

Auggie's Story: A Child with Huntington Disease

by

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Part I – DNA Replication and Errors

Dr. Schubert was concluding a lecture she had been giving to the college science majors in her genetics course. “Well class, that’s enough for today. But you will need to do some work on your own before our next meeting,” the professor said. “Go online and watch the assigned HHMI Biointeractive animations that summarize DNA replication and errors in DNA replication. Then answer the questions for homework.”

Kaitlyn, a biology major, left the classroom eager to watch the assigned videos, but she was a little worried about trying to remember the details of DNA replication. Freshman year, when she had taken general biology, seemed like a very long time ago, and she hadn’t thought much about the topic since. She definitely needed a refresher.



Follow along with Kaitlyn; watch the videos and answer the questions below.

Videos

- DNA Replication Advanced Detail. Running time: 2:19 min.
<<https://www.biointeractive.org/classroom-resources/dna-replication-advanced-detail>>
- Trinucleotide Repeat. Running time: 1:08 min.
<<https://www.biointeractive.org/classroom-resources/trinucleotide-repeat>>

Questions

1. Distinguish between the role of helicases and DNA polymerases in DNA replication.
2. Compare and contrast the leading and lagging strands in DNA synthesis. Include in your answer a definition of an Okazaki fragment.
3. Errors in DNA replication can result in sections of repeating nucleotides. As shown in the animation, what can cause an expansion of these repeats?

Part II – Trinucleotide Repeats

Two days later, Kaitlyn was back again in genetics class listening to Dr. Schubert.

“Some genes contain multiple repeats of three-nucleotide sequences. Increased numbers of these trinucleotide repeats, CAG for example, are associated with several genetic disorders, including Huntington disease and fragile X syndrome. Maybe you’ve heard about Huntington disease, which is caused by a CAG repeat expansion in protein-coding portions, or exons, of specific genes. But the larger the expansion, the faster the onset of the disease. Did you know that a small percentage of Huntington disease patients have juvenile onset?”

Kaitlyn turned to her classmate; they were both surprised to hear that children could also have this disease. They recalled hearing about Huntington disease in freshmen biology, but thought it was a disease you only “got” when you reached middle age.

“Professor, does Huntington disease run in families?” Kaitlyn inquired.

“That’s exactly the question everyone is to research now,” was the reply.

Dr. Schubert ended class by reminding students that DNA replication must precede cell division. She instructed the class to explore the HHMI Biointeractive “Genetic Mutations and Disease” interactive module, which would help them to answer the homework questions.



Follow along with Kaitlyn; once you access the interactive module, select the “Launch Interactive” button. After you review the information, answer the questions below.

Interactive Module

- Genetic Mutations and Disease.
<<https://www.biointeractive.org/classroom-resources/genetic-mutations-and-disease-0>>

Questions

1. Does Huntington disease run in families? Is the mode of inheritance recessive or dominant? How do you know?
2. An error in DNA replication can lead to mutations in offspring. Does the gene mutation for Huntington disease reside in germline or somatic cells?
3. Would a mutation in a parent’s somatic cell be passed on to their offspring? Justify your answer.
4. Is there a correlation between the CAG nucleotide repeat length and age of onset of the disease?

Part III – Meet Auggie

Dr. Schubert began her next lecture by presenting the medical case of an adolescent named Auggie. In 2007, Auggie, short for August, was born happy and healthy. When he was a few months old, he suffered a seizure and around that same time, developed allergies to eggs and soy. He walked by his first birthday and continued to meet all developmental milestones as a young child.

In kindergarten, what started as a trigger finger (where the digit locks in a bent position) progressed to rigidity in his hand, and soon his whole arm. His behaviors in the classroom also caused concern as he exhibited increased impulsivity and anger. In first grade, his walking gait became irregular, and he fell frequently. Soon, he went from being able to run, to only being able to walk, then only able to crawl, before being unable to move around without his mobility devices. What were once full sentences and conversations became only brief phrases. Occasional grand mal seizures were less common, while petite mal seizures became increasingly common.

In 2014, Auggie underwent genetic testing and was diagnosed with juvenile-onset Huntington disease and 88 CAG repeats. At age 35, his father was diagnosed with adult-onset Huntington disease and found to have 40 CAG repeats. Several paternal aunts and uncles as well as his paternal grandfather were also found to have a history of the disease.

Evaluations in 2015 and 2016 at the University of Iowa Children's Hospital showed Auggie's general intellectual abilities to be in the extremely low range, with deficits in word knowledge, visual-motor skills, spatial perception and motor dexterity.

However, his mood is consistently described as happy and cheerful, and he exhibits no signs of anxiety or worry. Auggie and his mother Nakiah know the reality of his disease, but they will not stop it from living their lives to the fullest.



Figure 1. Meet Auggie! His mother, Nakiah Chinchilla, is on Auggie's left and Elizabeth Manheim, one of the authors of this case study, is on his right. Dr. Manheim has known Auggie since birth. This picture was taken in April, 2018.



Watch the following of Auggie's story that was filmed in April 2018 by the case study authors at Auggie's home in California. Ask your instructor for recommended sources to help you answer the questions below.

Video

- Auggie's Story. Running time: 4:59 min.
<<https://youtu.be/3D-PdRLyn5s>>

Questions

1. If you were not told that Auggie has juvenile-onset Huntington disease, what neurological or genetic disorders might you suspect? Explain why.
2. What therapeutic interventions (pharmaceutic and nonpharmaceutic) are recommended for Huntington disease patients?
3. What would you anticipate is Auggie's prognosis? Justify your response.

Part IV – RNA Interference: Therapy of the Future?

Kaitlyn was inspired by Auggie’s story. She asked Dr. Schubert for further details when she arrived at her next genetics class. “At 13 years of age, Auggie has very limited verbal ability and eats via a nasogastric tube, but he still attends school and socializes with friends. His mother ensures he can still go to the beach with his motorized wheelchair. In 2019, he had electrodes implanted into his brain for deep brain stimulation (DBS) as an experimental treatment to reduce the incidence and severity of his seizures. Auggie still enjoys life with his limitations and not in spite of them.”

Dr. Schubert then displayed a slide showing the genetics of Huntington disease (Figure 2). She continued, “The Huntingtin protein (htt) is encoded by a dominant gene on human chromosome 4, and whereas the normal *HTT* gene has 10 to 26 CAG nucleotide base repeats, the Huntington disease gene mutation has more than 35 CAG repeats.

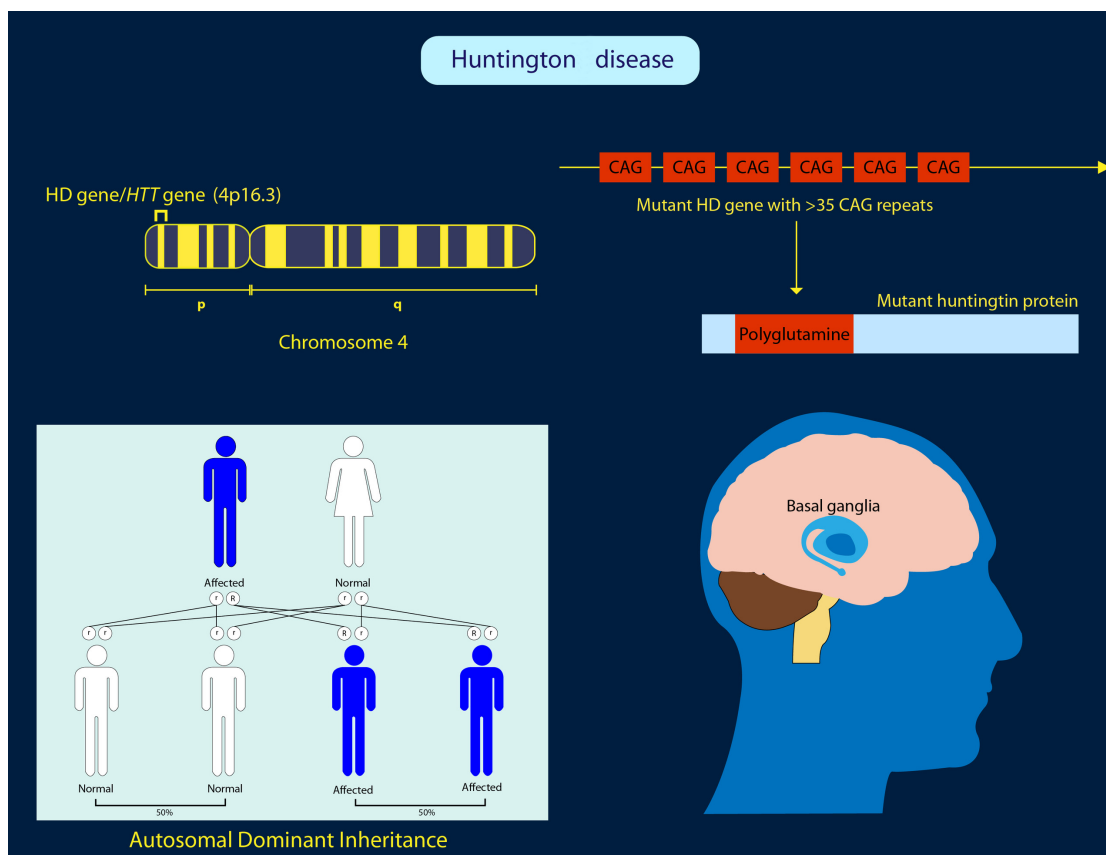


Figure 2. Genetics of Huntington disease. Credit: Meletios Verras | Dreamstime, ID 52510583.

“The htt protein may serve to facilitate the production and transport of brain-derived neurotrophic factor, a protein that promotes the survival and maintenance of neurons. These repeats cause the gene product, the abnormal htt protein, to contain an elongated stretch of glutamate that aggregates and impacts protein function.”

Dr. Schubert finished her lecture by assigning her students a set of homework questions about using RNA interference as a therapeutic strategy for Huntington disease. To help them answer the questions, she directed them to return to the HHMI Biointeractive website and explore the interactive module “Central Dogma and Genetic Medicine.”



Explore the following interactive module. After selecting the “Launch Interactive” button, use the scroll down bar or the next arrowheads to follow the flow of genetic information from DNA to RNA to protein. Click on the pink “+” sign that is labeled “RNA Interference Huntington’s disease” to reveal and read the Genetic Medicine and Case Study Tabs (be sure to open the “Learn more” links too). Then answer the questions on the next page.

Interactive Module

- Central Dogma and Genetic Medicine.
<<https://www.biointeractive.org/classroom-resources/central-dogma-and-genetic-medicine>>

Questions

1. What is the role of mRNA in the central dogma of molecular biology?
2. What structural changes occur in the brain of a Huntington disease patient? Specifically, what area of the brain atrophies?
3. Explain how in clinical trials, small interfering RNA (siRNA) is being tested as a potential therapeutic for Huntington disease. Include the goal of such therapy and any negatives to siRNA therapy.