Integrating Brain Imaging and Genetics to Uncover Risk for Alzheimer’s Disease

Robyn A. Honea, DPhil
Assistant Professor,
KUMC Department of Neurology
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Late Onset Alzheimer’s Disease Risk = Nuclear Genes + Mitochondrial Genes + Environment
We Need Complex Tools for a Complex Disease; Imaging Genetics

Environment

Brain Imaging

Genes:
- multiple susceptibility alleles each of small effect

Cells:
- subtle molecular changes, i.e., neurogenesis

Systems:
- change in cortical morphometry and brain function

Behavior:
- complex functional interaction and emergent phenomena

Cognition

Physical Performance

Environment
“Imaging Genetics”
A model to study complex diseases

- Characterize Disease Using Imaging
- Define Imaging Endophenotype- *a heritable trait
- Identify Genetic Variants
- Study Impact of Genetic Variation on Disease Endophenotype, or quantifiable trait
Heritability of Brain Morphometry

Gray matter volume

Cortical Thickness and Surface Area

Alzheimer’s Genes and Brain Atrophy

Multilocus genetic profiling to empower drug trials and predict brain atrophy


Table:

<table>
<thead>
<tr>
<th>Rank</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>CLU</td>
</tr>
<tr>
<td>4</td>
<td>ABCA7</td>
</tr>
<tr>
<td>5</td>
<td>CR1</td>
</tr>
<tr>
<td>6</td>
<td>PICALM</td>
</tr>
<tr>
<td>7</td>
<td>MS4A6A</td>
</tr>
<tr>
<td>8</td>
<td>CD33</td>
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<tr>
<td>9</td>
<td>MS4A4E</td>
</tr>
<tr>
<td>10</td>
<td>CD2AP</td>
</tr>
</tbody>
</table>

Honea et al. in preparation
BDNF- also associated Brain Atrophy

- Brain Derived Neurotrophic Factor is a neurotrophins that regulates cortical neuron survival, proliferation, and synaptic growth.
- Study: 645 participants from ADNI
- Six SNPs were significantly associated with hippocampal and/or whole brain atrophy, including Val66Met, which affects intracellular packing and secretion of neurotrophin

BDNF rs6265
Val> Met Carriers
Hippocampal Atrophy
*p<.02 FWE corrected

Honea et al. Plos One 2013
25% of all people over 55 have a family history of dementia (Loy C, Lancet 2014)

Nuclear Genes….are contributed by both parents

However, more often subjects have an affected mother than an affected father AD (Heyman A 1983, Edland SD 1996)

### Table 2

<table>
<thead>
<tr>
<th>Reference</th>
<th>AD cases</th>
<th>No affected parents</th>
<th>FH−</th>
<th>FHm</th>
<th>FHp</th>
<th>Mother:father ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heyman et al. 81</td>
<td>68</td>
<td>11</td>
<td>84%</td>
<td>10%</td>
<td>6%</td>
<td>1.8:1</td>
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<tr>
<td>Duara et al. 77</td>
<td>311</td>
<td>69</td>
<td>78%</td>
<td>17%</td>
<td>5%</td>
<td>3.6:1</td>
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<td>Edland et al. 78</td>
<td>118</td>
<td>24</td>
<td>80%</td>
<td>16%</td>
<td>4%</td>
<td>3.8:1</td>
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<tr>
<td>Farrer et al. 70</td>
<td>251</td>
<td>61</td>
<td>76%</td>
<td>16%</td>
<td>8%</td>
<td>1.9:1</td>
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<tr>
<td>Gomez-Tortosa et al. 80</td>
<td>2594</td>
<td>817</td>
<td>68%</td>
<td>23%</td>
<td>9%</td>
<td>2.6:1</td>
</tr>
</tbody>
</table>

FH− = No family history of AD; FHm = maternal history of AD; FHp = paternal history of AD.
Maternal Family History and Imaging Phenotypes of Alzheimer’s

- progressive atrophy in AD-regions (Honea et al., Neurology 2010, 2011)
- reduced glucose consumption (PET) (Mosconi et al. PNAS 2007)
- progressive reductions in glucose metabolism over time (Mosconi et al. Neurology 2009)
- Increased amyloid-beta load in key brain areas (Mosconi et al. PNAS 2010, Honea et al. JAD 2012)
- Hypoperfusion (reduced cerebral blood flow) in hippocampal and parietofrontal regions (Okonkwo OC et al. Cerebral Cortex 2014)
- Alterations in Resting State Connectivity (Wang et al. 2012; Honea et al in preparation)
- MCI with a maternal family history have more markers of AD pathophysiology (CSF, PiB, glucose metabolism) (Honea et al. JAD 2012, Mosconi et al. JAD 2014)
So, many nuclear genes relate to brain morphometry…

- What about the mitochondrial genome?
- Maternally inherited mutations of mtDNA may play a role in AD….but it is still unclear.

Mitochondria have DNA of their own, creating structures!!
Mitochondrial Haplogroups

Haplogroups are the major branch points on the mitochondrial phylogenetic tree which began with Mitochondrial Eve in Africa.
Association between Mitochondrial Genes and Temporal Cortex Atrophy

- ADNI longitudinal volume and thickness data
- Haplotype-based Treescanning approach to analyze evolutionarily meaningful groups of genes together for their association with phenotype
- 4 significant clades in Haplogroups U and K
- Next step, Next Generation mtDNA sequencing of 500 individuals from our KU Alzheimer’s Disease Center

Mitochondrial Genetic Haplogroup Tree

Ridge, P. et al PlosOne 2013
Gene X Environment Interactions

- Analyzing data from two 6 month exercise interventions, one in healthy elderly (R01AG033673-Burns PI) and one in Alzheimer’s Disease (R01AG34614- Burns PI) with imaging and genetic data.
Thank you!

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Cognitively healthy individuals with a maternal family history have more AD-like cortical thinning patterns.