NIAGADS Update: Fall 2023

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COI: Nothing to Disclose

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NIAGADS At a Glance

Data Sharing

102 datasets

>183,000 samples

492 Unique Requests

221 Institutional Certifications

Userbase

>250 articles cite U24

>3,515 verified users

ADSP

70 cohorts

26 current grant subawards

Exomes

20,503

Genomes

~350% increase from 2021 to 2024

(16,905 in 2021 to ~60,000 genomes in 2024)

ADSP Support

14 workgroups /

5 consortia

309 members

49 institutions

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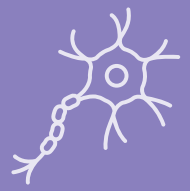
ADSP August 2023 R4 WGS QC Release

Released August 2023

R4 QC'd genotypes for bi-allelic autosomes (>36k genomes)

Individual level structural variant calls



Phenotypes

- updates
- Instructional **quick guide**
- Script to combine phenotype files for a standard AD case/control analysis

Identity by descent (IBD), Principal Component Analysis Coordinates, and other additional information that can be used in genetic association analysis

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Planned ADSP R4 WGS Releases

Coming Soon

November 2023	R4 WGS Annotation PHC 2023 Release
Early 2024	SV joint genotype called pVCF QC'd chrX/multi-allelic pVCF

ADSP-PHC 2023 Deliverables

ng00067.v11

✓ Included in ng00067.v11

Harmonization in Progress; to be included in future release

Domain data not available for harmonization

Cohorts	Autopsy	Cardiovascular Risk Factors	Cognition	Fluid Biomarkers	Imaging – DTI	Imaging – FLAIR	Imaging – PET	Imaging – T1
A4	N/A		✓	N/A	N/A	✓	✓	
ACT	✓		✓	N/A			N/A	
ADNI	N/A	✓	✓	✓	✓		✓	✓
ADFBS (NIA-LOAD)	✓	✓	✓	N/A	N/A	N/A	N/A	N/A
EFIGA		✓	✓	N/A	N/A	N/A	N/A	N/A
Knight ADRC			✓	✓				
NACC	✓	✓	✓	✓	✓	✓	✓	✓
ROS/MAP/MARS	✓	✓	✓	N/A	✓		N/A	
WHICAP			✓	N/A		✓		✓
UPenn				✓				
WHICAP		✓	✓			✓	N/A	
WRAP	N/A	✓	✓		✓		✓	✓

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ADSP-PHC 2023 Deliverables
ng00067.v11

Cognition	Fluid Biomarker	Neuropathology	Vascular Risk Factors
•Harmonized composite scores (PHC_EF, PHC_MEM, PHC_LAN, PHC_VSP)	•Amyloid ß,Tau, pTau •Z-scores •A/T classification •Raw data •Platform Information	•Mapped AD Phenotypes (NIA-AA ABC score, Thal phasing, Braak staging, CERAD score) •Cerebral amyloid angiopathy, lewy bodies, vascular brain injury, TDP-43 proteinopathy and hippocampal sclerosis	•Vascular Composite (Hypertension, diabetes, heart disease [myocardial infarct, congestive heart failure, etc.], BMI, height, weight, stroke, smoking, medication, blood pressure, CVR score)

Imaging – DTI	Imaging – FLAIR	Imaging – MRI	Imaging – PET
•PreQual Processed Data (Image-Based BIDS) •Free Water Corrected Metrics •Scanner Harmonization •Multi-Site Calibration •FA and MD Scalars	•Total WMH Volume	•Preprocessed Imaging Collection •MUSE Regions of Interest •FreeSurfer Regions of Interest •SPARE-AD Scores •AD Signature (Schwartz)	•Preprocessed Imaging Collection •Global SUVRs •Centilloid Values •GMM Probabilities •Amyloid Status

adsp PHC PHENOTYPE HARMONIZATION CONSORTIUM

Courtesy Tim Hohman / Vanderbilt: timothy.j.hohman@vumc.org

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ADSP R5 WGS Release

Coming in Q1 2024

ADSP Release	Primary Ancestry/Ethnicity	Cases	Controls	Other	Totals
GCAD Release 5	Black/African American	2,926	6,754	777	10,457
	Asian	1,273	4,083	5	5,422
	Latino/Hispanic	4,065	9,407	2,832	19,320
	Non-Hispanic White	9,124	14,459	6,067	31,663
	Total	**17,108**	**33,557**	**9,662**	**60,327**

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

ADRC samples in next batch release

- **4,590 exomes** (**22%** of total ADSP WES)
- **12,629 genomes** (**20%** of total ADSP WGS)

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ADRC GWAS Data Release

ADC1–7

- NHW available on NIAGADS currently
- Moving over to DSS

ADC1-15

Being prepared to release on NIAGADS DSS:

- QC'd GWAS, Covariate files, and TOPMed Imputation for all populations
- Standardizing Subject IDs across all file types
- Updating GWAS PLINK files to forward strand, on GRCh38

Anticipate end of 2023 release.

ADC16

~1,600 samples selected for genotyping. Plating at NCRAD.

Totaling GWAS SNP Array Data for 29,676 ADRC Samples Passing QC and available for request.

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Supporting Data Use

User Support

NIAGADS is always looking to improve user experience. Over the next year we are planning to introduce several new resources:

Office Hours

2nd office hour just completed

Video Tutorials

First video tutorials posted
https://www.youtube.com/@niagads1814

NIAGADS Roadshow

Glad to talk at your ADRC and meet colleagues!

Awareness

Expanding NIAGADS reach through increase investigator awareness will be accomplished through informational outreach sessions at AAIC, ASHG, and Neuroscience 2023 in 2023

Exhibit Hall Booth

Poster Presentations

ADSP Session at AAIC

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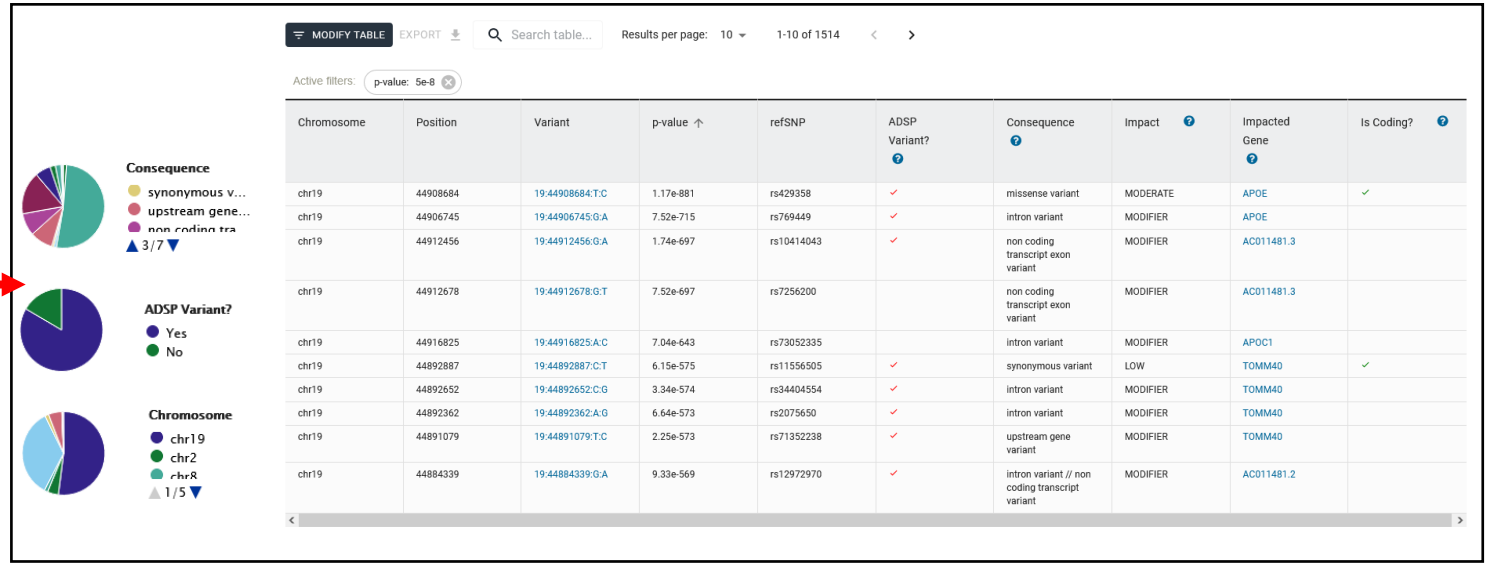
NIAGADS Knowledgebases – Web and API

- FILER[1]: https://tf.lisanwanglab.org/FILER/
  - 75,207 standardized functional genomics tracks
- ADVP[2]: https://advp.niagads.org
  - curated AD-GWAS catalog, documenting >18k published associations
- GenomicsDB[3]: https://www.niagads.org/genomics
  - GWAS summary statistics
  - >260M annotated ADSP Variants (17K R3)
  - detailed gene and variant reports
  - mine datasets and annotations in real-time
  - compare GWAS summary stats to FILER functional genomics tracks and ADSP variant annotations using the NIAGADS IGV Genome Browser

Explore these on the web

or leverage the new (alpha) NIAGADS API at https://api.niagads.org

to programmatically access these knowledgebases and incorporate annotations and data tracks in analysis pipelines.



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, in press. *Alzheimer's & Dementia*

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The NIAGADS Genome Browser

https://www.niagads.org/genomics/app/visualizations/browser

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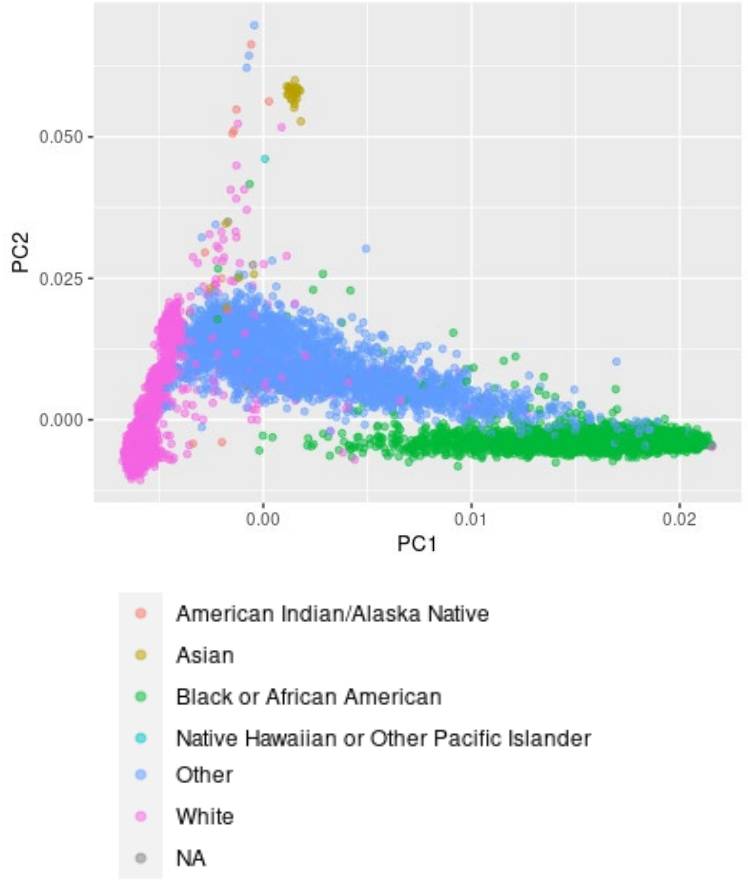
SNV and INDEL Analysis of ADSP Data

- Common variants and aggregates of rare coding/noncoding variants in 13,371 individuals with WGS data
  - 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 doi.org/10.1101/2023.09.01.23294953, https://www.medrxiv.org/content/10.1101/2023.09.01.23294953v1

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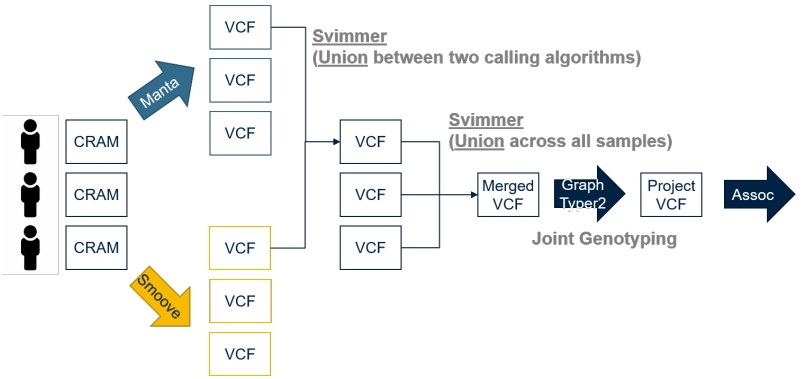
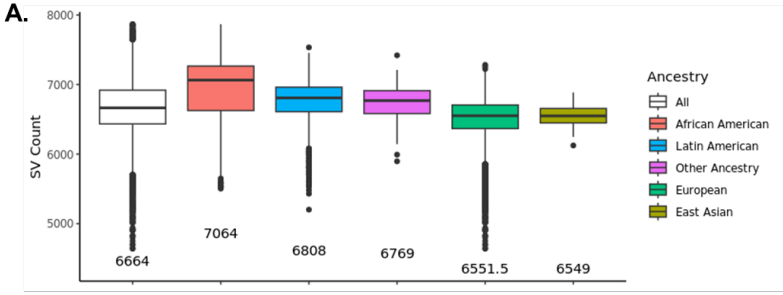
Structural Variant Analysis of ADSP Data

- Novel pipeline for calling SVs in WGS data
- Ultra-rare protein-altering SVs within AD-related genes, ABCA7, APP, PLCG2, and SORL1
- APP duplications in three early-onset AD cases
- Linkages between SVs and known AD risk-associated SNPs
- Reported 16 SVs linked to AD and 13 SVs associated with AD-related pathological endophenotypes
- Uncovering an over-representation of SVs within pathways related to neuronal function





H Wang et al., Structural Variation Detection and Association Analysis of Whole-Genome-Sequence Data from 16,905 Alzheimer's Diseases Sequencing Project Subjects
https://doi.org/10.1101/2023.09.13.23295505
https://www.medrxiv.org/content/10.1101/2023.09.01.23294953v1