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Molecular Evolution of APP Gene in Alzheimer's Disease

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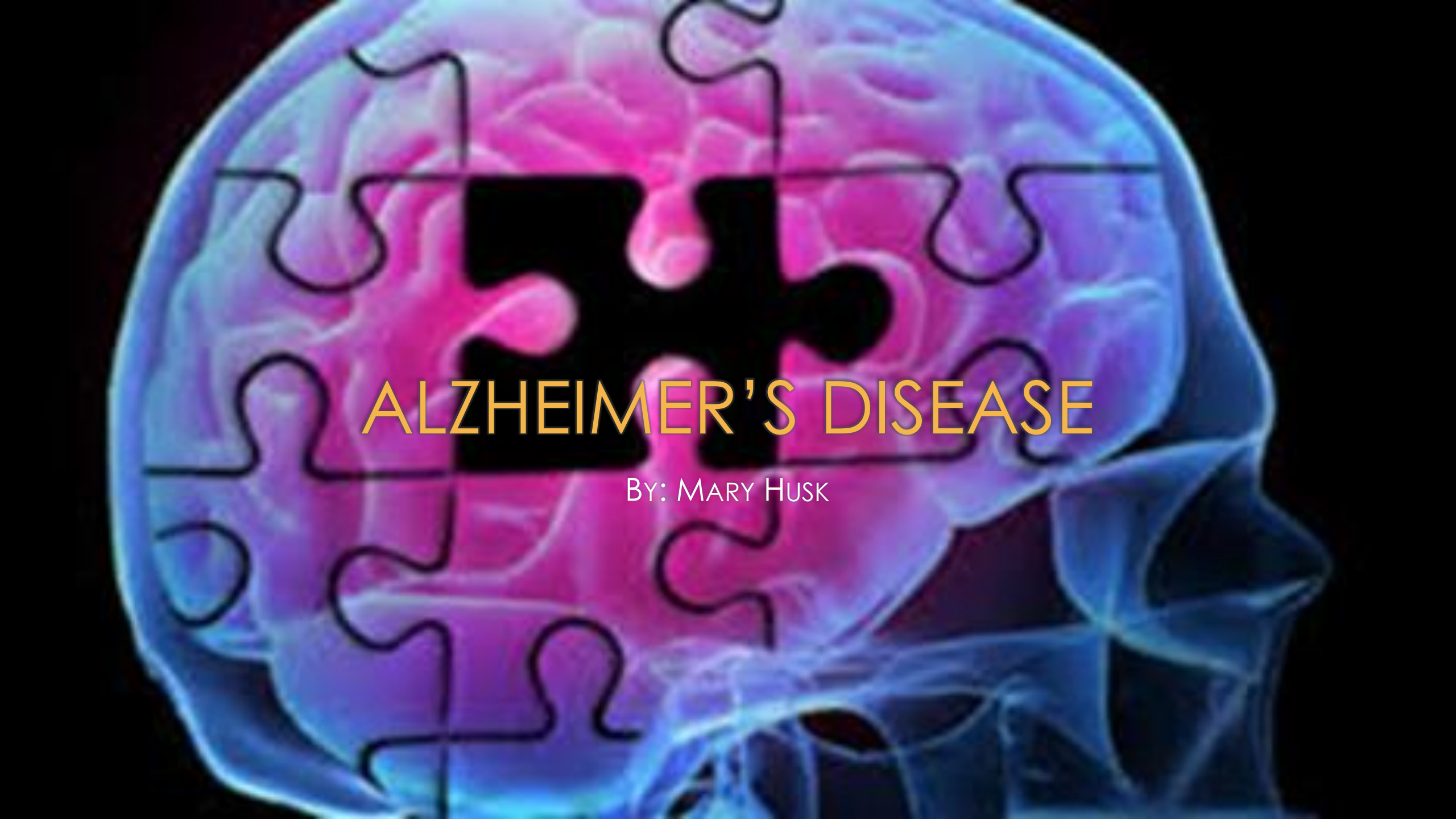


ALZHEIMER'S DISEASE

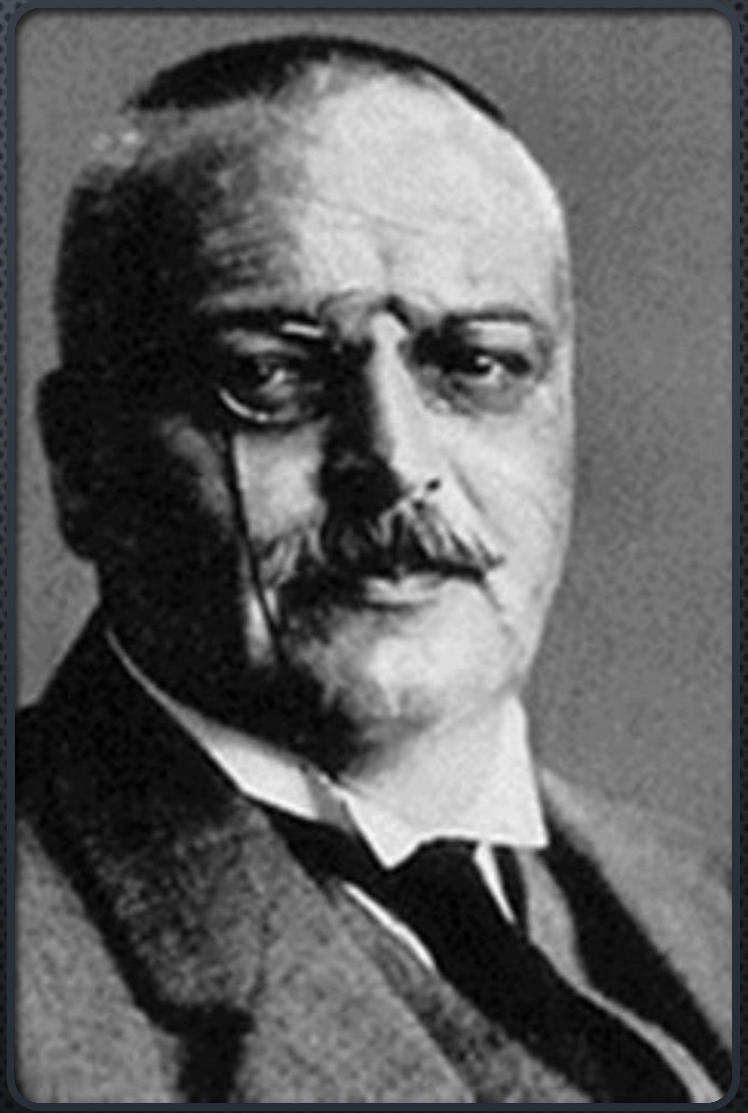
By: Mary Husk

Background

- Alzheimer's Disease:
  - degenerative brain disease of unknown cause
  - Progressive memory loss, impaired thinking, disorientation, changes in mood and personality
- Became generally accepted as most common basis for senile dementia in 1960's (Blessed, Tomlinson, and Roth)
- Found on chromosomes 21, 14, and 1
- Major leading cause of dementia in elderly

Alois Alzheimer

- Discovered Alzheimer's disease
- a German psychiatrist and neuropathologist
- 1901: met Auguste Deter; 51 year old female
- 1906: Deter died; Alzheimer had brain and records sent to him in Munich
  - Autopsy revealed shrinking of cortex and presence of neurofibrillary tangles and neuritic plaques
  - Diagnosed as senile dementia (later known as Alzheimer's disease)

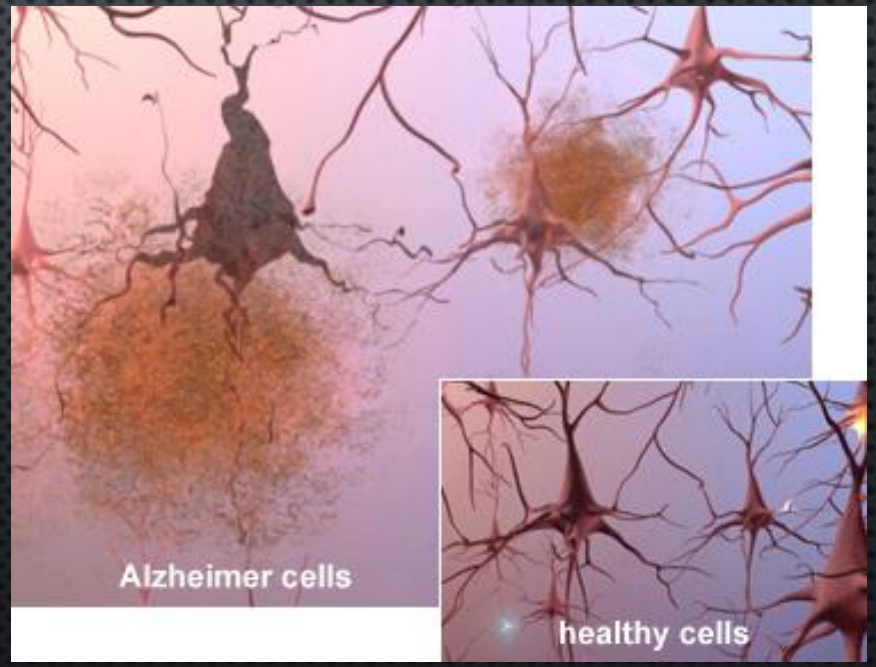


Down Syndrome to Alzheimer's Disease

- A strong homology between the amyloid b protein peptides from DS and AD brains was first indication of common genetic mechanism
  - Both found on chromosome 21
- Patients with DS inevitably develop characteristic Alzheimer's disease
- People with Downs syndrome have an extra copy of chromosome 21 which duplicates the APP gene

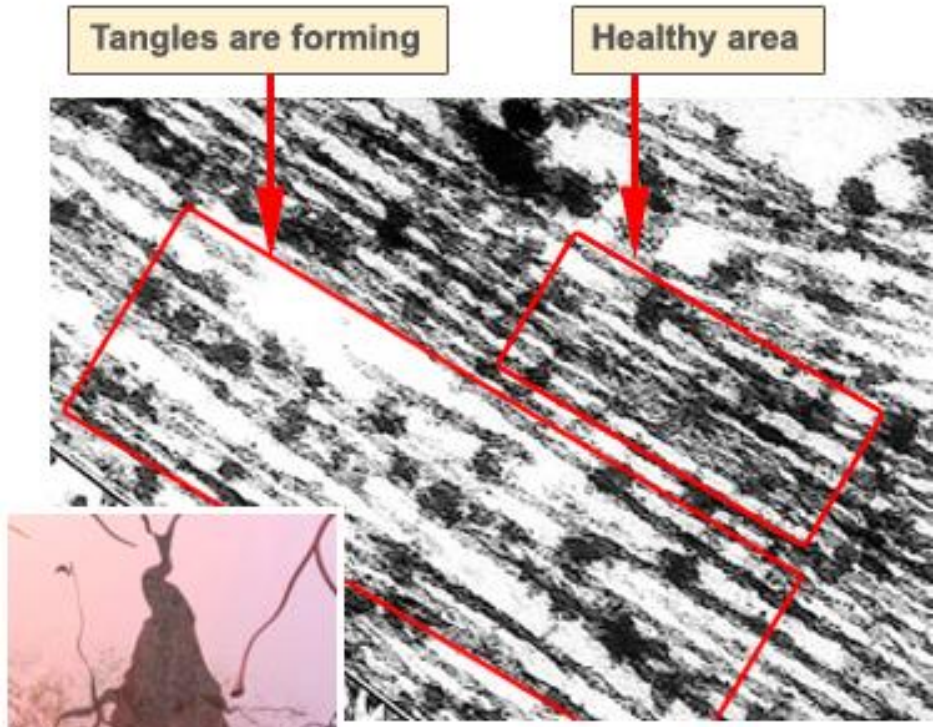
PLAQUES

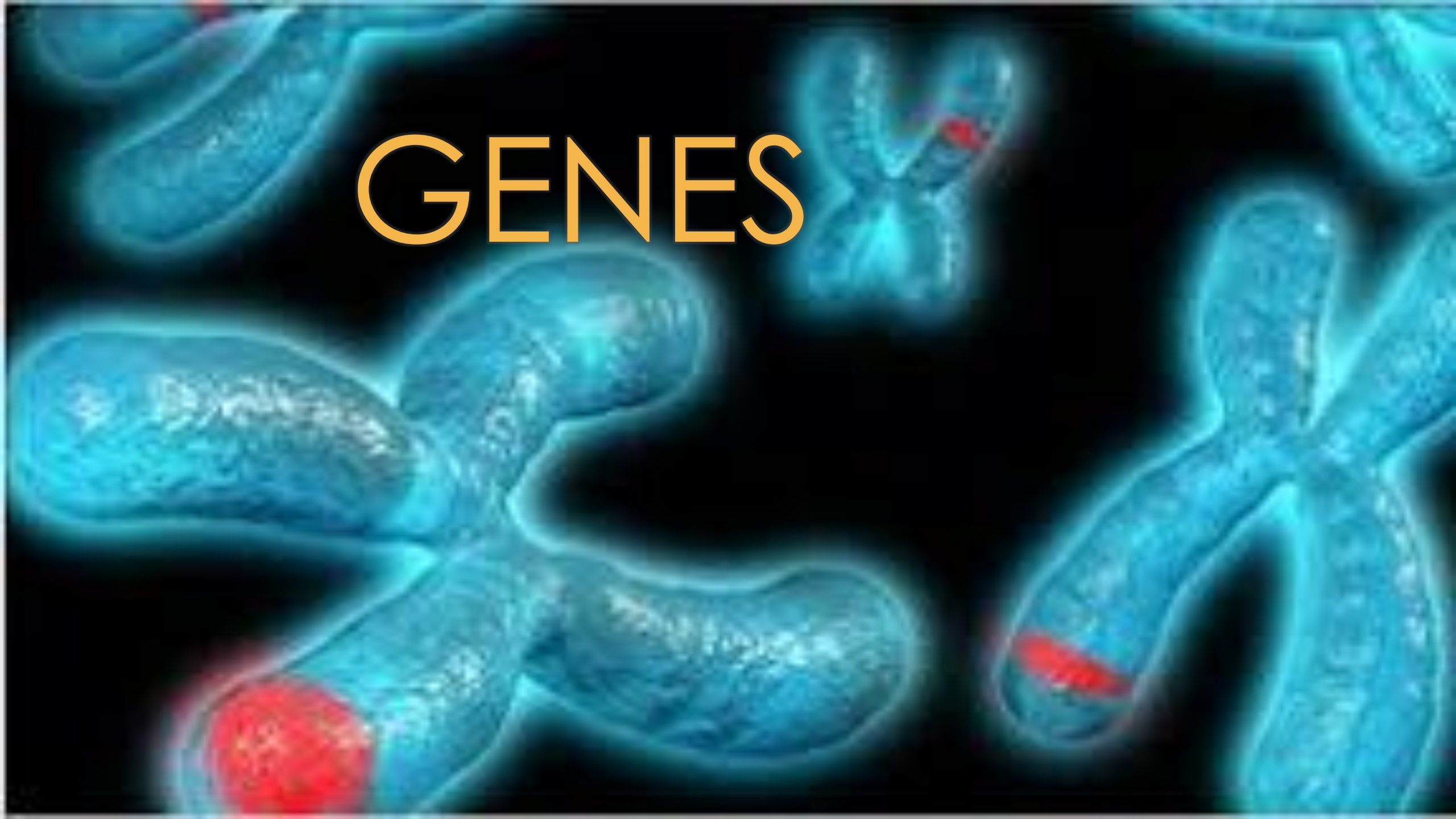
- Plaques occur when pieces of beta amyloid clump together
- Individuals with Alzheimer's disease develop plaques at an increased rate
- Usually start in areas of the brain dealing with learning



TANGLES

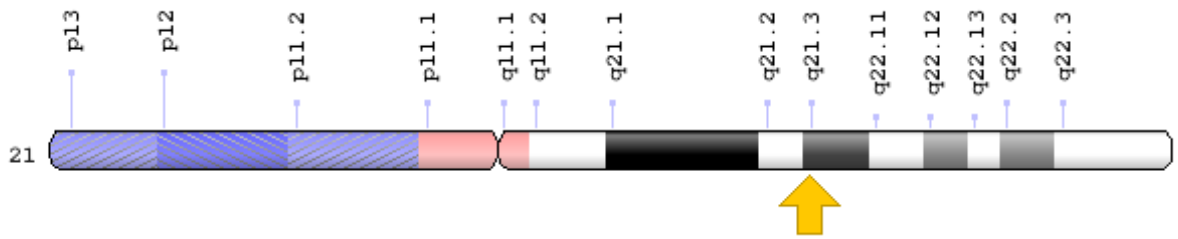
- A PROTEIN CALLED TAU HELPS KEEP THE TRACKS STRAIGHT
- TAU COLLAPSES INTO TWISTED STRANDS CALLED TANGLES
- THEY FALL APART AND DISENTIGRATE




GENES

APP GENE

- Located on chromosome 21
- Provides instructions for making protein called amyloid precursor protein
- Found in many tissues like brain and spinal cord
- APP is cut by enzymes to create smaller fragments, some of which are released outside of the cell

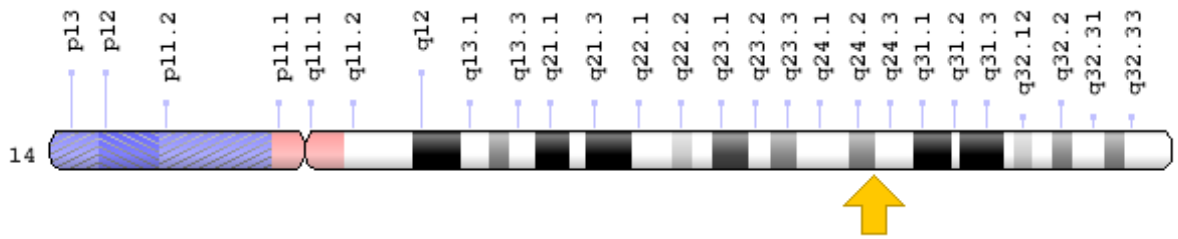


APP GENE MUTATION

- Accounts for less than 10% of early onset cases
- Mutation in APP gene at codons 717 and 716 (new)
  - Replaces amino acid valine with amino acid isoleucine at 717
- Double mutation at codons 670 and 671
- Common feature of mutations is to increase the concentration of Aβ ending at Aβ42
- Overexpression of APP inhibits cell proliferation; may promote AD pathogenesis

PSEN1

- Located on chromosome 14
- Makes presenilin 1 protein
- Subunit of gamma secretase
- Known as proteolytic subunit

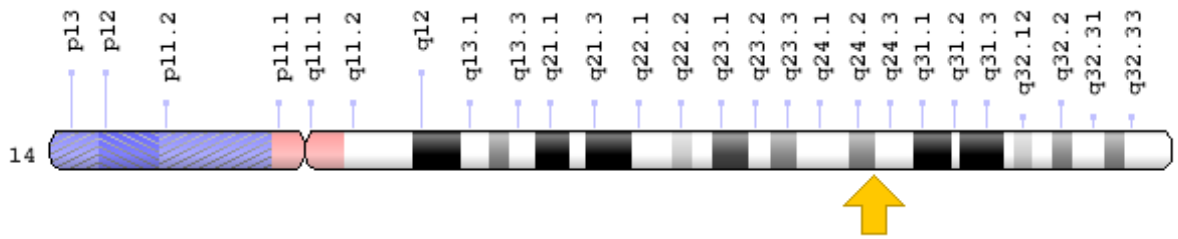


PSEN 1 MUTATION

- More then 150 mutations
- Accounts for up to 70% of early onset cases
- Results in production of abnormal PSEN1 which interferes with the function of gamma secretase complex
- Leads to longer, toxic version of amyloid beta peptide

PSEN2

- Located on chromosome 1
- Best known for its role in processing APP
- Makes protein presenilin 2
- Helps process proteins that transmit chemical signals from the cell membrane into the nucleus
  - Activates genes that are important for cell growth and maturation



PSEN 2 MUTATION

- At least 11 mutations
- Accounts for less than 5% of early onset cases
- Changes the amino acid asparagine to amino acid isoleucine at position 141
- Changes amino acid methionine to amino acid valine at position 239
- Disrupts processing of APP leading to build up of amyloid precursor protein

PHYTOTHERAPY

- Garden Angelica (*Angelica archgangelica*) and Catterall (*Treculia obovoidea*)
  - More than 80% inhibition of AchE
- Tumeric (*Curcuma longa*)
  - regulates multiple targets
  - Safe for humans
  - Targets growth factors
  - Considerable affinity for Ab 1-42 fibrils

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