Assessing a Network-Specific Polygenic Risk Score for Alzheimer's Disease in the Midwestern Amish and Across Diverse Ancestries

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Background: Alzheimer's disease (AD), the most common type of dementia, has a complex etiology with a strong genetic component. Many genetic risk variants for AD have been identified including *APOE*, the largest known genetic risk factor. However, most of this research has examined only broad populations of individuals with European ancestry and there is mounting evidence that effect sizes vary by population. Here, we investigate the transferability of polygenic risk scores (PRSs), including a network-specific PRS, in the midwestern Amish and across diverse ancestries.

Method: Data from 1,091 Amish adults with AD diagnosis by consensus were considered for analysis from the Collaborative Amish Aging & Memory Project. Genotype data (Illumina GSA and MEGA^{EX}) were imputed using the Haplotype Reference Consortium panel. We also analyzed 15,745 individuals from the Alzheimer's Disease Sequencing Project (ADSP) r3 with three predominant race/ethnicity groups: African American (AA; n=2,937), Hispanic (n=3,047), and non-Hispanic White (NHW; n=9,708). An AD network-specific PRS was constructed by including variants from AD-implicated molecular networks in the Kyoto Encyclopedia of Genes and Genomes. A comprehensive pruning and thresholding PRS considering all variants was calculated for comparison. Effect estimates from Kunkle et al. (2019) were used. PRS-only models, sex and age covariate-only, and full models were constructed for each group and the full ADSP data.

Results: We observed that PRS-only predictive ability was similar between the comprehensive PRS (AUC=0.56) and the network-specific PRS (AUC=0.55) in the full ADSP r3 data. Network-specific PRS performance was similar in the Amish (AUC=0.55). However, we observed better predictive ability with the comprehensive PRS compared to the network-specific PRS in each of the subgroups (Amish AUC: 0.61 vs. 0.55; NHW: 0.70 vs. 0.53; AA: 0.56 vs. 0.53, Hispanic: .61 vs. 0.56). These trends were consistent after inclusion of sex and age covariates.

Conclusion: We demonstrated that a network-specific PRS performed similarly to a comprehensive PRS in a combined diverse population and the Amish but confers less predictive ability when investigating individual subgroups. Thus, the network-specific PRS has potential as a component of a risk model in diverse populations because it may successfully account for effects that are consistent across subgroups.

Mosaic Loss of Chromosome Y in Peripheral Blood Cells and Cognitive Status in the Amish

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Background: Mosaic loss of chromosome Y (mLOY) refers to acquired aneuploidy in a fraction of somatic cells. In aging men, mLOY has been suggested as a possible biomarker for increased risk of numerous diseases, including Alzheimer's disease (AD). We investigated mLOY as a risk factor for AD in the Mid-Western Amish, a founder population with homogeneous lifestyle, reducing the effect of confounding environmental factors.

Method: The median of the log R ratio (mLRRY) from SNP array data within the male-specific region of chromosome Y was used to measure the degree of mLOY. A mLRRY value lower than the 99% confidence limit of the experimental distribution was scored to estimate the frequency of mLOY. The cognitive status was assigned via consensus review of cognitive examination results. Men in 3 age groups (65-74, 75-84, >=85) were included. The linear mixed model with a polygenic component to account for relatedness and a transformation to address non-normality was used to estimate familial correlations and heritability. A likelihood ratio test of association was performed with age at blood sampling and age of cognitive exam as covariates.

Result: After extensive QC, 533 participants (mean age=75.42±6.17) were included and 39 (7.9%) had a detectable level of mLOY. mLOY frequency increased with age ($p<1.0x10^{-6}$): 1.0% (65-74; n=103), 8.4% (75-84; n=334) and 14.3% (85+; n=96). Heritability of mLOY was 0.53 and the residual sibling correlation was 0.27 (n=201, $p<1.0x10^{-2}$). A subset of 423 individuals were assigned to the cognitively impaired (n=134) or unimpaired (n=289) groups and mLOY was significantly higher in the cognitively impaired group (p<0.0001). After adjusting for covariates and the relatedness, the association was no longer significant (p=0.098), but the direction of effect was the same.

Conclusion: The sibling correlation was significant for mLOY. We observed the same trend as reported in other European descent populations: mLOY increased with age and was more frequent in cognitively impaired individuals. The frequency of mLOY in Amish was lower than reported, overall and in each age stratum. Our results along with the lower prevalence of AD in Amish reinforces mLOY as a promising biomarker for the risk of AD.

Detecting genetic loci for preservation of cognition in the Midwestern United States Amish

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Background: Alzheimer's Disease (AD) is the most common form of dementia and has limited treatments. While AD risk has a large genetic component, under 50% of the genetic risk has been identified. By focusing on identifying genetic variants that delay or prevent the onset of AD, our goal is to identify new associated genes and variants. To detect such loci, we studied cognitive preservation in the Midwestern Amish, a genetically and culturally isolated population of European descent.

Methods: We studied 946 Amish individuals (ages 76-95) from Ohio and Indiana. Participants were classified as cognitively impaired (33.8%) or cognitively unimpaired (66.2%) by consensus review of cognitive examinations. These individuals were all connected in a 15-generation 8,222-person pedigree. This pedigree was divided into 104 sub-pedigrees via PedCut for linkage analysis. MERLIN was used for autosomal linkage analysis, while MINX was used for X-chromosome linkage analysis. The association analysis, corrected for genetic relationship, used GENESIS for autosomes and XWAS for the X chromosome.

Results: Over 250,000 SNPs were used for association and two-point linkage analyses, and a subset of 5,294 uncorrelated SNPs was used for multipoint linkage analyses. Linkage analysis identified significant (LOD > 3.3) regions on 15 different chromosomes, with the highest two-point heterogeneity LOD score (HLOD = 5.85) on chromosome 2 (~79Mb) and highest multipoint HLOD (3.55) on chromosome 12 (~25Mb), neither overlapping with known AD genes. Two linkage results overlapped with known AD genes (Chr 6: CD2AP; Chr 11: PICALM). Significant ($p \leq 6.4x10^{-7}$) and suggestive ($p \leq 1x10^{-4}$) thresholds for association were determined using SimpleM. While no significant associations were found, suggestive associations were found for 103 SNPs (11 loci) across 10 chromosomes. Three of these (chr 11: MS4A2; chr 14: SLC24A4; chr 16: IQCK) fall near known AD genes. These significant and suggestive regions are being followed up currently with fine mapping.

Conclusion: Preliminary analyses suggest that using cognitive preservation as our phenotype of interest identifies both known AD loci and novel regions that warrant further evaluation and may lead to a further understanding of both AD and cognitive preservation.

Distinct features of rapidly progressive Alzheimer's disease

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Background: Rapidly progressive Alzheimer's disease (rpAD) has been recognized as a subtype of Late-Onset Alzheimer's disease (LOAD) characterized by accelerated cognitive decline and/or reduced survival. The cause of variable progression rates of AD is largely unknown, and information regarding unique clinical features of rpAD is limited in longitudinal cohorts.

Method: A retrospective analysis was performed on AD patients in the National Alzheimer's Coordinating Center (NACC) database from 2015 to 2021. Patients with rpAD were identified by reduced survival time (time from symptom onset to death <= three years) or accelerated cognition decline (defined as Mini-Mental State Exam [MMSE] decrease >= 6 points/year or Clinical Dementia Rating scale [CDR] global score increase to 2 or 3 within three years). Demographic, clinical, and neuropsychological measurements were compared between patients with rpAD, typical "slow" progressive AD, and normal controls. rpAD patients and normal controls with Whole Genome Sequencing (WGS) data available from the Alzheimer's Disease Sequencing Project (ADSP) were selected for a pilot genome-wide association study (GWAS).

Result: Among 43,746 NACC participants, 983 patients met our criteria for rpAD. rpAD patients had a mean survival of 2.8±0.5 years and their decline in MMSE was 6.4±5.9 points/year. Compared to controls, rpAD patients were older (72.6±8.6 vs 70.0±8.6, $p < 0.001$), more likely to be male (39% vs 33%, $p < 0.001$) and had fewer years of education (14.6±3.6 vs 15.9±3.0, $p < 0.001$). Compared to AD patients who progressed slowly, rpAD patients showed a more rapid decline in neuropsychological tests measuring working memory, language, attention, and executive function (p values < 0.001). GWAS was performed on 175 rpAD patients and 525 age- and sex-matched NACC controls. 49 genetic variants showed significant associations with rpAD (p-values < 1×10^{-5}).

Conclusion: In the longitudinal NACC cohort, rapidly progressive AD constitutes an important subset, featuring a short survival with rapid decline of cognitive and neuropsychological functions. Previously known genetic risk variants for AD were not found in this rpAD cohort. Further examination of rpAD cohort could help identify unique mechanisms that drive the rate progression in AD for different groups of patients.

Identifying context-specific genetic variants and molecular pathways associated with resilience to Alzheimer's disease in the induced immune response

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Background: It is increasingly recognized that neurodegenerative pathologies consistent with Alzheimer's disease (AD) are common in older adults even among those without any cognitive symptoms. Genome-wide association studies (GWAS) have identified loci that are associated with better-than-predicted cognitive performance for a given level of neuropathology, sometimes described as resilience to AD symptoms. Transcriptome-wide association studies (TWAS) provide powerful mechanistic insights possibly bridging the association between loci and phenotype by implicating genes. We hypothesize that genetic variants influence resilience phenotypes by altering the function and response of monocytes, one of the premier immune cells involved in neuroinflammation. As a step toward testing this hypothesis, we have developed monocyte TWAS reference panels based on expression from a naïve state and following *in vitro* stimulations which can reveal important associations only seen in an inflammatory context.

Methods: Genetic data of CD14+ monocytes produced by Fairfax et. al 2014 were obtained and SNPs not directly genotyped imputed on the Michigan Imputation Server using samples available on the Haplotype Reference Consortium. Plink 1.9 was used for standard quality control. Corresponding monocyte expression data was downloaded from ArrayExpress, and a custom script was used to match Illumina microarray probe IDs to probe sequences, gene names, and genomic positions using the IlluminaHumanV4.db R package. Probes not overlapping with regions containing common SNPs (MAF > 0.05) and mapping to single genes were extracted. Cis-eQTL analysis was then performed assessing the additive relationship between gene expression values and genotypes using the MatrixeQTL R package. The final gene expression prediction panels were constructed by fitting elastic-net regularized regression models using the PredictDB pipeline.

Results: Our data processing and quality control pipeline has been validated through showing concordance between our results and those of the Fairfax group with respect to the rs1179625 SNP and its context-specific direction of effect on the gene expression of *HIP1*. Further, genotype imputation enabled the identification of thousands of additional eQTLs and response-eQTL's (re-eQTL's) across the genome—illustrating the importance of studying these cells in an appropriate environment. TWAS analyses of their collective impact on resilience phenotypes are ongoing.

Conclusion: We expand the available tissues and cell types for TWAS of AD by generating reference panels that account for the dynamic biology of monocytes in different states. These panels enable analyses that may have specific importance for cognitive resilience, and may provide concrete biological mechanisms as to how some individuals can manifest the neuropathology of AD and yet remain asymptomatic.

Leveraging the use of meta-analysis summary statistics to improve gene expression prediction models

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Background: Genetically regulated gene expression as assessed via Transcriptome-wide association studies (TWAS) can be used to elucidate the mechanistic basis of Alzheimer's Disease. A limitation of current TWAS approaches is the requirement for individual-level datasets with both genotypes and gene expression measures to produce effective prediction models. We sought to improve the predictive performance of existing gene-based models by leveraging easily accessible summary statistics that are powered by large sample sizes.

Methods: Brain *cis*-eQTL data produced from a large-scale meta-analysis was restricted to data from European-descent individuals and samples taken from Brain-Cortex (Average_N=2,547). The effect size estimates, and their standard errors from the individual cohorts (N=14) were used to re-run a meta-analysis excluding GTEx data via METAL. To perform gene-based elastic-net regressions using the produced summary statistics, the *lassosum* R package produced by Mak et al. 2017 was applied to genotype data from the 1,000 Genomes data (GRCh38) serving as a reference panel and GTEx_v8 genotype, normalized Brain-Cortex gene expression, and covariate data (N=205) serving as a testing panel for model validation and dynamic selection of the optimal mixing/penalty parameters. The maximum R2 produced by this pipeline was compared to elastic-net models generated by PredictDB using Brain-Cortex GTEx_v8 data where the mixing parameter was set at 0.5.

Results: Our pipeline produced gene-based models that had an improved predictive performance averaging 9.8% (SD: 7%) based on R2 over PredictDB models in 93.7% of genes tested (N=3,965) when restricting our pipeline to SNPs found in PredictDB. The optimal mixing parameter dramatically differed from PredictDB with a median of 0.009 highlighting the utility of including variants with small effects. Even restricting the mixing parameter to 0.5 for genes with a converged model, our pipeline outperformed PredictDB in 85% of genes (N=369). By examining expression prediction metrics for genes from the KEGG Alzheimer's Disease pathway (hsa05010), our pipeline had improved performance in 100% of matched genes (N=30).

Conclusion: We demonstrate improvement upon existing TWAS reference panels and increase gene-expression predictive performance by leveraging the power of summary statistics. Our findings show AD association studies based on TWAS approaches may be improved by meta-analysis reference panels.

A Haptoglobin (HP) Exon Deletion Polymorphism Alters the Effect of APOE Alleles on Alzheimer's Disease in European-Descent People with APOEε4

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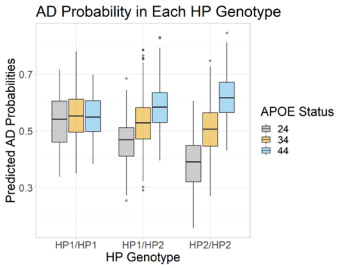
Background: Haptoglobin (HP) is an antioxidant of apolipoprotein E (APOE) – the strongest risk gene for sporadic Alzheimer's disease (AD). The *HP* gene has two functional alleles, *HP2* and *HP1*, which contains a two-exon deletion that changes its protein structure conformation. We hypothesize that this structural variation is associated with AD.

Method: To investigate this, we imputed the *HP* genotypes for 12,403 cases and 11,699 normal controls from the Alzheimer's Disease Genetics Consortium (ADGC), respectively within each cohort of 18 European-descent cohorts, using a custom reference panel. We then evaluated the association between *HP* genotype and the AD status using logistic regression, adjusting for sex, age, and the first 3 principal components.

Result: The imputed *HP1* frequency is 0.376. We found *HP* influences AD given an *APOEε4* genetic context. In individuals with ≥1 *APOEε4* allele (n=10,054), *HP1* homozygotes attenuate the effect of the second *APOE* allele; both the protective effect of the *ε2* allele and the risk effect of the *ε4* allele are dramatically reduced (odds ratio, OR=0.92, p=0.415 of *ε2* versus *ε3*, OR=1.09, p=0.415 of *ε4* versus *ε3*). However, the *HP2* allele accentuates the effect of the second *APOE* allele, both the protective effect of the *ε2* allele and the risk effect of the *ε4* allele (OR=0.80, p= 0.003 of *ε2* versus *ε3*, OR=1.25, p=0.003 of *ε4* versus *ε3*). This effect is even stronger in *HP2* homozygotes (OR=0.64, p=0.003 of *ε2* versus *ε3*, OR=1.55, p=0.003 of *ε4* versus *ε3*). In addition, we analyzed time to AD diagnosis with a cox proportional hazard regression model within the more consistently examined National Alzheimer's Coordinating Center (NACC) cohorts (n=7,448). A cox model shows that *HP2* alleles additively decrease the hazard of AD (hazard ratio=0.94, p=6.85e-3).

Conclusion: *HP* impacts AD risk in people with *APOEε4*. Furthermore, this risk is different in people with *APOEε24*, *APOEε34*, and *APOEε44* genotypes. Though the mechanism still awaits investigation, based on the current knowledge of HP function our results suggest a possible differential anti-oxidative ability of HP proteins for distinct APOE proteins. As such, the HP protein may be an imminently translatable therapeutic target for AD in *APOEε4* carriers.


AD Probability in Each HP Genotype
Predicted AD Probabilities
0.7
0.5
0.3
HP1/HP1
HP1/HP2
HP2/HP2
HP Genotype
APOE Status
24
34
44

Modeling gene expression on the X chromosome in the brain for transcriptome-wide association studies

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Background: Analysis of sex chromosomes is under-reported in Alzheimer's disease (AD) studies. As we gain more knowledge of disease associations and tissue-specific regulatory effects of autosomal loci, there is a growing interest in building prediction models of gene expression in the brain to model the cumulative functions of non-coding variants on the sex chromosomes. Transcriptome-wide Association Studies (TWAS) can identify disease-associated genes using these prediction models built for specific tissues by integrating genotype, imputed gene expression, and phenotype information. A key challenge of this approach for sex chromosome analysis is how to model copy number differences between males and females: genetic variants on the X chromosome are hemizygous for males, while females are heterozygous or homozygous diploid.

Method: We explore modeling approaches on the X chromosome using WGS and RNA-seq data in 13 Brain sub-regions retrieved from the GTEx project, currently restricting analyses to males. We used elastic-net regression, with a balanced LASSO-ridge penalty (mixing parameter α=0.5), as recommended by Wheeler et al. 2016. We tuned the penalization parameter λ for each gene in each tissue and assessed the model performance. There are 2392 genes on chromosome X, with only approximately 800 genes expressed in each GTEx brain tissue. SNPs (MAF>0.05) within the gene's 1M bp flanking window were used to train the model. We used mean squared error to determine the penalization parameter and select the best models.

Result: We built 761 prediction models in 13 Brain sub-regions on the expression of 503 genes. For example, we fit the prediction model of Gene COL4A6 (ENSG00000197565) in the Cortex, using 89 males. 83 cis-SNPs were kept in the final model (λ=0.015). The model R2 is 0.20, suggesting that 20% of the variance of expression levels in males can be explained.

Conclusion: These models predict the *cis*-regulated gene expression on the X chromosome in males. We can then use these estimated gene expression weights to impute male expression levels to identify (putative) causal genes for AD with TWAS.

Spatial Distribution of Rare Missense Variants Within Protein Structures is Associated with AD Risk.

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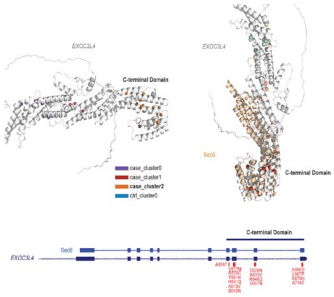
Background: Despite large genome-wide association studies, only ~30% of the heritability of Alzheimer's disease is explained. The Alzheimer's Disease Sequencing Project Whole Exome Sequencing (ADSP WES) has identified millions of genetic variants, over 97% of which are rare (MAF<1%), with 23% appearing in only one person. These rare variants could provide valuable information about new and previously identified risk loci for AD. However, current analysis strategies do not have power to detect associations for such rare variants.

Method: We have developed a protein structure-based approach that evaluates rare missense variants based on their spatial distribution in a known protein structure rather than on their allele frequency. We hypothesize that AD cases exhibit clustering of rare variants within a protein structure relative to cognitive normal controls. We applied our approach to the ADSP WES Discovery Dataset with 5,522 AD cases and 4,919 controls on 5,969 genes with known structures from the Protein Data Bank (PDB) and 17,450 genes with Alpha Fold2 predicted structures. Only rare variants(MAF<0.05) were included in the analysis. We validated the identified genes within an independent dataset with multi-ancestry individuals (ADSP WGS Replication) and a European-ancestry dataset with 15,078 individuals (ADSP validation dataset).

Results: We identified three significant genes (*TREM2*, *SORL1*, and *EXOC3L4*) and one suggestive gene (*CSF1R*) with AD-associated spatial clusterings from the ADSP WES data. For *TREM2*(PDB:6XDS; p-value=3.592E-07) and *SORL1*(PDB:3WSY;p-value=6.701E-05), two known AD genes, the spatial clusters are significant after excluding known AD risk variants, indicating the presence of additional low-frequency risk variants within these genes. *EXOC3L4*(AlphaFold2:Q17RC7;p-value=2.504E-05) is a novel AD risk gene that has a cluster of variants primarily shared by AD cases around the C terminal end of the Sec6 domain. This cluster replicated with significant associations in the ADSP WGS Replication and ADSP validation dataset.

Conclusion: Our result suggests multiple rare missense variants in *TREM2*, *SORL1*, *EXOC3L4*, and likely *CSF1R* are associated with AD risk by spatial clustering within the protein structure. These spatial clusterings have been replicated in two additional datasets. These spatial patterns may indicate potential functional regions in the protein structure associated with AD risk and are prime targets for further experimental validation.


EXOC3L4
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case_cluster1
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Sec6
C-terminal Domain
C-terminal Domain
Sec6
EXOC3L4

Title: African-ancestry based polygenic risk scores improve Alzheimer disease risk prediction in individuals of African Ancestry.

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Background: Polygenic risk scores (PRS) may be a useful approach to predict the risk of the complex disease and to be an important clinical tool for early intervention. PRS studies in Alzheimer Disease (AD) have focused on individuals of European Ancestry resulting in a >75% prediction accuracy. PRS generated from genome wide data in one population often provides reduced predictive accuracy in other populations. This is particularly problematic for underserved groups. In this study, we assessed and compared the PRS prediction accuracy of AD in individuals of African Ancestry (AA) using both AA and non-Hispanic White (NHW) Genome Wide Association (GWAS) studies.

Methods: As part of the Research in African American Alzheimer Disease Initiative (REAAADI) and ADGC, two TOPMED imputed AA datasets were generated (REAAADI:AD=234, cognitively unimpaired (CU)=676 and ADC9: AD cases=109, CU=224). We assessed the PRS using the effect sizes from summary statistics from the NHW (Kunkle et al. 2019) and the AA (Kunkle et al. 2021) studies. To model the effect of *APOE* we excluded *APOE* region in PRS constructing and included APOE alleles as separate terms in the prediction model. First, we generated PRS scores on the REAAADI dataset, and validated our model in ADC9 dataset. To assess the PRS performance, we employed the logistic regression modeling (covariates-only (age, sex, and PC1:3), PRS-only, and full (PRS+*APOE*+covariates) model) to construct receiver operator (ROC) curves.

Results: European ancestry-derived PRS has the poor prediction power (AUC=0.53) in the REAAADI dataset whereas the AA-derived PRS predicts better (AUC= 0.87). Further validation of the AA PRS in ADC9 dataset using covariates-only, PRS-only and full models validated that inclusion of African ancestry derived PRS significantly improves the accuracy of AD prediction in AA individuals ($AUC_{covariates\text{-}only}$=0.59; $AUC_{PRS\text{-}only}$=0.74 and AUC_{full}=0.81).

Conclusions: Our results showed that AA-derived PRS significantly improves AD risk prediction in AA individuals over European ancestry-derived PRS. Our findings demonstrate the importance of increasing the diversity in genetic studies to improve precision medicine approaches. Moreover, the development of more accurate PRS models that can detect the risk of AD in all in all groups paves the way for more accurate prevention, early detection, and intervention of AD.

Title: Fine-mapping of chromosome 9p21 linkage in Puerto Rican Alzheimer disease families.

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Background: We previously reported strong linkage on chromosome 9p21 in multiplex Alzheimer disease (AD) families from Puerto Rico. Nine families had the highest linkage contribution. 3/9 families shared seven coding variants with displayed evidence for AD association in similar ancestral population. Although these variants reside in genes with neuronal expression and functionality, they do not explain the linkage signal in all families. Here, we performed a fine-mapping analysis to identify non-coding variants that can contribute to the AD trait previously observed.

Method: We analyzed whole genome sequencing (WGS) from 9 families, 43 AD and 15 cognitively intact individuals. Chromatin interaction and cis-regulatory element (CREs) were used to prioritized relevant non-coding variants. Induced pluripotent stem cells (iPSC) derived neurons were generated from five individuals for characterization.

Result: We found an average of 300,000 non-coding variants per family. Following filtering steps including segregation, allele frequency and chromatin association, we identified ~400 variants per family. These variants were analyzed using the CREs derived from ENCODE, which left us with 31 (8%) variants falling in promoters. 5/31 variants were shared among four or more families, and fall in the promoter of genes *FBXO10*, *ACO1*, *NDUFB6* and *DNAJA1*. Six families shared variants in *FBXO10* making it our top candidate gene, a F-box protein family with a role in apoptosis and immunity. Interestingly, another F-box protein (*FBXL7)* has been associated with AD in a Caribbean Hispanic population.

Conclusion: These results reiterate the importance of family-based studies and fine-mapping as a resourceful tool to identified functional variants in AD. Transcriptomic profile and functional characterization of iPSC derived neurons will aid to understand the implication of prioritized genes in the linkage association previously observed.

Title: Exploring effect of known Alzheimer disease genetic loci in the Peruvian population

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Abstract Text:

Background: Native American populations are substantially underrepresented in Alzheimer disease (AD) genetic studies. The Peruvian (PE) population with up to ~80 of Amerindian ancestry (AI) provides a unique opportunity to assess the role of AI ancestry in AD. We performed whole-genome sequencing in PE case-control study to assess the effect of the known AD loci in PE population.

Methods: Whole-genome sequencing was performed in 96 AD cases and 145 unrelated cognitive healthy controls from PE population. We calculated the global ancestry (principal components) using the EIGENSTRAT approach. We tested 21 AD lead variants from the recent large non-Hispanic White (NHW) GWAS of AD (Kunkle et al. 2019). We performed association analyses using logistic regression model with accounting for age, gender, and population substructure (first three principal components). We used Bonferroni approach for multiple test correction.

Results: Logistic regression analysis confirmed association of *APOE* with AD (rs429358, OR=3.6, CI:1.9-7.0; pv < 8.4e-05) in PE population. *CLU* loci (rs9331896, pv=9.3e-04) passed the significance threshold after Bonferroni multiple test correction. Two AD loci demonstrated nominal associations (pv<0.05), which were *EPHA1* (rs10808026, pv = 0.028), and *FERMT1* (rs17125924, pv=0.022) loci.

Conclusion: Our results showed that known AD *APOE* and *CLU* loci are significantly associated with AD in PE population. Some of the genes demonstrated suggestive associations, but further analysis with a larger sample size is on-going to determine if these reflect true associations.

Title: Admixed ancestral composition with Amerindian predominance at the Peruvian Alzheimer Disease Initiative (PeADI)

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Background: Current genetic studies for AD and other dementias are making efforts to incorporate underrepresented populations including admixed Latinos. Peruvian population is characterized by admixed ancestry with a significant Amerindian component, which varies according to specific regions across Peru. The Peruvian Alzheimer Disease initiative (PeADI) was developed to ascertain a cohort for AD and other related dementias for genetic studies in Peru. We aim to determine the patterns of continental ancestry by regions across Peru.

Methods: Over the last 3 years, The PeADI study has recruited 212 unrelated cognitive participants through collaborative health centers and community outreach ascertainment strategies. Cases were assessed by neurologists following NINDS-ADRDA criteria. Controls were screened using MMSE, Clock drawing test and Pfeffer functional activities questionnaire. Genome-wide genotyping was performed by Illumina screening array. PC-AiR and model-based. The cohort was divided into five regions (Northern, Southern, Lima, Central Highlands, and Amazonian) based on place of birth of the participant or the ancient known ancestor.

Results: The global Admixture analysis showed that Peruvians have a substantial Amerindian component (63.6%), followed by European (35.9%), African (2.5%) and East Asian (2.1%) components. When analyzed by regions, we found that the Central region concentrates the highest Amerindian ancestry (72.7%), followed by the Northern region (58.2%), Lima and Callao (57%), the Amazonian region (55.6%), and the Southern region (55.1%). The highest European ancestry is located in the Amazonian region (42.1%), while the Central region has the lowest (26.6%). African and East Asian ancestry has little influence in Peru, being the Northern with the higher African component (4.1%), and Lima and Callao the region with the higher East Asian component (3.5%). There is no significant for Amerindian component across five regions (p=0.054); however, Central highlands region has higher Amerindian component compared to Lima (p=0.005), the Northern (p=0.005) and Southern(p=0.017) regions.

Conclusion: Our results confirmed the ancestry admixture of the Peruvian population with predominance of the Amerindian component. The Central region concentrates the highest Amerindian ancestry compared with other regions across Peru.

Title: Genomic assessment of early-onset AD identifies novel risk loci and an incomplete genetic overlap with late-onset AD.

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Background: Early Onset Alzheimer Disease (EOAD, age at onset [AAO] <= 65) is a severe form of AD, often occurring when patients are still caring for children or adults. Despite this, most genetic studies of EOAD have focused on autosomal dominant forms, and there is little understanding of similarities and differences between early and late onset forms of AD (LOAD, [AAO]>65). To address this, we present a genome-wide association study of non-Mendelian EOAD and compare it to LOAD GWAS.
Methods: Primary single-variant analyses were performed using two additive logistic regression for case-control models (full: SNPs, PCs, sex and *APOE*-ε4 dosage as covariates; reduced: SNPs and PCs); secondary models included PCs+sex and PCs+APOE. Models were applied on data derived from the Alzheimer Disease Genetics Consortium (ADGC), composed by unrelated individuals. Samples varied from 1293-1459 cases and 8894-9366 controls for EOAD, and 8795-9508 cases and 9702-10273 controls for LOAD, depending on the considered model. The SNP heritability (h2) and genetic correlation (rg) were estimated using LD score regression. Gene-based and pathway analysis (gene sets from Msigdb-v7.0) were performed using FUMA/MAGMA-v1.6.

Results: We identified two novel loci associated with EOAD: Chromosome 4 (full model: chr4:102027610, P=2.98x10-08, near *PPP3CA* gene) and Chromosome 12 (PCs+sex model: rs117001070, P=2.11x10-08, intergenic between *LINC02444* and *LINC02882*). We additionally confirmed *BIN1* and *APOE* in the EOAD subset. Several known genes also showed a significant association with LOAD. Heritability analyses showed higher h2 values for EOAD (h2 = 0.29, 0.29, 0.29 and 0.27) than LOAD (h2= 0.19, 0.16, 0.19, and 0.15), for full, reduced, PCs+sex and PCs+APOE models respectively. Genetic correlation showed moderate but incomplete genetic correlation between EOAD and LOAD. Other than *APOE* (p=3.89x10-12), gene-based tests showed nominal association for EOAD *C8orf44-SGK3* (p=9.95x10-06), *SGK3* (p=2.01x10-05) and *HIST1H2AC* (p=3.04x10-05), and plausible pathways such as HDL remodeling (p= 5.50x10-05) and positive regulation of cholesterol efflux (p= 9.79x10-05). These pathways were nominally associated with LOAD (p=0.04 and p=4.05x10-03).

Conclusions: We identified two novel loci associated to EOAD not previously reported by LOAD studies. Heritability and genetic correlation results suggest that the genetic etiology of EOAD has an incomplete genetic overlap with LOAD.

Title: Examining the impact of a rare protein-truncating *SORL1* variant on AD pathology

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Background: Recent analyses of rare variants using whole exome sequencing have found an enrichment of *SORL1* loss-of-function (LoF) variants in early onset Alzheimer's disease (EOAD). This makes *SORL1* one of the highest risk factors for AD, along with other candidate EOAD genes such as APP, PS1, and PS2. *SORL1* encodes an endocytic receptor involved in the trafficking of amyloid-β precursor protein (APP) and the secretion of amyloid-β. Furthermore, *SORL1* functions in the endolysosomal pathway with other EOAD genes, highlighting the potential for novel treatment avenues by targeting common pathways. We identified a family with multiple individuals affected with EOAD carrying a single base pair deletion (c.4293del) in *SORL1*, resulting in a frameshift and premature termination of the protein (p.Cys1431fs). Several recent studies have demonstrated that haploinsufficiency of *SORL1* can induce AD-related phenotypes in cultured neurons. However, the functional consequences of specific variants remain largely undefined. In this study, we used patient-specific induced pluripotent stem cell (iPSC)-derived neurons to evaluate the effect of a rare LoF *SORL1* variant on AD-related pathology.

Methods: Patient-specific iPSC lines were derived from two related heterozygous mutation carriers with EOAD. Each line was validated for pluripotency through immunocytochemical staining and RT-PCR. Karyotypic stability was assessed by G-banding. To evaluate the functional consequences of the *SORL1* deletion, patient and control iPSC lines were differentiated into cortical neurons and assessed for AD-related phenotypes.

Results: The iPSC lines were successfully differentiated into cortical neurons, characterized by immunostaining for various neuronal markers. Our data show that neurons bearing the p.Cys1431fs *SORL1* mutation have increased levels of APP accumulated in EEA1+ endosomes compared to neurons from unaffected individuals. Additionally, analysis of synaptic density revealed that neurons carrying the p.Cys1431fs variant show a significant reduction of SYN1+ puncta compared to controls.

Conclusions: Our results indicate that patient-derived neurons carrying the p.Cys1431fs variant have cellular defects associated with AD pathology while replicating, at least in part, previous *in vitro* findings on *SORL1* haploinsufficiency. Studies are currently being carried out in matched-pairs of isogenic patient and control iPSC-derived neurons to further elucidate the impact of the p.Cys1431fs *SORL1* variant on the endolysosomal pathway.

Title: Association of mitochondrial haplogroups and cognitive impairment in the Amish

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Background: Mitochondrial dysfunction is an important feature of Alzheimer's Disease (AD) pathogenesis. Reduced glucose utilization and increased oxidative stress are intermediates through which impaired mitochondria may promote AD-associated brain changes. Association between groups of variants ("haplogroups") in the mitochondrial genome and AD have been reported for haplogroups U, J, and K. To test these effects in the Amish, we looked for evidence of association between AD-associated haplogroups and cognitive impairment in a sample of aged Amish individuals.

Method: Cognitive status in adult Amish participants (n=670) with whole-genome sequence (WGS) data was determined based on modified mini-mental status exam results (3MS). An outcome of cognitively impaired (CI) was assigned to individuals with an education-adjusted 3MS < 87 at any age. A status of cognitively unimpaired (CU) was assigned to those aged ≥ 75 scoring ≥ 87 on the 3MS. Mitochondrial variants detected by WGS were used to derive broad haplogroups for each sample using Haplogrep2. Mixed model association testing was performed in GENESIS with CI as the outcome, and haplogroup (U, J, or K), *APOE* ε4 carrier status (ε4 vs no ε4), sex, and age as predictors. Based on reports of sex-specific haplogroup U effects on AD, a sex-stratified analysis was conducted. A random-effect kinship matrix was used to account for relationships.

Result: Association between mitochondrial haplogroups U, J, or K and CI was not observed at a 5% significance level. The sex-stratified analysis showed the strongest association of CI with haplogroup U (OR 1.8, 95% CI 0.92-3.5) among women. Among men, the estimated effect was 0.77 (95% CI 0.37-1.62). The overall direction of association was opposite in men and women, though neither was statistically significant at 5%.

Conclusion: Although significant evidence of a haplogroup effect on cognitive status was not observed, the moderate sex dependent effect of haplogroup U on impairment warrants further examination in an expanded dataset. Previously, haplogroup U was proposed as an AD risk factor among men, whereas it appears as a risk factor for CI in women in the present study.

Title: The Relationship of Alzheimer's Disease, Stroke and Ancestry in the Puerto Rican Alzheimer Disease Population.

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Background: The Puerto Rico Alzheimer and Related Dementias Initiatives (PRADI) patient cohort was developed to investigate AD and the associated genetics factors in the Puerto Rican population. PRADI recruitment was a snowball sampling, with both island-wide geographic distribution, and extensions of the PR communities in the continental US. A prior analysis suggested that stroke is a contributing factor to AD in the PR population. In this study we further evaluated the association between stroke and AD, while considering also age, gender, and ancestry.

Method: We assessed 1063 elderly PR individuals for dementia and obtained a medical history. Affection status or mild cognitive impairment was established using standard AD clinical criteria (NINCDS-ADRDA). Medical history was obtained by a self-report or informant report. The global ancestry was assessed through the ADMIXTURE program. Differences between affected and cognitively unimpaired (CU) individuals were initially evaluated using a chi-square test (for age, gender, global ancestry, and stroke) and at-test for the age at the exam time. Follow-up analyses on stroke were performed using logistic regression with age-at-exam, gender, and global ancestry proportions as covariates in the model. Initially we assess how stroke is associated with AD, while accounting for age, sex, and global ancestry analysis without *APOE,* results on the first table. The first table is the model without *APOE.* Then a second tab turns it around and looks at what factors are associated with Stroke, in the context of AD.

Result: In the PRADI population stroke is associated with an increased risk of AD dementia (p=0.012); this association persists even after accounting for *APOE* dosage (p=0.017). Additionally, age, gender and *APOE* dosage were all also associated with increased AD risk ($p < 0.05$) (table 1). AD correlated with Stroke (p=0.013). Gender was also associated with stroke, with females having a decreased risk of stroke (p=0.0021). *APOE* dosage and ancestry proportions measured through ADMIXTURE approach were not associated with stroke (table 2).

Conclusion: Stroke was independently associated to AD after controlling for *APOE* dosage. In contrast, age and gender were associated with stroke whereas global ancestry and *APOE* dosage were not.

Title: Alzheimer Disease candidate variants are associated with cerebral amyloid angiopathy

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Background: The hallmark lesions of Alzheimer Disease (AD) include tangles and plaques; however, these seldom appear alone. Lesions of AD-related dementias such as vascular and Lewy body dementias often co-occur with AD. These co-occurring lesions and total lesion burden are associated with a higher likelihood of dementia and severe cognitive impairment. Even amongst other lesions, cerebral amyloid angiopathy (CAA) presents a strong risk for more severe cognitive impairment. CAA also shows moderate correlations to AD (rho = 0.31), suggesting that CAA pathology could present an underlying or related process of AD pathology. We hypothesize that there is a genetic overlap between CAA and AD and therefore we investigate the influence of known AD genes on CAA.

Methods: Data come from 3,495 autopsied individuals with neuropathology and array data from the National Alzheimer's Coordinating Centers (NACC). CAA was measured according to NACC neuropathology form guidelines. We used ordinal logistic regression to model *APOE* genotype and 22 other known AD variants with CAA severity while adjusting for sex, age at death, and AD pathology. For the 22 other known AD variants, we tested the lead variants reported by Kunkle et al. and labeled by closest gene. We modeled *APOE* by carrier status and genotype.

Results: We confirmed associations for APOE with CAA severity, when modeling *APOE* as e4 dosage (OR=2.34, $p<0.001$) or by genotype (e3/e4: OR=1.96, $p<0.001$; e4/e4: OR=5.76, $p<0.001$). However, we did not see a significant association between CAA severity and *APOE*e2 carriers, as others have reported. Association persisted when including AD pathology terms in the model, even when extending to interaction-based models. Genetic variations in 7 of the 22 known AD genes (BIN1, HLA-DRB1, TREM2, CLU, PICALM, SORL1, SLC24A4) showed significant associations with CAA while accounting for AD pathology.

Conclusions: We confirmed strong associations of *APOE*e4 with CAA in a large clinical population. We modeled other known AD genes and 7 of them showed significant associations with CAA, demonstrating genetic overlap between AD and CAA pathologies. This study suggests that there is genetic overlap between CAA and AD pathology that could point to shared disease mechanisms for the targeting and treatment of AD.

Title: Analysis of Alzheimer Disease Plasma Biomarker pTau-181 in Individuals of Diverse Admixed Ancestral Backgrounds

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Background. Plasma proteins, including phosphorylated threonine-181 of Tau (pTau181) are used as biomarkers for differential diagnosis and preclinical detection of Alzheimer disease (AD). However, observation and measurement of these biomarkers are mostly from individuals of non-Hispanic, European ancestry. Given differences in AD risk, generalizability of these findings is not assured in individuals of diverse ancestry. This study evaluates the utility of plasma pTau181 in discriminating clinically diagnosed AD from cognitively intact, age-matched controls in ancestrally diverse, admixed cohorts.

Methods. We measured pTau181 with Simoa chemistry using the pTau181 AdvantageV2 on the Quanterix HD-X. Our cohorts consisted of 642 African Americans (162 AD and 480 controls), 906 Puerto Ricans (385 AD and 521 controls), 149 Peruvians (49 AD and 100 controls), 60 Cubans (26 AD and 34 controls), 246 individuals of non-Hispanic, European ancestry (22 AD and 224 controls), and 58 autopsy confirmed AD cases of European ancestry with plasma isolated from EDTA blood tubes. Samples were randomized, measurements performed in duplicate, and non-parametric Kruskal-Wallis tests used to detect differences in biomarker concentrations between cases and controls in each cohort.

Results. Median pTau levels in cases was higher than controls in all cohorts assayed: African Americans (2.30±1.14pg/mL vs 1.15±2.99pg/mL, $p_{corr}=2.0x10^{-27}$); Puerto Ricans (2.33±1.82pg/mL vs 1.44±1.21pg/mL, $p_{corr}=8.2x10^{-32}$); Peruvians (2.63±1.64pg/mL vs 2.13±1.42pg/mL, $p_{corr}=0.02$); Cubans (2.09±1.16pg/mL vs 1.35±0.67pg/mL, $p_{corr}=0.02$); and European ancestry (2.40pg/mL±0.78pg/mL vs 1.54pg/mL ±1.44pg/mL, $p_{corr}=0.02$). The pTau levels in the autopsy confirmed cases (2.96±2.29 pg/mL) were not significantly higher than AD cases in the other ancestries.

Conclusion. This study suggests pTau181 as a biomarker is generalizable across genetic ancestries, though potential sex and age effects remain to be determined. Ultimately, combining genomic and biomarker data, including pTau181 and other AD related plasma biomarkers such as A□40 and A□42, from diverse individuals will increase understanding of genetic risk and refine clinical diagnoses in individuals of diverse ancestries.

Title: Transcriptomic Analysis of Whole Blood in Admixed Latinx Alzheimer Disease Cohorts

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Background: Identifying the genes and biological pathways involved in Alzheimer disease (AD) is critical in the effort to develop effective therapies. Significant work has identified genetic variants conferring risk and protection for AD in individuals of diverse ancestries, but identification of downstream functional effects including modulation of gene regulation is lacking, particularly in individuals of diverse ancestries. Therefore, to explore transcriptional changes between clinically diagnosed AD and cognitively intact age-matched controls, herein we analyzed RNA sequencing data from peripheral blood collected from individuals of admixed genetic backgrounds.

Methods: Total RNA was extracted from peripheral whole blood stored in PAXGene tubes from 47 Cubans (22 AD and 25 controls), 85 Peruvians (41 AD and 44 controls), and 168 Puerto Ricans (88 AD and 80 controls). PolyA selected mRNA was sequenced to more than 40 million paired end read per sample on the Illumina NovaSeq 6000. The bioinformatic pipeline included mapping to the human reference genome (GRCh38), gene quantifications against the GENCODE v35 annotation set, and differential expression was calculated using DESeq2 with sex, age at blood draw, and count of *APOEe4* alleles as covariates. Functional categorization was performed by gene set enrichment of gene ontology and KEGG pathways.

Results: Across the cohorts, a total of 358 protein-coding genes (FDR ≤ 0.05, Fold change ≥ 1.25) were differentially expressed with 238 down-regulated and 120 up-regulated in AD relative to controls. Despite the few genes overlapping between ethnicities, pathway analysis revealed common pathways including up-regulation of genes involved in inflammation and RNA processing and down-regulation of genes involved in cellular detoxification and lipid transport, among others. Interestingly, while few specific genes overlap in differential expression overlap with a published set of genes from non-Hispanic Europeans and African Americans (Griswold et al, 2018), the pathways identified are similar.

Conclusion: Our analysis reveals a signature of gene expression that implicates increased inflammation and decreased cellular detoxification based on gene expression analysis in admixed Latinx AD. Convergence of pathways across these and African American and European cohorts supports the idea of distinct genes but similar underlying pathological processes contributing to AD across individuals of diverse ancestries.

Title: Ancestral Analysis of the Presenilin-1 G206A Variant Reveals it as a Founder Event on an African Haplotype in the Puerto Rican Population

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Background: Variants in the presenilin-1 gene (*PSEN1*) are known to be pathogenic for Alzheimer disease (AD). The change of glycine at amino acid 206 to alanine (G206A) in *PSEN1* has been identified in AD Caribbean Hispanic families from Puerto Rico with variable ages of onset and incomplete segregation (Athan et.al., 2001). Here we set out to confirm the role of G206A in the genetic etiology of AD in Puerto Rico while investigating its ancestral history and founding haplotype.

Methods: We performed genotyping and whole genome sequencing (WGS) of 43 AD families (N=182: 87 AD, 41 MCI, and 44 cognitively unimpaired) and 272 AD, 145 MCI, and 297 cognitively unimpaired unrelated individuals of Puerto Rican background and identified carriers of G206A. Genotyping data were phased using SHAPEIT to identify local ancestry of the *PSEN1* haplotype followed by RFMix to estimate the genetic ancestral background (African, European, or Amerindian). Haplotype modeling was performed using MERLIN software.

Results: We identified 19 carriers of G206A among individuals with sequencing data in eight of the 43 families (14 AD, two MCI, one neuropsychiatric disorder, and two cognitively unimpaired individuals under 65 years old). G206A did not completely explain AD in these eight families as six other AD cases in the families did not carry the variant. In the unrelated cohort, we identified 13 carriers (nine AD, one MCI, one Pick's disease, and two cognitively unimpaired under 65 years old). Local ancestry indicated that the mutation arose on an African ancestral haplotype. However, in screening WGS of individuals of primarily African ancestry from Ibadan, Nigeria (63 AD and 648 controls) and African Americans part of the Alzheimer Disease Sequencing Project (1347 AD, 2290 controls) no other carriers were identified.

Conclusion: Our results support that G206A contributes to AD in the Puerto Rican population, but in AD families does not completely explain the genetic risk. We also show that this variant occurs on a common haplotype across carriers representing a founder event on an African haplotype background in Puerto Rico.

Title: Diverse Ancestral Populations and the Alzheimer's Disease Sequencing Project (ADSP)

Authors: Brian W. Kunkle, PhD, MPH[1,2] for the Alzheimer's Disease Sequencing Project (ADSP)

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Background: A major goal of the ADSP is to fully reveal the genetic architecture of AD/ADRD across diverse ancestral populations with the hope that new discoveries and the therapeutic or prevention strategies they enable will benefit all ancestral groups.

Methods: While the project's 'Discovery Phase' (2012–2017) sequenced predominantly non-Hispanic White individuals of European ancestry (NHW-EA) [whole-exome sequencing: N=10,061; whole-genome sequencing (WGS): 197 NHW-EA and 351 Hispanic/Latino (HL) familial individuals], the 'Discovery-Extension Phase' of the project added WGS on 1,183 NHW-EA, 1,141 HL, and 1,070 non-Hispanic Black individuals with African ancestry (NHB-AA). The ADSP's current phase, the Follow-Up Study (FUS) (2018–2023) has targeted existing ancestrally diverse and unique cohorts with clinical AD/ADRD data. Over 40,000 individuals have been ascertained and ~32,000 sequenced to date (ancestry distribution: 9,192 NHB-AA; 9,952 HL; 13,531 NHW-EA, 4,600 East Asian, 2,760 Indian, 89 Amerindian).

Results: Despite relatively small sample sizes, important instances of unique AD/ADRD genetic variation have been identified in HL and NHB-AA studies, including population-specific rare/low-frequency variants, and evidence of the importance of ancestral background in conferring risk for genetic factors such as *APOE ε4*. Power studies show ~16,100 cases and ~16,100 controls are needed per ancestry for discovery of risk/protective variants with minor allele frequency (MAF) of 0.5% and odds ratios (OR) of 2.0 at genome-wide significance ($P=5x10^{-8}$). Using region-based testing ~10,000 cases and ~10,000 controls are needed for finding variants with MAF=0.005% and ORs=1.4.

Conclusions: To this end, the next phase of the ADSP, the "ADSP-FUS 2.0: The Diverse Population Initiative" NIH PAR-21-212 aims to ensure there are enough study participants to achieve statistical power for rare variant analysis in the largest US populations, with a particular focus on HL, NHB-AA, and Asian populations. Initiatives such as the Asian cohort for Alzheimer's disease (ACAD), focusing on increasing recruitment of Asians in AD/ADRD studies, are also in development. These datasets, some of which will include data for assessing social and environmental influences of AD/ADRD, will be an invaluable resource for the AD research community and will enhance ongoing efforts for the identification of shared and novel genetic risk factors for AD/ADRD across populations.

Title: Characterization of a diverse Frontotemporal Dementia cohort, enriched for Caribbean Hispanic patients.

Autors: Anisley Martinez, Farid Rajabli, Esther Gu, Sergio Tejada, Erika Negro, Humberto Acosta, Baumel, Camargo, Sun, Jeff Vance, Mike Cuccaro, Margaret Pericak-Vance, Karen Nuytemans.

Background:

The vast majority of biomedical data currently available for any disease is derived from studies in non-Hispanic white (NHW) populations. Specifically, clinical information, genetic factors as well as biomarkers for frontotemporal dementia (FTD) have been studied predominantly in those NHW populations. To increase representation in biomedical research, we set out to enroll and characterize a diverse FTD patient cohort enriched for Caribbean Hispanic patients.

Method:

Our current cohort consists of 89 FTD patients (30% NHW, 67% Hispanic), with continuing enrollment from the University of Miami Hospital Neurology Department in Miami, FL and the Caribbean Center for the Study of Memory and Cognition in San Juan, PR. All patients were evaluated using NACC approved Uniform DataSet (UDS) or equivalent in their preferred language. For ~65% of the cohort we also completed the NACC FTD module forms. We generated genotyping data (Illumina GDA+Neurobooster array) as well as whole genome sequencing and plasma biomarker data (Quanterix Simoa Neuroplex-3; A 40, A 42, and total tau) for a subset of the cohort.

Results:

Initial genetic analyses showed none of the Hispanic patients are carriers of known FTD mutations originally identified in NHW patients, including the *C9orf72* repeat expansion and reported pathogenic variants in *MAPT* or *GRN*. We did not identify a significant difference in age-at-onset or Clinical Dementia Rating scores at time of enrollment between NHW and Hispanic patients. Additionally, biomarker data on Aβ40/Aβ42 ratio and total tau levels in a subset of 22 FTD patients (~12/10 Hispanic/NHW) did not show significantly different levels between patients of both ethnicities.

Conclusion:

Genetic analyses of FTD in underrepresented population groups is necessary as genetic information from research in NHW is not always generalizable across race/ethnicity. We are currently working to expand our efforts to include identification of novel genetic risk factors for FTD in the Hispanic patients using whole genome sequencing, full evaluation of the Neuroplex as well as p-tau181 and NfL biomarkers in the complete cohort and comparison of clinical presentations between ethnicities. The biomedical characterization of FTD across race/ethnicity will help the understanding of disease mechanisms in all patients ultimately preventing further health disparities.

Title: The Alzheimer's Disease Sequencing Project Follow Up Study (ADSP-FUS): increasing ethnic diversity in Alzheimer's disease (AD) genetics research.

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Abstract Text:
Background: The ADSP-FUS is a National Institute on Aging (NIA) initiative focused on identifying genetic risk and protective variants for Alzheimer Disease (AD) by expanding the ADSP Discovery and Discovery Extension cohorts beyond non-Hispanic Whites of European Ancestry (NHW-EA). Given the lack of diversity in the ADSP, the ADSP-FUS was designed to sequence existing ethnically diverse and unique cohorts. The upcoming phase for ADSP-FUS, ADSP- FUS 2.0: The Diverse Population Initiative, focuses on Hispanic/Latino (HL), non-Hispanic Black with African Ancestry (NHB-AA), and Asian populations (e.g., the Asian cohort for Alzheimer's disease). The ADSP-FUS enables the utility of new discoveries for individuals from all populations.

Method: ADSP-FUS cohorts consist of studies of AD, dementia, and age-related conditions. Clinical classifications (AD, dementia, and cognitively intact) are assigned based on standard criteria and derived from clinical measures and history. Data dictionaries are curated for each cohort by the FUS clinical staff. The ADSPFUS initiatives intend to sequence over 100,000 individuals from diverse ancestries.
Biospecimens are processed and DNA is prepared and allocated for whole genome sequencing (WGS) at designated NIA sequencing centers. All raw sequence data is transferred to the Genome Center for Alzheimer's Disease (GCAD) for processing and harmonization following QC analysis at the University of Pennsylvania and University of Miami, resulting in analysis-ready genotype and sequence data. All clinical, genotype and sequence data are housed at the NIA Genetics of Alzheimer Disease Data Storage Site (NIAGADS), which stores, manages, and distributes ASDP-FUS data to AD researchers.

Results: Over 50,152 samples have been ascertained with ancestry groupings as follows: 10,166 NHB-AA; 10,531 HL; 22,002 NHW-EA (including 1,400 EOAD and 3,745 autopsy); 89 Amerindian; and 7,364 Asian (Korean and Indian) individuals. Currently, we have sequenced up to a total of 31,990 individuals.

Conclusion: The ADSP-FUS continues to identify shared and novel genetic risk factors for AD among diverse populations. This genomic resource is crucial to expanding our knowledge of potential genetic risk and protective variants for AD across all populations with the hope of developing new treatments for everyone.

Title: Characterization of chromosome 5q35 risk locus in African Ancestry population.

Authors: Karen Nuytemans, Farid Rajabli, Melissa Jean-Francois, Larry D. Adams, Takiyah D. Starks, Patrice L. Whitehead, Brian W. Kunkle, Allison Caban-Holt, The NIA-LOAD Family-Based Study, Mike L. Cuccaro, Jeffery M. Vance, Jonathan L. Haines, Christiane Reitz, Goldie S. Byrd, Gary W. Beecham, Margaret A. Pericak-Vance

ABSTRACT

Background. As part of the Research in African American Alzheimer Disease Initiative (REAAADI) and Late-Onset AD Family Study (LOAD), genotyping array and whole genome sequencing (WGS) data were generated for 51 families (160 affected and 318 unaffected). Multipoint linkage analyses identified a peak LOD score on chr5q35 (HLOD=3.20). Additionally, a suggestive locus flanking the 1-LOD score was previously identified in an AA GWAS study (p-value=2.6×10^{-6}) (Kunkle et al, 2019). Here, we further characterize this locus and its role in AD.

Method. We performed region-wide association analysis in an independent REAAADI dataset of ~240 cases and ~650 controls to fine map the signal in the locus. Additionally, we analyzed the WGS data to prioritize variants in the consensus regions based on segregation with disease among affected individuals and rarity (MAF<0.01). All variants were annotated for putative function including protein changes for coding variants and evidence for regulatory activity (ENCODE, RoadMap Epigenome) and chromatin interactions (publicly available HiC and promoter capture C) for noncoding variants.

Results. Region-wide association analysis identified two regions of rare (MAF~0.01) variants downstream ($p=3.0\times10^{-8}$) and upstream ($p=3.7\times10^{-6}$) of the 1-LOD linkage region. Segregation analysis using WGS data identified 111 rare variants (MAF<0.01) segregating with disease in the AD individuals of the family with the highest LOD score contributing to the linkage peak. These include a 3'UTR and synonymous variant in *INSYN2B/FAM196B* as well as a promoter variant in *WWC1/KIBRA*. Interestingly, four other AA families contributing to the chr5 linkage signal harbor different within-family shared variants located in *INSYN2B*'s promoter or in enhancer regions with evidence for interaction with *INSYN2B*'s promoter. *WWC1*, expressed in astrocytes, was previously reported in AD context, whereas novel candidate *INSYN2B* encodes an inhibitory synaptic factor active in oligodendrocytes and neurons.

Conclusions. Our initial analyses provide evidence for two candidate genes contributing to AD genetics in the AA population. Additional work for functional validation of these candidates for AD is ongoing. This AA population-specific finding shows the importance of diversifying population-level genetic data to better understand the genetic determinants of AD on a global scale.

Title: A Novel Protective locus significantly reduces the ApoE ε4 risk for Alzheimer's Disease in African Ancestry.

Authors: Marina Lipkin-Vasquez[1], Farid Rajabli[1], Gary W. Beecham[1,2] ,Hugh C. Hendrie[3], Olusegun Baiyewu[4], Adesola Ogunniyi[4], Sujuan Gao[5], Nicholas A. Kushch[1], Kara L. Hamilton-Nelson[1], Juan Young[1,2], Derek M. Dykxhoorn[1,2], Karen Nuytemans[1,2], Brian W. Kunkle[1,2], Liyong Wang[1,2], Fulai Jin[6] , Xiaoxiao Liu[6], Briseida E. Feliciano-Astacio[7], Alzheimer's Disease Sequencing Project, Alzheimer's Disease Genetic Consortium, Clifton L. Dalgard[8], Anthony J. Griswold[1,2], Goldie S Bird[9], Christiane Reitz[10], Jonathan L. Haines[11], Margaret A. Pericak-Vance[1,2], Jeffery M. Vance[1,2].

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Background: African ancestry populations have a lower risk for developing Alzheimer disease (AD) from *ApoE*ε4 compared to other populations. Understanding this mechanism of protection could lead new therapeutic insights for AD. Our goal is to identify areas of the genome that interact with *ApoE*ε4 in African ancestry that result in the lowered risk for developing AD in this population.

Methods: We performed association analyses using a logistic regression model with *ApoE*ε4 allele as an interaction term and adjusted for genome-wide ancestry, age, and sex. Discovery analysis included imputed SNP data from 1,850 African American (AA) individuals with AD and 4,331 AA controls. We performed replication analysis on whole-genome sequenced (WGS) data from 1) 63 Ibadan (Nigerian) AD individuals and 648 Ibadan controls; 2) WGS 273 Puerto Rican (PR) AD individuals and 275 PR controls; and 3) SNPs imputed from 8,463 non-Hispanic White (NHW) AD individuals and 11,365 NHW controls.

Results: We identified a significant interaction with the *ApoE* ε4 allele and the SNP rs10423769_A allele, that reduces the odds ratio for AD risk from 7.2 for *ApoE*ε4/ε4 without the A allele to 2.1 for allele *ApoE*ε4/ε4 carriers with the A allele. rs10423769 (frequency = 0.11 in AA, NHW= 0.003) is located approximately 2 megabases distal *to ApoE*, in a large cluster of pregnancy specific beta-1 glycoproteins on chromosome 19 and lies within a long noncoding RNA, ENSG00000282943. rs10423769 is reported to be a splicing QTL (sQTL) for TMEM145, whose highest brain expression is in the cerebellum. This interaction analysis was identified in the discovery AA dataset (β=-0.54, SE=0.12,p-value=7.50×10^{-6}), and this finding was replicated in both the Ibadan (β = -1.32,SE = 0.52,p-value = 1.15×10^{-2}) and PR (β=-1.27,SE=0.64,p-value=4.91×10^{-2}) datasets while it trended but was not significant in the NHW dataset.

Conclusion: This study identified a new African-ancestry specific locus that reduces the risk effect of *ApoEε4* for developing AD by approximately 75%. The genes lying near this protective locus are novel and thus suggest potential new protective mechanisms for AD development.

Title: The Peruvian Alzheimer Disease Initiative (PeADI): An international effort model to increasediversity in AD research

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Abstract Text:Background: Peru is one of the five largest countries in Latin America and harboring a highAmerindian ancestry component in this population. The Latin American population, including Peruvians,are underrepresented in research studies of Alzheimer disease (AD).We have developed aninternational collaborative research initiative to ascertain a Peruvian cohort for AD and other relateddementias for genetic studies of Amerindian individuals.

Methods: The Peruvian Alzheimer Disease initiative (PeADI) was developed to recruit and enrollPeruvian adults aged 65 and older to a comprehensive genetic AD study. Individuals will get wholegenome sequencing and plasma biomarkers. Participants included cases with AD and ADD,healthycontrols as well as multiplex AD families. Since 2019, we have established a multisource ascertainmentapproach including recruitment at main hospitals, outreach community activities and more recently dueto the COVID19 pandemic remote recruitment and home visits. Our recruitment has expanded sinceour initial efforts in which we enrolled individuals from Lima, the capital city. We are now ascertainingparticipants in three regions from the Andes highlands (Puno,Huancayo, and Cusco) and one regionfrom the southern coast (Tacna).All participants are enrolled using a standard protocol administered byneurologists and neuropsychologists. This protocol includes clinical interviews and neurocognitiveassessment.

Results: As of December 2021, we have enrolled 103 AD and other dementia cases, 202 controls and4 multiplex AD families. While the majority of participants are from Lima, 25% controls and 1% of caseshave been recruited in regions outside Lima. We have confirmed a significant association betweenAPOE and AD in Peruvian Population higher than we have observed in non-Hispanics. In addition toascertainment activities, we are working closely with the respective sites to develop a network for ADresearch across Peru. To date, we have developed local research capacities within eachregion,including training opportunities for investigators, coordinators and lab technicians. In addition, weare developing resources for health and medical support and basic equipment for all regions.

Conclusion: The PeADI study shows the importance of equitable international north-south cooperationand local network cooperation to increase representation of understudied admixed populations to helpus understand Amerindian ancestry in drug target discovery.

Title: Intragenic loci within *TOMM40* enhances *APOE* expression in human microglia

Authors: Oded Oron, PhD1, Aura Maria Ramirez, PhD1, Liyong Wang, Ph.D.1,2, Marina Lipkin Vasquez, PhD1, BrookeA DeRosa, PhD1, Katrina Celis, MD1, Alessandra Chesi, PhD3,4, Struan F.A. Grant, PhD3,4, Juan Young, PhD1,5, Karen Nuytemans, Ph.D.1,2, Jeffery M. Vance, MD, PhD1,2,5,6 and Derek M. Dykxhoorn, Ph.D.1,2, (1)John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL, USA, (2)Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine, Miami, FL, USA, (3)University of Pennsylvania, Philadelphia, PA, USA, (4)The Children's Hospital of Philadelphia, Philadelphia, PA, USA, (5)University of Miami Miller School of Medicine, Miami, FL, USA, (6)Department of Neurology, University of Miami Miller School of Medicine, Miami, FL, USA

Abstract Text:
Background: Previously, we demonstrated that the ancestry-related risk for Late Onset Alzheimer's Disease (LOAD) is driven by a local genomic region (termed Local Ancestry; LA) around *APOEε4*. Furthermore, we showed that in the brain of individuals bearing European LA there is higher expression of *APOEε4* compared to those with African LA. In a follow-up study, utilizing reporter assays and Capture-C data we located two intronic regions within the European LA, both in the *TOMM40* gene (named B10 and B13), that increased *APOE* expression in microglia and astrocytes. In this study, we sought to validate their regulatory role in *APOE* expression using CRISPR interference/activation (CRISPRi/a).

Method: Human Microglial Clone 3 (HMC3) CRISPRi/a lines were produced by transducing inducible dCas9-VP64 (Activation), dCas9-KRAB (Interference) or dCas9 (control) using lentiviral vectors. To direct the dCas9 constructs to our regions of interest, we generated multiplex vectors that encode 4 short-guide RNAs (sgRNAs) targeting either B10 or B13. We used 4 different sgRNAs in each case to ensure fulllength coverage of the tested regions (~850bp size). An empty multiplex vector was used as a control. We then transduced either of the multiplex vectors into the HMC3 CRISPRi/a lines. We induced expression of the dCas9 constructs for 2 or 6 days with Doxycycline (2ug/ml). RNA was extracted and the expression of *APOE* and *TOMM40* was measured by qRT-PCR.

Result: *APOE* expression significantly increased when targeting B10 or B13 (p=0.001; p=0.003 respectively) with dCas9-VP64 after 2 days of Doxycycline treatment. Six days after treatment the significance persisted only when targeting B10 (p=0.01). No significant changes in *APOE e*xpression were observed in the cells bearing the dCas9-KRAB presumably due to low endogenous APOE levels. Expression of *TOMM40* did not vary under any treatment.

Conclusion: These preliminary results support our previous findings that regions B10 and B13 may act as regulators for *APOE* expression as demonstrated by the elevation of ApoE expression when targeting an activator to these regions. The expression of *TOMM40* did not vary across cell lines in the evaluated time points supporting that the effect observed is specific for *APOE*.

Title: Plasma pTau181 is associated with impaired cognition in the Old Order Amish and adds additional information beyond the known genetic risk factors for AD

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Background: As plasma biomarker assays have become more widely available, they are increasingly being used to characterize AD and related dementias. The Old Order Amish are a cultural and genetic isolate in the US that have participated in genetic studies for decades. This study investigated plasma phosphorylated tau at threonine-181 (pTau181) in an Old Order Amish cohort to determine if the association with cognitive status is reproducible in this population.

Method: Old Order Amish individuals over age 65 (n=467, mean age = 81.3, 60.6% female) in Indiana and Ohio were examined using a modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery. Each individual was assigned Impaired (n=155, mean age = 82.5, 56.8% female) or Unimpaired (n=312, mean age = 80.8, 62.5% female) cognitive status via consensus review of these examination results. The level of plasma pTau181 was measured using the pTau181 Advantage V2 assay from Quanterix. Genetic Risk Scores (GRS) were calculated using genome-wide significant variants from Kunkle et al. (2019), weighted by log odds ratio estimates. A t-test was used to compare plasma pTau181 levels between the Impaired and Unimpaired groups. Logistic regression was then used to model the contribution of age, sex, GRS, and plasma pTau181 on cognitive status.

Result: We found that the average level of plasma pTau181 was significantly higher in the Impaired group (2.46 pg/mL) compared to the Unimpaired group (2.01 pg/mL) at $p<0.0001$. A multivariable model found increasing age (OR=1.10, p=0.0002), male sex (OR=1.60, p=0.04), increasing GRS (OR=1.97, $p<0.0001$), and increasing plasma pTau181 (OR=1.46, p=0.001) associated with impaired cognitive status. The effect of GRS is mostly attributable to *APOE*.

Conclusion: The result of these analyses indicates that pTau181 is associated with impaired cognitive status in the Old Order Amish, adding additional information beyond the known genetic risk factors for AD.

Title: Exploring effect of known Alzheimer disease genetic loci in the Peruvian population

Authors:
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Background
Native American populations are substantially underrepresented in Alzheimer disease (AD) genetic studies. The Peruvian (PE) population with up to ~80 of Amerindian ancestry provides a unique opportunity to assess the role of AI ancestry in AD. We performed whole-genome sequencing in PE case-control study to assess the effect of the known AD loci in PE population.

Methods
Whole-genome sequencing was performed in 96 AD cases and 145 unrelated cognitive healthy controls from PE population. We calculated the global ancestry (principal components) using the EIGENSTRAT approach. We tested 21 AD lead variants from the recent large non-Hispanic White (NHW) GWAS of AD (Kunkle et al. 2019). We performed association analyses using logistic regression model with accounting for age, gender, and population substructure (first three principal components). We used Bonferroni approach for multiple test correction.

Results
Logistic regression analysis confirmed association of *APOE* with AD (rs429358, OR=3.6, CI:1.9-7.0; pv < 8.4e-05) in PE population. *CLU* loci (rs9331896, pv=9.3e-04) passed the significance threshold after Bonferroni multiple test correction. Two AD loci demonstrated nominal associations (pv<0.05), which were *EPHA1* (rs10808026, pv = 0.028), and *FERMT1* (rs17125924, pv=0.022) loci.

Title: Using Oligodendrocytes for studies in Alzheimer disease

Authors: Aura M. Ramirez, Jihanne Shepherd, Shaina Simmon, Oded Oron, Marina Lipkin, Sofia Moura, Maria Muniz, Farid Rajabli, Liyong Wang, Xiaoxiao Liu, Fulai Jin, Brian Kunkle, Karen Nuytemans, Anthony Griswold, Juan Young, Derek M. Dykxhoorn, Jeffery M. Vance.

Introduction:

Genomic regulatory architecture (GRA) has been primarily studied in European ancestry. As part of the functional Consortium of the Alzheimer Disease Sequencing Project, we are determining the GRA in African and Amerindian ancestries. Oligodendrocytes (OLs) are the largest glial population in the adult central nervous system. While their main role is to support neuronal metabolism and connectivity, few studies have examined their importance in Alzheimer's disease (AD), despite reports of low numbers of oligodendrocytes and reduced myelin in the early stages of AD and a demonstrated role of myelinating oligodendrocytes in learning and memory. Several studies have reported the derivation of OLs from pluripotent cells, such as induced pluripotent stem cells (iPSC) to be challenging. Here, we optimized a protocol to derive oligodendrocytes from iPSC for studies in AD patients with different ancestries and how ancestry-specific genomic differences drive the onset and pathogenesis of AD.

Methods:

iPSC lines derived from AD patients were cultured and differentiated into oligodendrocytes using different induction media, as well as different seeding densities. The cells in each treatment were compared at multiple time points using immunocytochemistry (ICC) and qRT-PCR for oligodendroglia lineage markers with the goal of identifying the culture conditions that increase the yield of $O4^+$ cells and myelinating oligodendrocytes.

Results:

Our results showed that increasing the initial seeding density positively correlates with the number of $Olig2^+$ cells that subsequently transitioned into mature O4+ cells capable of producing myelin. Additionally, we showed that the addition of N2 supplement to the induction media was necessary to maintain the cell viability during the initial stage of differentiation.

Conclusions

We have optimized a protocol to derive OLs from human iPSC lines. We determined that both the seeding density and the media supplements used during the initial stage of differentiation directly influence viability and, consequently the amount $Olig2^+$ cells that could be obtained to be terminally differentiated into $O4^+$ and myelinating cells. Our optimized protocol will be used to evaluate the GRA and functionality of potential GWAS driving loci in cultured oligodendrocytes from individuals of African and Amerindian ancestries.

Title: Sex-specific DNA methylation differences associated with Alzheimer's disease

Authors: Juan I. Young, Achintya Varma, Lisette Gomez, Hannah Dykxhoorn, Brian Kunkle, Lily Wang, Eden R. Martin

Background: There is compelling evidence that women have a greater risk of developing Alzheimer disease (AD) as well as sex differences in AD neuropathology. The causes for sex differences in AD are still unclear and could include differences in brain structure and function, and differences in susceptibility to developing AD in response to genetic and environmental factors. Since expression of genes directly relates to all these factors, we explored the role of sex in AD by performing a meta-analysis of gene expression data from multiple human brain postmortem studies. Multiple brain regions were included to identify genes with sex-differential effects between AD cases and controls.

Method: We analyzed a total of eight microarray datasets. Data were quantile normalized after stratifying datasets by tissue and sex. Quality control of samples and probes included excluding outlier samples from Principal Component Analysis, and probes with expression in the bottom 10^{th} percentile in over 80% of samples. Surrogate Variable Analysis was used to detect and adjust additional unknown sources of noise. First, we analyzed each brain region (dorsolateral prefrontal cortex, visual cortex , cerebellum, entorhinal cortex, temporal cortex, Middle Temporal Gyrus, and hippocampus) separately. To identify genes with sex-specific effects in gene expression, a fixed-effects inverse variance weighted meta-analysis was then used to combine cohort-specific association between AD and gene expression stratified by sex. In addition, we also applied a sex-interaction model that allowed us to identify genes with differential sex effects between the sexes.

Results: We compared differentially expressed genes (both sex-stratified and sex-interacting) in different brain regions using an overlap analysis. We found a number of female-specific and male-specific differentially expressed genes were common in several brain regions, such as *KCNK12* (F) and *SOHLH1* (M). Sex-interacting genes shared by multiple regions included *SLC16A6* and *LIPL1*. Pathway analysis showed differentially expressed genes were enriched in pathways of neurodegeneration, synaptic signaling and inflammatory processes in AD.

Conclusion: Our meta-analysis shows AD brains exhibit a transcriptomic profile that has a sex-specific component. The identification of sex-specific transcriptional regulation in AD may help us to better understand sex differences in disease etiology and facilitate personalized medicine.

Title: Harnessing Chromatin 3D interactions to Understand Ancestry-Specific Alzheimer Disease (AD) risk

Authors: Liyong Wang, Ph.D.1,2, Xiaoxiao Liu3, Oded Oron, PhD1, Wanying Xu3, Jack Trittipo1, Farid Rajabli, PhD1, Derek M. Dykxhoorn, Ph.D.1,2, Anthony J. Griswold, PhD1,2, Margaret A. Pericak-Vance, PhD1,2, Juan Young, PhD1,2, Fulai Jin, PhD3,4 and Jeffery M. Vance, MD, PhD1,2, (1)John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL, USA, (2)Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine, Miami, FL, USA, (3)Case Western Reserve University, School of Medicine, Cleveland,
OH, USA, (4)4. Department of Computer and Data Sciences, Case Western Reserve University, Celveland, OH, USA

Background:
Ancestry-specific Alzheimer Disease (AD) genetic risk is well recognized. Chromatin 3D interaction map in ADrelevant cells with different ancestries is lacking but needed to understand the genetic/epigenetic basis for AD indiverse populations. We have shown that the local ancestry (LA) block (~2Mb in size) surrounding *APOE* confers differential genetic risk for *APOE ε4* carriers in Non-Hispanic Whites (NHW) and African Americans (AA). Recently, we reported that NHW *APOE ε4* carriers have a higher *APOE ε4* expression and higher number of astrocytes compared to their AA counterparts in the frontal cortex. We therefore sought to characterize chromatin 3D interactions in astrocytes within different *APOE* LA.

Method:
Induced pluripotent stem cells (iPSCs) with African or European LA block (N=2 individuals for each) were differentiated into astrocytes. Chromatin Hi-C libraries were constructed with 4-cutter enzyme and sequenced targeting 500 million pair-end reads per library. Spatial genome structure was examined at compartment, topological associated domain (TAD), and loop levels. To better define enhancer-promoter interaction (EPI), high-resolution contact matrices were built using the *HiCorr* and *DeepLoop* algorithms.

Result:
Each library generated over 250 million uniquely mapped, non-redundant reads for Hi-C analysis. Compartment and TAD had limited variability among samples (correlation co-efficiency = 0.62~0.90 for compartment, 0.84~0.94 for TAD). Chromatin loop, which usually represents EPI, displays higher variability among samples (correlation coefficiency= 0.38~0.75). In the 5kb-contact-matrix analysis, a chromatin interactive event involving *APOE* was detected, which is supported by Capture-C data. The higher-resolution 500bp-contact-matrix analysis revealed multiple better-defined interactions within the event. Of particular interest, an interaction between the 5'end of *TOMM40* and *CLPTM1* (about 100 kb apart from each other) surrounding *APOE* is only observed on European butnot African LA background.

Conclusion:
Chromatin loop displays more inter-individual variations compared to other spatial genome structures and therefore is more informative in elucidating the epigenetic basis for inter-ancestry differences in gene expression regulation. While identifying chromatin loop from Hi-C data at higher resolution is challenging, it has the potential to delimitate EPI and offers insights on the ancestry-specific AD genetic risk by providing functional mechanisms underlying A Dassociated genetic varian.

Title: Depressive Symptoms Associated with an Earlier Age at Onset Differ as a Function of Race-Ethnicity: An Exploratory Analysis

Authors: Andrew Zaman, PhD[1], Pedro Ramon Mena, MD[2], Larry D. Adams[1], Maricarmen Contreras, BA[1], Faina C Lacroix, MPH[1], Sergio Tejada, MD[1], Takiyah D. Starks, BS, MS[1], Briseida E. Feliciano-Astacio, MD[3], Concepcion Silva, MBA[3], Allison M Caban-Holt, PhD[4], Goldie S. Byrd, PhD[4], Izri Martinez, MD[5], Temitope Ayodele, BS[5], Penelope Baez[5], Gabrielle Blackshire[6], Sara Kennedy, PhD[6], Christiane Reitz, PhD, MD[7], Jonathan L. Haines, PhD[8,9], Jeffery M. Vance, MD, PhD[1], Margaret A. Vance, PhD[1] and Michael L. Cuccaro, PhD[1],

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Introduction: Depression (DEP) is a known risk factor for AD. However, DEP symptoms vary by race-ethnicity (e.g. greater somatization among African Americans). The relationship between DEP and AD progression in underrepresented groups is not well-understood. We hypothesize that certain DEP symptoms will be associated with earlier AAO, and that this relationship is moderated by race-ethnicity.

Method: Self-declared Non-Hispanic White (NWH), African American (AA), and Hispanic (HI) participants with AD and CDR data were identified from a larger genetic study. Our dataset consisted of 549 persons with a self-completed GDS (mean CDR = 0.6; 15% NWH, 43% AA, 42% HI), 334 persons with informant completed CSDD (CDR = 1.7; 41% NWH, 20% AA, 39% HI), and 266 persons with self-reported DEP and anxiety in a medical history exam (CDR = 0.7; 26% NWH, 23% AA, 51% HI). All measures were completed after the onset of AD. Univariate linear regressions examined the relationship between AAO and DEP (total scores and individual items), and race-ethnicity x DEP interactions after controlling for sex, race-ethnicity, disease duration, and *APOE-e4*.

Results: Self-reported anxiety (p = 0.04), informant-reported anxiety (CSDD) (p = 0.02), and self-reports of *feeling empty* (GDS) (p = 0.02) were associated with an earlier AAO across all groups. Informant-reported *poor self-esteem* (CSDD) was associated with an earlier AAO overall (p < 0.01), but an interaction showed that this was not significant in HI (p = 0.03). Unique items associated with an earlier AAO in NHW included higher GDS total score (p = 0.01), and GDS items *feeling bored (GDS)* (p < 0.01), and *perceived problems with memory* (GDS) (p < 0.01). In AA, self-reported DEP was associated with an earlier AAO (p = 0.02). No items were uniquely associated with AAO in HI.

Conclusion: Self- and informant-reported anxiety and self-reported feelings of emptiness were associated with an earlier AAO in all groups. However, several DEP symptoms associated with earlier AAO differed as a function of race-ethnicity. We believe our findings suggest that the occurrence of DEP may be culturally or ancestrally influenced, which in turn has a differential impact on AAO in underrepresented groups.

Novel circling SWAT for deep learning based diagnostic classification of Alzheimer's disease: Application to metabolome data

Taeho Jo, Junpyo Kim, Paula Bice, Kevin Huynh, Tingting Wang, Peter J. Meikle, Rima Kaddurah-Daouk, Kwangsik Nho* and Andrew J. Saykin*, for the Alzheimer's Disease Neuroimaging Initiative (ADNI), Alzheimer's Disease Metabolomics Consortium (ADMC) and AI4AD Consortium

Background

Recent advances in deep learning have allowed multi-omics data to be used to detect early stages of Alzheimer's disease (AD). The metabolome, as the end-product of biological cascades including the genome, transcriptome, and proteome, may have informative elements that could serve as potential AD biomarkers. We report a novel two-step deep learning method to detect AD and progression using lipidomics data.

Methods

We used serum-based cross-sectional lipidome data with 781 lipids from the Alzheimer's Disease Neuroimaging Initiative (ADNI) including 216 cognitively normal (CN), 635 MCI, and 382 dementia (AD). Phenotype influence scores (PIS) was derived by deep learning-based circling Sliding Window Association Test approach (Circling SWAT) (Fig. 1-A), an extension of SWAT (Jo et al., 2022) with correlation heatmap and dendrogram analysis for omics data with minimal features. We used convolutional neural networks (CNN) to classify AD from CN based on top-scoring metabolites. The AD classification model was used to predict conversion of MCI to AD within two years using 146 MCI-convertors who developed AD and 190 MCI-Stable who did not develop AD over two years from baseline. We removed two deDE lipids, deDE(18:2) and deDE(20:4), because their associations with AD were driven mainly by AD-related medication.

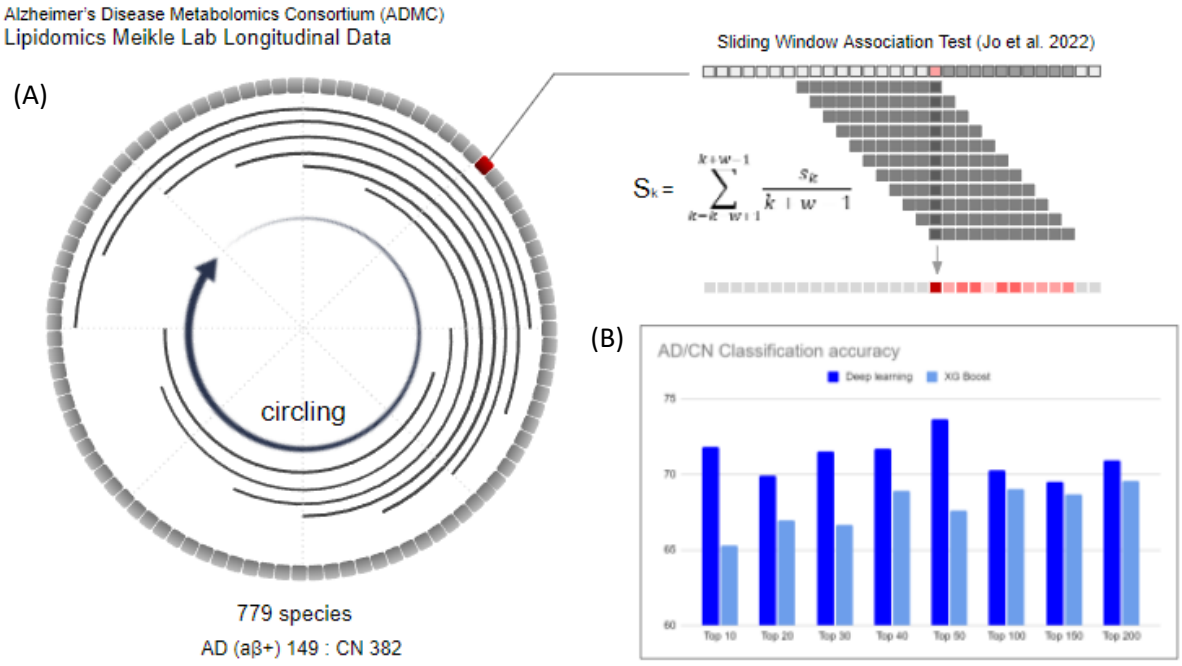
Results

Phenotype influence scores (PIS) were calculated for each lipid using circling SWAT to determine their impacts on AD. The metabolites with the highest PIS were LPE(22:6), PC(39:5), and PC(15-MHDA_22:6). When CNN was applied to the top 50 lipids by PIS, AD and CN classification accuracy was 73.6% (Fig. 1-B), which was 5.1% higher than the accuracy obtained using only age, sex, and *APOE* ε4. For MCI conversion to AD, the AD/CN classifier accuracy was 69.9% or 8.8% higher than a model using only age, sex, and *APOE* ε4.

Conclusions

The circling SWAT method appears promising for the analysis of lipidome data as it was able to identify several AD-related lipids and predict disease progression.

Figure 1. Circling SWAT is an extension of SWAT(Jo et al. 2022) for small datasets. In (A), circling SWAT is applied to metabolites sorted by heatmaps and dendrograms, and results are shown in (B). The highest accuracy was achieved by applying the top 50 metabolites based on phenotype influence score.



Reference

1. Jo, T., Nho, K., Bice, P., Saykin, A. J., & Alzheimer's Disease Neuroimaging Initiative. (2022). Deep learning-based identification of genetic variants: application to Alzheimer's disease classification. *Briefings in Bioinformatics*, *23*(2). *https://doi.org/10.1093/bib/bbac022*

Genome-wide meta-analysis employing the African Genome Resources panel identifies novel Alzheimer disease risk loci in African-Americans

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Background: In the largest Alzheimer disease (AD) genome-wide association studies to date for African-Americans (AA; Reitz et al. JAMA 2013; Kunkle at al. JAMA Neurol 2021) we previously identified in addition to *APOE* several novel susceptibility loci, including *ABCA7, API5, RBFOX1* and *IGF1R*. We followed up these analyses with an increased sample size (2,913 cases, 5,802 controls) employing the African Genome Resource (AGR) panel.

Methods: Single-variant association analysis was conducted adjusting for age, sex, principal components and subsequently *APOE*, applying logistic regression for case-control and general estimating equations for family-based datasets. Within-study results were meta-analyzed using METAL. Gene-based and pathway analyses were conducted via MAGMA.

Results: In addition to the previously reported AA risk loci, we identified three novel signals reaching genome-wide significance at chromosomes 3p24 (*TOP2B*; $P=4.7 \times 10^{-8}$), 3q26 (*NCEH1*; $P=3.7 \times 10^{-8}$) and 9p23 (*MPDZ*; $P=1.7 \times 10^{-8}$), and seventeen novel loci reaching suggestive significance at $p \leq 9 \times 10^{-7}$. *NCEH1* modulates cholesterol metabolism and is neuroprotective against α-synuclein toxicity; *MPDZ* encodes a scaffolding protein involved in cytoskeleton remodeling. *Top2B* encodes a DNA topoisomerase involved in DNA transcription. Gene-based analyses identified *SLC39A3* ($P=2.9 \times 10^{-6}$), involved in zinc transport, as a novel candidate gene. Pathway analyses support the notion that besides immunity, synaptic function, transcription/DNA repair, lipid processing, and intracellular trafficking, which overlap with the major AD-associated pathways in non-Hispanic Whites, also renal function is involved in AD etiology in African Americans.

Conclusions: We identified several novel candidate loci for AD in AA. While the major pathways involved in Alzheimer disease etiology in African American individuals are similar to those in non-Hispanic White individuals, the disease-associated loci within these pathways differ. Identification of a significant number of loci at suggestive significance indicates that future studies with further increased sample size will be valuable to identify additional disease-associated loci in this ethnic group.

Keywords: Alzheimer's disease, GWAS, African-American

No added value of Sex and *APOE**4 stratification for Alzheimer's Disease Genetic Risk Scores

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336/350 words

Background

Genetic risk scores (GRS), be it polygenic risk scores (PRS) or polygenic hazard scores (PHS), have shown promise to support genetic risk prediction and clinical trial recruitment for Alzheimer's disease (AD). A recent study further suggested that sex-matched AD PHS (e.g., male-to-male) outperform sex-mismatched PHS (e.g., male-to-female), while no benefit was observed for PRS. Similar benefits may be expected for matching by *APOE**4 positivity status, but this question has remained unexplored. The prior sex-stratified work neither evaluated whether full sample GRS (males+females) outperform sex-matched GRS, nor compared polygenic (including many variants regardless of significance) to oligogenic (including fewer more significant variants) effects. Here, we performed the largest-to-date sex-stratified, and first *APOE**4-stratified, evaluation of AD GRS.

Methods

The study design is detailed in **Figure-1**: genome-wide association studies (GWAS) were performed in a Discovery cohort (LMM-BOLT v.2.3.5) and GRS were constructed and evaluated in an independent Replication cohort (PRSice-2 & R v3.6). All analyses performed multiple linear regression on an AD-age score that models resilience to age-related risk for AD (**Figure-2**). Models adjusted for sex, *APOE**4/*APOE**2 dosage (rendering GRS estimates/effects independent of *APOE*), the first five genetic principal components (PC-AiR; GENESIS; R v3.6), and array/sequencing center. GRS were evaluated at different P-value thresholds to elucidate oligogenic versus polygenic effects, while all GRS with other covariates were combined to evaluate predictive performance in the Replication.

Results

Stratified discovery GWAS are shown in **Figure-3**. GRS tended to perform best at more stringent P-value thresholds (i.e., oligogenic) and GRS derived from the full-sample discovery virtually always outperformed

stratified GRS (**Figure-4-5**). Predictive performance was similarly the highest for GRS derived from the full-sample discovery (**Table-1**).

Conclusions

Our results were consistent with emerging literature supporting that AD is oligogenic and showed that the performance of sex- or *APOE**4-stratificatied GRS was outweighed by using full-sample derived GRS. While not shown here, we made consistent observations when using a case-control model (thus equivalent to PRS) without age adjustment. These findings have important implications to guide further efforts at translating AD GRS into clinical practice.

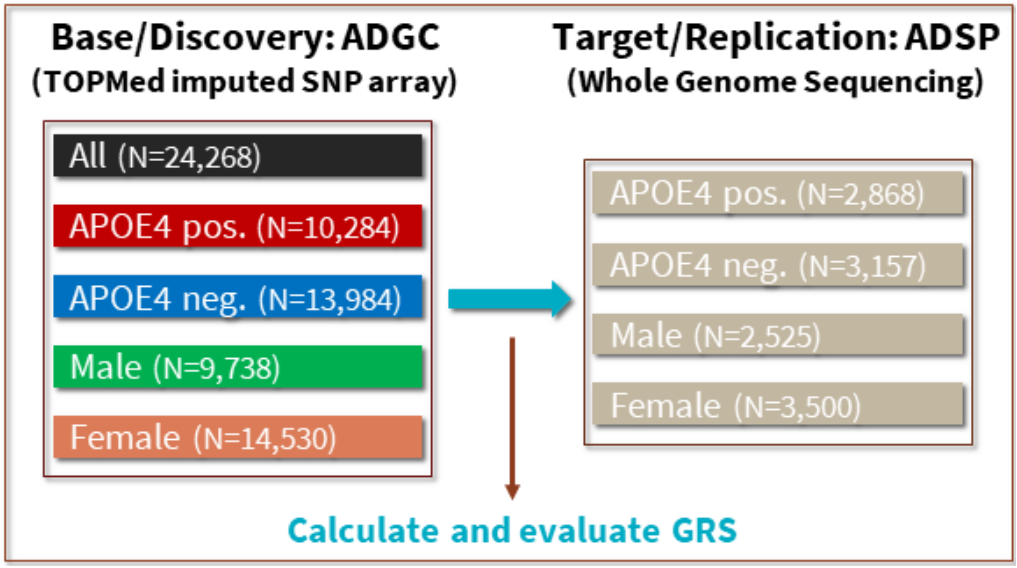

Figure-1. Study design and basic demographics. Participants were ages 60+, of European ancestry (>=75%; SNPweights v.2.1), and diagnosed as cases or controls. Subjects in the Replication were independent from the Discovery (down to first degree relatedness as determined by identity-by-descent). Variants included to calculate GRS had a minor allele frequency > 1% in both the discovery and replication, had at least 95% genotyping rate in each stratum, were intersecting across all strata, and excluded a 7MB region centered around *APOE*. GRS were constructed using clumping (distance=250kb, Linkage Disequilibrium R^2>0.1; P-value thresholds ranging from 10^{-8} to 1). *Abbreviations: Alzheimer's disease Genetics Consortium, ADGC; Alzheimer's disease Sequencing Project, ADSP; Genetic Risk Score, GRS.*

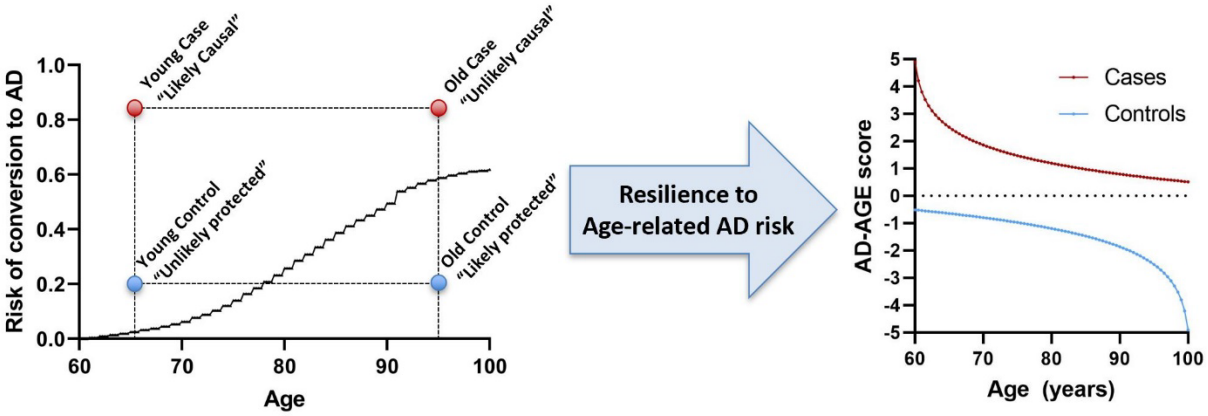

Figure-2. Schematic of the AD-age-score phenotype. Cumulative risk for AD shows subjects display (lack of) resilience depending on their age, providing the basis for an AD age-related resilience score. This approach integrates age information directly with the AD diagnosis and was shown to perform equivalent or better than Cox proportional hazard regression on AD age-at-onset (Le Guen & Belloy et al., 2021).

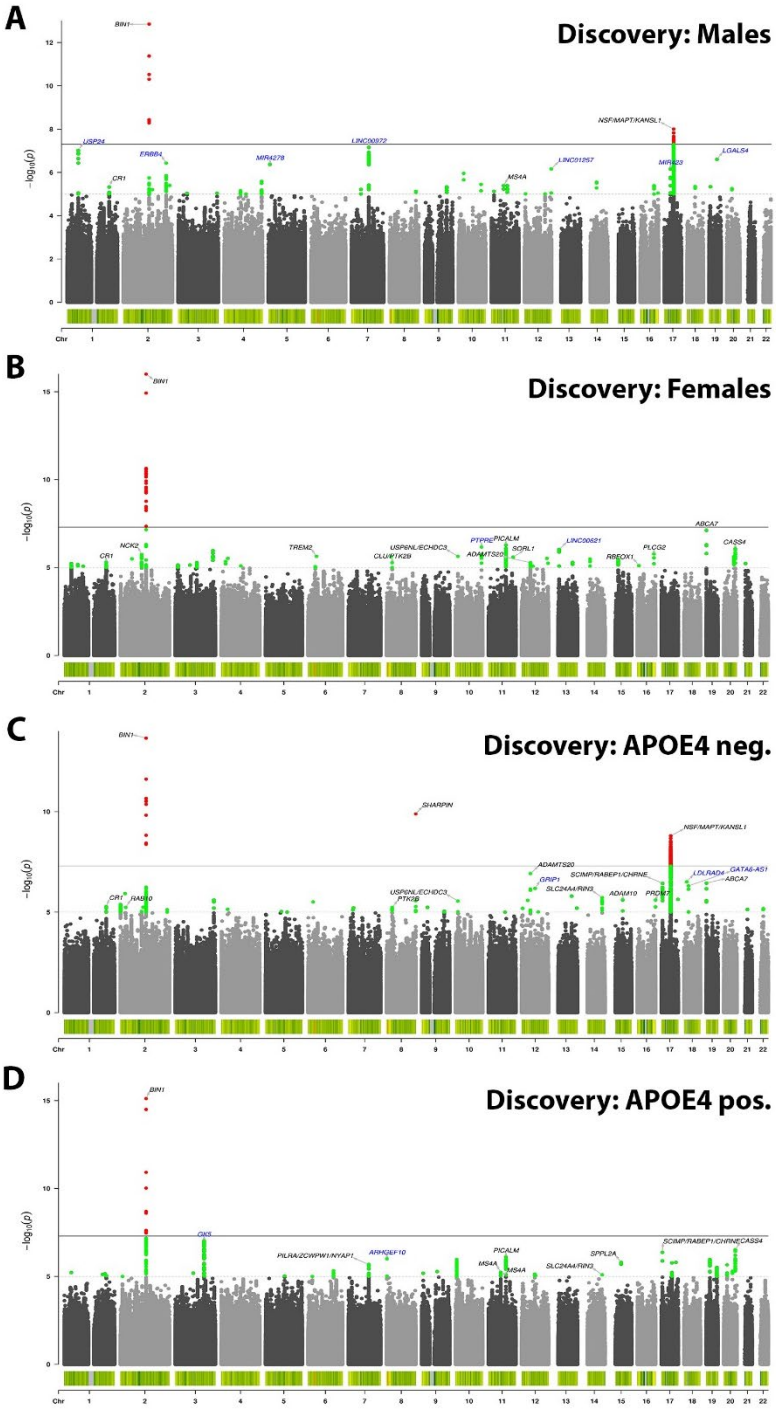

Figure-3. Manhattan plot of stratified Discovery GWAS. Green and red dots respectively indicate suggestive and genome-wide significance. Top variants passing below a P-value of 10^{-5} within 500Kb of known AD loci were annotated in black. Top variants passing below a P-value of 10^{-6} in novel loci were annotated with the nearest gene from the NCBI RefSeq curated gene set in blue. Note that the *MAPT* locus was genome-wide significant in *APOE**4 neg. subjects, consistent with Jun et al. 2016, and in males.

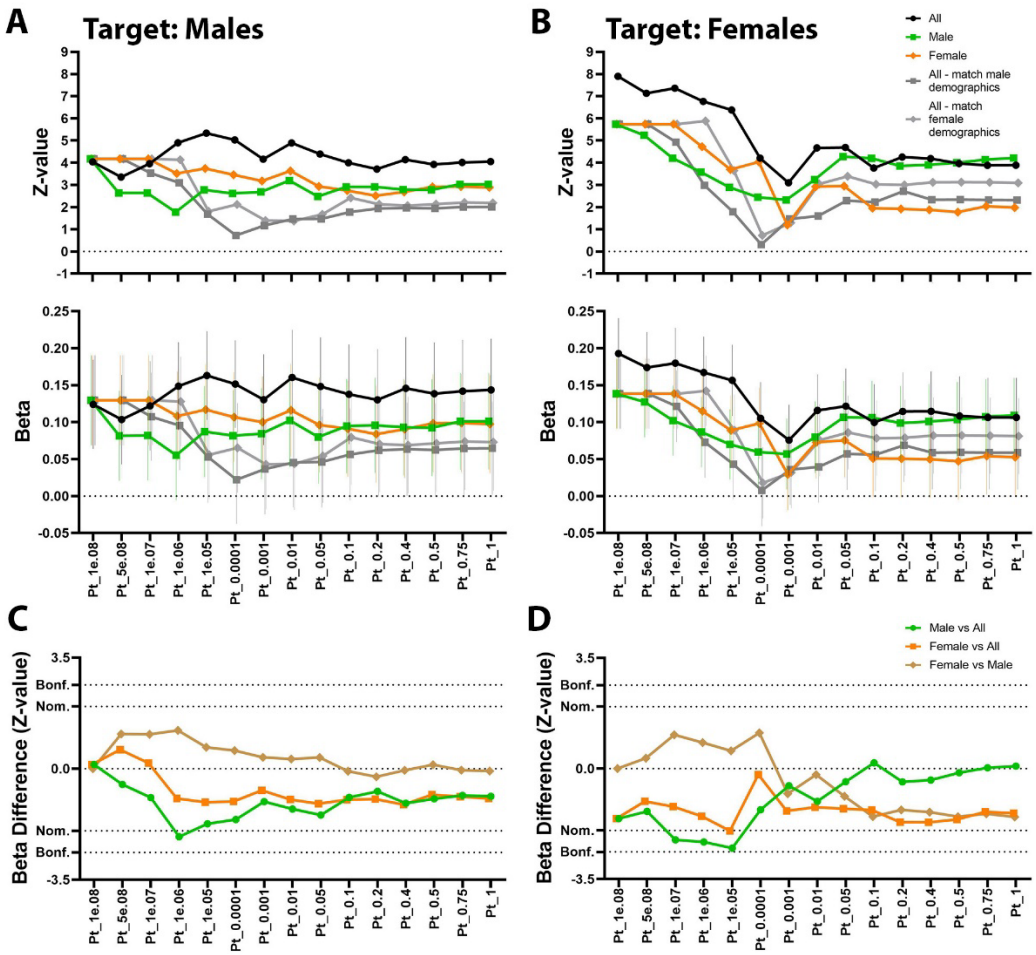

Figure-4. Evaluating genetic risk scores across sex strata. Associations of GRS (for different P-value thresholds (Pt)) with the AD-age-score in the replication are shown in males (left; **A&C**) and females (right, **B&D**). For comparison, additional GRS were computed for non-stratified discovery samples with demographics matched to male and female Discovery samples (grey traces; cf. legend). **A-B)** Top panels show Z-values and bottom panels show Beta values with 95% confidence intervals. **C-D)** Z-values for comparisons between Beta values from GRS derived from different Discovery strata, evaluated in the respective target stratum. Y-axis indicates the threshold for nominal significance of P=0.05 (Nom.) or Bonferroni correction of P=0.05/6 (Bonf.; 3 primary Discovery strata (all, males, females) evaluated in two Replication strata (males, females))

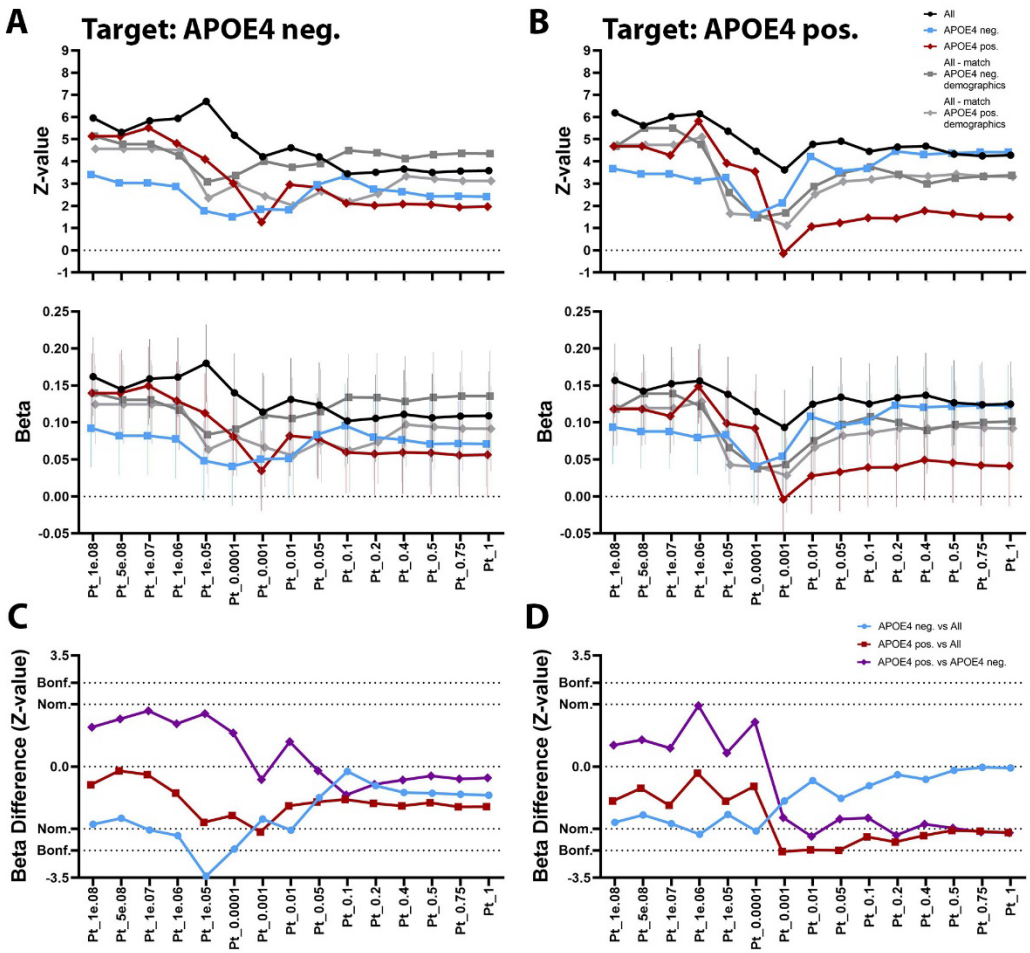

Figure-5. Evaluating genetic risk scores across *APOE4 positivity strata.** Associations of GRS (for different P-value thresholds (Pt)) with the AD-age-score in the replication are shown in *APOE**4 neg (left; **A&C**) and *APOE**4 pos (right, **B&D**). For comparison, additional GRS were computed for non-stratified discovery samples with demographics matched to *APOE**4 neg and *APOE**4 pos Discovery samples (grey traces; cf. legend). **A-B)** Top panels show Z-values and bottom panels show Beta values with 95% confidence intervals. **C-D)** Z-values for comparisons between Beta values from GRS derived from different Discovery strata, evaluated in the respective target stratum. Y-axis indicates the threshold for nominal significance of P=0.05 (Nom.) or Bonferroni correction of P=0.05/6 (Bonf.; 3 primary Discovery strata (all, *APOE**4 neg., *APOE**4 pos.) evaluated in two Replication strata (*APOE**4 neg., *APOE**4 pos.))

		Adjusted R2						
Base stratum	**Target stratum**	**sex**	**sex+APOE**	**sex+PRS**	**sex+APOE +PRS**	**APOE gain**	**PRS gain**	**PRS gain / APOE gain**
All	Males	0	0.07216	0.03761	0.10533	0.07216	0.03317	0.45967
Male	Males	0	0.07216	0.02157	0.09034	0.07216	0.01818	0.25194
Female	Males	0	0.07216	0.02291	0.09419	0.07216	0.02203	0.30529
All match male demographics	Males	0	0.07216	0.01177	0.08358	0.07216	0.01142	0.15826
All match female demographics	Males	0	0.07216	0.01543	0.08616	0.07216	0.01400	0.19401
All	Females	0	0.07357	0.03039	0.10333	0.07357	0.02976	0.40451
Male	Females	0	0.07357	0.02261	0.09426	0.07357	0.02069	0.28123
Female	Females	0	0.07357	0.01963	0.09314	0.07357	0.01957	0.26601
All match male demographics	Females	0	0.07357	0.01288	0.08630	0.07357	0.01273	0.17303
All match female demographics	Females	0	0.07357	0.01786	0.09082	0.07357	0.01725	0.23447
All	APOE4 neg.	0.00652	0.01023	0.03608	0.03961	0.00371	0.02938	7.91914
APOE4 pos.	APOE4 neg.	0.00652	0.01023	0.02305	0.02673	0.00371	0.01650	4.44744
APOE4 neg.	APOE4 neg.	0.00652	0.01023	0.02102	0.02427	0.00371	0.01404	3.78437
All match APOE4 pos. demographics	APOE4 neg.	0.00652	0.01023	0.02614	0.02885	0.00371	0.01862	5.01887
All match APOE4 neg. demographics	APOE4 neg.	0.00652	0.01023	0.03080	0.03366	0.00371	0.02343	6.31536
All	APOE4 pos.	0.00359	0.03472	0.04180	0.07104	0.03113	0.03632	1.16672
APOE4 pos.	APOE4 pos.	0.00359	0.03472	0.02333	0.05360	0.03113	0.01888	0.60649
APOE4 neg.	APOE4 pos.	0.00359	0.03472	0.02670	0.05735	0.03113	0.02263	0.72695
All match APOE4 pos. demographics	APOE4 pos.	0.00359	0.03472	0.02479	0.05530	0.03113	0.02058	0.66110
All match APOE4 neg. demographics	APOE4 pos.	0.00359	0.03472	0.02673	0.05751	0.03113	0.02279	0.73209

Table-1. Predictive performance of stratified and non-stratified genetic risk scores in the Replication. All models were fit in the target/replication data using the covariates sex, array/sequencing center, and genetic PCs 1-5. Different conditions were evaluated by further adding *APOE**2/*APOE**4 dosage and/or GRS (for all P-value thresholds) as covariates, followed by using these variables in addition to sex to predict the AD-age-score outcome measure (adjusted R2 linear regression fits). The *APOE* gain (*APOE**2/*APOE**4 dosage) was quantified as the differences between sex+*APOE* versus sex, while the PRS gain was the difference between sex+*APOE*+PRS versus sex+*APOE*.

Diverse Ancestral Populations and the Alzheimer's Disease Sequencing Project (ADSP)

Brian W. Kunkle, PhD, MPH[1,2] for the Alzheimer's Disease Sequencing Project (ADSP)

Background: A major goal of the ADSP is to fully reveal the genetic architecture of AD/ADRD across diverse ancestral populations with the hope that new discoveries and the therapeutic or prevention strategies they enable will benefit all ancestral groups.

Methods: While the project's 'Discovery Phase' (2012–2017) sequenced predominantly non-Hispanic White individuals of European ancestry (NHW-EA) [whole-exome sequencing: N=10,061; whole-genome sequencing (WGS): 197 NHW-EA and 351 Hispanic/Latino (HL) familial individuals], the 'Discovery-Extension Phase' of the project added WGS on 1,183 NHW-EA, 1,141 HL, and 1,070 non-Hispanic Black individuals with African ancestry (NHB-AA). The ADSP's current phase, the Follow-Up Study (FUS) (2018–2023) has targeted existing ancestrally diverse and unique cohorts with clinical AD/ADRD data. Over 40,000 individuals have been ascertained and ~32,000 sequenced to date (ancestry distribution: 9,192 NHB-AA; 9,952 HL; 13,531 NHW-EA, 4,600 East Asian, 2,760 Indian, 89 Amerindian).

Results: Despite relatively small sample sizes, important instances of unique AD/ADRD genetic variation have been identified in HL and NHB-AA studies, including population-specific rare/low-frequency variants, and evidence of the importance of ancestral background in conferring risk for genetic factors such as *APOE ε4*. Power studies show ~16,100 cases and ~16,100 controls are needed per ancestry for discovery of risk/protective variants with minor allele frequency (MAF) of 0.5% and odds ratios (OR) of 2.0 at genome-wide significance ($P=5x10^{-8}$). Using region-based testing ~10,000 cases and ~10,000 controls are needed for finding variants with MAF=0.005% and ORs=1.4.

Conclusions: To this end, the next phase of the ADSP, the "ADSP-FUS 2.0: The Diverse Population Initiative" NIH PAR-21-212 aims to ensure there are enough study participants to achieve statistical power for rare variant analysis in the largest US populations, with a particular focus on HL, NHB-AA, and Asian populations. Initiatives such as the Asian cohort for Alzheimer's disease (ACAD), focusing on increasing recruitment of Asians in AD/ADRD studies, are also in development. These datasets, some of which will include data for assessing social and environmental influences of AD/ADRD, will be an invaluable resource for the AD research community and will enhance ongoing efforts for the identification of shared and novel genetic risk factors for AD/ADRD across populations.

Association Analysis on Alzheimer's Disease Sequencing Project (ADSP) 16,905 Whole-Genome Sequence Data

Wan-Ping Lee, PhD[1,2], Gina M Peloso, PhD[3], Achilleas N Pitsillides, PhD[3], Nancy Heard-Costa, PhD[4,5], Hui Wang, PhD[1.2], Yuk Yee Leung, PhD[1.6], Jonathan L. Haines, PhD[7.8], Anita L. Destefano, PhD[3.4] and Collaboration on Alzheimer's Disease Research (CADRE), and The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)

Background: The Alzheimer's Disease Sequencing Project (ADSP) has released the R3 dataset of whole- genome sequencing (WGS) from 16,905 samples collected by 17 study cohorts across three major populations including 10,651 Non-Hispanic Whites, 3,212 Hispanics, 2,874 African Americans, and 168 others. The release also includes a callset of 206 million biallelic single nucleotide variants (SNVs), 16 million biallelic insertion/deletions (INDELs), and 28 million multiallelic variants. Leveraging this dataset, we are conducting association analysis for variants, genes, and gene sets to identify genetic risk for Alzheimer's Disease (AD).

Method: We assembled the sample list, kept only genetically unique individuals, and removed samples with unclear AD diagnoses. Samples were further removed if they had >10 Standard Deviation (SD) on any ADSP provided quality metrics including genotype missing rate, singleton rate, heterozygous/homozygous ratio, and transition/transversion ratio. Multiallelic variants were split into biallelic variants and, after QC, merged with the biallelic callset. We filtered variants if they did not obtain the GATK "pass", were monomporphic, has an allele balance for heterozygous (ABHet) were <0.25 or >0.75, or had a genotype missing rate >0.05. RUTH was used to perform a robust unified Hardy-Weinberg equilibrium test. We applied GENESIS PC-AiR to conduct principal component (PC) analysis. We are performing association analyses with two approaches: using all samples while adjusting for genetic ancestry, and within population-specific groups defined by PC clustering (10 SD) around reference populations from the Human Genome Diversity Project. Our analytical model will adjust for sex, PCs, *APOE,* and technical covariates.

Result: The merged biallelic and multiallelic callset contained 223 million variants. The minor allele frequency distribution (MAF) is 88.2% MAF<0.001, 6.5% 0.001<=MAF<0.01, 2.3% 0.01<=MAF<0.05, and 3.0% MAF>=0.05. PCs within the ADSP data have been generated. We are initiating association analyses including single variant analysis (using GENESIS), gene based analyses (using SKAT-O) and rare noncoding variant set based testing (using STAAR).

Conclusion: With this project, we will examine known and identify novel AD-related variants. The dataset consists of participants from diverse genetic ancestry that will enable us to investigate how AD-associated genetic risk factors differ by populations.

Multi-Ancestry Genome-wide Association Analysis of Late-Onset Alzheimer's Disease (LOAD) in 60,941 Individuals Identifies a Novel Cross-Ancestry Association in LRRC4C

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Background: Increasing diversity in genomic studies is critical for defining the genetic architecture of LOAD by improving power to identify variants more prevalent in or specific to a given ancestry. In this study, we constructed and analyzed a multi-ancestry collection of GWAS datasets in the Alzheimer's Disease Genetics Consortium (ADGC) to identify novel LOAD susceptibility loci and characterize shared and unique features of LOAD genomic risk profiles between ancestry groups.

Methods: The ADGC multi-ancestry dataset collection includes GWAS genotype and phenotype data on 38,774 non-Hispanic White (NHW), 7,454 African American (AA), 11,436 Hispanic (HI), and 3,277 East Asian (EAS) subjects, all imputed to the NHLBI TOPMed v5 haplotype reference panel. We performed a two-stage analysis: (1) single-variant association analyses using score-based logistic regression for case-control and cohort studies and generalized linear mix-model for family-based datasets with covariate adjustment for onset/exam age, sex, principal components for population substructure, and *APOE* ε2/ε3/ε4 genotype, followed by within-ancestry fixed-effects meta-analysis using METAL; and (2) cross-ancestry meta-analysis of within-ancestry summary statistics using the random-effects model (RE2) in METASOFT.

Results: In addition to *APOE* region associations, we identified five loci with cross-ancestry genome-wide significant associations ($P \leq 5\times10^{-8}$) including chromosomes 2q14 (*BIN1*; $P=2.4\times10^{-19}$), 7q22 (*NYAP1*; $P=4.9\times10^{-8}$), 11p2 (*LRRC4C*; $P=4.6\times10^{-8}$), 11q12 (*MS4A6A*; $P=2.6\times10^{-8}$), and 11q14 (*PICALM*; $P=2.3\times10^{-10}$). 21 loci reached suggestive significance ($P<10^{-5}$), including 10 associations driven by AA ancestry in or near *ABCA7*, *APP*, *TAF1B*, and *CEP44*); five by NHW (*CR1*, *CD2AP*, *SORL1*, *ECHDC3*, and *ABCA1*); four by HI (*TREM2*, *IQCK*, *DIRC3*, and *FAR1*); and one by EAS (*VPS41*), some with highly heterogeneous cross-ancestry associations. Follow-up analyses including cross-ancestry fine-mapping, gene-based analyses, eQTL (expression) analyses, and functional analyses are in progress.

Conclusions: Cross-ancestry GWAS meta-analyses identified a novel LOAD susceptibity locus, *LRRC4C*, as well as several suggestive loci driven by individual ancestry groups. *LRRC4C* (Leucine-Rich Repeat Containing 4C; MIM:608817) encodes NGL1, a ligand of Netrin-G1 in the netrin family of axon guidance molecules and has been shown to regulate development and function of thalamocortical axons. Multi-ancestry studies with even larger sample sizes will provide even more powerful for further elucidating the genomic underpinnings of LOAD.

African-ancestry based polygenic risk scores improve Alzheimer disease risk prediction in individuals of African Ancestry.

Bilcag Akgun, Kara L. Hamilton-Nelson, Nicholas A. Kushch, Larry D. Adams, Takiyah D. Starks, Izri M. Martinez Soto, Renee A. Laux, Patrice L. Whitehead, Brian Kunkle, Alzheimer's Disease Genetic Consortium, Michael L. Cuccaro, Jeffery M. Vance, Christiane Reitz, Goldie S. Byrd, Jonathan L. Haines, Gary W. Beecham, Margaret A. Pericak-Vance, Farid Rajabli.

Background: Polygenic risk scores (PRS) may be a useful approach to predict the risk of the complex disease and to be an important clinical tool for early intervention. PRS studies in Alzheimer Disease (AD) have focused on individuals of European Ancestry resulting in a >75% prediction accuracy. PRS generated from genome wide data in one population often provides reduced predictive accuracy in other populations. This is particularly problematic for underserved groups. In this study, we assessed and compared the PRS prediction accuracy of AD in individuals of African Ancestry (AA) using both AA and non-Hispanic White (NHW) Genome Wide Association (GWAS) studies.

Methods: As part of the Research in African American Alzheimer Disease Initiative (REAAADI) and ADGC, two TOPMED imputed AA datasets were generated (REAAADI:AD=234, cognitively unimpaired (CU)=676 and ADC9: AD cases=109, CU=224). We assessed the PRS using the effect sizes from summary statistics from the NHW (Kunkle et al. 2019) and the AA (Kunkle et al. 2021) studies. To model the effect of *APOE* we excluded *APOE* region in PRS constructing and included APOE alleles as separate terms in the prediction model. First, we generated PRS scores on the REAAADI dataset, and validated our model in ADC9 dataset. To assess the PRS performance, we employed the logistic regression modeling (covariates-only (age, sex, and PC1:3), PRS-only, and full (PRS+*APOE*+covariates) model) to construct receiver operator (ROC) curves.

Results: European ancestry-derived PRS has the poor prediction power (AUC=0.53) in the REAAADI dataset whereas the AA-derived PRS predicts better (AUC= 0.87). Further validation of the AA PRS in ADC9 dataset using covariates-only, PRS-only and full models validated that inclusion of African ancestry derived PRS significantly improves the accuracy of AD prediction in AA individuals ($AUC_{covariates\text{-}only}$=0.59; $AUC_{PRS\text{-}only}$=0.74 and AUC_{full}=0.81).

Conclusions: Our results showed that AA-derived PRS significantly improves AD risk prediction in AA individuals over European ancestry-derived PRS. Our findings demonstrate the importance of increasing the diversity in genetic studies to improve precision medicine approaches. Moreover, the development of more accurate PRS models that can detect the risk of AD in all in all groups paves the way for more accurate prevention, early detection, and intervention of AD.

Fine-mapping of chromosome 9p21 linkage in Puerto Rican Alzheimer disease families.

Katrina Celis, Farid Rajabli, Shaina A. Simon, Liyong Wang, Kara L. Hamilton-Nelson, Larry D. Adams, Pedro R. Mena, Sergio Tejada, Patrice L. Whitehead, Derek J. Van Booven, Briseida E. Feliciano-Astacio, Angel Chinea, Nereida I. Feliciano, Heriberto Acosta, Clifton L. Dalgard, Jonathan L. Haines, Fulai Jin, Jeffery M. Vance, Michael L. Cuccaro, Gary W. Beecham, Derek M. Dykxhoorn, Anthony J. Griswold, Margaret A. Pericak-Vance.

Background: We previously reported strong linkage on chromosome 9p21 in multiplex Alzheimer disease (AD) families from Puerto Rico. Nine families had the highest linkage contribution. 3/9 families shared seven coding variants with displayed evidence for AD association in similar ancestral population. Although these variants reside in genes with neuronal expression and functionality, they do not explain the linkage signal in all families. Here, we performed a fine-mapping analysis to identify non-coding variants that can contribute to the AD trait previously observed.

Method: We analyzed whole genome sequencing (WGS) from 9 families, 43 AD and 15 cognitively intact individuals. Chromatin interaction and cis-regulatory element (CREs) were used to prioritized relevant non-coding variants. Induced pluripotent stem cells (iPSC) derived neurons were generated from five individuals for characterization.

Result: We found an average of 300,000 non-coding variants per family. Following filtering steps including segregation, allele frequency and chromatin association, we identified ~400 variants per family. These variants were analyzed using the CREs derived from ENCODE, which left us with 31 (8%) variants falling in promoters. 5/31 variants were shared among four or more families, and fall in the promoter of genes *FBXO10*, *ACO1*, *NDUFB6* and *DNAJA1*. Six families shared variants in *FBXO10* making it our top candidate gene, a F-box protein family with a role in apoptosis and immunity. Interestingly, another F-box protein (*FBXL7)* has been associated with AD in a Caribbean Hispanic population.

Conclusion: These results reiterate the importance of family-based studies and fine-mapping as a resourceful tool to identified functional variants in AD. Transcriptomic profile and functional characterization of iPSC derived neurons will aid to understand the implication of prioritized genes in the linkage association previously observed.

Ancestral Analysis of the Presenilin-1 G206A Variant Reveals it as a Founder Event on an African Haplotype in the Puerto Rican Population

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Background: Variants in the presenilin-1 gene (*PSEN1*) are known to be pathogenic for Alzheimer disease (AD). The change of glycine at amino acid 206 to alanine (G206A) in *PSEN1* has been identified in AD Caribbean Hispanic families from Puerto Rico with variable ages of onset and incomplete segregation (Athan et.al., 2001). Here we set out to confirm the role of G206A in the genetic etiology of AD in Puerto Rico while investigating its ancestral history and founding haplotype.

Methods: We performed genotyping and whole genome sequencing (WGS) of 43 AD families (N=182: 87 AD, 41 MCI, and 44 cognitively unimpaired) and 272 AD, 145 MCI, and 297 cognitively unimpaired unrelated individuals of Puerto Rican background and identified carriers of G206A. Genotyping data were phased using SHAPEIT to identify local ancestry of the *PSEN1* haplotype followed by RFMix to estimate the genetic ancestral background (African, European, or Amerindian). Haplotype modeling was performed using MERLIN software.

Results: We identified 19 carriers of G206A among individuals with sequencing data in eight of the 43 families (14 AD, two MCI, one neuropsychiatric disorder, and two cognitively unimpaired individuals under 65 years old). G206A did not completely explain AD in these eight families as six other AD cases in the families did not carry the variant. In the unrelated cohort, we identified 13 carriers (nine AD, one MCI, one Pick's disease, and two cognitively unimpaired under 65 years old). Local ancestry indicated that the mutation arose on an African ancestral haplotype. However, in screening WGS of individuals of primarily African ancestry from Ibadan, Nigeria (63 AD and 648 controls) and African Americans part of the Alzheimer Disease Sequencing Project (1347 AD, 2290 controls) no other carriers were identified.

Conclusion: Our results support that G206A contributes to AD in the Puerto Rican population, but in AD families does not completely explain the genetic risk. We also show that this variant occurs on a common haplotype across carriers representing a founder event on an African haplotype background in Puerto Rico.

Characterization of chromosome 5q35 risk locus in African Ancestry population.

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Background: As part of the Research in African American Alzheimer Disease Initiative (REAAADI) and Late-Onset AD Family Study (LOAD), genotyping array and whole genome sequencing (WGS) data were generated for 51 families (160 affected and 318 unaffected). Multipoint linkage analyses identified a peak LOD score on chr5q35 (HLOD=3.20). Additionally, a suggestive locus flanking the 1-LOD score was previously identified in an AA GWAS study (p-value=2.6×10^{-6}) (Kunkle et al, 2019). Here, we further characterize this locus and its role in AD.

Method: We performed region-wide association analysis in an independent REAAADI dataset of ~240 cases and ~650 controls to fine map the signal in the locus. Additionally, we analyzed the WGS data to prioritize variants in the consensus regions based on segregation with disease among affected individuals and rarity (MAF<0.01). All variants were annotated for putative function including protein changes for coding variants and evidence for regulatory activity (ENCODE, RoadMap Epigenome) and chromatin interactions (publicly available HiC and promoter capture C) for noncoding variants.

Results: Region-wide association analysis identified two regions of rare (MAF~0.01) variants downstream ($p=3.0\times10^{-8}$) and upstream ($p=3.7\times10^{-6}$) of the 1-LOD linkage region. Segregation analysis using WGS data identified 111 rare variants (MAF<0.01) segregating with disease in the AD individuals of the family with the highest LOD score contributing to the linkage peak. These include a 3'UTR and synonymous variant in *INSYN2B/FAM196B* as well as a promoter variant in *WWC1/KIBRA*. Interestingly, four other AA families contributing to the chr5 linkage signal harbor different within-family shared variants located in *INSYN2B*'s promoter or in enhancer regions with evidence for interaction with *INSYN2B*'s promoter. *WWC1*, expressed in astrocytes, was previously reported in AD context, whereas novel candidate *INSYN2B* encodes an inhibitory synaptic factor active in oligodendrocytes and neurons.

Conclusions: Our initial analyses provide evidence for two candidate genes contributing to AD genetics in the AA population. Additional work for functional validation of these candidates for AD is ongoing. This AA population-specific finding shows the importance of diversifying population-level genetic data to better understand the genetic determinants of AD on a global scale.

A Novel Protective locus significantly reduces the ApoE ε4 risk for Alzheimer's Disease in African Ancestry.

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Background: African ancestry populations have a lower risk for developing Alzheimer disease (AD) from *ApoE*ε4 compared to other populations. Understanding this mechanism of protection could lead new therapeutic insights for AD. Our goal is to identify areas of the genome that interact with *ApoE*ε4 in African ancestry that result in the lowered risk for developing AD in this population.

Methods: We performed association analyses using a logistic regression model with *ApoE*ε4 allele as an interaction term and adjusted for genome-wide ancestry, age, and sex. Discovery analysis included imputed SNP data from 1,850 African American (AA) individuals with AD and 4,331 AA controls. We performed replication analysis on whole-genome sequenced (WGS) data from 1) 63 Ibadan (Nigerian) AD individuals and 648 Ibadan controls; 2) WGS 273 Puerto Rican (PR) AD individuals and 275 PR controls; and 3) SNPs imputed from 8,463 non-Hispanic White (NHW) AD individuals and 11,365 NHW controls.

Results: We identified a significant interaction with the *ApoE* ε4 allele and the SNP rs10423769_A allele, that reduces the odds ratio for AD risk from 7.2 for *ApoE*ε4/ε4 without the A allele to 2.1 for allele *ApoE*ε4/ε4 carriers with the A allele. rs10423769 (frequency = 0.11 in AA, NHW= 0.003) is located approximately 2 megabases distal *to ApoE*, in a large cluster of pregnancy specific beta-1 glycoproteins on chromosome 19 and lies within a long noncoding RNA, ENSG00000282943. rs10423769 is reported to be a splicing QTL (sQTL) for TMEM145, whose highest brain expression is in the cerebellum. This interaction analysis was identified in the discovery AA dataset (β=-0.54, SE=0.12,p-value=$7.50x10^{-6}$), and this finding was replicated in both the Ibadan (β = -1.32,SE = 0.52,p-value = $1.15x10^{-2}$) and PR (β=-1.27,SE=0.64,p-value=$4.91x10^{-2}$) datasets while it trended but was not significant in the NHW dataset.

Conclusion: This study identified a new African-ancestry specific locus that reduces the risk effect of *ApoEε4* for developing AD by approximately 75%. The genes lying near this protective locus are novel and thus suggest potential new protective mechanisms for AD development.

Novel Loci for Alzheimer Disease Identified by Genome Wide Association Study in Ashkenazi Jews

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Background: Previous studies identified associations of Alzheimer's disease (AD) risk primarily in outbred European ancestry (EA) populations. We focused on Ashkenazi Jews (AJs) who descended from a founder population in eastern Europe.

Methods: We discriminated AJs in the multiethnic Alzheimer's Disease Genetic Consortium (ADGC) TOPMed imputed GWAS dataset (n=53,502) and whole genome sequencing (WGS, n=16,815) and whole exome sequencing (WES, n=20,504) datasets assembled by the Alzheimer's Disease Sequencing Project using a reference GWAS dataset including persons with four AJ grandparents (n=3,435). Principal component (PC) analysis was performed for each AD dataset combined with the AJ reference data, and a Gaussian mixture model was applied for population clustering. GWA analyses were performed by combining AJs discriminated from the ADGC and WGS subjects (G1) using genome-wide data and from all three datasets using variants called from exome capture (G2). Separate analyses of individual common (MAF$\geq$1%) and rare (MAF<1%) variants and gene-based analyses including rare variants were performed using models adjusting for age, sex, and PCs.

Result: Totals of 2,956, 738 and 1,062 unique AJs were identified in the ADGC, WGS and WES datasets, respectively. After filtering duplicate and closely related individuals, the sample sizes were 1,355 cases and 1,661 controls for G1 and 1,504 cases and 2,047 controls for G2 analyses. Excluding the *APOE* region, G1 analyses revealed a genome-wide significant (GWS) association ($P<5.0\times10^{-8}$) with the *TREM2* R47H missense mutation ($P=9.66\times10^{-9}$) and suggestive associations with rs541586606 near *RAB3B* ($P=5.01\times10^{-8}$), rs545690149 near *ZNF890P*, ($P=5.77\times10^{-8}$) and rs1225737296 near *ANXA10* ($P=6.32\times10^{-8}$). In G2 analyses, we obtained GWS associations with *GBA* intronic SNP rs3115534 ($P=3.20\times10^{-13}$) and *TREM2* R47H ($P=2.64\times10^{-10}$), and suggestive associations with rs1003710 in *SMAP2* ($P=1.91\times10^{-7}$) and rs200698976 in *ZNF890P* ($P=3.49\times10^{-7}$). No GWS rare variant associations were identified. Significant gene-based association was identified with *GIPR* (7.34×10^{-7}).

Conclusions: Among the novel findings, *GBA* was previously associated with Parkinson disease and Lewy body dementia (LBD). Remarkably, rs3115534 is located 35 bp from, but not in linkage disequilibrium with, N370S that is associated with LBD in AJs. Moreover, rs3115534 (MAF=0.027 AJ controls) is rare in EAs (MAF=0.0015). Our results highlight the efficacy of GWAS in founder populations.

Multiple Viruses Detected in Human DNA are Associated with Alzheimer Disease Risk

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Background: Multiple infectious agents, including viruses, bacteria, fungi, and protozoa, have been linked to Alzheimer disease (AD) by independent lines of evidence.

Methods: We mapped and quantified DNA sequence reads from whole exome and whole genome sequencing data in 37,000 AD cases and controls from of the Alzheimer Disease Sequencing Project that did not align to the human genome to 318 viral reference sequences. After quality control, the sample included 1,696 samples derived from brain (cases=1,314, controls=382) and 14,588 derived from blood (cases=5,813, controls=8,775). We tested individual and cumulative normalized viral read counts, both free and inserted in the host genome, for association with AD using multiple machine learning (ML) classifiers, selecting the top 30 viral species according to an algorithm based on the species' predictive rank weighted by the model's overall predictive accuracy across models. These top 30 viruses were tested for association with AD using logistic regression models adjusted for PCR amplification, sequencing site, sex, *APOE* genotype, and ancestry. Analyses were stratified by tissue source.

Results: We detected sequence reads from 175 unique viral species, herpes simplex virus 1 (HSV-1) being the most common. Viral read counts varied significantly by sequence center, tissue source, sex, PCR use, and ancestry in both the WES and WGS datasets. ML results indicated that herpes viruses (1, 2, 4, 5, 6A, 6B, 7, and 8), HIV, Hepatitis C, Molluscum contagiosum, several Torque Teno virus species (TTV), HPV-71, Coronavirus 229E, Tick-borne encephalitis, human Mastedenovirus, human polyomavirus 2, variola virus, primate t-lymphotropic virus 1, human endogenous retrovirus K, and total normalized mapped viral reads were significant predictors of AD. Subsequent meta-analyses of results stratified by tissue source showed that AD was significantly associated with HSV-1(OR_{meta}=4.07, P_{meta}=2.22x10^{-5}), Human papillomavirus type 71(OR=3.26, P=0.006), TTV-10 (OR=22.11, P=0.004) , and cumulative viral read count (OR=7.34, P=0.03).

Conclusions: These results support the hypothesis that viral infections, especially HSV-1, is associated with AD risk and demonstrate the potential of using deep sequencing technology to detect microbial agents in multiple tissues and discerning here-to-for unrecognized associations of infectious agents and AD.

Variants near X-Chromosome Genes NLGN4X and PTCHD1 are Significantly Associated with Alzheimer's Disease Risk

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Background: Genome-wide association studies (GWAS) for AD have identified numerous associated loci but have been focused only on the autosomes. We sought to identify novel AD-associated genes on X-Chromosome (X-Chr).

Methods: We evaluated the association of AD with X-Chr variants in GWAS datasets assembled by the Alzheimer Disease Genetics Consortium including 26,322 non-Hispanic White (NHW) individuals using logistic regression models with covariates for age, sex and principal components of ancestry. The number of independent SNPs in X-Chr was calculated by linkage disequilibrium pruning yielding a study-wide significance threshold of $P<7.58x10^{-7}$. Genes near SNPs surpassing this threshold were further evaluated by expression quantitative trait locus (eQTL) in the BRAINEAC database and differential gene expression analyses using RNA-seq data obtained from autopsied brains contained (GEO: GSE44772 and GSE33000). We also tested association of AD with missense or splicing variants with minor allele count (MAC)≥10 in the same genes using GENESIS and whole exome sequencing (WES) data obtained by the Alzheimer Disease Sequencing Project (ADSP) for 11,172 NHWs.

Results: We identified novel associations with variants near *NLGN4X* (rs34056759; minor allele frequency [MAF]=0.15, OR=1.15, $P=5.14x10^{-7}$) and *PTCHD1* (rs5970663; MAF=0.30, OR=1.13, $P=8.26x10^{-7}$). The rs5970663 risk allele *C* was significantly associated with increased expression of *PTCHD1* in the medulla region, and *PTCHD1* expression was significantly higher in AD cases than in controls in the prefrontal cortex ($P<2.1x10^{-8}$) and visual cortex ($P<2.3x10^{-4}$). Rs34056759 was not associated with *NLGN4X* expression, but *NLGN4X* expression was significantly lower in AD cases compared to controls in the prefrontal cortex ($P<8.7x10^{-7}$). A rare *PTCHD1* variant (rs201933353; MAF = 0.001) was nominally associated with AD among 6,318 women (OR=3.72, P=0.06).

Conclusion: We identified novel associations of AD with X-Chr variants near *NLGN4X* and *PTCHD1*, loci that were previously associated with autism spectrum disorder. We plan to replicate, fine-map, and annotate the candidate loci identified in this study using large whole genome sequencing ADSP datasets.

Identification of Genetic Variants and Serum Metabolites Associated with Blood-derived Mitochondrial DNA Copy Number

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Background: Mitochondrial DNA Copy Number (mtDNA-CN) can be used to estimate mitochondrial function and it varies across tissues and cell types. Blood-derived mtDNA-CN has been studied in aging-related diseases including Alzheimer's Disease (AD). However, little is known about the genetic contribution to variation of blood-derived mtDNA-CN and how this variation affects the level of serum metabolites.

Methods: We developed a fast computational pipeline to accurately estimate mtDNA-CN using whole genome sequence data from blood samples from European ancestry (EA, 2,885 AD cases and 2,777 controls), African American (AA, 1,118 AD cases and 1,725 controls), and Caribbean Hispanic (CH, 1,022 AD cases and 1,949 controls) participants of the Alzheimer's Disease Sequencing Project (ADSP). In the combined sample and within each population group, we tested association of blood-derived mtDNA-CN with 17,569,705 variants (minor allele count≥20) genome-wide using a linear mixed effect model including covariates for age, sex, sequencing center, PCR, AD status, polygenic risk score of blood cell count, and principal components of ancestry. We also tested the associations of mtDNA-CN and levels of 175 serum metabolites in 1,521 subjects from Alzheimer's Disease Neuroimaging Initiative.

Results: In the total sample, we identified genome-wide significant (GWS) associations with variants from 24 independent loci. The top-ranked SNP (rs1455130415 in *NDUFS8*, ($p=3.25x10^{-42}$) was also GWS in EAs ($p=3.96x10^{-28}$) and AAs ($p=2.20x10^{-27}$). SNP rs997412864 ($p=5.13x10^{-9}$) in *GCAT* was found associated with mtDNA-CN in EAs, but not in other groups. Association of SNP rs1237233197 ($p=1.40x10^{-8}$) in *NDUFS7* was specific to AAs. Measurements of two long-chain acylcarnitine, C14:2-OH ($p=4.91x10^{-7}$) and C18:2 ($p=1.81x10^{-5}$), were negatively associated with mtDNA-CN after Bonferroni correction ($P<2.9x10^{-4}$). Ornithine, a non-proteinogenic amino acid, was also negatively associated with mtDNA-CN ($p=2.32x10^{-4}$).

Conclusions: We identified GWS association of blood-derived mtDNA-CN with a SNP in a nuclear-encoded mitochondrial gene, *NDUFS8*, which encodes a subunit of Complex I. In addition, mtDNA-CN was significantly associated with two acylcarnitine metabolites and ornithine whose levels were previously reported to be decreased in blood of AD patients. These results provide more insight about the role of mitochondrial function in AD pathogenesis and suggests that blood-derived mtDNA-CN may be a useful biomarker for AD.

Association of short tandem repeats with neuropathological features in late-onset of Alzheimer's disease brains

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Background: Late-Onset Alzheimer's Disease (LOAD) is characterized by genetic heterogeneity and there is no single model explaining the genetic mode of inheritance. Short tandem repeats (STRs), which are hyper-mutable sequences in the human genome could explain some of the missing heritability in LOAD. STRs are involved in several neuro-degenerative disorders. We systematically evaluated the impact of 31 disease-associated STRs on neuropathological LOAD features.

Methods: From whole-genome sequencing (WGS) data in for 1,134 unrelated individuals of European ancestry from Religious Orders Study (ROS) and Rush Memory and Aging project (MAP) cohorts, we identified known pathogenic STRs in 31 loci using ExpansionHunter. WGS was generated from DNA extracted from blood and brain tissues. We tested the association of STRs with a) neuropathological LOAD status, b) beta-amyloid levels, c) neurofibrillary tangle (NFT) burden, d) global measure of pathology based on the scaled scores of 5 brain regions and e) estimated slope of global cognition using longitudinal measurements. Regression models adjusting for age, sex and first three principal components. Subsequently, we examined if STRs influenced gene expression in dorsolateral prefrontal cortex (DLPFC), posterior cingulate cortex (PCC) and the anterior cingulate (AC) and tested if the association of STRs with neuropathological traits were mediated by altered gene expression.

Results: TGC repeat in *ATXN1* was associated with cognitive decline (b=-0.007, p=0.014) and risk of clinical AD (b=0.126, p=0.03). Variations in CAG repeats in *ATN1* was associated with cognition (b=0.004, p=0.022) and risk of pathological AD (b=-0.069, p=0.035). Longer Repeats *ATXN1* increased gene expression in DLPFC (b=0.012, p=0.049) and PCC (b=0.019, p=0.006) and repeats in *ATN1* altered DLPFC (b=0.01, p=0.016) and PCC (b=0.01, p=0.026) expression. Mediation analysis determined that the effect of the CAG repeats in *ATN1* on tau was mediated by gene expression in PCC (p=0.004).

Conclusions: We demonstrate that disease causing STRs influence the underlying gene expression in brain and are associated with neuropathological and cognitive endophenotypes of AD. This suggests that STRs could explain some of the missing heritability in LOAD.

APOE missense variant R145C is associated with increased Alzheimer's disease risk in African ancestry individuals with the *APOE ε3/ε4* genotype

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1. Background

The *APOE* gene has two common missense variants that greatly impact the risk of late-onset Alzheimer's disease (AD). Here we examined the risk of a third *APOE* missense variant, R145C, that is rare in European-Americans but common in African-Americans and always in phase with *APOEε3* (**Table 1**).

2. Methods

We included 11,790 individuals of African ancestry (**Table 2**). The discovery sample was composed of next generation sequencing data (2,888 cases and 4,957 controls), and the replication was composed of imputed data (1,201 cases and 2,744 controls). In primary analyses, the AD risk associated with R145C was estimated using a linear-mixed-model regression on case-control diagnosis. In secondary analyses, we estimated the influence of R145C on age-at-onset using linear-mixed-model regression, and risk of conversion to AD using competing risk regression.

3. Results

In *ε3/ε4*-stratified meta-analyses (**Table 3**), R145C carriers had a nearly three-fold increased risk compared to non-carriers (OR=2.75[1.84;4.11]; $P=8.3x10^{-7}$) and had a reported AD age-at-onset nearly 6 years younger (β=-5.72[7.87;3.56]; $P=2.0x10^{-7}$). Competing risk regression showed that the cumulative incidence of AD grows faster with age in R145C carriers compared to non-carriers (HR=2.42[1.81;3.25]; $P=3.7x10^{-9}$; **Figure 1**).

4. Conclusions

The R145C variant is a potent risk factor for AD among African ancestry individuals with the *ε3/ε4* genotype. Our findings should enhance AD risk prediction in African ancestry individuals and help elucidate the mechanisms linking the apoE protein to AD pathogenesis. The findings add to the growing body of evidence demonstrating the importance of including ancestrally-diverse populations in genetic studies.

Table 1. *APOE* R145C (rs769455) allelic breakdown by *APOE* genotype. Rs769455 alternate allele (T) is not observed in *APOE ε2/ε2*, *ε2/ε4*, *ε4/ε4*, and is only present in the homozygous state in *APOE ε3/ε3*, supporting the finding in sequening databases that the alternate allele is always found in phase with *APOE ε3*. Note that rs769455 is located between rs7412 (99 bp apart) and rs429358 (39 bp apart) which define the *APOE* allele genotype. CN: cognitively normal, AD: Alzheimer's disease, N: number of individuals.

			APOE ε2/ε2		*APOE ε2/ε3*		*APOE ε3/ε3*		*APOE ε2/ε4*		*APOE ε3/ε4*		*APOE ε4/ε4*	
Sample	**rs769455**	**N total**	**CN**	**AD**	**CN**	**AD**	**CN**	**AD**	**CN**	**AD**	**CN**	**AD**	**CN**	**AD**
Discovery	C C	7561	41	11	691	221	2490	1086	179	111	1269	1041	118	303
	C T	279	0	0	18	4	129	57	0	0	19	52	0	0
	T T	5	0	0	0	0	3	2	0	0	0	0	0	0
Replication	C C	3793	26	5	366	75	1236	416	120	42	765	468	117	157
	C T	148	0	0	11	1	78	14	0	0	21	23	0	0
	T T	4	0	0	0	0	4	0	0	0	0	0	0	0

Table 2. Demographics per *APOE* genotype. DX: diagnosis, CN: cognitively normal, AD: Alzheimer's disease, N: number of individuals, %Females: percentage of female individuals, μ and σ: mean age and standard error.

			APOE ε2/ε2		*APOE ε2/ε3*		*APOE ε3/ε3*		*APOE ε2/ε4*		*APOE ε3/ε4*		*APOE ε4/ε4*	
Sample	**DX**	**N**	**N (%Females)**	**Age μ(σ)**	**N (%Females)**	**Age μ(σ)**	**N (%Females)**	**Age μ(σ)**	**N (%Females)**	**Age μ(σ)**	**N (%Females)**	**Age μ(σ)**	**N (%Females)**	**Age μ(σ)**
Discovery	CN	4957	41 (58.5%)	77.6 (9.2)	709 (69.7%)	77.6 (8.6)	2622 (72.7%)	77.2 (8.3)	179 (76.5%)	75.2 (8.8)	1288 (72.2%)	75.8 (8.4)	118 (67.8%)	73.0 (7.8)
	AD	2888	11 (81.8%)	81.3 (5.4)	225 (71.1%)	79.6 (8.7)	1145 (68.0%)	78.2 (8.5)	111 (67.6%)	77.7 (8.7)	1093 (68.9%)	75.2 (8.7)	303 (68.6%)	70.7 (8.2)
Replication	CN	2744	26 (69.2%)	82.2 (6.7)	377 (67.4%)	80.7 (7.6)	1318 (69.0%)	78.7 (9.5)	120 (67.5%)	79.4 (8.8)	786 (67.3%)	78.3 (9.4)	117 (76.9%)	75.8 (9.9)
	AD	1201	5 (60.0%)	78.2 (8.0)	76 (57.9%)	77.4 (9.7)	430 (69.5%)	76.4 (9.7)	42 (64.3%)	77.3 (8.4)	491 (72.7%)	73.9 (9.9)	157 (64.3%)	71.4 (8.6)

Table 3. R145C is associated with increased AD risk and with younger age-at-onset specifically in *APOE ε3/ε4* individuals. Since R145C is in phase with *APOE ε3*, stratified analyses were limited to *APOE ε2/ε3*, *APOE ε3/ε3*, and *APOE ε3/ε4* genotypes. Discovery sample is composed of next generation sequencing data, while replication sample included microarray data imputed on the TOPMed reference panel. *APOE ε3[R145C]/ε4* individuals have significantly higher AD risk, younger onset, and higher risk of conversion from healthy aging to AD than *APOE ε3/ε4* individuals. N: number of individuals, MAC: minor allele count, OR: odds ratio, β: parameter estimate in the regression, HR: hazard ratio, P: p-value.

		AD Case-Control Regression				AD Age-at-onset Regression				Competing Risk Regression			
	Sample	N	MAC	OR [95% CI]	P	N	MAC	β [95% CI]	P	N	MAC	HR [95% CI]	P
APOE ε2ε3	*Discovery*	934	22	0.73 [0.26; 2.04]	0.55	222	4	-6.96 [-15.56; 1.64]	0.11	918	22	1.14 [0.35; 3.69]	0.82
	Replication	453	12	0.78 [0.11; 5.35]	0.80	53	1	-18.42 [-39.23; 2.38]	0.08	430	12	3.05 [0.33; 28.09]	0.32
	Meta-analysis	1387	34	0.74 [0.3; 1.84]	0.52	275	5	-8.63 [-16.58; -0.69]	0.03	1348	34	1.42 [0.5; 3.99]	0.51
APOE ε3ε3	*Discovery*	3767	196	1.06 [0.78; 1.46]	0.71	1108	58	-1.68 [-3.87; 0.5]	0.13	3646	187	1.09 [0.82; 1.45]	0.57
	Replication	1748	100	0.85 [0.48; 1.53]	0.60	347	8	-1.36 [-8.29; 5.58]	0.70	1656	94	0.80 [0.41; 1.57]	0.51
	Meta-analysis	5515	296	1.01 [0.77; 1.34]	0.94	1455	66	-1.65 [-3.74; 0.43]	0.12	5302	281	1.04 [0.8; 1.35]	0.79
APOE ε3ε4	*Discovery*	2381	71	3.01 [1.87; 4.85]	**6.0×10^{-6}**	1063	51	-5.87 [-8.35; -3.4]	**3.4×10^{-6}**	2315	70	2.66 [1.86; 3.8]	**8.5×10^{-8}**
	Replication	1277	44	2.20 [1.04; 4.65]	**0.04**	421	21	-5.23 [-9.58; -0.87]	**0.02**	1195	42	2.00 [1.19; 3.35]	**8.7×10^{-3}**
	Meta-analysis	3658	115	2.75 [1.84; 4.11]	**8.3×10^{-7}**	1484	72	-5.72 [-7.87; -3.56]	**2.0×10^{-7}**	3510	112	2.42 [1.81; 3.25]	**3.7×10^{-9}**

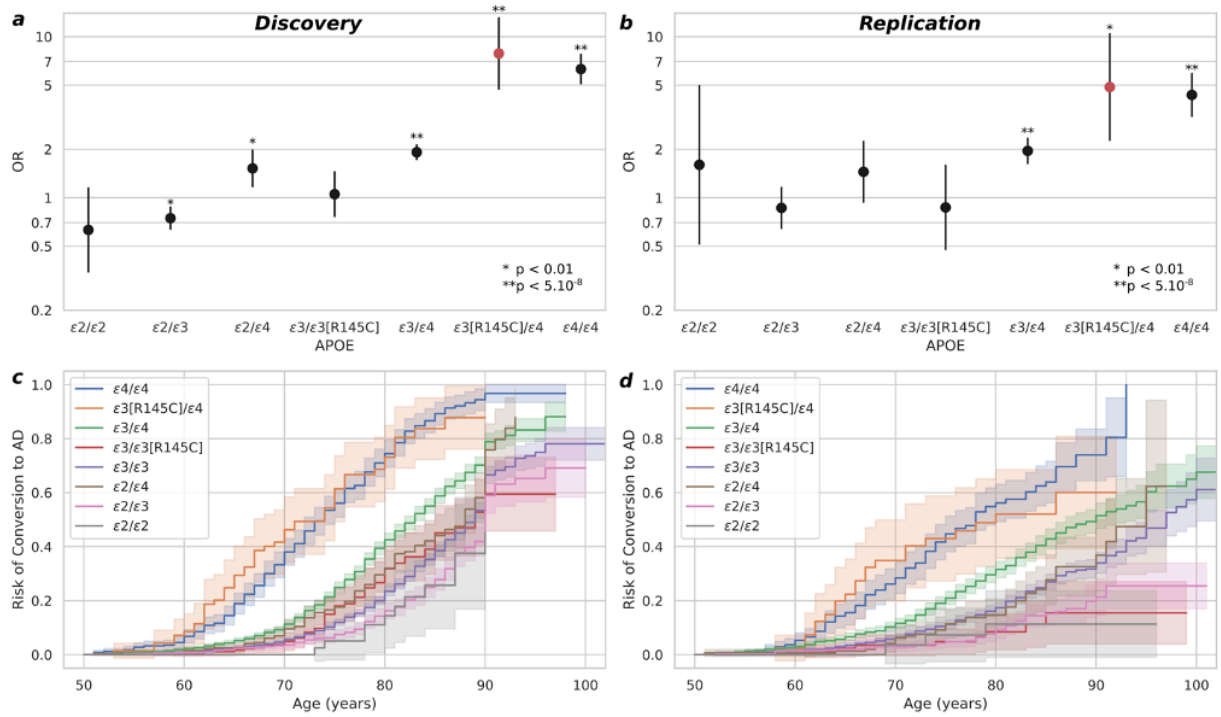

Figure 1. *APOE ε3/*R145C]/*ε4* individuals have an AD risk comparable to *APOE ε4/ε4* individuals. Alzheimer's disease (AD) risk per *APOE* genotype assessed compared to the *APOE ε3/ε3* reference group (i.e., odds ratio (OR) *APOE ε3/ε3* equals 1) in (**a**) our discovery sample composed of next generation sequencing data from the ADSP dataset, and in (**b**) our replication composed of microarray data imputed on the TOPMed reference panel. AD cumulative incidence per *APOE* group, from the competing risk regression analysis accounting for the censored individuals (last visit or reported death), in the discovery (**c**) and replication (**d**).

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ADSP Functional Genomics: from gene, to function to mechanisms and targets

Carlos Cruchaga, on behalf of the ADSP Functional Genomics Consortium

Genetic studies have been highly successful in identifying genetic regions associated with Alzheimer's disease, and we are now at the exciting juncture of applying this knowledge to understanding disease mechanisms. The ability to generate and mine clinical and omicdata is advancing our understanding of neurodegeneration. The Alzheimer's Disease Sequencing Project (ADSP) Functional Genomics Consortium (FunGen-AD; https://adsp-fgc.niagads.org/) aims to apply cutting-edge genomics technologies, high-throughput genetic screening and cutting edge disease modeling to understand the functional consequences of genetic susceptibility and resilience to Alzheimer's Disease, and to identify genetics-guided targets for the prevention, diagnosis, and treatment of Alzheimer's disease and related dementias (AD/ADRD).

The investigators of the FunGen-AD consortium are using multiple approaches, including brain single cell data acquisition, human stem cell modeling and high through put CRISPR-based screens, to understand how AD variants lead to changes across molecular networks, and understand how specific risk variants affect disease in diverse populations. Multi-omic data generated in well characterized cohorts are being used to identify systems-level alterations in and provide insight into the mechanisms underlying genetic variants.

The FunGen-AD consortium is organizing and facilitating large collaborative projects. Currently we are working on a xQTL project putting together data from multi-tissue (brain, myeloid cells, CSF and plasma), and multi-omic layers (transcriptomic in bulk and at single cell level, epigenetic, proteomic, and metabolomic). In order to fully understand the biology of AD we recognize that multiple tissues, and -omic layers need to be studied. All the omic data are being processed, harmonized and analyzed using standard pipelines, and mapping on a reference genome and annotation developed by the group. This QTL atlas will be used to perform colocalization and identify the functional genes within AD risk loci, and Mendelian Randomization to identify novel causal genes, proteins and druggable targets. This xQTL project will provide a rich resource of multi-omics datasets, analysis pipelines, and an xQTL atlas for the research community studying AD/ADRD and other complex neurodegenerative traits.

In summary, the FunGen-AD consortium is using multidisciplinary and collaborative research approaches to identify genetics-guided targets for the prevention, diagnosis, and treatment of AD/ADRD.

Title: Pleiotropic effect of *LRRK2* on Parkinson-associated proteins and processing of pathological alpha-synuclein in myeloid cells

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Background: Mutations in the *LRRK2* gene, which encodes leucine-rich repeat kinase 2 (LRRK2), are a cause of autosomal dominant Parkinson's disease (PD). Single-nucleotide polymorphisms (SNP) in the *LRRK2* locus are one of the most consistently replicated in multiple genome-wide association studies in sporadic PD and with inflammatory diseases. We recently found that a PD-associated risk SNP (rs76904798, $p=2.0\times10^{-28}$) in the *LRRK2* locus is also associated with cerebrospinal fluid (CSF) levels of granulins (*PGRN,* $p=8.6\times10^{-9}$), glycoprotein nmb *(GPNMB,* $p=2.3\times10^{-9}$), Ectonucleoside triphosphate diphosphohydrolase-1 (*ENTPD1,* $p=2.3\times10^{-9}$) also known as CD39 and Cathepsin B (*CTSB,* $p=2.5\times10^{-4}$). Yet, functional validation in cellular models is lacking.
Methods: Human monocytic cells (U937) were differentiated (dU937) into macrophages to test the effect of LRRK2 on CTSB, CD39, GPNMB, PGRN and alpha-synuclein (aSyn). LRRK2 kinase activity and expression level were modulated using pharmacological inhibitors and lentivirus-mediated overexpression. Protein levels were assessed using western blotting and ELISA. dU937 cells were treated with human aSyn pre-formed fibrils (haSyn PFFs). We analyzed CSF somaLogic data from the Parkinson's Progression Marker's Initiative (PPMI) cohort (Data accessed November 2021).
Results: *LRRK2* mutation (G2019S and R1441G) carriers from the PPMI cohort exhibit significantly increased CSF levels of PGRN ($p=2.1\times10^{-22}$), GPNMB ($p=1.6\times10^{-29}$), CTSB ($p=2.5\times10^{-16}$) and CD39 ($p=1.8\times10^{-18}$) compared to age and gender-matched non-carriers (N=1158). dU937 cells overexpressing LRRK2 showed an increase in the phosphorylation of LRRK2-Ser935 and Rab10-T73 and intracellular levels of lysosomal proteins CTSB and Saposin D without affecting LAMP1 or M6PR. LRRK2 also reduced extracellular CD39, PGRN and GPNMB levels and the levels of intracellular endogenous aSyn dimers in dU937 cells. HaSyn PFF treatment induced a time-dependent reduction of CTSB and GPNMB levels, increased PGRN levels and altered intracellular aSyn processing pattern in dU937 cells overexpressing LRRK2. Pharmacological LRRK2 kinase inhibition decreased intracellular CTSB levels. LRRK2 co-immunoprecipitates with PGRN in cells and in human brain.
Conclusions: LRRK2 modifies lysosome-associated proteins and regulate aSyn proteostasis. Pathogenic *LRRK2* mutations increased CSF levels of PGRN, GPNMB, CTSB and CD39 in the PPMI cohort. Our in vivo and in vitro data supports a pleotropic role of the *LRRK2* locus as a genetic modifier of PD-associated proteins.

Comparative analysis of CSF biomarker measurement in Alzheimer's disease by multiplex SOMAscan platform and immunoassay-based ELISA approach

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Background:
The multiplex, aptamer based SOMAscan assay has an advantage over classic immunoassay-based methods because of its ability to measure a large number of proteins in a cost-effective manner. This high-throughput nature of SOMAscan panel enables the possibility of quantification of more human proteins in future. However, the performance of this novel technology in comparison to the tried and tested gold standard, such as ELISA, needs to be evaluated. In this study, we performed a comparative analysis of SOMAscan and ELISA protein measurement for the following five classic cerebrospinal fluid (CSF) biomarkers in Alzheimer's disease (AD): NFL, NGRN, TREM2, VILIP1 and SNAP-25.

Method:
We obtained measures of the five biomarkers in ADNI (N=689), MAP (N=870), DIAN (N=115), and Pau (N=94) cohort through SOMAscan and ELISA. Samples between the platforms were matched based on subject ID and CSF draw date. Because several cohorts had ELISA based measures for only a subset of biomarkers, sample size for each biomarker varied. In SOMAscan, there were more than one aptamer targeting TREM2 and VILIP1, and comparisons were performed for all of them. For each protein, raw values were log10 transformed and scaled with mean 0 and variance 1. Pearson's correlation coefficients were calculated subsequently. In addition, we obtained receiver operating characteristic (ROC) curve and area under the curve (AUC) value to compare prediction accuracy of these biomarkers between the two platforms.

Results:
For NGRN and VILIP1, we found high correlation between SOMAscan and ELISA measures (correlation > 0.9). NFL also showed a strong correlation (correlation = 0.83). TREM2 had a fair correlation (>0.6), whereas SNAP-25 showed weak correlation (correlation = 0.097). Measures in both platforms provided similar predicted performance for AD status for all biomarkers. The findings were consistent for most biomarkers when correlations and prediction accuracy was examined in each cohort.

Conclusion:
In four of the five CSF AD biomarkers (NFL, NGRN, TREM2, and VILIP1), we found that SOMAscan measures were comparable to ELISA measures. Our study shows a promise for using SOMAscan as an alternative to traditional immunoassay-based ELISA. Follow-up study will be required for SNAP-25 and other additional established biomarkers.

CSF proteo-genomic studies identify an interaction between LRRK2 genetic variants and GRN, GPNMB, CTSB, and ENTPD1

Lihua Wang[1,2], Chengran Yang[1,2], Samira Mafi Moghaddam[1,2], Jigyasha Timsina[1,2], Priyanka Gorijala[1,2], Fengxian Wang[1,2], Ignacio Alvarez[3], Miiquel Aguilar[3], Agustin Ruiz[4,5], Pau Pastor[4,5], Yun Ju Sung[1,2,6] , Carlos Cruchaga[1,2,7]

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Background: Parkinson's disease (PD) is a movement disorder characterized by dopaminergic neurodegeneration in the substantia nigra of the brain. Another neurodegenerative disorder, Alzheimer's disease (AD), is a progressive memory loss disorder with pathological changes mainly at hippocampus and entorhinal cortex. As dementia is also present in late stage of PD, there might be common molecular mechanism between the pathogenesis of AD and PD. Evidence has nominated Leucine Rich Repeat Kinase 2 (LRRK2), Progranulin (GRN), Glycoprotein nonmetastatic melanoma protein B (GPNMB), Cathepsin B (CTSB), and ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1) since these proteins were linked to AD and PD. Identifying genetic variants of 5 proteins will be critical to shed lights on common disrupted pathways shared by AD and PD.

Methods: To identify genetic variants associated with these 5 proteins, we performed protein quantitative trait loci (pQTL) analyses of log10 transformed CSF GRN, GPNMB, CTSB, ENTPD1 and LRRK2 assayed in SomaScan platform. We considered ~11 million sequenced variants from 787 individuals recruited at PPMI in the discovery and ~4.3 million imputed variants from 799 Knight ADRC samples in replication. Age, sex and 10 principal components were included as covariates. Genome-wide threshold (5.0×10^{-8}) was used in the meta-analyses of discovery and replication for significance.

Results: On chromosome 12, exonic missense LRRK2 variant rs33939927 (MAF=1.4%) was identified as shared pQTL for GRN ($P=7.87\times10^{-10}$), CTSB ($P=8.99\times10^{-9}$), GPNMB ($P=3.59\times10^{-9}$), and ENTPD1 ($P=1.24\times10^{-13}$). The second LRRK2 exonic missense variant rs34637584 (MAF=11%) was pQTL consistent for 3 proteins (GRN: $P=2.34\times10^{-8}$, GPNMB: $P=8.55\times10^{-13}$, and ENTPD1: $P=1.75\times10^{-13}$). The third LRRK2 exonic missense variant rs35303786 (MAF=3.4%) was identified for GPNMB ($P=1.53\times10^{-8}$) and ENTPD1 ($P=2.31\times10^{-8}$). The risk allele of 3 SNPs were associated with higher amount of corresponding CSF proteins. No significant LRRK2 pQTL was identified. Additional analyses including colocalisation with AD and PD GWAS results are ongoing.

Conclusions: Two low frequency exonic missense LRRK2 variants (rs33939927 and rs35303786) and one common exonic missense LRRK2 variant (rs34637584) were pQTL shared by GRN, CTSB, GPNMB, and ENTPD1. Our findings indicate that the LRRK2 exonic variants are the key genetic regulators of LRRK2 activity and CSF level of GRN, CTSB, GPNMB, and ENTPD1.

Large-scale pQTL analysis of over 3,000 CSF samples

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Abstract:

Introduction: Expression quantitative trait locus (eQTL) studies have been influential in identifying new gene targets for many complex diseases. However, levels of mRNA often do not correlate well with levels of the protein that they encode, due to rates of degradation, translation, or alternative splicing, among other reasons. By correlating protein levels to genetic variation, pQTLs can elucidate a more accurate genetic architecture that underlies the disease. While few large-scale studies have considered cerebrospinal fluid (CSF) protein levels, CSF biomarker levels are one of primary diagnostic tools in Alzheimer's disease (AD), highlighting CSF's relevance to brain aging and AD pathology. Here, we present CSF pQTL analysis of over 3,000 individuals.

Methods: We generated CSF levels of 7,584 analytes for 3,065 samples using the aptamer-based SOMAscan 7k platform. CSF levels of 4,884 analytes for additional 1,158 samples were also included. After stringent quality control, 3,107 unrelated European samples were selected for analysis. We performed pQTL analysis using a linear model with protein levels as the outcome variable, using a three-stage study design: discovery, replication, and meta-analyses. We performed colocalization of our pQTLs with eQTLs and GWAS loci, and compared our pQTL results to pQTLs reported by smaller CSF studies and plasma studies to identify CSF-specific pQTLs. We used Mendelian Randomization (MR) to identify proteins potentially causative for both AD and other traits.

Results: This study represents the first use of the SOMAscan 7k platform in CSF, as well as the largest pQTL analysis of CSF to date. Analyses are ongoing.

Conclusions: We previously performed pQTL analysis of CSF using the SOMAscan 1.3k platform, where 425 pQTLs were identified and 3 proteins (PTP1B, Siglec-3, and SLAF5) were found through MR to be involved in AD risk, as well as 48 additional protein associations for other neurodegenerative diseases. This study expands on those findings by including 6,000 more proteins and much larger samples, allowing for greater power. This study will be vital for identifying novel proteins involved in AD and elucidate novel drug targets for AD and other neurodegenerative disorders.

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Using amyloid PET as a biomarker to detect progression of early Alzheimer disease

Muhammad Ali, PhD[1,2], Samira Mafimoghaddam, PhD[1,2], Yun J. Sung, PhD[3,4,5], Fengxian Wang, PhD[1,2,6], Maria Victoria Fernandez, PhD[7], Derek B Archer, PhD[8,9], Timothy J. Hohman, PhD[10], Claudia L Satizabal, PhD[11,12,13], Qiong Yang, PhD[14,15], Alexa S Beiser, PhD[15,16], Ruiqi Wang, MS[17], Brian A. Gordon, PhD[18,19,20], Tammie L.S. Benzinger, MD, PhD[18,19,20], Chengjie Xiong, PhD[1,19], John C. Morris, MD[1,18], Randall J. Bateman, MD[1,6,21], Celeste M. Karch, PhD[2,6,20], Eric McDade, DO[1,21], Alison Goate, DPhil[22], Sudha Seshadri, MD[15,16], Richard Mayeux, MD[23], Reisa Sperling, MD[24], Rachel F. Buckley, PhD[24], Michael J Properzi[24], Keith A. Johnson, MD[25], Dominantly Inherited Alzheimer Network (DIAN)[26], Alzheimer's Disease Neuroimaging Initiative (ADNI)[27] and Carlos Cruchaga, PhD[1,2,18], (1)Washington University in St. Louis School of Medicine, St. Louis, MO, USA, (2)NeuroGenomics and Informatics Center, St. Louis, MO, USA, (3)Washington University in St. Louis School of Medicine, St Louis, MO, USA, (4)Neurogenomics and Informatics Center, St. Louis, MO, USA, (5)Hope Center for Neurological Disorders, St Louis, MO, USA, (6)Hope Center for Neurological Disorders, St. Louis, MO, USA, (7)Washington University School of Medicine, St Louis, MO, USA, (8)Vanderbilt Memory & Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN, USA, (9)Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA, (10)Vanderbilt Memory & Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN, USA, (11)Framingham Heart Study, NHLBI, Framingham, MA, USA, (12)Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, University of Texas Health Sciences Center, San Antonio, TX, USA, (13)Boston University and the NHLBI's Framingham Heart Study, Boston, MA, USA, (14)Boston University School of Public Health, Boston, MA, USA, (15)The Framingham Heart Study, Framingham, MA, USA, (16)Boston University School of Medicine, Boston, MA, USA, (17)Boston University, Boston, MA, USA, (18)Hope Center for Neurological Disorders, Saint Louis, MO, USA, (19)Knight Alzheimer Disease Research Center, Saint Louis, MO, USA, (20)Washington University School of Medicine, St. Louis, MO, USA, (21)Knight Alzheimer's Disease Research Center, St. Louis, MO, USA, (22)Ronald M. Loeb Center for Alzheimer's disease, New York, NY, USA, (23)The Institute for Genomic Medicine, Columbia University Medical Center and The New York Presbyterian Hospital, New York, NY, USA, (24)Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, (25)Gordon Center for Medical Imaging, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, (26)Washington University in St. Louis, Washington, MO, USA, (27)Harvard University, Cambridge, MA, USA

Abstract Text:

Background: Alzheimer's disease (AD), the most common form of dementia, is a complex polygenic disease with genetic, cellular, pathologic, and clinical heterogeneity. Recently, significant attempts have been made for identifying AD biomarkers for reliably tracking disease progression in its early asymptomatic stages. To this end, amyloid PET imaging has provided useful information tracking accumulation of parenchymal amyloid beta (Aβ) deposits in the brain. Previous investigations have conducted genetic association studies of CSF Aβ42, both continuously as well as using a threshold for amyloid positivity, and identified novel genes and loci potentially contributing to the preclinical stage in AD. In a recent case-control based study using amyloid PET as a quantitative trait, Raghavan et al., identified a novel locus for amyloidosis within RBFOX1 gene in 4,314 participants, however, further investigations are needed to replicate and expand on these findings.

Method: In order to investigate the underlying genetic basis for brain amyloidosis in AD, we systematically analyzed the largest collection of amyloid imaging data (N=6,320), across multiple ethnicities from multicenter cohorts (ADRC, A4, DIAN, ADNI, ADNIDOD, UPitt, and HABS) as a quantitative trait to identify the functional variants and genes driving the association of AD. Furthermore, we have conducted

diagnosis-, gender-, and APOE-stratified analyses to investigate the effect of these variables on the brain amyloidosis.

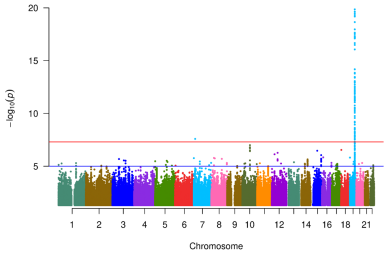
Result:

Preliminary results found a strong APOE signal in chr19 (min P = 1e-185) and a genome-wide significant hit (P = 2e-08) in the chromosome 7 (potentially, associated to *TMEM106B* gene) warranting further investigation (Fig. 1). Moreover, some suggestive signals were detected in chr10 (P = 1e-07) and chr12 (P = 5e-07). Consistent with previous finding, we found *RBFOX1* to be associated with increased amyloid burden (β = 0.07), however, the signal was only nominally significant (P = 0.03). Additional analyses including multi-ancestry meta-analysis using FHS, AIBL, and EISAI cohorts and post-GWAS analyses are ongoing.

Conclusion: The identification of pre-clinical AD-specific molecular signatures and pathways will enable the characterization of appropriate therapeutic targets for the prevention and/or treatment of AD. Results generated from our investigation will further serve to generate prediction models for amyloid positivity and Mendelian Randomization (MR) analyses.

Tables and Figures:

Manhattan_amyloid_imaging.png (126.8KB)



Title:
Using amyloid PET as a biomarker to detect progression of early Alzheimer disease

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Preferred Presentation Format:
Oral Presentation Preferred, but will do Poster Presentation if so assigned

Was this research funded by an Alzheimer's Association grant?
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Theme:
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Identification of novel genetic variants and biomarkers for cognitive decline in Alzheimer's disease

Muhammad Ali, PhD[1,2], Fengxian Wang, PhD[1,3], Samira Mafimoghaddam, PhD[1,2], Jack Euesden, PhD[4], Chloe Robins, PhD[4], David J. Pulford, PhD[4] and Carlos Cruchaga, PhD[1,2,3,5], (1)Washington University in St. Louis School of Medicine, St. Louis, MO, USA, (2)NeuroGenomics and Informatics Center, St. Louis, MO, USA, (3)Hope Center for Neurological Disorders, St. Louis, MO, USA, (4)GlaxoSmithKline Medicines R&D, Stevenage, SG1 2NY, UK, Hertfordshire, United Kingdom, (5)Knight Alzheimer Disease Research Center, Saint Louis, MO, USA

Abstract Text:

Background:

Alzheimer’s disease (AD) is a complex, multifactorial disease that is incurable in the aging population. The success of genome-wide association studies (GWAS), as a cross sectional design, to identify novel genetic risk factors for AD in recent years is well known; however, case-control studies are less likely to uncover genetic factors that influence other aspects of the disease, such as progression and onset.

Method:

In order to identify common and rare genetic variants associated with rates of cognitive decline in AD, we aim at systematically analyzing the largest collection of longitudinal and GWAS data (N = 7,241), across non-Hispanic white individuals from multicenter cohorts (Knight-ADRC, ADNI, NACC, and GSK) with at least 1.5 years of follow up after being diagnosed with AD. We also aim at exploring if genetic risk factors, alone or interacting with other genetic factors, are associated rate of cognitive decline in patients with AD when aggregated together into a single Polygenic Risk Score (PRS). Furthermore, external proteomics data will be combined with the genetics data for Mendelian Randomization (MR) analyses in order to discover causal biomarkers for cognitive decline and AD risk.

Result:

Preliminary results found a suggestive signal in chr21 (min P = 8.7e-8) approaching close to the genome-wide significance threshold. Moreover, some other suggestive signals were detected in chr2 (min P = 3.8e-06) and chr1 (min P = 3.7e-06) that warrant further investigation. Further results and key findings of the post-GWAS analyses will be presented during the AAIC meeting.

Conclusion:

We have leveraged these datasets to generate prediction models for rate of cognitive decline in AD. The identification of AD-specific genetic variants and biomarkers will enable the characterization of appropriate therapeutic targets for slowing or halting the AD progression.

Title:
Identification of novel genetic variants and biomarkers for cognitive decline in Alzheimer's disease

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Sex-specific molecular profiling to understand pathology and identify causal genes and drug targets for Alzheimer's disease

Yun J Sung, PhD[1], Anh Do, PhD[1], Jigyasha Timsina, MS[2], Lihua Wang, PhD[3], Fengxian Wang, PhD[2] and Carlos Cruchaga, PhD[2,4], (1)Washington University School of Medicine, St Louis, MO, USA, (2)NeuroGenomics and Informatics Center, St. Louis, MO, USA, (3)Department of Psychiatry, Saint Louis, MO, USA, (4)Hope Center for Neurological Disorders, St. Louis, MO, USA

Abstract Text:

Background: Alzheimer's disease (AD) is a highly heterogeneous multifactorial disease. Genetic influences on AD are strong as shown by several pathogenic genes and over 50 AD GWAS loci. There are also clear sex differences in AD risk and progression. Women are at a higher risk of developing AD and present faster progression. A recent GTEx study also highlights sex differences in the genetic regulation of gene expression. Despite these established sex differences, sex-specific molecular findings in AD are still limited.

Method: We generated and performed analysis using 713 CSF proteomic data that passed QC obtained from Knight-ADRC and DIAN samples. The sample includes 190 late onset clinical AD patients and 509 age- and gender-matched cognitively healthy individuals. Age at lumbar puncture and surrogate variables (to account for unmeasured heterogeneity) were included as covariates. To evaluate sex-specific molecular signatures, we performed sex-stratified analysis by separately analyzing 333 males and 366 females.

Result: In male CSF tissues, 99 proteins significantly associated with late onset AD status (FDR $P < 0.05$) and 131 proteins in female CSF tissues. Those proteins were enriched in pathways involved in the endolysosome and proteasome pathway including HSP70. We identified 44 proteins presenting a suggestive evidence of sex-specific effects on AD status. In particular, several proteins that were previously reported to be associated with AD risk show sex-specific effects. Downregulation of LRIG3 improves cognitive impairment and alleviate neuronal damage in hippocampus tissues in AD rats through modulating the PI3K/Akt pathway. We found that LRIG3 was associated in males only and would not have been identified through a combined analysis that simply included sex as a covariate ($P = 3.4\times10^{-3}$ in males; $P > 0.5$ in females; $P = 0.067$ in all).

Conclusion: This study demonstrates that 800 proteins in 700 CSF tissues can provide a suggestive information on sex-specific proteomic profiles. We will extend our sex-specific analysis using our recently generated 7000 proteomic data to fully understand the biology of the disease and determine the role of sex in disease, create sex-specific genes and prediction models. This will provides insights for clinically translatable interventions for prevention and treatment.

Title:
Sex-specific molecular profiling to understand pathology and identify causal genes and drug targets for Alzheimer's disease

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Identification of genetic regulators of human metabolites in CSF

Ciyang Wang[1], Samira Mafimoghaddam, PhD[2,3], Brenna C Novotny, MS[2,4], Yun J Sung, PhD[5,6,7], Fabiana H.G. Farias, PhD[8,9], Chengran Yang, PhD[7,10,11], Fengxian Wang, PhD[2,3,12], Marta Marquié, MD, PhD[13,14], Mercè Boada, MD, PhD[13,15], Itziar de Rojas, MSc[13,15], Ignacio Alvarez, MSc[13,15], Miquel Aguilar, Msc[15,16], Victoria Fernandez, PhD[11,17,18], Oscar Harari, PhD[2,4,12] and Carlos Cruchaga, PhD[2,3,12,17,19], (1)Division of Biology and Biomedical Sciences, Washington University in St. Louis, St. Louis, MO, USA, (2)NeuroGenomics and Informatics Center, St. Louis, MO, USA, (3)Washington University in St. Louis School of Medicine, St. Louis, MO, USA, (4)Washington University School of Medicine, St. Louis, MO, USA, (5)Washington University in St. Louis School of Medicine, St Louis, MO, USA, (6)Neurogenomics and Informatics Center, St. Louis, MO, USA, (7)Hope Center for Neurological Disorders, St Louis, MO, USA, (8)Washington University School of Medicine in St. Louis, St. Louis, MO, USA, (9)Hope Center for Neurological Disorders, Washington University, St Louis, MO, USA, (10)NeuroGenomics and Informatics Center, St Louis, MO, USA, (11)Washington University School of Medicine, St Louis, MO, USA, (12)Hope Center for Neurological Disorders, St. Louis, MO, USA, (13)Networking Research Center on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain, (14)Research Center and Memory Clinic. Ace Alzheimer Center Barcelona. Universitat Internacional de Catalunya, Barcelona, Spain, (15)Research Center and Memory Clinic, ACE Alzheimer Center Barcelona, Universitat Internacional de Catalunya, Barcelona, Spain, (16)Networking Research Center on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III, Barcelona, Spain, (17)Hope Center for Neurological Disorders, Saint Louis, MO, USA, (18)NeuroGenomics and Informatics Center, Washington University School of Medicine, St. Louis, MO, USA, (19)Knight Alzheimer Disease Research Center, Saint Louis, MO, USA

Abstract Text:

Background:

Brain metabolism perturbation in dementia is not well understood. Metabolite levels are quantitative traits that have been linked to genetic loci. Existing metabolite quantitative trait loci (MQTL) were found mostly using tissues other than cerebrospinal fluid (CSF) and brain, which being less than ideal for studying neurodegenerative diseases. The first CSF MQTL study was published last year, but with limited power. Therefore, we hope to expand our knowledge on MQTL in the central nervous system to better understand neurological disorders.

Method:

We performed metabolome-wide genome-wide association study (M-GWAS). More than 400 metabolites passed QC in CSF from 2329 participants recruited from five cohorts (CASTLE project). We performed a three-stage study design: discovery (1224 CASTLE participants), replication (meta-analysis of results from 1087 CASTLE participants and 291 CSF participants (Panyard, D.J. et. al 2021)) and meta-analyses. Linear regression model includes age, sex, genetics principal components, genotyping array, and cohort information as covariates. We defined an association region to be 1 Mb interval centered on the index SNP (lowest study-wide P value) by performing clumping of signals using plink1.9. We merged association regions if they share overlapping chromosome location to identify genetic locus associated with metabolite level traits. Future plan includes association study including rare variants, functional annotation of each locus, conditional analysis to identify independent signals, replication of identified signals, M-GWAS for Brain metabolomics datasets (1169 samples in total), comparing features of identified associations amongst multi-tissue (CSF, brain and blood) using mashr in R. In addition, colocalization and Mendelian randomization analysis will be performed to discover metabolites contributing to neurological disorders.

Result:

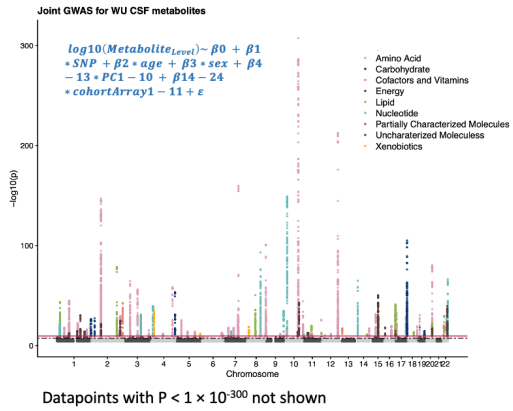
The preliminary CSF M-GWAS study jointing five cohorts identified 165 associations in 125 metabolites from 90 loci. Meta-analysis on the discovery and replication results will be utilized for the downstream functional annotation, tissue comparison, and disease mechanistic exploration.

Conclusion:

We present the largest CSF M-GWAS study so far and showed a substantial number of genetic association findings for metabolites. We not only expect to replicate a number of our findings using studies with blood and CSF tissues, but also expect to discover novel signals that has potential for being unique to CSF.

Tables and Figures:

Figure 1. M-GWAS.png (111.7KB)



Title:
Identification of genetic regulators of human metabolites in CSF

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Preferred Presentation Format:
Oral Presentation Preferred, but will do Poster Presentation if so assigned

Was this research funded by an Alzheimer's Association grant?
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Genome-Wide Association Study for CSF Aβ42, Tau, and pTau in a Large Multi-cohort Study to Identify Novel AD Genetic Variants

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Background

Previous studies have identified more than 20 genetic loci to be associated with AD risk. However, these reported loci do not account for all the estimated heritability nor report enough information on the undelaying biological mechanism. Genome-wide association studies (GWAS) of endophenotypes have been successful in identifying new loci associated with Alzheimer's disease (AD). To better understand AD pathology and to identify new variants implicated in AD much larger samples size is needed. In this study, we conducted a GWAS of Amyloid-beta (Aβ42) tau, and phosphorylated tau (ptau) in cerebrospinal fluid (CSF) to detect novel variants associated with AD.

Methods

AD CSF biomarkers Aβ42, Tau, and pTau were measured in 7282 individuals from 24 different cohorts. Samples were genotyped using different array technology. Stringent quality control (QC) standards were applied to each dataset before combining datasets. The minimum call rate for single nucleotide polymorphism (SNP) and individuals was 99.85%. SNPs not in Hardy–Weinberg equilibrium ($P < 1 \times 10^{-6}$) were excluded. X-chromosome SNPs were analyzed to verify sex identification. Duplicates and cryptic relatedness (Pihat ≥ 0.25) among samples were tested by pairwise genome-wide estimates of proportion identity-by-descent. PLINK was used to calculate principal component analysis (PC). Previous to combining the data for analysis, CSF biomarker levels of were log10-transformed to approximate a normal distribution with the mean standardized to zero for each dataset to account for the variability on the different platforms used to measure proteins levels. One-stage joint-GWAS to maximize the power in our analysis. Post-GWAS analysis such as colocalization (COLOC) was implemented to detect genetic colocalization of two potentially related signals phenotype or signals to discern whether they shared common genetic causal variants. Also, Mendelian randomization (MR) and LD score regression LDSC was implemented to evaluate the overlap in the genetic architecture between CSF biomarkers and the risk factor in AD. Additionally, GTAC analysis was applied to estimate the proportion of phenotypic variance explained by all Genome-wide SNPs for the trait of interest.

Results

This study represents one of the largest multi-cohort GWAS analyses on CSF AD biomarkers. Several genome-wide significant hits were found including *APOE*. Additional analyses are underway.

Conclusions

CSF Aβ42, tau, and ptau are well established AD endophenotypes with a clear genetic association with *APOE* genotype and AD risk. Genetic studies on endophenotypes provide enough power to detect association with a smaller sample size than case-control studies helping us to better understand the biological mechanism of the disease. With this study we aim to identify novel variants implicated in AD.

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Use of the human reference genome 38 enhances integration of the multi-tissue proteomics with genetics and disease

Heng Yi, MS[1,2], Qijun Yang[1,2], Jigyasha Timsina, MS[1,2], Fengxian Wang, PhD[1,2], Lihua Wang, PhD[1,2], Carlos Cruchaga, PhD[1,2,3] and Yun Ju Sung, PhD[1,2], (1)Washington University in St. Louis School of Medicine, St. Louis, MO, USA, (2)NeuroGenomics and Informatics Center, St. Louis, MO, USA, (3)Hope Center for Neurological Disorders, St. Louis, MO, USA

Abstract Text:

Background: Most existing protein quantitative trait locus (pQTL) studies focus on a single tissue and use the reference Genome Reference Consortium Human Build 37 (GRCh37/hg19) published in 2009. GRCh38/hg38 was updated in 2013 with correcting thousands of sequencing artifacts that cause false SNPs and updating non-nuclear genomic sequence. Many papers strongly recommend switching to GRCh38/hg38. The goal of this study is to use multiple tissues (brain, CSF and plasma) to explore the genetic architecture of protein levels in neurologically relevant tissues and to update the human reference genome as hg38 to compare the findings.

Method: In this study, 805 CSF samples and 871 proteins, 529 plasma samples and 953 proteins and 378 brain samples and 1,300 proteins passed quality control process. We performed genome-wide association analyses of over 8 million autosomal variants (MAF ≥ 0.01) imputed using the most updated hg38 TOPMed imputation panel to identify cis/trans pQTLs. We performed conditional analysis to identify independent pQTLs. After removing pleiotropic loci and including Alzheimer's disease (AD) variants, Mendelian randomization (MR) was applied to detect the casual associations between proteins and AD risk. To decrease unmeasured pleiotropy effect, we used co-localization analysis to get more supporting information among multiple traits. Finally, we replicated our findings in much larger studies.

Result: In brain tissue, we identified 4269 pQTLs in hg38 compared to 2418 pQTLs in hg19 with a threshold of 5×10^{-8} for cis-pQTLs and 5×10^{-8}/(number of independent proteins) for trans-pQTLs. We found the independent SNPs and highlight the complexity of regions with multiple independent local pQTLs. Analysis for CSF and plasma is underway.

Conclusion: This study is to apply the hg38 as the human reference genome to detect much more pQTLs and correct possible false findings in the previous hg19 study. With the following analysis, we could get more valuable and confirmed information about the additional GWAS loci and identify the function of certain proteins on the disease risk. The multiple tissue samples and multiple traits could help us detect the complex genetic architecture of protein levels in neurologically relevant tissues.

Title:
Use of the human reference genome 38 enhances integration of the multi-tissue proteomics with genetics and disease

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GWAS for CSF TREM2 levels identify new variants implicated on TREM2 biology and Alzheimer disease

Samira Mafimoghaddam, PhD[1,2], Lihua Wang, PhD[1,2], Priyanka Gorijala, Msc[1,2], Jigyasha Timsina, Msc[1,2], Niko Nykanen, PhD[1,2], Fengxian Wang, PhD[1,2], Marta Marquié, MD, PhD[3,4], Mercè Boada, MD, PhD[3,4], Ignacio Alvarez, MSc[5], Miquel Aguilar, Msc[5], Pau Pastor, MD, PhD[5], Agustín Ruiz, MD, PhD[3,4], Yun Ju Sung, PhD[1,2] and Carlos Cruchaga, PhD[1,2,6], (1)NeuroGenomics and Informatics Center, St. Louis, MO, USA, (2)Washington University in St. Louis School of Medicine, St. Louis, MO, USA, (3)Networking Research Center on Neurodegenerative Disease (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain, (4)Research Center and Memory Clinic, Fundació ACE Institut Català de Neurociències Aplicades - Universitat Internacional de Catalunya (UIC), Barcelona, Spain, (5)Memory Disorders Unit, Department of Neurology, Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Terrassa, Spain, (6)Hope Center for Neurological Disorders, St. Louis, MO, USA

Abstract Text:

Background: It is demonstrated that the soluble TREM2 in the cerebrospinal fluid (CSF) is associated with Alzheimer disease (AD). Recent studies by our group found that it is the *MS4A4A* and/or MS4A6A locus that plays a role in modulating sTREM2 and is also associated with AD risk. The goal of this study is to validate and extend findings from previous studies using a larger cohort, identify functional genes, and determine the overlap of the genetic architecture of CSF TREM2 levels with other traits.

Method: We used 3,033 individuals from Knight ADRC, ADNI, DIAN, and PPMI, and 8,499,039 variants (MAF >0.01) to identify protein quantitative trait loci (pQTLs) that modify TREM2 levels via a linear regression including age, sex, first 10 genetic principal components and array/cohort as covariates. TREM2 protein measurements were obtained from SomaScan 7k platform. Colocalization analyses were conducted for AD risk as well as functional genes from eQTLGen. LDSC and GNOVA and Mendelian randomization (MR) is being used to determine the overlap of the genetic architecture of sTREM2 levels with those for AD risk, onset and progression, as well as cardiovascular and lipid traits.

Result: The pQTL analysis identified the previously discovered *MS4A* gene region on chr11 (rs72918674, *P* = 7.009e-58) as well as a peak on chr3 (rs73823326, *P* = 2.227e-09). The lead variant resides in the intron of *MS4A6A* gene. Conditional analysis on this variant revealed rs10897026 as an additional independent signal located in the intron of *MS4A4A*. Chr11 peak colocalized with AD risk (PP-H4=0.97) and *MS4AE* and *MS4A6A* expression QTL in blood (PP-H4=0.97 and 0.96, respectively). Four regulatory region variants are in high linkage disequilibrium (LD) with chr3 index variant. *RBMS3* and *TGFBR2* are two genes flanking the chr3 peak, both expressed in microglia.

Conclusion: This is the largest study to date aiming at identifying genetic modifiers of CSF sTREM2. The findings validated discoveries from previous studies and identified a novel signal on chr3 at genome-wide significance. We propose two new genes, *RBMS3* and *TGFBR2* on chr3, could be involved in TREM2 biology. Our findings provide new insight to unravel sTREM2 modulators and their role in AD.

Title:
GWAS for CSF TREM2 levels identify new variants implicated on TREM2 biology and Alzheimer disease

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A large-scale genome-wide association study of early-onset Alzheimer disease

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Background

Early-onset (≤65 years old) Alzheimer Disease (EOAD), which accounts for approximately 10% of all AD cases, is sometimes equated with dominantly inherited forms of AD (i.e., caused by known mutations in *APP*, *PSEN1* or *PSEN2*). However, 90% of EOAD cases remain unexplained by these variants. This project aims to identify novel EOAD-associated variants through a large-scale, multi-ethnic genome-wide association (GWA) study.

Methods

We have leveraged the Alzheimer Disease Genetics Consortium (ADGC) GWAS dataset that is aligned to GRCh38 and imputed with the TOPMed imputation server. This includes 39 studies from non-Hispanic Whites (NHW; CA=3,202; CO=5,782), 17 from African American (CA=139; CO=253), six from Asian (CA=133; CO=474), and seven from Hispanic (CA=199; CO=59) cohorts. Only the younger (≤65yo) and older participants (>80yo) were included for analysis as cases and controls, respectively. The genetic background was confirmed using PCA. We are performing single-variant analysis to identify variants that confer a higher risk for EOAD.

Results

Our preliminary single-variant association analysis (using sex, PC1-PC10 as covariates) emerging from the largest NHW cohort (CA=3,202; CO=5,782) have revealed nine different loci that were associated with EOAD at a suggestive P-value<1×10^{-6}. The strongest signal from our analysis was in the *APOE* region. Additionally, we identified three novel genome-wide significant (P-value <5×10^{-8}) loci of interest at *HLA-DRB9* (rs9268852, P-value=2.9×10^{-9}, OR=1.22); *FAM86B3P* (rs73199790, P-value=3×10^{-11}, OR=1.32); and *MSMB* (rs2075895, P-value=2.83×10^{-16}, OR=1.26); while also confirming the previously identified loci at *MS4A4A* (rs7108663, P-value=1.13×10^{-10}, OR=0.80) and *CR1* (rs6656401, P-value=2.54×10^{-12}, OR=1.32). We will perform qualitative associations on the other three ethnicities to confirm the transferability of these signals.

Conclusion

Our single-variant analysis has identified three novel loci associated with EOAD. This study is the largest genetic screening for risk and protective variants in EOAD and will be instrumental to identifying novel variants and pathways implicated in unexplained EOAD. Our future analysis includes gene-based association and pathway analyses per ethnicity to identify variants that confer a higher risk for EOAD, followed by transethnic analysis to validate the comprehensive nature of these risk factors. Additionally, we have also generated GWAS data from the Knight-ADRC participants, which will be merged with the ADGC datasets for our future analysis.

Genetic architecture of plasma Alzheimer disease biomarkers

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Abstract:

Background: Case-control genome-wide association studies (GWAS) have identified loci associated with risk for Alzheimer disease (AD), but they require very large sample sizes and identify variants with small effect sizes. GWAS of informative endophenotypes for disease have more power to identify novel variants and provide information about biological mechanisms. By analyzing data from 1,269 individuals, we previously identified risk variants for AD that were associated with CSF levels of tau and p-tau, including a novel variant associated with AD risk. Recent technological developments have led to new assays in plasma for Aβ, p-tau and NFL with high predictive power. However, no GWAS have been performed using these plasma biomarkers as quantitative trait.

Methods: Plasma Aβ and NFL were obtained from 882 individuals from the Knight-ADRC, plasma Aß from 160 individuals from the Human Connectome Project, and plasma Aß, NFL, tau and p-tau from 1,694 individuals from ADNI. GWAS and sequencing data is also available from these samples. We performed linear regression to determine single nucleotide polymorphisms (SNPs) associated with these plasma AD biomarkers. SKAT-O was used to perform gene-based analyses including rare non-synonymous variants. GCTA and LDSC was used to determine the proportion of biomarker variability explained by genetic variants. We used colocalization to determine if the loci associated with plasma biomarker levels are also associated with AD risk, onset or progression. Mendelian randomization and LDSC was used to determine the overlap in the genetic architecture of plasma AD biomarkers with other traits, including cardiovascular and inflammation-related traits.

Results: This represents the largest GWAS for plasma AD biomarkers measured with the novel and more powerful assays. We found several genome-wide significant hits, including *APOE*. Additional analyses are ongoing.

Conclusions: Previous studies using CSF biomarker levels as quantitative traits identified novel genes implicated in AD risk, onset and progression. This current study using plasma biomarker levels as quantitative traits can be critical to identification of novel genes that impact AD and more accurate interpretation of plasma biomarker levels.

GWAS of Genetic Resilience to Age-Related Risk for Alzheimer's Disease in Admixed African Ancestry Individuals

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350/350 words

Background

We sought to identify genetic variants that confer resilience to age-related Alzheimer's disease (AD) risk in subjects of admixed African ancestry.

Methods

Participants were ages 60+, of African ancestry (>=25%), and diagnosed as cases or controls. Genetic data were available from SNP arrays imputed to TOPMed, whole genome sequencing (WGS), or whole exome sequencing (WES). Genome-wide association studies (GWAS) were performed per data type, split by Hispanic/non-Hispanic participants (**Table-1**), followed by meta-analysis (Plink v2.0; GWAMA v2.2.2). GWAS performed multiple linear regression on an AD-age score that models resilience to age-related risk for AD (Le Guen & Belloy et al. 2021; **Figure-1**). Models adjusted for sex, *APOE**4/*APOE**2 dosage, the first five genetic principal components (PC-AiR; GENESIS; R v3.6), and array/sequencing center. Brain amyloid Positron Emission Tomography (PET) qualitative reads together with SNP array data imputed to TOPMed were also available for African American individuals in A4. These data were independent from the primary GWAS and were used to evaluate significant GWAS variants for their association with binarized amyloid outcome (negative/positive), using a consistent model that additionally adjusted for age-at-scan.

Results

We found a novel protective genome-wide significant intergenic variant (rs77450754) ~200kb downstream of *ATXN8OS*/*KLHL1* (**Figure-2-3**). It has a MAF of 13% in African ancestry samples, but is rare (0.1%) in Europeans and (<2%) Latino/Admixed Americans in gnomAD v.3. The latter may explain why effects appeared less pronounced in the considered Hispanic samples (since linkage to potential causal nearby variants may differ) (**Figure-3**). The variant also displayed a protective, non-significant, association

with brain amyloid in African ancestry samples (**Table-2**). Interestingly, *KLHL1*, also known as *MRP2*, is a member of the superfamily of ATP-binding cassette (ABC) transporters, and has potential functions related to neurite outgrowth and efflux transport at the blood-brain barrier, supporting its potential relevance to AD pathogenesis.

Conclusions

Our results provide new insights into genetic resilience to AD across aging and emphasize the importance of including ancestrally-diverse populations in genetic studies. Our results also highlight the need for the field to compose ancestrally-diverse multi-omics and endophenotype data to support further validation analyses of genetic risk loci prioritized from GWAS.

Samples	Participants (N)	Cases (N (%))
ADGC Imputed - non-Hispanic	2,508	317 (12.6 %)
ADSP WGS - non-Hispanic	2,683	1,060 (39.5 %)
ADSP WES - non-Hispanic	1,843	570 (30.9 %)
ADGC Imputed - Hispanic	1,067	556 (52.1 %)
ADSP WGS - Hispanic	1,012	401 (39.6 %)
ADSP WES - Hispanic	384	115 (29.9 %)
Total	9,497	3,019 (31.8 %)

Table-1. Demographics. All included subjects had >= 25% African ancestry and were unrelated to one another down to 2nd degree relatedness (determined through identity-by-descent). *Abbreviations: Alzheimer's disease Genetics Consortium, ADGC; Alzheimer's disease Sequencing Project, ADSP.*

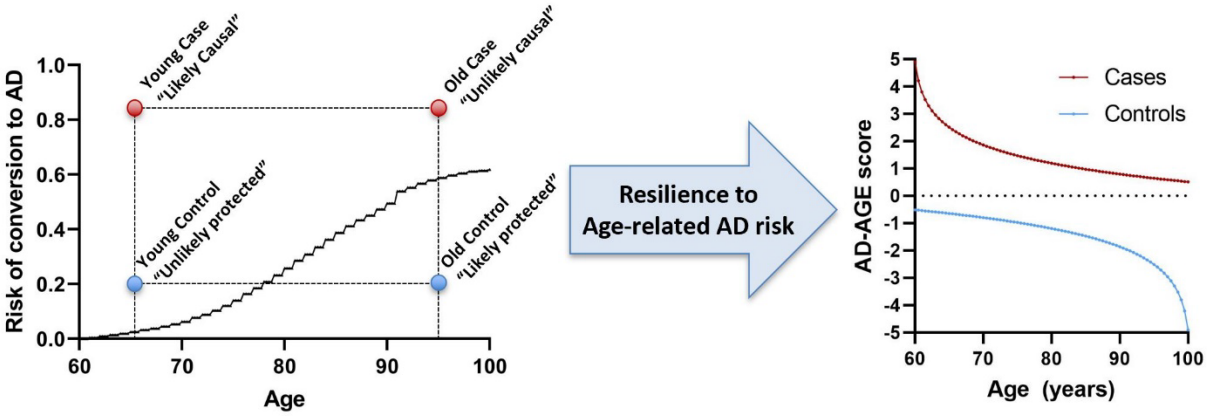

Figure-1. Schematic of resilience phenotype. Cumulative risk for AD shows subjects display (lack of) resilience depending on their age, providing the basis for a resilience score.

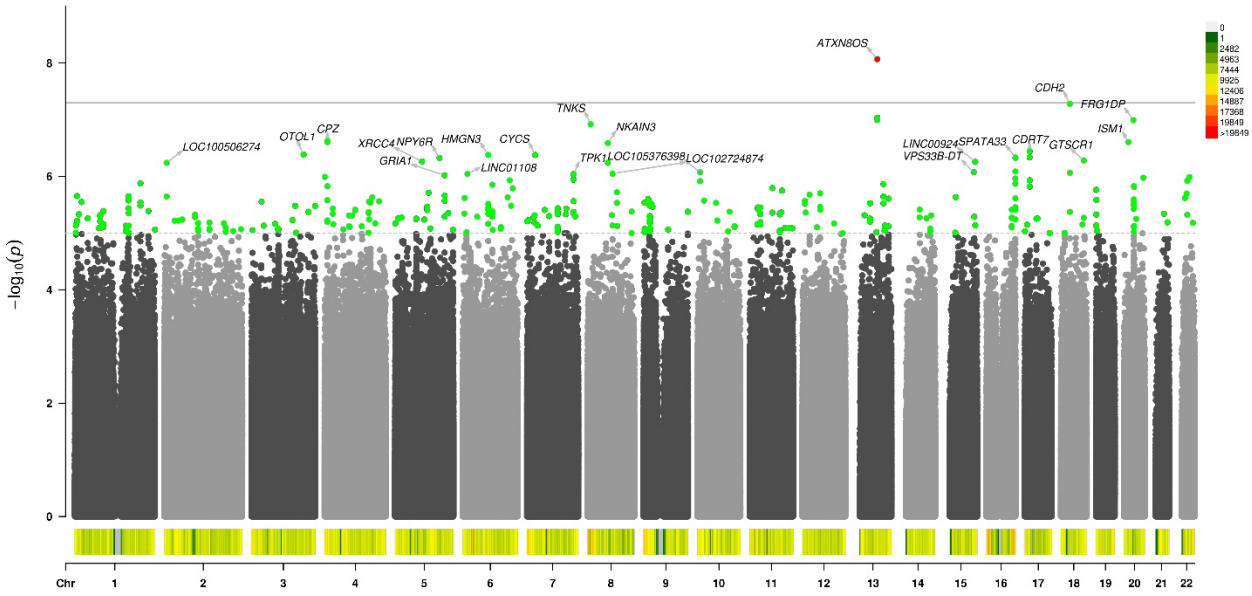

Figure-2. Manhattan plot. Green and red dots respectively indicate suggestive and genome-wide significance. Top variants passing below a P-value of 10^{-6} were annotated with the nearest gene from the NCBI RefSeq curated gene set.

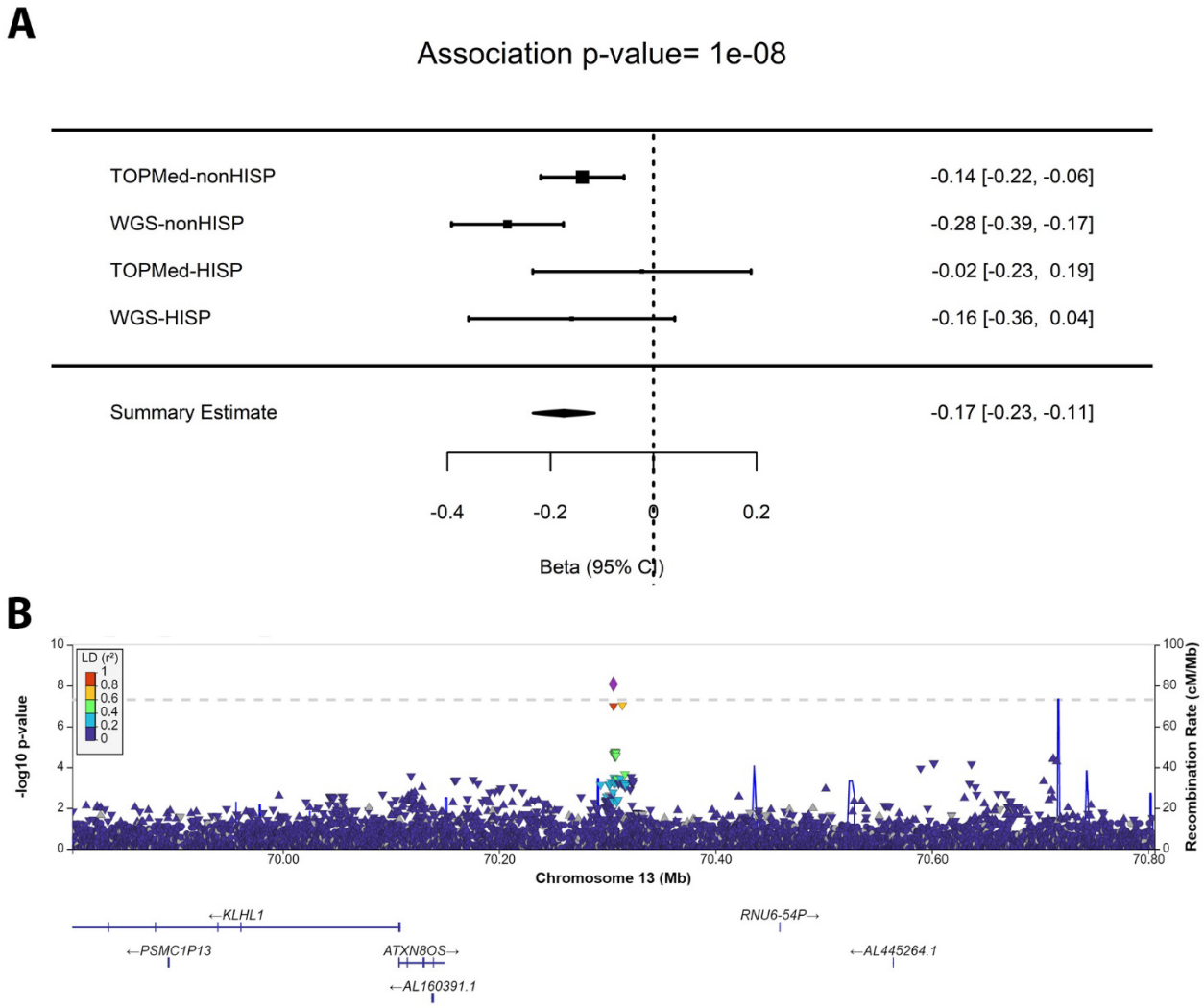

Figure-3. Top hit rs77450754. A) Forest plot. **B)** Locus zoom plot.

SNP	No. Amy- (MAF %)	No. Amy+ (MAF %)	OR (95% CI)	P-value
rs77450754*C	102 (11.3%)	31 (6.5%)	0.43 (0.11, 1.64)	0.22

Table-2. Association of rs77450754 with amyloid status in A4 samples. All included subjects were cognitively normal at the time of PET scan, had >= 25% African ancestry, and were independent from the primary GWAS (almost all subjects were non-Hispanic). Note that the lack of significance and large confidence interval reflect the limited sample size, highlighting the need for more ancestrally-diverse endophenotype samples. *Abbreviations: Amyloid, Amy; Odds ratio, OR; Confidence Interval, CI; Minor Allele Frequency, MAF.*

Overlap of genetic risk for Lewy body and Alzheimer's disease pathology

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July 1, 2022

Abstract

Background: Lewy body (LB) pathology is relatively understudied compared to Alzheimer's disease (AD) pathology, and the genetic risk overlap between the two remains unclear. Chia *et al.* (2021) identified five genomic loci significantly associated with LB pathology in a genome-wide association study (GWAS) of LB dementia cases and controls (N = 6,618), where 69% of cases and 15% of controls were pathologically confirmed. Here we gathered a largely distinct set of individuals (5.1% overlap) with genetic data and postmortem assessment for both AD and LB pathology (N = 6,002) to estimate the odds ratio (OR) for risk of sole AD pathology (AD^+LB^-), sole LB pathology (AD^-LB^+), and dual AD-LB pathology (AD^+LB^+) for the five variants reported by Chia *et al.* We compared our results for *APOE* to ORs reported by Tsuang *et al.* (2013). **Method:** Our initial study population comprised 4,579 subjects from the National Alzheimer's Coordinating Center and 1,423 from the Rush University Medical Center assessed for AD and LB pathology. We separately used criteria from Tsuang *et al.* and from Kaivola *et al.* (2021) to classify subjects as AD^+LB^+, AD^+LB^-, AD^-LB^+, or AD^-LB^-. We performed a GWAS for three phenotypic contrasts: each of AD^+LB^-, AD^-LB^+, and AD^+LB^+ against AD^-LB^-. We estimated ORs for the variants of interest. **Result:** We found that rs769449 (*APOE* locus) was associated with AD^+LB^+ and AD^+LB^- at the genome-wide significance level and nominally associated with AD^-LB^+, though with OR estimates lower than those reported by Tsuang *et al.* We obtained qualitatively similar results for rs6733839 (*BIN1*). The lead variants reported at the *GBA*, *TMEM175*, and *SNCA-AS1* loci (or proxies in high linkage disequilibrium) were not associated with a pathological phenotype, although an independent intronic variant of *GBA* was nominally associated with AD^+LB^+ and AD^-LB^+. **Conclusion:** Our results suggest that *APOE* and *BIN1* are associated with both AD and LB pathology, while *GBA* is associated with LB but not AD pathology. The ORs reported by Tsuang *et al.* for *APOE*-associated risk for single and dual AD-LB pathology may overestimate the true population values. Overall, AD and LB pathology share *APOE* and *BIN1* as risk factors.

References

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Figures and tables

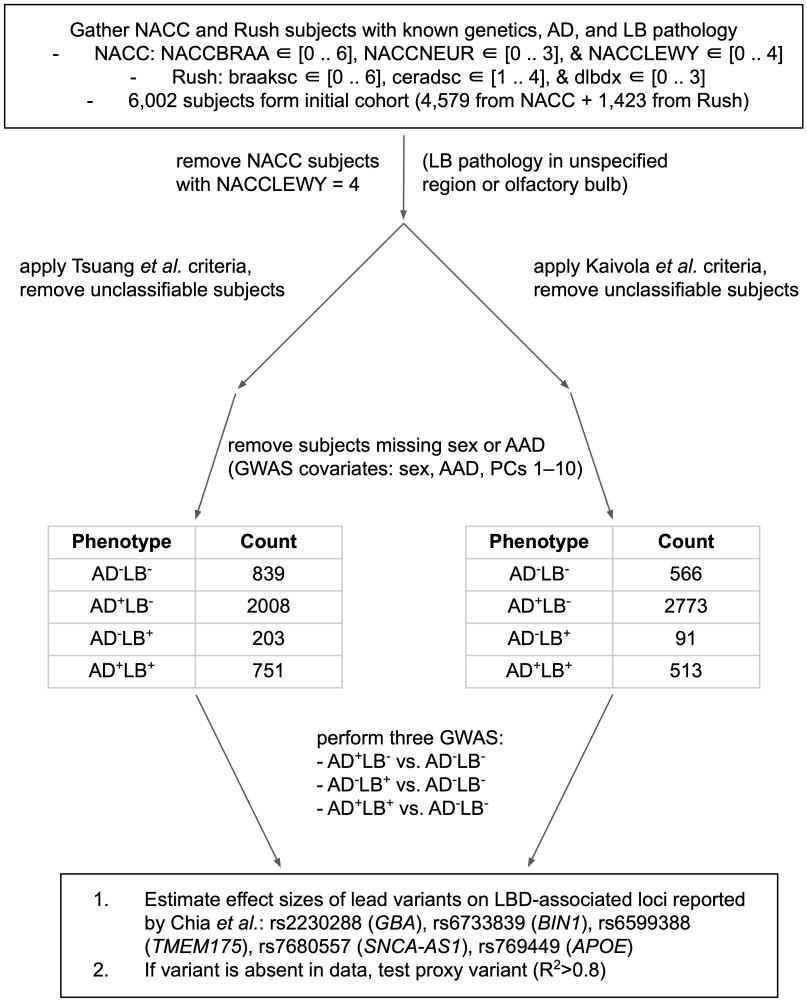

Figure 1: Flowchart of the pipeline used to determine odds ratios for risk of single and dual AD-LB pathology. AD is Alzheimer's disease, LB is Lewy body, AAD is age at death, GWAS is genome-wide association study, PC is principal component, $AD^{+}LB^{-}$ is AD single pathology, $AD^{-}LB^{+}$ is LB single pathology, $AD^{+}LB^{+}$ is AD-LB dual pathology, and LBD is Lewy body dementia.

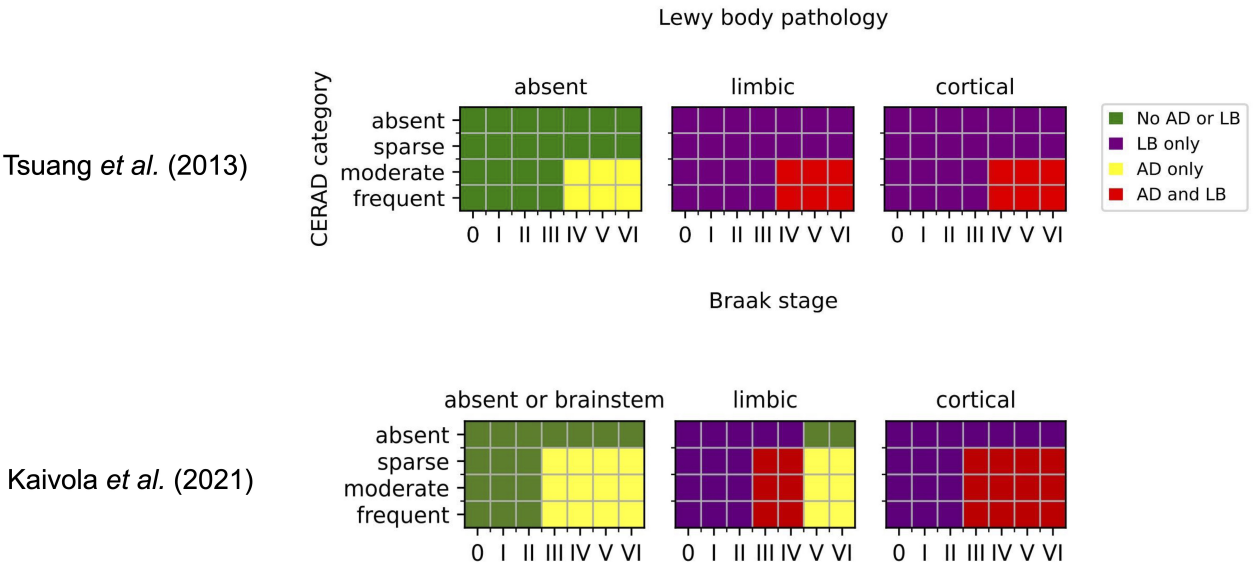

Figure 2: Categories used to define AD and LB pathology. Schemes from the literature used to classify individuals as $AD^{+}LB^{+}$, $AD^{+}LB^{-}$, $AD^{-}LB^{+}$, or $AD^{-}LB^{-}$ based on tau (Braak stage), amyloid neuritic plaque (CERAD score), and Lewy body pathology criteria.

Table 1: *APOE* locus association with AD or/and LB pathology. Association of rs769449 (*APOE* locus) with $AD^{+}LB^{-}$, $AD^{-}LB^{+}$, and $AD^{+}LB^{+}$ in our data compared with results for rs429358 (*APOE-ϵ4*) reported by Tsuang *et al.* and Kaivola *et al.* The two variants are in linkage disequilibrium ($R^2 = 0.766$ in European-ancestry individuals).

	NACC + RUSH (Tsuang *et al.* criteria)				Tsuang *et al.* (2013)				NACC + RUSH (Kaivola *et al.* criteria)				Kaivola *et al.* (2021)			
Phenotype	OR	CI	P	N (case/control)	OR	CI	P	N (case/control)	OR	CI	P	N (case/control)	OR	CI	P	N (case/control)
$AD^{+}LB^{-}$	3.52	[2.94, 4.21]	1.06×10^{-42}	2008/839	9.9	[6.4, 15.3]	1.2×10^{-24}	244/269	4.76	[3.77, 6.00]	1.55×10^{-39}	2773/566			N/A	
$AD^{-}LB^{+}$	1.66	[1.21, 2.29]	1.92×10^{-3}	203/839	6.1	[3.5, 10.5]	1.3×10^{-10}	91/269	1.14	[0.64, 2.03]	6.68×10^{-1}	91/566	0.75	[0.43, 1.30]	3.1×10^{-1}	88/2928
$AD^{+}LB^{+}$	3.40	[2.75, 4.20]	8.14×10^{-30}	751/839	12.6	[8.1, 19.8]	2.1×10^{-28}	224/269	4.66	[3.51, 6.18]	1.36×10^{-26}	513/566	4.25	[3.35, 4.39]	1.29×10^{-32}	341/2928

Table 2: *BIN1* locus association with AD or/and LB pathology. Association of rs6733839 (*BIN1* locus) with $AD^{+}LB^{-}$, $AD^{-}LB^{+}$, and $AD^{+}LB^{+}$ in our data.

	NACC + RUSH (Tsuang *et al.* criteria)				NACC + RUSH (Kaivola *et al.* criteria)			
Phenotype	OR	CI	P	N (case/control)	OR	CI	P	N (case/control)
$AD^{+}LB^{-}$	1.48	[1.30, 1.67]	8.15×10^{-10}	2008/839	1.50	[1.30, 1.72]	9.21×10^{-9}	2773/566
$AD^{-}LB^{+}$	1.27	[1.01, 1.60]	4.43×10^{-2}	203/839	1.12	[0.79, 1.57]	5.31×10^{-1}	91/566
$AD^{+}LB^{+}$	1.59	[1.36, 1.86]	7.10×10^{-9}	751/839	1.70	[1.41, 2.06]	2.76×10^{-8}	513/566

Table 3: *GBA* locus association with AD or/and LB pathology, testing the signal reported by Chia *et al.* Association of rs71628662 (*GBA* locus) with $AD^{+}LB^{-}$, $AD^{-}LB^{+}$, and $AD^{+}LB^{+}$ in our data compared with results for rs2230288 reported by Kaivola *et al.* rs2230288, absent in our data, is also the variant reported by Chia *et al.* The two variants are in linkage disequilibrium ($R^2 = 1$ in European-ancestry individuals).

	NACC + RUSH (Tsuang *et al.* criteria)				NACC + RUSH (Kaivola *et al.* criteria)				Kaivola *et al.* (2021)			
Phenotype	**OR**	**CI**	**P**	**N (case/control)**	**OR**	**CI**	**P**	**N (case/control)**	**OR**	**CI**	**P**	**N (case/control)**
$AD^{+}LB^{-}$	0.58	[0.33, 1.04]	6.89×10^{-2}	2008/839	0.72	[0.39, 1.32]	2.85×10^{-1}	2773/566			N/A	
$AD^{-}LB^{+}$	2.06	[0.99, 4.32]	5.46×10^{-2}	203/839	1.46	[0.55, 5.56]	3.40×10^{-1}	91/566	4.52	[1.94, 10.44]	4.0×10^{-4}	88/2928
$AD^{+}LB^{+}$	0.92	[0.47, 1.80]	8.07×10^{-1}	751/839	1.56	[0.75, 3.25]	2.38×10^{-1}	513/566	1.45	[0.69, 3.01]	3.2×10^{-1}	341/2928

Table 4: *GBA* locus association with AD or/and LB pathology, testing a signal independent from that reported by Chia *et al.* Association of rs147830103 (*GBA* locus) with $AD^{+}LB^{-}$, $AD^{-}LB^{+}$, and $AD^{+}LB^{+}$ in our data compared with results for rs2230288 reported by Kaivola *et al.* The two variants are not in linkage disequilibrium, nor are rs71628662 and rs147830103 ($R^2 = 0.0009$ in European-ancestry individuals for both pairs).

	NACC + RUSH (Tsuang *et al.* criteria)				NACC + RUSH (Kaivola *et al.* criteria)				Kaivola *et al.* (2021)			
Phenotype	**OR**	**CI**	**P**	**N (case/control)**	**OR**	**CI**	**P**	**N (case/control)**	**OR**	**CI**	**P**	**N (case/control)**
$AD^{+}LB^{-}$	0.94	[0.58, 1.54]	8.15×10^{-1}	2008/839	1.16	[0.68, 1.99]	5.83×10^{-1}	2773/566			N/A	
$AD^{-}LB^{+}$	2.14	[1.04, 4.41]	3.98×10^{-2}	203/839	1.46	[0.49, 4.32]	4.95×10^{-1}	91/566	4.52	[1.94, 10.44]	4.0×10^{-4}	88/2928
$AD^{+}LB^{+}$	2.26	[1.35, 3.80]	1.94×10^{-3}	751/839	2.41	[1.31, 4.42]	4.54×10^{-3}	513/566	1.45	[0.69, 3.01]	3.2×10^{-1}	341/2928

Sex-specific genetic predictors of memory, executive function, and language performance

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Abstract Text:

Background: Alzheimer's disease (AD) is more prevalent in women than men, and robust evidence shows sex differences in the biological response to the AD neuropathological cascade. However, there is a lack of large-scale genetic studies on sex-specific genetic predictors of AD-related cognitive outcomes. Thus, we sought to elucidate the sex-specific genetic etiology of memory, executive function, and language performance.

Method: This study included six cohorts of cognitive aging (N_{males}=7,267, $N_{females}$=9,518). We applied psychometric approaches to build harmonized memory, executive function, and language composite scores. Next, for all domains, we calculated slopes from the cognitive scores (two or more timepoints) with linear mixed effects models. Then we performed sex-stratified and sex-interaction GWAS on these phenotypes, covarying for baseline age and the first three genetic principal components. We meta-analyzed across cohorts with a fixed-effects model. Sensitivity analyses for all models restricted the sample to cognitively unimpaired individuals.

Result: In addition to well-established associations with cognition at the *APOE* locus, we identified three genetic loci that showed sex-specific effects with cognition. A chromosome 16 locus (rs114106271), a splicing-quantitative trait locus for *RP11-152O14.4* and *LINC02180* in the testis (GTEx), associated with baseline memory performance in men (β=0.13, P=2.40×10-8; $P_{Interaction}$=8.96×10-6; Figures 1-2) but not in women (β=-0.01, P=0.76). A chromosome 14 locus (rs34074573), an expression-quantitative trait locus (GTEx) for *HOMEZ* (a homeobox gene), and for *BCL2L2* (a previously reported AD risk gene), associated with longitudinal memory performance in men (β=-0.01, P=4.15×10-8; $P_{Interaction}$=5.83×10-7; Figures 3-4) but not in women (β=0.001, P=0.09). Finally, a chromosome 6 locus (rs9382966) associated with longitudinal language performance in men with near genome-wide significance (β=-0.004, P=6.29×10-8; $P_{Interaction}$=2.01×10-4) but not in women (β=-0.0003, P=0.61).

Conclusion: Our results highlight some key sex differences in the genetic architecture of cognitive outcomes. Findings further suggest that some sex-specific genetic predictors have domain-specific associations, providing an exciting opportunity to better understand the molecular basis of memory, executive function, and language through genomic analysis. Although our findings need to be replicated, our GWAS analyses highlight the contribution of sex-specific genetic predictors beyond the *APOE* locus in conferring risk for late-life cognitive decline.

Tables and Figures:

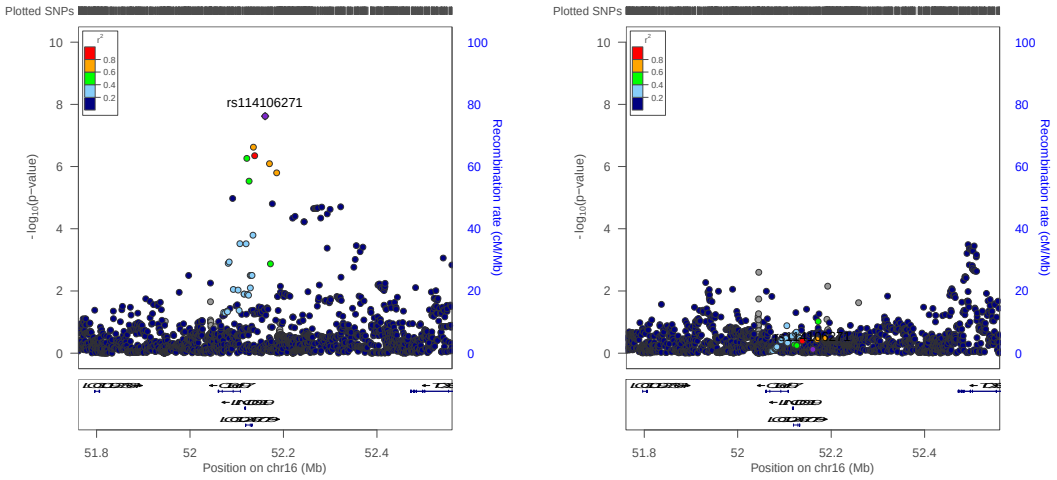

Figure 1. Genomic region around chromosome 16 locus associated with baseline memory performance in men. 400kb region flanking genome-wide significant SNP, rs114106271, which is associated with baseline memory performance in men (A) but not in women (B).

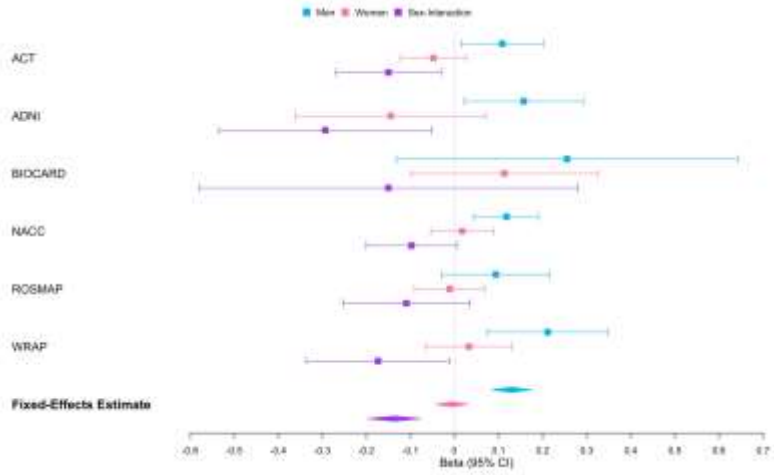

Figure 2. 95% confidence intervals for rs114106271 association with baseline memory performance in men. Baseline memory performance GWAS betas and standard errors with a 95% confidence interval are plotted for each cohort, as well as for the fixed-effects meta-analysis estimates across cohorts. Estimates in men are plotted in blue, women in pink, and sex-interaction in purple.

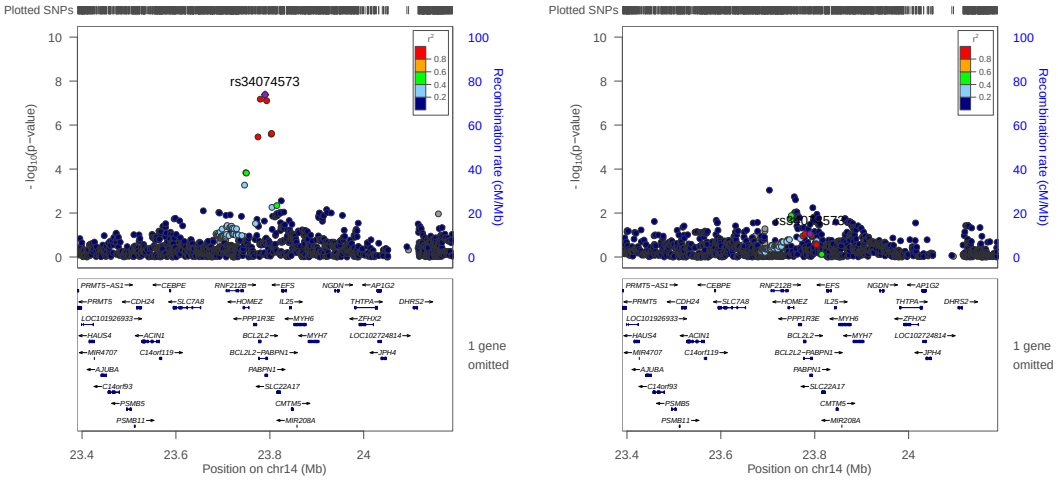

Figure 3. Genomic region around chromosome 14 locus associated with longitudinal memory performance in men. 400kb region flanking genome-wide significant SNP, rs34074573, which is associated with longitudinal memory performance in men (A) but not in women (B).

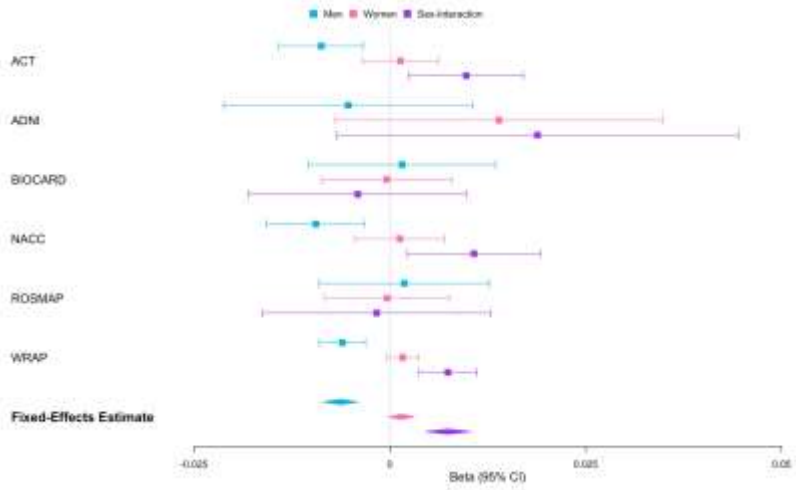

Figure 4. 95% confidence intervals for rs34074573 association with longitudinal memory performance in men. Longitudinal memory performance GWAS betas and standard errors with a 95% confidence interval are plotted for each cohort, as well as for the fixed-effects meta-analysis estimates across cohorts. Estimates in men are plotted in blue, women in pink, and sex-interaction in purple.

Abstract Title: Sex differences in white matter microstructure in aging and Alzheimer's disease: A multi-site free-water imaging study

Authors: Derek B. Archer[1,2], Niranjana Shashikumar[1], Varuna Jasodanand[1], Elizabeth E. Moore[1], Kimberly R. Pechman[1], Murat Bilgel[3], Lori L. Beason-Held[3], Yang An[3], Shannon L. Risacher[4,5], Bennett A. Landman[6,7,8], Angela L. Jefferson[1,2,9], Andrew J. Saykin[4,5], Susan M. Resnick[3], Timothy J. Hohman[1,2]

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Background: Sex differences in gray matter alterations in aging and AD have been reported, but there have been few large-scale studies evaluating white matter microstructure. The goal of this study is to leverage multi-site diffusion MRI data in tandem with free-water (FW) imaging to determine sex-specific differences in white matter microstructure in aging and AD.

Methods: The dataset used in this study leveraged cross-sectional data from several cohorts of aging [Alzheimer's Neuroimaging Initiative (ADNI), Baltimore Longitudinal Study of Aging (BLSA), Vanderbilt Memory & Aging Project (VMAP)]. This dataset included 1,898 participants (72±9 years, 59% female). Data was processed using standard preprocessing techniques and followed up with FW postprocessing. FW and FW-corrected intracellular metrics of fractional anisotropy (FA_T), radial diffusivity (RD_T), and axial diffusivity (AD_T) were then quantified within seven white matter tractography templates (**Figure 1A**) and harmonized using the ComBat technique. The sex differences for each microstructural metric were then determined using a linear regression model covarying for age, cognitive status, education, and *APOE*-ε4 carrier status. Secondary analyses were conducted to determine *sex x cognitive status* interactions on white matter microstructure.

Results: While we found no sex differences in FW, there were significant associations in all intracellular metrics. Females had significantly lower FA_T in the association ($p_{FDR}=6.62x10^{-10}$), limbic ($p_{FDR}=5.28x10^{-9}$), motor transcallosal (TC) ($p_{FDR}=0.008$), prefrontal TC ($p_{FDR}=6.34x10^{-6}$), and projection ($p_{FDR}=4.74x10^{-20}$) tracts and significantly lower AD_T in the association ($p_{FDR}=5.23x10^{-10}$), limbic ($p_{FDR}=1.84x10^{-6}$), prefrontal TC ($p_{FDR}=4.41x10^{-11}$), and projection ($p_{FDR}=5.29x10^{-17}$) tracts. For RD_T, females exhibited higher RD_T in all tracts (p_{FDR} range: $4.94x10^{-16}$ – 0.022). Illustrations of these results can be found in **Figure 1**. Sex differences were compared across cohorts and were similar (**Figure 2**). The only significant *sex x cognitive status* interaction was for the projection tract RD_T measure ($p_{FDR}=0.043$, **Figure 3**).

Discussion: This study suggests intracellular microstructural values (i.e., FA_T, AD_T, RD_T) exhibit strong sex differences, whereby females have lower FA_T/AD_T and higher RD_T compared to males. We also found a *sex x cognitive status* interaction for projection tract RD_T, whereby females with AD exhibited lower RD_T, but larger studies with more AD cases would be needed to further explore this finding.

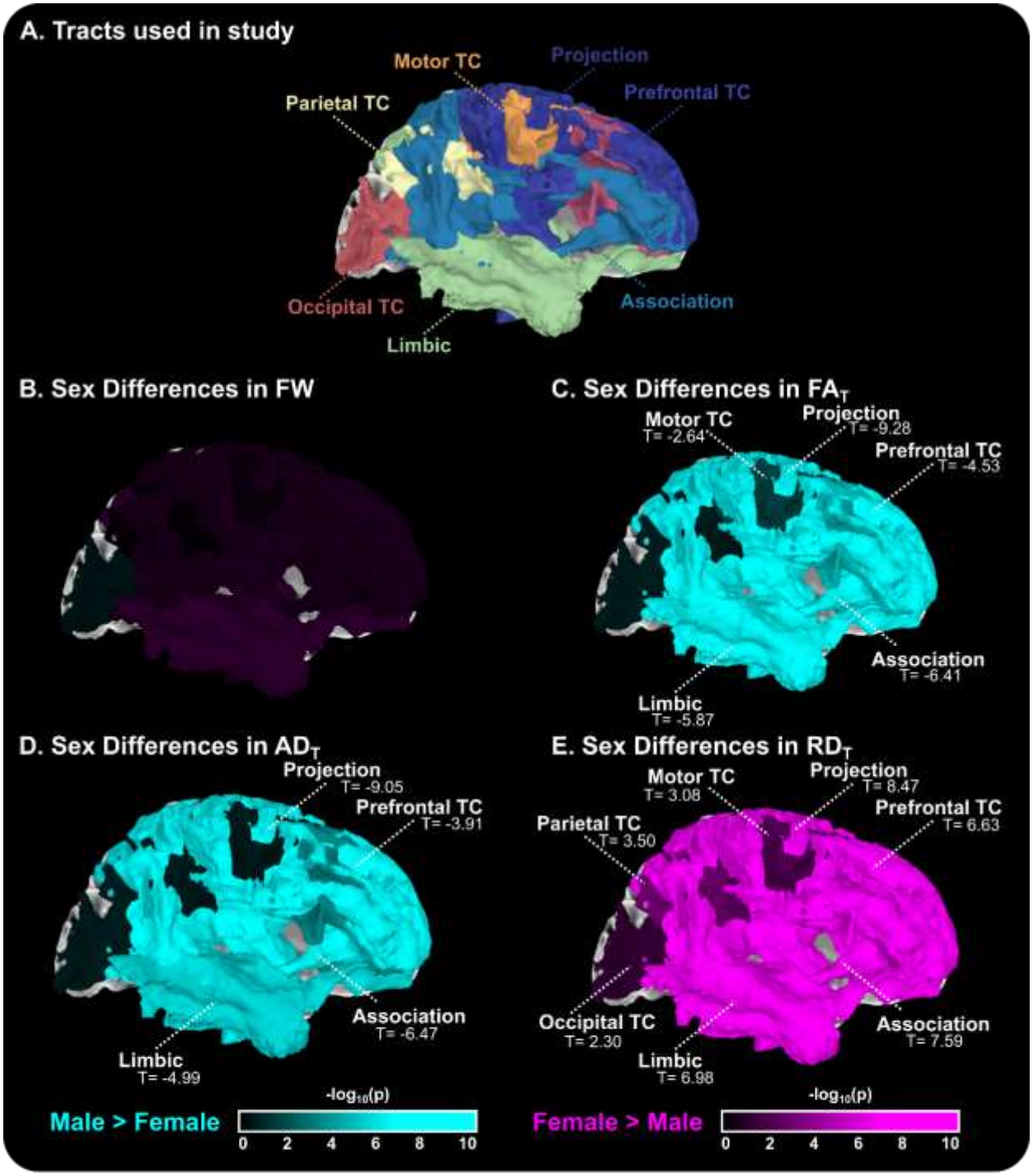

Figure 1. Using several white matter tract templates (**A**), this study used free-water diffusion MRI analysis to find that there no sex-specific differences in FW (**B**), but there are significant difference in FA_T (**C**), AD_T (**D**), and RD_T (**E**).

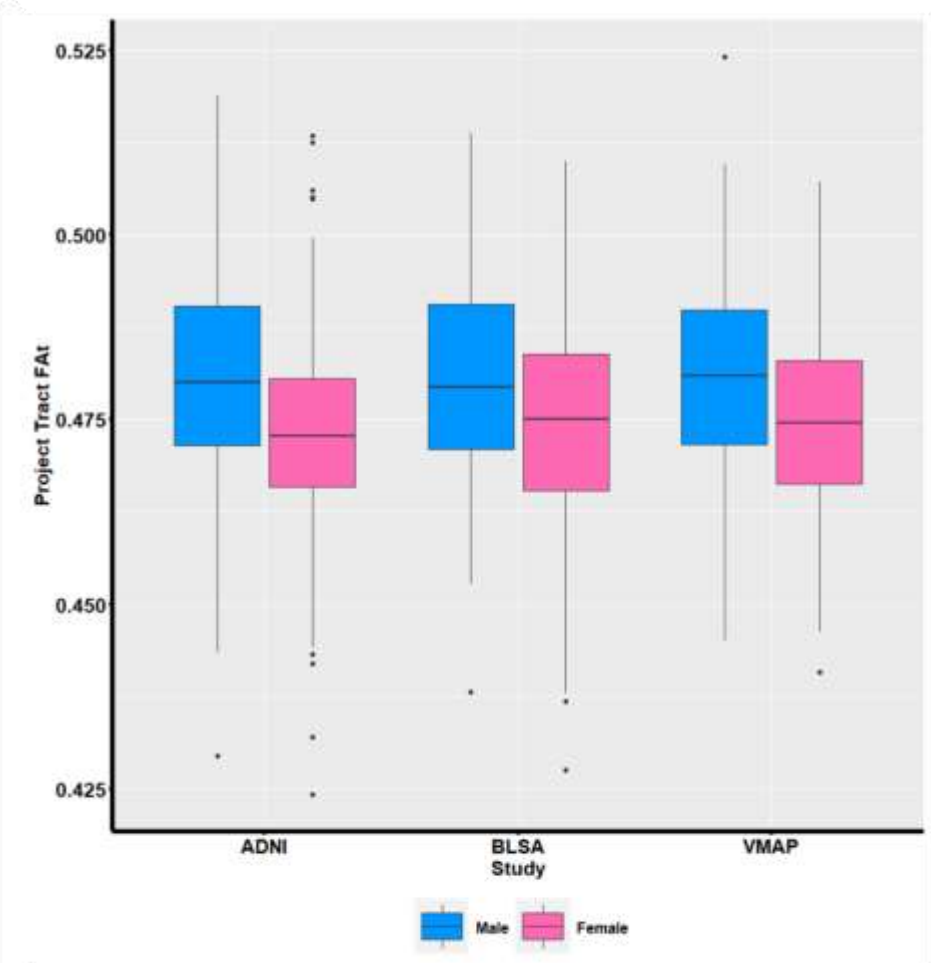

Figure 2. A grouped bar chart demonstrating the cross-cohort consistency in projection tract FA_T sex differences.

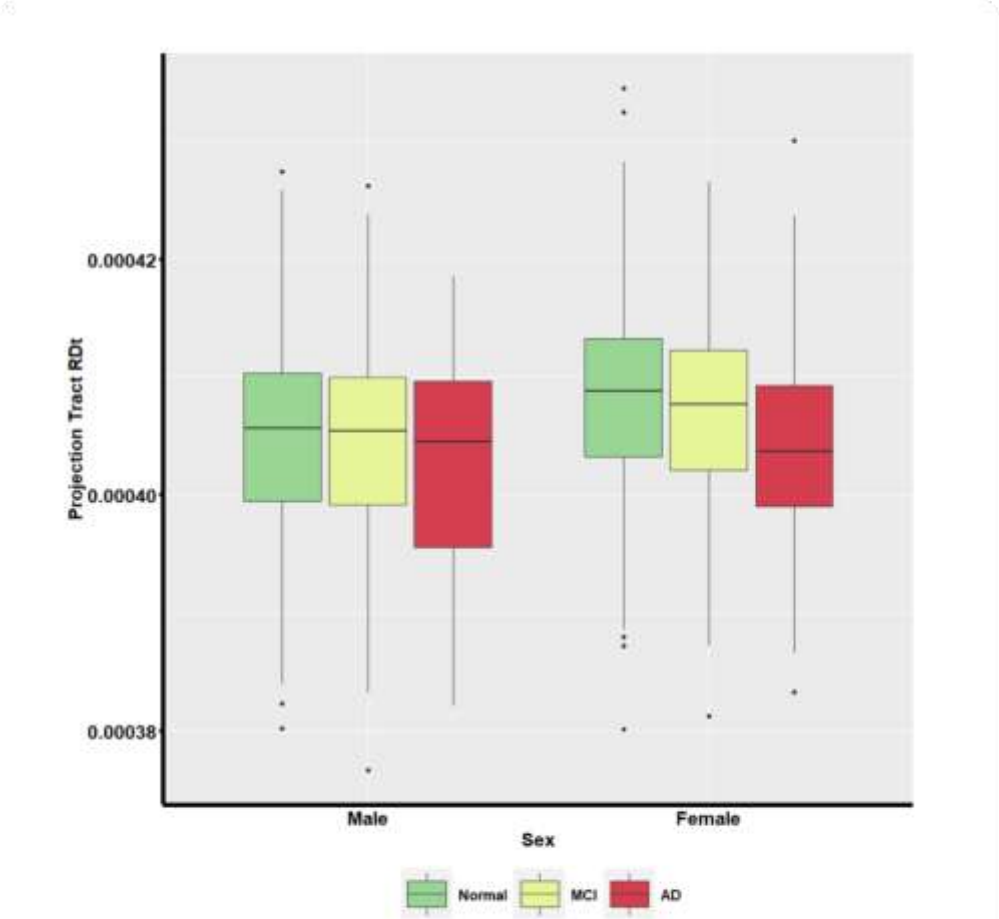

Figure 3. A significant *sex x cognitive status* interaction was found for RD_T in the projection tracts.

Abstract Title: Leveraging longitudinal, multi-site diffusion MRI data in conjunction with free-water analysis to characterize patterns of white matter neurodegeneration in aging

Authors: Derek B. Archer[1,2], Niranjana Shashikumar[1], Varuna Jasodanand[1], Elizabeth E. Moore[1], Kimberly R. Pechman[1], Murat Bilgel[3], Lori L. Beason-Held[3], Yang An[3], Andrea Shafer[3], Shannon L. Risacher[4,5], Bennett A. Landman[6,7,8], Angela L. Jefferson[1,2,9], Andrew J. Saykin[4,5], Susan M. Resnick[3], Timothy J. Hohman[1,2]

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Background: Several prior studies have used diffusion MRI to investigate the relationship between white matter microstructure and aging; however, many of these studies used conventional diffusion MRI measures and single site data. The goal of the study is to leverage multi-site harmonized diffusion MRI data in conjunction with a novel post-processing technique [i.e., free-water (FW) correction] to quantify the aging related tract-specific changes in white matter microstructure.

Methods: The dataset used in this study was collated using several well-established longitudinal cohorts of aging [Alzheimer's Neuroimaging Initiative (ADNI), Baltimore Longitudinal Study of Aging (BLSA), Vanderbilt Memory & Aging Project (VMAP)]. In total, this dataset included 1,909 participants (mean age at baseline: 72±9 years, 59% female) and 4,844 imaging sessions (mean number of visits: 4 ± 2 years, interval range: 1–12 years). Data was processed using standard approaches and uncorrected fractional anisotropy (FA_U) was quantified with seven white matter tractography atlases (see **Figure 1A**). Data was then post-processed using the FW correction technique and FW and FW-corrected FA (FA_T) values were quantified. Data were then harmonized using the ComBat technique and linear mixed-effects regression was conducted on each microstructural measure, covarying for age at baseline, sex, cognitive status, education, *APOE*-ε4 carrier status, and *APOE*-ε2 carrier status. The effect of aging was modelled using an *Age_at_Baseline x Interval* interaction term.

Results: Age was associated with lower FA_U in all seven tracts (p_{FDR} range: $4.77x10^{-10}$ to -0.01). In the FW analysis, age was associated with higher FW in all seven tracts (p_{FDR} range: $7.81x10^{-12}$ to $1.33x10^{-6}$). For FA_T, however, age was only associated with lower FA_T in the limbic tracts (p_{FDR}=0.024) in addition to the occipital ($p_{FDR}=1.19x10^{-8}$), parietal ($p_{FDR}=2.32x10^{-4}$), and prefrontal (p_{FDR}=0.024) TC tracts. **Figure 1B-D** illustrates our findings.

Discussion: This study suggests that while there are global associations with FA_U and age, these associations are attenuated once correcting for partial volume effects. Leveraging FW analysis, we found a global association with FW and age, whereby age is associated with higher FW. Further, we found that age is associated with reductions in FA_T in the limbic and occipital/parietal/prefrontal TC tracts.

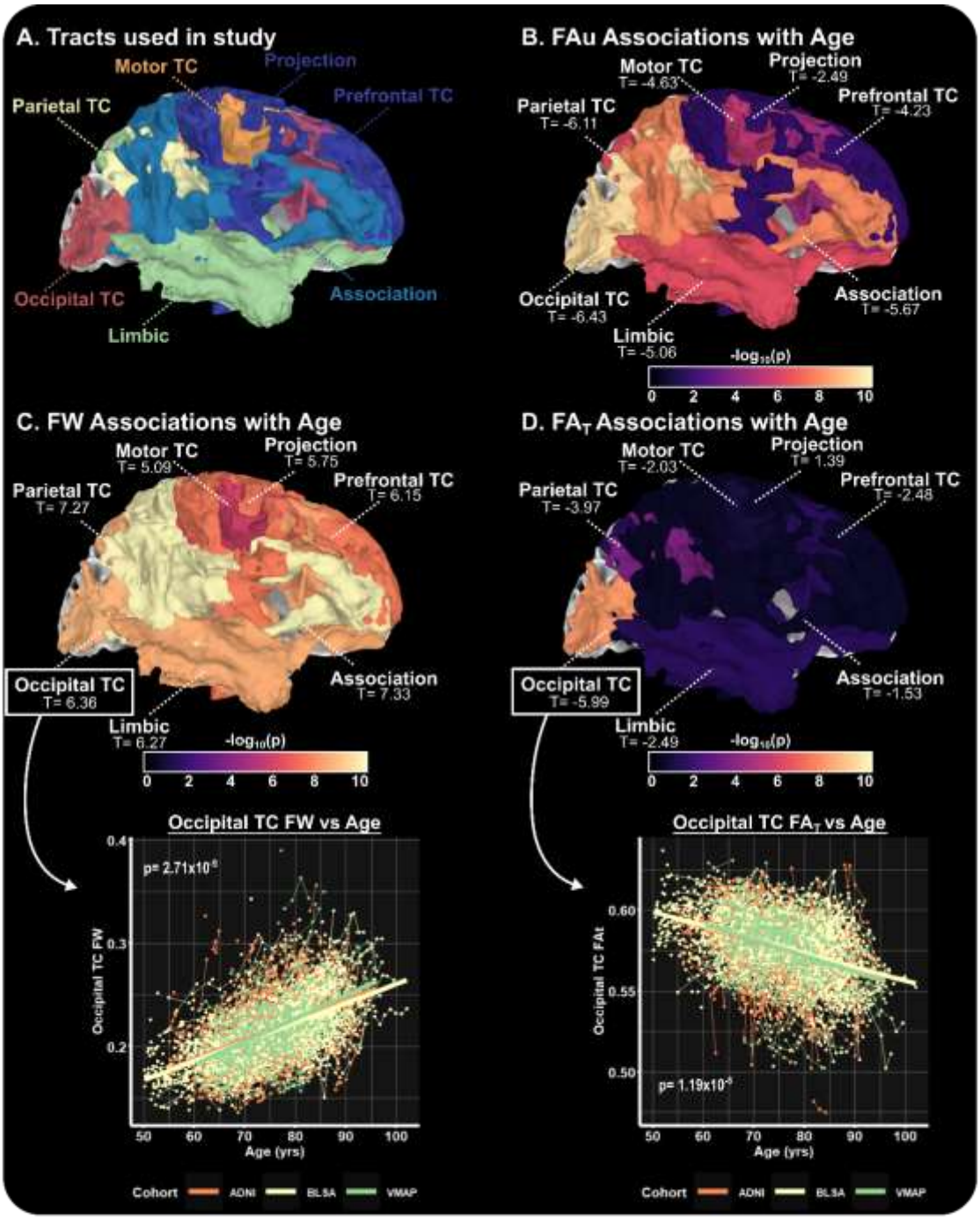

Figure 1. Using several white matter templates (**A**), this study used conventional diffusion MRI analysis to find that uncorrected fractional anisotropy (FA_U) is strongly associated with age [significant tracts (p_{FDR}<0.05) labelled, **B**]. Leveraging free-water (FW) analysis in the same cohort, this study found that while there are global associations with FW [significant tracts (p_{FDR}<0.05) labelled, **C**], there are tract-specific associations with FW-corrected FA (FA_T) [significant tracts (p_{FDR}<0.05) labelled, **D**]. As an example, occipital transcallosal (TC) FW and FA_T associations with age are shown for each cohort used in this study.

Learning Objectives

1. Explain why free-water correction is superior to conventional diffusion MRI analysis.
2. Differentiate between different types of white matter tracts.
3. Name which white matter tracts are most vulnerable to aging and AD.

Keywords

ISTAART Professional Interest Area: Neuroimaging

magnetic resonance imaging (MRI)

white matter disease

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Native American Ancestry is associated with lower risk of Alzheimer's Disease: results from the Genetic of Alzheimer's disease in Peruvian Populations (GAPP) study.

Nilton Custodio, PhD, MD[1], Marcio Soto-Añari, PhD[2], Rosa Montesinos, MD[3], Maritza Pintado Caipa, MD[1], Maria Fernanda Ore-Gomez, PhD[4], CLAUDIA RIVERA-FERNANDEZ, Psicóloga[5], Dolly Reyes-Dumeyer, BS[6] and **Giuseppe Tosto, MD, PhD**[6], (1)Cognitive impairment diagnosis and dementia prevention unit, Instituto Peruano de Neurociencias, Lima, Peru, (2)Universidad Católica San Pablo, Arequipa, Peru, (3)Instituto Peruano de Neurociencias, Lima, Peru, (4)Instituto Peruano de Neurociencia, Lima, Peru, (5)Universidad Nacional de San Agustín de Arequipa, AREQUIPA, Peru, (6)Columbia University Irving Medical Center, New York, NY, USA

Abstract Text:

Background: Alzheimer's Disease Related Dementias (ADRD) is not equally distributed among racial and ethnic groups. The *APOE-ε4* allele alone does not explain the different frequency of the disease. In fact, Hispanics (HI) and African Americans *e4* non-carriers still show a two-to-four-fold higher incidence of ADRD, compared with non-Hispanic Whites. Ancestry is an understudied yet a critical aspect of health disparities, as it may explain observed differences in frequency of ADRD across ethnic groups. We recently launched a genetic study in Peruvians, whose genome is characterized by large Native-American ancestry proportions (higher than other HI populations such as Caribbean Hispanics or Mexicans), and studied the association between Ancestry, *APOE-e4* and ADRD.

Method: We recruited 264 Peruvians across three main sites in Peru (Lima, Arequipa, Puno). Genotyping was conducted on GSA Illumina platform, and, after QC, global ancestries (Native American [NAT], European [EUR], African [AFR]) were estimated using the Human Genome Diversity Project as reference (Figure 1). Number of *APOE-e4* alleles were entered as predictor along with proportion of global ancestries in regression models, adjusting for age, sex and education. AD status was employed as main outcome; episodic memory scores were used as secondary outcomes in healthy controls.

Result: 51 were diagnosed with AD, 213 were healthy controls (mean age 72 years old). Average ancestry was estimated to be 73.0% NAT, 23.8% EUR, 3.2% AFR. *APOE-e4* was found associated with AD (OR [95%CI]= 4.09 [1.98-8.47], p<0.001). NAT ancestry proportion was found protective at trend in the whole cohort (OR=0.73[0.50-1.06], p=0.096). When restricted to *e4* non-carriers, NAT ancestry was found significantly associated with lower AD risk (OR=0.57[0.36-0.91], p=0.019). Consistently, higher NAT ancestry was associated with better episodic memory scores in healthy controls (e.g. delayed recall: $beta_{standardized}$=0.26, p<0.001).

Conclusion: To our knowledge, this is the largest collection of individuals with predominant Native American ancestry showing protective effect towards ADRD. This is particularly evident in those individuals not carrying the *APOE-e4* allele. *APOE* is confirmed as strong risk factor for ADRD (larger than other HI populations).

Tables and Figures:

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Hearing loss and dementia in Peruvian populations

Nilton Custodio, PhD, MD[1], Virgilio E Failoc-Rojas, MA[2], Diego Chambergo-Michilot, MS[3], Diego Malaga[2], Maria Fernanda Ore-Gomez, PhD[4], CLAUDIA RIVERA-FERNANDEZ, Psicóloga[5], Marcio Soto-Añari, PhD[6], Dolly Reyes-Dumeyer, BS[7], Sandro Casavilca-Zambrano[8], Rosa Montesinos, MD[2] and Giuseppe Tosto, MD, PhD[7], (1)Cognitive impairment diagnosis and dementia prevention unit, Instituto Peruano de Neurociencias, Lima, Peru, (2)Instituto Peruano de Neurociencias, Lima, Peru, (3)Facultad de Ciencias de la Salud, Universidad Científica del Sur, Lima, Peru, (4)Instituto Peruano de Neurociencia, Lima, Peru, (5)Universidad Nacional de San Agustín de Arequipa, AREQUIPA, Peru, (6)Universidad Católica San Pablo, Arequipa, Peru, (7)Columbia University Irving Medical Center, New York, NY, USA, (8)Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru

Abstract Text:

Background: Hearing loss is prevalent in older adults, affecting a third of this population. Hearing loss is a modifiable and treatable factor. It has been shown that hearing loss can lead to social isolation and later to dementia. In addition, the corresponding cortical area has a close relationship with auditory and cognitive processing. In this study we aimed to evaluate the association between dementia and hearing loss.

Method: A multicenter cross-sectional study was carried out in three locations of different altitude in Peru: Lima, Arequipa and Puno. Participants over 50 years of age with an available informant were recruited in memory clinics. The Hughes Clinical Dementia Rating (CDR) was employed to rate dementia (0 being healthy, 0.5 being questionable dementia, and greater than 1 being dementia). The exposure variable was reported hearing loss, which was defined as current hearing problems for more than six months. A descriptive analysis was performed and to evaluate the association between these variables, multinomial logistic regression with robust variances was used to estimate prevalence ratios (PR) with 95% confidence intervals.

Results: We evaluated 295 patients. The mean age was 71.9 years. More than a half was female (68.8%). The prevalence of hearing loss was 19.6%. In the crude model, hearing loss were associated with increased prevalence of dementia, with older age and education being associated with higher and lower CDR scores, respectively. After adjusting for confounders and geographic clustering, the association between hearing loss and dementia showed a PR of 3.39 (95% CI: 1.11-10.39) that in those without dementia.

Conclusion: In our cohort of Peruvian participants, we found that hearing loss was associated with dementia in line with previous investigations. Further follow-up studies are needed to better assess and characterize this association.

Title:
Hearing loss and dementia in Peruvian populations

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IMPACT OF THE COVID-19 PANDEMIC IN ADRD PATIENTS AND CAREGIVERS IN A LATIN-AMERICAN COUNTRY

Nilton Custodio, PhD, MD[1], Diego Malaga[2], Diego Chambergo-Michilot, MS[3], Maria Fernanda Ore-Gomez, PhD[4], CLAUDIA RIVERA-FERNANDEZ, Psicóloga[5], Marcio Soto-Añari, PhD[6], Dolly Reyes-Dumeyer, BS[7], Virgilio E Failoc-Rojas, MA[2], Sandro Casavilca-Zambrano[8], Rosa Montesinos, MD[2] and Giuseppe Tosto, MD, PhD[7], (1)Cognitive impairment diagnosis and dementia prevention unit, Instituto Peruano de Neurociencias, Lima, Peru, (2)Instituto Peruano de Neurociencias, Lima, Peru, (3)Facultad de Ciencias de la Salud, Universidad Científica del Sur, Lima, Peru, (4)Instituto Peruano de Neurociencia, Lima, Peru, (5)Universidad Nacional de San Agustín de Arequipa, AREQUIPA, Peru, (6)Universidad Católica San Pablo, Arequipa, Peru, (7)Columbia University Irving Medical Center, New York, NY, USA, (8)Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru

Abstract Text:

Background: Alzheimer Disease and Related Dementia (ADRD) patients and caregivers have been significantly affected by the coronavirus disease 2019 (COVID-19) pandemic and have seen their access to healthcare disrupted. ADRD has emerged as a key comorbidity of COVID-19. Little is known about the impact of the pandemic in ADRD patients living in countries with reduced vaccinations rates. Our objective was to assess the impact of the pandemic in ADRD patients and caregivers in Peru, which has one of the world's highest COVID-19 death rate.

Method: As part of the Genetics of Alzheimer's disease In Peruvian Populations (GAPP) study, we performed a cross-sectional study in ADRD patients and caregivers. We employed the National Alzheimer Coordination Center COVID-19 survey to evaluate the impact of the pandemic in our cohort. We also considered the severity of cognitive impairment, measured by the Cognitive Dementia Rating Scale (CDR).

Result: the GAPP cohort had 52 ADRD cases and 213 controls. The median age was 72 (54-95 IQR 12), and 68.68% were females. A third of patients reported COVID-19 symptoms; of those, 2.71% were hospitalized in the Intensive Care Unit (1 patient needed respirator). Over 50% of participants reported at least some cognitive or behavioral changes (with memory being the most predominant), with no difference between cases and controls. Overall, participants felt moderately concerned with infection and social distancing, with no differences between groups. Caregivers reported higher degrees of concern, especially for ADRD participants. 25% of caregivers reported being affected significantly by the pandemic, mainly because of decreased takeover by family or friends, especially among those looking after ADRD participants. Over 50% considered their income reduced. Finally, their willingness to participate in research projects was not impacted significantly.

Conclusion: The COVID-19 pandemic has impacted ADRD patients (especially those with higher CDR) and their caregivers, reducing their financial income and their caregiving ability. These results could help in developing COVID-19 public health policies that include specific needs for ADRD patients.

Title:
IMPACT OF THE COVID-19 PANDEMIC IN ADRD PATIENTS AND CAREGIVERS IN A LATIN-AMERICAN COUNTRY

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Association between nutritional status and dementia staging among Alzheimer's disease patients in Peru: Preliminary results of the Genetic of Alzheimer's Disease in Peruvian Population Study

Rosa Montesinos, MD[1], Diego Chambergo-Michilot, MS[2], Diego Malaga[1], Maria Fernanda Ore-Gomez, PhD[3], CLAUDIA RIVERA-FERNANDEZ, Psicóloga[4], Marcio Soto-Añari, PhD[5], Dolly Reyes-Dumeyer, BS[6], Virgilio E Failoc-Rojas, MA[1], Sandro Casavilca-Zambrano[7], **Nilton Custodio, PhD, MD**[1,8] and Giuseppe Tosto, MD, PhD[6], (1)Instituto Peruano de Neurociencias, Lima, Peru, (2)Facultad de Ciencias de la Salud, Universidad Científica del Sur, Lima, Peru, (3)Instituto Peruano de Neurociencia, Lima, Peru, (4)Universidad Nacional de San Agustín de Arequipa, AREQUIPA, Peru, (5)Universidad Católica San Pablo, Arequipa, Peru, (6)Columbia University Irving Medical Center, New York, NY, USA, (7)Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru, (8)Cognitive impairment diagnosis and dementia prevention unit, Instituto Peruano de Neurociencias, Lima, Peru

Abstract Text:

Background: Alzheimer's Disease Related Dementias (ADRD) is estimated to increase up to 152 million in 2050. Dementia-related mortality increases with older age, male sex, neuropsychiatric symptoms, faster cognitive decline, physical impairment and disease severity. Malnutrition is an important ADRD complication due to its impact on several domains. Prior studies showed that malnutrition is associated with behavioral and cognitive impairment (emotional disinhibition and behavior disturbance, memory impairment) and higher mortality risk among ADRD patients. Prevalence of malnutrition is heterogeneous and may depend on disease severity. We aimed to assess the association between malnutrition and dementia severity in an outpatient cohort of Peruvians, part of the Genetic of Alzheimer's Disease in Peruvian Population (GAPP) Study.

Method: A cross-sectional study was carried out in three different sites of different altitude in Peru. We included individuals aged >50 years who attended memory clinics. We used the Mini-Nutritional Assessment (MNA) scale to assess the nutritional status, and the Clinical Dementia Rating (CDR) to grade the dementia. We stratified the nutritional status in normal (MNA score: 12-14) and malnourished or risk of malnourished (MNA: 11 or less).

Result: We assessed 295 patients; mean age was 71.9 (SD: 8.3) and 68.8% were females; proportion of demented (CDR>=1) was 23%. Prevalence of malnourishment and risk of malnourishment was 6.4% and 35%, respectively. When adjusted by demographic covariates and geographical recruitment site, we found malnourishment scores significantly associated with CDR scores (e.g. CDR 2-3: PR 2.27, 95% CI: 1.95-2.62). Malnourishment was not associated with cardiovascular risk factors or diseases.

Conclusion: In our Peruvian cohort, malnourishment or risk of malnourishment was found associated with higher risk of ADRD. Prevalence of malnourishment or risk of malnourishment was in line with those reported in other South American countries. Further longitudinal studies should confirm this association.

Title:
Association between nutritional status and dementia staging among Alzheimer's disease patients in Peru: Preliminary results of the Genetic of Alzheimer's Disease in Peruvian Population Study

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Collection of genetic data in ethnic-based studies across Aymaras, Quechuas and Mestizos: the challenges of the Genetics of Alzheimer's in Peruvian Population (GAPP) study.

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Background. The Genetics of Alzheimer's Disease in Peruvian Population (GAPP) study aims to investigate genetic and environmental risk factors for Alzheimer's Disease (AD) in Peru. The project is led by Columbia University (CU, New York, US) and the Instituto Peruano de Neurociencias (IPN, Lima, Peru). For the past year and a half, despite the ongoing COVID-19 pandemic, the study has collected data on cognitive function, health, diet and numerous clinical and biological risk factors for AD. In addition, we collected blood samples for DNA extraction as well as serum and plasma to look at core AD biomarkers.

Method. Recruitment prioritized populations from south Peru, the Quechuas and Aymaras, because of their high proportion of Native American ancestry (or, in other words, low admixture with European ancestry) as well as Mestizo (mixed Native-European ancestry). Three recruitment sites were established in Lima, Puno and Arequipa. Interviewers were trained to clinically and cognitively assessed the participants and collect and ship blood samples to the main site (IPN). DNA samples were then sent to CU for processing. Serum and plasma samples were processed in Lima and stored at -80C for batch shipping to CU. DNA samples were sent to CD Genomics and Children's Hospital of Philadelphia for *APOE* genotyping and GWAS, respectively.

Result. A database with 350 participants has been created. Blood samples from all participants were collected; 268 successfully underwent GWAS and *APOE* genotyping. An additional 82 samples are pending QC and genotyping. No samples were dropped at extraction, and only 0.7% failed DNA quality standards for genotyping.

Conclusion. Sample collections for genetic studies in South American indigenous populations such as Peru represent important logistic challenges. The use of blood as a main source of DNA provides an effective and reliable source for genetic data analysis. Plasma and serum biomarkers will provide additional insights into the disease manifestations and validation of the clinical diagnosis in these underrepresented populations. Ongoing recruitment will augment the analytical power of the cohort by collecting blood, serum and plasma samples from additional GAPP participants.

AAIC 2022

Sex differences in *APOE* effects on cognition are domain-specific

Authors: Alex G. Contreras, Skylar Walters, Shubhabrata Mukherjee, Michael L. Lee, Seo-Eun Choi, Phoebe Scollard, Emily H. Trittschuh, Jesse Mez, William S. Bush, Corinne D. Engelman, Qiongshi Lu, David W. Fardo, Keith F. Widaman, Rachel Buckley, Elizabeth Mormino, Brian Kunkle, Adam C. Naj, Lindsay R. Clark, Katherine A. Gifford, The Alzheimer's Disease Neuroimaging Initiative (ADNI)*, Alzheimer's Disease Genetics Consortium (ADGC), The Alzheimer's Disease Sequencing Project (ADSP), Michael L. Cuccaro, Carlos Cruchaga, Margaret A. Pericak-Vance, Lindsay A. Farrer, Li-San Wang, Gerard Schellenberg, Jonathan L. Haines, Angela L. Jefferson, Sterling C. Johnson, Walter A. Kukull, Marilyn S. Albert, C. Dirk Keene, Andrew J. Saykin, Eric B. Larson, Reisa A. Sperling, Richard Mayeux, Paul M Thompson, Eden R. Martin, David A. Bennett, Lisa Barnes, Julie A. Schneider, Paul K. Crane, Timothy J. Hohman, and Logan Dumitrescu

Background: Two-thirds of Alzheimer's disease (AD) patients are women and there are well-established sex differences in the association between *APOE* and cognitive impairment in AD. However, it is not clear whether sex-specific cognitive consequences of *APOE* emerge across all cognitive domains or in a domain-specific manner.

Methods: Data were obtained from 38,386 participants in four longitudinal studies of aging and AD. The average age of participants at baseline was 75±8 years (10% AD, 42% male, 12% African American [AA], 12% *APOE*-ε2 carriers, and 36% *APOE*-ε4 carriers). Based on detailed neuropsychological exams, harmonized composite scores for memory, executive function, and language were generated using latent variable modeling. Linear regression assessed *APOE**sex interactions on each baseline cognitive domain score. Mixed-effects regression models assessed sex interactions with *APOE* on cognitive trajectories, including fixed and random effects for both the intercept and the slope (years from baseline). All models adjusted for age at baseline, sex, and race/ethnicity. Exploratory analyses of the potential effect of race/ethnicity were also performed using an *APOE**sex*race interaction term in the model.

Results: As expected, *APOE*-ε4 was associated with worse cognitive performance, and *APOE*-ε2 was associated with better performance in all domains, both at baseline and longitudinally ($p<0.001$). At baseline, we observed a significant sex**APOE*-ε4 interaction on memory ($\beta=-0.06$, $p<0.001$) and significant sex**APOE*-ε2 interaction on memory ($\beta=0.05$, $p=0.03$). In both cases, the association between *APOE* and memory was significantly stronger in females compared to males. Notably, despite the large sample size, no interactions were observed in the two other cognitive domains or in the longitudinal analysis. Additionally, we observed a significant interaction between sex**APOE*-ε2*race on baseline memory ($\beta=-0.19$, $p=0.02$), whereby the *APOE*-ε2*sex interaction was significant in non-Hispanic whites ($\beta=0.06$, $p<0.01$) but not in AA ($\beta=-0.11$, $p=0.10$).

Conclusion: We provide new evidence that the sex difference in *APOE* in cognition is most pronounced in relation to memory performance and is particularly driven by differences in baseline performance rather than trajectories of performance over time. Future work will examine intersections with clinical diagnosis to better differentiate sex differences in *APOE* associations in the context of normal aging and neurodegenerative disease.

Cognitive resilience polygenic risk score sensitive to preclinical disease changes

Jaclyn M. Eissman, BS[1,2], Omair A. Khan, MAS[3], Dandan Liu, PhD[3], Vladislav A Petyuk, PhD[4], Katherine A. Gifford, PsyD[1], Logan Dumitrescu, PhD[1,2], Angela L. Jefferson, PhD[1] and Timothy J. Hohman, PhD[1,2], (1)Vanderbilt Memory & Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN, USA, (2)Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA, (3)Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA, (4)Biological Sciences Division and Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory, Richland, WA, USA, Richland, WA, USA

Abstract Text:

Background: Alzheimer's disease (AD) polygenic risk scores (PRS) are often derived from case/control GWAS, which are typically not sensitive to preclinical disease changes, limiting their clinical utility. To overcome this pitfall, we built and evaluated the performance of multiple PRS of AD-related endophenotypes, including resilience to cognitive impairment in the presence of amyloid.

Method: Four PRS were derived from GWAS of baseline memory, memory decline, cognitive resilience (Dumitrescu et al., 2021), and AD (Kunkle et al. 2019). PRS were built in an independent cohort that was free of dementia, the Vanderbilt Memory and Aging Project (N=255). We used linkage disequilibrium clumping on TOPMed-imputed genotypes, and a threshold of P=0.01. We ran linear models with baseline memory score as the outcome, and baseline age, sex, and PRS as predictors. Linear mixed effects models, with identical predictors, were used when longitudinal memory was the outcome, letting individual slope and intercept vary. Finally, we tested a CSF Aβ42-by-PRS interaction term to assess if PRS modified associations between amyloid and cognition. Sensitivity analyses excluded *APOE* from PRS calculations.

Result: As expected, the baseline memory PRS related to baseline memory (β=0.12, P=0.04), and the memory decline PRS related to longitudinal memory (β=0.04, P=0.001). Without *APOE*, the baseline memory PRS and the memory decline PRS results attenuated. The AD PRS related to both baseline memory (β=-0.19, P=0.002) and longitudinal memory (β=-0.03, P=0.01), but results attenuated without *APOE*. The resilience PRS did not have a main effect on baseline or longitudinal memory. However, interestingly, the resilience PRS interacted with CSF Aβ42 on baseline memory (β=-0.001, P=0.02; Figure 1), whereby the resilience PRS related to memory among amyloid-positive individuals (β=0.44, P=0.01) but not amyloid-negative individuals (β=0.06, P=0.46). No other PRS was predictive of memory among amyloid-positive individuals, and resilience PRS results remained consistent without *APOE*.

Conclusion: Our results demonstrate that a resilience PRS appears to be predictive of individual cognitive performance downstream of amyloidosis. Future work is needed to replicate this finding, but our preliminary findings highlight the potential utility of resilience PRS for predicting individual risk for AD-related cognitive impairment during the preclinical stages of disease.

Tables and Figures:

Table1. Main effects results for PRS associations with baseline memory and longitudinal memory performance.

	Baseline Memory		Longitudinal Memory	
	β	P	β	P
AD PRS	-0.186	0.0015	-0.0326	0.0099
Baseline Memory PRS	0.119	0.0444	0.0201	0.1076
Memory Decline PRS	0.1041	0.0811	0.0395	0.0014
Resilience PRS	0.0867	0.1424	0.0134	0.2804

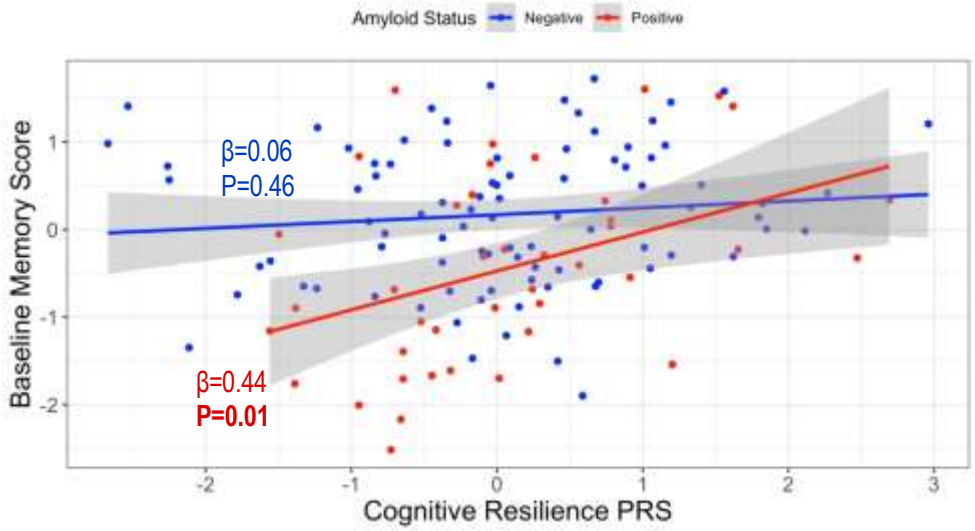

Figure 1. Cognitive resilience PRS performs better in amyloid-positive individuals. Association of the cognitive resilience PRS and baseline memory scores for individuals in the Vanderbilt Memory and Aging Project is plotted above. The linear regression lines, stratified by amyloid status, show that the resilience PRS significantly predicts baseline memory performance in amyloid-positive individuals but not in amyloid-negative individuals.

AAIC 2022

Title: Longitudinal GWAS Identifies Novel Genetic Variants and Complex Traits Associated with Resilience to Alzheimer's Disease

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AAIC 2022

Background: We completed a large genetic analysis of resilience to cognitive decline in Alzheimer's Disease (AD) and discovered novel variants, genes, and complex traits associated with better-than or worse-than-expected cognitive performance given an individual's age, sex, and *APOE* genotype.

Methods: Leveraging 15,933 non-Hispanic white participants across four longitudinal cohort studies of aging and AD (Figure 1), our group determined the effects of genetic variants on resilience metrics using mixed-effects regressions. Models adjusted for age, sex, *APOE* ε4 allele count, presence of the *APOE* ε2 allele and all covariate interactions with interval (years from baseline). The outcomes of interest were residual cognitive resilience, quantified from residuals in three cognitive domains (memory, executive function, and language), and combined resilience, summarized as the covariance of educational attainment with residual cognitive resilience. Post-GWAS analyses included gene tests using MAGMA and estimates of genetic correlation with 65 complex traits using GNOVA.

Results: We observed genome-wide significant associations at multiple established AD loci, including *BIN1* and *CR1* (Figure 2). We observed a novel association with combined resilience on chromosome 13 (top SNP: rs11838654, MAF=0.06, $P=4.7x10^{-8}$; Figure 3) and a novel signal on chromosome 1 approaching significance (top SNP: rs2817183, MAF=0.41, $P=5.1x10^{-8}$). Interestingly, rs11838654 is an eQTL for four genes in hippocampus (*WBP4*, *COG6*, *MRPS31*, and *NHLRC3I*; Braineac database). We also observed an association with residual cognitive resilience on chromosome 5 that approached genome-wide significance (top SNP: rs4482935, MAF= 0.25, $P=5.5x10^{-8}$; Figure 2). Gene-level tests identified associations of *CD2AP* (P.fdr=0.027) and *ZNF146* (P.fdr=0.049) with residual cognitive resilience and combined resilience, respectively. Additionally, we identified negative genetic correlations of combined resilience with ischemic stroke and coronary artery disease (all $P.fdr<2.5x10^{-2}$; Figure 4).

Conclusion: Compared to models of resilience that regress out the effects of AD neuropathology on cognition, the present models benefit from larger sample size at the cost of molecular precision. Although the genetic architecture of resilience from these less precise models more closely resembles that of clinical AD, we uncovered novel genetic drivers of resilience through this approach. Such findings will require future replication but suggest a trajectory-based definition of resilience holds substantial promise for discovery.

	ACT	ADNI	NACC	ROSMAP
N	2099	969	10918	1947
Age at Baseline (years)	75.29±6.35	74.69±6.59	74.29±7.84	78.58±7.39
Education (years)	14.33±3.1	15.92±2.86	15.98±2.82	16.34±3.52
Number of Visits	6.01±2.82	6.59±2.86	5.05±2.93	9.86±5.38
Residual Cognitive Resilience	0.23±0.72	0.01±0.95	0.02±0.93	0.03±0.99
Combined Resilience	-0.07±0.31	0.05±0.31	0.05±0.31	0.09±0.36
% AD Diagnosis	26%	14%	32%	5%
% Female	58%	41%	54%	71%
% APOE4 Carrier	25%	45%	41%	25%

Figure 1. Participant characteristics table. Values are mean ± standard deviation or number of samples (per cent of the group).

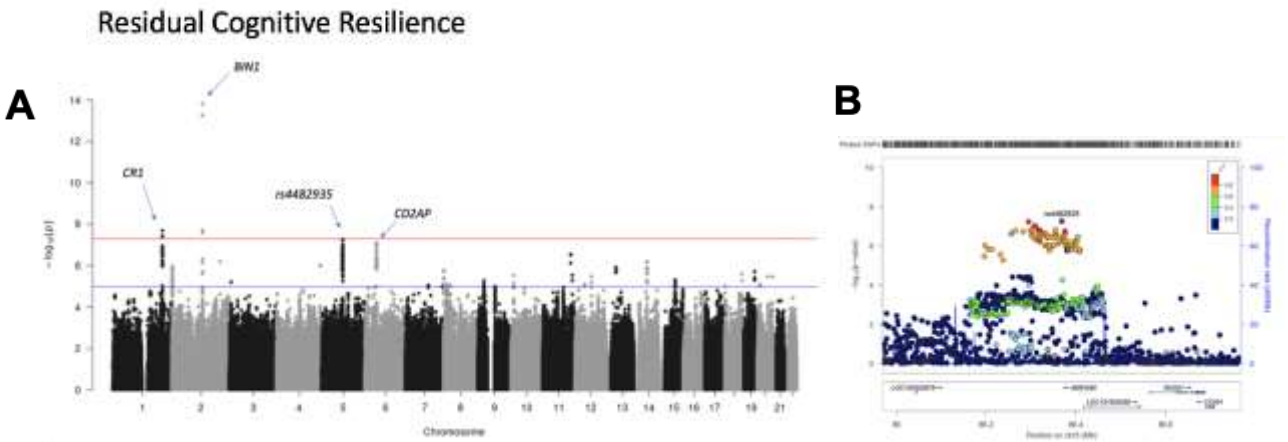

Figure 2. A) Manhattan plot of results from GWAS analysis of residual cognitive resilience. GWAS significance (5×10^{-8}) is indicated by the red line, while suggestive significance (1×10^{-5}) is indicated by the blue line.
B) LocusZoom plot of the top SNP on chromosome 5, rs4482935. Colors denote linkage disequilibrium with the most statistically significant SNP.

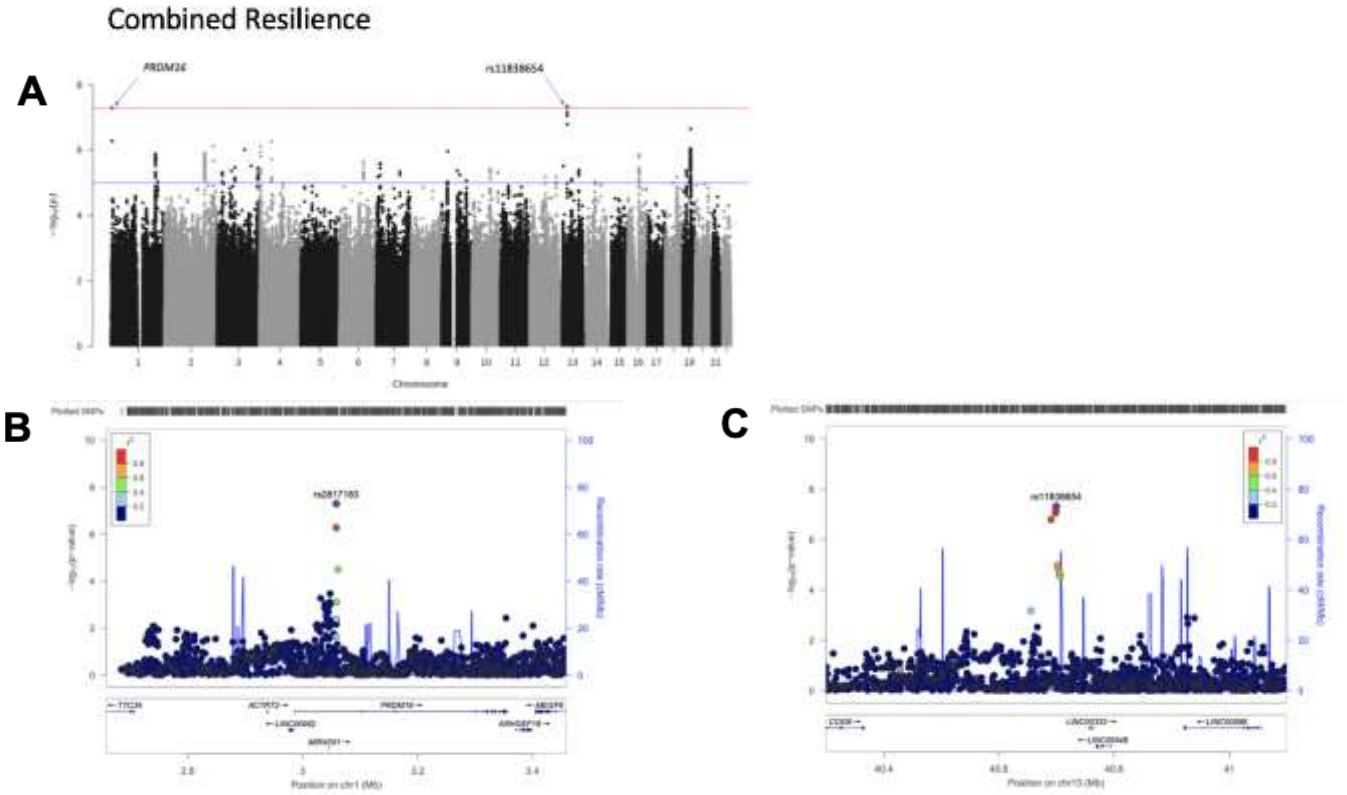

Figure 3. A) Manhattan plot of results from GWAS analysis of combined resilience. B) LocusZoom plot of the top SNP on chromosome 1, rs2817183. C) LocusZoom plot of the top SNP on chromosome 13, rs11838654.

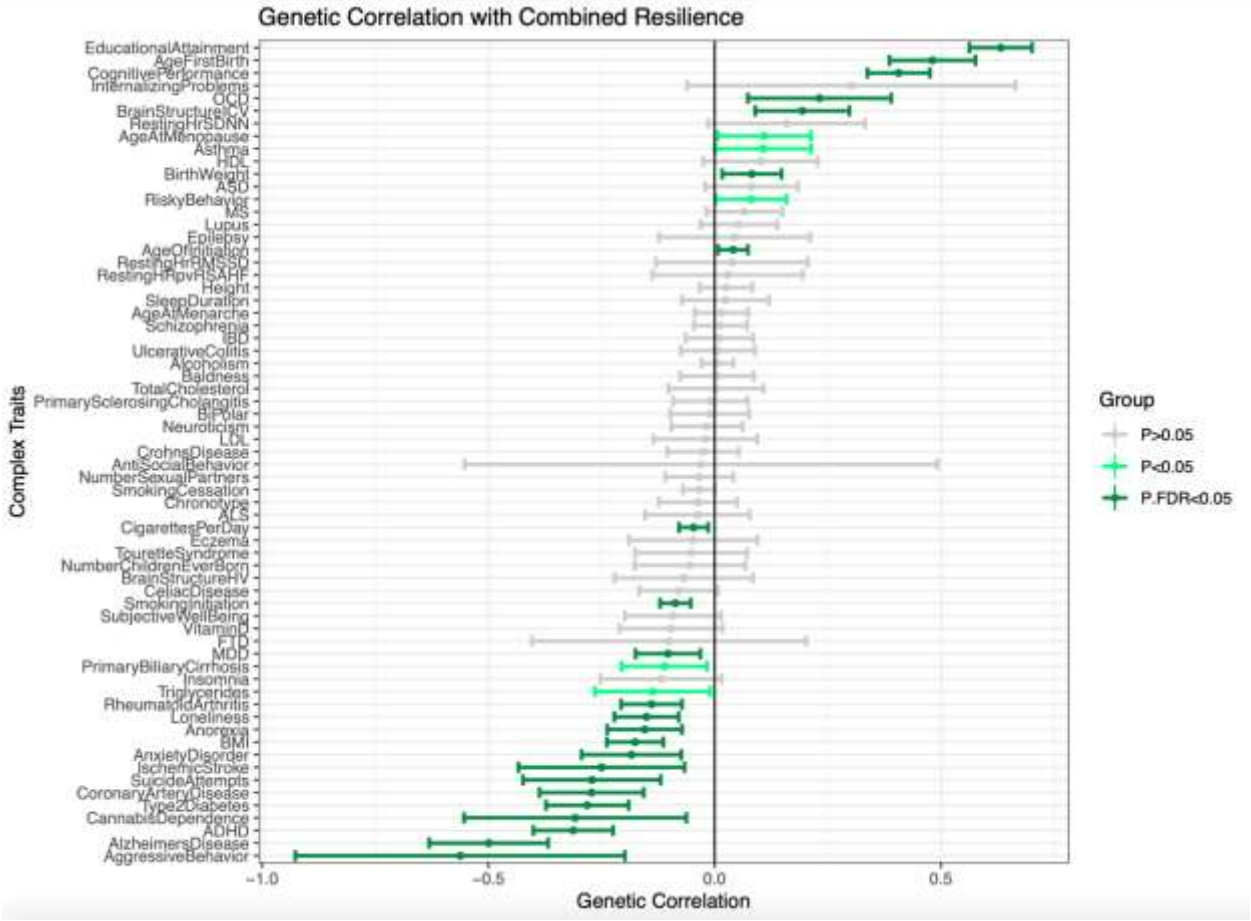

Figure 4. GNOVA plot of genetic correlation of combined resilience with 65 complex traits. We confirmed previously observed positive associations of combined resilience with age at first birth and obsessive-compulsive disorder. In addition, we identified novel negative correlations with the genetic architectures of ischemic stroke and coronary artery disease (all P.fdr<$2.5x10^{-2}$). These results suggest that genetic risk for certain cardiovascular traits may contribute to susceptibility to cognitive decline.

Rare Genetic Risk in Progressive Supranuclear Palsy

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Background: Genetic risk in common variants have been identified for Progressive Supranuclear Palsy (PSP), but common variants only account for a portion of disease heritability. A proportion of the remaining disease heritability is likely contributed by rare variants identifiable via sequencing. Leveraging whole-genome sequencing of 1719 PSP cases and 2940 controls from the Alzheimer's Disease Sequencing Project, we detected single nucleotide variants (SNVs), insertion/deletions (INDELs), and copy number variants (CNVs). Note that all samples are non-Hispanic whites with identity by descent (IBD) >0.25, and no outlier is >6 standard deviation in the principal component analysis. We conducted association analysis for variants, genes and gene sets to identify rare genetic risk for PSP.
Method: After quality control (variants and genotypes notated PASS by the calling algorithms), we detected 85,228,234 rare SNVs/INDELs and 163,987 rare CNVs (minor allele frequency (MAF) < 1%). For rare SNVs/INDELs, the Sequence Kernel Association Test Optimized was performed to identify rare genetic PSP risk from protein truncating variants (PTV) and damaging missense variants (MAF<0.01%) in both protein coding genes and gene sets that were previously associated with PSP based on protein co-expression networks. For rare CNVs, a permutation-based association test implemented in Plink was performed to identify CNVs associated with PSP.
Result: Combining protein truncating variants (PTV) and damaging missense variants, we identified one genome-wide significant gene, FBXO38 (FDR=0.0003, OR=1.78). We also found enrichment of PTVs and damaging missense variants in genes comprising the C2 module, a neuronal module previously identified in post mortem PSP brain (FDR=0.0016). For CNV analysis, there were 17 significant deletions and 2 significant duplications that were associated with PSP (P_{adjust} < 0.05). The deletion (18:58488230-58488489) in ALPK2, which has been identified as an Alzheimer's Disease risk gene, was the only CNV that conferred a higher-risk for PSP. Particularly, one deletion (17:46009357-46009595) was in linkage disequilibrium with MAPT H2 haplotype which has been associated various neurodegenerative diseases including PSP.

Conclusion: We identified several new genes and a protein co-expression network in which risk variants were associated with PSP. These genes and pathways provide potential candidate drug targets for future investigation.

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Beyond the Uniform Data Set (UDS): Benefits of incorporating additional items for the measurement of memory, executive functioning, and language from the University of Pittsburgh Alzheimer's Disease Research Center

Seo-Eun Choi, PhD[1], Shubhabrata Mukherjee, PhD, MS[2], Laura E Gibbons, PhD[1], Emily H. Trittschuh, PhD[3,4,5], Michael L. Lee, PhD, MPH[1], Phoebe Scollard, MA[1], R. Elizabeth Sanders, BA[1], Beth E Snitz, PhD[6,7], Robert Sweet[6,8], Oscar L. Lopez, MD[6,7], Jesse B. Mez, MD, MS[9,10,11], Andrew J. Saykin, PsyD[12,13,14], Timothy J. Hohman, PhD[15,16,17] and Paul K. Crane, MD, MPH[1,2], (1)University of Washington, Seattle, WA, USA, (2)Department of General Internal Medicine, University of Washington School of Medicine, Seattle, WA, USA, (3)Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA, USA, (4)VA Puget Sound Health Care System, Seattle Division, Seattle, WA, USA, (5)Geriatric Research, Education, and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA, (6)University of Pittsburgh, Pittsburgh, PA, USA, (7)Alzheimer's Disease Research Center, Pittsburgh, PA, USA, (8)VA Pittsburgh Healthcare System, Pittsburgh, PA, USA, (9)Department of Neurology, Boston University School of Medicine, Boston, MA, USA, (10)Boston University Alzheimer's Disease Research Center, Boston, MA, USA, (11)Boston University School of Medicine, Boston, MA, USA, (12)Department of Radiology and Imaging Services, Indiana University School of Medicine, Indianapolis, IN, USA, (13)Indiana University, Indianapolis, IN, USA, (14)Indiana University School of Medicine, Indianapolis, IN, USA, (15)Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA, (16)Vanderbilt Memory and Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN, USA, (17)Vanderbilt Memory & Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN, USA

Abstract Text:

Background:

Alzheimer's Disease Research Centers (ADRCs) administer prescribed cognitive batteries – the Uniform Data Set (UDS) – and report UDS data to the National Alzheimer's Coordinating Center (NACC). ADRCs may administer other items beyond the UDS. We used data from the University of Pittsburgh ADRC (Pitt) to determine psychometric implications of UDS items alone versus UDS items plus additional Pitt-specific items.

Method:

We used confirmatory factor analyses to co-calibrate Uniform Data Set 1 and 2 (UDS1/2, broadly overlapping, 2005-2015) and UDS3 (2015-2020) data for memory, executive functioning, and language. We added Pitt-specific items for each domain. We compared measurement properties of UDS scores vs. UDS plus Pitt scores, including measurement precision and projected sample sizes needed to show a 25% reduction in rate of decline over 12 months for people with Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD).

Result:

There were 2,726 participants with 8,602 visits across UDS1, 2, and 3 (**Table 1)**. **Figure 1** summarizes findings for memory. **Figure 1a** shows boxplots for memory scores for normal cognition (NC), MCI, and AD for UDS1/2 (green) and UDS3 (purple). **Figure 1b** shows corresponding boxplots and standard error of measurement (SEM) curves for UDS1/2 (left) and UDS3 (right). Incremental improvements in measurement precision can be seen with the lower SEM curve for the UDS plus Pitt curves. **Figures 2 and 3** summarize similar findings for executive functioning and for language. In each case UDS Plus Pitt has less measurement error than UDS alone. Proportions of scores with standard errors >0.30 (a commonly used

threshold for individual decision-making) during UDS1/2 and UDS3 are in **Table 2**. Pitt-specific items reduced the proportion with imprecise scores for every comparison with the exception of executive functioning in UDS1/2. Sample sizes needed to show a 25% reduction in the rate of decline are shown in **Table 3.** Improved precision from additional items was associated with greater power to show change over time.

Conclusion:

Integrating additional data beyond UDS1/2 and UDS3 results in better measurement precision and increased statistical power.

Tables and Figures:

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Table 1. Baseline demographic characteristics by UDS wave.

	UDS1/2 (2005-2015) n =1564	UDS3 (2015-2020) n =1040
Female, n (%)	906 (58%)	592 (57%)
Age in years, mean (SD)	74.3 (7.9)	73.9 (7.8)
Education in years, mean (SD)	14.8 (3.1)	15.6 (2.9)
≥1 *APOE-ε4* allele, n (%)*	740 (47%)	414 (40%)

* *APOE* genotype was missing for 40 people in UDS1/2 and 128 people in UDS3.

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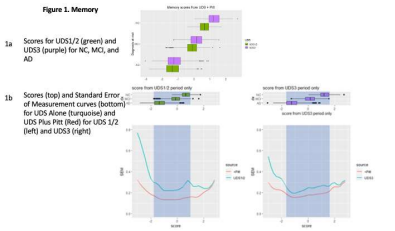

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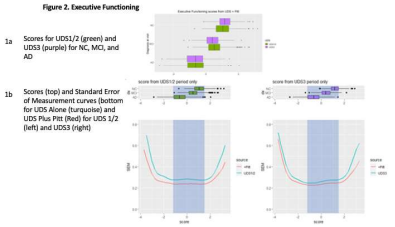

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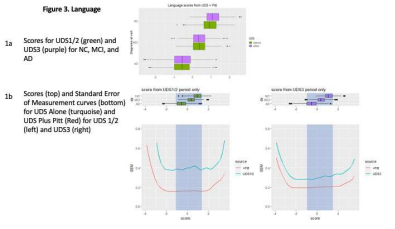

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Table 2. Number and proportion of people in the UDS1/2 and UDS3 eras who have standard errors >0.30 for each domain by diagnosis and overall

	UDS 1/2					UDS3				
		UDS Only		UDS Plus Pitt				UDS Only		UDS Plus Pitt
Group	N of visits	N	%	N	%	Group	N of visits	N	%	N	%
Memory										
NC	929	929	100	84	14.0	NC	592	592	100	291	75.4
MCI	823	822	100	22	2.7	MCI	620	586	94.5	159	25.7
AD	2104	2094	99.5	118	5.6	AD	303	412	45.4	63	7.0
Other	809	808	99.9	85	9.5	Other	847	790	93.3	402	47.5
Total	4951	4339	99.7	309	7.1	Total	2782	2120	78.5	875	32.4
Executive Functioning*											
NC	575	110	19.1	161	28.0	NC	316	316	100	91	28.8
MCI	881	106	12.0	173	19.6	MCI	551	551	100	106	19.2
AD	2260	572	25.3	836	37.0	AD	793	793	100	119	15.0
Other	1007	216	21.4	321	31.9	Other	753	753	100	183	24.3
Total	4723	1004	21.3	1491	31.6	Total	2413	2413	100	499	20.7
Language											
NC	575	575	100	112	19.5	NC	320	240	75.0	43	13.4
MCI	880	880	100	140	15.9	MCI	583	271	46.5	56	9.6
AD	2275	2275	100	193	8.5	AD	898	179	20.0	44	4.9
Other	1014	1014	100	172	17.0	Other	791	440	55.6	93	11.8
Total	4744	4744	100	617	13.0	Total	2592	1130	43.6	236	9.1

* Results for executive functioning surprised us, as adding additional items should improve measurement precision. We confirmed the accuracy of these results. The bulk of the distribution of standard errors was indeed improved with the UDS Plus Pitt scores for UDS1/2, but at the specific *a priori* threshold of 0.30 the results are as shown here. (For example, findings with a threshold of 0.40 instead of 0.30 were as expected, with more visits characterized by higher standard errors with the UDS Only scores than with the UDS Plus Pitt scores.)

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Table 3. Sample sizes needed to show a 25% change in the rate of decline for each domain

Baseline diagnosis	UDS1/2 only	UDS1/2 plus Pitt	UDS3 only	UDS3 plus Pitt
MCI				
Memory	7830	5736	37921	14637
Executive Functioning	6346	4333	17900	7941
Language	6730	3496	3349	2608
AD				
Memory	1808	869	1515	943
Executive Functioning	2633	1330	1503	640
Language	1387	632	457	335

Composite scores for memory, executive functioning, and language performance harmonized across waves from the National Alzheimer's Coordinating Center (NACC)

Michael Lee, Shubhabrata Mukherjee, Seo-Eun Choi, Phoebe Scollard, Elizabeth Sanders, Laura E. Gibbons, Jessica Culhane, Kathryn Gauthreaux, Gary Chan, Sarah Biber, Kari Stephens, Walter Kukull, Emily Trittschuh, Jesse Mez, Andrew J. Saykin, Timothy Hohman, Paul K. Crane

Background: Alzheimer's Disease Centers and Research Centers (ADRCs) collect standardized data and report them centrally to the National Alzheimer's Coordinating Center (NACC). The cognitive battery has been modified several times over the years. We developed harmonized and calibrated composite scores for three cognitive for all participants and visits prior to March 2020.

Methods: Based on content, an expert panel assigned items to a single domain – memory, executive functioning, language or visuospatial. For each domain except visuospatial, which had too few items, we used confirmatory factor analysis to estimate scores for in-person NACC visits. We used a common-anchoring approach involving data from NACC and other studies to co-calibrate across the three rounds of the Uniform Data Set (UDS1, UDS2, and UDS3). Items in UDS1/2 were identical, while UDS 3 introduced new non-proprietary cognitive test items to replace similar tests with licensing restrictions. In the case of the memory domain, items between UDS1/2 and UDS 3 are mutually exclusive, and direct comparison would not be possible without harmonization and calibration. We compare composite scores of first visit and last visit for people with longitudinal data.

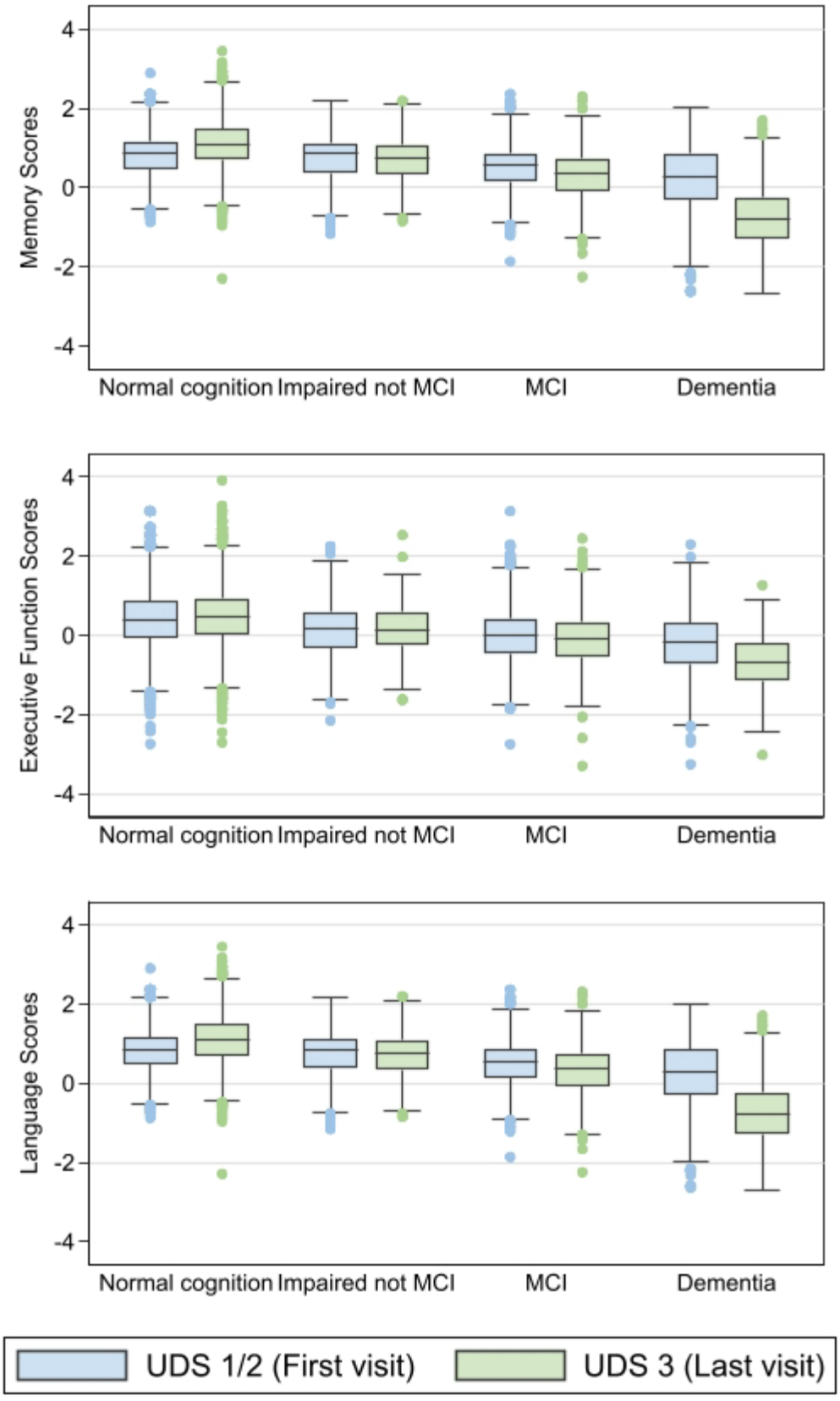
Results:
NACC includes in person collected data from 41,459 individuals with at least 2 data points between 2005 and 2019. (Table 1). 32,764 people enrolled during UDS 1/2. Of these, 24,077 (74%) had all of their visits during UDS1/2, and 8,687 (26%) also had data collected during UDS3. An additional 8,695 individuals were enrolled during UDS3 (See Table 1). Figure 1 shows first (blue) and last (green) visit domain scores, split by last visit diagnosis for participants that were cognitively normal at enrollment in UDS1/2, and had their last during UDS 3. UDS 3 scores decrease with worsening dementia diagnosis. Cognitively normal participants in UDS1/2 diagnosed with dementia in UDS 3 had lower baseline memory scores than those without dementia diagnosis at their last UDS 3 visit.

Discussion
Co-calibrated composite scores for memory, executive functioning, and language allow for comparisons and analysis across UDS 1/2 and UDS 3, addressing the challenge of different batteries administered. Composite scores will be made available through NACC.

Table 1. Number of participants by cognitive status at first and last NACC visit.

First and last visits: UDS1/2	Baseline visit: Normal Cognition	Impaired, not MCI	MCI	Dementia	Total
Last Visit					
Normal Cognition	5,682	216	628	354	6,880
Impaired, not MCI	178	583	160	109	1,030
MCI	327	161	3,232	1,416	5,136
Dementia	19	25	103	10,884	11,031
Total	6,206	985	4123	12,763	24,077
First visit: UDS1/2 Last visit: UDS3					
Normal Cognition	4,174	151	281	19	4,625
Impaired, not MCI	178	106	115	12	411
MCI	631	109	614	45	1,399
Dementia	375	80	706	1,091	2,252
Total	5,358	446	1,716	1,167	8,687
First visit and last visits: UDS3					
Normal Cognition	3,735	64	109	6	3,914
Impaired, not MCI	47	261	40	3	351
MCI	116	60	1,640	19	1,835
Dementia	15	7	245	2,328	2,595
Total	3,913	392	2,034	2,356	8,695

Figure 1. First and last visit cognitive domain scores, split by last visit diagnosis, for participants who were cognitively normal during their UDS 1/2 baseline visit and had their last visit in UDS 3. Individuals are categorized based on dementia status at most recent UDS 3 visit. Box plots: blue=UDS1/2 visit, green=UDS 3 visit


Memory Scores
4
2
0
-2
-4
Normal cognition
Impaired not MCI
MCI
Dementia
Executive Function Scores
4
2
0
-2
-4
Normal cognition
Impaired not MCI
MCI
Dementia
Language Scores
4
2
0
-2
-4
Normal cognition
Impaired not MCI
MCI
Dementia
UDS 1/2 (First visit)
UDS 3 (Last visit)

Title: *KDM6A* expression is associated with a sex-disease interaction in activated microglia

Authors: Logan Brase, Amy Dunn, Logan Demitrescu, Catherine Kaczorowski, Timothy Hohman, Celeste Karch, Oscar Harari, Bruno A. Benitez

Background: There is increasing evidence indicating sex-specific patterns in disease manifestation and sex differences in the rates of cognitive decline and brain atrophy. Women are protected, relative to men, at the prodromal phases but later exhibit steeper cognitive decline and higher brain atrophy rates[1]. Sex-related differences in AD-associated genes are starting to emerge. The X-linked gene, *KDM6A*, avoids X-inactivation and the resulting elevation in expression confers resilience in women[2]. *KDM6A* is also dysregulated in disease associated microglia (DAM) in the 5XFAD mouse model[3]. We sought to identify if activated microglia was the effector cell type for the *KDM6A* resilience effect in the brain using single-nucleus RNA-seq (snRNA-seq).

Methods: Using snRNA-seq data from the parietal cortex of 56 pathologically confirmed control, sporadic AD (sAD), and autosomal dominant AD (ADAD) samples from the Knight ADRC and DIAN cohorts[4], we applied a linear mixed model to confirm the female specific upregulation of *KDM6A* in the major brain cell types and their alternative transcriptional states. We then applied a sex-AD interaction linear mixed model to identify the cell types and expression states that potentially contribute to disease resilience through *KDM6A* expression.

Results: *KDM6A* is expressed in all major brain cell types, with the highest expression in oligodendrocytes, followed by endocytes, microglia, astrocytes, OPCs, and neurons (http://ngi.pub/SNARE/). All cell types showed increased *KDM6A* expression in females compared to males (oligo $P=4.22\times10^{-15}$, microglia $P=1.07\times10^{-41}$, astro $P=1.30\times10^{-13}$, OPC $P=2.55\times10^{-5}$, neuron $P=7.55\times10^{-8}$). We identified a sex-AD interaction in *KDM6A* expression within activated microglia (sAD $P=9.12\times10^{-3}$; ADAD $P=2.28\times10^{-3}$; Fig. 1), but no evidence in the overall DAM signature. Female sAD and ADAD samples showed higher expression compared to controls, while male sAD and ADAD samples had less expression than controls. Furthermore, we observed sex differences in *KDM6A* expression within transcriptional states of oligodendrocytes, OPCs, astrocytes and neurons. We are validating these results in additional generated data and publicly available data sets.

Conclusion: These results suggest that the role of *KDM6A* in AD resilience could be mediated through activated microglia, but current data cannot rule out additional cell types as effectors in *KDM6A* resilience.

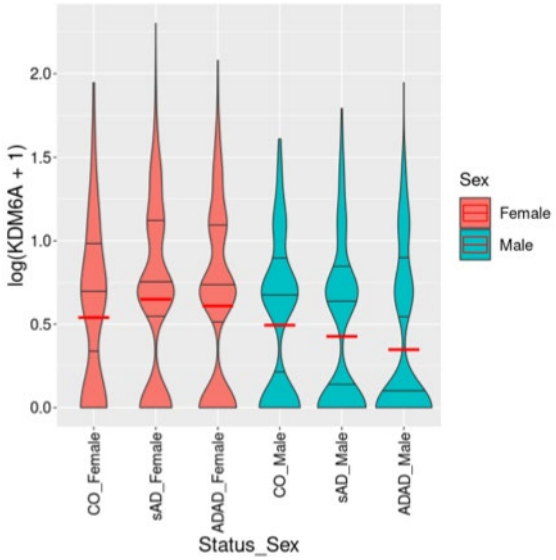


Figure 1. Sex*AD interaction influences KMD6A expression in activated microglia. Violin plot of the log KMD6A gene expression grouped by sex and AD status (CO = control, sAD = sporadic AD, ADAD = autosomal dominant AD). Black horizontal bars in the violins depict the quantiles. Red horizontal bars depict group mean expression.

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Characterizing Disrupted Cellular Crosstalk Signaling Networks in Alzheimer's Disease Using Single-Nuclei Transcriptomics

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* Co-corresponding authors

Background: Genetics and molecular studies have implicated multiple genes, pathways, and cell types in Alzheimer's disease (AD) risk and progression. How these genes and pathways perturb and are modulated by brain cellular crosstalk networks have not been deeply characterized.
Method: We generated single-nuclei transcriptomic profiles (snRNA-seq) of parietal lobes from 67 donors from the Knight ADRC and DIAN brain banks, representing neuropathological-free controls and AD cases from pre-symptomatic and AD[1]. We estimated cellular crosstalk patterns among the brain cell types based on the expression of known ligand-receptor pairs[2] and reconstructed the co-expression network upstream and downstream of these ligand-receptor pairs to determine how these signals are propagated across cells[3].
Result: We analyzed ~294K high-quality nuclei and identified six major cell populations[1]. We observed changes in cellular crosstalk patterns between controls and AD, with the largest involving microglial interactions (increased in AD, OR=1.31, p=8.94e-11). Cellular interactions directly involving AD-related genes[4] as either the receptor or the ligand were enriched for neuron-microglia pairs (OR=2.74, p=4.41e-15), and the majority (64.9%) codified for microglial cell membrane receptors, supporting the role for these cells in AD. We observed an increase in the frequency of a subset of interactions involving AD-related genes in microglia when comparing pre-symptomatic and AD individuals, suggesting correlation with pathological burden. These included TREM2-semaphorin (neuron-microglia, 4.38-fold increase). We performed a comprehensive study of the microglial co-expression networks up/downstream of these interactions and provided additional evidence of their association with Braak stage. The TREM2-semaphorin neuron-microglia interaction is predicted to directly propagate signals into a sub-network associated with microglia activation, involving four genes from the HLA family previously implicated in AD. Furthermore, the neuronal co-expression network had significant enrichment for AD-related genes including CELF2 (OR=2.10, p=5.32e-3), consistent with AD-related genes in neurons propagating signals into microglia. We replicated these results in public snRNA-seq studies and are currently validating these findings experimentally.
Conclusion: This study reveals the role of cellular crosstalk in AD biology and identifies disruptions in neuron-microglia interactions as an important component of AD pathology. In addition, we show that cellular crosstalk networks can directly modulate genes previously associated with AD (**Figure 1**).

References:[1]DOI:10.1101/2021.11.30.21267072;[2]PMID:32103204;[3]PMID:33853780;[4]PMID:30820047

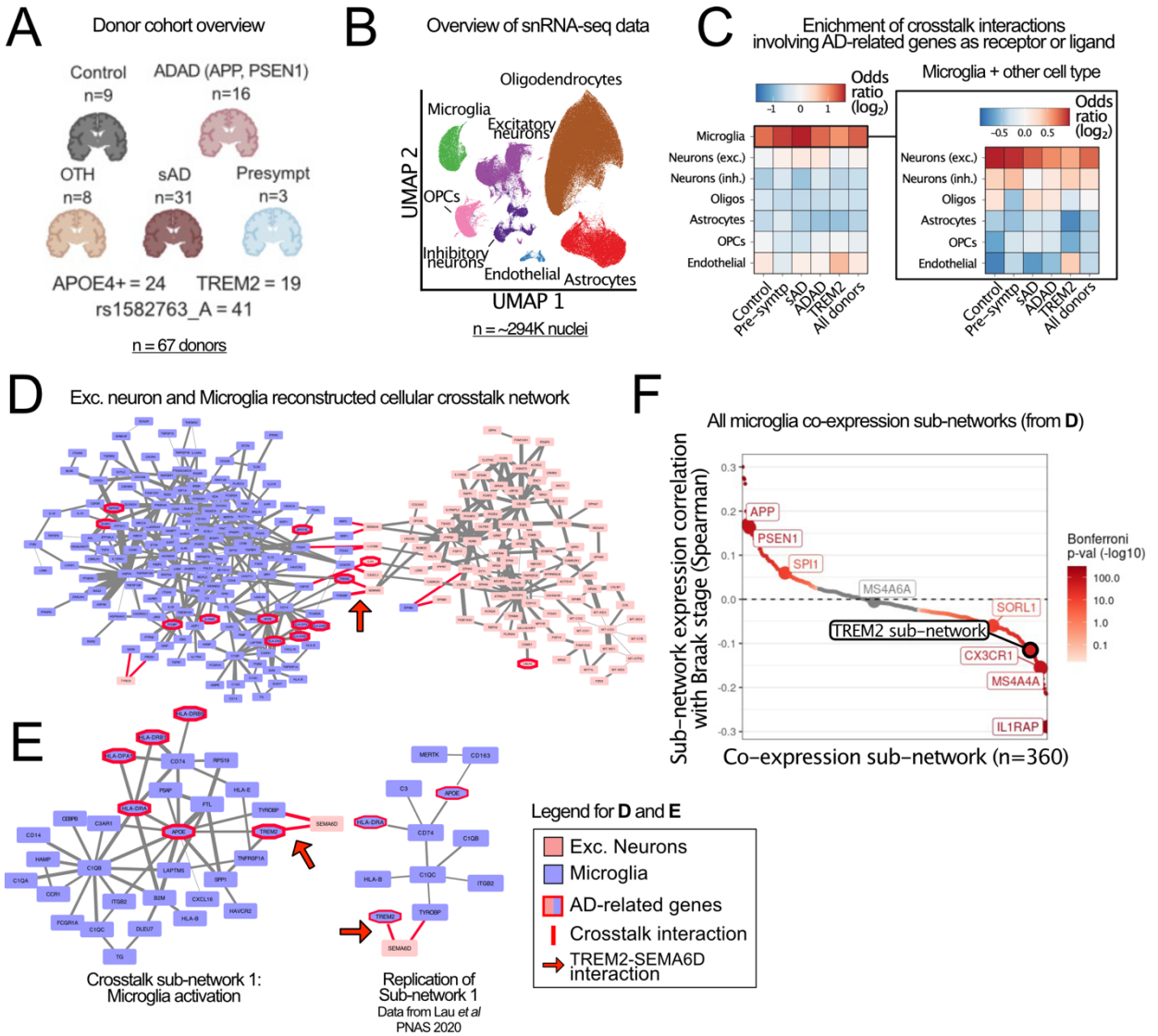

Figure 1: (**A**) Overview of donor cohort used for this study. Parietal cortex samples were obtained from the Knight-ADRC and DIAN brain banks. (**B**) snRNA-seq identifies seven major brain populations based on transcriptional profiles. (**C**) Microglia and Exc. neurons are enriched for cellular crosstalk interactions involving AD-related genes as either the ligand or receptor. (**D**) Reconstructed co-expression network of exc. neurons and microglia crosstalk identifies AD-related genes downstream of crosstalk interactions. (**E**) TREM2-SEMA6D crosstalk interaction propagates signals into a sub-network associated with microglia activation. (**F**) Transcriptional signatures of a subset of microglia co-expression sub-networks are positively or negatively correlated with Braak stage.