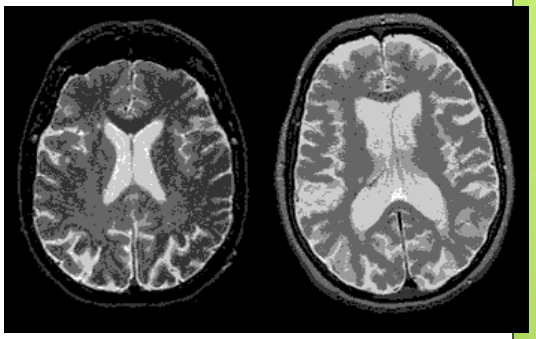
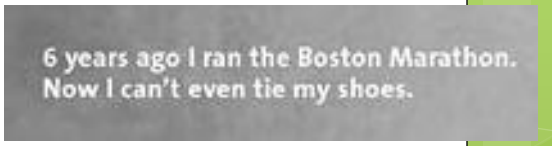
Huntington's Disease:

-Nancy Huang

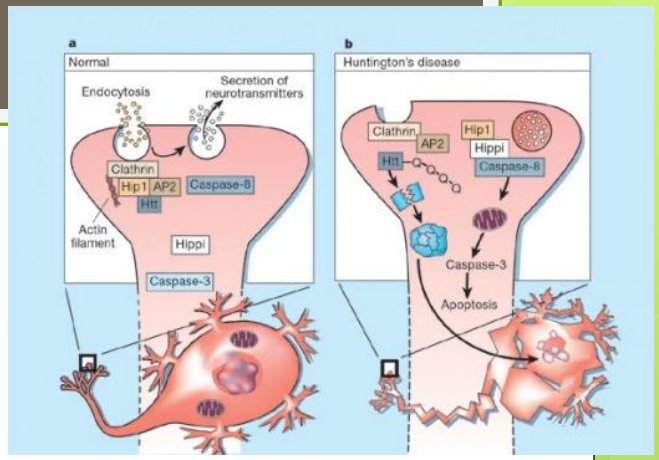
Physiology



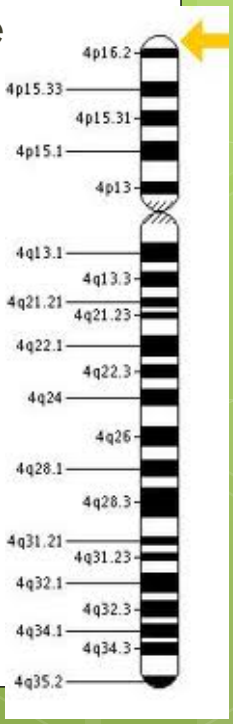
- Normally late-onset(30's-40's)
  - Can be symptomatic at adolescence
- "normal" stage=pre-symptomatic
- Motor and cognitive impairment
  - Chorea, muscle weakness, incoordination
  - Twitches, wide gait
  - Slurring, dysphagia, slowed reflexes
  - Depression, paranoia, hallucinations
  - Mental retardation, seizures, death
  - Loss of brain tissue
- incorrectly diagnosed as Parkinson's, schizophrenia, Neuroacanthocytosis, Huntington's disease-like 2

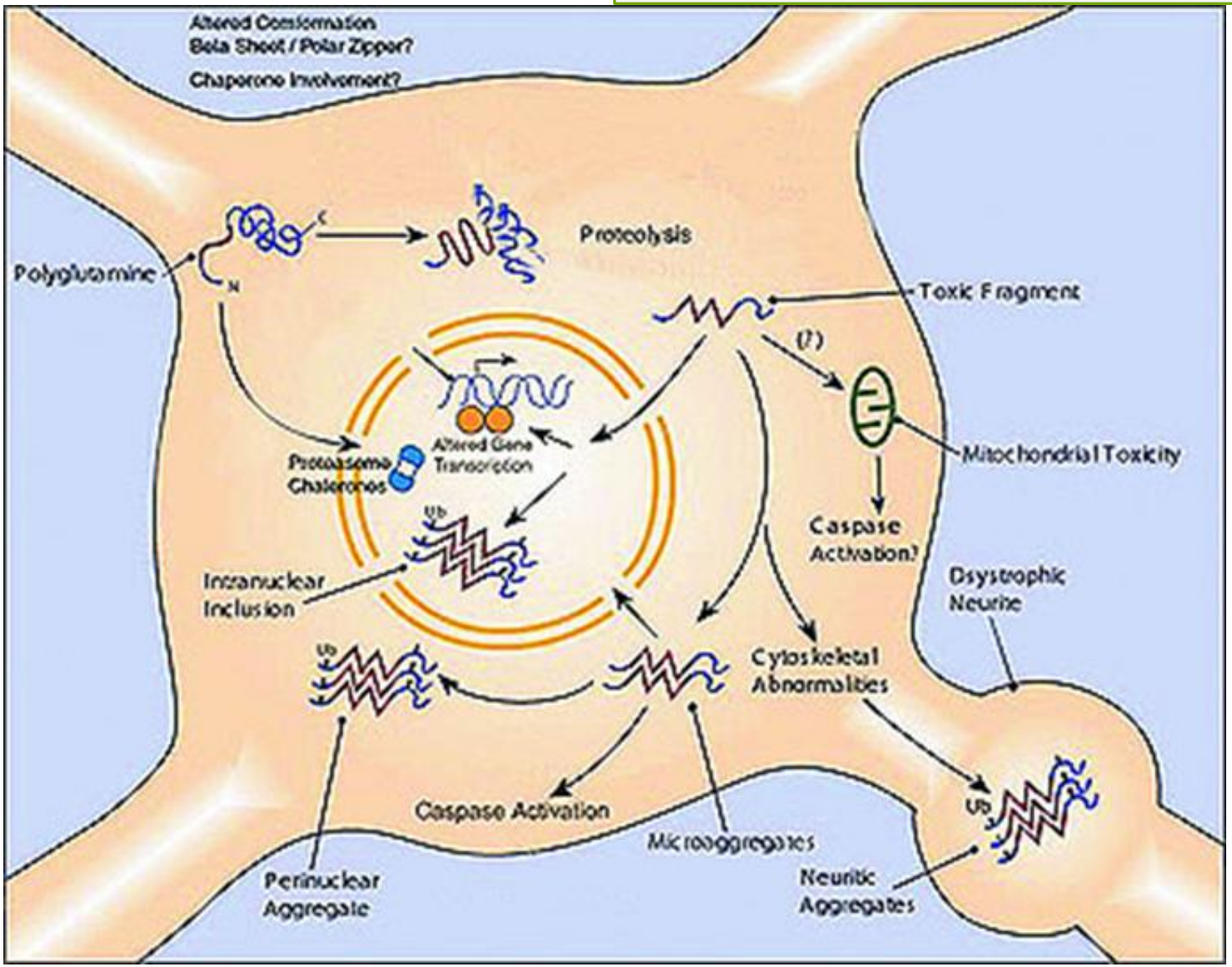


Molecular Cause



- Autosomal dominant(2 alleles=more severe)
- Expansion of CAG on chromosome 4p16.2
  - Normally 20 codons, but HD has 40+
  - CAG->glutamine->polyglutamine/polyQ strands
- misfolded Hungtingtin(Htt)->aggregates->nuclear inclusion
- Normally Htt regulates vesicles, transcription, apoptosis
- Mutated Htt will bind with smaller proteins causing them to lose function
- Retains binding sites, but NES is messed up
- Affects the Ubiquitin-Proteasome System
  - mHtt can't be degraded->bundling/clumping->neuron degeneration
- Toxic gain of function: cleavage caused by caspases
- Limits transcription
- Antibody 3B5H0: glows in contact with Htt-producing neuron about to die




Altered Conformation
Beta Sheet / Polar Zipper?
Chaperone Involvement?
Proteolysis
Polyglutamine
Toxic Fragment
Mitochondrial Toxicity
Caspase Activation?
Dystrophic Neurite
Altered Gene Transcription
Proteasome Chaperones
Intranuclear Inclusion
Cytoskeletal Abnormalities
Caspase Activation
Microaggregates
Perinuclear Aggregate
Neuritic Aggregates
Ub

Current Treatments

- No cure->available symptom treatments
- Therapies: physiotherapy, speech, occupational
  - Require aide of a companion
- Drug:
  - Tetrabenzine(TBZ): prevents VMATs from storing dopamine and inhibits dopamine receptors
  - Pridopidine/Hentexil: adjusts the levels of dopamine in the cortex and striatum(low: glutamate, high: bind to receptors)
  - Prozac: increase levels of serotonin- reduce agitation
- Gene therapy: gene silencing & RNAi

Proposed Cure

- Study the HEAT sites, UPS, and neuron insensitivity
- Start treatment for asymptomatic patients
- Allele specific silencing for the Huntington gene
- double stranded RNA packed in adeno-avirus
- Long RNA strand diced into siRNA->forms a RISC

->cleaved and separated into single strands->targets mRNA in neuron->RNA fragments are formed and discarded as wastes

- Identify SNPs that only the Huntington gene contains and not the normal allele
- Viral vector based delivery system(need a lipid bilayer to get past immune system)

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