Huntington’s Disease – 2008

The Genetics of HD

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Disclosures

- Dr Moore has nothing to disclose
George Huntington - 1911
Huntington observed that there were families in his practice that had an inherited disorder characterized by involuntary movements (chorea).
Huntington’s Disease

George Huntington
“On Chorea”
Medical and Surgical Reporter
Philadelphia
1872: 26, 317-321

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872

Kussmaul, A and Nothnagel CHW (1872)
In Virchow-Hirsch Jahrbuch fur 1872, Berlin, p.175.
Annotation of Huntington’s paper
Noted by JM Charcot, Paris
Some Introductory Biology
A Note on Cells

Generic Cell

Nerve Cell

Dendrites

Cell body

Axon

Direction of message

Axon terminals synapse with dendrites on target cell

Axon
HD – A Genetic Disorder Affecting Nerve Cells

Nerve Cell - Brain

Nucleus
Genetics of HD

• Terminology
• DNA - deoxyribonucleic acid, a self-replicating material present in nearly all living organisms as the main constituent of chromosomes. It is the carrier of genetic information.
Genetic Material (DNA) Is Located in the Nucleus in Chromosomes

Chromosomes
22 Autosomes
2 Sex chromosomes, x and y
Chromosomes Contain Strings of DNA
Genes Are Made From DNA

DNA is made up of four nucleic acids:
- Adenine - A
- Cytosine - C
- Guanine – G
- Thymine – T

Three consecutive bases in a gene code for an amino acid.
E.g., CAG--Glutamine
Gene Expression
Genetics of HD
Gene Location in HD

Chromosomal location of a gene

- chromosome # 7
- short arm p
- Centromere
- long arm q
- long arm q
- region # 3
- band # 1
- sub-band # 2

Example gene: CFTR

Chromosomal location:
7 q 3 1 . 2

Chromosome 4
Genes Code for Proteins

[Diagram showing the process of gene expression: DNA to mRNA to Protein]
HD
The HD Gene

- **121**
- **36**
- **11**

\[(\text{CAG})_n\]

- **9750 bp**

\[\text{Huntington's disease gene}\]

\[(\text{Q})_n\]

- **350 kDa**

\[\text{Huntingtin}\]
The Molecular Disorder

Huntingtin - Normal

Polyglutamine Repeat Zone

Huntingtin - Mutant

Protein Folding Abnormality
Mutant Protein Accumulation Results in Nerve Cell Degeneration

- Mutant Protein
- Abnormal Protein Degradation
- Neuronal Protein Accumulation
- Nerve Cell Death