NIAGADS Fall 2022 Update

Alzheimer’s Disease Sequencing Project and Improving Cohort Diversity in Alzheimer’s Disease Genetics Research

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No financial conflict of interest
NIA Genetics of Alzheimer’s Disease Data Storage Site

*NIA-designated repository for ADRD human genetic/genomic data*

- **89** Datasets
- **144,242** Samples
- **18** Genomic Data Types
## Alzheimer’s Disease Sequencing Project: From Genetic Signals to Targeted Therapeutics

### Target Discovery
- Loci and genes associated with disease risk

### AD Biology
- Causal genes for pathogenesis
- Underlying molecular mechanisms and pathways

### Therapeutic Development
- Therapeutic strategy
- Genetics-driven clinical trials

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### Follow-Up Sequencing 2.0
- Diversity cohorts
  - Genome sequencing
  - Variant discovery

### Phenotype Harmonization

### Biomarker Discovery

### Infrastructure
- Sequencing / Sample Management / Computing Infrastructure / Data Sharing

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### Functional Genomics

### AI/Machine Learning

### Biomarker Discovery
ADSP R4 Data Release (ng00067.v9)

• 19,456 new genomes
  • Sequencing read alignments (CRAM)
  • Genomic Variant Call files (gVCF)
  • Basic Phenotypes

• Cumulative joint-genotype call for all 36,361 ADSP genomes

• 393,874,470 variants with GATK PASS quality
Deep Phenotypic Data from ADSP Phenotype Harmonization Consortium (ADSP-PHC)

First batch of harmonized phenotypes

README, data dictionaries, and harmonized data files are available for the following domains:

- Cognitive
- fluid biomarker
- neuropathology

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Cognition</th>
<th>Biomarker</th>
<th>Neuropath</th>
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<td><strong>14661</strong></td>
<td><strong>2036</strong></td>
<td><strong>5992</strong></td>
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ADSP Gene Verification Committee
Top Gene and Loci List

To clarify which loci and genes are valid versus potential false positives, the GVC is reviewing published human genetic studies of AD and dementia to determine the quality of evidence supporting a genetic signal (locus) or a specific gene.

Ryan Corces, Gladstone Institutes
Anita DeStefano, Boston University
Lindsay Farrer, Boston University
Alison Goate, Icahn School of Medicine at Mount Sinai
Brian Kunkle, University of Miami
Fanny Leung, University of Pennsylvania
Edoardo Marcara, Icahn School of Medicine at Mount Sinai
Richard Mayeux, Columbia University
Gerard Schellenberg (chair), University of Pennsylvania
Badri Vardarajan, Columbia University

https://adsp.niagads.org/index.php/gvc-top-hits-list/
Updated ADSP Website (Winter 2022)

List of ADSP investigators and grants
Quick Data Guide
Data Request Procedure
Publications
Gene Verification Committee Top Gene List
ADSP Cohorts and Global Map
WGS Sequencing Progress
Bottleneck: Alzheimer’s Research Needs More Diversity

Genetic risks vary across populations ... yet we know little about diverse ancestry groups

**APOE e4 variant increases risk of AD by...**

- **3.4-fold** in Europeans
- **2.3-fold** in Africans
- **5-fold** in Asians

Source: PubMed (Publication ID: 32015339, 23571587, 31426376)

Source: AD Variant Portal (advp.niagads.org)
ADSP Follow-Up Sequencing (FUS) 2.0: Diversity Initiative (PAR-21-212)

- 18,500 cases and 18,500 controls each from the three populations of African, Hispanic, and Asian ancestry to achieve statistical significance for rare variants
  -> Estimate 130,000~150,000 genomes by 2027-2028

- Supports generation of data, primary from cohorts with African, Hispanic/Latino, Asian Ancestry; includes Amer-Indian populations

Sample acquisition / sequencing and genotyping
Variant calling & QC / data harmonization & sharing
Analysis / Functional Genomics / Machine Learning


## ADSP Foreign Cohorts with Asian Samples

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<tr>
<th>Study</th>
<th>PI</th>
<th>Korea site PI</th>
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<tr>
<td>Gwangju Alzheimer’s &amp; Related Dementias (GARD) Study – Korea</td>
<td>Lindsay Farrer (Boston University)</td>
<td>Kunho Lee (Chosun University)</td>
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<td>KBASE2: Korean Brain Aging Study, Longitudinal Endophenotypes and Systems Biology</td>
<td>Andrew Saykin (Indiana University)</td>
<td>Don Young Lee (Seoul National University)</td>
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<td>Aspirin in Reducing Events in the Elderly (ASPREE) Trial cohort – Australia</td>
<td>Paul Lacaze (Monash University)</td>
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<tr>
<td>Longitudinal Aging Study in India – Diagnostic Assessment of Dementia (LASI-DAD) – India</td>
<td>Jinkook Li (University of Southern California)</td>
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</table>
Challenges in Recruiting AAPIs for AD Genetics Research

We need resources to invest in the infrastructure and networks to meaningfully include AAPIs in ADRD genetics and other clinical and caregiving research.
Asian Cohort for Alzheimer’s Disease

- Supported by a two-year R56 to recruit 1,000 Chinese in US and Canada
- Eventual Goal: 5,000 participants in 5 years: Chinese / Korean / Vietnamese Ancestry in US and Canada
- Culturally appropriate recruitment and assessment
- DNA for genetics and plasma for blood-based biomarkers
# ACAD Protocol

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<thead>
<tr>
<th>Categories</th>
<th>Initial</th>
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<tr>
<td>CDR</td>
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<td>✓</td>
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<td>Early Life Enrichment</td>
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<tr>
<td>Medical conditions / Medications</td>
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<td>GDS</td>
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<tr>
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</tr>
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<td>Additional Cognitive Tests</td>
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<tr>
<td>Family History of Dementia</td>
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<td>Clinician’s Judgement of Symptoms</td>
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<td>Imaging Data</td>
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<td>Neurological Diagnosis</td>
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<td>Factors Affect Testing</td>
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<tr>
<td>Consensus Worksheet</td>
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![Diagram](image)

*Diagram illustrates the flow of data collection and processing for the ACAD Protocol.*
Summary

• Diverse cohorts increase statistical power for gene discovery
• Leverage existing cohorts/infrastructure to increase sample size quickly
• Long term investment for minority populations underrepresented in medical research
• Culturally sensitive assessment protocols and recruitment strategies; build trust with communities
We thank the contributions by researchers from these projects (partial list):

- Alzheimer’s Disease Sequencing Project (ADSP)
- Alzheimer’s Disease Genetic Consortium (ADGC)
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We are grateful to participants, families/caregivers and staff of the offices, University of Pennsylvania.

Funding support from National Institute on Aging and National Institutes of Health.

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- Alzheimer’s Disease Sequencing Project (ADSP)
- NGHRIs for Common Disease Genomics (CCDG)
- NIAD Genetics of Alzheimer’s Disease Data Storage Site (NIAGDS)
- Genome Center for Alzheimer’s Disease (GCAD)
- Asian Cohort for Alzheimer’s Disease (ACAD)

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