Molecular Evolution of APP Gene in Alzheimer's Disease

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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)
A strong homology between the amyloid β 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 Down’s 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
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 Ab ending at Ab42
- 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 pre-senilin 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 archangelica*) and Catterall (*Treculia obovoidea*)
  - More than 80% inhibition of AchE

- **Turmeric** (*Curcuma longa*)
  - Regulates multiple targets
  - Safe for humans
  - Targets growth factors
  - Considerable affinity for Ab 1-42 fibrils
REFERENCES

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• Wu, Y., & Zhang, S., & Xu, Q., & Zou, H., & Zhou, W., & Cai, F., & Li, T., & Song, W. Regulation of global gene expression and cell proliferation by APP. Scientific Reports. DOI: 10.1038/srep22460. HTTPS://WWW.NCBI.NLM.NIH.GOV/PUBMED/26936520


