Zetzsche T., Rujescu D., Hardy J., Hampel H. (2010). Advances and perspectives from genetic research: development of biological markers in Alzheimer's disease.Expert Rev. Mol. Diagn. 10, 667–690.

* 35.9 million patients in 2010
* projected increase in 2050 to over 115 million sufferers
* Most people (95%) have late-onset AD (LOAD)
* some people have autosomal dominnt familial AD (FAD) with prevalent early-onset AD (EOAD)
  + LOAD and EOAD have diff genetic backgrounds
* Behavioral and psychological symptoms of dementia (BPSD)

Brain changes

* Deposition of senile plaques (amyloid peptides)
* Neurofibrillary tangles
* Loss of neurons in hippocampus and other regions

Genetics of AD

* Mendelian AD caused by mutations in 3 genes

1. APP
2. Presenilin 1 (PSEN1)
3. Presenilin 2 (PSEN2)

* Mutations🡪altered production of Abeta
* Symptoms variable
* Causes familial forms of AD (EOAD)
* These genes found in > 80% of EOAD patients
* > 200 genes suggested for LOAD
  + no major AD locus
  + Apolipoprotein E (APOE) is a susceptibility gene. 3 isoforms:
    1. ε2
    2. ε3
    3. ε4
    - polymorphisms determined by two SNPs
    - ε3 and ε4 heterozygotes 2-3x more likely to develop AD compared with ε3 homozygotes
    - ε4 homozygotes >2x the risk of ε3 and ε4 heterozygotes
    - ε2 heterozygotes have a reduced risk
    - ε4 allele is a risk factor for LOAD
    - APOE lipid metabolism protein and may be involved in amyloid processing
  + Possible link with atherosclerosis (plaque builds up inside arteries🡪limit of flow of blood)
    - Many LOAD patients also have cerebrovascular damage
    - Univeristy of Texas found that the presence of atherosclerotic risk factors and cardiovascular comorbidieties and risk factors didn’t influence rate of AD progression
  + AlzGene.org
    - Summarizes scientific literature on topic
    - Provides results of allele-based meta-analyses for most polymorphisms
      * Highlight >20 diff potential AD genes
    - Show the class how cool this is
  + Neuronal nicotinic acetylcholine receptor beta2 subunit and transferrin show most consistent risk effects (after of course APOE)
  + So many other possibilities 🡪use alzgene.org to show that

Epigenetics in AD

* Histone acetylation and DNA methylation implicated in etiology of AD
  + Amyloid plaques formed by deposition of Abeta peptides
  + Abeta peptides formed by cleavage of APP by beta and gama secretase
  + This cleavage also generates an APP intracellular domain which can interact with the histone acetyltransferase TIP60 and coact as a transcriptional activator
  + AD associated with increase in histone acetylation
* Hypomethylation of promoter region of PSEN1🡪 incrase presenilin expression and enhanced Abeta formation

There’s tons more but this isn’t a genetics paper so ignore it

# Adlard, P. et al. (2014). A review of β-amyloid neuroimaging in Alzheimer’s disease. *Frontiers in Neuroscience, 8*(327).

Figure 2

* A)
  + 1. PET scan of Axial view of human AD patient tagged with PIB (which images beta amyloid plaques)
  + 2-4. PET scans of coronal views of diff transgenic mouse models
* B) MRI scans of an APP/PS1 AD transgenic mouse brain (24 months)
  + A&D: different ways to capture images on an MRI. Different pulse sequences
  + G: DAB enhanced iron staining
    - Possible iron accumulation in AD plaques
  + J: thioflavine S amyloid staining
  + M: anti-Abeta peptide immunohistochemistry

Drugs in the works (alz.org)

Solanezumab (alzforum.org)

* Humanized monoclonal Immunoglobulin G 1 (IgG1) antibody
* Directed at the soluble monomeric Abeta peptide (not fibrillar Abeta)
* Still in the works. Questionable whether it’s actually effective

MK-8931 (verubecestat)

* Disrupts Beta-secreatase (BACE) which is the enzyme that cuts APP and makes it possible for Abeta to form
* Still in progress. May be working

AADvac1

* Vaccine that stimulates body’s immune system to attack abnormal form of tau protein that destabilizes structure of neurons

CSP-1103

* Microglial modulator aimed at reducing inflammation in the brain

Airoldi, C. et al. (2011), Aβ Monomers, Oligomers and Fibrils: Structural Features. *Current Bioactive Compounds, 7*, 202-217.

* Accumulation of misfolded amyloid β peptides in the form of oligomers and fibrils in brain🡪AD
* Monomers tend to aggregate and form Aβ oligomers which eventually produce A β fibrils
* Β-sheet formation by A β promoted at low pH
  + AD brain has low pH maybe because of A β deposits

Klein, W. L. (n.d.). Cytotoxic Intermediates in the Fibrillation Pathway: Aβ Oligomers in Alzheimer’s Disease as a Case Study. *Protein Misfolding, Aggregation, and Conformational Diseases Protein Reviews,* 60-81

* Abeta 42 form is insoluble and likely the bad one that causes AD
* Assumed that fibrillar state required for neurotoxicity
* Oligomer structure actually probably the toxic structure (stable in that structure, not converting to fibrils)
  + Exposure of hippocampal slices to fibril-free oligomer preparations completely inhibits LTP (Lambert et al., 1998; Wang et al., 2002)
    - Confirmed in vivo too
  + Beta-Amyloid Derived Diffusible Ligands with a dementing activity (ADDLs): globular Abeta oligomers that inhibit LTP

Let’s talk about Oligomers

* Oligomers might directly insert into membranes after partially unfolding
  + But theyre super water soluble and SDS stable (hydrophobic domains hidden within structure)🡪prob don’t actually insert into plasma membrane lipids
* Deff bind nonrandomly (like totally bind to hippocampal cells)
* Specifically target synapses
* Three hypotheses as to what happens in the synapses after oligomers attach:
  + Oligomers generate ion flux via transmembrane pores
  + Oligomesr could generate synaptically localized oxidative damage
  + Binding to specific toxin receptors could lead indirectly to a downstream impact on signaling pathways