829	T	C	0.31%	0.29	0.16	0.53	6.6E-05	0.27	0.15	0.47	**7.0E-06**	0.98	0.96	PASS	ok
PTPRD-AS1	9	8880476	rs138987427	A	G	0.27%	3.49	1.83	6.68	1.6E-04	4.06	2.19	7.55	**9.3E-06**	0.99	0.99	PASS	ok
LINGO2	9	28300621	rs4587420	G	C	38.87%	0.85	0.79	0.91	**2.4E-06**	0.85	0.80	0.91	**1.8E-06**	1.6E-03	0.16	PASS	ok
C9orf85	9	71914326	rs113367159	T	TG	0.22%	5.66	2.75	11.67	**2.8E-06**	3.60	1.77	7.33	4.0E-04	0.99	0.99	LCR	discordant
SHC3	9	89033784	rs1537144	A	C	19.51%	0.84	0.77	0.91	3.5E-05	0.83	0.76	0.90	**4.2E-06**	0.92	0.43	PASS	ok
RAD23B	9	107355656	rs10739241	T	A	41.20%	0.86	0.80	0.91	**5.1E-06**	0.87	0.81	0.93	1.5E-05	0.21	0.39	PASS	ok
LINC00844	10	58995166	rs140004050	T	C	0.77%	2.06	1.41	3.01	1.8E-04	2.29	1.59	3.29	**7.4E-06**	0.98	0.98	PASS	ok
ATE1	10	121774625	rs775805330	C	T	0.18%	0.16	0.07	0.35	**6.3E-06**	0.25	0.11	0.53	3.0E-04	0.97	5.2E-03	PASS	ok
MIR4300HG	11	81712477	rs200761787	A	AG	1.52%	0.53	0.41	0.70	**5.2E-06**	0.56	0.43	0.72	**8.7E-06**	0.97	0.95	PASS	ok
ARHGAP42-AS1	11	100680925	rs758006599	A	T	0.38%	0.29	0.17	0.50	**8.5E-06**	0.33	0.20	0.56	3.4E-05	0.98	0.96	LCR	ok
LOC101928535	11	106426120	rs117682555	T	C	2.21%	1.58	1.26	1.99	9.0E-05	1.65	1.33	2.06	**7.2E-06**	0.96	0.11	PASS	ok
ETV6	12	11698764	rs2724652	G	T	45.30%	0.85	0.80	0.91	**5.4E-06**	0.86	0.80	0.91	**3.0E-06**	6.65E-05	0.38	PASS	ok
CAPRIN2	12	30718899	rs188591971	T	G	0.64%	2.30	1.52	3.48	8.7E-05	2.46	1.66	3.66	**7.9E-06**	0.97	0.02	PASS	ok
LINC02451	12	42653330	rs184022552	A	G	7.45%	0.74	0.65	0.84	**4.6E-06**	0.76	0.67	0.86	1.5E-05	2.7E-04	0.15	PASS	ok
LINC02451	12	42657809	rs141146804	C	T	7.36%	0.74	0.65	0.85	**8.1E-06**	0.75	0.66	0.85	**5.0E-06**	2.7E-04	0.09	PASS	ok
ATP8A2	13	25623164	rs547117207	A	G	0.25%	3.87	1.97	7.61	8.1E-05	4.41	2.31	8.41	**6.5E-06**	0.99	0.99	PASS	ok
VWA8	13	41939480	rs796820552	TA	T	0.40%	3.69	2.17	6.28	**1.6E-06**	1.95	1.12	3.40	0.02	0.98	0.98	non-PASS	discordant
DNAJC15	13	43061521	rs143663531	G	A	0.60%	2.70	1.75	4.17	**7.3E-06**	2.50	1.65	3.78	1.6E-05	0.98	0.99	PASS	ok
MIR4704	13	66170147	rs9540673	T	G	16.61%	0.82	0.75	0.89	**1.0E-05**	0.83	0.76	0.91	3.2E-05	0.60	0.97	PASS	ok
MIR4539	14	105778867	rs188538741	T	A	0.61%	2.74	1.79	4.22	**3.9E-06**	2.51	1.66	3.78	1.1E-05	0.98	0.08	PASS	ok
LOC102723493	15	67048252	rs78650348	C	A	1.82%	0.59	0.46	0.76	3.4E-05	0.57	0.45	0.72	**3.6E-06**	0.90	0.09	PASS	ok
CALML4	15	68164398	rs148101423	G	A	0.21%	0.19	0.09	0.39	**1.0E-05**	0.21	0.10	0.42	1.2E-05	0.97	0.99	PASS	ok
FAM169B	15	98506192	rs4465592	G	C	35.69%	1.17	1.10	1.26	**5.1E-06**	1.16	1.08	1.24	1.2E-05	0.87	0.76	PASS	ok
FAM169B	15	98528459	rs72766230	G	A	13.74%	1.22	1.11	1.35	5.0E-05	1.23	1.13	1.35	**7.9E-06**	0.60	0.27	PASS	ok
BMERB1	16	15459834	rs56189737	A	G	2.43%	1.66	1.34	2.06	**3.9E-06**	1.57	1.28	1.93	1.8E-05	0.79	0.06	PASS	ok
PIRT	17	10902147	rs34731238	T	C	7.06%	0.74	0.65	0.85	**8.4E-06**	0.77	0.68	0.87	5.0E-05	0.02	0.38	PASS	ok
KIF2B	17	54042628	rs137879811	C	T	0.66%	2.70	1.79	4.09	**2.7E-06**	2.59	1.74	3.84	**2.5E-06**	0.98	0.98	PASS	ok
LOC105371855	17	62716778	rs12602916	G	A	39.26%	1.16	1.08	1.24	2.5E-05	1.16	1.09	1.24	**6.3E-06**	0.90	0.96	PASS	ok
LOC105371855	17	62722776	rs34113842	A	AT	6.54%	0.74	0.64	0.84	**7.3E-06**	0.76	0.66	0.86	2.1E-05	0.81	0.98	PASS	ok
TNFRSF11A	18	62385675	-	CCG	C	0.52%	0.34	0.21	0.55	**7.7E-06**	0.38	0.24	0.59	2.6E-05	0.01	0.93	PASS	discordant
ZNF600	19	52762647	rs564984950	G	A	1.86%	0.57	0.44	0.73	**6.6E-06**	0.61	0.48	0.77	3.0E-05	0.96	0.32	PASS	ok
MCM5	22	35469225	rs28620909	A	G	31.56%	0.84	0.79	0.91	**3.7E-06**	0.85	0.80	0.91	**5.6E-06**	0.42	0.10	PASS	ok
APOBEC3A	22	38960570	rs6001341	A	G	0.25%	0.24	0.12	0.47	3.2E-05	0.22	0.12	0.43	**6.7E-06**	0.98	0.98	PASS	ok

eTable 10. Comparing current ADSP WES association statistics for AD risk genes/variants identified in a prior study, using a similar model and largely overlapping data. Table shows variants identified in Le Guen et al. 2021, considering the case-control analyses not adjusting for age. We additionally highlight the rs3764645 variant on *ABCA7*, which was not present in the prior study, but was identified at suggestive signicance level here (the prior study indicated a different significant variant on *ABCA7*). Not all variants were shared across the current and prior study, which is mainly due to the differences in data releases (the prior study used the original ADSP WES and WGS discovery samples, covering fewer participants than considered here). Note that associations findings were highly consistent across both studies.

Gene	rsID	current P-value	Le Guen et al. 2021 - P-value
KIF21B	rs2297911	1.60E-03	2.00E-04
USH2A	rs111033333	2.40E-03	4.00E-03
RAB10	rs149622307	0.31	0.06
TREM2	rs75932628	8.20E-11	3.00E-10
PILRA	rs2405442	-	2.10E-05
MS4A6A	rs12453	8.90E-05	9.00E-06
RIN3	rs150221413	1.80E-03	7.00E-03
TAOK2	rs4077410	-	6.10E-05
NSF/MAPT/KANSL1	rs199533	9.10E-05	5.10E-06
ABCA7	rs547447016	-	1.10E-04
ABCA7	rs3764645	3.80E-06	-

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