Updates:

Alzheimer’s Disease Genetics Consortium
ADGC

Alzheimer’s Disease Sequencing Project
ADSP

Partners:

National Alzheimer Coordinating Center – NACC
National Cell Repository for Alzheimer’s Disease - NCRAD
National Institute on Aging Genetics of Alzheimer’s Disease Storage site - NIAGADS
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>532</td>
<td>1,571</td>
</tr>
<tr>
<td>ADC1</td>
<td>1,549</td>
<td>512</td>
</tr>
<tr>
<td>ADC2</td>
<td>727</td>
<td>156</td>
</tr>
<tr>
<td>ADC3</td>
<td>894</td>
<td>586</td>
</tr>
<tr>
<td>ADC4</td>
<td>304</td>
<td>377</td>
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<tr>
<td>ADC5</td>
<td>286</td>
<td>505</td>
</tr>
<tr>
<td>ADC6</td>
<td>213</td>
<td>338</td>
</tr>
<tr>
<td>ADC7</td>
<td>500</td>
<td>790</td>
</tr>
<tr>
<td>ADC8</td>
<td>1,061</td>
<td>1,597</td>
</tr>
</tbody>
</table>

ADGC Cohorts

ADGC

<table>
<thead>
<tr>
<th>Consort</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADCs</td>
<td>5,534 cases</td>
<td>4,861 controls</td>
</tr>
<tr>
<td>10,395 total</td>
<td></td>
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</tr>
</tbody>
</table>
ADGC Major Projects – in progress

Exome Chip
- 8,158 Cases, 6,703 Controls
- Replicate in 17,000 IGAP samples

Rare Variant GWAS
- Previous analysis – impute to HapMap, MAF ~> 2%
- Impute to 1,000 Genomes – MAF to 0.5% to 2%
- Validate by Sanger sequencing
- Replicate in 19,000 subjects from IGAP

Transethnic analysis
- Caucasian
- African American
- Asian
- Caribbean Hispanic
Very Rare Variant GWAS

Previous analysis – Impute to 1,000 Genomes
MAF to 0.5% to 2.0%
Impute using ~30,000 genome reference panel
MAF to 0.1% or lower (?) to 1.5%

Goals: Identify AD rare variants
Replicate findings from the ADSP

Whole exome sequencing – 3,200 African American subjects
ADC subjects
507 cases
668 controls

ADGC Major Projects – new

Imputation in progress

Fall 2015 – Spring 2016
Add cohorts to the ADGC sample

HANDLS
HEALTH ABC
MESA
REGARDS
SOF
NHS
MrOS
SOL
WHS
SWAN
WHIM
Kaiser Permanente

2015-2020

Goals:
Increase sample size
Increase minority samples
Add deep-phenotype data
Alzheimer’s Disease Sequencing Project (ADSP)

Whole exome sequencing:

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

Whole-genome sequencing: 585 subjects
111 multiplex families

All sequencing completed
QC completed (WGS and WES)
VCF files (genotypes) available

Replication planning
Alzheimer’s Disease Sequencing Project (ADSP)

Analysis:

<table>
<thead>
<tr>
<th>Family-based study:</th>
<th>linkage analysis <em>(in press)</em></th>
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</thead>
<tbody>
<tr>
<td>WGS data</td>
<td>genes in linked regions</td>
</tr>
<tr>
<td></td>
<td>single variant analysis</td>
</tr>
<tr>
<td></td>
<td>gene-based analysis</td>
</tr>
<tr>
<td></td>
<td>pathway/gene cluster analysis</td>
</tr>
</tbody>
</table>

| Case-control:       | single variant analysis       |
|                     | gene-based analysis           |
|                     | pathway/gene cluster analysis |

Structural variants – insertions, deletions, copy number variation, inversions, rearrangements. 1bp to very large
Data Access – all subjects

SNP array data – all subjects/studies
Published data sets: NIAGADS
Most recent data: SAG process
3 page application to ADGC
74 approved SAGs
2 under review

ADSP Sequence data
dbGaP – all data, de-identified
available now

Li-San Wang will describe how to obtain subject level information a little later.
Alzheimer’s Disease Genetics Consortium

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NIA/NIH, Alzheimer’s Association