DEGENERATIVE DISORDERS

INHERITED METABOLIC DISORDERS

- *Tay Sachs*
  > AR, HEXA @ chr15

NOT METABOLIC

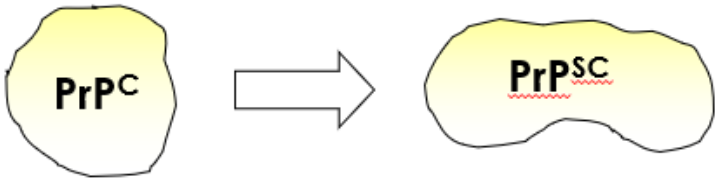
- *Variant Cruietzfeldt-Jackob (BSE)*
  > prions
- *Parkinsons's Disease*
  > AD (chr4)-SNCA mutation
  > AR (chr6)- Parkin mutation
  > sporadic
- *Huntington's Disease*
  > AD mutation-Huntingtin (htt)
- *Alzheimer's Disease*
  > idiopathic
  > Traumatic brain injury
  > APP @ chr21
  > Presinilin @ chr1&14
  >ApoE4
- *Multiple Sclerosis*
  > autoimmune

TAY SACH'S DISEASE

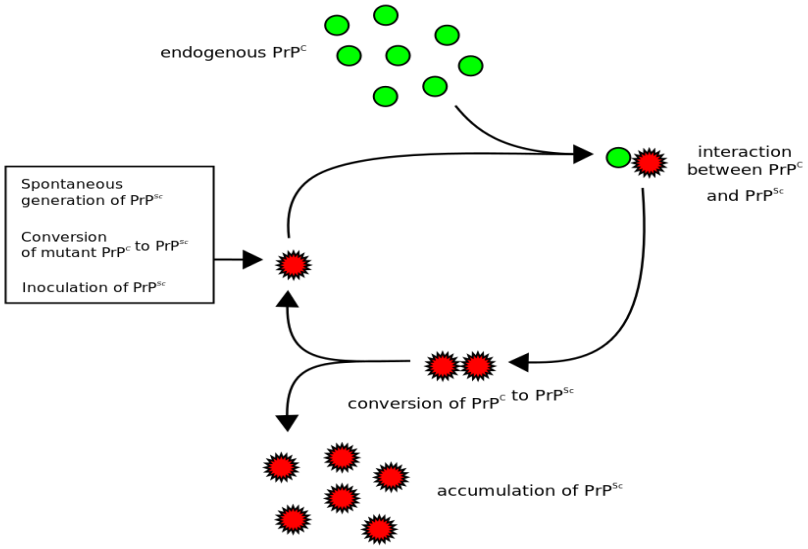
- Causes brain to **swell** and **damage itself** against the inside of the skull and dura mater
- Metabolic "storage" disease; a type of **sphingolipidosis**.
  - **1 or more enzymes are missing**, waste products cannot be destroyed by lysosomes.
  - Lysosomes get larger, cells get larger, **brain swells**
- **Symptoms**: begin around 4 months
  - Exaggerated startle response
  - Listlessness
  - Irritability
  - Spasticity
  - Seizures
  - Dementia
  - death
- **inherited: AR ; a genetic mutation in the *HEXA* genes on chromosome 15**.
  - Results in problems with an enzyme called **beta-hexosaminidase A** which results in the buildup of the molecule **GM2 ganglioside** within cells, leading to toxicity.
- **Diagnosis**: by measuring the blood hexosaminidase A level or genetic testing.

CREUTZFELDT JAKOB DISEASE

- **Transmissible Spongiform Encephalopathies (TSE)**
  - Contagious brain disease whose degenerative process gives the brain a **sponge-like appearance**.
    - **Bovine Spongiform Encephalopathy (BSE)**
    - **Creutzfeldt-Jakob Disease (CJD)**
    - **Fatal familial insomnia**
- **Prions** – protein that can exist in **two** forms that differ only in their **3-D shape**.
  - Normal prion protein (synaptic protein)→Development and learning and memory
  - Accumulation of misfolded prion protein is responsible for TSE.
  - **PrP^{c} (normal) and PrP^{sc} (prion infected)**



  - PrP^{SC} -**protease-resistant** (prion protein also **heat-resistant**)
  - Abnormal protein taken up into neuron by **retrograde transport**
- **Stanley Prusiner (discovered 1986), Nobel Prize (1997)**
- Encephalopathy gives the brain a **'swiss cheese'-like appearance**



- **Symptoms:**
  - Rapidly progressive dementia & memory loss
  - personality changes & hallucinations
  - **Physical problems** such as speech impairment, jerky movements, balance and coordination dysfunction (ataxia), changes in gait, rigid posture, and seizures
  - **Death**
- **Long incubation periods** (4-40 years)
- 50,000 BSE-infected cattle are estimated to have entered the human food chain before its recognition in 1986

PARKINSON'S DISEASE

- A disease caused by **degeneration of the nigrostriatal system** – the **dopamine**-secreting neurons of the substantia nigra (send axons to BG)
- **Lewy Body** – abnormal circular structures with a dense core consisting of **α-synuclein** protein (presynaptic protein); found in dopaminergic nigrostriatal neurons of Parkinson's patients.
- 1% of people over 65
- **Symptoms:**
  - Muscular rigidity
  - Slowness of movement
  - Resting tremor
  - Postural instability
  - Difficulties with handwriting or making facial expressions
- **Causes**:

Mutation on chromosome 4

- Gene that codes for **alpha-synuclein (SNCA)** – located in presynaptic terminal of DA cells
- Toxic **gain of function (production of a protein w/ toxic effects)**
- **Dominant**
- Abnormal SNCA becomes misfolded, forms aggregations - make up **lewy bodies**

Sporadic

- ~95% of cases
- **Causes**:
  - Toxins present in environment
    - Insecticides
  - Faulty metabolism
  - Unidentified infectious disorder
- Toxic chemicals inhibit mitochondrial functions which leads to the aggregation of misfolded **alpha-synuclein**, in DA neurons, kills the cell

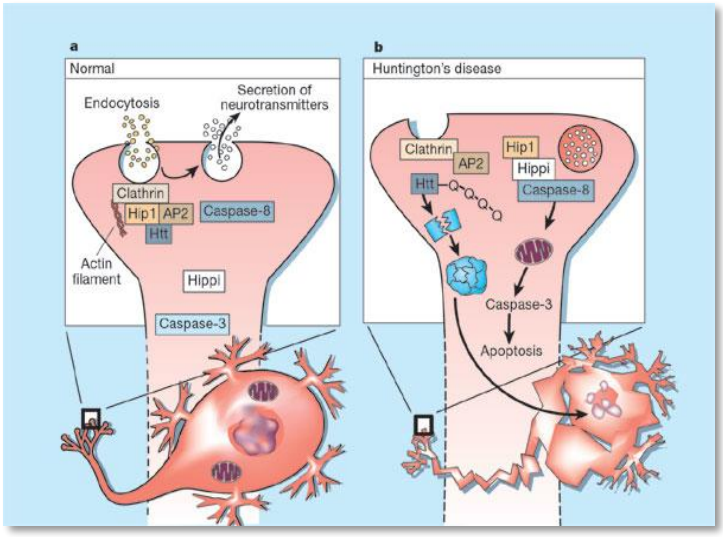
Mutation on chromosome 6- produces an abnormal Parkin protein

- **Recessive disorder**
- **Loss of function**
- Normal Parkin plays a role in **Trafficking defective/misfolded proteins to proteasomes for destruction (recycling)**
- Defective Parkin:
  - Allows abnormally high levels of defective proteins to accumulate in dopaminergic neurons
  - Fails to ubiquinate abnormal proteins
  - Ubiquitination – targets the abnormal proteins for destruction by the proteasomes
  - Kills the cell

- **Treatment:**
  - **Stimulation of subthalamus** (deep brain stimulation)
    - Implant electrodes in subthalamic nucleus and attach a device that permits PD patient to electrically stimulate the brain.
    - Fewer side effects (compared to surgery)
  - **Gene Therapy**: Genetically modified virus into the subthalamic nucleus of PD patients
    - Delivered a gene for **GAD** (enzyme that makes GABA)
    - Production of GAD turned some of the glutamate neurons into inhibitory, GABA neurons
    - **Activity of GPi decreased, activity of supplementary motor area increased, symptoms improved.**

HUNTINGTON'S DISEASE

- **Aka Huntington's Chorea**
- Degeneration of **caudate nucleus** and **putamen**
- Uncontrollable movements, jerky limb movements
- Progressive, cognitive and emotional changes
- **Death (10-15 years)**
- **Cause**:
    - **AD mutation** in either of an individual's two copies of a gene called **Huntingtin**, which means any child of an affected person typically has a 50% chance of inheriting the disease.
    - **Normal Huntingtin (htt)**
        - Forms complex with clatherin, Hip1 and AP2
        - Involved in endocytosis and NT release
        - facilitates the production and transport of **brain derived neurotropic factor** (BDNF)
            - **BDNF**: neurotropic factor critical for the survival of neurons
            - produced in cortex and transported to basal ganglia
    - **Huntington's Disease**
        - Htt protein has abnormally long glutamine tract
        - May lead to abnormal endocytosis and secretion of NTs
        - Striatal death by **apoptosis** - Caspase-3
        - Interferes w/ BDNF-2 ways:
            - **Inhibits** the expression of the BDNF gene
            - Interferes with the **transport** of BDNF from the cerebral cortex to the BG
- **Epidemiology**:
    - The disease can affect both men and women
    - Physical symptoms of Huntington's disease can begin at any age from infancy to old age, but usually begin between 35 and 44 years of age.
    - About 6% of cases start before the age of 21 years with an **akinetic-rigid syndrome**; they progress faster and vary slightly.
- **Neurodegeneration in the putamen**
    - First: Inhibitory neurons (GABAergic)
    - Removes inhibitory control of motor areas in cortex (***hyperkinetic***)
    - As the disease progresses, neural degeneration occurs in many other regions
- **Inclusion bodies**:
    - Role is unclear in Huntington's Disease
    - Tissue infected with abnormal htt produces inclusion bodies
    - Neurons with inclusion bodies had lower levels of abnormal htt elsewhere in the cell, cell lived longer than cells without inclusion bodies
    - Neuroprotective?



ALZHEIMER'S DISEASE

- Degenerative brain disorder of **unknown origin**; causes **progressive memory loss, motor deficits, and death**.
- **Severe degeneration** of the:
    1. Hippocampus
    2. entorhinal cortex
    3. neocortex (prefrontal and temporal association areas)
    4. Locus coeruleus
    5. Raphe nucleus
- **Signs:**
    1. Memory loss that disrupts daily life
    2. Challenges in planning or solving problems
    3. Difficulty completing familiar tasks at home, at work or at leisure
    4. Confusion with time or place
    5. Trouble understanding visual images and spatial relationships
    6. New problems with words in speaking or writing
    7. Misplacing things and losing the ability to retrace steps
    8. Decreased or poor judgment
    9. Withdrawal from work or social activities
    10. Changes in mood and personality

Amyloid Plaque:

= Extracellular deposit containing a dense core of defective **β-amyloid** (Aβ) protein surrounded by:

- degenerating axons and dendrites
- activated microglia
- reactive astrocytes.

*** Gene**:

- encodes the production of the **β-amyloid precursor protein** (APP; ~700 a.a. long)
- APP is then cut in 2 places by **secretases** to produce **β-amyloid protein**
    - **β-secretase**
    - **γ-secretase**
- Results in **Aβ-40** or **Aβ-42**
- Normal brain **~95% of Aβ is short**
- **AD brain Aβ-42 is as high as 40%**
    - Folds improperly and form aggregates
    - System cannot ubiquinate the high amounts of long Aβ proteins

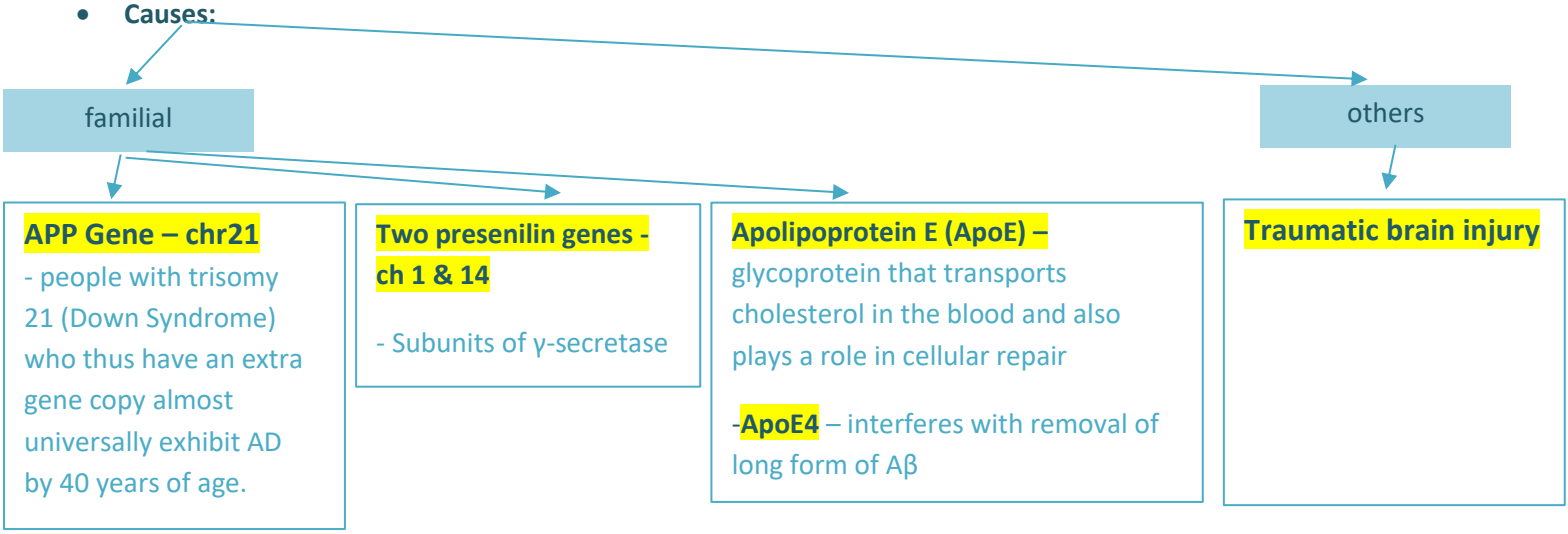
- Aβ inside cell (not plaques) is the cause of neural degeneration
- Aggregated forms of amyloid (Aβ oligomers) interact with **microglia**, causing an ***inflammatory response*** that triggers the release of toxic cytokines
- trigger XS release of **glutamate by glial cells**, causes **excitotoxicity** (increased inflow of Ca2+ through neural NMDA receptors)
- Cause synaptic dysfunction and suppress the formation of **LTP**

Neurofibrillary Tangles:

= a dying neuron containing intracellular accumulations of abnormally phosphorylated **tau-protein** filaments that formerly served as the cell's internal skeleton.

- **The tau hypothesis** states that excessive or abnormal phosphorylation of tau results in the transformation of normal adult tau into **PHF-tau** (paired helical filament) & **NFTs** (neurofibrillary tangles).
- **Tau protein** (**τ proteins**, after the Greek letter) are:
    - a ***highly soluble*** **microtubule-associated protein (MAP)**
    - proteins that stabilize **microtubules**.
    - **abundant** in neurons of the CNS and are less common elsewhere, but are also expressed at **very low levels** in CNS astrocytes and oligodendrocytes.
    - Pathologies and dementias of the nervous system such as **Alzheimer's disease** and **Parkinson's disease** are associated with tau proteins that have become defective and no longer stabilize microtubules properly.
    - are the product of ***alternative splicing*** from a single gene that in humans is designated ***MAPT*** (microtubule-associated protein tau)
        - located on chromosome **17q21**
    - Transport is disrupted, cell dies.

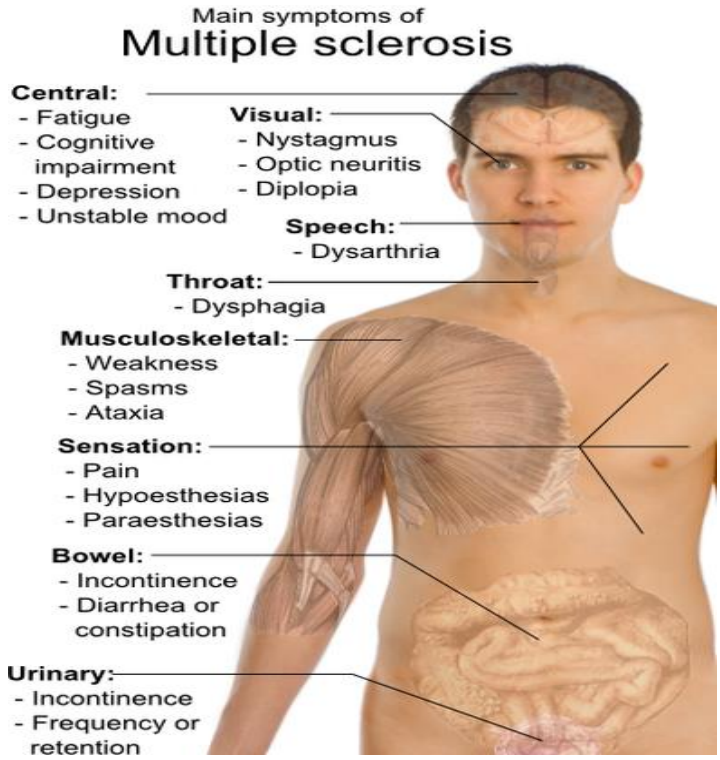
- **Epidemiology**:
    - 10% of the population over 65 years old and 50% of the population over 85
    - Alzheimer's is the sixth leading cause of death in the United States.
- **Causes:**



- **Treatment:**
    - Decline in ACh levels
    - **Cholingeric agonists** (AChE inhibitors)
    - **NMDA receptor antagonist** (memantine)
    - **Immunotherapeutic** approach
        - **Amyloid vaccine** to reduce plaque deposits and improve performance on memory tasks in a transgenic mouse model
            - Mixed results
            - Dangerous side effects

MULTIPLE SCLEROSIS

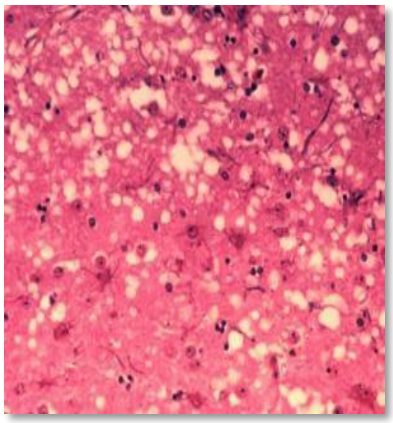
- **Autoimmune demyelinating disease**.
    - The immune system attacks the protective sheath (myelin) that covers nerve fibers and causes communication problems between your brain and the rest of your body
- **Sclerotic plaques**
- **Myelin damage:**
    - myelin in the CNS becomes detached and eventually destroyed.
    - This creates a lesion that may cause **numbness, pain or tingling** in parts of the body.
- **Epidemiology**
    - More women than men
    - Late 20s-30s
    - Childhood in colder climates
    - **Canada** has amongst the highest MS incidence estimates in the world; 55,000 – 75,000



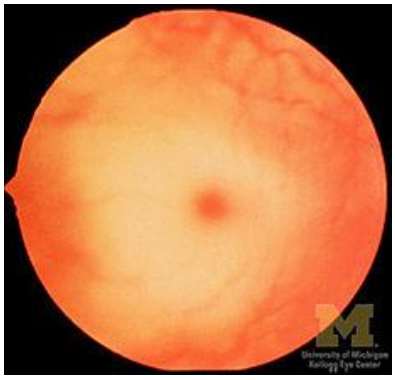
- **Treatment:**
    - **Interferon β**
        - Modulates the responsiveness of the immune system
        - Treatment slows the progression and severity of the attacks
    - **Glaterimer acetate (copaxone)**
        - Peptides composed of random sequences of **glutamate**, **alanine** and **lysine** **(glu-ala-lys)**
        - May stimulate anti-inflammatory responses

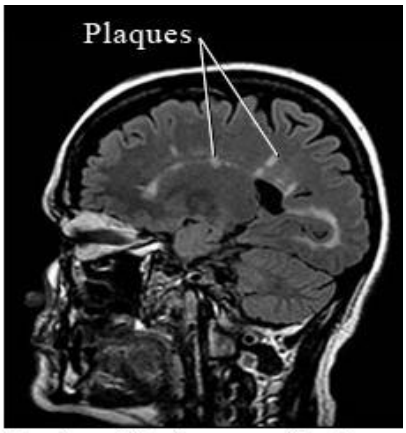
Clinical/histopathology Pictures in the lecture:

⇓Creutzfeldt-Jakob Dz

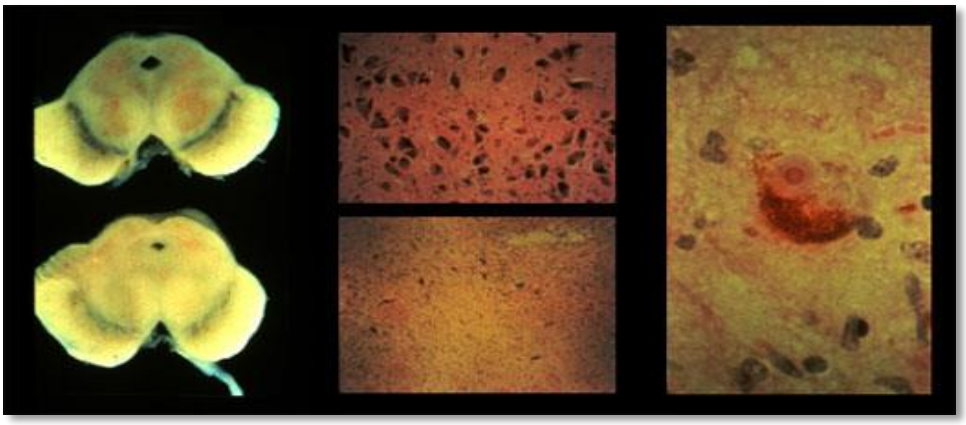


⇓Tay-sachs



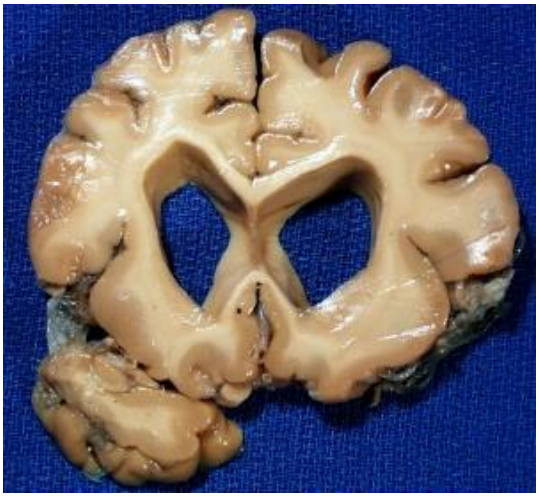


Brain with damage (lesions or plaques) caused by MS

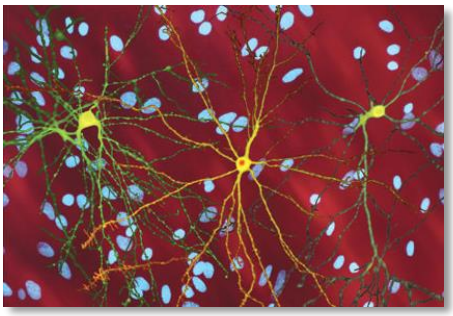


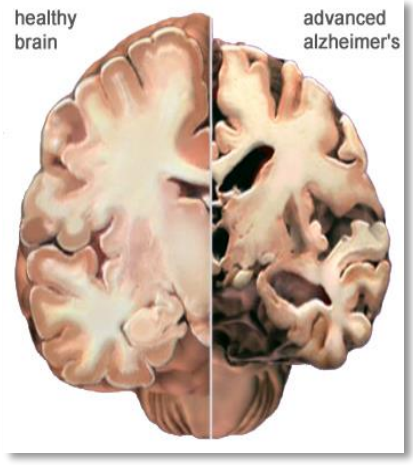
<-Parkinson's Dz

– Lewy Body



<-Huntington's Dz⇓





<-Alzheimer's⇓