ADGC and NIAGADS Update

October 2014 ADC Director's Meeting

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ADGC
Alzheimer's Disease Genetics Consortium

NIAGADS

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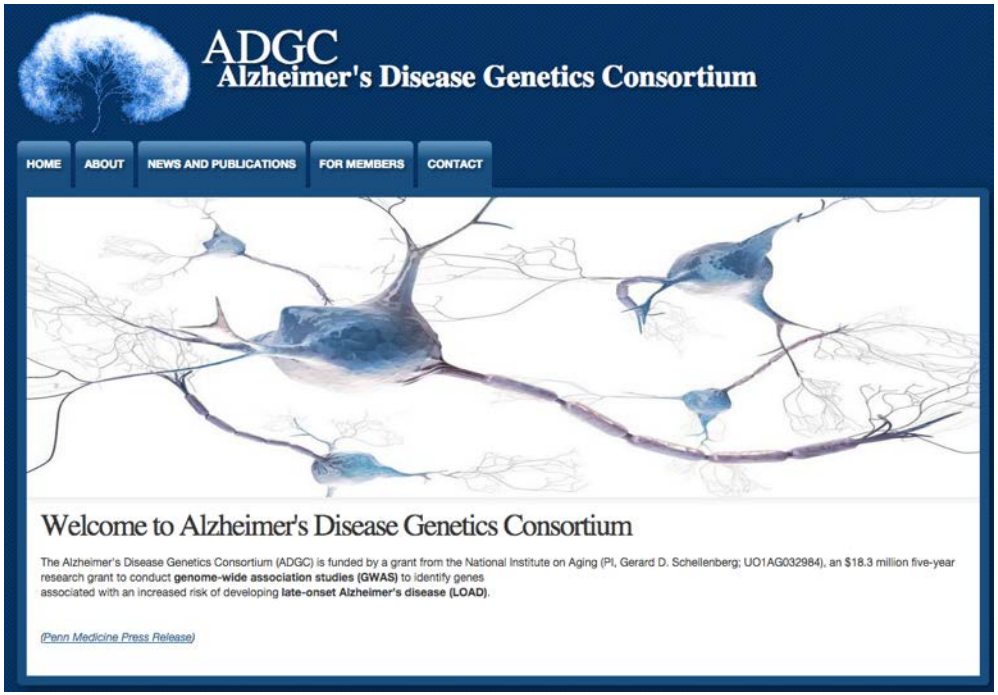
ADGC



The Alzheimer's Disease Genetics Consortium (ADGC) is funded NIA (PI: Gerard Schellenberg) to conduct genome-wide association studies (GWAS) to identify genes associated with an increased risk of developing late-onset Alzheimer's disease (LOAD).

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ADGC / ADC Sample Update

- GWAS Phase I: **4,464** ADC subjects
  - Data available via **NACC** (relabeled to patient IDs) and **NIAGADS** (using NACC IDs)
- GWAS Phase II: As of October 3, 2014, total **11,376** ADC subjects genotyped by ADGC GWAS

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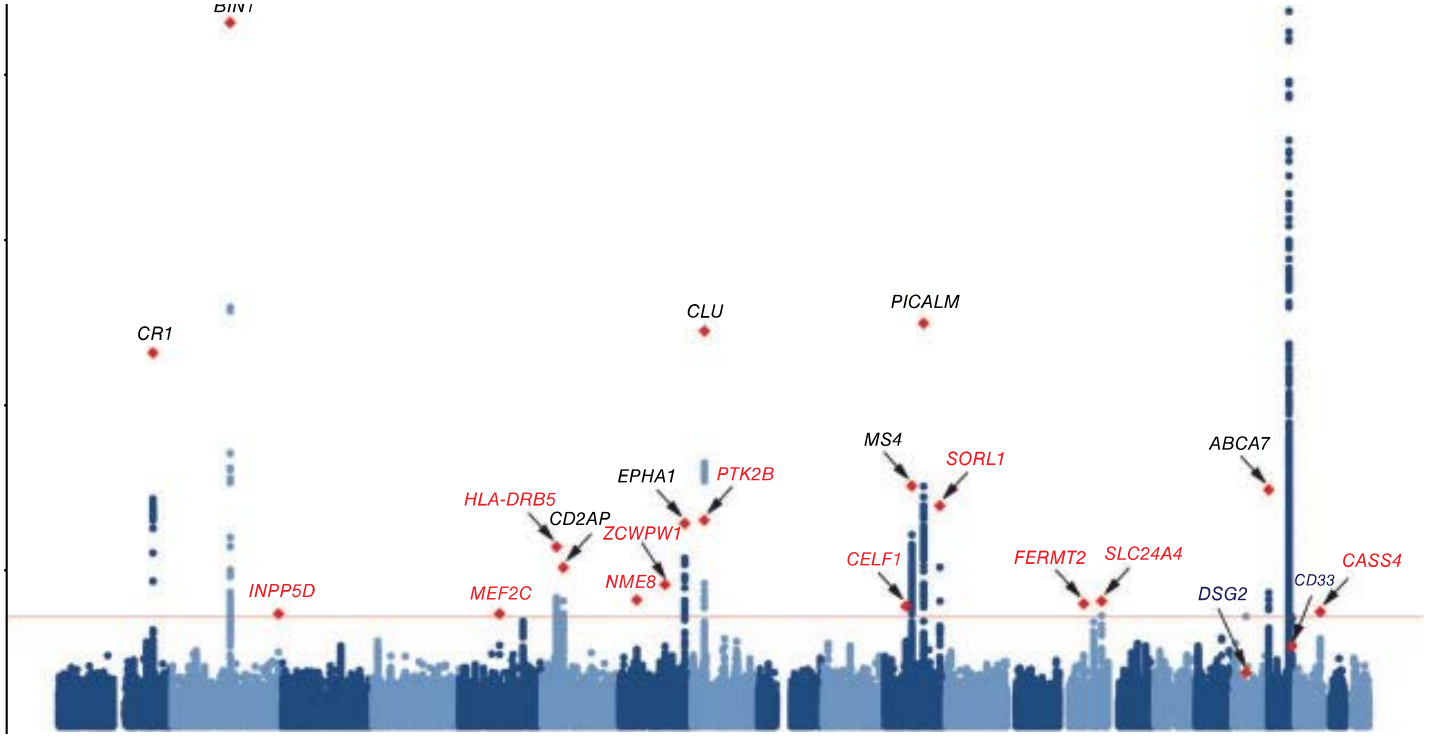
Lambert et al 2013 IGAP GWAS



Lambert 2013

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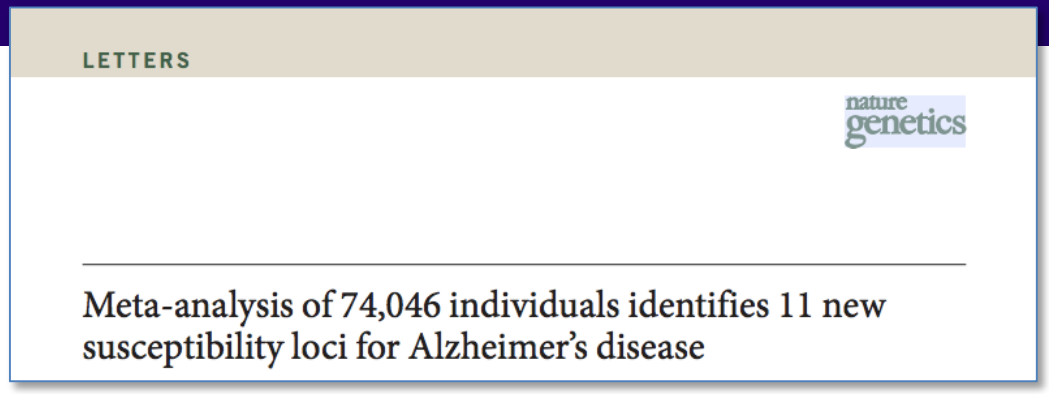
IGAP


LETTERS

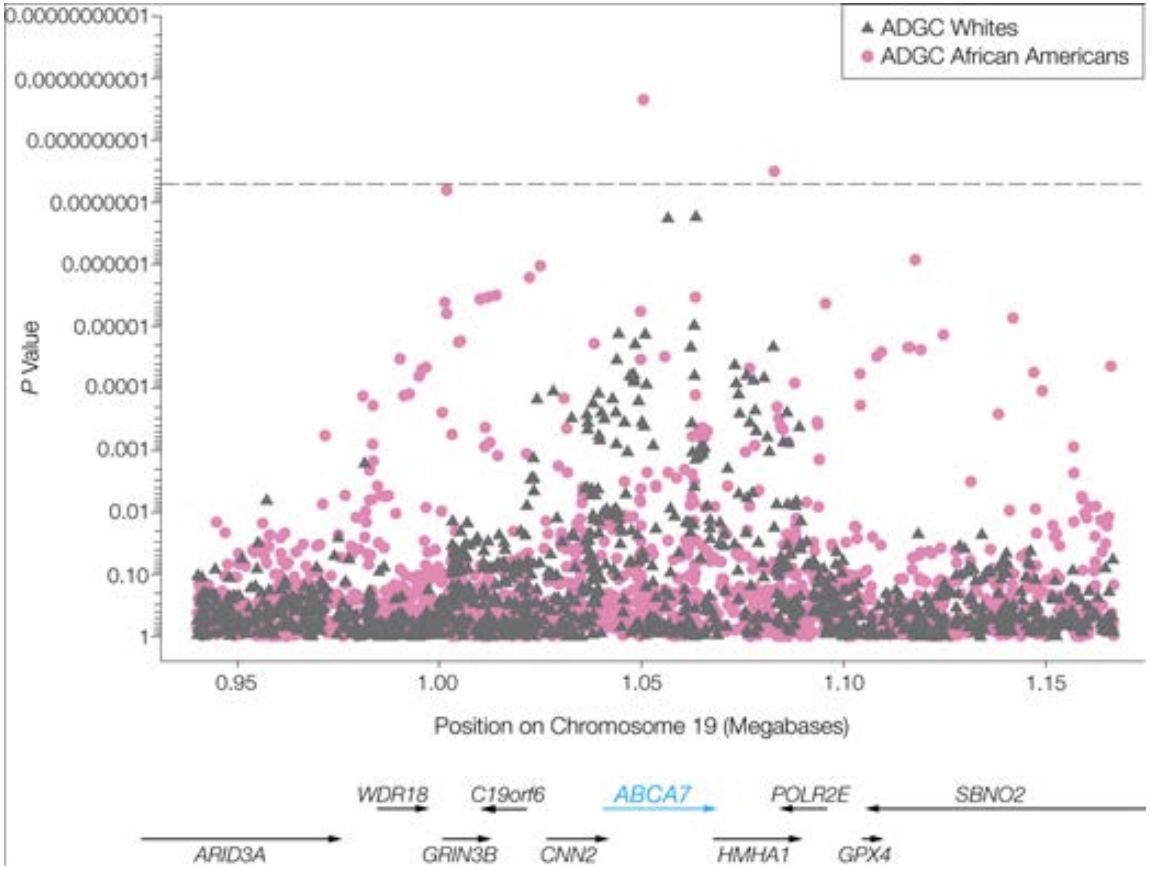
nature genetics

Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease

- IGAP (Lambert et al. Nature Genetics 2013)
- Genome-wide summary statistics with non-identifiable information: P-value / HapMap Allele frequency / OR
- **go.nature.com/tumaG2** has the following URL to data access

  http://www.pasteur-lille.fr/en/recherche/u744/Igap_stage1.zip
- NIAGADS is working to cross-list the dataset

Reitz 2013 GWAS on African American population



Effect size for rs429358 (in ABCA7) comparable with APOE ϵ4–SNP

OR: 2.31 [95% CI, 2.19-2.42]
$P = 5.5 \times 10^{-47}$

Reitz 2013

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36 publications since 2009

16 published or in press in 2014; 10 submitted and under review

Benitez et al. *Missense variant in TREML2 protects against Alzheimer's Disease*. Neurobiol Aging. 2014 Jun;35(6):1510.e19-26. ◆ **Ruitz et al.** *International Genomics of Alzheimer's Disease Project identifies TRIP4 as a novel susceptibility gene*. Transl Psychiatry 2014 Feb 4;4:e358. ◆ **Escott-Price et al.** *Gene-wide analysis detects two new susceptibility genes for Alzheimer's disease*. PLOS One 2014 Jun 12;9(6):e94661. ◆ **Naj et al.** *Effects of Multiple Genetic Loci on Age at Onset in Late-Onset Alzheimer Disease: A Genome-Wide Association Study*. JAMA Neurol. 2014 Sep 8. ◆ **Nelson et al.** *ABCC9 gene polymorphism is associated with hippocampal sclerosis of aging pathology*. Acta Neuropathologica 2014 Jun;127(6):825-43. ◆ **Allen et al.** *Association of MAPT haplotypes with Alzheimer's disease risk and MAPT brain gene expression levels*. Alzheimer's Research and Therapy (in press) ◆ **Jones et al.** *Convergent genetic and expression data implicate immunity in Alzheimer's disease*. Alzheimers and Dementia (in press) ◆ **Wang al.** *APP Mutation A673T; A protective variant for Alzheimer's disease in the United States?* JAMA Neurology (in press) ◆ **Beecham et al.** *Genome-wide association meta-analysis of neuropathologic features of Alzheimer's disease and related dementias*. PLOS Genetics. 2014 Sept 4;10(9) ◆ **Jun et al.** *PLXNA4 is Associated With Alzheimer Disease Risk and Modulates Tau Protein Phosphorylation*. Ann Neurol. 2014 Sep;76(3):379-92. ◆ **Logue et al.** *Two Rare AKAP9 Missense Variants are Associated with Alzheimer Disease in African Americans*. Alzheimers Dement. 2014 Aug 26. ◆ **Ramirez et al.** *SUCLG2 identified as both a determinator of CSF Aβ1-42-levels and an attenuator of cognitive decline in Alzheimer's disease*. Hum Mol Genet. 2014 Jul 15 ◆ **Barral et al.** *Genetic variants in a 'cAMP element binding protein' (CREB)-dependent histone acetylation pathway influence memory performance in cognitively healthy elderly individuals*. Neurobiol Aging. 2014 Jun 28. ◆ **Barral et al.** *Common genetic variants on 6q24 associated with exceptional episodic memory performance in the elderly.* JAMA Neurology (In press). ◆ **Wetzel-Smith et al.** *A rare mutation in UNC5C predisposes to Alzheimer's disease and increases neuronal cell death*. Nature Medicine (In press). ◆ **Schreiber et al.** *Alzheimer's Disease Genetics*. Current Behavioral Neuroscience Reports (In press).

New findings

- Follow-up of IGAP study
  - **TRIP4** (rs74615166)
  - **TP53INP1** and **IGHV1-67** via gene-wise analysis
- **TREML2** (rs3747742) is a protective variant
- **ABCC9** (rs704178) associated with hippocampal sclerosis
- **PLXNA4**: NIA-LOAD and Framingham family studies
- **SUCLG2** associated with $A\beta_{1\text{-}42}$ and cognitive decline in AD
- Rare variants in **AKAP9** associated with AD in African Americans
- GWAS using neuropath-confirmed subjects with stronger effect sizes
- **CR1**, **BIN1**, and **PICALM** associated with age at onset

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Association with age at onset [Naj 2014]

					Age at Onset						LOAD Risk	
					Minimal Adjustment Model			Extended Adjustment Model				
SNP	CH:MB	Nearest Gene	Minor Allele	MAF	β (95% CI)	*P* Value	*P* Value for Het	β (95% CI)	*P* Value	*P* Value for Het	OR (95% CI)	*P* Value
rs6701713	1:207.8	*CR1*	*A*	0.24	−0.41 (−0.65 to −0.17)	7.2×10^{-4}	.405	−0.41 (−0.69 to −0.12)	4.9×10^{-3}	.422	1.16 (1.11 to 1.22)	4.6×10^{-10}
rs7561528	2:127.9	*BIN1*	*A*	0.37	−0.31 (−0.52 to −0.09)	4.8×10^{-4}	.855	−0.32 (−0.57 to −0.08)	9.9×10^{-3}	.684	1.17 (1.13 to 1.22)	4.2×10^{-14}
rs9349407	6:47.5	*CD2AP*	*C*	0.32	−0.03 (−0.25 to 0.19)	.765	.266	−0.14 (−0.40 to 0.11)	.273	.860	1.12 (1.07 to 1.18)	1.0×10^{-6}
rs11767557	7:143.1	*EPHA1*	*C*	0.18	0.03 (−0.26 to 0.32)	.830	.861	0.07 (−0.24 to 0.39)	.659	.657	0.87 (0.83 to 0.92)	2.4×10^{-7}
rs1532278	8:27.5	*CLU*	*T*	0.37	0.05 (−0.18 to 0.28)	.661	.137	0.0038 (−0.26 to 0.27)	.977	.108	0.89 (0.85 to 0.93)	8.3×10^{-8}
rs4938933	11:60.0	*MS4A4A*	*C*	0.36	0.09 (−0.14 to 0.31)	.448	.454	0.018 (−0.23 to 0.27)	.887	.584	0.88 (0.85 to 0.92)	1.7×10^{-9}
rs561655	11:85.8	*PICALM*	*G*	0.38	0.33 (−0.12 to 0.55)	2.2×10^{-3}	.915	0.32 (0.07 to 0.57)	.011	.957	0.87 (0.84 to 0.91)	7.0×10^{-11}
rs3752246	19:1.1	*ABCA7*	*G*	0.34	−0.27 (−0.55 to 0.02)	.064	.700	−0.19 (−0.51 to 0.13)	.242	.748	1.15 (1.09 to 1.21)	5.8×10^{-7}
Haplotype rs7412/ rs429358	19:45.4	*APOE*	ε4	0.35	−2.45 (−2.68 to −2.21)	3.3×10^{-96}	.094	−0.24 (−0.75 to 0.27)	.360	.874	3.02 (2.86 to 3.20)	2.2×10^{-320}
rs3865444	19:51.7	*CD33*	*A*	0.20	0.10 (−0.13 to 0.33)	.377	.596	0.13 (−0.13 to 0.38)	.338	.872	0.89 (0.86 to 0.93)	1.1×10^{-7}

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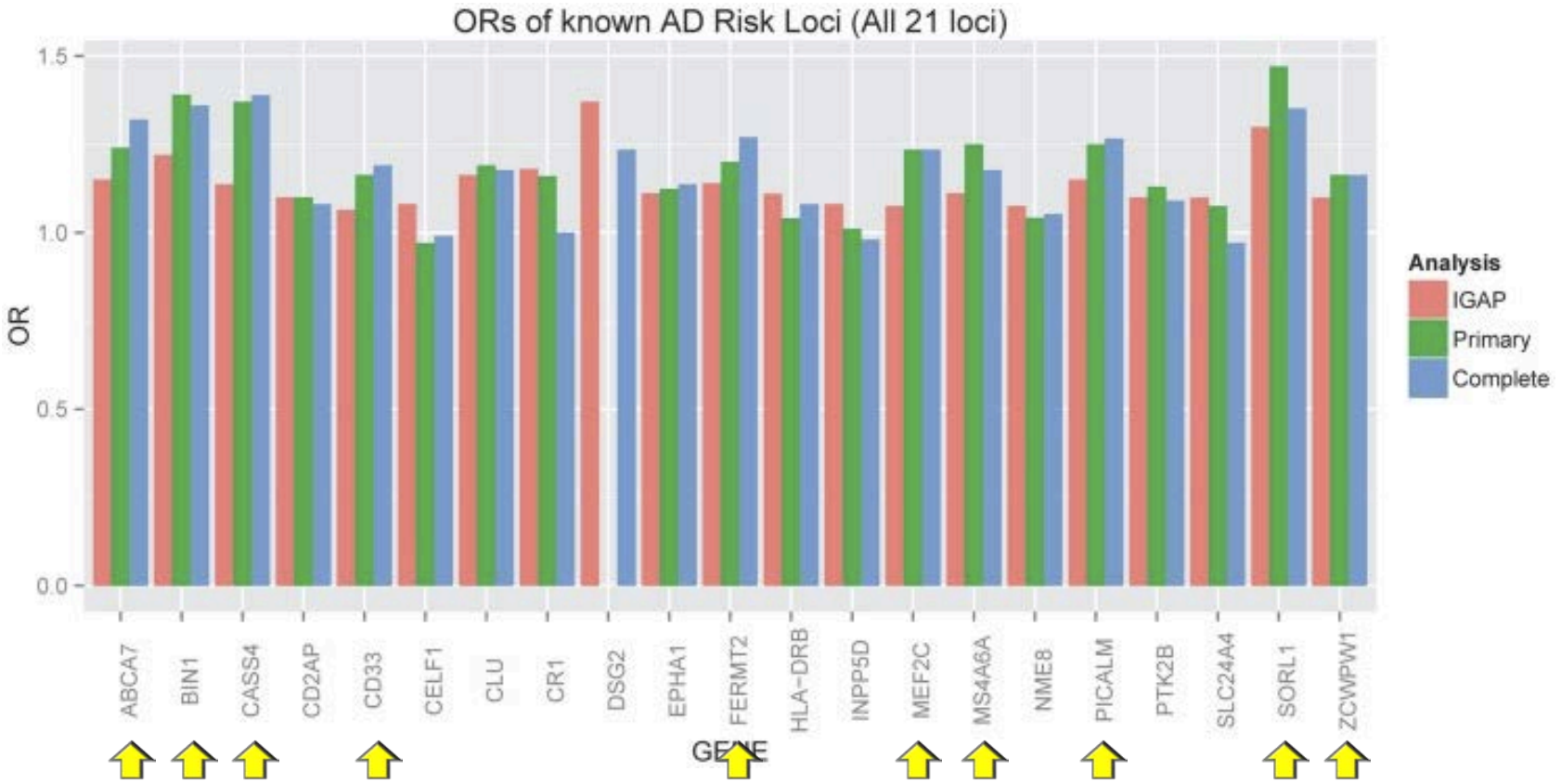
Stronger effect size using neuropath-confirmed subjects [Beecham 2014]



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ADGC GWAS Data available at NIAGADS

- 13 ADGC GWAS datasets from Naj et al. (2011) and Lambert et al (2013) available at NIAGADS
- *GWAS data*
- *Phenotype*
- *Imputation*
- *Naj et al. Nature Genetics 2011 Summary Statistics*

Round	Platform	Cases/Controls	Link
Discovery (Stage 1)			
ACT	Illumina Human660	354/1981	NG00034
ADC1	Illumina Human660	1566/515	NG00022
ADC2	Illumina Human660	738/160	NG00023
ADNI	Illumina Human610	268/173	Access Data
GenADA	Affymetrix 500	669/713	Coming Soon!
Genetic Differences	Illumina Human660	213/0	NG00034
UM	Illumina Human660/1M Duo/Affymetrix 6.0	1186/1135	Coming Soon!
VU			Coming Soon!
MSSM			Contact PI
MIRAGE	Illumina Human610/330	509/753	NG00031
NIA-LOAD	Illumina 610	1852/1991	NG00032
OHSU	Illumina HumanCNV370v1_C	647	NG00017
TGEN2	Affymetrix 1M	864/493	NG00028
Replication (Stage 2)			
ADC3	Illumina OmniExpress	897/588	NG00024
MAYO	Affymetrix 6.0	728/1173	Coming Soon!
ROSMAP	Affymetrix 6.0	296/776	NG00029
UPitt	Illumina HumanOmni1-Quad	1440/1000	NG00026
WashU	Illumina Human610	403/225	NG00030

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ADGC vs NIAGADS: Data Access

	ADGC	NIAGADS
Objective	AD genetics **research**	AD genetics / genomics data **resource**
Data control jurisdiction	Collaborators contribute data. New analysts NEED approval from original data contributors	Data delegated to NIAGADS via *NIA data sharing plan.* New analysts DO NOT NEED approval from original data contributors
Apply for data access	As **ADGC collaborator** with a specific analysis plan. Needs sponsoring ADGC member. No-surprises, no overlap with primary analysis	As an **independent Investigator**. Data access application
Type of data	Access to **pre-publication** data	Only **published** data
Manuscript review	Reviews findings and methodology	Only check for acknowledgement
Authorship & Acknowledg-ement	**ADGC as co-author.** Acknowledge ADGC and study funding	**NIAGADS is not co-author**. Acknowledge study funding and NIAGADS

ADGC ADC data types

- Complete data
  - GWAS
  - Phenotype
  - Imputation
  - Genome-wide association results
- Specific subset
  - Genotypes for top SNPs (in preparation, will be available via NACC)
  - Association results for specific SNPs are available via NIAGADS Genomics DB

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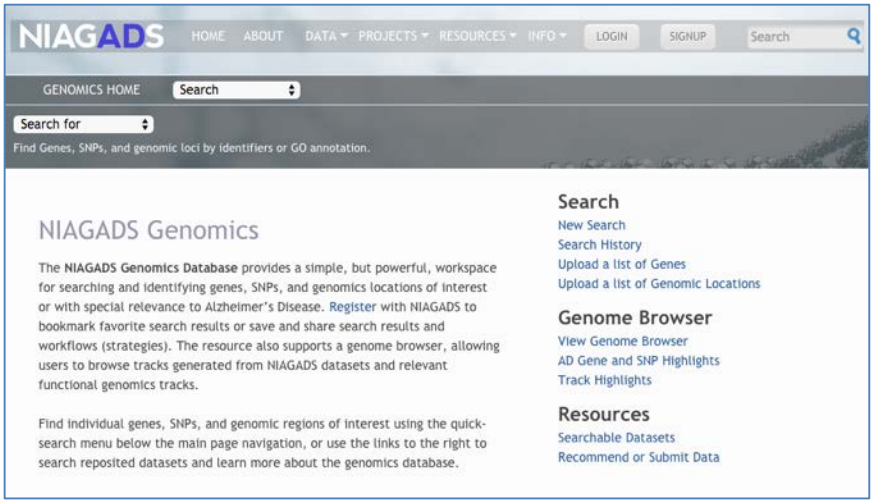
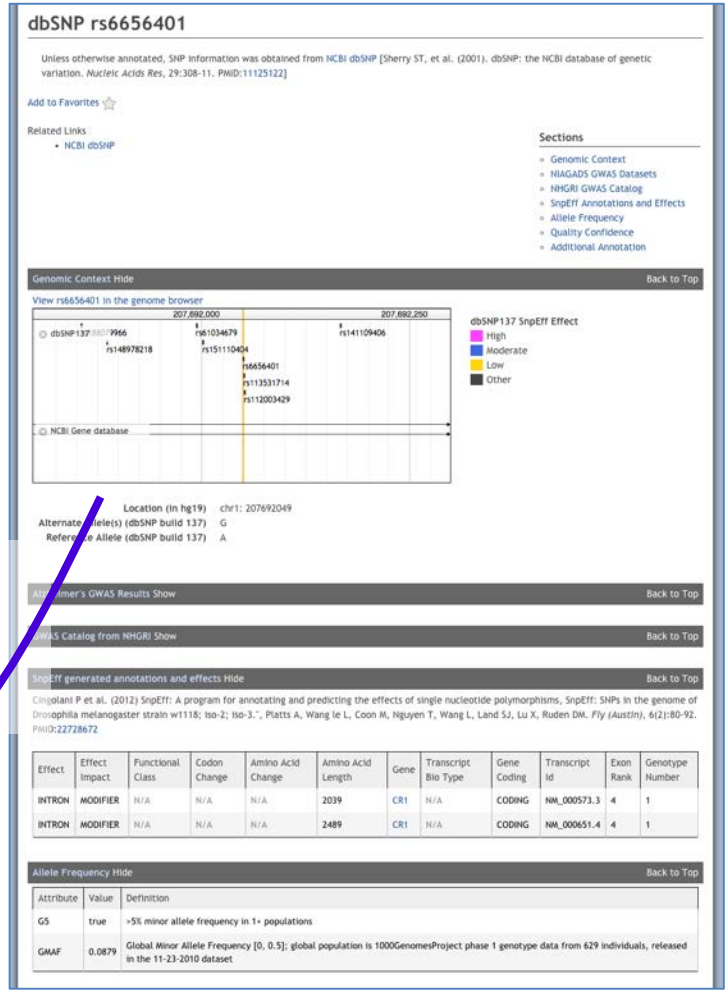
https://www.niagads.org/genomics/



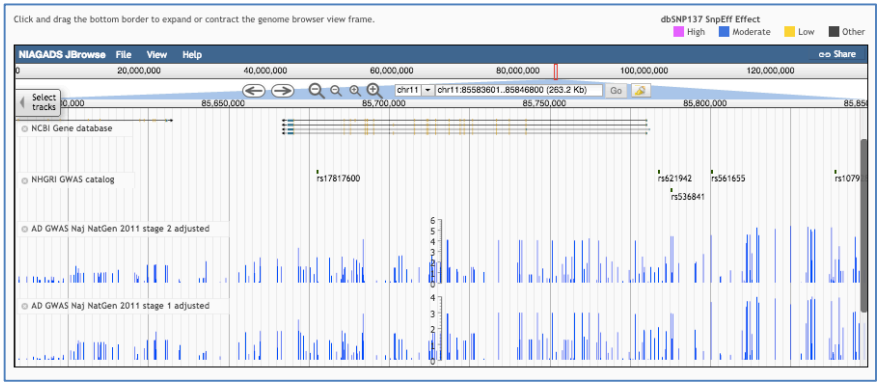
Query by gene or SNPID

Gene / SNP report



View genomic context

Genome Browser



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AD Sequencing Project

- Announced in February 2012 by DHHS and NIH

adsp
Alzheimer's Disease Sequencing Project

- Participants
  - NIA, NHGRI
  - LSSP sequencing centers (Broad/Baylor/WashU)
  - ADGC and CHARGE
  - NIAGADS (data coordinating center)
- Study design available at **www.niagads.org/adsp**

Photo from http://nihrecord.od.nih.gov/newsletters/2012/03_02_2012/story5.htm

ADSP Progress

- 578 whole genomes from 111 multiplex families available in March 2014
- 10,939 samples/10,959 subjects with Whole Exome Sequencing will be available late October
- **3,264 are ADC subjects**
- See ADSP website (www.niagads.org/adsp) for more information on
  - Study design
  - Apply for data access

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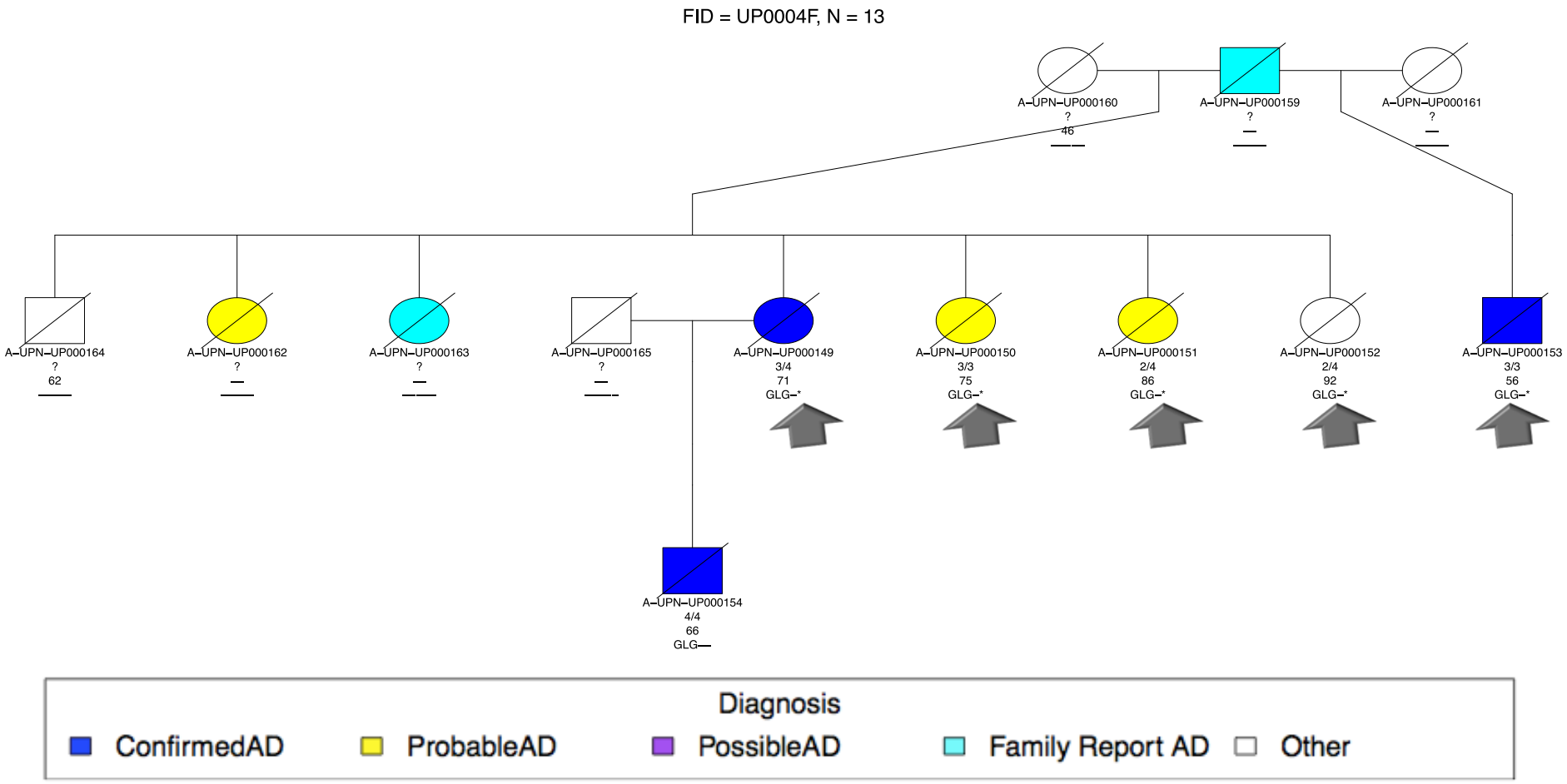
Example ADSP pedigree



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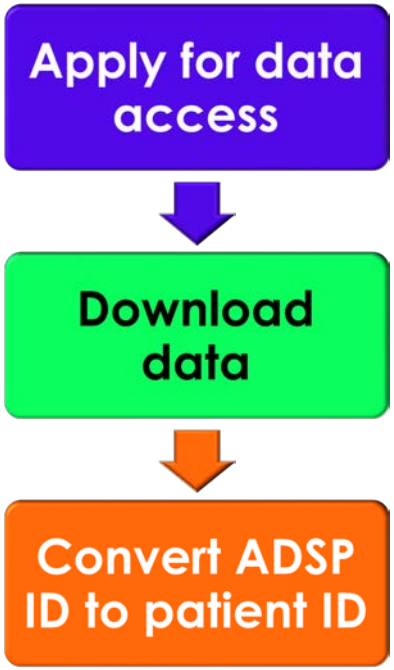
ADSP Whole-Exome Sequencing Data



- ~10,939 subjects, 3,264 are ADC subjects
  - BAM (*raw sequences*) end of October
  - VCF (*SNPs and indels*) at later date
- **Apply for access now!** Contact NIAGADS for help
- **ADSPID to ADC PatientID mapping** via NACC for each center (*A NACC/NCRAD/ADGC/NIAGADS Collaboration!*)

See **www.niagads.org/adsp** for more information

Or just contact NIAGADS **data@niagads.org**

ADGC Alzheimer's Disease Genetics Consortium NIAGADS

Apply for ADSP data access

Go to **www.niagads.org/adsp** , click **Apply for Data**

- All applications will be submitted to dbGaP and reviewed by NIH
- The dbGaP dataset ID for ADSP is **phs000572**.
- ADSP requires the following additional information:
  - **Description of the secondary data** that will be generated by your study and deposited into NIAGADS
  - Signed **NIA Data Sharing Plan** and **NIAGADS Data Distribution Agreement** for ADSP
- Contact NIAGADS (data@niagads.org) for data application, we'd be glad to help step-by-step

University of Pennsylvania
- Gerard Schellenberg
- Laura Cantwell
- Beth Dombroski
- Sherry Beecher

Familial AD
- Richard Mayeux
- Deborah Blacker

Clinical Group
- John Morris
- Debbie Tsuang

Neuropathology Group
- Tom Montine
- Eric Reiman

Biomarker Group
- Alison Goate
- Andy Saykin

Prospective Cohort Group
- David Bennett
- Bernadino Ghetti
- Brad Hyman
- Denis Evans
- Eric Larson
- Paul Crane
- John Hardy
- Ilyas Kamboh
- Eric Reiman
- Nilifur Taner
- Julie Schneider
- Steve Younkin
- Denis Dickson
- Charlie DeCarli
- Douglas Galasko
- Elaine Peskind
- Neil Graff-Radford
- Matthew Frosch
- John Trojanowski
- Vivianna Van Deelin
- John Morris

NACC
- Bud Kukull
- Duane Beekly

NCRAD
- Tatiana Foroud
- Kelly Michelle Faber

University of Miami
- Peggy Pericak-Vance
- Adam Naj
- Gary Beecher
- Paul Gallins
- Eden Martin

Boston University
- Lindsey Farrer
- Gyungah Jun
- Jacqueline Buros

Case Western
- Jonathan Haines

NIA/NIH, Alzheimer's Association

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Alzheimer's Disease Genetics Consortium

NIAGADS

EADI

Philippe Amouyel
Jean-Charles Lambert

GERAD

Julie Williams
Paul Hollingworth
Denise Harold
Peter Holmes

ADGC

Gerard Schellenberg
Peggy Pericak-Vance
Jonathan Haines
Richard Mayeux
Lindsay Farrer
Gyungah Jun
Jacqueline Buros
Gary Beecham
Adam Naj
Eden Martin
Li-San Wang

CHARGE

Sudha Seshadri
Cornelia van Duijn
Lenore Launer
Ainta DeStefano

IGAP
INTERNATIONAL
GENOMICS OF ALZHEIMER'S PROJECT

NIA/NIH, Alzheimer's Association

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ADSP Project

experimental design
power calculations – drive design
case/control selection
family selection
data flow and database planning
existing genetic data – submit to dbGap
phenotype data – submit to dbGaP
conference calls: 3-6/week, past 30 months
DNA samples to sequencing centers

ADSP Project

Gerard Schellenberg
Gary Beecham
Amanda Partch
Laura Cantwell
Adam Naj
Richard Mayeux
Lindsay Farrer
Peggy Pericak-Vance
Jonathan Haines
Li-San Wang
Wendy Raskind/Tom Bird
Tatiana Foroud
Kelley Faber
Anita DeStefano
Marilyn Miller

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NCRAD
NACC
NIAGADS


NIH
National Institute on Aging
Turning Discovery Into Health


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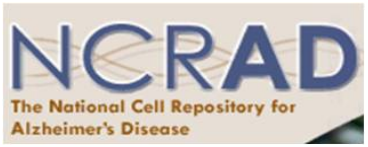
Alzheimer's Disease Genetics Consortium


NIAGADS


alzheimer's association


CHGR
center for human genetics research
VANDERBILT UNIVERSITY


NCRAD
The National Cell Repository for Alzheimer's Disease


NACC
National Alzheimer's Coordinating Center


University of Pittsburgh


ADNI


BOSTON
UNIVERSITY


COLUMBIA UNIVERSITY
MEDICAL CENTER

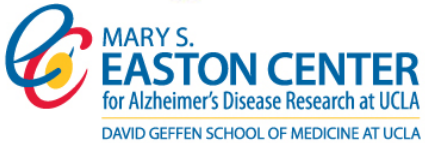

GroupHealth.


UCSF


UNIVERSITY OF PITTSBURGH


MAYO CLINIC
Jacksonville, Florida


UNIVERSITY OF MIAMI
MILLER SCHOOL OF MEDICINE
HUSSMAN INSTITUTE
for HUMAN GENOMICS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research center


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Shiley-Marcos
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Research Center


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Langone Medical Center
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USF
HEALTH


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UNIVERSITY


INDIANA UNIVERSITY


Washington University in St.Louis


JOHNS HOPKINS MEDICINE


School of Medicine

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Alzheimer's Disease Research Center

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KENTUCKY

University of Michigan
Health System

Alzheimer's Disease
EMORY
ADRC
Research Center