MIT Introduction to Technology, Engineering, and Science

HTT Hunters

Amal, Genesis, Jacob, Millani

Biological Engineering

Abstract:

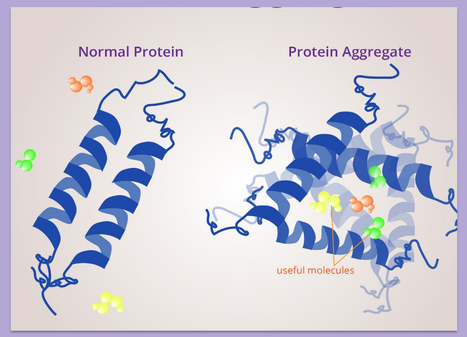
Huntington's disease (HD) is a rare disorder that begins from a mutation on chromosome 4 where 'CAG' sequence repeats itself. Scientists continue to research Huntington's on a surface, and molecular level to try and determine possible treatments, or experiments that can be completed to insure a better quality of life for those experiencing the disease.

Our methods in approaching HD are experimental gene editing. This is the most effective procedure to figure out how to correct the mutated gene, but also discover new ways to prohibit the mutation from passing down through sexual reproduction.

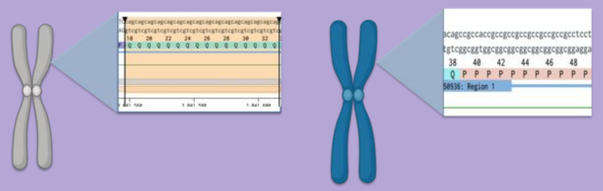
What is Huntington's Disease?

- Huntington's disease is a single-gene disorder and is autosomal dominant inheritance
- In Huntington's Disease, there is a repeat of the three nucleotides "CAG," which encodes the amino acid glutamine.
- The severity of the disease is determined by how many repeats of this CAG there are in the patient's gene.
- Huntington's is a rare disease, and anyone can develop Huntington. It tends to run in people of European descent (having family members who came from Europe)

Diagram of HTT Gene structure:

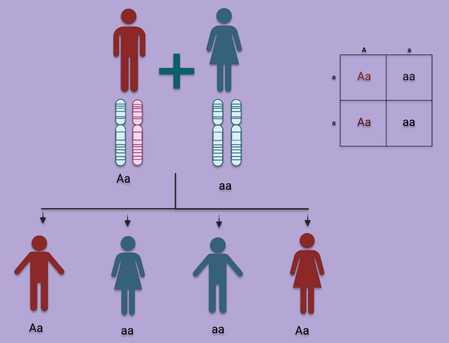


Genetic basis of the disease:



Brain:

Family Tree:



What are current treatments?

- The current treatments help reduce the amount of symptoms and improve their life with Huntington's like Tetrabenazine which treats Chorea

Why we need a new solution?

The current treatments are primarily to address the symptoms rather than trying to cure the disease at hand.

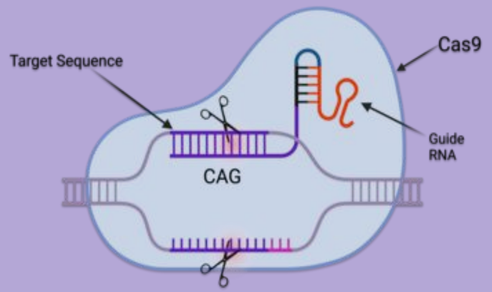
Possible treatment plans

- Bioengineering - Gene editing
  → CRISPR/ Cas9
- Replace gene or use editing to inhibit mutated gene from being passed down

Negative effects

- Off-target / Experimental mutations
- Non-homologous end joining vs. Homology directed repair

CRISPR



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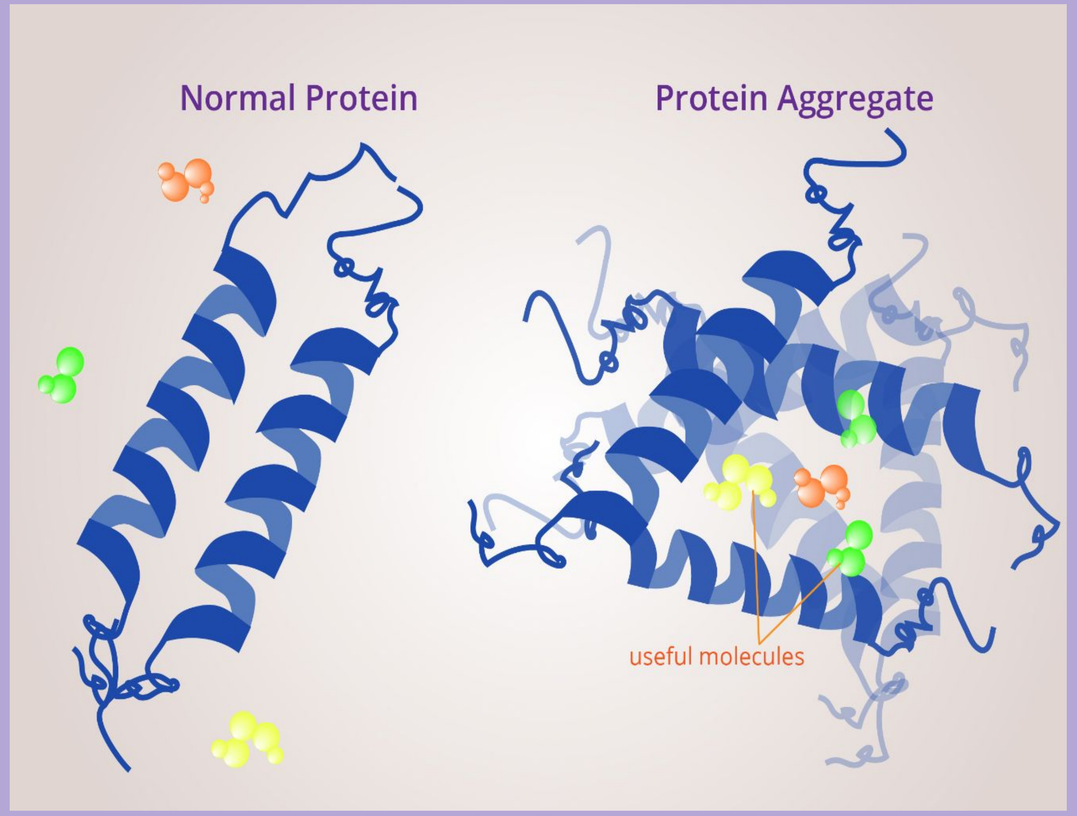
Normal Protein:

→ Folds structures neatly

Natural folding makes it easier for the protein to use it's useful and important molecules



Mutated Protein:

→ Folds into structures that make it challenging for the useful molecules to work together

Unnatural folding creates the large clumps formed! This traps useful molecules, causing a malfunction in the folding process

https://hopes.stanford.edu/prion-like-behavior-in-the-huntingtin-protein/

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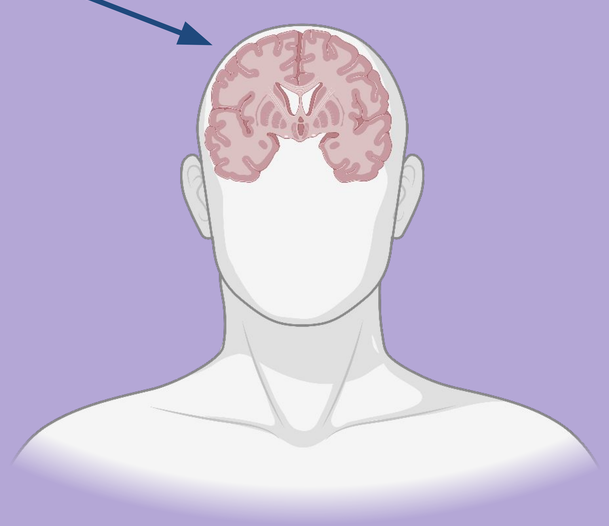
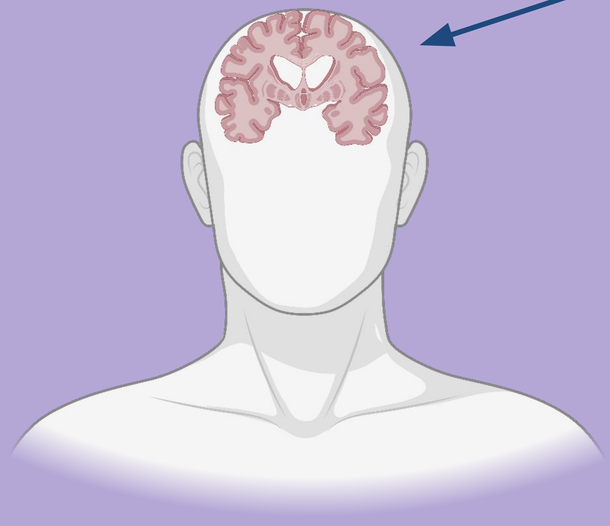
Brain of someone without Huntington's Disease



Brain of someone with Huntington's Disease



- emotional disturbances
- loss of intellectual abilities
- uncontrolled movements

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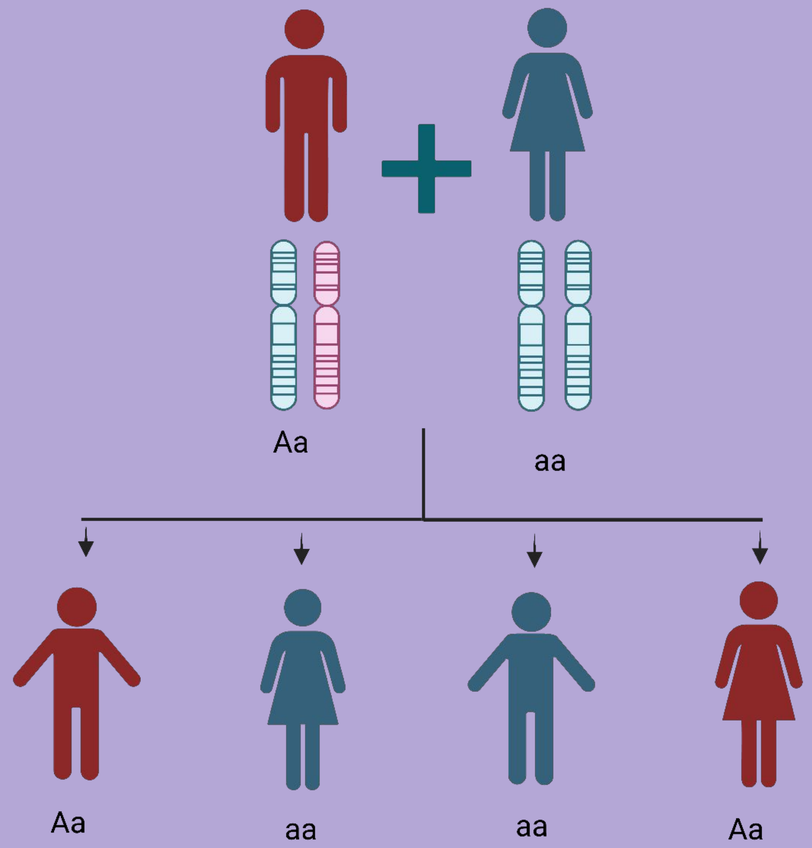

	A	a
a	Aa	aa
a	Aa	aa

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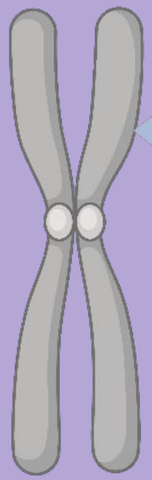
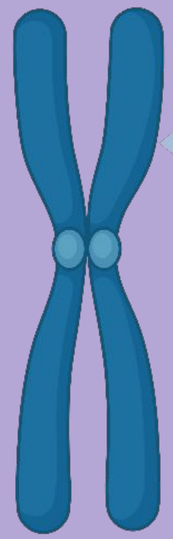
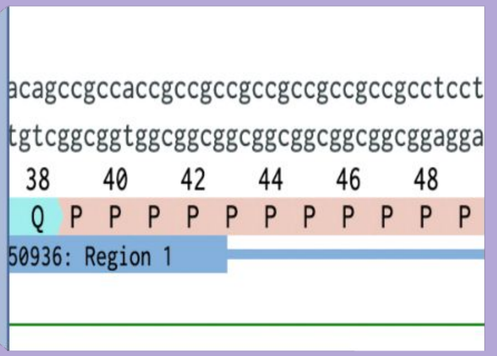
Q = Quantitative marking of CAG repeats



Mutated





Normal

Repeat count	Classification	Disease status	Risk to offspring
<27	Normal	Will not be affected	None
27–35	Intermediate	Will not be affected	Elevated, but <50%
36–39	Reduced Penetrance	May or may not be affected	50%
40+	Full penetrance	Will be affected	50%

Severity of Huntington's!

https://pubmed.ncbi.nlm.nih.gov/17240289/

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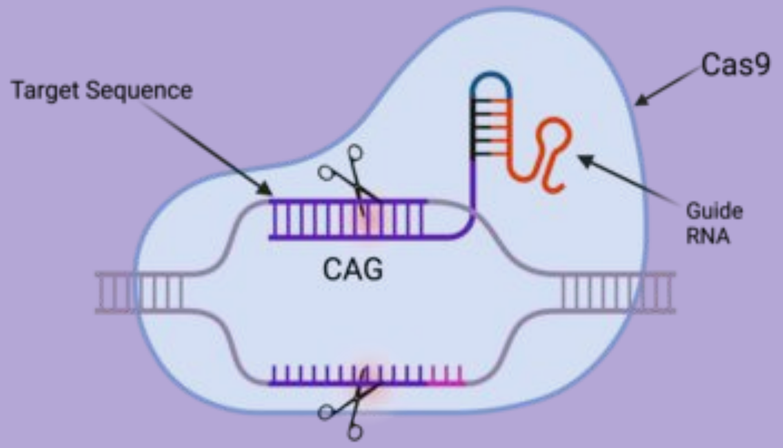
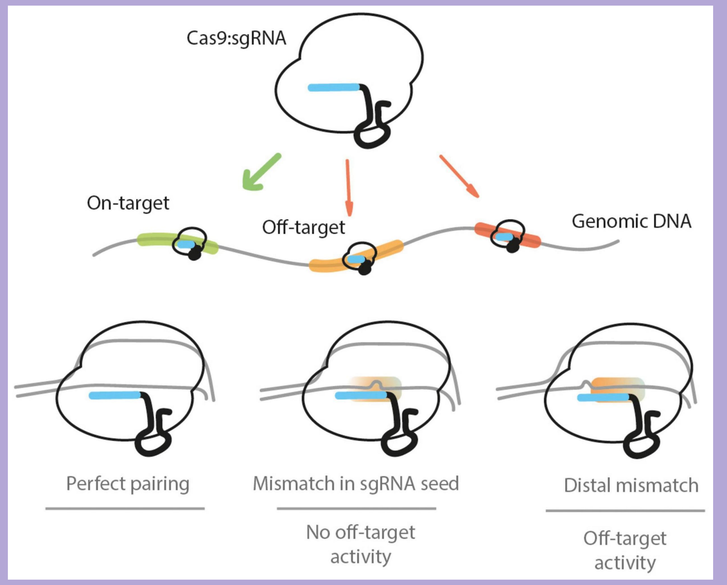


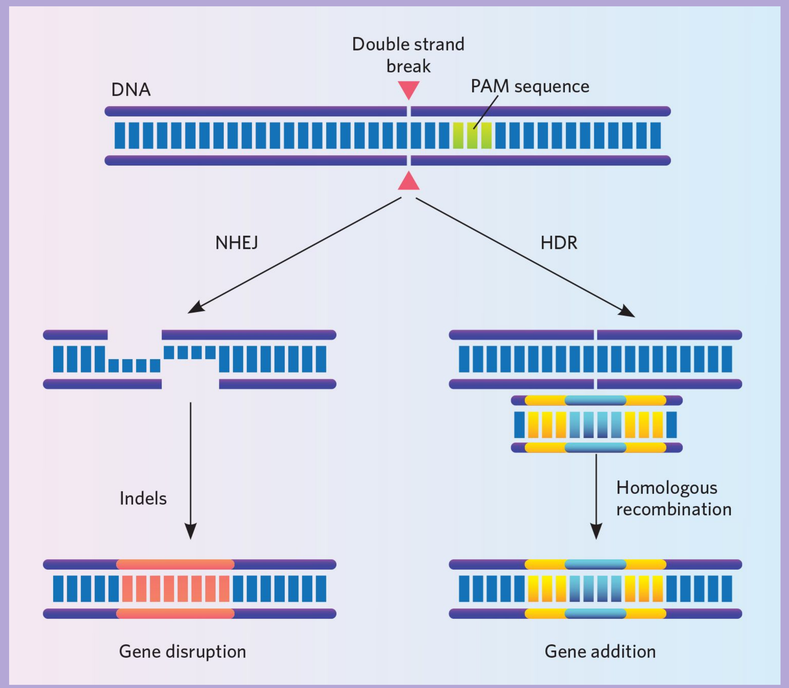
CRISPR PROCESS

1. Target sequence
2. Guide RNA + Cas9
3. PAM sequence (_GG)



OFF- TARGET

- Cas9 binds, and cuts the incorrect segment
- Can lead to more mutations



NON-HOMOLOGOUS

- Cut is made, and there are outlying strands
- Gene uses proteins to fix cell damage
- Can result in more mutations

HOMOLOGY DIRECTED

- (Blunt) Cut is made in the middle of sequence
- Gene can be inserted in the middle