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Admixture mapping identifies novel Alzheimer disease risk regions in African Americans

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Abstract

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CONFLICTS OF INTEREST

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Background—This study used admixture mapping to prioritize the genetic regions associated with Alzheimer disease (AD) in African American (AA) individuals, followed by ancestry-aware regression analysis to fine-map the prioritized regions.

Methods—We analyzed 10,271 individuals from 17 different AA datasets. We performed admixture mapping and meta-analyzed the results. We then used regression analysis, adjusting for local ancestry main effects and interactions with genotype, to refine the regions identified from admixture mapping. Finally, we leveraged *in silico* annotation and differential gene expression data to prioritize AD-related variants and genes.

Results—Admixture mapping identified two genome-wide significant loci on chromosomes 17p13.2 ($p=2.2\times10^{-5}$) and 18q21.33 ($p=1.2\times10^{-5}$). Our fine mapping of the chromosome 17p13.2 and 18q21.33 regions revealed several interesting genes such as the *MINK1, KIF1C, and BCL2*.

Discussion—Our ancestry-aware regression approach showed that AA individuals have a lower risk of AD if they inherited African ancestry admixture block at the 17p13.2 locus.

Keywords

ancestry; admixture; admixture mapping; African American; local ancestry; global ancestry

1. BACKGROUND

Alzheimer disease (AD) is the most common form of dementia and is characterized by the loss of memory and other cognitive functions. AD studies showed that disease affects individuals of all races and ethnicities with the higher prevalence and incidence in African American (AA) and Hispanic populations than non-Hispanic whites (NHW)[1,2]. Large-scale genetic studies have successfully identified more than 30 susceptibility loci for AD[3–6]. Most of these studies have focused on NHW populations; yet genetic studies in diverse populations have found ethnic-specific variations in several genes influencing disease[5,7]. The effect of the polymorphisms in the *APOE* gene on AD is a notable example of how different ethnic backgrounds may lead to differential effects in different populations[8]. Studies in admixed populations have shown that the effect of the *APOE ε*4 allele is correlated with the genetic ancestral background and suggested that regions of African ancestry around the *APOE* gene are likely to harbor protective variant(s) that mitigate the effect of the known *APOE* risk variant[9,10]. Another example of ethnic-specific effects is the *ABCA7* locus. Genome-wide association studies (GWAS) in AAs found that *ABCA7* influences risk in AAs more strongly than in NHW[7]. Follow-up studies identified a pathogenic 44 bp deletion in *ABCA7* associated with AD exclusively in individuals with African ancestral background[11]. Such findings highlight the need to study diverse populations to understand the differences in genetics effects on disease and discover ethnic-specific variants that would be missed otherwise.

There is an emerging effort to include diverse populations in AD genetic studies; yet the largest AA GWAS to date was performed in case-control study of ~8,500 AA individuals, which is less than one-tenth of the size of the largest GWAS of AD in NHW individuals of ~95,000 individuals[3,5]. Because of the substantial underrepresentation of AAs in genetic studies of AD relative to NHW, SNP-based GWAS in AAs have reduced statistical power for

novel variant discovery and have limited power to assess genetic factors identified in NHW populations.

The AA population is a two-way admixed population with genetic ancestry from African and European ancestors. Admixture in AAs creates mosaic chromosomes containing discrete segments of European and African ancestry, referred to as local ancestry. This mosaic pattern varies among the individuals, though the proportion of each ancestry across the genome (global ancestry) tends to be similar. Admixture mapping is a complementary statistical approach to SNP-based GWAS that maps the risk loci in admixed populations by leveraging the local ancestry estimates. This approach is based on the hypothesis that the causal risk alleles with large frequency or effect-size differences between the parental ancestries (African and European for AAs) will result in deviation of the expected local-ancestry proportions at the risk loci. Figure 1A illustrates a two-way admixed population (parental ancestries “A” and “B”) with the excess of “B” local ancestry among cases at the risk locus. This excess results in a spike of “B” ancestry percentage (Figure 1B). Admixture mapping identifies such risk loci by calculating the deviation of the local-ancestry proportions from the genome-wide averages. Moreover, admixture mapping has a lower multiple testing burden than SNP-based GWAS studies, since recent admixture (~20 generations) in AAs created admixture blocks, which are larger than linkage disequilibrium (LD) blocks (Supplemental Figure 1).

In the present study, we performed the largest AA admixture-mapping analysis to date with 9,322 total AA individuals. The sample includes the 5,644 participants previously analyzed by Hohman et al[12] and increased the number of subjects by 65%. Taking advantage of the large sample size and potential power of admixture mapping, this study aims to identify ancestry-specific genetic loci associated with AD in AAs using twostep approach: (i) admixture mapping to prioritize the genetic regions associated with AD, and (ii) multipronged fine-mapping strategy to translate the findings from associated genetic regions to potential causal gene(s) (Figure 2).

2. METHODS

2.1. Study samples

This study included 3,166 AD cases and 6,156 controls of self-reported African Americans from 17 datasets: the Adult Changes in Thought (ACT) Study[13], the National Institute on Aging (NIA) Alzheimer’s Disease Centers (ADCs)[14], the University of Miami/Vanderbilt University (UM/VU)[15,16], the Mount Sinai School of Medicine (MSSM) Brain Bank[17], the Washington Heights Inwood Columbia Aging Project (WHICAP)[18], The African American Alzheimer’s Disease Genetics (AAG) Study[19], the MIRAGE Study[20], NIA-LOAD/NCRAD[21], the Mayo Clinic[22], the Rush University Alzheimer’s disease Center[23–26] (ROS/MAP, MARS/CORE), the Chicago Health and Aging Project (CHAP)[27], the Indianapolis Ibadan Dementia Study (Indianapolis)[28], the Genetic and Environmental Risk Factors for Alzheimer’s Disease Among African Americans (GenerAAtions) Study[29], the University of Pittsburgh (UP)[30], Washington University (WU)[31–34] and Research in African American Alzheimer Disease Initiative (REAAADI)[35]. All participants were consented under IRB protocols approved by the appropriate Institutional Review Board. Participants

were assessed by following NINCDS-ADRDA criteria for possible and probable AD[36]. The detailed description of the study samples, diagnosis of AD, and age of onset are described elsewhere[7]. Three datasets have family data. The details of the family numbers within these datasets are provided in Supplemental Table 1.

Genotype quality control: Genome-wide genotyping was performed using different array chips, full details of array genotyping explained elsewhere[7]. Quality control analyses were performed individually for each dataset using the software PLINK v.2[37]. Genotypes with a call rate less than 95% or deviating from Hardy-Weinberg equilibrium (HWE) ($p<1.e-6$) were eliminated. The concordance between reported sex and genotype-inferred sex was verified using X-chromosome data. The relationships among individuals within families were confirmed using "identical by descent" (IBD) allele sharing.

Genotype Imputation: All genotype-array datasets were individually phased and imputed to the TOPMed R2 version panel (build of GRCh38) using the TOPMed Imputation server[38]. The TOPMed R2 reference panel provides information on ~308 million genetic variants and contains 97,256 samples. Most of samples are predominantly from non-European populations and ~25% of the samples are from African-descent populations.

2.2. Assessment of genetic ancestry

We assessed the global ancestry using the PC-AiR approach, which is robust to known and cryptic relatedness[39]. We calculated PCs without population reference datasets and performed the Tracy-Widom test to select PCs for covariates in the genome-wide admixture-mapping analysis[40].

To assess local ancestry, first we combined our array genotype data with HGDP reference panel using PLINK v2 software[37, 41] and phased the data using the SHAPEIT tool ver. 2 with default settings and 1000 Genomes Phase 3 reference panel[42,43]. Then, we performed RFMix, a discriminative modeling approach, to infer the local ancestry at each locus across the genome[44].

2.3. Statistical analysis

Admixture mapping: We performed admixture mapping separately within each of 17 AA datasets using the GENESIS software. First, we encoded copies of African local-ancestry calls as dosage values (0,1, or 2; number of African haplotypes at a locus). Then, to test for an association between AD and local ancestry at a genomic location, we used a logistic mixed model. The model includes local ancestry (LA_{AF}) as main and the genetic relationship matrix (GRM) as a random effect to adjust for the sample relatedness, and was adjusted further for age, sex, and genome-wide ancestry (PC1:3) (equation 1).

$$AD \sim age + sex + PC1{:}3 + LA_{AF} + GRM \quad LA_{AF} \in \{0,1,2\} \qquad \text{(equation 1)}$$

Meta-analysis: To meta-analyze the 17 AA datasets, which were separately analyzed using admixture mapping, we first aligned the genetic positions across the datasets, and

then we performed meta-analysis using METASOFT software[45]. To replicate the findings, we conducted a meta-analysis with an independent study of imputed genotype data from 11,424 Caribbean Hispanic (CHI) individuals (full details of array genotyping, imputation, and QC are described elsewhere[46]). We used the random effects approach proposed by Han and Eskin (RE2) that is more powerful than traditional random-effect models for detecting small-effect heterogeneous genetic associations[45]. The RE2 model assumes no heterogeneity under the null hypothesis, the average genetic effect (μ) and between-study variance (τ^2) are zero: $H_0: \mu = 0 \; and \; \tau^2 = 0$ vs $H_1: \mu \neq 0 \; or \; \tau^2 > 0$. (Ancestry and statistical analysis methods are described in detail in Supplemental methods).

2.4 Adjustment for multiple testing and power analysis

Because of the highly correlated tests in admixture mapping analysis, we implemented the STEAM software to estimate the admixture mapping significance threshold and control the family-wise error rate at level 0.05[47]. To calculate an appropriate significance threshold for admixture mapping STEAM accounts for the number of ancestral populations, generations since admixture, population structure, and density of markers tested[47]. We performed power analysis by using multi-ancestry admixture mapping (PAMAM) software[48].

2.5 Fine Mapping

Admixture mapping identifies regions of interest that may span multiple megabases (mB). We used a multipronged fine-mapping strategy to translate the findings from associated genetic regions to potential causal gene(s). First, to identify risk loci that correlate with ancestral background within the relatively broad regions identified by admixture mapping (p-value < 0.001), we conducted what we refer to as an “ancestry-aware regression analysis”. In this model, affection status is modeled as a function of the risk genotype, LA and an interaction term (LA x genotype). Significance of the interaction term suggests that association between genotype and the risk of AD depends on the ancestral background of the genotype. Specifically, LA modifies the effect of the risk loci such that risk allele has a modified effect on the risk of AD with increasing or decreasing dosage of specific ancestry. This can be an effective fine-mapping tool because conditioning on LA removes signals at variants that are in LD with the causal variant due only to the admixture of the population[49].

We conducted ancestry-aware analyses in the AA imputed datasets with the local ancestry and genotype (G) as main effects and the interaction term, also adjusted for age, sex, and genome-wide ancestry (PC1:3) and included the genetic relationship matrix (GRM) as a random effect to adjust for the sample relatedness (equation 2). We used a parametric bootstrap[50] to get precise p-value for each test, using a large number of bootstrap permutations that substantially exceeds the number of independent tests in the prioritized genetic regions. An adjusted p-value was calculated by multiplying the p-value obtained through the parametric bootstrap by the number of independent tests. To identify the number of independent tests we implemented a linkage disequilibrium (LD)-based pruning step to remove SNPs in high LD (r^2>0.1) with any nearby SNP (< 250 Kilobase), based LD estimates from publicly available 1000 Genomes phase3 ASW (African ancestry in Southwest USA) and YRI (Yoruba in Ibadan, Nigeria) populations data (The code used

in this study to perform admixture mapping and ancestry-aware analysis is available here https://github.com/hihg-um/ad-admixture-mapping).

$$AD \sim age + sex + PC1{:}3 + G + LA_{AF} + G{*}LA_{AF} + GRM \quad LA_{AF} \in \{0,1,2\} \qquad \text{(equation 2)}$$

For further prioritization of ancestry-aware analysis results, we used the web-based platform FUMA to prioritize a set of variants and genes using the functional annotation and the LD pattern with the lead variant (r^2>0.6)[51]. All variants were annotated by ANNOVAR, combined annotation dependent depletion (CADD) scores, and RegulomeDB (RDB) scores[52–54]. We also examined genes for differential expression using results from RNA sequencing of peripheral blood collected from 234 AA (115 AD cases, 119 controls) and 240 NHW (121 AD cases, 119 controls). Analyses and datasets are described elsewhere[55]. Finally, we validated the prioritized genes using Accelerating Medicines Partnership in Alzheimer's Disease (AMP-AD) AGORA knowledge portal (https://agora.ampadportal.org/genes), where the data on differential expression of genes across the brain regions from NHW individuals are available. These data are from Mount Sinai Brain Bank Study (MSBB) (number of individuals = 164), Religious Orders Study (ROS) and Memory and Aging Project (MAP) (number of individuals = 241), and Mayo RNASeq Study (number of individuals = 179).

3. RESULTS

3.1. Estimates of Genetic Ancestry

The average proportions of African and European local ancestry across the 17 cohorts, based on the autosomes only, were similar (Supplemental Figure 2, Supplemental Table 2). The average African ancestry proportion across all studies was 0.782 (SD=0.023). We did not observe any significant differences in global ancestry proportions (based on average LA) between cases and controls. The overall African-ancestry proportion in cases was 0.783 (SD = 0.032) and in controls was 0.782 (SD = 0.024).

3.2. Admixture Mapping

We estimated 7.3e-5 as a threshold for statistical genome-wide significance for this study using the analytic approximation approach in STEAM software. Using this threshold, we identified two loci genome-wide significantly associated with AD: one on chromosome 17p13.2 (p-value = 2.20×10^{-5}) and one on 18q21.33 (p-value = 1.20×10^{-5}) (Figure 3). Both regions were genome-wide significant in the meta-analysis of our AA results with results from the CHI dataset from Sariya et al.[46] (Supplemental Figure 3) (17p13.2: p-value = 2.01×10^{-5}; 18q21.33: p-value = 1.96×10^{-5}).

3.3. Fine Mapping

The admixture blocks span the large genomic region, so identifying the causal gene(s) from the admixture mapping is challenging. The mean of admixture block sizes in the largest dataset of AA individuals (~2,900) in our study was ~36Mb. Supplementary Figure 4 illustrates the distribution of the admixture block sizes in AAs. In this study, we leveraged

several sources of information to prioritize genes and causal variants. We overlapped information from ancestry-aware regression analysis followed by comprehensive *in silico* fine-mapping, and differential gene expression data to prioritize AD related genes and variants at the loci identified through the admixture mapping.

3.3.1 Ancestry-aware Analysis—We defined two regions of small p-values (p-value < 0.001) around the genome-wide significant results at chromosome 17p13.2 (spanning from ~4.8 Mb to ~8.6 Mb) and at chromosome 18q21.33 (spanning from ~58.0 Mb to ~61.0 Mb) for fine-mapping (build of GRCh37). The ancestry-aware regression model identified a significant interaction term (G x LA) on chromosome 17p13.2 with the genotypes of the lead SNP rs72835045 (β = 0.97; SE = 0.28; p-value=7.93×10^{-5}; parametric bootstrap FDR < 0.05). Figure 4 illustrates the ancestry-aware regression model results across the chromosome 17p13.2 locus for the G X LA interaction term. Significance of the interaction term at the chromosome 17p13.2 locus implies that association between rs72835045 genotype and the risk of AD depends on the LA background of the genotype. Specifically, LA modifies the effect of the rs72835045 genotype risk allele (A) such that allele "A" has a greater effect on the risk of AD with increasing dosage of European ancestry (or conversely decreasing dosage of African ancestry). We did not observe any significant G x LA interactions for the chromosome 18q21.33 locus (Supplement Figure 4).

3.3.2. Functional Mapping and Annotation—FUMA identified 157 variants, which are in LD (r^2>0.6) with the lead variant rs72835045 on chromosome 17q. The resulting output of the interaction model for these variants is shown in Supplemental Table 3. We used pre-calculated LD structure based on 1000G European populations as the European local ancestry were increasing the AD risk in rs72835045_A allele carriers. Figure 5A illustrates the distribution of 157 variants across the rs72835045 genotype LD region. There are 6 exonic variants, two of which are missense variants (rs2283568 in the *INCA1* gene, rs74744272 in the *PFN1* gene). Both missense variants have CADD score > 10, and missense variant rs2283568 has a regulatory potential with RDB score of 2b. The synonymous exonic variant rs17707385 in *KIF1C* gene has the highest CADD score of 18.04 and the RDB score 1f. Functional annotation shows that in total 23 variants have a strong regulatory potential with the RDB score ≤ 2, and 18 variants have possible deleterious effect with CADD score ≥ 10. The whole list of annotated variants by ANNOVAR, CADD scores, and RDB scores are presented in the Supplemental Table 4.

FUMA mapped the variants to 14 genes based on ANNOVAR annotation. The FUMA GENE2FUNC process provided tissue specific expression patterns based on GTEx v6 RNA-seq data. Figure 5B illustrates the expression levels for 14 genes in the heatmap for 13 brain tissue types. Eight genes (*PLD2, KIFC1, SLC25A11, PFN1, RNF167, SPAG7, CAMTA2,* and *MINK1*) show consistent high expression pattern among all brain tissue types.

3.3.3. Differential Gene-expression Analysis

Peripheral blood from AA and NHW individuals: We examined the genes on the chromosome 17p13.2 that were in LD with the rs72835045 genotype and all the genes located on the chromosome 18q21.33 that spans the admixture mapping signal.

We identified differential expression (DE) for three genes in the chromosome 17p13.2 locus in the joint AA and NHW gene-expression analyses and DE in one gene in the chromosome 18q21.33 locus in the NHW gene-expression analysis (Table 1). All genes in the chromosome 17p13.2 locus were upregulated in AD and the gene on the chromosome 18q21.33 locus was downregulated in AD. A complete list of expression results for the genes on the chromosome 17p13.2 and 18q21.33 is provided in Supplemental Table 4.

AMP-AD data: We queried the 14 genes from chromosome 17p13.2 locus and 11 genes from chromosome 18q21.33 using web-based database Agora to further investigate the differential gene expression in 7 types of post-mortem brain tissues, which were dorsolateral prefrontal cortex (DLPFC) from ROSMAP, temporal cortex (TCX) and cerebellum (CBE) from Mayo, and inferior frontal gyrus (IFG), superior temporal gyrus (STG), frontal pole (FP), and parahippocampal gyrus (PHG) from MSBB. Out of 14 genes from the chromosome 17p13.2 locus, eight genes showed significant DE in various brain tissues, where four of them (*SLC25A11, MINK1, KIF1C,* and *CAMTA2)* showed significant DE in more than one brain tissue type. Seven genes from the chromosome 18q21.33 locus showed significant DE, where five genes showed DE in two type of tissues. Supplemental Figures 6A and 6B shows the forest plots of eight genes from the 17p13.2 locus and five genes from the 18q21.33 locus, respectively.

4. DISCUSSION

We identified two genome-wide significant admixture mapping signals: on chromosomes 17p13.2 and 18q21.33. Our results showed that 18q21.33 locus contributes to increased risk for AD in AAs with the increased frequency of African local ancestry, whereas European local ancestry increases the risk effect of the 17p13.2 locus. These genetic regions are novel in AA populations. Our study with the increased sample size and new ancestry-aware statistical approaches was able to identify the regions that were not previously found in AA genome-wide association studies or the previous AA admixture mapping study[7,12].

The finding at the 17p13.2 locus is intriguing because this genetic region was identified as a genome-wide significant AD risk locus in three NHW AD meta-analysis of GWAS's with sample sizes over 100,000[4,6,56]. Our follow-up ancestry-aware analysis narrowed the 17p13.2 locus to an interval of 200 kilobase, that is likely to harbor risk variants explaining the admixture peak at the 17p13.2 locus. We compared the variants prioritized through the ancestry-aware fine mapping with previous studies in NHW and AA AD GWAS studies[3,5]. The lead marker showing significant interaction with European local ancestry (rs72835045; p-value=7.93×10^{-5}) was significantly associated with AD risk in NHW GWAS study[3] (p-value = 3.28×10^{-4}), whereas it was not found as a risk marker in AA GWAS study[5] (p-value=0.61). Supplemental Table 6 summarize and compare the prioritized markers through this study with NHW and AA GWAS studies[3,5]. Our findings at the 17p13.2 locus suggest that AA samples inherit their risk allele from European ancestors and have a lower risk of AD if they inherited a segment of African ancestry at the 17p13.2 locus. This finding supports the hypothesis that the variation of both genetic risk loci and their effect across the populations is most likely related to genetic ancestry that is surrounding the risk locus (local ancestry) and not related the overall ancestry (global ancestry)[9,10].

Our fine-mapping and multi-omics approach homed in on three genes at the 17p13.2 locus: the Kinesin Family Member 1C *(KIF1C),* Profilin 1 (*PFN1*) and Misshapen Like Kinase 1 (*MINK1*). These genes show strong evidence of regulatory potential and deleterious effect on protein function. All genes are highly expressed in several GTEx brain tissue types. *KIF1C and MINK1* genes were differentially expressed between AD and non-AD brain tissues, and additionally *KIF1C* showed significant differential expression in blood. The *KIF1C* variant rs17707385 has strong evidence of regulatory potential and deleterious effect on protein function and was in strong LD ($r^2 = 0.62$) with the lead variant from the ancestry-aware regression analysis. *KIF1C* encodes a motor protein involved in retrograde transport from the Golgi to the endoplasmic reticulum, suggesting a role of intracellular trafficking processes[57]. Studies have also shown a link between the deficits in the active transport of gene products and neurodegenerative disorders[58]. The *PFN1* gene encodes a member of the profilin family of small actin-binding proteins involved in actin polymerization, and its dynamics are essential for the basic cellular activities[59]. Rare, missense mutations within the *PFN1* gene were associated with the neurodegenerative disorder Amyotrophic lateral sclerosis[60]. A recent AD study found a variant within the *MINK1* gene with significant pleiotropic genetic effect in AD and cardiovascular disease[61]. Intriguingly, the pleiotropic *MINK1* gene variant identified by Broce et al and colleagues is in strong LD (r^2=0.97) with the lead variant identified in ancestry-aware regression analysis.

Our follow up using available AD gene expression data revealed an interesting candidate gene at the 18q21.33 locus: *BCL2*. This gene is highly expressed in several brain tissue types and was differentially expressed between AD and non-AD brain tissues and blood. *BCL2* gene play an important role in regulating the autophagy[62]. Studies have shown that overexpression of *Bcl2* gene improves the place recognition memory in mice, protects neuronal cells *in vitro* from the Aβ-related death, influences the tau processing, and reducing the number of NFTs[63,64].

Our study, with the substantially increased sample size, found nominal significance for four regions out of seven regions that were identified in the previous AA admixture mapping study[12]. All nominally replicated regions showed a similar direction of effect. Notably, the *ABCA7* region showed the strongest association compared to other regions ($p - value < 2 \times 10^{-3}$). The sample size of this study was much larger (~65% more) than the previous AA AD admixture mapping study. Additionally, the approaches were different. In our study, the association between AD and local ancestry was assessed within each dataset separately by conducting logistic regression controlled for age, sex, global ancestry (PC1:3), and known and cryptic relatedness, followed by meta-analysis. The study by Hohman et al. did not account for global ancestry in their models, and they performed joint analysis of a combined dataset using Wilcoxon rank-sum test.This study has several limitations. First, our dataset is underpowered to identify association between the local ancestry and AD when the risk-allele frequencies and their effect sizes are similar across the ancestral groups (e.g., African and European). Larger samples will be required to detect these more subtle AD-associated admixture blocks. Second, we combined the AA samples in one discovery dataset to maximize the power of the study and relied on NHW and AA GWAS and gene expression data from peripheral blood and AMP-AD data for validation[3,5,55,]. An additional

independent dataset is needed for replication analysis. Third, ancestry-aware fine-mapping analysis is not well powered in our study for the large genomic region on chromosome 18q21.33 prioritized through admixture mapping. Increasing the sample size in the AA dataset can help to translate the findings from associated genetic regions to potential causal gene(s).

We provided robust evidence for two genomic regions to be associated with the AD risk and prioritized several candidate genes and markers through the fine-mapping approaches. Further investigation of the prioritized loci through long-read sequencing may allow for more comprehensive and accurate detection of variation, especially structural variation. As a next step, integrating the prioritized variants with the cell-type specific data can help to translate the findings into clinically actionable gene sets.

In summary, we identified two novel genome-wide significant loci (17p13.2 and 18q21.33) associated with the increased risk of AD in AAs. Our study generalized known European genetic AD risk locus (17p13.2) to the AA population. The lack of identification of the 18q21.33 region previously in large NHW and incomparably smaller AA GWAS studies, and excess of African ancestry in AD AA individuals at this locus suggest that genetic risk factor(s) is(are) likely to be African-ancestry specific. We found that the overall proportion of African ancestry does not differ between the cases and controls. The similar proportions of parental ancestries in AA cases and controls suggest that African genetic ancestry alone is not likely to explain the AD prevalence difference between AA and NHW populations. Thus, it is likely that social and environmental determinants in concert with the ancestral and genetic factors influence the susceptibility to AD[65].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1. **Systematic review:** The authors reviewed the literature using PubMed. The African American (AA) population is substantially underrepresented in Alzheimer disease (AD) genetic studies, yet its admixed genetic ancestry provides a unique opportunity to identify novel genetic factors associated with AD and related to genetic ancestry.
2. **Interpretation**: This study identified two genome-wide significant loci on chromosomes 17p13.2 and 18q21.33. These genetic regions are novel in AAs. Ancestry-aware approach showed that AA individuals have a lower risk of AD if they inherited African ancestry admixture block at the 17p13.2 locus.
3. **Future directions:** Further investigation of the prioritized loci through long-read sequencing may allow for more comprehensive and accurate detection of variation, especially structural variation. As a next step, integrating the prioritized variants with the cell-type specific data can help to translate the findings into clinically actionable gene sets.

Highlights

- We identified two genome-wide significant admixture mapping signals: on chromosomes 17p13.2 and 18q21.33, which are novel in African American populations.
- Our ancestry-aware regression approach showed that AA individuals have a lower risk of AD if they inherited African ancestry admixture block at the 17p13.2 locus.
- We found that the overall proportion of African ancestry does not differ between the cases and controls that suggest African genetic ancestry alone is not likely to explain the Alzheimer disease prevalence difference between African American and non-Hispanic White populations.

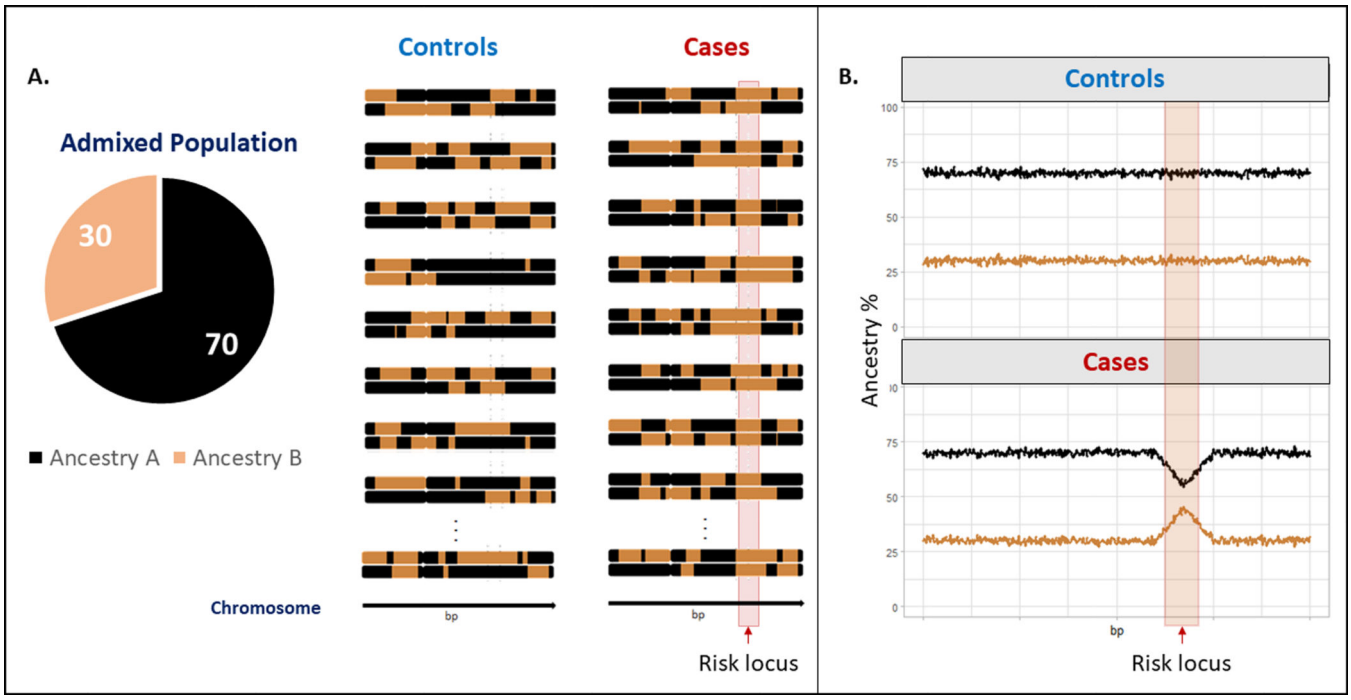

Figure 1.

(A) An example of a two-way admixed population ("A" and "B") with the uniform distribution of the local ancestries in controls and excess of the "B" local ancestry at the risk locus in cases. (B) The proportion of "A" and "B" ancestries in cases and controls across the chromosome with the spike of "B" ancestry at the risk locus in cases.

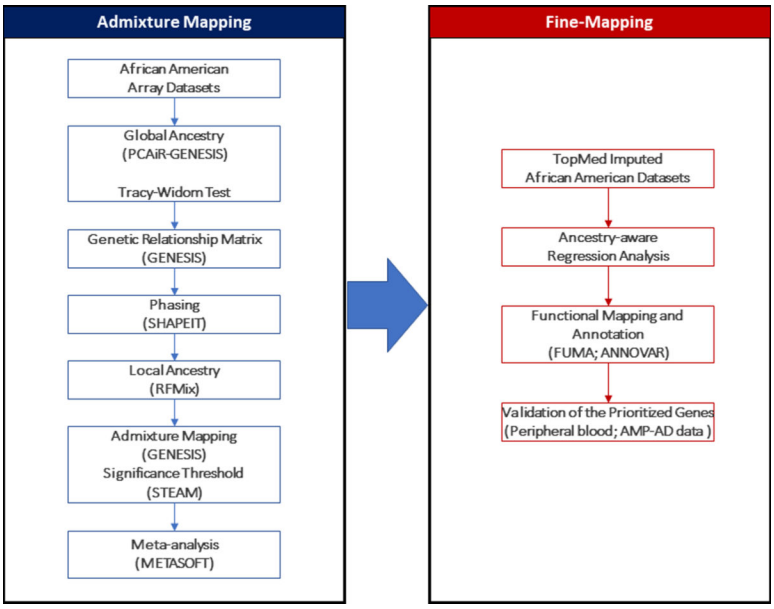

Figure 2.
Schematic illustration of the admixture mapping and fine-mapping analysis.

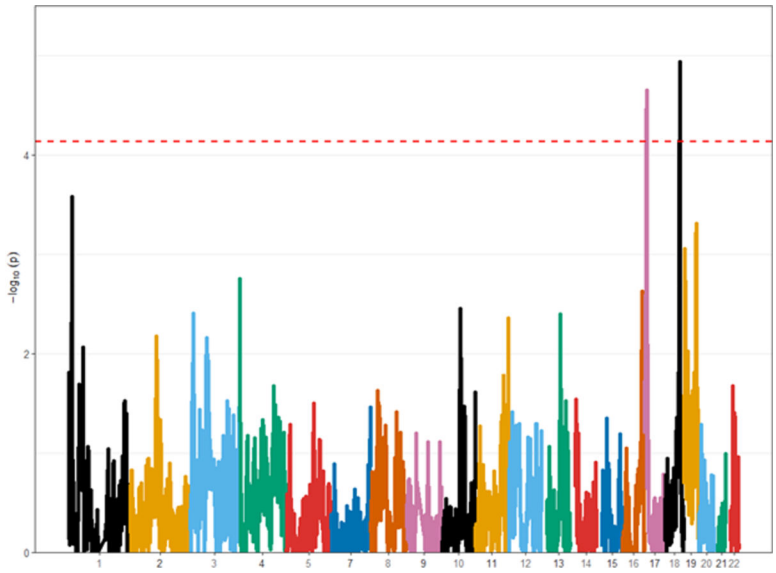

Figure 3. Admixture mapping Manhattan plot of meta-analysis African American datasets.
Genomic coordinates are displayed along the X-axis, with each color representing a different chromosome. Negative logarithm of the association p-value for the ancestral allele is displayed on the Y-axis. The red dotted horizontal line represents the significance threshold after multiple testing correction, i.e. those dots falling above the line are considered study-wise significant

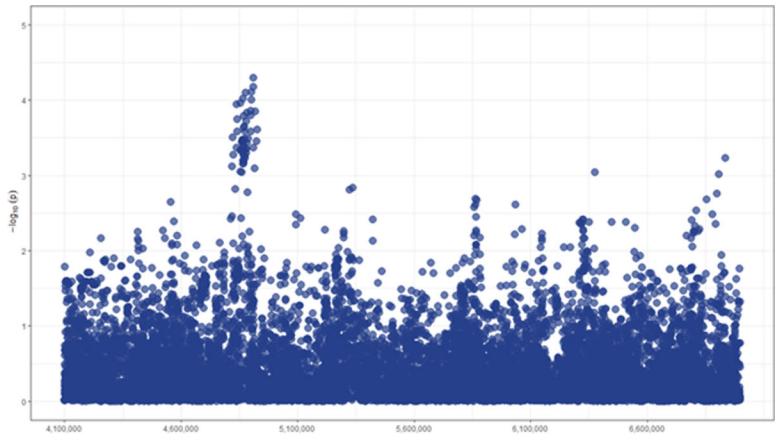

Figure 4. Region plot of ancestry-aware regression analysis for the 17p13.2 region.
Genomic coordinates are displayed along the X-axis. Negative logarithm of the ancestry-aware regression approach p-value for the interaction term (G x LA) is displayed on the Y-axis.

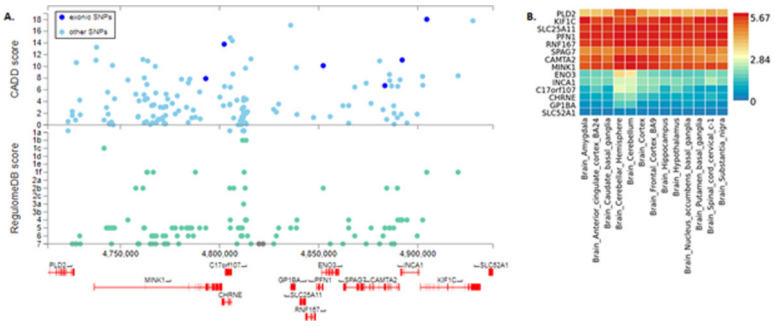

Figure 5. Follow up 17p13.2 locus using functional mapping and annotation

A-Regional plot of the 17p13.2 locus, which includes prioritized genes and variants with CADD and RequlomeDB scores. B-Gene expression heatmaps constructed with GTEX v6 13 brain tissues types. Genes and tissues are ordered by clusters for the GTEX heatmap.

Table 1.

Significantly differentially expressed genes between Alzheimer disease and controls in non-Hispanic Whites (NHW), non-Hispanic Whites and African Americans joint analysis (NHW+AA).

Gene	Locus	Fold Change	P-Value	FDR	Study
GP1BA	17p13.2	*1.21*	*0.0036*	*0.03*	*NHW+AA*
SLC25A11	17p13.2	*1.08*	*0.0063*	*0.05*	*NHW+AA*
KIF1C	17p13.2	*1.07*	*0.0068*	*0.05*	*NHW+AA*
BCL2	18q21.33	*−1.17*	*0.0006*	*0.04*	*NHW*