‘How the HD Gene works’

Jeff Carroll PhD

Ed Wild MD PhD
We don’t know.
How does HD science work?

Jeff Carroll PhD

Ed Wild MD PhD
This, we know.
Presenter Disclosures

Dr Ed Wild and Dr Jeff Carroll

The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

No relationships to disclose or list

Huntington’s Disease Society of America
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Ode to HD research
Ronald Roberts

On top of all the stress and strain,
The fears, the loss, the psychic drain,
Now comes the jargon of the lab
As science shares its chatty gab.

Now one more way our stomachs churn,
And one more language we must learn.
Ode to HD research
Ronald Roberts

Take ganglionic eminence
And other terms that make no sense.
There’s not a one of them routine.
Explain striatal dopamine.
There’s C-A-G and R-N-A
With dorsal caudate interplay,
And neurons that degenerate,
And aspartate and glutamate!
Excitotoxic neuron death-
There’s hardly time to catch your breath.
The other losses that depress
Are worse by far than this, I guess.
But still this abstract language mess
Is one more insult, I confess!
Before science, how’d we get here?
ON CHOREA.

By George Huntington, M. D.,
Of Pomeroy, Ohio.

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

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the dancing propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and char-
(1) Any person suffering from a hereditary disease may be rendered incapable of procreation by means of a surgical operation (sterilization), if the experience of medical science shows that it is highly probable that his descendants would suffer from some serious physical or mental hereditary defect.

(2) For the purposes of this law, any person will be considered as hereditarily diseased who is suffering from any one of the following diseases: –

(5) Hereditary Chorea
I DONT HAFTA PAY YOU BARMAN A DIME
MY OLD CHOREA MAKES ME DIZZY ALL TH' TIME
GOD MAKES ALL KINDSA SICKNESS AND MISERY
AN' CHOREA FITS ME JUST FINE
NO I DONT HAFTA PAY YOU BARTENDERS ONE DIME,
CHOREEAY MAKES ME DRUNKY AN' DRUNK ALLA TH' TIME
GOD MAKES ALL KINDSA SICKNESS AN' MISERY
MY CHOREAAEA FITS ME FINE

MY CHOREEY AINTA KETCHIN AND I FEEL NO PAINS
JUSTA DIZZERY BLUNDERY STAGGERY WALK BUT IT'S NOT MY BRAIN
GOD MAKES ALL KINDSA SICKNESS AND MISERIES
AN' MY CHOREA SUITS ME JUST FINE
I'VE GOTA STAGGER MY SIXTY SIX DOLLERS WORTH
BFORE I CAN GIT MY PENSION CHECK Cash'D
GOD MAKES ALL KINDSA SICKNESS AND MISERY
MY CHOREA FITS ME FINE

Words & Music: Woody Guthrie
A Novel Gene Containing a Trinucleotide Repeat That Is Expanded and Unstable on Huntington's Disease Chromosomes

The Huntington's Disease Collaborative Research Group*

Summary

The Huntington's disease (HD) gene has been mapped in 4p16.3 but has eluded identification. We have used haplotype analysis of linkage disequilibrium to spotlight a small segment of 4p16.3 as the likely location of the defect. A new gene, IT15, isolated using cloned trapped exons from the target area contains a polymorphic trinucleotide repeat that is expanded and unstable on HD chromosomes. A (CAG)n repeat longer than the normal range was observed on HD chromosomes from all 75 disease families examined, comprising a variety of ethnic backgrounds and 4p16.3 haplotypes. The (CAG)n repeat appears to be located

Introduction

Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by motor disturbance, cognitive loss, and psychiatric manifestations (Martin and Gusella, 1986). It is inherited in an autosomal dominant fashion and affects ~1 in 10,000 individuals in most populations of European origin (Harper et al., 1991). The hallmark of HD is a distinctive choreic movement disorder that typically has a subtle, insidious onset in the fourth to fifth decade of life and gradually worsens over a course of 10 to 20 years until death. Occasionally, HD is expressed in juveniles, typically manifesting with more severe symptoms including rigidity and a more rapid course. Juvenile onset of HD is associated with a preponderance of paternal transmission of the disease allele. The neuropathology of HD also displays a distinctive pattern, with selective loss of neurons that is most severe in the caudate

*The Huntington’s Disease Collaborative Research Group consists of investigators in the United States and Europe who are studying the genetic and molecular basis of Huntington’s disease.

References


Lookout, here comes some science
Stars in our galaxy = 100 thousand million ($10^{11}$)
Gene

TCCTTTTC\textcolor{red}{CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG}

Protein

S F Q Q Q Q Q Q
More “CAG” units, earlier HD

But, disease duration is same
CAG “Expansion”

\[
\begin{align*}
2 & \quad \cdots \text{CAGCAG}\cdots \\
7 & \quad \cdots \text{CAGCAG}\cdots \\
18 & \quad \cdots \text{CAGCAG}\cdots \\
27 & \quad \cdots \text{CAGCAG}\cdots \\
42 & \quad \cdots \text{CAGCAG}\cdots 
\end{align*}
\]
Ok, this all makes sense.

But how do all these extra CAG’s kill brain cells?
Normal huntingtin protein

Mutant huntingtin protein
Change in shape causes Change in function
‘Animal models’ of HD
All these animals have an HD gene. None of them, as far as we know, ever gets HD because their CAG tracts don’t grow like ours do.

But, what if we could manipulate them to artificially give them a long “C-A-G” repeat in their HD gene, would that make them sick?
Mouse (0.4g)

Rat (2g)

Monkey (95g)

Human (1400g)

Courtesy of Dr. Russ Lonser
Motor signs of Huntington’s Disease
Is this testing HD?
Research in HD patients
Quantitative motor
RECAP
Agilent 1100 Series HPLC Applied Biosystems API 2000

Biological Sample
Luna 5µm NH2 column
STHdhQ111/Q7

0.2 0.4 0.6 0.8 1.0
0 5000 10000

Time (minutes)
Peak Size (Counts per second)

4ng
10ng
20ng
40ng

Taurine

Cells

Patients

Animal Models

Cells

Animal Models
Drug discovery
Identifying targets, finding or making molecules

Preclinical phase
Testing in cells and animals

Clinical trials
In humans

Phase 1
Healthy volunteers

Phase 2
Small numbers of patients

Phase 3
Large numbers of patients

Approval