Alzheimer’s Disease Genetics

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Genetics of AD

Autosomal dominant inherited (monogenic) forms
early onset (30-60 yrs of age); < 1%
- amyloid precursor protein (APP)
- presenilin 1 (PS1)
- presenilin 2 (PS2)

Sporadic forms (genetic components variable)
late onset (60+ yrs of age)
- apolipoprotein E (APOE) (e4 isoform)
- many other potential genes
  - genome-wide association studies (GWAS)
  - multigenic risk

Formation of Aβ peptides

Amyloid precursor protein (APP)
β-secretase
γ-secretase
Plaques
A Word (or Two) on Mouseheimer’s Disease

- Gamma-secretase clips many proteins besides APP (Notch, N-Cadherin, p75, etc)
- PS1 mutation carriers differ significantly from sporadic AD (white matter disease, spinal cord, etc)
- Typical mouse models are double- or triple-transgenic (PS1 + APP + MAPT)
- Despite this, progressive, age-related neuronal loss is not a typical feature

APOE (and the others)

- Three common variants: 2, 3, 4
- 4 confers risk (65% of AD), 2 protective
- Moves age of onset earlier
- Not useful as a general screening tool
- E4 effect weaker in some groups
- Increases diagnostic accuracy in young patients with unusual clinical picture

Apolipoprotein E

Lambert et al., Nature Genetics 2013

Mayeux et al., NEJM, 1998
APOE4 Domain Interaction

Huang et al., Trends Mol Med, 2010

Increased Amyloid Deposition with E4

Morris et al., Ann Neurol, 2010

Sex Modifies the APOE4 Effect (case-control data)

Farrer et al, JAMA, 1997

Sex Modifies the APOE4 Effect (longitudinal conversion data)

Altmann et al, Ann Neurol, 2014

Clinical conversion from healthy aging to MCI or AD

4500+ older controls
- 1320 E3/E4
- 3210 E3/E3
**Genetics of Alzheimer’s Disease**

- PSEN1, APP, PSEN2
- APOE
- SORL1
- BIN1
- CLU
- CR1...

**McCarthy et al., Nat Rev Genetics, 2008**

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**Stanford Extreme Phenotypes in Alzheimer’s Disease (StEP AD) Cohort**

- ADRC-supported study to find rare genetic variants that either
  - protect APOE4 carriers from getting AD
  - cause early-onset AD in non-APOE4 carriers
- Whole-genome sequencing in
  - Healthy controls with 1 or 2 APOE4 copies over age 70
  - AD patients with onset before age 65 and negative for APOE4, PS1/PS2/APP

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**Conclusions**

- Rare autosomal dominant mutations provide human and animal model insights into sporadic AD
- APOE has most clinical relevance
- Other GWAS hits less clinically relevant but important for molecular pathways
- Missing heritability
  - Extreme phenotypes/WGS
  - X-chromosome is unexplored
  - Gene-gene interactions

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**Acknowledgments**

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**Funding**

NIH: P50 AG047366 (ADRC); RO1 AG060747; The Show Me Charity Foundation; The J. W. Bagley Foundation