Loosening the Gordian Knot: Unraveling Alzheimer Disease Biology and Finding Therapeutic Targets Using Genetic Approaches

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No Disclosures
ALZHEIMER DISEASE

- Progressive loss of memory and cognition
- Onset in most cases after age 65 years, but can occur as early as age 30
- No effective treatment or cure
DIAGNOSIS OF ALZHEIMER DISEASE

- Pathologic confirmation (“Gold Standard”)
- Neuropsychological and brain imaging tests
- Rule out other organic causes (e.g., stroke)
- Progression for at least one year
NEUROPATHOLOGY OF ALZHEIMER DISEASE

- β-amyloid deposition in
  - parenchymal senile plaques
  - cerebral blood vessel walls

- Neurofibrillar tangles in neurons of cerebral cortex and hippocampus
Neuropathology of Alzheimer Disease
Alzheimer Disease is a Public Health Menace

- Affects 13% of people >age 65; 43% ages 85+
- 7th leading cause of death in US (5th among >65)
- More than 5.4 million Americans afflicted
- AD patients fill more than 50% of all nursing home beds and consume an estimated $172 billion per year in health care resources
Established Gene Loci for Alzheimer Disease

**Deterministic Mutations:**
- Amyloid Precursor Protein (APP)
- Presenilin-1 (PS-1)
- Presenilin-2 (PS-2)

**Susceptibility Polymorphism:**
- Apolipoprotein E (APOE)
## Gene Defects Causing Autosomal Dominant Alzheimer Disease

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Number of Mutations</th>
<th>Onset Age (Range)</th>
<th>Relative Frequency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>APP</td>
<td>21</td>
<td>33</td>
<td>37 – 65</td>
<td>5%</td>
</tr>
<tr>
<td>PS1</td>
<td>14</td>
<td>185</td>
<td>29 – 60</td>
<td>70%</td>
</tr>
<tr>
<td>PS2</td>
<td>1</td>
<td>13</td>
<td>40 – 82</td>
<td>5% – 10%</td>
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</tbody>
</table>

* These effects account for <<1% of all AD cases
Established Gene Loci for Alzheimer Disease

Deterministic Mutations:
- Amyloid Precursor Protein (APP)
- Presenilin-1 (PS-1)
- Presenilin-2 (PS-2)

Susceptibility Polymorphism:
- Apolipoprotein E (APOE)
• Plasma protein involved in cholesterol transport

• Produced in liver and in astrocytes in central and peripheral nervous system

• Encoded by gene on chromosome 19

• 3 alleles (ε2, ε3, and ε4) resulting from amino acid substitutions at positions 112 or 158

• ε2, ε4 associated with hyperlipidemia, type III hyperlipoproteinemia and hypertriglyceridemia (decreased binding to lipoprotein receptors)
Risk of Alzheimer's Disease by ApoE Genotype

Myers et al, Neurology 1996; 46:673-677

- ApoE 33
- ApoE 34
- ApoE 44
Odds of Alzheimer Disease by APOE and Age in Caucasians

Farrer et al. JAMA 1997; 278:1349-1356
Relative Odds of Alzheimer’s Disease by APOE Genotypes, Age and Sex in Caucasians

Farrer et al. JAMA 1997; 278:1349-1356

- By early 2007, 968 association studies in 398 candidate genes reported on AlzGene (http://www.alzforum.org/res/com/gen/alzgene)

- None other than APOE with robust confirmation

- Reasons include:
  - Initial results false positive
  - Lack of power in replication studies (false negatives)
  - Locus heterogeneity
  - Clinical heterogeneity
  - Lack of informative markers
  - Intralocus (non-allelic) heterogeneity
Mutations Causing Alzheimer Disease cause mis-processing of APP

APP is cleaved at sites which require subcellular trafficking of APP
Generation of Aβ requires trafficking into selected subcellular compartments

**Study Design**

**Retromer complex:**
VPS26 (10q21)
VPS35 (16q12).

**VPS10-containing sorting receptors:**
SORT1 (1p21-p13)
SORCS1 (10q23-q25)
SORCS3 (10q23-q25)
SORCS2 (4p16)
SORL1 (11q23-q24)

**Candidate Genes In Retromer Pathway**

**Gene(s) associated with AD**

**More SNPs**

**Functional Assays**

**Replicate in independent datasets**

≥ 2 SNPs/gene in 2 family cohorts:
North European: 124
Hispanic: 228

3 independent cohorts:
Mayo Clinic

4 independent cohorts:
North European case-controls: 178/142
MIRAGE Caucasian: 276
MIRAGE African American: 238
Israeli-Arab: 111/114

4 independent cohorts:
North European case-controls: 178/142
MIRAGE Caucasian: 276
MIRAGE African American: 238
Israeli-Arab: 111/114
<table>
<thead>
<tr>
<th>Ethnic origin</th>
<th>Carib Hispanic FAD **</th>
<th>Israeli Arab</th>
<th>NE FAD **</th>
<th>NE spAD</th>
<th>MIRAGE Caucasian</th>
<th>MIRAGE African American</th>
<th>Mayo Jack</th>
<th>Mayo Roch</th>
<th>Mayo Aut</th>
<th>All Caucasian</th>
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</thead>
<tbody>
<tr>
<td># AD samples</td>
<td>605</td>
<td>111</td>
<td>321</td>
<td>178</td>
<td>279</td>
<td>244</td>
<td>549</td>
<td>433</td>
<td>423</td>
<td>1583</td>
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<tr>
<td>Haplo p-value</td>
<td>0.005</td>
<td>0.0085</td>
<td>0.005</td>
<td>0.045/0.005</td>
<td>-</td>
<td>0.0025</td>
<td>&lt;0.003</td>
<td>-</td>
<td>0.003</td>
<td>&lt;0.02</td>
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</table>

Identical alleles are associated with AD in Israeli Arabs, Hispanics and some European Caucasians.

Identical alleles associated with AD in European Caucasians; Different haplotype associated with AD in African Americans.

SORL1 is reduced specifically in cortical neurons in late onset AD

How are sequence variants in SORL1 functionally associated with AD?

- Do not affect coding sequence or splicing;

- Intronic variants may affect tissue-specific regulation of transcription

- CTT_{22-24} haplotype associated with reduced transcription in lymphoblasts (*not very robust*);

- Genotype accounts for 14% of variance in expression level;

- **Corollary:** modifiers of SORL1 expression could be other causes of AD or potential therapies.

Suppressing SORL1 gene does not alter expression of APP or PS1 but increases BACE and γ-secretase cleavage of APP (more Aβ peptide and APPsβ)
SORL1 is a sorting receptor for APP

SORL1 is a sorting receptor for APP

APPsα → ADAM17 → SORL1-dependent switch → APP

SORL1 → BACE1 → Late endosomal pathways

Late endosomal pathways → PS1

ER-Golgi Secretory Pathway

Recycling Endosomes → VPS26, VPS35

SORL1 is a sorting receptor for APP

SORL1-dependent switch

Late endosomal pathways

APPsβ

APP-CTFβ

PS1

APP-CTFα

APPsα

ADAM17

APP

SORL1

BACE1

Aβ

AICD

ER-Golgi Secretory Pathway

Recycling Endosomes

Intracellular Trafficking of APP
May You Live in Interesting Times…

Since 2005, about 1400 genome-wide association studies have identified robust associations with genetic variants for more than 220 common, complex diseases and traits:

• 10 Mar 2005: Age-related macular degeneration
• 30 Apr 2006: QT interval prolongation
• 19 Oct 2006: “Wet” AMD
• 26 Oct 2006: Inflammatory bowel disease
• 11 Feb 2007: Type 2 diabetes
• 5 Mar 2007: Crohn’s disease
• 12 Apr 2007: Obesity
Published Genome-Wide Associations through 09/2011
1,617 published GWA at $p \leq 5 \times 10^{-8}$ for 249 traits

NHGRI GWA Catalog
www.genome.gov/GWASStudies
“There have been few, if any, similar bursts of discovery in the history of medical research...”

Unique Aspects of GWA Studies

• Permits examination of inherited genetic variability at unprecedented level of resolution
• Permits "agnostic" genomewide comparison
• Most robust associations in GWA studies have not been with genes previously suspected of being related to the disease
• Some associations in regions not even known to harbor genes

“The chief strength of the new approach also contains its chief problem: with more than 500,000 comparisons per study, the potential for false positive results is unprecedented.”

<table>
<thead>
<tr>
<th>Source</th>
<th>Population</th>
<th>Markers Examined</th>
<th>Most Significant Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coon et al, 2007</td>
<td>1411 cases and controls (autopsy and clinical series)</td>
<td>Affy 500K</td>
<td>APOE; GAB2 (among APOE ε4 carriers)</td>
</tr>
<tr>
<td>Reiman et al, 2007</td>
<td>103 LOAD and 170 1st-degree relatives from large Dutch pedigree</td>
<td>Affy 500K</td>
<td>linkage to 1q21-q25 &amp; 10q22-24 (confirm); and 3q23</td>
</tr>
<tr>
<td>Liu et al, 2007</td>
<td>5 case-control samples; total 1808 AD &amp; 2062 controls</td>
<td>17,343 cSNPs</td>
<td>APOE; GALP, TNK1, PCK1</td>
</tr>
<tr>
<td>Li et al, 2008</td>
<td>753 cases, 736 controls (Can) 418 cases, 249 controls (UK)</td>
<td>Affy 500K</td>
<td>APOE; GOLPH2, ch. 9 ATP8B4/SLC27A2</td>
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</tbody>
</table>
## Genome Wide Association Studies (continued)

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<tr>
<th>Source</th>
<th>Population</th>
<th>Markers Examined</th>
<th>Most Significant Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertram et al, 2008</td>
<td>410 NIMH Study families</td>
<td>Affy 500K</td>
<td>APOE; intergenic SNP on chr 14q31</td>
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<tr>
<td>Beecham et al, 2009</td>
<td>492 LOAD cases, 498 controls</td>
<td>Illumina 550K</td>
<td>APOE; chr 12q13 SNP in vitamin D receptor</td>
</tr>
<tr>
<td>Carrasquillo et al, 2009</td>
<td>844 LOAD cases, 1,255 controls</td>
<td>Illumina 317K</td>
<td>APOE; PCDH11X (Xq21.3)</td>
</tr>
</tbody>
</table>
Genome Wide Association Study

University of Miami Hussman Institute for Human Genomics

University of Pennsylvania School of Medicine

Boston University School of Medicine
Discovery Meta-Analysis
## Strongest Associations

<table>
<thead>
<tr>
<th>SNP</th>
<th>CH:MB</th>
<th>Nearest Gene</th>
<th>MA</th>
<th>MAF</th>
<th># SNPs</th>
<th>( \text{OR}_{\text{stage } 1+2} ) (95% CI)</th>
<th>( P_{\text{stage } 1+2} )</th>
<th>( \text{OR}_{\text{stage } 1+2+3} ) (95% CI)</th>
<th>( P_{\text{stage } 1+2+3} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs6701713</td>
<td>1:207.8</td>
<td>CR1*</td>
<td>A</td>
<td>0.20</td>
<td>7</td>
<td>1.16 (1.11-1.22)</td>
<td>4.6x10^-10</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>rs7561528</td>
<td>2:127.9</td>
<td>BIN1*</td>
<td>A</td>
<td>0.35</td>
<td>10</td>
<td>1.17 (1.13-1.22)</td>
<td>4.2x10^-14</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>rs9349407</td>
<td>6:47.5</td>
<td>CD2AP</td>
<td>C</td>
<td>0.27</td>
<td>1</td>
<td>1.12 (1.07-1.18)</td>
<td>1.0x10^-6</td>
<td>1.11 (1.07-1.15)</td>
<td>8.6x10^-9</td>
</tr>
<tr>
<td>rs11767557</td>
<td>7:143.1</td>
<td>EPHA1†</td>
<td>C</td>
<td>0.19</td>
<td>1</td>
<td>0.87 (0.83-0.92)</td>
<td>2.4x10^-7</td>
<td>0.90 (0.86-0.93)</td>
<td>6.0x10^-10</td>
</tr>
<tr>
<td>rs1532278</td>
<td>8:27.5</td>
<td>CLU*</td>
<td>T</td>
<td>0.36</td>
<td>2</td>
<td>0.93 (0.89-0.97)</td>
<td>8.3x10^-8</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>rs4938933</td>
<td>11:60.0</td>
<td>MS4A4A</td>
<td>C</td>
<td>0.39</td>
<td>22</td>
<td>0.88 (0.84-0.92)</td>
<td>1.7x10^-9</td>
<td>0.89 (0.87-0.92)</td>
<td>8.2x10^-12</td>
</tr>
<tr>
<td>rs561655</td>
<td>11:85.8</td>
<td>PICALM*</td>
<td>G</td>
<td>0.34</td>
<td>36</td>
<td>0.87 (0.84-0.91)</td>
<td>7.0x10^-11</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>rs3752246</td>
<td>19:1.1</td>
<td>ABCA7%</td>
<td>G</td>
<td>0.19</td>
<td>2</td>
<td>1.15 (1.09-1.21)</td>
<td>5.8x10^-7</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>rs3865444</td>
<td>19:51.7</td>
<td>CD33*</td>
<td>A</td>
<td>0.30</td>
<td>1</td>
<td>0.89 (0.86-0.93)</td>
<td>1.1x10^-7</td>
<td>0.91 (0.88-0.93)</td>
<td>1.6x10^-9</td>
</tr>
</tbody>
</table>
New Gene Loci for Alzheimer Disease

Genome Wide Association Study:
Phosphatidylinositol binding clathrin assembly protein (PICALM)
Clusterin (CLU)
Bridging Integrator 1 (BIN1)
Complement component (3b/4b) receptor 1 (CR1)
(Harold et al. & Lambert et al. Nat Genet 2009; Seshadri et al. JAMA 2010)

Pathway Candidate Gene Analysis:
Sortilin-related receptor, LDLR class A repeats-containing (SORL1)
(Rogaev et al. Nat Genet 2007)
New Gene Loci for Alzheimer Disease

Genome Wide Association Study:

CD33 antigen (CD33)

Membrane-spanning 4-domains, subfamily A (MS4A)

Ephrin type-A receptor 1 (EPHA1)

CD2-associated protein (CD2AP)

(Naj et al. Nat Genet 2011)
Genetics AD: Where do we go next?

- Genomic convergence
  Compare results from GWAS with results from other sources:
  - expression arrays
  - siRNA knockdown experiments
  - proteomic databases
- Identify Functional Variants (may be rare)
- Biomarkers and Endophenotypes
The Endophenotype Advantage

• APOE + 10 GWAS loci account for ~ 35% of genetic variance for AD

• Where is the “missing heritability?”

   Answer: Small(er) effect loci, rare variants, structural variants, gene-gene & gene-environment interactions

   ➔ Requires extremely large samples to address

• AD complex phenotype

• Endophenotypes (MRI, cognitive, biomarker) can increase signal-to-noise ratio
Study Populations for MRI Trait GWAS

Multi Institutional Research in Alzheimer’s Genetic Epidemiology (MIRAGE) Study

- Caucasian and African American families containing primarily discordant sib pairs
- Cross-sectional, single time-point
- Semi-quantitative MRI measures of neurodegeneration (HV, TCV) and cerebrovascular disease (WMH) included in study

Alzheimer’s Disease Neuroimaging Initiative (ADNI)

- Unrelated subjects
- Quantitative volumetric measures
- Baseline + Longitudinal follow-up

<table>
<thead>
<tr>
<th>AD</th>
<th>MCI</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
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</tbody>
</table>
# Subject Characteristics

<table>
<thead>
<tr>
<th>Class</th>
<th>AD</th>
<th>MCI</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>168</td>
<td>336</td>
<td>188</td>
</tr>
<tr>
<td>Age</td>
<td>75.4</td>
<td>75.2</td>
<td>75.0</td>
</tr>
<tr>
<td>(S.D.)</td>
<td>(7.6)</td>
<td>(7.1)</td>
<td>(4.9)</td>
</tr>
<tr>
<td>Freq APOE ε4</td>
<td>0.420</td>
<td>0.342</td>
<td>0.144</td>
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</tbody>
</table>

**PHASE ONE**

(Genome Wide)

**ADNI**
## Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PHASE ONE</th>
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<th>MIRAGE Caucasian</th>
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<tbody>
<tr>
<td></td>
<td>(Genome Wide)</td>
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<tr>
<td></td>
<td>ADNI</td>
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<td>MCI</td>
<td>CON</td>
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<td>(7.6)</td>
<td>(7.1)</td>
<td>(4.9)</td>
</tr>
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<td>0.420</td>
<td>0.342</td>
<td>0.144</td>
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<tr>
<td></td>
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<td>0.291</td>
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## Subject Characteristics

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<tr>
<th></th>
<th>PHASE ONE (Genome Wide)</th>
<th>PHASE TWO (Regions)</th>
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<tr>
<td></td>
<td>ADNI</td>
<td>MIRAGE Caucasian</td>
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<tr>
<td>Class</td>
<td>AD</td>
<td>MCI</td>
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<tr>
<td>Sample Size</td>
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<tr>
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</tr>
<tr>
<td>Freq APOE ε4</td>
<td>0.420</td>
<td>0.342</td>
</tr>
</tbody>
</table>
Phase 1: GWAS in Two Caucasian datasets

ADNI

MIRAGE CAUCASIAN

META ANALYSIS

P-VALUE (META) ≤ 1 X 10^{-5}
P-VALUE (EACH) ≤ 0.05

MOST SIGNIFICANT SNP FROM EACH REGION SELECTED

CANDIDATE REGIONS FOR EVALUATION IN PHASE 2
GWAS (Phase 1) Regions of Interest

<table>
<thead>
<tr>
<th>Trait</th>
<th>Number</th>
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<tbody>
<tr>
<td>Hippocampal Volume</td>
<td>14</td>
</tr>
<tr>
<td>Total Cerebral Volume</td>
<td>3</td>
</tr>
<tr>
<td>White Matter Hyperintensities</td>
<td>5</td>
</tr>
</tbody>
</table>

ROI’s Tested in African Americans in Phase 2
Hippocampal Volume

Caucasian  
African American  
Combined

rs6703865
P = 1.1 x 10^{-9}
Hippocampal Volume Genes

Factor V
- essential co-factor of blood coagulation cascade
- Leiden variant associated with risk of vascular dementia and perhaps AD in Rotterdam Study

P-Selectin
- Granule membrane protein that mediates interaction of activated endothelial cells or platelets with leukocytes
- Stellos et al. *J Cereb Blood Flow Metab* 2010
  - Higher levels – AD fast cognitive decline
  - Lower levels – AD slow cognitive decline
Whole Genome Sequencing…

The New Frontier

• First human genome to be sequenced took 10 years, multiple laboratories and billions of dollars

• Today, whole genome can be sequenced in a few days for < $5,000

• Still technical issues in capturing all of the sequence and aligning all of the fragments

• Biological relevance of most of sequence still unknown

• Most researchers use whole exome sequencing (~ 3% of genome) or targeted gene re-sequencing which costs < $1,200 per exome or sequencing lane.

• Data management and bioinformatic analysis significant
NEXT GENERATION SEQUENCING TO IDENTIFY ALZHEIMER’S GENES

With thanks to Dr. Clinton Baldwin
Overall Strategy

Alzheimer Subjects and Controls

Genetic Association Study

High-Throughput Sequencing

Bio - Informatic Analysis

Generate Testable Hypothesis about Disease Mechanism, Develop Authentic Models
Sequencing of Wadi Ara AD samples

- Inbred Arab Community in Northern Israel – lower genetic complexity?
- High Prevalence of AD
- Whole EXOME sequence for 2 cases/2 controls
- Candidate gene custom sequencing (intron plus exon) for AD related genes including SORL1 in 7 cases and controls selected based on genotype

Sequencing effort directed by Dr. Clint Baldwin
Summary of Whole Exome Sequencing in Wadi Ara

<table>
<thead>
<tr>
<th>Sample</th>
<th>5B</th>
<th>6A</th>
<th>7</th>
<th>8A</th>
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<tbody>
<tr>
<td>Alzheimer Status</td>
<td>Control</td>
<td>Control</td>
<td>Case</td>
<td>Case</td>
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<tr>
<td>Total Reads</td>
<td>35743353</td>
<td>62468267</td>
<td>52598715</td>
<td>45570929</td>
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<td>Reads Aligned</td>
<td>11876829</td>
<td>18025538</td>
<td>31719546</td>
<td>12823442</td>
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<tr>
<td>Percent Aligned</td>
<td>33.23%</td>
<td>28.86%</td>
<td>60.30%</td>
<td>28.14%</td>
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<tr>
<td>Multi Aligned Reads</td>
<td>2377789</td>
<td>5875571</td>
<td>3197036</td>
<td>2087745</td>
</tr>
<tr>
<td>Percent Multi Aligned Reads</td>
<td>6.65%</td>
<td>9.41%</td>
<td>6.08%</td>
<td>4.58%</td>
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<tr>
<td>SNPs</td>
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<td>22417</td>
<td>47641</td>
<td>17426</td>
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<tr>
<td>Non-synonymous SNPs</td>
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<td>4723</td>
<td>6149</td>
<td>3941</td>
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<table>
<thead>
<tr>
<th>Sample</th>
<th>Known SNPs</th>
<th>Novel SNPs</th>
<th>Total Ann</th>
<th>Total Sequenced</th>
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<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Unknown</th>
<th>Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 cases and 0 controls</td>
<td>1953</td>
<td>148</td>
<td>1805</td>
</tr>
<tr>
<td>2 controls and 0 cases</td>
<td>1589</td>
<td>168</td>
<td>1421</td>
</tr>
<tr>
<td>all 4 subjects</td>
<td>3601</td>
<td>3469</td>
<td>132</td>
</tr>
<tr>
<td>At least one case and 0 controls</td>
<td>39776</td>
<td>17606</td>
<td>22170</td>
</tr>
<tr>
<td>At least one ctrl and 0 cases</td>
<td>15845</td>
<td>4546</td>
<td>11299</td>
</tr>
<tr>
<td>At least one case and 0 ctrl (not 7)</td>
<td>5960</td>
<td>2009</td>
<td>3951</td>
</tr>
</tbody>
</table>
The mutation (red circle) is located in the central portion of the extracellular cysteine rich domain at the WNT binding site. This region of the protein is highly conserved among related proteins (gi accession numbers shown) and are generally glutamic acid or aspartic acid at that position.
LETTER

A mutation in APP protects against Alzheimer’s disease and age-related cognitive decline

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Table 1 | APP A673T protects against Alzheimer’s disease

<table>
<thead>
<tr>
<th>Analysis</th>
<th>1/OR</th>
<th>OR</th>
<th>P value</th>
<th>Frequency (%)</th>
<th>Nchip</th>
<th>Nsilico</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD versus population controls</td>
<td></td>
<td></td>
<td></td>
<td>0.13</td>
<td>2,199</td>
<td>849</td>
</tr>
<tr>
<td>AD versus population controls aged 85 or greater</td>
<td>4.24</td>
<td>0.236</td>
<td>4.19 x 10⁻⁶</td>
<td>0.45</td>
<td>57,174</td>
<td>22,074</td>
</tr>
<tr>
<td>AD versus cognitively intact controls at age 85</td>
<td>5.29</td>
<td>0.189</td>
<td>4.78 x 10⁻⁷</td>
<td>0.62</td>
<td>7,653</td>
<td>1,350</td>
</tr>
<tr>
<td>AD versus cognitively intact controls at age 85</td>
<td>7.52</td>
<td>0.133</td>
<td>6.92 x 10⁻⁶</td>
<td>0.79</td>
<td>827</td>
<td>407</td>
</tr>
</tbody>
</table>

The table shows association results, comparing patients with Alzheimer’s disease (AD) to three different control groups (top line gives numbers for patients with Alzheimer’s disease only). Nchip, number of individuals with chip-based genotype information; Nsilico, number of individuals with genealogy-based genotype information.
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http://genetics.bumc.bu.edu