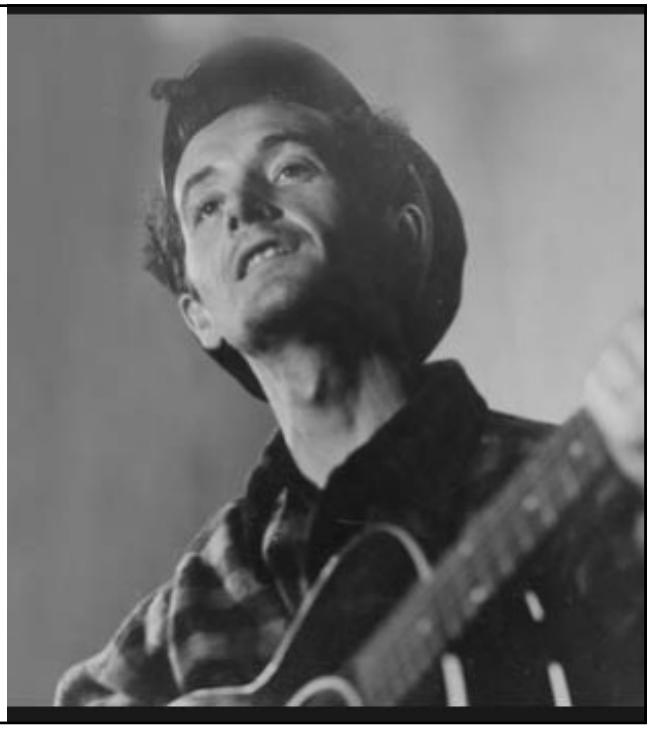
Huntington's Disease

1

Huntington's Disease

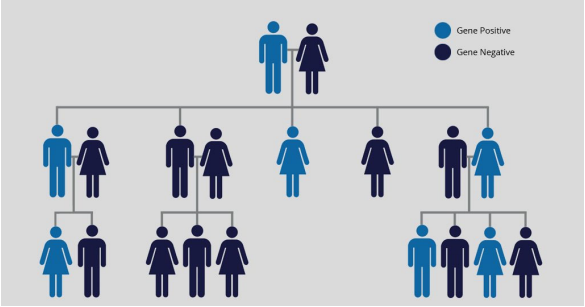
- Rare neurodegenerative disorder causing a combination of motor, cognitive, and psychiatric symptoms
- Symptoms most often begin in middle life
- Relentlessly progressive with death occurring 15-20 years after diagnosis



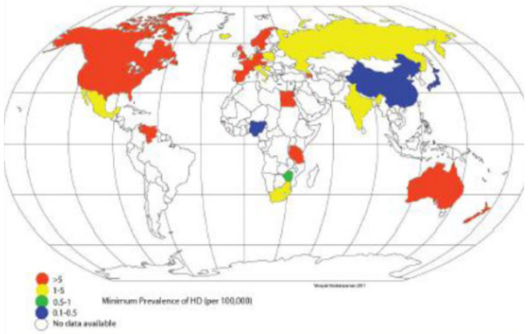
2

Epidemiology

- 5 per 100,000
- 40,000 adults in US
- 250,000 at 50% risk



HDSA.org



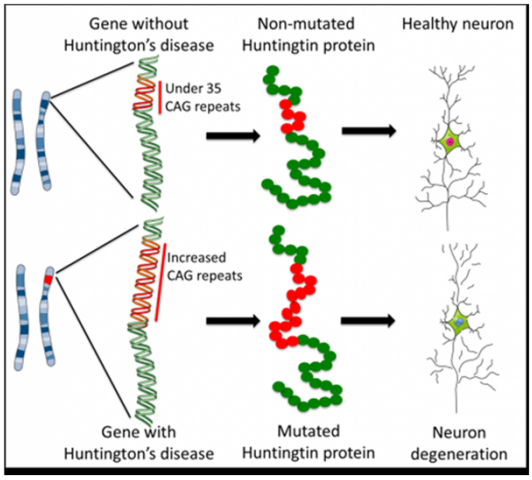
Warby et al. 2009

3

Genetics of Huntington's Disease

- Expanded (40+) CAG repeat on HTT gene encoding huntingtin

- Huntingtin protein
  - Incompletely understood
  - Ubiquitously expressed
  - Plays a role in multiple critical processes necessary for neuronal development and health



https://blog.cirm.ca.gov/tag/hd-ipsc-consortium/

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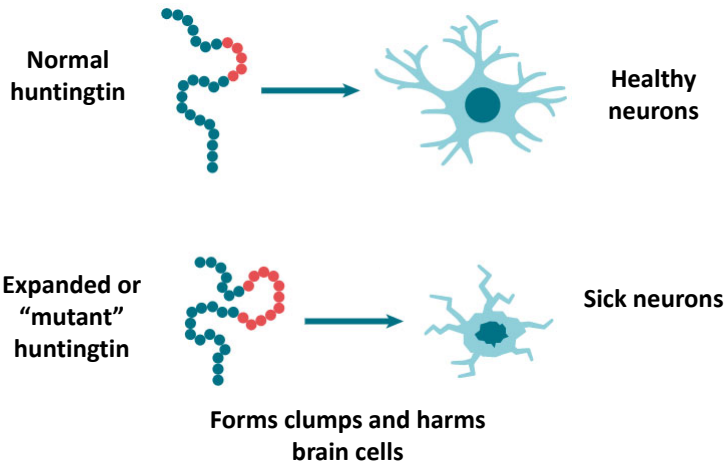
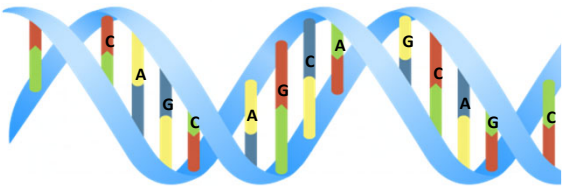
Expanded huntingtin harms brain cells



5

The *huntingtin* gene

CAG CAG CAG CAG CAG CAG CAG CAG CAG



10-26 repeats is typical; >40 leads to HD

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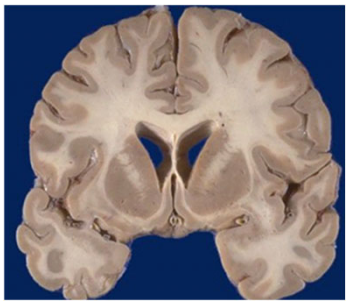
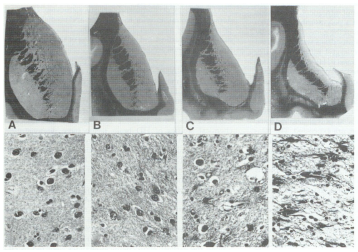
Neuropathological findings of HD



Normal brain

HD brain



Rosas et al, Neurology 2001;57:1025-8

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Motor symptoms of HD

- Involuntary movements
  - Chorea, dystonia
  - Tics, stereotypies
- Loss of balance and coordination
  - Difficulty walking, falls
- Bradykinesia, slowness of voluntary movements
  - Impaired dexterity
  - Dysphagia

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Cognitive changes

- Difficulty with planning, organizing, calculations
- Change in personality
- Slowness and decreased flexibility of processing
- Impaired judgement, loss of awareness, impulsivity
- Memory loss

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Psychiatric symptoms

- Mood
  - Depression
  - Anxiety
  - Apathy
- Obsessive-Compulsive Disorder
- Impulsivity
- Irritability, anger outbursts
- Psychosis
  - Hallucinations
  - Paranoia
  - Delusions
- Suicide

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Huntington's Disease progression

- Exact symptoms vary from person to person
- Usually starts in 30-50's, progressively worse over time
- Eventually, a person with HD relies completely on other people for their personal care
- The disease is always fatal
- Has emotional, psychological, social, and economical impact on the entire family
  - Impacts all relationships

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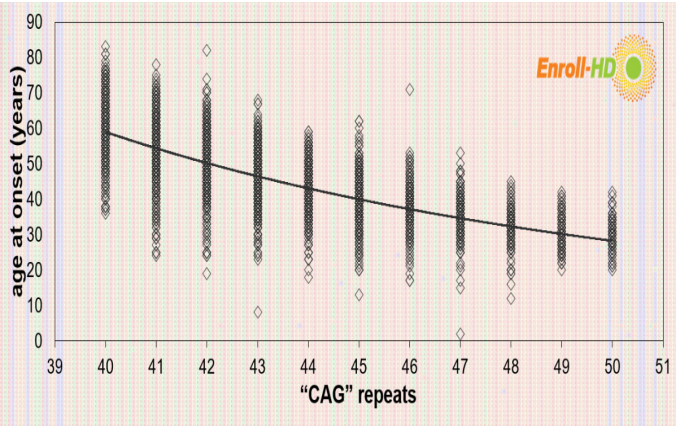
Age of onset

- Inversely correlated with CAGn
- Modified by genetic and probably environmental factors



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Symptom management - medications

- Chorea
  - Tetrabenazine (Xenazine), deutetrabenazine (Austedo), valbenazine (Ingrezza)
  - Antipsychotic medications (off-label)
- Psychiatric symptoms
  - Treat the same as those without HD
  - SSRIs, antipsychotic medications
- There are no effective medications for cognitive symptoms of HD

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Symptom management – non-pharmacologic

- Physical therapy
  - Balance, gait, fall prevention
- Speech therapy
  - Dysphagia, dysarthria
- Nutrition
  - Weight loss
- Occupational therapy
  - Functional decline
- Social work
  - Everything!

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Potential therapies of the future

- Very exciting research is being done to develop therapies that may be able to slow or stop the disease progression
- Approaches to disease modification
  - Huntingtin lowering
  - Gene editing
  - Clean up toxic huntingtin
  - Protect neurons from damage
    - Improve cell health
    - Decrease inflammation
    - Improve mitochondrial dysfunction

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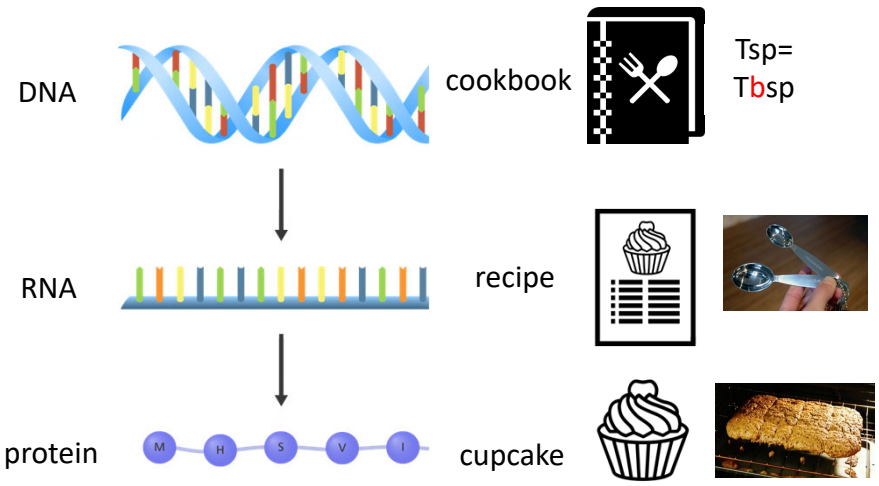
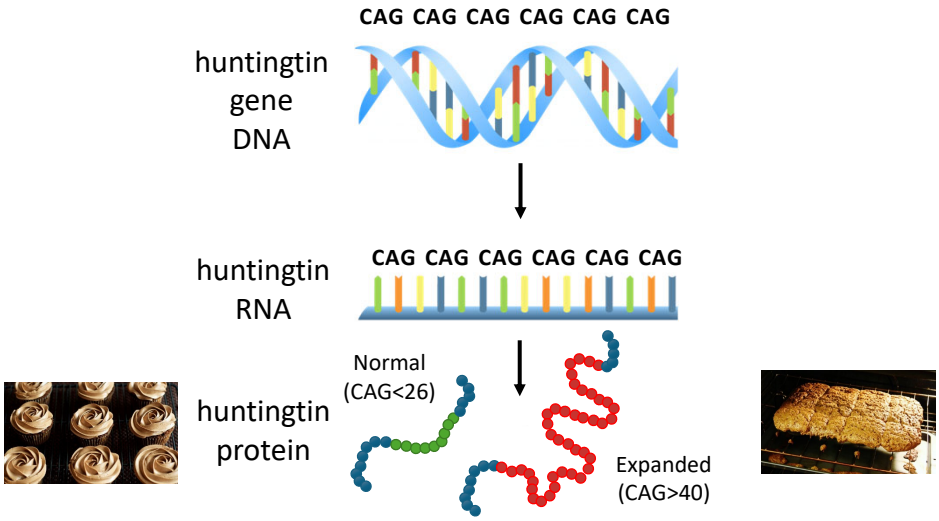
Genetics and cupcakes



16

Genetics of Huntington's disease



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Huntingtin lowering: getting rid of the bad cupcakes

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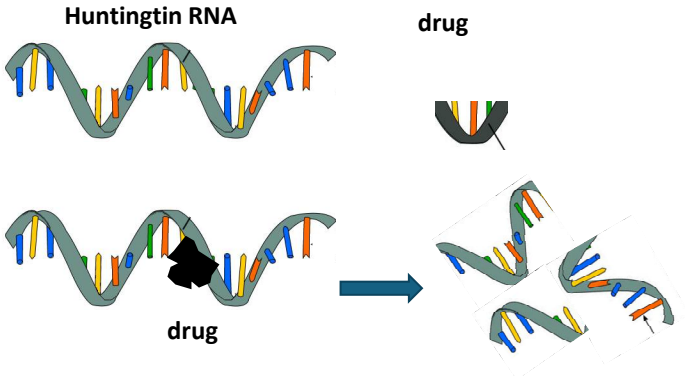
Huntingtin lowering drugs target the RNA "recipe"



Less huntingtin RNA = less harmful protein

Clinical trials are testing if this strategy could slow down the symptoms of HD

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Huntingtin lowering therapies

- Antisense Oligonucleotides
  - Tominersen
  - WVE-003
- RNA interference
  - AMT-130
- Small molecules
  - Branaplam
  - PTC 518

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Tominersen

- Tominerson was not effective overall in GENERATION-HD1
- New analysis of halted GENERATION-HD1 trial showed tominersen may have been helpful for younger participants with less severe symptoms
- Roche is currently running a **new GENERATION-HD 2 trial in earlier HD:** lower doses of the drug spaced 4 months apart
- Recruiting people with very early HD, age 25-50

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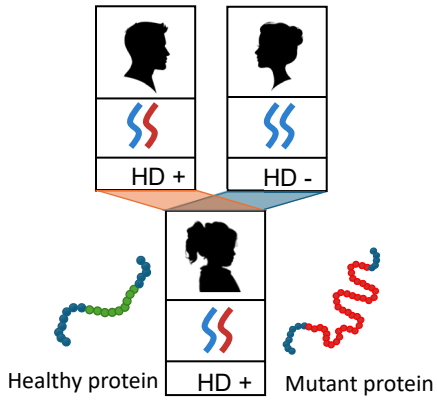
LF [2]0

SELECT-HD (WVE-003)



- Selective huntingtin-lowering (toxic form)
- Redesigned chemistry and adaptive trial
- SELECT-HD enrolled 1st participant in Sept 2021 (sites in Europe, Australia, Canada)
- Encouraging data in animals (huntingtin-lowering and delivery)

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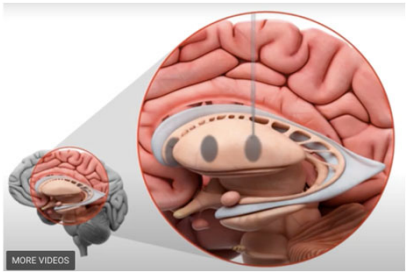
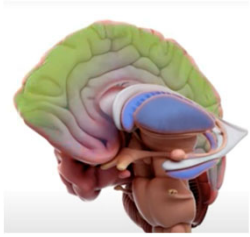
Slide 22

LF [2]0 could potentially add some of the info and images from here to the previous slide
Leora Fox, 2022-02-23T21:51:07.624

uniQure

HD-GeneTRX1 + 2 (AMT-130)





- First gene therapy trial for HD; drug is packaged in a virus and delivered via brain surgery
- Small ongoing safety studies in Europe (15 people) and USA (26 people)
- June 2022: safety analysis of the first, low-dose U.S. cohort revealed no safety concerns and lowering of mHTT by over 50% one year after dosing
- August 2022: Last 2 high dose surgeries postponed because of safety concerns after surgery
- November 2022: High dose surgeries resume with longer monitoring after surgery and prescription of anti-inflammatories
- UPDATE December 2023: safe and well-tolerated

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LF [2]0

NOVARTIS

Branaplam

- An oral drug developed for children with SMA, discovered also to lower huntingtin
- Trial in people with HD May 2022
- August 22: We learned that dosing of branaplam was stopped due to participants in the trial developing peripheral neuropathy
- December 2022: Novartis announced they will not move forward with developing branaplam for HD

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Slide 23

LF [2]0 this is out of date but could potentially add this picture to previous slide
Leora Fox, 2022-02-23T21:52:40.660

Slide 24

LF [2]0 could potentially add this picture to previous slide
Leora Fox, 2022-02-23T21:52:24.296

PTC THERAPEUTICS™

PIVOT HD (PTC-518)

- Oral huntingtin-lowering therapy (splice modulator)
- Positive safety data in Phase I trial of healthy adults
- **PIVOT-HD trial** initiated April 2022 in USA, Europe, Australia, enrolling 160 people age 25+, very early HD symptoms, goals safety and huntingtin-lowering
- October 18th 2022: trial ongoing, but US recruitment paused. Not for safety - FDA needs more data to lengthen the study
- June 2023: Well-tolerated and lowers blood levels of huntingtin protein.

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Other ways to get rid of the bad cupcakes

Cookbook typo

Bad recipe

Weird, exploded cupcakes

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Gene editing

- Able to decrease harmful huntintin protein by 40% while leaving the healthy protein intact in mice
- Working to make sure it does not edit the wrong genes

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Other ways to get rid of the bad cupcakes

Cookbook typo

Bad recipe

Weird, exploded cupcakes

28

VTx-003

- Antibody to bind mutant huntintin
- Triggers elimination of the protein

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INT41 Vybion

- Blocks the harmful effects of toxic huntintin protein
- Motor and cognitive benefits in animal studies

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ORIGAMI Therapeutics ORI-113 and ORI-503

- Developing therapies to correct or eliminate toxic huntingtin
- Early discovery phases

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Approaches to disease modification

- Huntingtin lowering
- Gene editing
- Clean up toxic huntingtin
- Protect brain cells from damage

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1

prilenia

PROOF-HD trial (recruited)

- Phase III PROOF-HD trial of pridopidine
- Testing effects on day-to-day function, movement and behavior in HD
- Fully recruited Oct 2021; fast-track designation from FDA
- Not found to be effective at slowing disease progression

KA0

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ANNEXON biosciences

ANX005

- Prevents inflammation in response to HD
- Phase 2 study completed with positive results
- Working on additional studies

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Slide 33

KA0 Have also opened open label extension, KINECT-HD 2, that is currently enrolling participants
Kelly Andrew, 2021-12-01T21:40:54.852

0 0 Awesome - added
, 2021-12-01T21:53:39.278

1 neurocrine & prilenia are in the same boat - perhaps put them both on the same slide? both trials fully recruited - waiting results. then, you could put Roche & Wave on the same slide but be careful to note that Wave has an ongoing trial so perhaps we should give them a little more real estate....
, 2021-12-01T22:00:31.237

1 0 Makes sense and done
, 2021-12-01T22:08:35.392

ReS18-H

- Improve the function of brain cells
- Oral medication
- Pre-clinical development

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