

# Overview: Alzheimer's Disease Genetics Projects

**No conflicts**



**Perelman School of Medicine  
University of Pennsylvania**

## Overview

- ADGC Alzheimer's Disease Genetics Consortium  
Schellenberg/Farrer/Haines/Mayeux/Pericak-Vance/Wang
- ADSP Alzheimer's Disease Sequencing Project  
Many investigators
- GCAD Genomic Center for Alzheimer's Disease  
Schellenberg/Wang/Farrer/Haines/Mayeux/Pericak-Vance
- NIAGADS NIA Genetics of Alzheimer's Disease Storage site  
Wang

## Partners

- ADCs Alzheimer's Disease Centers  
Many investigators
- NACC National Alzheimer Coordinating Center  
Bud Kukull
- NCRAD National Cell Repository for Alzheimer disease  
Tatiana Foroud

# Alzheimer's Disease Genetics Consortium

- **Expand sample size**
- **Exome chip project (in press)**
- Rare-variant Analysis (1,000 genome imputation)
- HRC imputation analysis (rare variants MAF < 0.01% - 0.001%)
- PrediScan analysis

# Alzheimer's Disease Genetics Consortium

Cohort	Cases	Controls
ADC1	1,549	512
ADC2	727	156
ADC3	894	586
ADC4	304	377
ADC5	286	505
ADC6	213	338
ADC7	566	878
ADC8	517	664
ADC9	728	908
ACT	532	1,571
ADNI	268	173
BIOCARD	6	112
CHAP	27	144
EAS	9	141
GSK	666	712
NIA-LOAD	1,788	1,559
MAYO	658	1,046
MIRAGE	491	738
MTV	256	189
NBB	80	48
OHSU	132	153
PFIZER	696	762
RMAYO	13	233
ROSMAP	354	986
TARCC	323	181
TGEN	668	365

ADCs  
5,784 cases  
4,924 controls  
10,708 total

Cohort	Cases	Controls
UKS	596	170
UMVUMSSM	1,177	1,126
UPITT	1,255	829
WASHU	339	187
WASHU2	38	94
WHICAP	73	560
<b>Totals</b>	<b>15,707</b>	<b>15,441</b>

**Grand total 31,608**

## New

Cohort	Cases	Controls	Total
MESA			8,224
WHICAP2			1,011
NIA-LOAD2	345	1,062	1,407 (672 families)
<b>Totals</b>			<b>10,642</b>

## IGAP


Consortium	Cases	Controls
ADGC	14,428	14,562
CHARGE	2,137	13,474
EADI	2,240	6,631
GERAD	3,177	7,277
<b>Totals</b>	<b>21,972</b>	<b>41,935</b>

# Cohorts

ACT	Crane/Larson
ADC	many
ADNI	Weiner
BIOCARD	Albers
CHAP	Bennet/Evans
EAS	Lipton
<b>EFIGA</b>	<b>Mayeux</b>
GSK	St George-Hyslop
MAYO	Peterson
MESA	Rich
<b>MIRAGE</b>	<b>Farrer/Green</b>
NBB	Riemenschneider
<b>NIA-LOAD</b>	<b>Foroud/Mayeux</b>
OHSU	Kramer
PFIZER	Whelan
RMAYO	Younkin
ROSMAP	Bennet

TARCC	Barber
TGEN	Reiman
UKS	Riemenschneider
UPITT	Kamboh
WASHU	Cruchaga/Goate
<b>WHICAP</b>	<b>Mayeux</b>
<b>UMVUMSSM</b>	<b>Pericak-Vance/Haines /Buxbaum</b>

## African American WES: by study

Study	Affected	Unaffected	Total
MIRAGE	105	125	230
Miami/Duke	180	309	489
North Carolina A&T	186	256	442
Case Western	44	60	104
 <b>Alzheimer's Disease Centers</b>	<b>572</b>	<b>740</b>	<b>1,312</b>
GenerAAtions	211	187	471
Rush	78	84	162
Total	1,376	1,761	3,210

**WES in progress – complete summer 2017**

# Exome Chip

- Stage 1: exome chip genotyping
- Stage 2: *de novo* genotyping,  $P < 10^{-4}$ ,  $n = 43$  SNVs
- Stage 3: ADGC HRC imputation – top 4 variants

## ILLUMINA ExomeBeadChip:

- ~247,870 assays
- 75% MAF  $< 0.5\%$
- protein-altering variants (non-synonymous coding, splice site, stop gain/stop loss)

# Exome Chip

- Stage 1: exome chip genotyping  
Stage 2: *de novo* genotyping,  $P < 10^{-4}$ ,  $n = 43$  SNVs  
Stage 3: ADGC HRC imputation – top 4 variants

	controls (n)	cases (n)	total (n)
Stage 1:	18,077	16,097	34,174
Stage 2:	21,921	14,041	35,692
Stage 3:	8,345	6,652	14,997
<b>Totals</b>	<b>48,402</b>	<b>37,022</b>	<b>85,133</b>



# Alzheimer's Disease Sequence Project

**ADSP**

## Case-control - whole exome sequencing:

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5,000 unrelated cases:

4,220 from the ADGC

**2,430 from ADC's**

5,000 elderly normal controls:

3,240 from the ADGC

**840 from the ADC's**

1,000 cases from multiplex families – one/family

Multiplex families - whole-genome sequencing:

585 subjects

111 multiplex families

Analysis  
in  
progress

In progress: sequencing completed  
data processing started

**415 subjects**

**old and new families**

## Case-control extension - WGS

Caucasians:	500 cases/500 normal controls
African Americans:	500 cases/500 normal controls
Caribbean Hispanics:	500 cases/500 normal controls

- Processing/QC – summer 2017

## Follow up sequencing - WGS

- ~10,000 cases – composition to be determined
- Controls – ethnically matched, cognitively normal

Controls are elderly cognitively normal subjects

# Collaborative Network Sequencing

Investigator/Study	Total samples	Total families	Cases	Controls	Notes
<b>Whole exome sequencing</b>					
Brkanac	77	0			Non-Hispanic white
Cruchaga	40	14	29	11	Non-Hispanic white
Mayeux/WHICAP	4059	0	1844	2215	Non-Hispanic Whites and Caribbean Hispanics
Kamboh	800	0	418	380	Non-Hispanic Whites
Kauwe/Cache County	30	0	30	0	Non-Hispanic Whites
ADGC	3200	0	1600	1600	African Americans
<b>Totals - WES</b>	<b>8206</b>		<b>3921</b>	<b>4206</b>	
<b>Whole genome sequencing</b>					
ADNI	818	0	128	267	Non-Hispanic white
Mayeux/WHICAP	143	0	143	0	African Americans
Mayeux/EFIGA	705	148			Caribbean Hispanics
Miami	150				African Americans
Mayeux/Foroud/NIA-LOAD	1193				
Kamboh/Pittsburgh (NYGC)	211	0	211	0	Non-Hispanic white
Kauwe/Cache County WGS	214	0	0	214	Non-Hispanic white
ADGC/ADC/Genentech	62	0	62	0	Non-Hispanic white
<b>Totals - WGS</b>	<b>3496</b>	<b>148</b>	<b>544</b>	<b>481</b>	

# ADSP + Collaborative Network Sequencing

Phase	WGS	WES
Family discovery + extension	1,008	
Case/control discovery		10,909
Case/control extension	3,000	
FUS	10,000	
FUS control (TOPMed) ?	10,000	
Collaborative Network	3,496	8,206
<b>Total sample/size</b>	<b>27,504</b>	<b>19,115</b>

# Genomic Center for Alzheimer's Disease

**GCAD**

## 1. Process all AD-relevant Sequence data

- ~30,000 WGS
- ~20,000 WES
- TOPMed controls – 20,000 WGS?
- CCDG controls – 20,000 WGS?
- HG38
- Call using common pipeline/protocols
- gVCF files (GATK, ATLAS)

## 2. Coordinate analysis

Goal: All variant positions  
called in all data sets

# NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS)

Data Coordinating Center  
for ADSP

One-step data access  
portal and community  
resource for AD genetics  
research

Other datasets:

41 Datasets (GWAS+others)

55.8K samples

24.6B genotypes

[www.niagads.org](http://www.niagads.org)

NIAGADS

DATA RESOURCES NEWS GENOMICS DB ABOUT CONTACT LOGIN/REGISTER

## The National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site

NIAGADS is the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site. NIAGADS is a national genetics repository created by NIA to facilitate access by qualified investigators to genotypic data for the study of genetics of late-onset Alzheimer's disease.

**BROWSE DATASETS**

DISEASE

DATA TYPE

SEARCH

**AVAILABLE DATA**

41 DATASETS

55,802 SAMPLES

24,582,306,146 GENOTYPES

*Kuzma et al., Alz Dem  
12(11): 1200-3, 2016*



# NIAGADS Genomics Database

Variants, gene annotations, AD-relevant functional genomics datasets allow AD researchers to easily identify and interpret genomic regions

**Table of Contents**

- Genomic Context
- Functional Genomics
- Co-located SNPs
- Functional Annotation

**Related Resources**

- NCBI: 348
- HUGO: HGNC:613
- ENSEMBL: ENSG00000130203
- VEGA: OTTHUMG00000128901
- OMIM: 107741

**Explore Further**

- PubMed
- StringDB
- ExAC Browser
- UCSC Genome Browser

**Expression**

- GTEx Portal
- Human Protein Atlas
- EMBL-EBI Expression Atlas

**APOE**  
apolipoprotein E  
Also known as: AD2, LDLCO5, LPG, APO-E

**Genomic Context**  
chr19, (45409039..45412650)

**Variant Effect Impact (snpEff)**

**Functional Genomics within Gene Promoter Region**

ChIP-Seq TFBS from ENCODE

To view functional genomics annotations on the provided button to load the tracks on the browser

Download (CSV) Copy to Clipboard View on Genome Browser

Hits	Track	Platform
1	CTCF TFBS ChIP-seq on human BE2-C	ChIP-seq
1	CTCF TFBS ChIP-seq on human Gliobla	ChIP-seq

**My Strategies:** New Opened (1) All (1) Basket Public Strategies (11)

**Strategy:** SNPs with genome-wide significance for established CSF biomarkers and Alzheimer's disease (IGAP)\*

CSF biomarkers 23 SNPs

IGAP 1089 SNPs

16 SNPs

**Expanded View of Step CSF biomarkers**

CSF ptau 12 SNPs

CSF tau 8 SNPs

CSF AB42 18 SNPs

23 SNPs

23 SNPs

**16 SNPs from Step 2**

**Strategy:** SNPs with genome-wide significance for established CSF biomarkers and Alzheimer's disease (IGAP)

**About the Result Table**

Filter results by putative impact of SnpEff-inferred effects

All SNPs Low (5) Moderate (0) High (0)

16 5

**SNP Results** Genome View

Advanced Paging

SNP	Reference Allele	Minor Allele/MAF	Strongest Effect Impact
rs11556505	C	T:0.114	LOW
rs12972156	C	G:0.08806	LOW
rs12972970	G	A:0.08806	LOW
rs1305082	G	C:0.3425	MODIFIER

NIAGADS Genome Browser File View Help

dbSNP 137 SnpEff Effect High Moderate Low Other

5,000,000 10,000,000 15,000,000 20,000,000 25,000,000 30,000,000 35,000,000 40,000,000 45,000,000 50,000,000 55,000,000

Select Tracks

chr19 chr19:45388781..45410160 (21.38 kb)

dbSNP 137

NCBI Gene database

NM\_001128916.1

NM\_001128917.1

NM\_000114.2

TOMM40

AD GWAS IGAP stage1

AD GWAS AA unadjusted for APOE

FANTOMS Enhancer expressed astrocyte

ENCODE Chromatin NH-A H3K27ac

ENCODE DNase NH-A

## **Collaborative Network PIs**

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Lindsay Farrer  
Jonathan Haines  
Richard Mayeux  
Peggy Pericak-Vance  
Li-San Wang  
Tatiana Foroud  
Walter “Bud” Kukull

## **University of Pennsylvania**

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Sherry Beecher  
Fanny Leong

## **Washington University**

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Alison Goate

## **Columbia**

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Badri Vardarajan  
Jennifer Manly

## **NIA**

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Marilyn Miller

NIA/NIH, Alzheimer’s  
Association

## **NACC**

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Duane Beekly

## **NCRAD**

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## **University of Miami**

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Kara Hamilton  
Brian Kunkle

## **Boston University**

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Kathryn Lunett  
Jaeyoon Chung

## **Case Western**

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Will Bush



# Alzheimer's Disease Genetics Consortium

## University of Pennsylvania

Laura Cantwell  
Beth Dombroski  
Sherry Beecher

## Familial AD

Deborah Blacker

## Clinical Group

Debbie Tsuang

## Neuropathology Group

Tom Montine

## Biomarker Group

Alison Goate  
Andy Saykin

## Prospective Cohort Group

David Bennett

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Denis Evans  
Eric Larson  
Paul Crane  
John Hardy  
Ilyas Kamboh  
Nilifur Taner  
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Steve Younkin  
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Elaine Peskind  
Neil Graff-Radford  
Matthew Frosch  
John Trojanowski  
**Christian Reitz**  
**Gyungah Jun**



**EADI** **Jean Charles Lambert**  
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Denise Harold  
Peter Holmes

**ADGC**

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NIA/NIH, Alzheimer's Association



The End