Alzheimer’s Disease Genetics Consortium (ADGC)

University of Pennsylvania School of Medicine
Goals

- Identify genetic variants that increase risk for AD
- Identify genetic variants that affect AD endophenotypes (Aβ load, tangle load, psychosis, biomarker levels, etc.)
Goals

- Identify genetic variants that increase risk for AD
- Identify genetic variants that affect AD endophenotypes (Aβ load, tangle load, psychosis, biomarker levels, etc.)

Bring together AD datasets for meta-analysis and combined analysis

Solve the genetics of Alzheimer’s disease
Mechanism

- Use existing AD case/control populations, data, DNA
- Genotype samples using high-density SNP platforms
- Analyze for genome-wide association
- *Meta*-analysis/combined analysis with other AD studies
- *Meta*-analysis with other neurodegenerative disease studies

Funding - NIA

- April 2009: UO1 is funded
- August 2009: initial genotyping
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Genome-wide Association Studies (GWAS)

- ApoE – association for one gene
- GWAS – test all (most) genes simultaneously
  Genotype 600,000 sites in cases and controls
  Test each for association with AD
- Correct for multiple comparisons
  Need p value < 5 x 10^{-7}
- Need large samples to detect small-effect genes
# ADGC Projects – years one and two

1. Meta-analysis existing studies:
   - Reiman-TGEN*
   - Framingham*
   - University of Miami/Vanderbilt*
   - ADNI*
   - Jacksonville Mayo*
   - LOAD study (Richard Mayeux)

2. ADC autopsy cases
   - ADGC: 2,000 AD cases
   - ADGC: 2,000 controls
     (supplement with UDS controls)

3. Samples with CSF biomarker data
   - Washington University: 431
   - University of Washington: > 500
   - ADNI: 491*
   - University of Pennsylvania: 283

* Not funded by the ADGC but data is/will be available
## ADGC Projects – years two - five

4. Prospective cohorts (European Ancestry)

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* Not funded by the ADGC but data is/will be available
ADGC Organization

Administration – UPenn team

Gerard D. Schellenberg, PI
Li-San Wang, bioinformatics/statistical analysis/database
Laura Cantwell, project manager
Otto Valderes, computer programmer
Caitlin Goodman, administrative assistant
Mi Ryung Han, research assistant

Laura Cantwell
lcant@mail.med.upenn.edu
gerardsc@mail.med.upenn.edu
## ADGC Organization

### Administration – UPenn team

- Gerard D. Schellenberg, PI Chair, University of Pennsylvania
- Li-San Wang, co-PI Database, University of Pennsylvania
- David Bennett, co-PI Cohort studies, Rush University Medical Center
- Deborah Blacker, co-PI Familial AD, Massachusetts General
- Richard Mayeux, co-PI Familial AD, Columbia University
- Lindsay Farrer, co-PI Analysis group, Boston University
- Margaret Pericak-Vance, co-PI Analysis group, University of Miami
- Tatiana Foroud, co-PI NCRAD, Indiana University
- Alison Goate, co-PI Biomarkers, Washington University
- Andy Saykin, co-PI Biomarkers, Indiana University
- Walter Kukull, co-PI NACC, University of Washington
- Thomas Montine, co-PI Neuropathology, University of Washington
- Eric Reiman, co-PI Neuropathology, Banner Alzheimer’s Institute
- John Morris, co-PI Clinical samples, Washington University
- Debbie Tsuang, co-PI Clinical samples, University of Washington
- Hakon Hakonarson, co-PI Genotyping, Children’s Hospital of Philadelphia
- Nilifer Tanner, member Data contributor, Jacksonville Mayo
- Marilyn Miller, Ex-officio National Institute on Aging, National Institutes of Health
- Tony Phelps, Ex-officio National Institute on Aging, National Institutes of Health

### Membership

- **PI/co-PI on U01**
- **Contribute data/samples**

### Executive Committee

- **Gerard D. Schellenberg**
  - PI Chair
  - University of Pennsylvania
- **Li-San Wang**
  - co-PI Database
  - University of Pennsylvania
- **David Bennett**
  - co-PI Cohort studies
  - Rush University Medical Center
- **Deborah Blacker**
  - co-PI Familial AD
  - Massachusetts General
- **Richard Mayeux**
  - co-PI Familial AD
  - Columbia University
- **Lindsay Farrer**
  - co-PI Analysis group
  - Boston University
- **Margaret Pericak-Vance**
  - co-PI Analysis group
  - University of Miami
- **Tatiana Foroud**
  - co-PI NCRAD
  - Indiana University
- **Alison Goate**
  - co-PI Biomarkers
  - Washington University
- **Andy Saykin**
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  - Indiana University
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  - University of Washington
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  - co-PI Genotyping
  - Children’s Hospital of Philadelphia
- **Nilifer Tanner**
  - member Data contributor
  - Jacksonville Mayo
- **Marilyn Miller**
  - Ex-officio National Institute on Aging
  - National Institutes of Health
- **Tony Phelps**
  - Ex-officio National Institute on Aging
  - National Institutes of Health
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<th>Name</th>
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<td>John Trojanowski</td>
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Walter Kukull                                  | National Alzheimer’s Coordinating Center  |
Hakon Hakonarson                                | Children’s Hospital of Philadelphia     |
Tatiana Foroud                                  | National Cell Repository for Alzheimer’s Disease |
Susan Resnick                                   | NIA                                     |
ADGC Organization

External Advisory Committee

Executive Committee

Administration – UPenn team

Investigator Committee

Analysis Committee

Biomarker Committee

Clinical Committee

Familial AD Committee

Neuropath. Committee

Prospective Cohort Committee
Alzheimer’s Disease Center Samples

29 ADCs

data cleaning

subject lists

NACC

ADGC

Phase 2

Selection of samples for GWAS

UDS Samples
Clinical committee

- John Morris chair, co-PI
- Debbie Tsuang co-PI
- Thomas Bird
- Helena Chui
- Jeffrey Cummings
- Charlie DeCarli
- Steven Ferris
- Douglas Galasko
- Neil Graff-Radford
- Richard Mayeux
- Elaine Peskind
- John Ringman
- Sandra Weintraub

- Walter Kukull NACC
- Gerard Schellenberg ADGC
Alzheimer’s Disease Center Samples

29 ADCs

DNA tissue

data cleaning

subject lists

list of samples received

NACC

ADGC

NCRAD

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Alzheimer’s Disease Center Samples

- 29 ADCs
- 29 ADCs
- 29 ADCs

Data Cleaning

Reimbursement (NACC subcontract)
- $10 DNA
- $50 brain

NACC
- ADGC

NCRAD
- ADGC

DNA Tissue

29 ADCs

Subject Lists

Received Samples

Samples received

29 ADCs

29 ADCs

29 ADCs
Alzheimer’s Disease Center Samples

29 ADCs

DNA tissue

NACC

data cleaning

subject lists

list of samples received

phenotype data

genotype data

ADGC

NCRAD ADGC

ADGC UPenn

Genotyping site CHOP
• Reiman – TGEN
• Younkin
• Framingham
• ADNI
• Welcome Trust control data (1958 cohort)
• University of Miami/Vanderbilt

• clean genotype data
• impute genotypes
• merge genotype/phenotype data
• assemble analysis package
  1. cleaned data
  2. original data
  3. Beadstudio package for CNVs

ADGC
UPenn

University of Miami analysis group
Margaret Pericak-Vance

Boston University analysis group
Lindsey Farrer

Special analysis groups (SAGs)
others
## Phase 1

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3,501 samples
Genotyping

- 660Quad Illumina
- 2,100 autopsy cases
- 862 controls (~200 from autopsied subjects)
- 462 subjects with CSF biomarker data
1. Replicate recent GWAS findings (ApoJ, etc)

- ADGC samples
- Miami/Vanderbilt data (Pericak-Vance/Haines)
- Framingham data
- Boston University data (Farrar)
- Mt. Sinai data (Buxbaum)
- LOAD data/Hispanic cohort - Columbia (Mayeux)
- ~5,000 cases/5,000 controls

Next 2 weeks
Goals

1. Replicate recent GWAS findings

2. New GWAS
   - ADGC (3,000 cases/3,000 controls)
   - Miami/Vanderbilt data (Pericak-Vance/Haines)
   - Framingham data
   - Boston University data (Farrar)
   - Mt. Sinai data (Buxbaum)
   - LOAD data - Columbia (Mayeux)
   - ~5,000 cases/5,000 controls

January, 2010
Phase 2

ARRA GO grant
9/30/2009 – 9/30/2011

Collect and Analyze UDS samples

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</table>

Expect 1,744 in October
The NIA recently awarded a 5-year, $19.5 million grant to the Alzheimer’s Disease Genetics Consortium (ADGC) to conduct a genome-wide association study (GWAS) to identify the remaining genes associated with an increased risk of developing late-onset Alzheimer’s disease (AD). Dr. Gerard D. Schellenberg of the University of Pennsylvania School of Medicine will lead the study.

GWAS requires a large number of samples to be studied to detect significant differences in genetic associations between people who have AD and those who do not. The ADGC is a collaborative effort of AD geneticists who are collecting more than 10,000 cases and 10,000 controls for such a study. In this study, investigators will look for genes that may influence the age of AD onset, rate of progression, and AD-related biomarkers. They will also be able to look for genes associated with age-related cognitive decline.

Identifying the remaining risk-factor genes will provide insight into new pathways that result in late-onset AD, a first step in the development of drugs to combat development of AD. It will also help identify people at high risk of developing late-onset AD, who would be prime candidates for prevention therapies and clinical trials.

- Press Release, Spotlight on Aging Research, NIA May 2009

<introductory note by Jerry>

GWAS Phase 1 Genotyping Initiated

Phase 1 of the ADGC genotyping, sponsored by the NIDCD, involved about 2,500

New ADGC Website

The ADGC website has been launched at:
http://alois.med.upenn.edu/adgc/

The site has information on the consortium, including members and committees, links to Alzheimer’s disease (AD) information, and will eventually list consortium publications. This will also be your resource for guidelines to submit analysis proposals, description of datasets available, and rules of data use. We welcome comments and suggestions to continually improve the website.

Special points of interest:
- View the new ADGC website
- Genotyping complete for over 2000 ADGC Phase 1 DNA
- New AD GWAS reports published online at Nature Genetics
ADGC Website

http://alois.med.upenn.edu/adgc/
The End