

Huntington's Disease: Etiology, Research Models and Treatment

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WRITERS' COMMENT: As a student in the social science discipline, my past writing has revolved around explaining psychological theory in practice. Although similar in style and method to writing any research paper in that one must focus on empirical evidence, this class pushed me to look past theory and focus on the topic's scientific background as well as its physical and psychological impact on the patient. Thus, when presented with this term paper for Professor Carey's Longevity class, I sought to challenge myself and research a topic I knew little about. I chose to explore Huntington's Disease as it intersected with many of the themes we discussed in class, including health, mortality, and the genetics of longevity. Huntington's disease is often discussed when highlighting heritable disorders; however, I aimed to approach the subject more holistically in my literature review. This influenced my decision to focus on the etiology, so readers can understand the condition's origins while also highlighting research models and treatment options available to those who live with the disease.

INSTRUCTOR'S COMMENT: Starting with her paper's title and ending with its last bibliographic entry, reading Maram's essay on one of the world's most devastating neurodegenerative diseases was as gratifying as it was informative. Her paper's organization is impeccable, her writing style engaging, direct and succinct, and her research due diligence thorough and complete but not excessive. Especially impressive was not only the time Maram invested in carefully cropping figures and re-typing their legends rather than simply cutting and pasting entire screenshots, but also in her meticulous use of typographical best practice (in her original in-class submission) including her choice of font and

typeface, exact line spacing, wide margins to create shorter lines for ease of reading, and assiduous use of both font emphasis (italics; bold) and font hierarchy (title, headings/subheadings). Her paper is the complete package from head to toe—a sight to behold, a joy to read, and a model to inspire.

—James R. Carey, Department of Entomology

Summary

Huntington's disease is a hereditary disease marked by both physical and cognitive deterioration. The disease is caused by a mutation in chromosome four that elongates a protein to include more Cytosine-Adenine-Guanine (C-A-G) repeats in the huntingtin gene. The number of mutations will determine the severity and onset of the disease, with more C-A-G repeats indicating earlier onset and more aggressive symptoms. This mutation inevitably causes the degenerative symptoms characteristic of the disease, including chorea, abnormal eye movement, difficulty in speech and swallowing, apathy, irritability, and the development of psychological disorders like depression. The disease typically progresses in four stages: prodromal stage, early-stage, moderate stage, and advanced-stage Huntington's disease. Progression between the stages is often slow and may take years or even decades, depending on the severity. Research on the disease has been ongoing since the discovery of the gene responsible. With the use of both small and large animal models, scientists have begun to develop possible therapies. One promising advance in the field is RNA interference, which hopes to directly reduce gene expression of huntingtin by turning off protein translation. This therapy is believed to reduce or hopefully eliminate the mutations altogether, and thus by conjunction, the symptoms seen in patients.

Introduction

The emergence of chromosome mapping in the 1980s enabled scientists to discover the gene responsible for Huntington's disease (HD), and with it came efforts to better understand and treat the condition. To obtain the necessary pedigree information for genetic mapping, scientists followed the disease in two communities. One was in a family in Ohio with a high incidence of the disease and another in the Lake Maracaibo region in Venezuela, where interbreeding has caused a large population of individuals with Huntington's (Chial, 2008). The researchers documented more than seven hundred individuals and tested them for several DNA markers. However, even with the abundance of data, it proved a difficult task. It took researchers over six years to find the DNA marker G8 that was linked to the disease (Gusella, 1984). Its discovery led to greater knowledge of the genes' role in the formation of the neurodegenerative disease, as well as possible therapies.

Overview

History

Huntington's disease was first documented by the Long Island doctor George Huntington who noticed cases of dementia and chorea, which are unpredictable movements, that seemingly ran in families. After seeing a similar pattern with his father's patients as well, Huntington began documenting in great detail the symptoms and onset by following generations of a family who exhibited the condition. Some hallmark symptoms of 'Hereditary Chorea' that he observed included muscle spasms or rigidity, slow and twitching eye movements, impaired cognitive abilities, and lack of impulse control. Perhaps his most astute observation was that if one or both parents showed signs of the disease, then their offspring will likely suffer from the condition as well (Bhattacharyya, 2016).

It is noteworthy that before the earliest medical accounts of

the disease in the 1840s, the condition was still present, although misunderstood and seldom documented. One explanation for this lapse in documentation is a result of the increased life expectancy of the population during the 19th century (Wexler, 2013). Before Huntington and his contemporaries documented the disease, individuals who carried the condition seldom lived long enough for the symptoms to manifest. This may have concealed the conditions' hereditary nature. It was not until advances in technology and the widespread acceptance of physicians that lifespan increased, and thus the progression of the disease could be witnessed more readily (Wexler, 2013).

Etiology

Huntington's disease is a degenerative disease that is caused by a mutation on chromosome four. A healthy individual will have up to 26 Cytosine-Adenine-Guanine (C-A-G) repeats in their DNA on the specific region on the chromosome responsible for the huntingtin protein (Langbehn et al., 2019). However, people with Huntington's disease have a higher prevalence of the sequence repeats due to a mutation, usually 40 or more, and will thus exhibit symptoms of the condition. The elongated protein will get cut into smaller sections that attach themselves to the neurons and thus disrupt the cells' functioning. The symptoms associated with the condition are caused by the changes occurring to the nerve cells as a result of the mutated huntingtin gene. Damage caused to the basal ganglia and cerebral cortex leads to disease symptoms associated with delayed or disrupted movements and conscious thoughts (Langbehn et al., 2019).

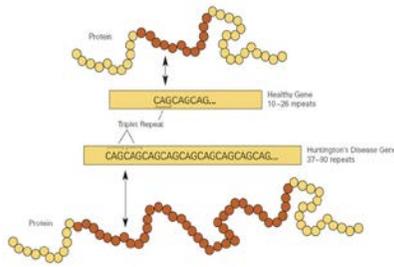


Figure 1: A strain of DNA that indicates the C-A-G repeats present in a healthy individual (on top) and one with Huntington's disease (Source: Australian Academy of Science, 2018).

Carriers of the gene will manifest the disease, with the number of C-A-G repeats indicating the severity of the symptoms. Scientists have categorized the disease into three subsets: adult-onset, which is the most common, and juvenile and infantile-onset, both rarer. Those with early-onset typically have more than 60 C-A-G repeats and thus show earlier signs. As the gene mutation is passed through the generations and is dominantly inherited, parents have a fifty percent chance of passing on the mutation to their children, and the risk of inheritance is no different for the sexes. However, research has shown that women display more symptoms and are more prone to developing depression than men (Hentosh et al., 2021). Individuals who carry between 27 and 35 repeats will not manifest the disease but will pass it on to their children, who are then at risk for developing it. This is because the mutation can enlarge and lead to increased anticipation, meaning the children may have an earlier onset compared to their parents (Mahalingam & Levy, 2014). However, individuals with more than 37 repeats of the mutation, as shown in figure 1, will undoubtedly get the disease and typically develop it as an adult, with symptoms beginning to manifest between the ages of 30 and 50. The elongated protein responsible for the HD mutation can disrupt the protein folding process and lead to synaptic dysfunction and brain damage characteristic of the condition (Shacham et al., 2019). As it is a progressive disease, the

earlier the onset, the more fatal and aggressive the symptoms will likely be (Hogarth, 2013).

Progression

Regardless of onset, the course of the disease is quite similar for those afflicted, with researchers and physicians usually categorizing the progression into four stages: prodromal, early stage, moderate stage and advanced stage Huntington's disease (HD) (Stages of Huntington's Disease, 2021). The progression of the disease can be seen in Figure 2 where motor, cognitive and psychiatric symptoms that are impacted are highlighted. Symptoms associated with the first prodromal stage typically occur 15-20 years before motor symptoms manifest. This stage is mostly categorized by mild cognitive and behavioral changes often only noticeable to the family. The second phase is Early Stage Huntington's, which is where more pronounced motor signs are seen. A major symptom is chorea which is unpredictable movements. This can include abnormal eye movements, changes in facial expressions, and speech. Other mood and cognitive symptoms include apathy, irritability, and the development of psychological disorders like anxiety, depression, and obsessive-compulsive disorder (NHS, 2021). Symptoms continue in moderate stage HD with the progression of symptoms listed above. The worsening of symptoms often leads to the loss of independence due to the faster decline in motor functions. The prevalence of suicide in this stage increases as well. The final stage is advanced-stage HD, where speech becomes very difficult, and around-the-clock care is necessary. Swallowing is impaired, which may lead to the patient being malnourished, susceptible to infection, and even heart failure (A Caregiver's Handbook, 1999).

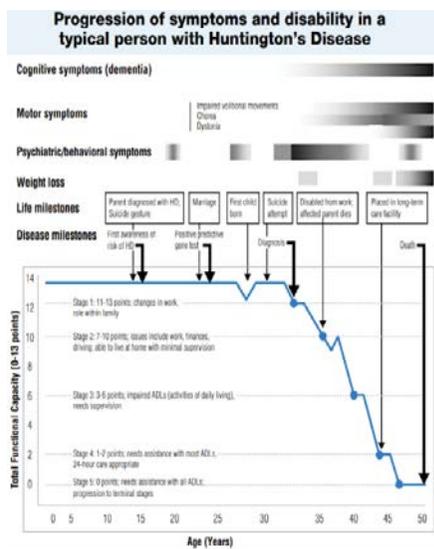


Figure 2: shows the symptoms associated with Huntington's Disease along with their progression and outlines the typical changes in a patient's life before and after diagnosis (Source: Nance et al., 2011)

Models

Small Animal

Many neurodegenerative disorders, including Huntington's disease, are markedly human conditions, making them difficult to mirror in models. However, models remain one of the few ways to test possible therapies, and so their importance has persisted. With the discovery of the mutated gene, it became possible to use models to better understand the disease and investigate potential therapies. The findings from animal models are especially important in illuminating the disrupted pathways caused by the diseases. Although invertebrates, including fruit flies and nematodes, have been used in the past, most research uses rodents,

as genetic engineering is advanced in the model and is quite accessible (Stricker-Shaver et al., 2018). In order to replicate the disease onset, the mice are engineered to express the huntingtin mutation and, as a result, exhibit the associated behavioral and anatomical symptoms. There are two main categories of genetic mouse models, transgenic in which the mice get randomly inserted with a portion of the mutated human gene, and knock-in, where the gene sequence where the mutation is found is altered through substitution (Ramaswamy et al., 2007). The transgenic model is the most widely used; however, it is important to note that specific species are better suited to model certain aspects of the disease (Pouladi et al., 2013).

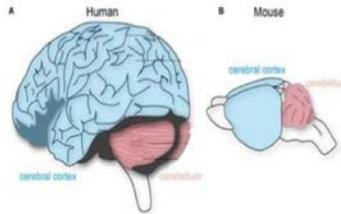


Figure 3: A human and mouse brain model showcasing the cerebral cortex, indicated in blue. Brains are not drawn to scale. (Source: Miterko et al., 2018).

Although the mouse model is necessary to understand Huntington's disease, its use in research does come with limitations. The most significant being the mouse's short lifespan. Huntington's disease is characterized by its progressive nature, and it takes up to forty years to manifest and decades more before a patient succumbs to the disease. This limitation restricts scientists' research as its short lifespan inhibits the possibility of a long-term study. Other models may be better suited for studying the progression at a closer time interval over which the condition progresses in humans. Another limitation is their small brain size which restricts the number of electrodes used when studying the organ. Although the mouse and human brain share 90% of the genes responsible for operating the brain, the human brain is markedly bigger (Kiderra & LaFee,

2021). For reference, as shown in figure 3, the cerebral cortex of a human is a thousand time larger than that of a mouse, and has 1,000 fold more neurons (Hodge et al., 2019). Their variance in size also means that treatment methods tested on mice need to be scaled up when used on humans. This difference makes it hard to scale therapies as it is difficult to determine whether patients need more or less drugs in their system.

Another issue is that rodent brains lack some of the key neuroanatomical characteristics that are present in human brains and that have an important connection to the disease. For instance, the basal ganglia and cerebral cortex of mice are considerably different in structure compared to the ones in humans. The difference in structure is important to note as the basal ganglia is responsible for smooth and coordinated movements (Gonzalez-Usigli, 2021) while the cerebral cortex controls language, motor activity and decision making, all agents that are impacted by Huntington's disease (Estrada-Sánchez & Rebec, 2013). These evolutionary distinctions can complicate scientists' ability to test a treatments effectiveness, and thus it is important for reserachers to understand a model's limits when developing therapies (Morton & Howland, 2013).

Large Animal

In order to address some of the pitfalls of employing mice as a model, research has moved to using large animal models. The ideal test subject would be a non-human primate, such as a chimpanzee, as we share much of our DNA and brain structure. However, research on primates has slowed and is quite costly, so it is rarely done (Morton & Howland, 2013). Thus, scientists have looked toward other large mammalian models, especially farm animals, as they come with some significant and practical benefits. For one, the farming industry already has breeding and rearing systems in place, which makes it a convenient model. Two models in use today are pigs and sheep. They both come with some

important benefits, including being outbred, domesticated, docile, and that housing, caring, and feeding them is relatively inexpensive as they live outside. Another advantage that is useful for clinical research is their weight, which is comparable to that of humans in some species. Their longer lifespan also helps researchers track progressive neurological diseases with greater accuracy than mice models. However, perhaps the most significant advantage is that they have a large and anatomically similar brain to that of humans. Vital structures such as the gyrencephalic cortex, basal ganglia and thalamic nuclei are present in models such as sheep that are not found in mice models (Morton & Howland, 2013). These advantages make it possible to look at the animal's brain structures through magnetic resonance imaging (MRIs) and test therapies that are meant to be delivered directly into the brain.

Sheep are promising models in the study of Huntington's disease as there are several naturally occurring mutations found in their DNA that can manifest into neurological disorders. Some have been found to show resemblance to human neurological disorders such as Batten's and Gaucher's Disease (Weber & Pearce, 2013). This implies that the huntingtin mutation may be able to cause a sheep to exhibit progressive symptoms of the disease as well. A recent study by Jacobsen and company uses transgenic sheep to model the disease and is in the process of being conducted. (Jacobsen et al., 2010) Although none of the sheep have yet to exhibit symptoms of the disease, this was expected, as the sheep are only five years old, and onset is not until late childhood. This study is promising as it paves the way for gene therapy and a better understanding of the disease.

Treatment Options

Pharmacological

Most pharmacological therapies prescribed to patients with Huntington's disease target the symptoms, most notably chorea, as

it is the most common. In 2008, the Food and Drug Administration approved the drug tetrabenazine, otherwise known as Xenazine, for treating chorea associated with Huntington's disease. It is thought that the jerky movements that characterize chorea result from an increase in the activity of monoamines, such as the neurotransmitters Dopamine and Serotonin (FDA, 2008).

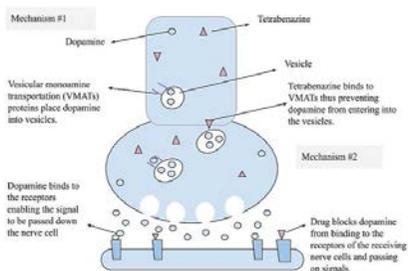


Figure 4: The effects of Tetrabenazine (Xenazine) on neurotransmitters and the two ways in which it operates. First, by binding to neurotransmitters and preventing their penetration into the vesicles and through sending the signals received to the nerve cell (Based on Source: Liou, 2010).

Monoamines are responsible for homeostasis and physiological functions, but more importantly, they are involved in nerve and muscle functions. As highlighted in figure 4, Xenazine operates by reducing the amount of the hormone in the brain, and it does

this in two ways. First, through blocking vesicular monoamine transporters (VMAT's), which are proteins responsible for transporting neurotransmitters to vesicles in the nerve cells. The drug binds to VMAT's and prevents them from storing excess dopamine in the vesicles. Xenazine also prevents dopamine from passing the signal to other receptors (Bio News Incorporated).

Although the drug has helped patients manage some of the disorder's symptoms, it does come with some risks, most notably an increase in depression and suicidal thoughts. This is a major risk for patients because as many as 33-69% of those with the disorder also show symptoms of a depressed mood (Epping & Paulsen, 2011). Also troubling is that reported rates of completed suicide are also high among the population ranging from 3-13%, with as

many as 25% of patients citing they have attempted suicide at least once during their illness (Epping & Paulsen, 2011). As a result, patients are notified of these adverse effects, and with the help of a physician, the need to address chorea in patients is weighed with knowledge on the patient's psychological wellbeing to prevent suicides. Patients should be screened, and Xenazine stopped if suicide ideation persists.

Therapeutic Advances

Since the literature has been expanding over the years and knowledge on the pathogenesis of the disease has broadened, several therapeutic approaches have been tested. One promising therapeutic tool being studied is RNA interference (RNAi) which works by directly reducing gene expression (Abdulrahman, 2011). In the case of Huntington's disease, it decreases the number of the mutant Htt proteins being produced. It can thus help delay the onset of symptoms for patients before debilitating neuropathology occurs. It selectively targets genes by binding to the mRNA of the selected gene and either blocking or hindering the transcription process (Aguilar et al., 2017).

There are two types of RNA interferences being studied that hold some promise. First, *in vitro* synthesis, which is double-stranded small interfering RNA (siRNA) and promoter-expressed short hairpin RNA (shRNA), which are made through viral vectors. Both silence genes; however, the methods differ in their persistence as siRNA needs repeated administration to suppress the gene, whereas shRNA's can be permanent if an appropriate viral vector is used (Harper, 2009). Several preclinical studies in model rats have been shown to be effective in improving Huntington phenotypes, including behavioral deficits. RNAi treatment is especially promising as it has a large therapeutic window and can be administered early to patients with Huntington's disease in hopes of treating the disease before extensive neuropathology occurs (Meghan & Neil, 2011). It may potentially be able to delay onset. However, the therapy does come with side effects, including

the activation of the immune responses and off-target effects if the mRNA binds to the incorrect gene (Meghan & Neil, 2011). The former can be especially problematic because it can change the expression of the non-target mRNA in unknown ways. As a result, it will take some time before this therapy is available to patients.

Conclusion

Since George Huntington's work on documenting the disease, knowledge on the subject has expanded. Over the past three decades, technological advances such as genetic engineering and animal models have enabled researchers to locate the specific gene mutation responsible for the disease. This has fortunately led to a better understanding of the condition. However, despite the efforts of the global community to find a cure, progress toward therapeutic treatment has been slow compared to the rapid success in finding the gene. Physicians can now treat specific symptoms of the disease, such as chorea and depression, with pharmaceutical options, yet a substantial cure has not been found. Thus, the disease remains largely untreatable, but a deeper understanding of the pathological process may lead to advances in the future.

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