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

Huntington's Disease

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

Huntington's Disease

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

Chorea

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

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

Huntington's Disease
Clinical Features - 2

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

Huntington's Disease
Clinical Features - 3

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

Huntington's Disease
Clinical Features - 4

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

Huntington's Disease
Clinical Features - 5

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

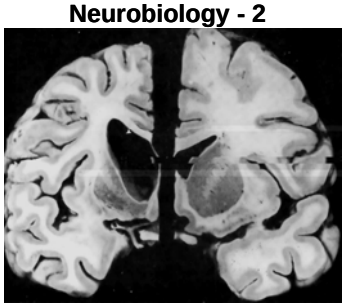
Huntington's Disease
Clinical Features - 6

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

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

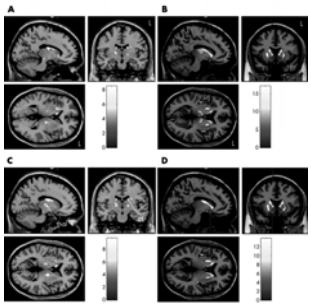
Huntington's Disease
Neurobiology - 2



Huntington's Disease
Neurobiology - 3

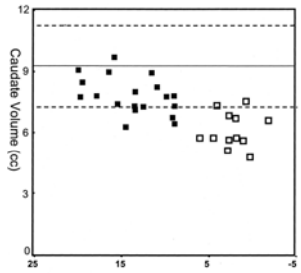
- *selective neuronal loss*
  - striatal projection neurons are affected
    - medium spiny neurons (GABA)
  - striatal interneurons are spared
    - SS/NPY
    - cholinergic

Figure 4 Results of the voxel based morphometric analysis of the Huntington's disease patient subgroups v age matched controls: panels A and B for the criterion motor deficits; panels C and D for the criterion cognitive deficits. All regions are shown where the corresponding subgroup (n = 12 each) had a significantly decreased grey matter density in comparison with an age matched group of normal controls (n = 15 each) at p



Kassubek J et al. J Neurol Neurosurg Psychiatry 2004;75:213-220

Figure 1. Caudate volume and estimated years to onset (YTO) in preclinical subjects

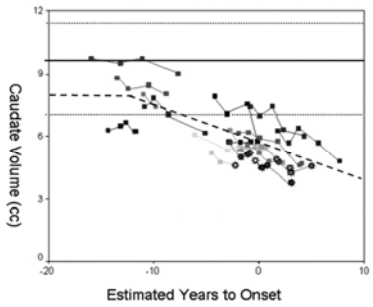


Aylward EH et al. Neurology 2004;63:66-72

NEUROLOGY

AMERICAN ACADEMY OF NEUROLOGY

Figure 2. Longitudinal change in caudate volume for preclinical subjects



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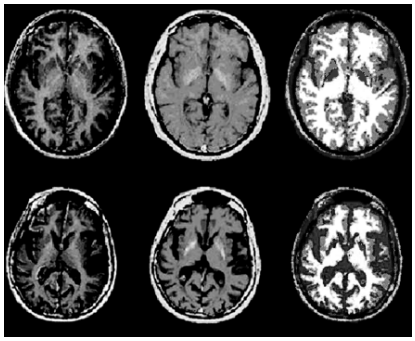
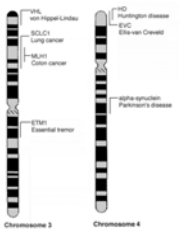


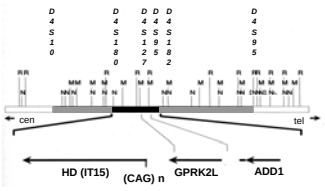
Ciarmiello A et al. J Nucl Med 2006; 47:215-222

Huntington's Disease
Genetics - 1

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



Huntington's Disease
Genetics - 2



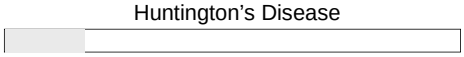
Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. ***Cell 1993;72:971-983***

Human IT15 Gene

Normal

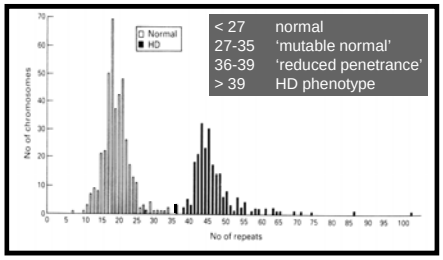
(CAG) $_{5 - 35}$

Huntington's Disease



(CAG) $_{40 - 240}$

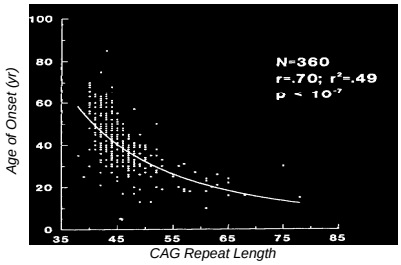
Huntington's Disease
CAG Repeat Number - 1



< 27	normal
27-35	'mutable normal'
36-39	'reduced penetrance'
> 39	HD phenotype

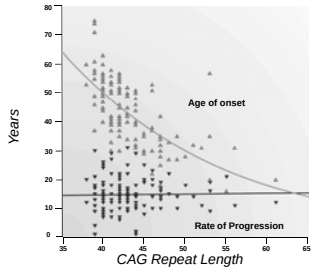
Crauford D, et al. J Med Genet 1993;30:1008-1011

Huntington's Disease
CAG Repeat Number - 2



Andrew SE, et al. Nature Genetics 1993;4:398-403

Huntington's Disease
CAG Repeat Number - 3



Nature Genetics Reviews

Huntington's Disease
Diagnosis

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

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

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

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

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)

Huntington's Disease
Cellular Mechanisms

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

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*

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

Huntington's Disease
Weak Excitotoxic Hypothesis

Impaired mitochondrial energy metabolism

⇩

↑ **Neuronal sensitivity to endogenous glutamate**

⇩

Gradual loss of neurons
(*final mechanism = excitotoxicity*)

Weak Excitotoxic Hypothesis

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

Huntington's Disease

Current Treatment

- symptomatic

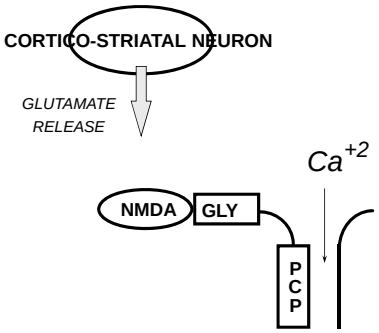
Huntington's Disease

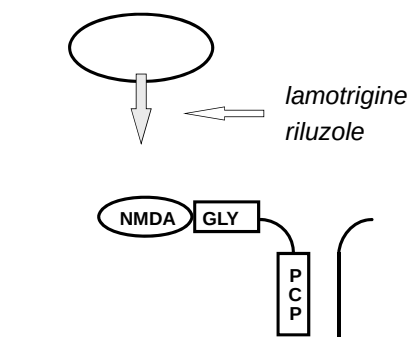
Experimental Treatment

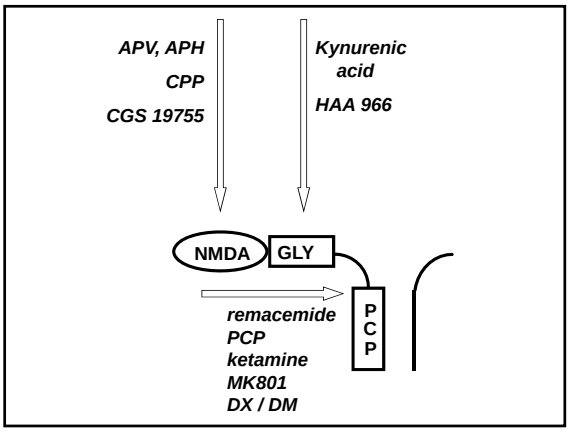
- goal
  - to delay or prevent the onset of symptomatic HD in the asymptomatic individual

Huntington's Disease
Experimental Treatment

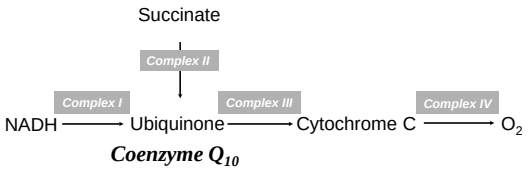
- postulated mechanisms
  - excitotoxicity
  - impaired mitochondrial metabolism







Electron Transport Chain



CARE - HD

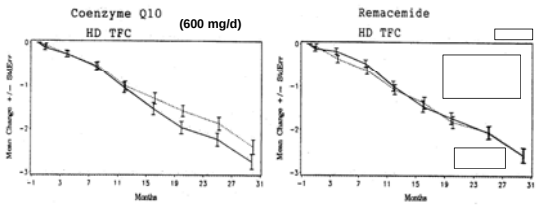
(Co-enzyme Q_{10} and Remacemide in HD)

- 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

CARE - HD
(Co-enzyme Q_{10} and Remacemide in HD)

- end-point =
  total functional capacity

The Huntington Study Group. **A randomized, placebo-controlled trial of coenzyme Q_{10} and remacemide in Huntington's disease.** ***Neurology 2001; 57:397-404***



Huntington's Disease
Experimental Treatment

- 2CARE
  – Co Q_{10} 2400 mg/d

Huntington's Disease
Experimental Treatment

- minocycline
  - caspase I inhibition