Alzheimer’s Disease Genetics

Mike Greicius, MD
Medical Director
Stanford Center for Memory Disorders
Department of Neurology and Neurological Sciences

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
**DIAN Study**

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

---

**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**

- 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

---

**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 (longitudinal conversion data)**

Altmann et al., *Ann Neurol*, 2014

---

**A Variant That Counteracts APOE4?**

Belloy et al., in prep
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

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