Alzheimer's Disease Genetics Consortium

Perelman School of Medicine
University of Pennsylvania

Alzheimer's Disease Genetics Consortium (ADGC)

Goal: Completely solve the genetics of Alzheimer's disease

- Common variants – susceptibility loci
- Rare strong effect variants
- CNVs/indels

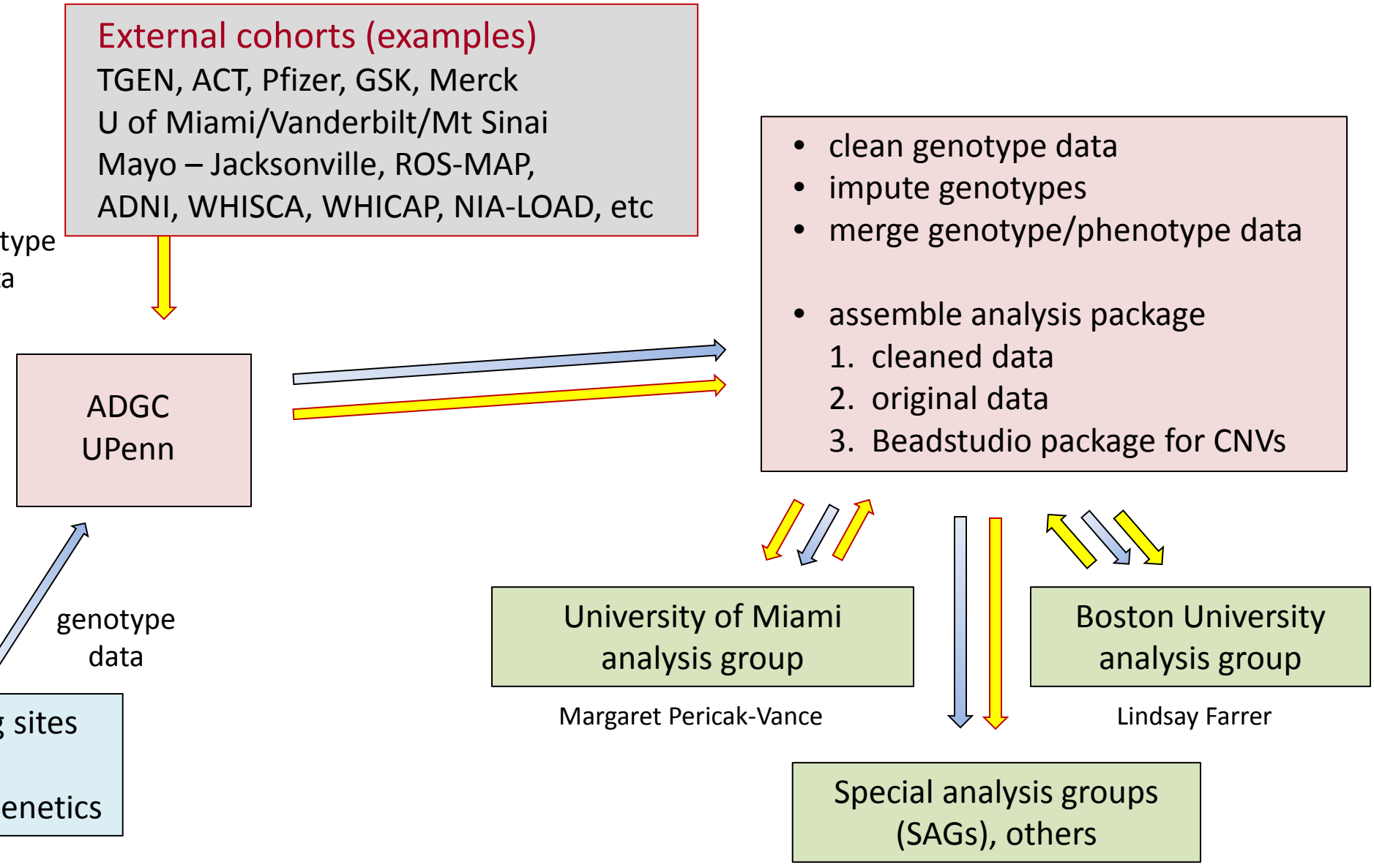
Alzheimer's Disease Genetics Consortium (ADGC)

Today's talk:

- Update you on what we have done (with your samples and your help).
- Outline projects in progress
- Encourage continuous participation by ADCs in getting blood samples/DNA to NCRAD

Samples and data:

- Alzheimer’s disease centers
- Collaborations with other studies
- Collaborations with other consortia


External cohorts (examples)
TGEN, ACT, Pfizer, GSK, Merck
U of Miami/Vanderbilt/Mt Sinai
Mayo – Jacksonville, ROS-MAP,
ADNI, WHISCA, WHICAP, NIA-LOAD, etc
type
a
ADGC
UPenn
genotype
data
g sites
enetics
clean genotype data
impute genotypes
merge genotype/phenotype data
assemble analysis package
1. cleaned data
2. original data
3. Beadstudio package for CNVs
University of Miami
analysis group
Margaret Pericak-Vance
Boston University
analysis group
Lindsay Farrer
Special analysis groups
(SAGs), others

ADC Contribution

	Phase 1 MDS	Phase 2 UDS	Total
NACC Subjects	4,727	24,190	28,817
Samples to NCRAD	3,774	10,550	14,324
Samples genotyped	2,990	5,477	8,467

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ADGC Genotyping

Cohort	Cases	Controls	Other	Total
ACT	20	7	372	399
ADC	4787	3121	559	8467
Miami	92	71	3	166
ROS/MAP	81	68	501	650
TARCC	203	97	0	300
Vanderbilt	17	81	4	102
WHICAP	82	605	0	687
CHAP*	16	54	778	848
Cache County*	0	1022	0	1022
EAS*	22	213	34	269
Total	**5320**	**5339**	**2251**	**12910**

*Genotyping not complete

Other Genotype Data Contributed

Cohort	Cases	Controls	Total
ACT	566	1696	2262
ADNI	268	173	441
GenADA	669	713	1382
London	61	137	198
Mayo	728	1173	1901
Merck/NYU	392	159	551
MIRAGE	509	753	1262
NIA-LOAD	1811	1575	3386
OHSU	132	153	285
Pfizer	733	792	1525
ROS/MAP	296	776	1072
TGen	864	493	1357
Univ Pittsburgh	1271	841	2112
Wash U	339	187	526
Total	**8639**	**9621**	**18260**

nature genetics

Common variants at *MS4A4/MS4A6E*, *CD2AP*, *CD33* and *EPHA1* are associated with late-onset Alzheimer's disease

The Alzheimer Disease Genetics Consortium (ADGC) performed a genome-wide association study of late-onset Alzheimer disease using a three-stage design consisting of a discovery stage (stage 1) and two replication stages (stages 2 and 3). Both joint analysis and meta-analysis approaches were used. We obtained genome-wide significant results at *MS4A4A* (rs4938933; stages 1 and 2, meta-analysis P (P_M) = 1.7×10^{-9}, joint analysis P (P_J) = 1.7×10^{-9}; stages 1, 2 and 3, $P_M = 8.2 \times 10^{-12}$), *CD2AP* (rs9349407; stages 1, 2 and 3, $P_M = 8.6 \times 10^{-9}$), *EPHA1* (rs11767557; stages 1, 2 and 3, $P_M = 6.0 \times 10^{-10}$) and *CD33* (rs3865444; stages 1, 2 and 3, $P_M = 1.6 \times 10^{-9}$). We also replicated previous associations at *CR1* (rs6701713; $P_M = 4.6 \times 10^{-10}$, $P_J = 5.2 \times 10^{-11}$), *CLU* (rs1532278; $P_M = 8.3 \times 10^{-8}$, $P_J = 1.9 \times 10^{-8}$), *BIN1* (rs7561528; $P_M = 4.0 \times 10^{-14}$, $P_J = 5.2 \times 10^{-14}$) and *PICALM* (rs561655; $P_M = 7.0 \times 10^{-11}$, $P_J = 1.0 \times 10^{-10}$), but not at *EXOC3L2*, to late-onset Alzheimer's disease susceptibility[1–3].

Adam C. Naj, Gyungah Jun, Gary W. Beecham, Li-San Wang, Badri Narayan Vardarajan, Jacqueline Buros, Paul J. Gallins, Joseph D. Buxbaum, Gail P. Jarvik, Paul K. Crane, Eric B. Larson, Thomas D. Bird, Bradley F. Boeve, Neill R. Graff-Radford, Philip L. De Jager, Denis Evans, Julie A. Schneider, Minerva M. Carrasquillo, Nilufer Ertekin-Taner, Steven G. Younkin, Carlos Cruchaga, John S.K. Kauwe, Petra Nowotny, Patricia Kramer, John Hardy, Matthew J. Huentelman, Amanda J Myers, Michael M. Barmada, F Yesim Demirci, Clinton T. Baldwin, Robert C. Green, Ekaterina Rogaeva, Peter St George-Hyslop, Steven E. Arnold, Robert Barber, Thomas Beach, Eileen H. Bigio, James D. Bowen, Adam Boxer, James R. Burke, Nigel J. Cairns, Chris S. Carlson, Regina M. Carney, Steven L. Carroll, Helena C. Chui, David G. Clark, Jason Corneveaux, Carl W. Cotman, Jeffrey L. Cummings, Charles DeCarli, Steven T. DeKosky, Ramon Diaz-Arrastia, Malcolm Dick, Dennis W. Dickson, William G. Ellis, Kelley M. Faber, Kenneth B. Fallon, Martin R. Farlow, Steven Ferris, Matthew P. Frosch, Douglas R. Galasko, Mary Ganguli, Marla Gearing, Daniel H. Geschwind, Bernardino Ghetti, John R. Gilbert, Sid Gilman, Bruno Giordani, Jonathan D. Glass, John H. Growdon, Ronald L. Hamilton, Lindy E. Harrell, Elizabeth Head, Lawrence S. Honig, Christine M. Hulette, Bradley T. Hyman, Gregory A. Jicha, Lee-Way Jin, Nancy Johnson, Jason Karlawish, Anna Karydas, Jeffrey A. Kaye, Ronald Kim, Edward H. Koo, Neil W. Kowall, James J. Lah, Allan I. Levey, Andrew P. Lieberman, Oscar L. Lopez, Wendy J. Mack, Daniel C. Marson, Frank Martiniuk, Deborah C. Mash, Eliezer Masliah, Wayne C. McCormick, Susan M. McCurry, Andrew N. McDavid, Ann C. McKee, Marsel Mesulam, Bruce L. Miller, Carol A. Miller, Joshua W. Miller, Joseph E. Parisi, Daniel P. Perl, Elaine Peskind, Ronald C. Petersen, Wayne W Poon, Joseph F. Quinn, Ruchita A. Rajbhandary, Murray Raskind, Barry Reisberg, John M. Ringman, Erik D. Roberson, Roger N. Rosenberg, Mary Sano, Lon S. Schneider, William Seeley, Michael L. Shelanski, Michael A. Slifer, Charles D. Smith, Joshua A. Sonnen, Salvatore Spina, Robert A. Stern, Rudolph E. Tanzi, John Q. Trojanowski, Juan C. Troncoso, Vivianna M. Van Deerlin, Harry V. Vinters, Jean Paul Vonsattel, Sandra Weintraub, Kathleen A. Welsh-Bohmer, Jennifer Williamson, Randall L. Woltjer, Laura B. Cantwell, Beth A. Dombroski, Duane Beekly, Kathryn L. Lunetta, Eden R. Martin, M. Ilyas Kamboh, Andrew J. Saykin, Eric M. Reiman, David A. Bennett, John C. Morris, Thomas J. Montine, Alison M. Goate, Deborah Blacker, Debby W. Tsuang, Hakon Hakonarson, Walter A. Kukull, Tatiana M. Foroud, Jonathan L. Haines, Richard Mayeux, Margaret A. Pericak-Vance, Lindsay A. Farrer & Gerard D. Schellenberg

Late-onset Alzheimer's disease susceptibility genes

APOE:[1]	apolipoprotein E
PICALM[4]:	phosphatidylinositol-binding clathrin assembly protein
CLU/APOJ[3]:	clusterin
CR1[3]:	complement receptor 1
CD2AP[6,7]:	CD2-associated protein
EPHA1[6,7]:	ephrin receptor
MS4A4/MS4A6[6,7]:	membrane-spanning 4-domains, subfamily A
CD33[6,7]:	CD33 antigen
ABCA7[6,7]:	ATP-binding cassette (ABC) transporter, member A7
BIN1[5]:	bridging integrator 1
SORL1[2]	sortilin related receptor 1

1. Strittmatter *et al.* P*roc. Natl. Acad. Sci. U.S.A.* **90**, 1977-1981 (1993).
2. Rogaeva *et al. Nat. Genet*. **39**, 168-177 (2007)
3. Lambert *et al. Nat Genet* **41**, 1094-1099 (2009).
3. Harold*et al.Nat Genet* **41**, 1088-U1061 (2009).
4. Seshadri *et al. JAMA* **303**, 1832-1840, (2010).
5. Naj *et al. Nat. Genet*. **43**, 436-441 (2011).
6. Hollingworth *et al.* Nat. Genet. **43**, 429-435 (2011).

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ABCA7[6,7]:	ATP-binding cassette (ABC) transporter, member A7
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- ADGC samples
- Japanese case-control samples
- Korean case-control samples

Genome-wide significant association with AD

African American GWAS: ADC + other cohorts

	Cases	Controls	Total
DNA received (ADGC genotyped)	1076	1909	3297
Genotypes contributed to ADGC	1243	2565	3808
Total All	2319	4474	7105

Analysis nearly complete

ADGC Ongoing Core Projects

- African American population
- Hispanic population
- Rate of cognitive change
- CSF biomarkers
- Neuropathologic markers
- Neuropathology versus clinical cases/controls
- Onset age GWAS
- *APOE* interaction GWAS
- Exome chip
- IGAP – international collaboration
- Whole exome (genome) sequencing

IGAP

International Genomics Alzheimer Project

• EADI – France and Europe	Philippe Amouyel
• ADGC – USA	Gerard Schellenberg
• CHARGE – USA + Europe population based cohorts	Sudha Seshadri
• GERAD – Great Britain	Julie Williams

IGAP

International Genomics Alzheimer Project

- Stage 1: ~20,000 cases
  ~20,000 elderly controls
  ~20,000 population controls (younger)

- Stage 2: custom chip from stage 1 data
  ~50,000 SNPs
  14,000 cases (?)
  14,000 controls (?)

Genotyping in progress!

IGAP

International Genomics Alzheimer Project

Analysis – June 2012?

Sub-projects:

- onset age analysis
- stratified APOE GWAS
- pathway analysis
- Incident AD
- burden analysis
- other ?

Rare variants

Rationale:

- detect genes that cannot be identified by GWAS
- detect large effect alleles at genes identified by GWAS

Approaches:

- exome chip
- whole-exome sequencing
- whole-genome sequencing

Exome Chip Experiment

Goal: To enable an intermediate experiment between current genotyping arrays, which focus on relatively common variants, and exome sequencing of very large numbers of samples, which will enable examination of coding variants, down to singletons.

- Variants detected in 24,000 chromosomes by whole exome sequencing
- Includes rare variants – seen 3 times across 2 data sets
- Common exon variants

Exome Chip Content

Non-synonymous Variants	243,094
Splice site variants	12,662
Stop Altering Variants	7,137
Previously Described GWAS Hits	5,325
Ancestry Informative Markers	
European descent versus African Americans	3,241
European descent versus Native Americans	998
Scaffold for Identity by Descent	5,710
Grid of common variants	5,286
Random set of synonymous variants	4,651
Fingerprint SNPs	259
Mitochondrial SNPs	246
Chromosome Y SNPs	128
HLA tag SNPs	2,459
Indels	181

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HLA tag SNPs	
Indels	

- Genotyping completed for 7,000 chips
- Genotyping in progress for 10,000 more (complete in several weeks)

ADGC Genotyping – CSF cohorts

Cohort	Cases	Controls	Other	Total
BIOCARD	0	244	105	349
Blennow/Sweden	300	0	0	300
Peskind/UW	0	0	269	269
Vanderbilt	17	81	4	102
Wash U	113	233	197	543
Mayo – Rochester	?	?	?	500
Total	**430**	**558**	**575**	**2,063**

All samples have tau, P-tau, and Aβ levels

Other projects

- African American GWAS
  - About 2300 cases and 4100 controls
    - 1000 cases and 1600 controls genotyped by the ADGC
- Exome Chip
  - ADC: 2673 cases and 4418 controls
  - Other: 4652 cases and 3892 controls
  - Total: 7325 cases and 8310 controls

ADGC Member Analysis Projects

1. Washington University
   Use of biological and evolutionary information to prioritize SNPs from the ADGC genome-wide association studies for follow-up
   Alison Goate (PI), Keoni Kauwe, Carlos Cruchaga
2. Vanderbilt University
   Detection of Gene x Gene Interactions in LOAD GWAS Data
   Jonathan Haines (PI), Marilyn Ritchie, Kim Luci
3. NIA and University College London
   Epigenetic and Expression Modifications Associated with AD Risk SNPs
   Hardy, Andrew Singleton, Michael Nalls
4. University of Kentucky
   Topic – ***GWAS to identify SNPs associated with pathologically-verified hippocampal sclerosis***
   Peter Nelson MD PhD (PI), Steven Estus PhD, and David Fardo PhD
5. Mass General (and University of Washington)
   A genome-wide association study of Alzheimer's disease with psychosis (AD+P)
   Deborah Blacker MD (PI), Alan Fung MD, Debby Tsuang MD
6. Columbia University
   Identification of mitochondrial DNA variants associated with Alzheimer's disease
   Investigators - Sandra Barral Rodriguez PhD (PI), Rong Cheng PhD, Joseph Lee DrPH,
7. University of Washington (and Boston University, Indiana University)
   Psychometrically sophisticated GWAS: Cognitive decline among AD cases in the ADGC
   Paul Crane MD (PI), S McKay Curtis MD, Robert C Green MD

(analysis projects cont.)

8. University of Pennsylvania

   CNV Analysis of the ADGC Phase 1+2 Dataset

   Li-San Wang PhD, Chiao-Feng Lin PhD, Gerard Schellenberg PhD

9. Mayo Clinic

   Analysis of variants in the chromosome 10 VR22/LRRTM3 region in the combined ADGC and Mayo Clinic Datasets

   Nilufer Ertekin-Taner MD PhD

10. University of Pennsylvania

    Pathway and eSNP Analysis of AD and Cognitive decline

    Li-San Wang PhD, Chiao-Feng Lin PhD, Otto Valladares, Gerard Schellenberg PhD

11. Washington University

    Analysis of ADGC GWAS data for association with cerebrospinal fluid (CSF) biomarkers for LOAD

    Alison Goate PhD, Carlos Cruchaga PhD, Tony Hinrichs PhD

12. Boston University

    Analysis of Gene Interactions for AD Risk Using a Cooperative Game Theory Approach

    Badri Vardarajan, Lindsay Farrer PhD, Adrienne Cupples PhD

13. New York University

    Analysis of Gene-Environment Interactions Involved in AD

    Iryna Lobach PhD (PI), Tatiyana Apanasovich PhD, Hongyu Zhao PhD

(analysis projects cont.)

14. University of Pennsylvania

    Evaluation of Mitochondrial Heteroplasmy in AD GWAS datasets

    Neal Sondheimer MD PhD (PI), Jack Tirone, Li-San Wang PhD

15. ROS/MAP

    Validation of a CR1 susceptibility allele

    Philip L. De Jager MD PhD (PI), Eric Reiman MD, David A. Bennett MD

16. Mayo Clinic

    Combined GWAS for brain gene expression levels and AD risk

    Dr. Nilufer Ertekin-Taner (PI), Dr. Steven G. Younkin, Dr. Fanggeng Zou

17. ROS/MAP

    Replication of Genome-wide Scans for AD-related Intermediate Phenotypes and Functional Validation in Drosophila

    Philip L. De Jager MD PhD (PI), Mel Feany MD PhD, David A. Bennett MD

18. Columbia University

    Multi-locus genotype patterns associated with episodic memory in the NIA-LOAD/NCRAD Study

    Sandra Barral PhD (PI), Richard Mayeux MD

19. University of Washington

    Pathway-wide association study (PWAS) of AD

    Paul Crane MD (PI), Shubhadbrata Mukherjee PhD, S. McKay Curtis PhD

(analysis projects cont.)

20. University of Pennsylvania

    Alzheimer's Disease and toxicity exposure: a gene-environment Interactions analysis

    Shin-Yi Chou (PI) and Rhea Bhatta (Lehigh University), Li-San Wang

21. Columbia University

    SORCS2, SORCS3 and SORT1 and risk of Alzheimer's disease

    Chistiane Reitz, MD PhD, Lindsay Farrer, PhD, and Richard Mayeux, MD MSc

22. Mayo Clinic

    Determine risk associated with TMEM106B SNP rs1990622 in AD

    Dr. Rosa Rademakers, Dr. Minerva Carrasquillo and Dr. Steven Younkin

23. Mayo Clinic

    Joint Analysis of Genomic and Transcriptomic Data to Identify Novel AD Risk Genes

    Dr. Nilufer Ertekin-Taner (PI), Dr. Steven G. Younkin, Dr. Fanggeng Zou

24. Oregon Health & Sciences University

    Replication of a GWAS for autopsy-confirmed AD cases and controls

    Patricia Kramer, Matthew Huentelman, Jason Corneveaux

25. Autopsy-confirmed Parkinson Disease GWAS Consortium (APDGC)

    ADGC Controls for Parkinson Disease GWAS

    Dr. William Scott, Dr. Gary Beecham and Cherylyn Jauregui

26. Bringham Young University

    Pleiotropy and Interactions in CSF Biomarkers for AD

    Keoni Kauwe, PhD, Alison Goate, PhD, Taylor Maxwell PhD

(analysis projects cont.)

27. Genentech

    Whole-genome sequence analysis of early-onset Alzheimer's disease in APOE 3/4 and 4/4 subjects

    Timothy Behrens, Ward Ortmann, and Robert C. Gentleman

28. Emory University

    The proportion of common SNPs that explain late-onset Alzheimer's disease

    Thomas Wingo, MD and David Cutler, PhD

29. North American Pancreatic Study Group (NAPS)

    Genetic risk in recurrent acute and chronic pancreatitis

    David Whitcomb, MD, PhD, Bernie Devlin, MD

30. Bringham Young University

    Remaining genetic variance in clinical diagnosis of Alzheimer's disease

    Keoni Kauwe, PhD, and Perry Ridge, MS

31. UCSF

    Investigation for genetic loci underlying depressive symptomatology in Alzheimer's Disease

    Jennifer Yokoyama (PI), Howard Rosen, MD (mentor), Bruce Miller, MD

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Samples to NCRAD	3,774	10,550	14,324
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Benefits – Alzheimer's Disease Center Participation

- Participate in exciting science
- Genotypes returned for own study (including *APOE*)
- If blood sent to NCRAD, DNA prepared/returned
- Propose analysis projects (pre-publication data)

National Institute on Aging

alzheimer's association

NACC
National Alzheimer's Coordinating Center

NCRAD
The National Cell Repository for Alzheimer's Disease

University of Pittsburgh

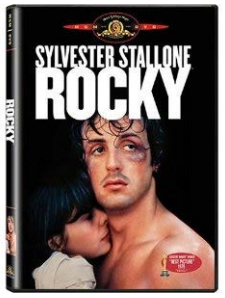
ADNI

BOSTON UNIVERSITY

Columbia University Medical Center

CHGR
center for human genetics research
VANDERBILT UNIVERSITY

UCSF



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UNIVERSITY of WASHINGTON

INSTITUTE for MEMORY IMPAIRMENTS and NEUROLOGICAL DISORDERS
UNIVERSITY of CALIFORNIA · IRVINE

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

USC

The eMERGE Network
electronic Medical Records & Genomics

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

Mount Sinai School of Medicine

RUSH UNIVERSITY MEDICAL CENTER

TGen

ARIZONA ALZHEIMER'S CONSORTIUM

UCDAVIS
UNIVERSITY OF CALIFORNIA

UT SOUTHWESTERN MEDICAL CENTER

MASSACHUSETTS alzheimer's disease research center

University of California, San Diego
Shiley-Marcos Alzheimer's Disease Research Center

NYU Langone Medical Center
Center of Excellence on Brain Aging

USF HEALTH

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INDIANA UNIVERSITY

Washington University in St. Louis
School of Medicine

JOHNS HOPKINS MEDICINE

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Jonathan Haines

NACC

Bud Kukull
Duane Beekly

NCRAD

Tatiana Foroud
Kelly Michelle Faber

NIAGADS

Li-San Wang

NIA

Marilyn Miller
Steve Snyder

NIA/NIH, Alzheimer's Association

The End