

**Huntington's Disease**

*Neuroscience 410  
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**Huntington's Disease**

- inherited neurodegenerative disorder
  - autosomal dominant
  - 100% penetrance
- age of onset: 35 - 45 yr
- juvenile variant
  - 5-10% of affected individuals

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**Huntington's Disease**

- motor, cognitive, and behavioural dysfunction
- inexorably progressive
  - death 15 - 20 yr after symptom onset

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**Huntington's Disease**

- prevalence
  - 10 / 100,000 population
- Movement Disorders Clinic
  - about 65 symptomatic patients

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**Chorea**

- irregular, unpredictable, purposeless, rapid movements that flow randomly from one body part to another
- Huntington's disease

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**Huntington's Disease  
Clinical Features - 1**

- motor dysfunction
  - chorea is usually the earliest sign
    - initially fingers, toes, face
    - progressive
  - motor impersistence
  - eye movement abnormalities
    - impaired initiation of saccades
    - slow saccades

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**Huntington's Disease**  
**Clinical Features - 2**

- motor dysfunction
  - dystonia and parkinsonism
  - progressive incoordination, unsteadiness, immobility, dysarthria, dysphagia
  - motor signs eventually appear in all

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**Huntington's Disease**  
**Clinical Features - 3**

- juvenile onset
  - rigidity, dystonia, bradykinesia, myoclonus
  - seizures
  - rapidly progressive dementia

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**Huntington's Disease**  
**Clinical Features - 4**

- cognitive impairment
  - executive function is thought to be selectively lost
  - cortical deficits absent (aphasia, agnosia, apraxia)

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**Huntington's Disease**  
**Clinical Features - 5**

- cognitive impairment
  - some degree of impairment is inevitable
  - occasionally minimal
  - rate of progression varies considerably

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**Huntington's Disease**  
**Clinical Features - 6**

- behavioural changes
  - gradual change in personality
  - affective disorders in 30-40%
  - schizophrenia and other psychoses in 10%
  - alcohol abuse; high suicide risk

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**Huntington's Disease**  
**Neurobiology - 1**

- pathology
  - striatal atrophy
  - neuronal loss and gliosis
    - most striking in, but not limited to striatum
    - diffuse cortical changes, primarily frontal
  - degree of pathology is related to the duration of symptomatic HD

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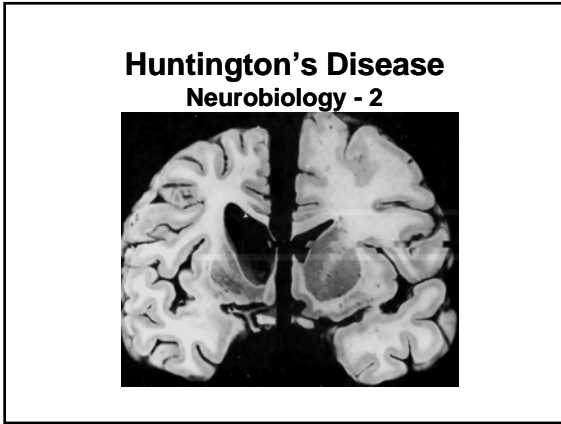
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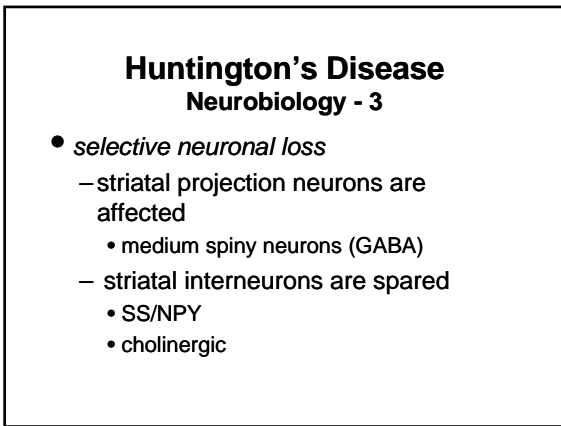
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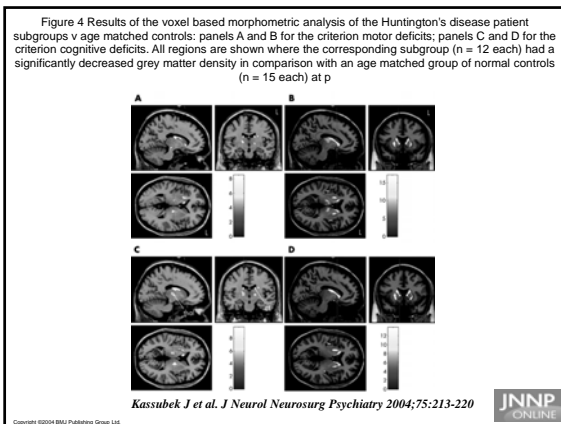
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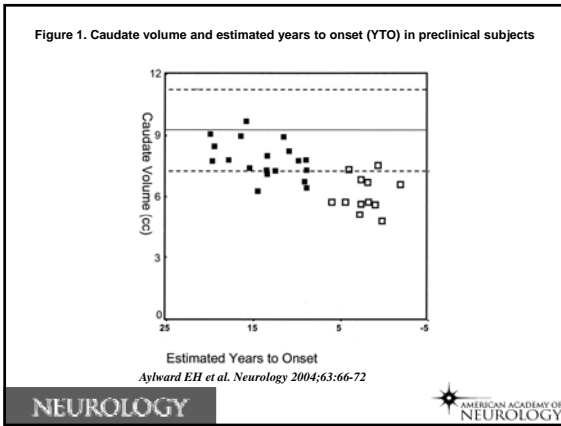
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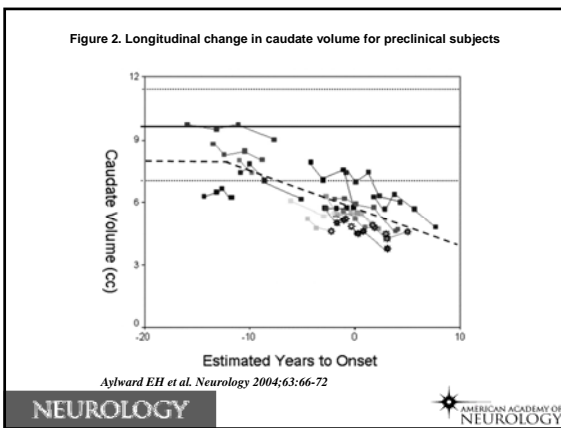
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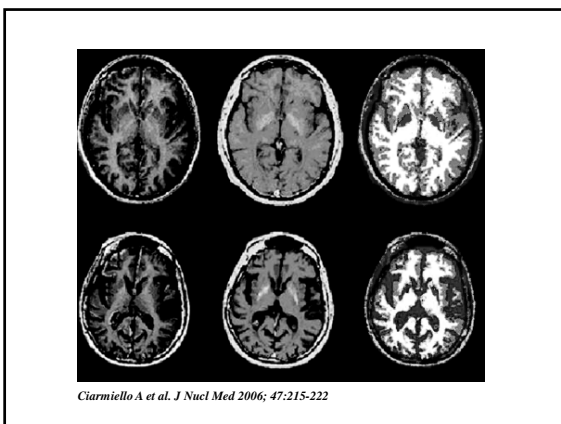
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### Huntington's Disease Genetics - 1

- autosomal dominant
- chromosome 4
- very low spontaneous mutation rate

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### Huntington's Disease Genetics - 2

|   |   |    |   |   |   |
|---|---|----|---|---|---|
| D | D | D  | D | D | D |
| 4 | 4 | 4  | 4 | 4 | 4 |
| 5 | 5 | 5  | 5 | 5 | 5 |
| 7 | 7 | 19 | 1 | 9 | 9 |
| 0 | 8 | 2  | 5 | 8 | 5 |
|   | 0 | 7  | 2 |   |   |

*Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. **Cell** 1993;72:971-983*

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### Human IT15 Gene

Normal

**(CAG)** <sub>5 - 35</sub>

Huntington's Disease

**(CAG)** <sub>40 - 240</sub>

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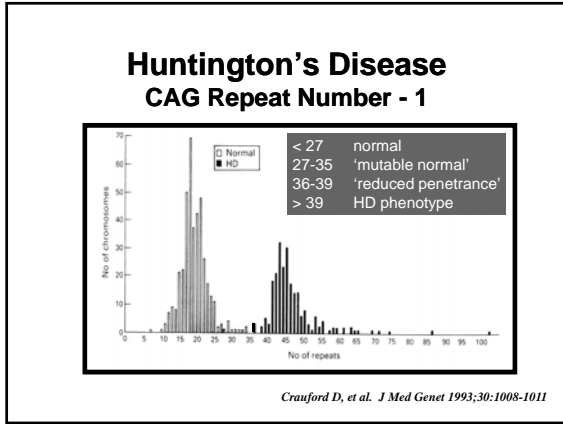
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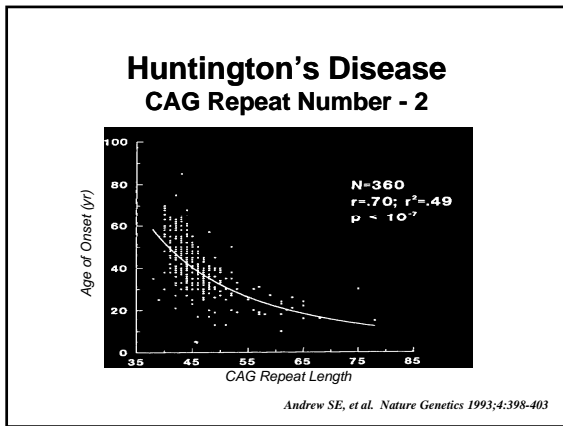
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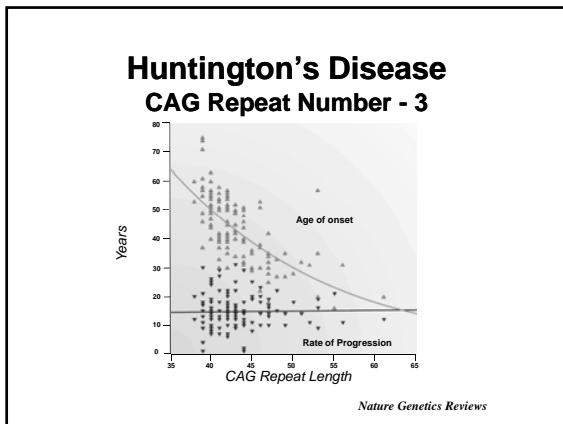
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**Huntington's Disease  
Diagnosis**

- CAG repeat analysis
  - determine the presence of the gene
- ***diagnosis of symptomatic HD is based on the clinical features***

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- supportive counselling is crucial before, during, and after DNA testing, regardless of whether or not the patient is symptomatic

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**IT15**

- universal expression in multiple tissues
- new class of protein important to neuronal function
  - *huntingtin*
  - 3144 amino acids, m.w. = 348 kDa
- no evidence of regional selectivity in brain
  - neurons and glia

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***huntingtin***

- transgenic mouse models
  - significantly reduced levels associated with aberrant brain development and perinatal lethality
  - normal levels, even of mutant huntingtin, is associated with normal brain development
- critical role in neurogenesis

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**Huntington's Disease  
Cellular Mechanisms**

- *huntingtin* - normally localized in cytoplasm
- *in HD* - neuronal intranuclear inclusions
  - huntingtin and ubiquitin
  - associated nuclear membrane changes
  - precedes phenotypic changes (transgenic mice)

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**Huntington's Disease  
Cellular Mechanisms**

- *translocation of mutant huntingtin from cytoplasm to nucleus may represent the dominant gain of function*

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**Huntington's Disease  
Pathophysiology**

- animal models
  - intrastriatal kainic acid
    - *McGeer EG, McGeer PL. Nature 1976;263:517-519*
    - *Coyle JT, Schwarcz R. Nature 1976;263:244-246*
  - intrastriatal quinolinic acid
    - *Beal F and others*

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**Huntington's Disease  
Pathophysiology**

- *excitotoxic hypothesis*
  - intrastriatal injection of excitotoxic amino acids mimics the characteristic pathology of HD
  - toxicity can be prevented by NMDA antagonists
  - **but** acute striatal lesion is unlike the slow insidious cell loss associated with neurodegenerative disease

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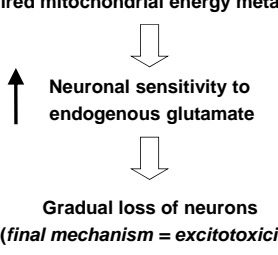
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**Huntington's Disease  
Weak Excitotoxic Hypothesis**

Impaired mitochondrial energy metabolism



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graph TD; A[Impaired mitochondrial energy metabolism] --> B[Neuronal sensitivity to endogenous glutamate]; B --> C[Gradual loss of neurons (final mechanism = excitotoxicity)];
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***Weak Excitotoxic Hypothesis***

- 3-NPA
  - inhibits succinate dehydrogenase and complex II
  - associated with striatal pathology similar to HD
  - blocked by NMDA antagonists

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**Huntington's Disease  
Current Treatment**

- symptomatic

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**Huntington's Disease  
Experimental Treatment**

- goal
  - to delay or prevent the onset of symptomatic HD in the asymptomatic individual

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**Huntington's Disease  
Experimental Treatment**

- postulated mechanisms
  - excitotoxicity
  - impaired mitochondrial metabolism

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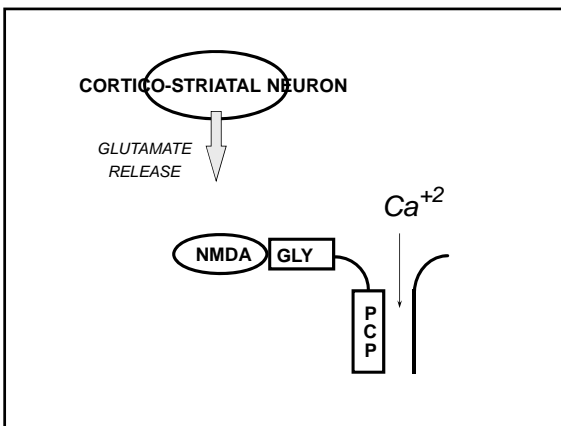
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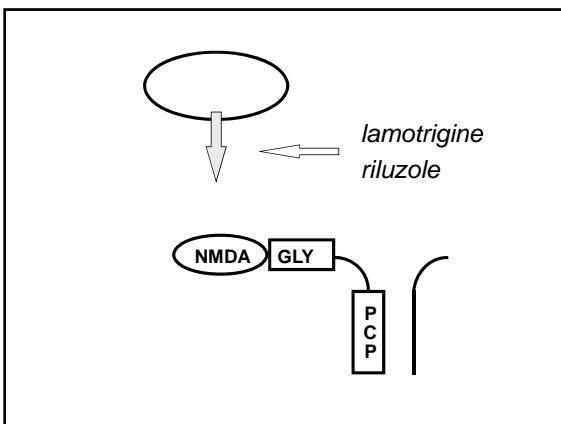
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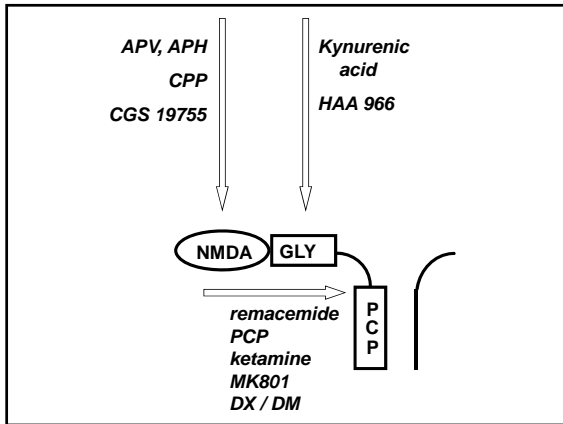
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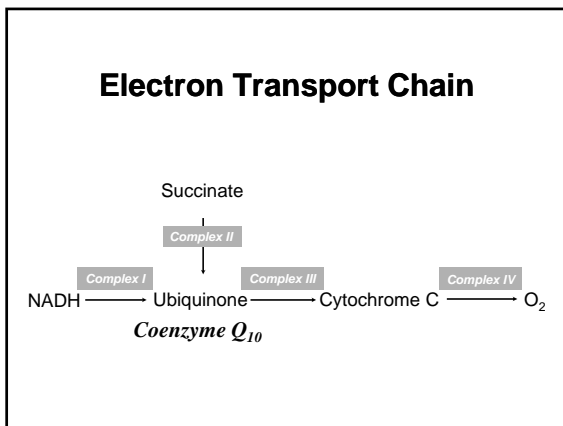
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### CARE - HD

(Co-enzyme Q<sub>10</sub> and Remacemide in HD)

- multi-centre, placebo-controlled, randomized, prospective trial
- 2 x 2 factorial design
- 347 patients with symptomatic HD
- 30 month follow-up, using validated clinical rating scales (UHDRS)
- Huntington Study Group; NIH funded

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**CARE - HD**  
**(Co-enzyme Q<sub>10</sub> and Remacemide in HD)**

- end-point =  
total functional capacity

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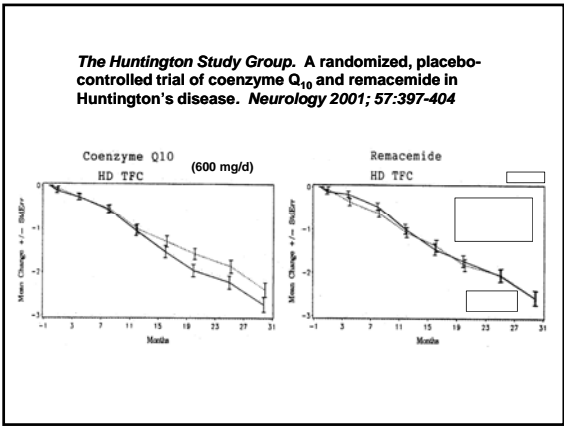
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**Huntington's Disease  
Experimental Treatment**

- 2CARE  
– Co Q<sub>10</sub> 2400 mg/d

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**Huntington's Disease**  
**Experimental Treatment**

- minocycline
  - caspase I inhibition

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