Current HD Clinical Trial Research: Ionis, Wave, and others.

North Carolina Research Day
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NC Biotech Center
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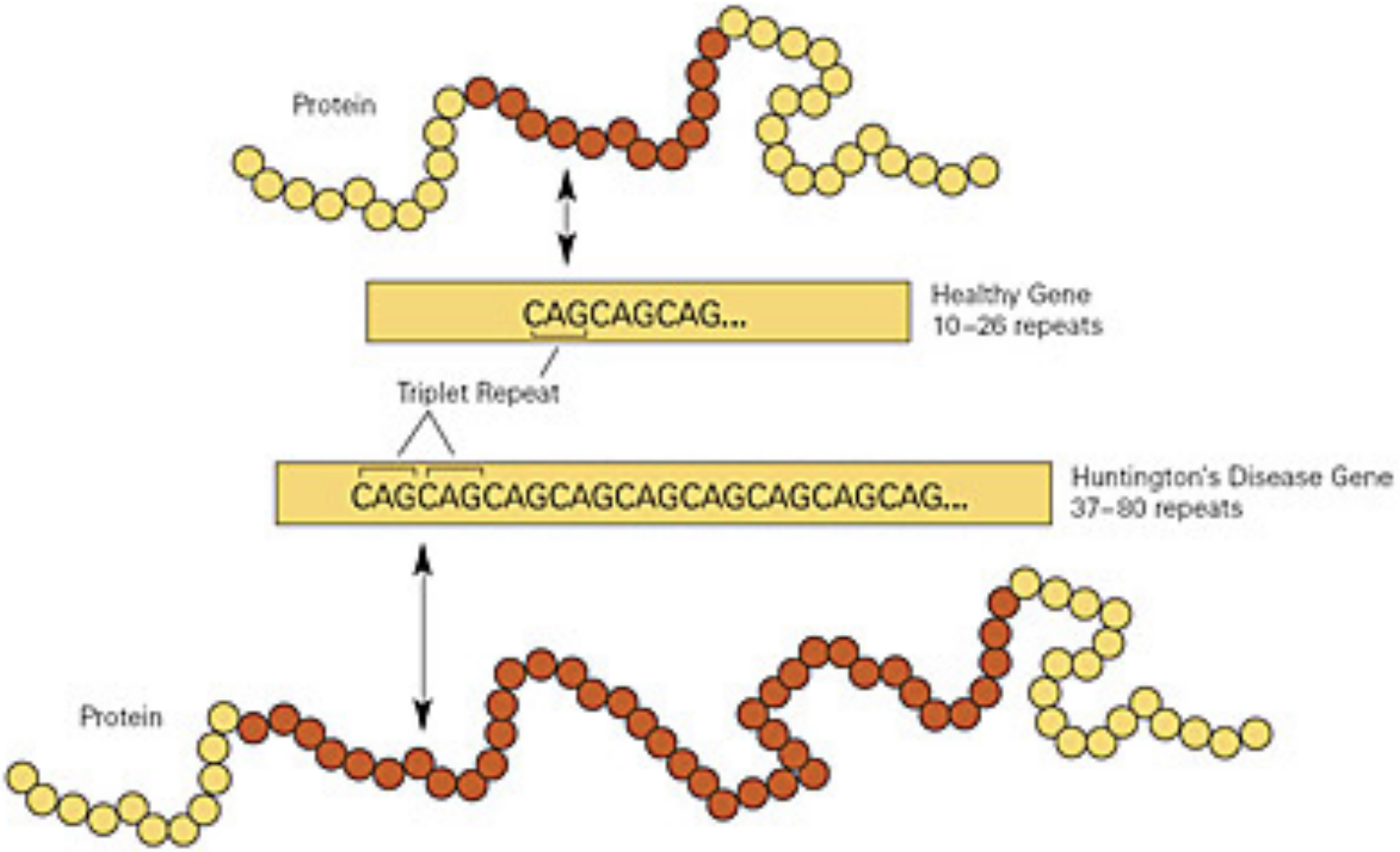
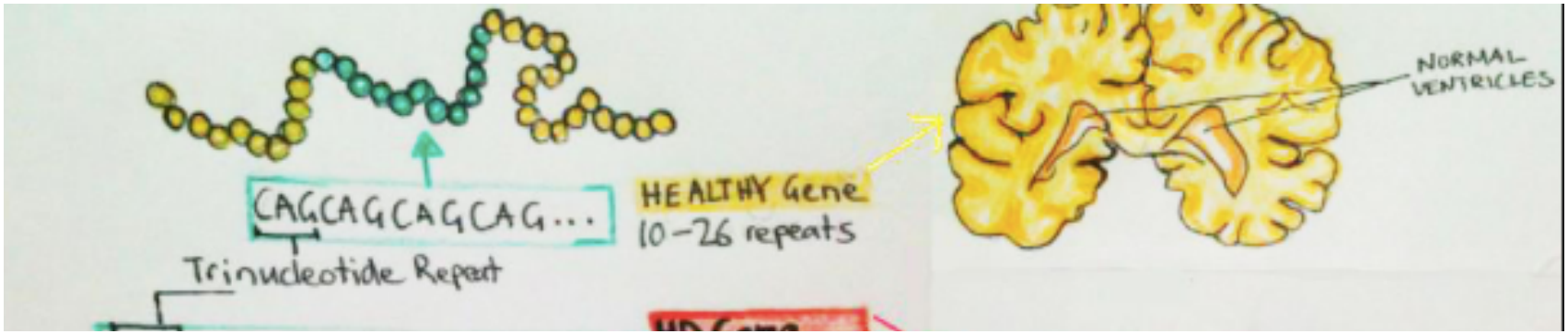
Introduction

- A little science
- New ways to attach the HD problem

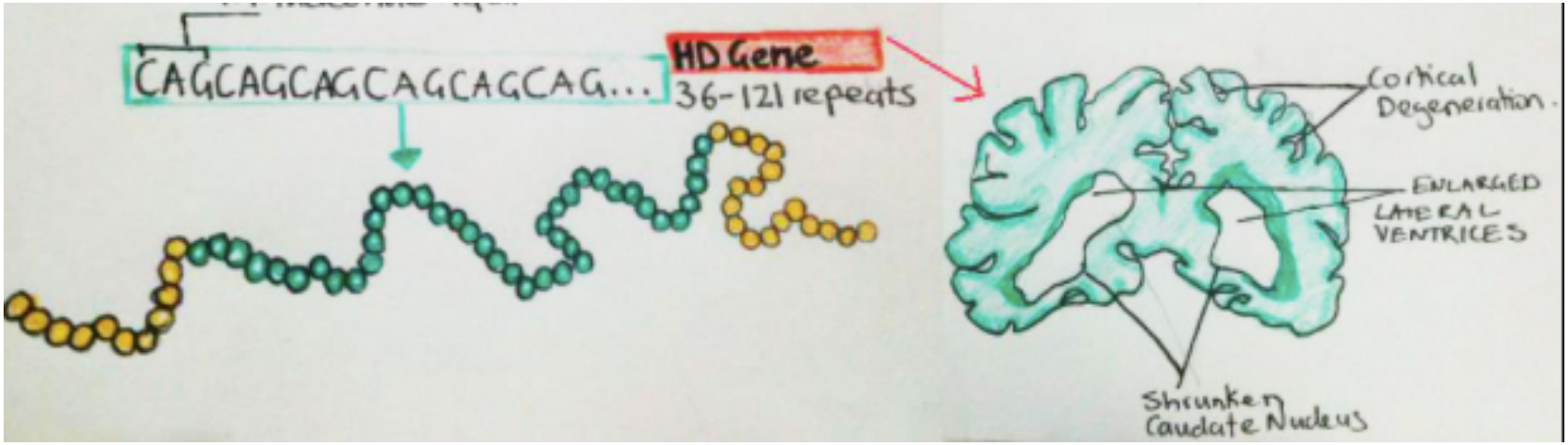
Healthy gene (top)—unhealthy gene (bottom)



If you have two healthy genes—your brain is OK



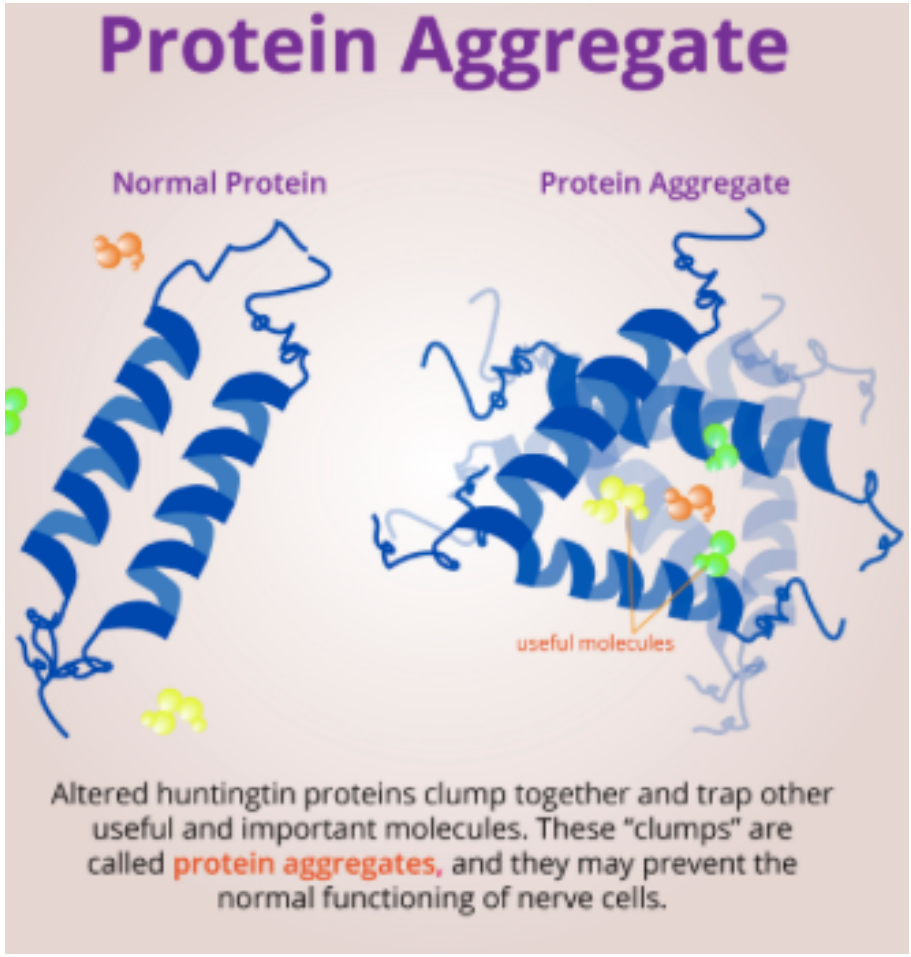
If you have even one unhealthy HD gene, eventually it affects the brain



So, why doesn't HD show up at birth?

- Well, its because the unhealthy gene still does its normal function pretty well
- The problem comes when the protein gets old and broken down
  - Instead of going into the cell's garbage disposal machinery, it forms clumps
  - The clumps can be digested, but very slowly
  - Over time they slowly accumulate
  - Then these clumps gum up the works

Mutant huntingtin clumps

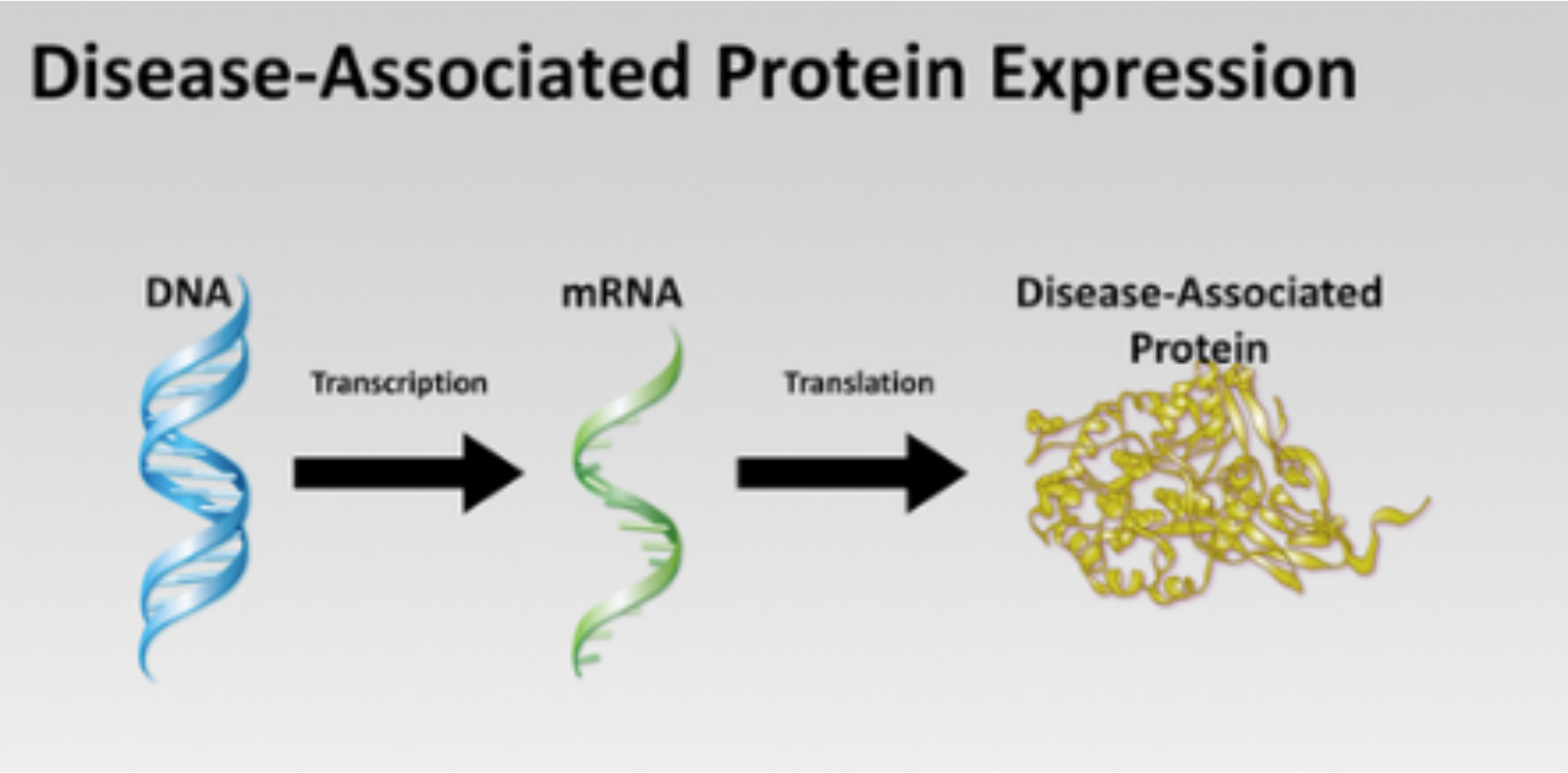


How do the clumps cause trouble?

- They interfere with other molecules in the cell
- They interfere with DNA and RNA communication in multiple areas
- They block of the normal protein disposal systems in the brain
- Cells can degrade/digest the clumps, it's just that they cannot keep up with the production, so slowly, gradually, over time trouble evolves.

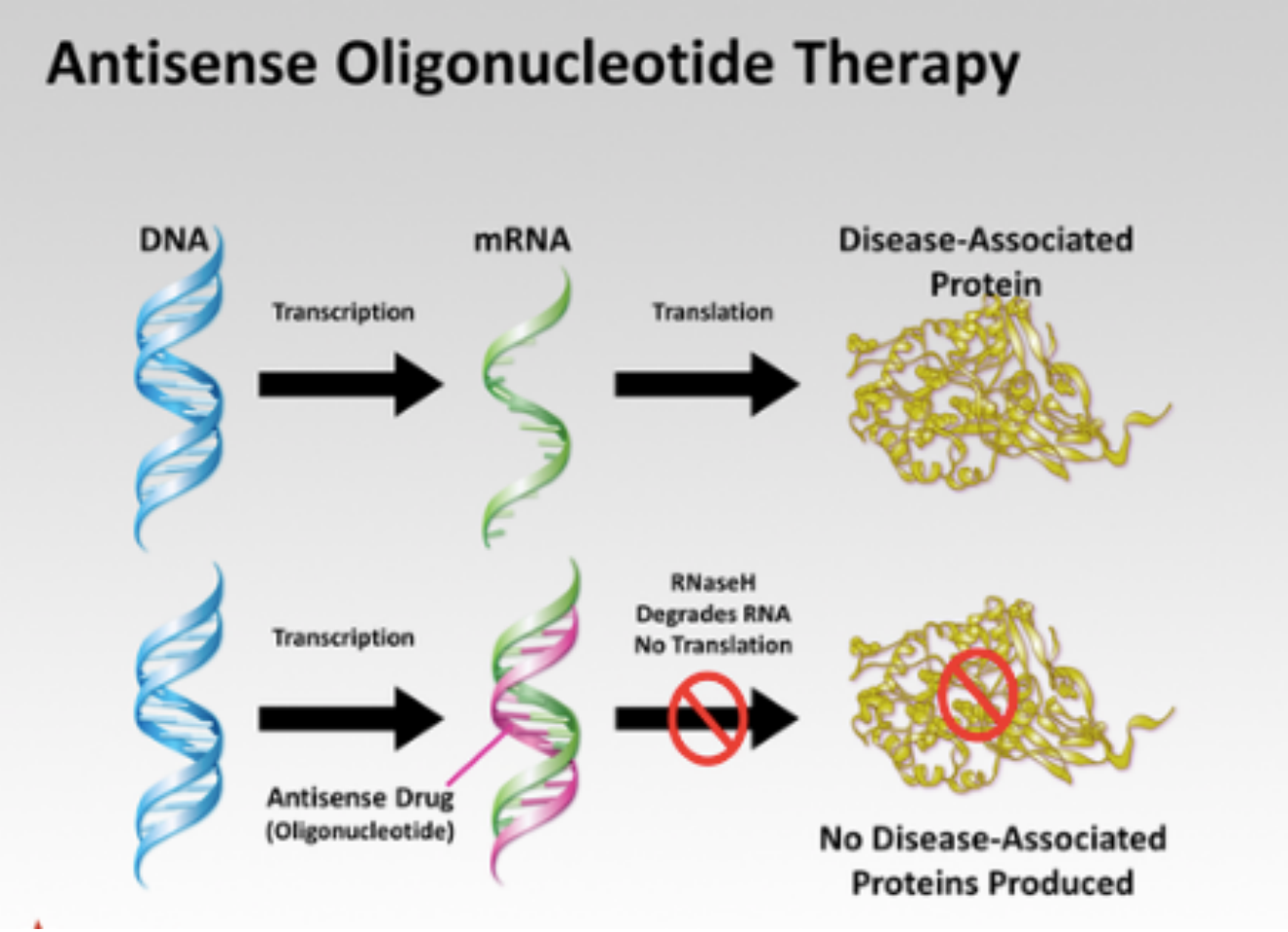
So why do things happen in HD?

Because the unhealthy gene causes a protein that cannot be gotten rid of easily



So, how do we fix HD?

By blocking or reducing the creation of the mutant HD protein

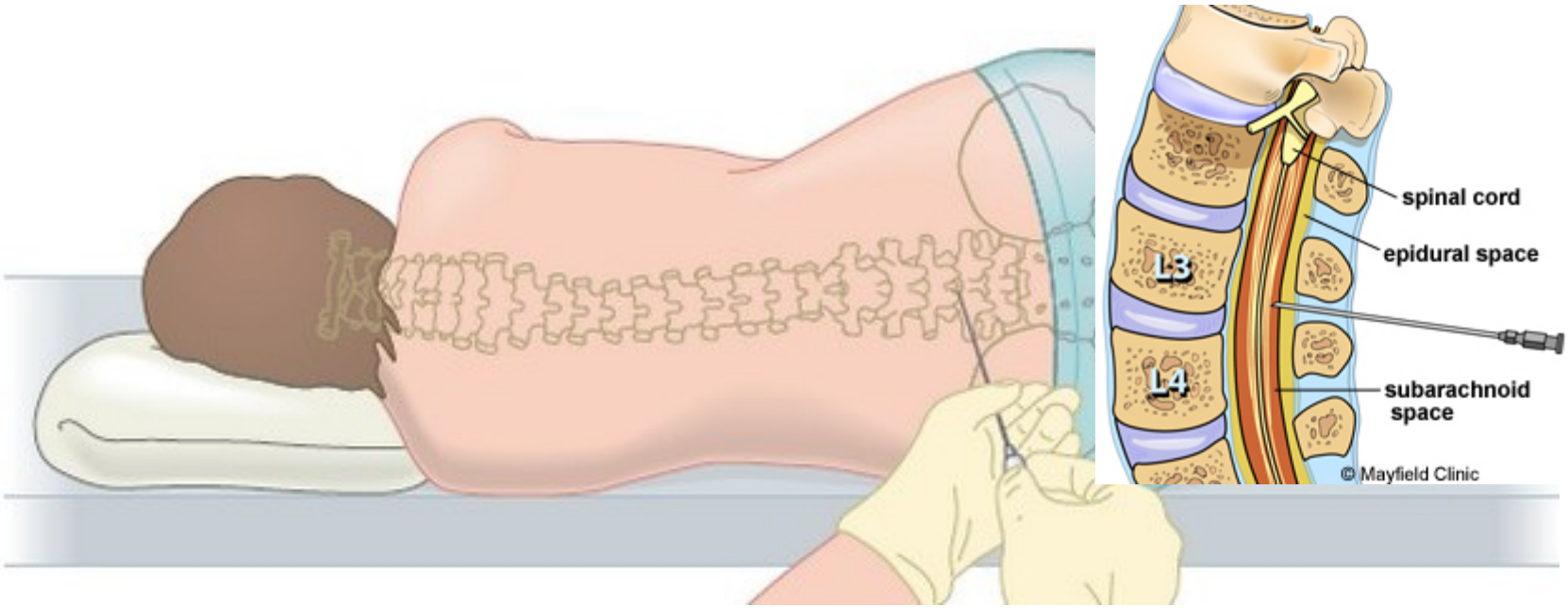


How do you block it

- Complicated genetic chemistry allows this to happen
- The molecules are very large, and cannot be taken as a pill or an IV (they require lumbar puncture or other approaches)
- One of the anti-sense oligonucleotide drugs blocks the production of both mutant and healthy huntingtin protein (IONIS)
- The other blocks only the production of the mutant huntingtin protein (Wave)

What is a spinal tap?

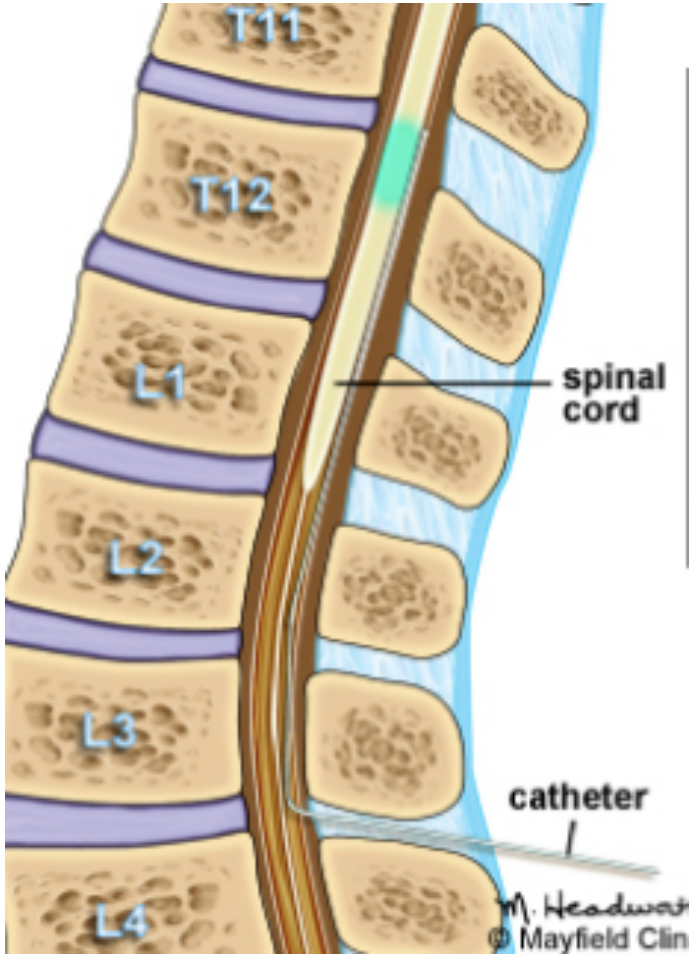
Lumbar puncture: Spinal tap



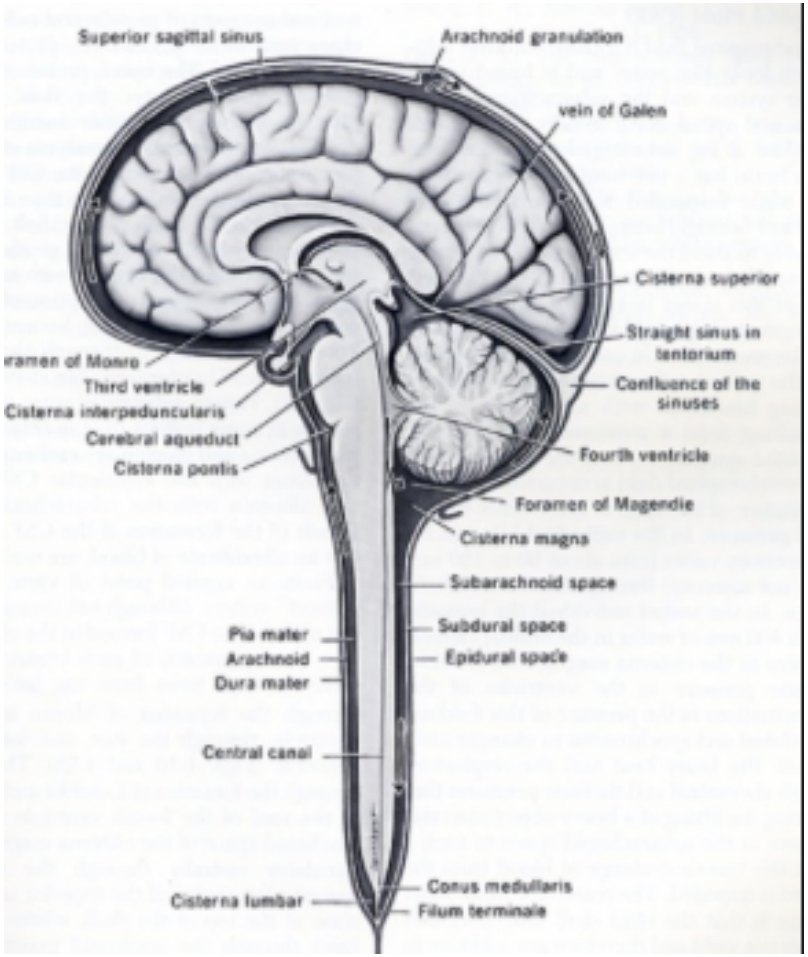
Spinal tap

- Done sitting up or lying down
- Ultrasound used to help mark best sites
- Very thin needle and local anesthesia
- Not much different than an “epidural”
- Very safe
- Post-lumbar puncture headache is a possibility (treatable!)

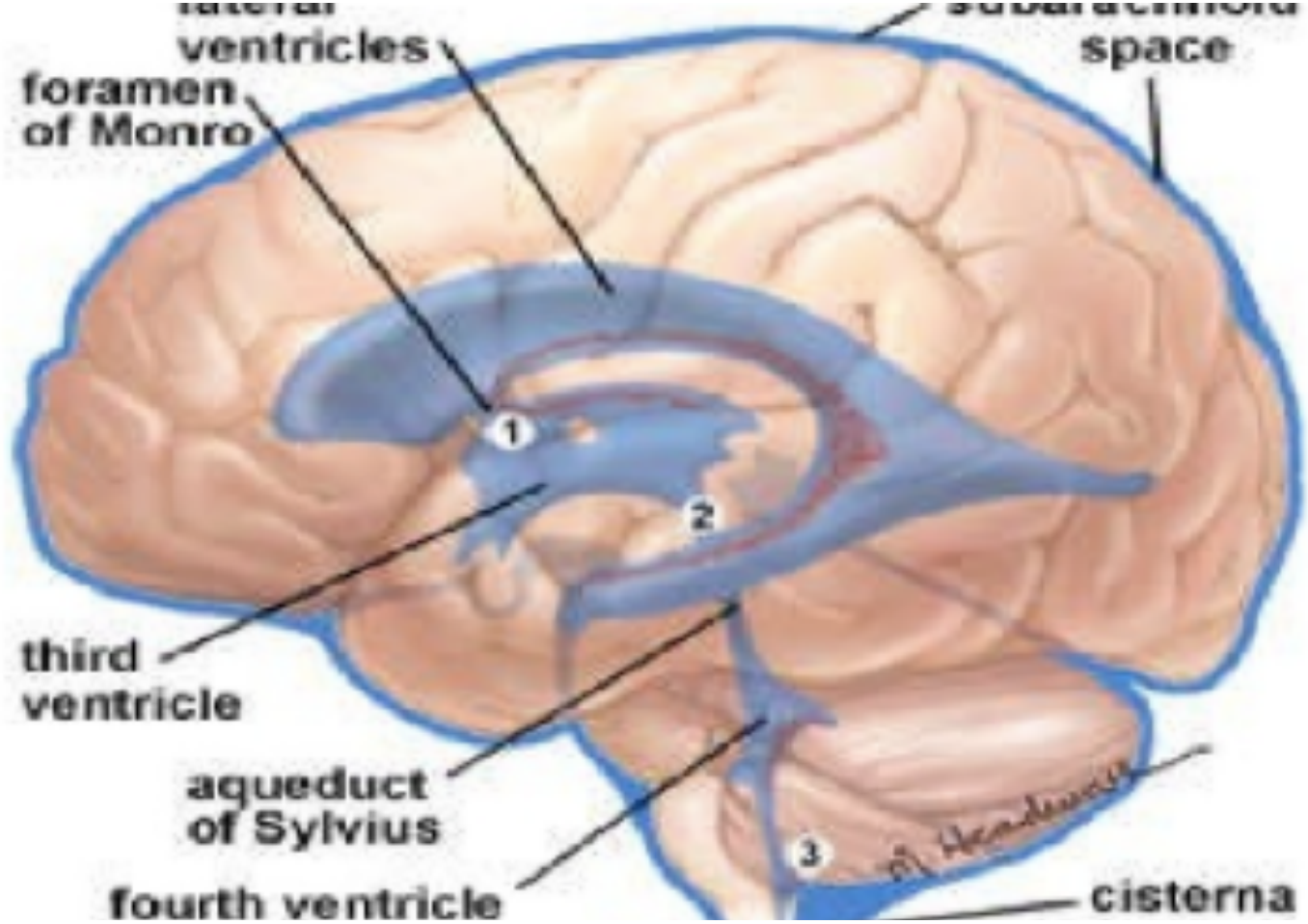
Administering therapy



CSF circulation



Where the CSF circulates in and around the brain



What's the difference between the IONIS and WAVE drugs?

IONIS drug

- Already completed an early human trial
- Safe and well tolerated
- Blocks both mutant and healthy huntingtin—but only partially
- Allows cells that are healthy to slowly get rid of the clumps
- It has shown to be able to reduce mutant huntingtin protein in the spinal fluid
- Therapy needs to be given several times a year
- Clinical benefits have yet to be shown!

Wave Life Sciences

- Clinical trials have started in Canada, soon in USA
- This compound also goes in by spinal tap
- **It only blocks mutant huntingtin, it leaves healthy huntingtin alone**
- Therapy needs to be given several times a year
- It can only be given to about 75% of HD patients (a blood test determines eligibility)
- So far, it seems safe

Which drug is better?

- We do not know if one is better than the other (or for that matter, if either will actually work in humans, and if they do, how well they will work)
- The good news is, that Ionis will likely set up the next round of clinical trials in the USA
- If you do not qualify for the Wave study, you might still be able to get into the Ionis study

Which drug is better?

- You would think the Wave compound might be better because it just blocks the mutant protein, but we do not know that
- These are brand new types of drugs so we do not have a lot of experience with efficacy and safety
- We worry that CSF circulation might not get the drug to all parts of the brain with either drug

Are there other treatments?

- You can administer gene therapy via viruses
- This approach cannot be administered in the spinal fluid
- This type of treatment goes directly in the brain by injection
- The effects are local, but you may need only one treatment
- Voyager (Boston) applying for FDA approval for this type of therapy

Is there any other research a person with HD or who cares about HD can participate in?

HD Clarity study

- A biomarker—not a treatment—study
- Looking to find something in the blood or spinal fluid that indicates disease severity
- Neurofilament light chain protein might be found in both
- Also, can measure mutant HD protein in the spinal fluid
- Involves getting a spinal tap and a blood test
- One or two visits—starting soon—we will need normal volunteers as well.

Why is this important

- We would like to see evidence that a drug is working quickly
  - If an antibiotic can break a fever you know that is a sign of efficacy
- Biomarkers can provide early signals of efficacy and mechanism of action of new drugs
- Biomarkers can significantly speed up clinical trials

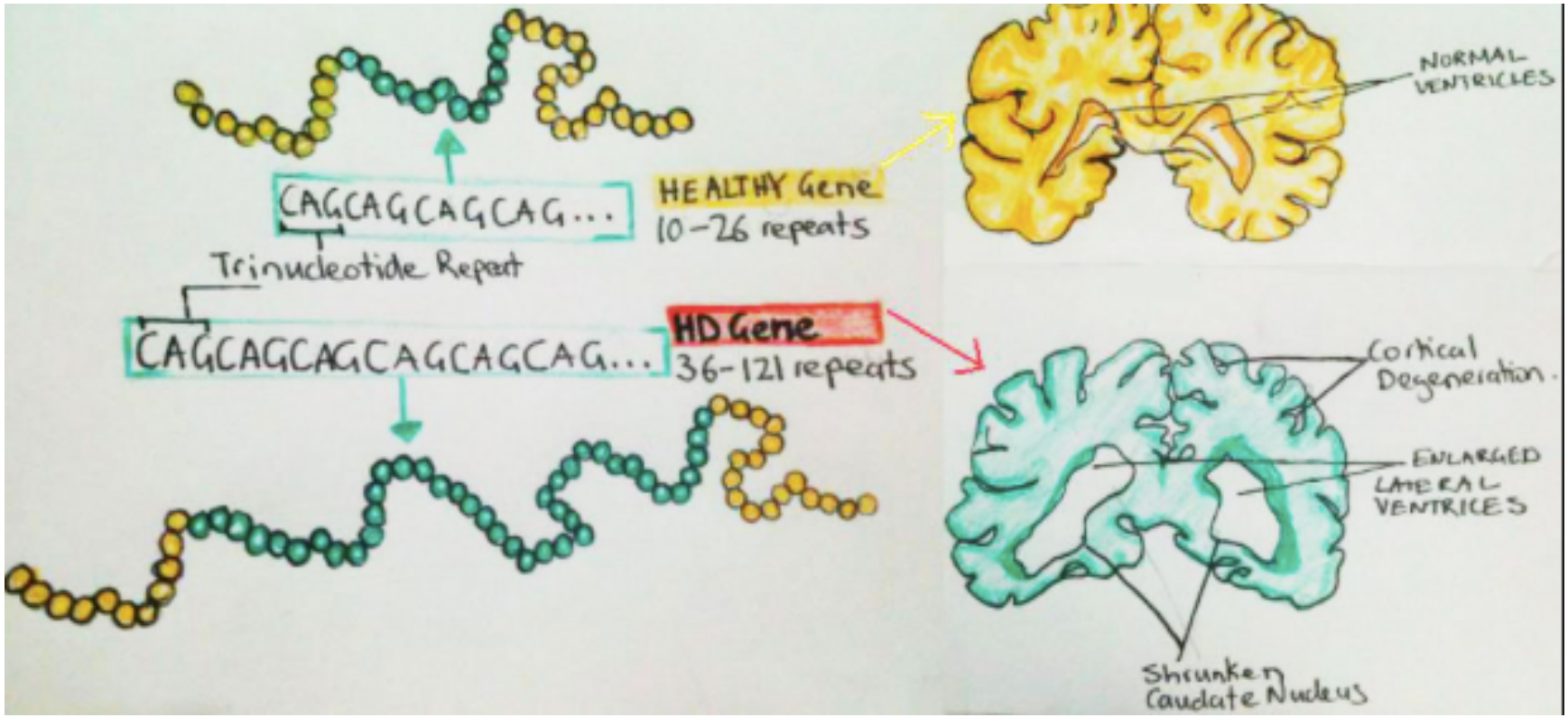
And, other studies are in the works

Summary

- Lots of exciting things are going on in HD
- There is room in clinical trials for anyone and everyone who wants to help
- Some of the newer treatments are more aggressive than what we have tested in the past, but they also show greater potential for success

Many thanks

Two healthy genes (top), one unhealthy gene (bottom)



IONIS study

- **Not** available in USA (currently).
- RNA compound that reduces production of *huntingtin* (via feedback loop in brain cells)
- Cells can catch up on digesting residual *huntingtin* clumps
- Must be administered by spinal tap
- Another Ionis RNA compound, also given by spinal tap, has recently proven effective in Spinal Muscular Atrophy (another gene disorder)

Wave Life Sciences

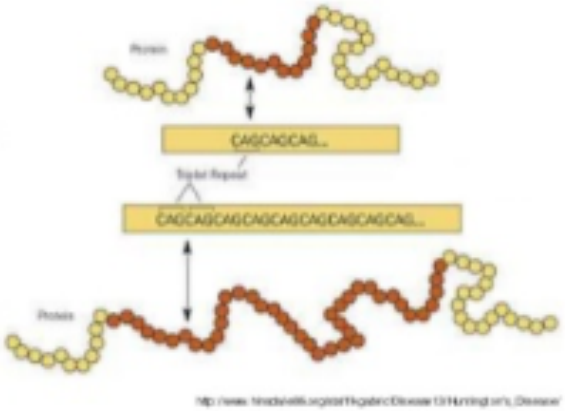
- Developing a study for sites in US using similar RNA technology
- It is selective for reducing only mutant huntingtin (but 20% of potential volunteers will be excluded based on a blood test)
- Only for individuals with early, diagnosed HD
- Will also be administered by spinal tap
- Maybe beginning this summer

How important is the healthy gene?

- How do we know an unhealthy gene still does most of its job?
  - Because, if you have two copies of the unhealthy gene, everything still goes along great, until later, when the clumps begin to cause problems.

Background- Htt and mHtt

- The Huntingtin Protein (Htt)
  - Normal Htt gene has less than ~36 glutamine trinucleotide repeats
  - Mutant form (mHtt) is responsible for HD
    - mHtt gene has over ~36 trinucleotide (CAG) glutamine repeats
  - Has many essential functions
    - Vesicular trafficking, early brain development
    - However, the numerous, exact functions of th Htt protein remain largely unknown



- Cell lines used in project
  - STHdhQ111
    - HD length- 111 glutamine repeats in polyglutamine tract
  - STHdhQ7
    - Normal length- 7 glutamine repeats in polyglutamine tract

Image:
Top- Normal Htt protein with typical glutamine repeat length

Bottom- Mutant Htt protein with elongated glutamine tract

Comments

- Christine O'Neill Research Coordinator
  - Research commentary
- Vicki P. Hunt RN HD nurse
  - Research and care commentary
- Questions for the Wake Forest Group