Alzheimer's Disease Genetics

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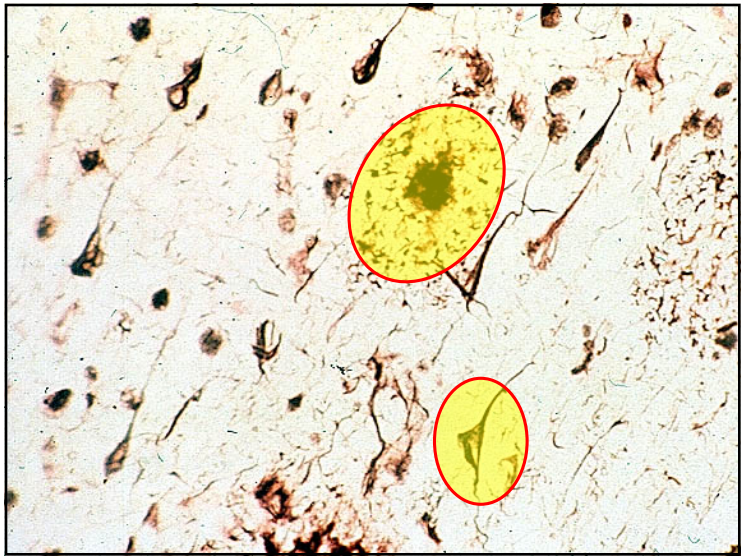
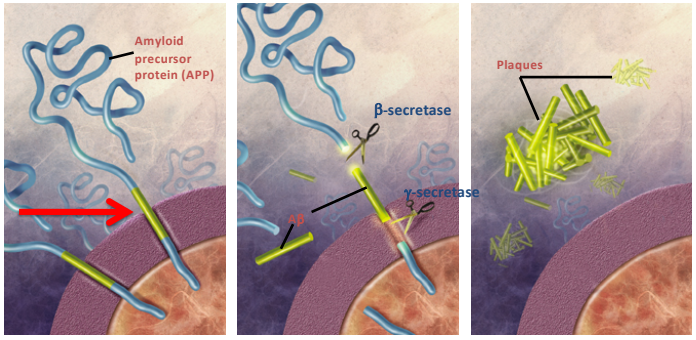
Genetics of AD

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

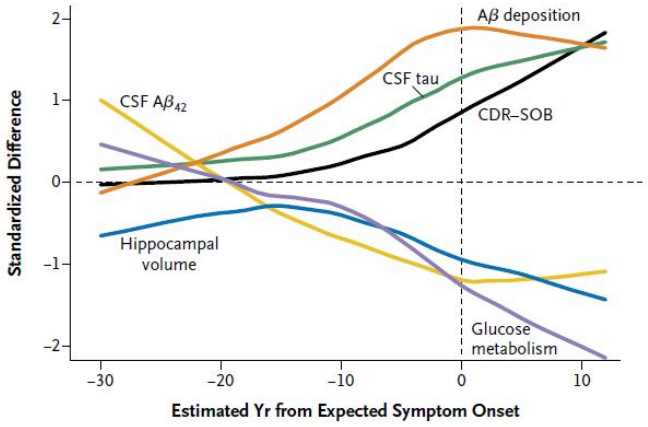


Formation of Aß peptides



NIH/NIA

DIAN Study

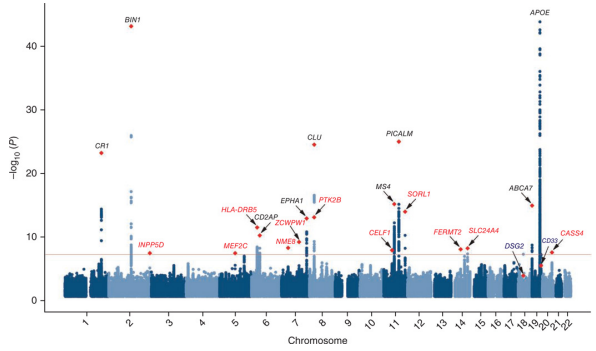


Bateman et al., *NEJM*, 2012

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)



Lambert et al., *Nature Genetics* 2013

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

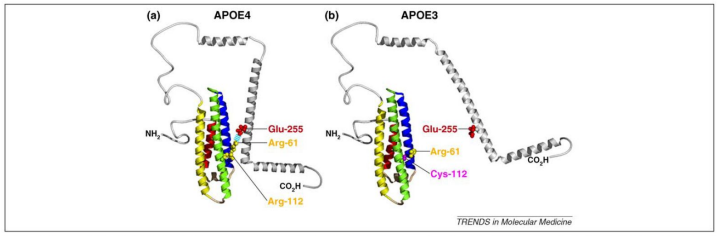
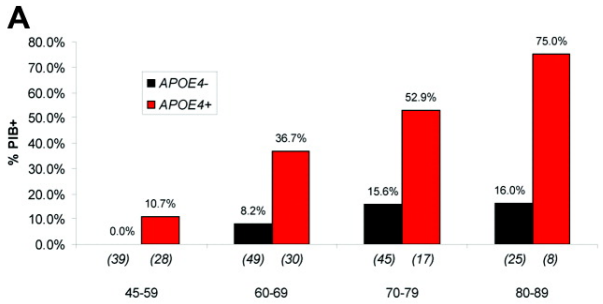


Figure 1. Domain interaction influences the conformation of APOE. **(a)** In APOE4, Arg-112 orients the side chain of Arg-61 into the aqueous environment where it can interact with Glu-255, resulting in a salt bridge between the N- and C-terminal domains. **(b)** In APOE3, Arg-61 does not interact with residues in the C-terminal domain, resulting in a very different overall conformation. For details, see reference [28].

Huang et al., *Trends Mol Med,* 2010

Increased Amyloid Deposition with E4

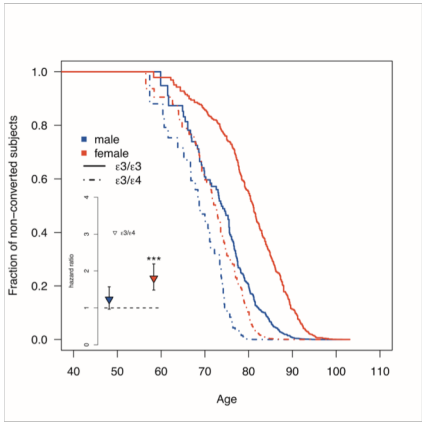


Morris et al., *Ann Neurol*, 2010

Sex Modifies the APOE4 Effect (longitudinal conversion data)

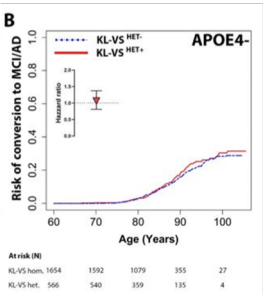
Clinical conversion from healthy aging to MCI or AD

4500+ older controls
-1320 E3/E4
-3210 E3/E3



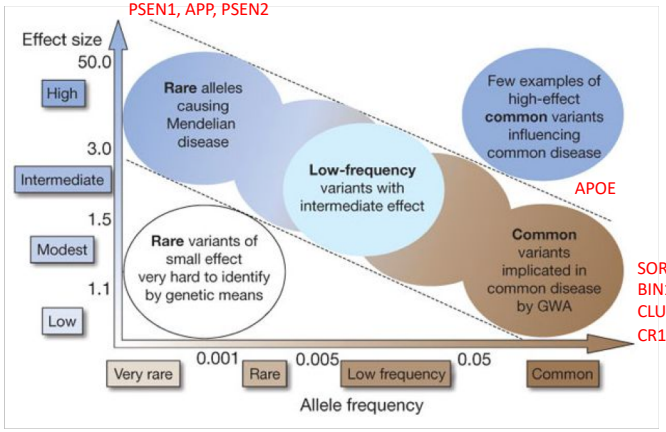
Altmann et al, *Ann Neurol*, 2014

A Variant That Counteracts APOE4?



Belloy et al., in prep

Genetics of Alzheimer's Disease



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

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