NIAGADS Update
Fall 2024

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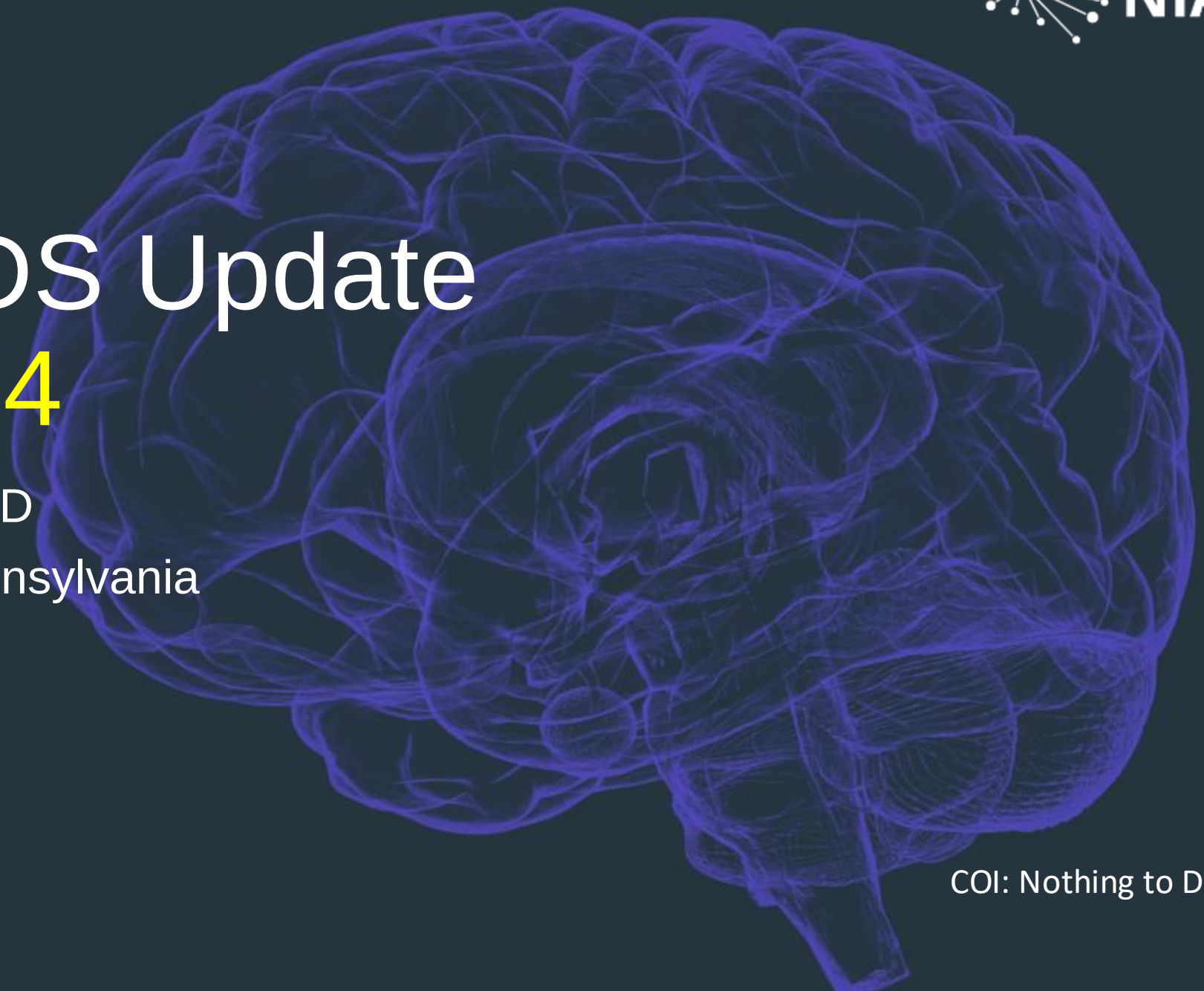
University of Pennsylvania



COI: Nothing to Disclose

NIAGADS at a Glance

NIAGADS

Data Sharing

127 datasets

>209,000 samples

497 unique requests

238 institutional certifications

Userbase

>330 articles cite U24

>4,900 verified users

ADSP

73 cohorts

23 current grant subawards

R4 Release

20,503 exomes

36,361 genomes

R5 Release

Increasing to

>60,000 genomes

ADSP Support

14 workgroups /

5 consortia

>500 members

52 institutions

ADSP 2024 Releases

NIAGADS

Released in 2024

October

Additional files added for R2, R3, and R4 releases

Structural Variant joint genotype calls, multi-allelic / chrX quality control results

Coming Soon in 2024

November

R5 Whole Genome Sequencing for ~24K new samples

Individual sample raw data (CRAMs)

Joint genotype calls preview pVCF across all ~60k genomes released by ADSP

December

Additional cohorts from the **Phenotype Harmonization Consortium** (PHC) released

ADSP Data Released in Oct 2024

NG00067v13; New files for R2, R3, and R4

Release	**R2:** 20K Whole Exomes (cumulative)	**R3:** 17K Whole Genomes (cumulative)	**R4:** 36K Whole Genomes (cumulative; including 17K from R3)
Files	20k WES **chrY and M joint genotype calls** (preview)	Population Structure Estimate: Principal Component Analysis **(PCA) results** from the 17k analysis	• **GDS format:** fully QC'd bi-allelic joint call pVCFs • **Bi-allelic chr X** QC'd pVCF (full & compact-filtered) • **Multi-allelic autosomal and chr X** QC'd pVCF (full & compact-filtered) • **GraphTyper joint-called SV** pVCF (manta + Smoove) • **FAVOR annotations** in GDS format (Open Access)

Next ADSP Data Release (Pending Nov 2024)

ADSP R5 – Up to 60K Whole Genomes

ADSP Release	Primary Ancestry/Ethnicity	Cases	Controls	Other	Totals
GCAD Release 5	Black/African American	2,646	5,608	777	9,031
	Asian	1,273	4,083	5	5,361
	Latino/Hispanic	4,488	10,248	2,777	17,513
	Non-Hispanic White	9,124	14,459	6,067	29,650
	Total	**17,531**	**34,398**	**9,626**	**61,555**

ADRC samples in R5

12,629
genomes
20% of total ADSP WGS

4,590
Exomes (previously released)
22% of total ADSP WES

Files in the Preview Release

- Sequence read mappings (CRAMs) for individual genomes
- Individual structural variant calls using GCAD pipeline
- Joint variant calls over all ADSP genomes (project level VCF)
- Data quality information / Documentation

ADRCs can get WGS/WES data from their own samples from us!
Send an email to niagads@pennmedicine.upenn.edu to initiate.

Next ADSP Data Release (Pending Dec 2024)

Additional Clinical Data from the Phenotype Harmonization Consortium (PHC)

Cohorts	Cognition	Fluid Biomarkers	Neuro-pathology	Vascular Risk Factors	Imaging - DTI	Imaging - FLAIR	Imaging - T1	Imaging - PET
ADNI			N/A					
WHICAP		N/A						N/A
EFIGA		N/A			N/A	N/A	N/A	N/A
NIA-AD FBS		N/A			N/A	N/A	N/A	N/A
WRAP			N/A			N/A		
ROS/MAP/MARS		N/A						N/A
ACT		N/A			N/A	N/A	N/A	N/A
NACC								
WashU (Knight ADRC)								
A4		N/A	N/A					
KBASE								
TARCC		N/A	N/A					
HABS-HD		N/A	N/A					
Miami Brain Bank	N/A	N/A		N/A	N/A	N/A	N/A	N/A
HIHG Brain Bank	N/A	N/A		N/A	N/A	N/A	N/A	N/A
Case Western	N/A	N/A		N/A	N/A	N/A	N/A	N/A

✓ Coming in December 2024

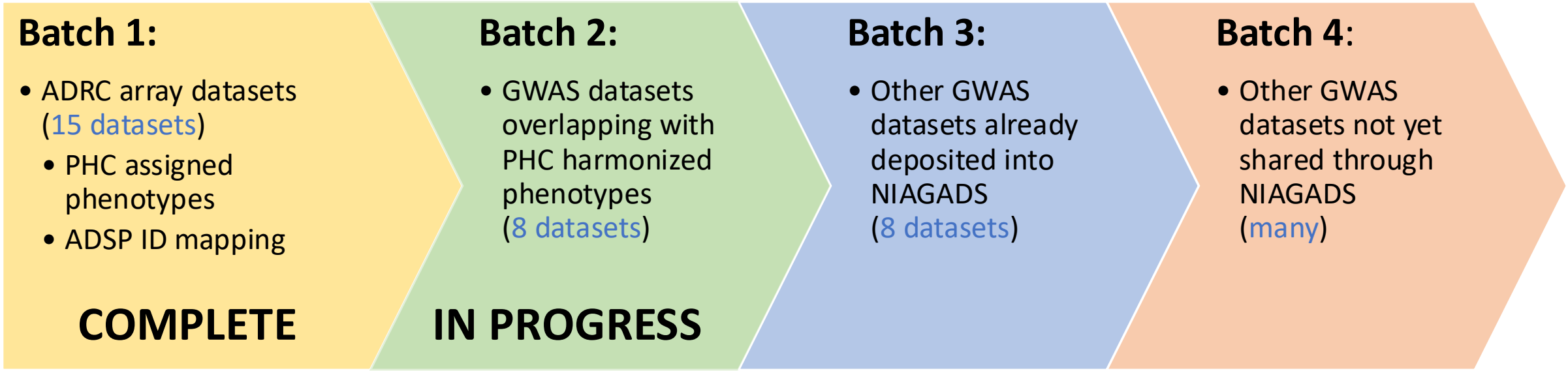
Harmonization in Progress; to be included in future release

N/A Domain data not available for harmonization

ADGC GWAS Data Release

NIAGADS

Leads: Adam Naj & Amanda Kuzma

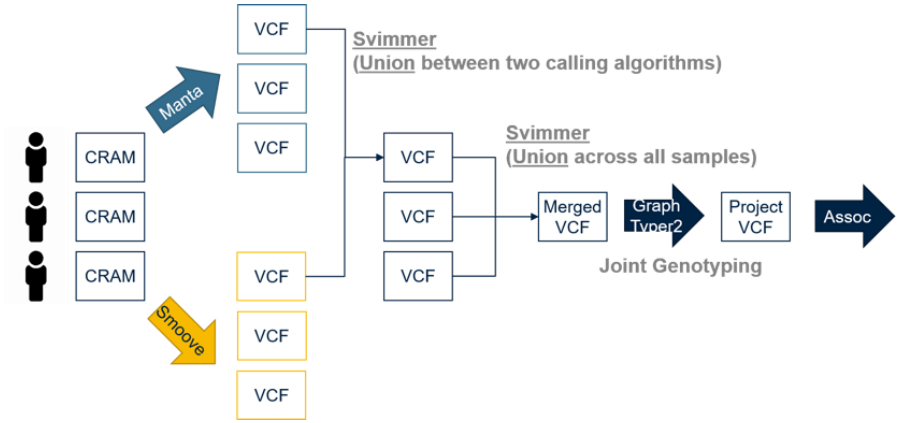


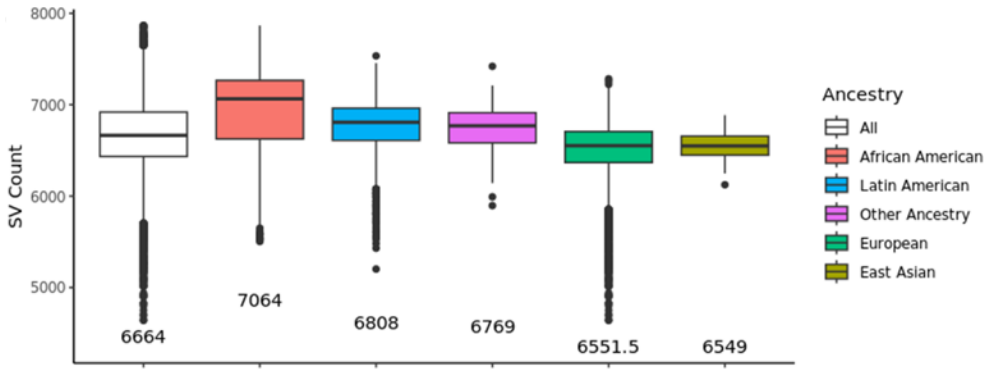
Release Features

- All subject IDs standardized using updated schema
- PLINK files converted to forward strand and lifted to GRCh38
- Covariate files updated with consistent variables/formatting
- Standardized file naming schema

Structural Variant Analysis of ADSP Data

ADSP Structural Variant Workgroup





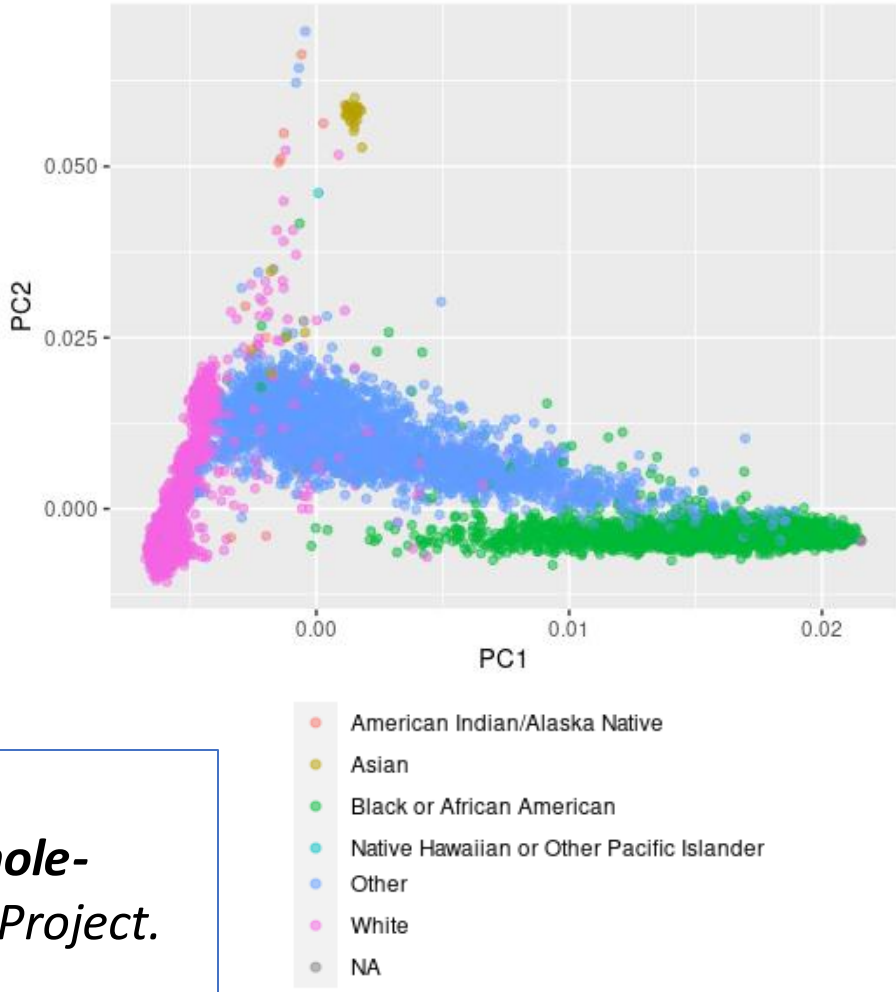
- Ultra-rare protein-altering SVs within ABCA7, APP, PLCG2, SORL1
- APP duplications in three early-onset AD cases
- Linkage disequilibrium between SVs and known AD risk-associated SNPs -> possible causal SV
- 16 SVs linked to AD and 13 SVs associated with AD-related pathological endophenotypes
- Enrichment of SVs in neuronal genes

H Wang et al., ***Structural Variation Detection and Association Analysis of Whole-Genome-Sequence Data from 16,905 Alzheimer's Diseases Sequencing Project Subjects.*** *Under review. DOI: 10.1101/2023.09.13.23295505*

SNV and INDEL Analysis of ADSP Data

NIAGADS

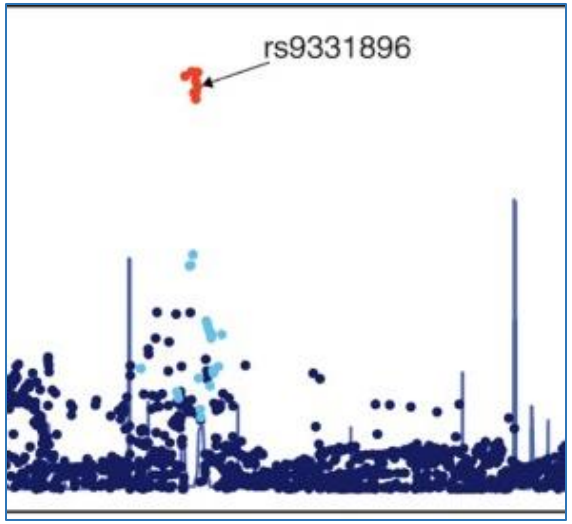
- Common variants and aggregates of rare coding/noncoding variants in 13,371 genomes
  - AD cases: 64.9% NHW, 15.7% Hispanics, and 17.4% AA
  - Controls: 45.4% NHW, 29.0% Hispanics, and 24.9% AA
- Significant findings
  - Common variants (MAF>0.5%) in or near *APOE, BIN1, LINC00320* and 14q24 ($p < 5x10^{-8}$)
  - Suggestive associations (p < 5x10-5) of rare coding variants in *ABCA7* and rare noncoding variants in the promoter of TOMM40 distinct of *APOE*

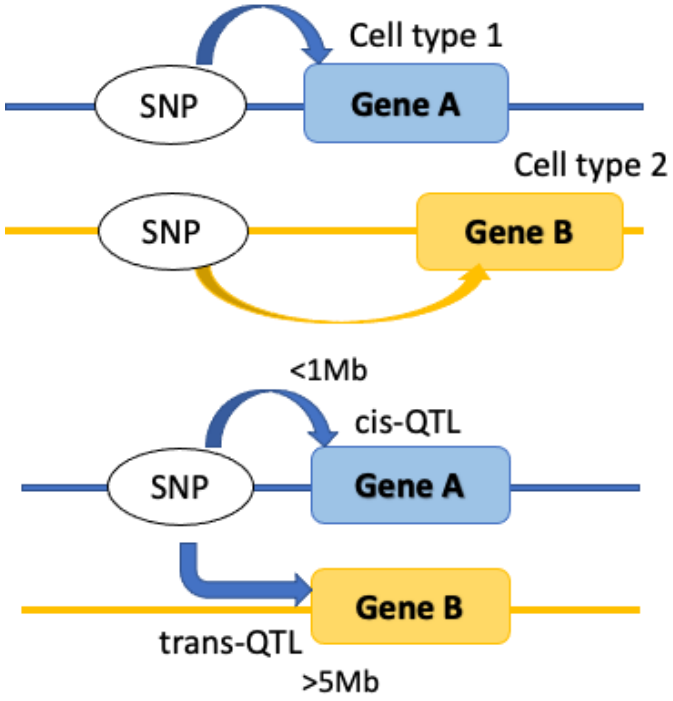


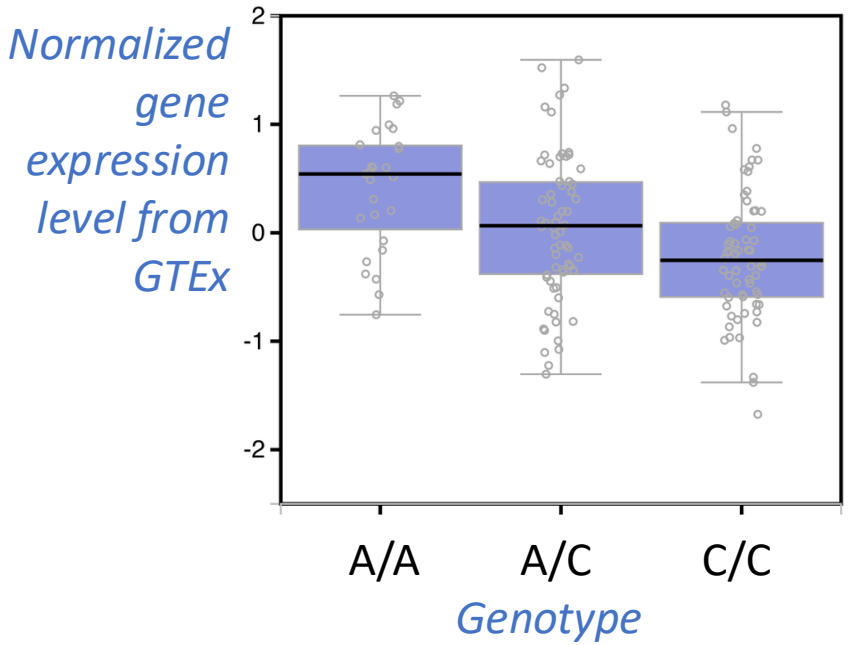
WP Lee et al., ***Association of Common and Rare Variants with Alzheimer's Disease in over 13,000 Diverse Individuals with Whole-Genome Sequencing from the Alzheimer's Disease Sequencing*** *Project. Alz & Dementia, In Press.* DOI: 10.1101/2023.09.01.23294953

ADSP Quantitative Trait Locus (QTL) Analysis

Find regulatory non-coding variants in AD susceptibility loci







Genetic Association Signal

Hypothesis: risk of AD due to gene expression regulation in relevant cell type

Evidence: linkage with regulatory SNP using QTL datasets

Provided by Fanny Leung

QTL Analysis by the XQTL Workgroup
ADSP FunGen Consortium

NIAGADS

Project Leads
Phil De Jager (Columbia)
Carlos Cruchaga (WashU)
Gao Wang (Columbia; analysis lead)
Fanny Leung (Penn; data coordination)

Raw Data from Collaborators

ROSMAP
Knight-ADRC
STARNET
EFIGA
MAGENTA
MSBB
MIGA

→ **Data Management** (NIAGADS)

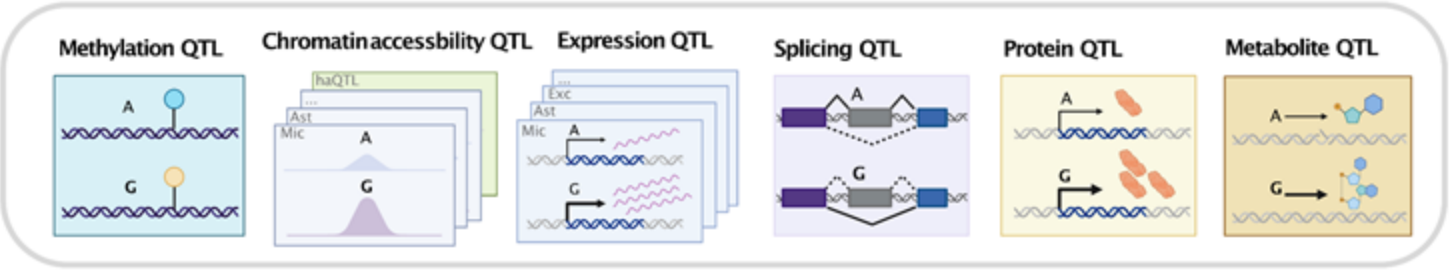
→ **Process and Standardize Data** (GCAD Genome Center for Alzheimer's Disease)

→ **Analyze Data**

→ **Generate Summary Statistics**

FunGen-AD ADSP Functional Genomics Consortium

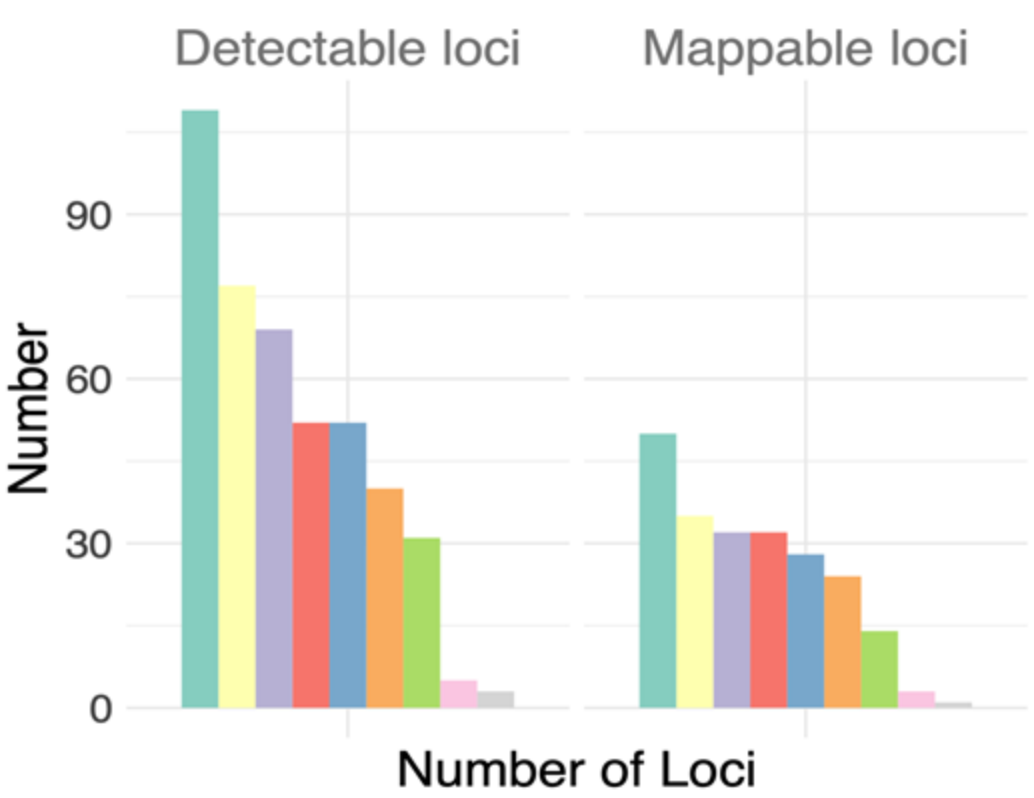
FunGen xQTL protocol

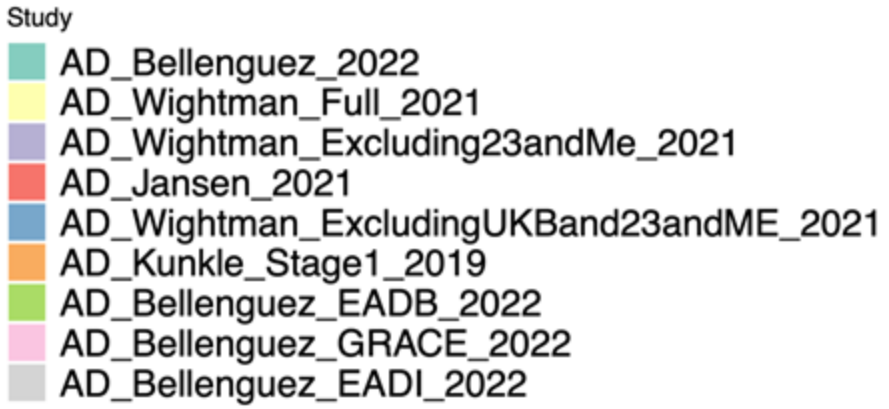


→ **Data Sharing**
NIAGADS
SageBionetworks
Repositories for respective QTL datasets

→ **Summary Statistics Data Sharing**
NIAGADS
filer
GenomicsDB

Analyzing Quantitative Trait Locus (QTL)





Detectable loci:
CS 95%

Mappable loci:
CS 95% with <= 3 variants

As of v0.3.0,

>90

AD GWAS loci are fine-mapped genome-wide at 95% credible level

Provided by Gao Wang

NIAGADS Open Access

Data and Annotation Resources

Unrestricted data and annotations (variant, gene, sequence) available for immediate access

dss NIAGADS

Open Access Portal

direct data downloads for GWAS summary statistics (p-values) and **ADSP Variant Annotations**

https://dss.niagads.org

filer [1]

75,207

standardized, searchable functional genomics tracks

https://tf.lisanwanglab.org/FILER/

advp [2]

curated AD-GWAS catalog, documenting

>18k

published associations

https://advp.niagads.org

GenomicsDB [3]

AD-genetics knowledgebase and **Genome Browser**, containing

>260M

annotated variants

https://www.niagads.org/genomics

1. Kuksa et al. 2022, *NAR Genomics and Bioinformatics,* 4(1): lqab123. 2. Kuksa et al. 2021, *Journal of Alzheimer's Disease,* 86(1): 461-477. 3. Greenfest-Allen et al. 20204, *Alzheimer's & Dementia,* 20(2):1123-1136

Supporting Data Use

User Support

NIAGADS offers several support resources launched over the last year:

Office Hours

Held at least once a quarter

Video Tutorials

https://www.youtube.com/@niagads1814

NIAGADS Support Portal

All NIAGADS documentation in one place, new informational pages to address user questions, dedicated FAQ page

Ticket Support

Users can now submit a ticket to work on resolving technical issues with the NIAGADS team.

Awareness

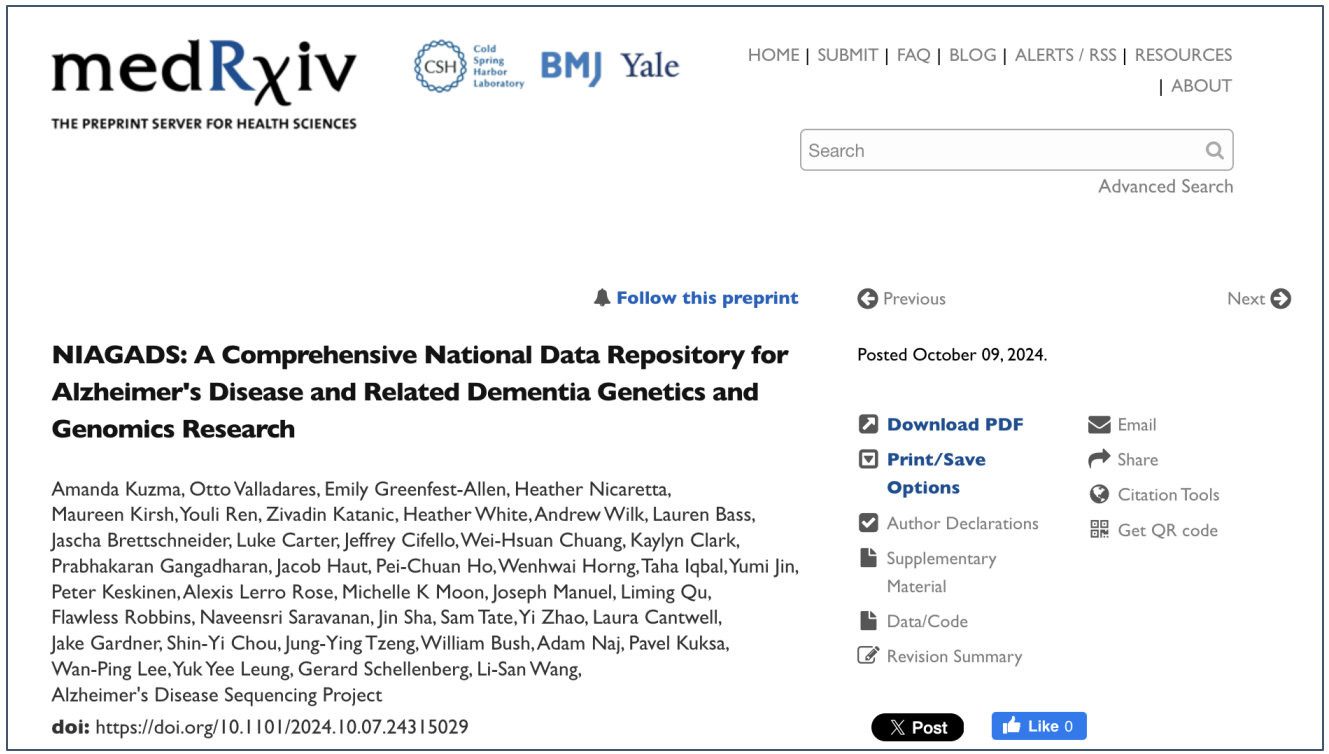
Expanding NIAGADS reach through increased investigator awareness was accomplished through informational outreach sessions at AAIC and will continue at ASHG in 2024

Exhibit Hall Booth

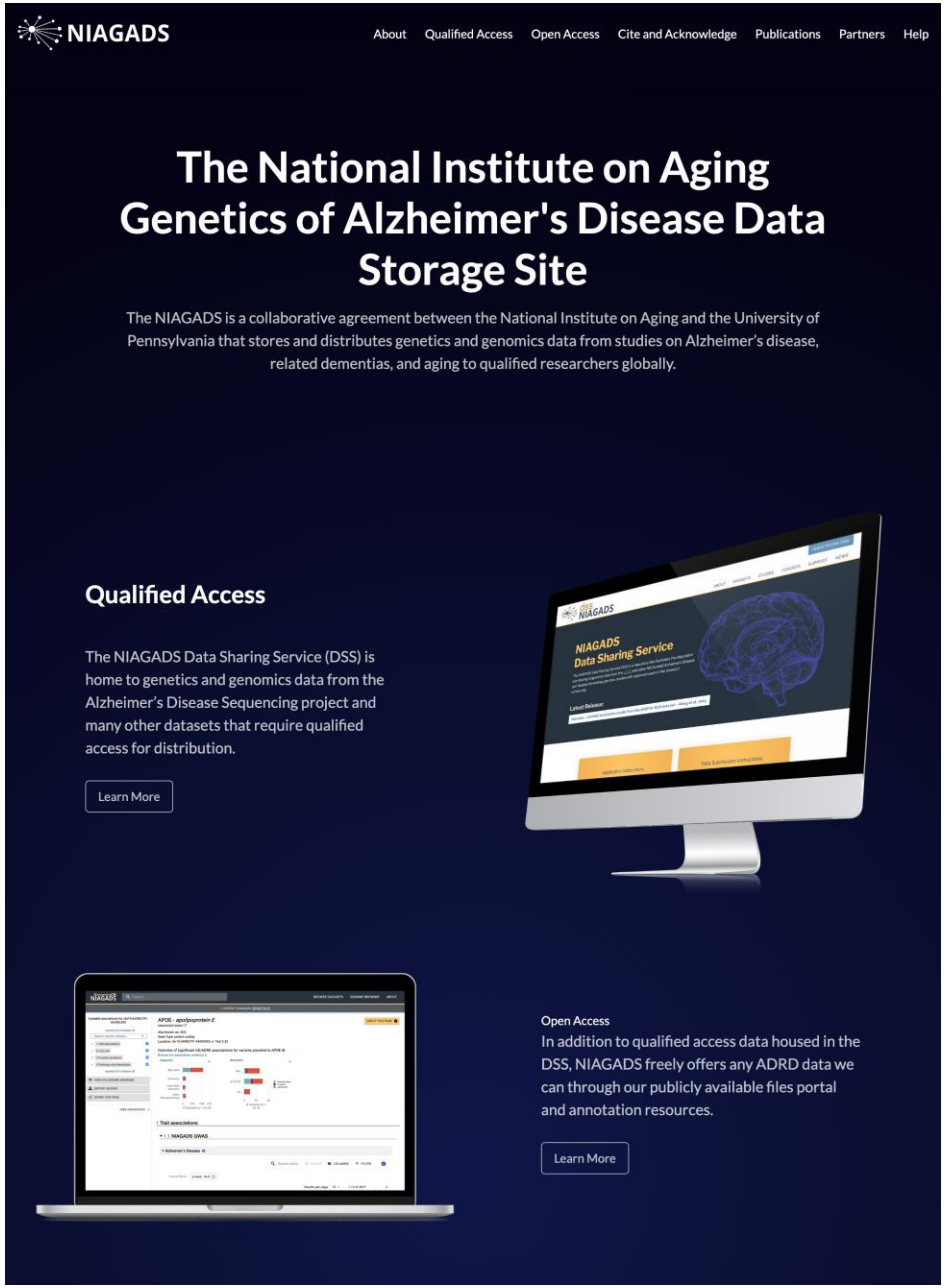
Visit us at booth 1023 at ASHG!

Poster Presentations

ADRC workshop at AAIC in partnership with NACC, Sage, and NCRAD



DOI: 10.1101/2024.10.07.24315029



ASHG 2024 Activities

ASHG Exhibit Hall Booth

*Visit us at booth **1023D** at ASHG*

See you this November in Denver!