Pathogenesis and Therapeutics of Huntington's Disease

Megan Bones

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Ersilia Mirabelli, Ph.D.
Thesis Chair

_____

William Moore, Ph.D.
Committee Member

_____

David Schweitzer, Ph.D.
Assistant Honors Director

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Date

Abstract

Huntington's disease (HD) is a rare, incurable, inherited neurological disease that causes the progressive breakdown of nerve cells in the brain. The mutant huntingtin gene contains 40 to 80 repeats of a CAG trinucleotide sequence. The pathogenesis of HD is multifaceted and includes pathways related to glutamine aggregation, mitochondrial and oxidative stress, mitochondrial dysfunction, and DNA damage. Currently two drugs, tetrabenazine and deutetrabenazine, are FDA approved for the treatment of HD. Otherwise, medications given to HD patients include general antipsychotics, antidepressants, and mood-stabilizer drugs. Other treatment methods include speech and physical therapy. This research provides an understanding of the various maladapted HD pathways, as well as a comparison of the current HD drug therapies and other methods of treatment.

Pathogenesis and Therapeutics of Huntington's Disease

Introduction

Huntington's disease (HD) is a rare congenital neurological disease that is characterized by choreiform movement as well as cognitive and psychiatric dysfunctions. Currently, there is no cure for HD (Illarioshkin et al., 2018). The cumulative HD frequency in the United States is 6.52 per 100,000 persons (Bruzelius et al., 2019). This rate is higher than the total HD global incidence and prevalence rates (Medina et al., 2022). The clinical description of HD was first established in 1872 by the American physician George Huntington, M.D., and in 1993, scientists identified the gene responsible for causing HD was identified (Huntington's Disease Society of America, 2023). This gene is located on chromosome 4 and is responsible for the production of a protein called huntingtin. The normal huntingtin protein plays an important role in axonal transport (Vitet et al., 2020). The mode of inheritance of this gene defect is dominant, meaning that only one copy of the defective gene passed from a carrier parent to offspring is enough to cause the HD phenotype (Myers, 2004). In the normal huntingtin gene, a three-base sequence, CAG, is repeated between 11-29 times. The mutant huntingtin gene contains 40-80 repeats of this CAG sequence (Myers, 2004).

History

In 1872, at 22 years of age, Dr. Huntington authored the paper entitled *On Chorea*, which established the clinical description of HD (Huntington's Disease Society of America, 2023). Chorea piqued Huntington's interest when he started practicing medicine in his hometown (Bhattacharyya, 2016). He observed dementia and chorea in middle-aged patients and noticed that these symptoms ran throughout families (Huntington's Disease Society of America, 2023).

Born into a family of physicians, Huntington noticed some of his father's and grandfather's cases that alluded to the same condition. Each family Huntington studied descended from the same ancestor; Jeffrey Francis, an immigrant from England in 1634 (Huntington's Disease Society of America, 2023). Although Huntington's paper was not the first to examine chorea, it was the most comprehensive report at the time.

58 years after Francis' immigration to America, in 1692, the Salem Witch Trials began in colonial New England. Around that time, several families in colonial New England presented with symptoms similar to HD (Bhattacharyya, 2016). Some have theorized that many of the victims burned during the Salem Witch Trials actually suffered from HD, as they were characterized with choreiform movements and odd behavior (Huntington's Disease Society of America, 2023). 180 years later, when Huntington published *On Chorea*, and theorized that Jeffrey Francis was a common ancestor for HD in the United States, historians favored the idea that Francis brought HD to the United States from England (Huntington's Disease Society of America, 2023). Huntington believed that over time, scientific research would reveal the unknown pathology of chorea, which had always intrigued him (Huntington's Disease Society of America, 2023).

Prevalence and Trends

Based on global studies from 1985 to 2010, the total new cases of HD were estimated as 0.38 per 100,000 persons and the total global prevalence was estimated as 2.71 per 100,000 persons (Medina et al., 2022). A study conducted from 2003-2016 estimated that the HD frequency rate was 6.52 per 100,000 persons in the United States (Bruzelius et al., 2019).

HD is an autosomal dominant inherited neurodegenerative disorder with varying age of onset (Myers, 2004). The average onset age is 40 years; however, patients have developed the disease as early as 2 years and as late as 80 years (Myers, 2004). If one parent has HD, their children have a 50% chance of developing the disease. After onset, patients live for an average of 17-20 years, however those with a late onset HD tend to progress more slowly than those with early onset HD (Myers, 2004). The onset and severity of progression of HD is determined by the number of CAG repeats in the gene and the instability of the HD repeat pattern (Illarioshkin et al., 2018). Trinucleotide CAG repeats of 40 or more are associated with HD. Repeats of 26 or less are considered normal. CAG repeats between 27-39 are considered intermediate. Patients that have an intermediate number of repeats may not have the disease, however they have repeat instability (Myers, 2004). Repeat instability is the phenomenon in which parents, usually fathers, who have an intermediate number of CAG repeats pass a higher number of repeats to their offspring. Therefore, children of parents with intermediate repeats may develop HD, even if their parents do not (Myers, 2004). Additionally, studies have found that juvenile onset HD, before the age of 21, disproportionally occurs when the individual inherited the huntingtin gene from his/her affected father (Myers, 2004). This trend is caused by the meiotic instability of the HD repeat pattern in paternal transmission versus stability in maternal transmission. Furthermore, affected fathers who pass the gene to their children tend to pass a relatively larger expansion of repeats compared to affected mothers (Pinto et al., 2020).

Testing and Diagnosis

The diagnosis for HD requires multiple types of tests. In addition to family and medical history, neurological exams, neuropsychological tests, psychiatric evaluations, general exams,

brain-imaging, and genetic tests are all collectively used to diagnose HD (Mayo Clinic, 2020). The neurological exam and general exam consist of basic questions and tests to examine motor, sensory, and psychiatric symptoms. The reflexes, muscle strength, balance, touch, vision, hearing, and mood are also examined (Mayo Clinic, 2020). The neuropsychological tests involve standardized tests designed to evaluate memory, reasoning, language, spatial reasoning, and mental agility. The psychiatric evaluation involves a deeper examination of the mood, emotional state, behavior patterns, quality of judgement, coping skills, and signs of disordered or unorganized thinking (Mayo Clinic, 2020). After these tests, the patient may be referred to get a brain-imaging test. Imaging techniques such as magnetic resonance imaging (MRI) or computed tomography (CT) scans are used to examine the structure and therefore functions of the brain.

If these tests are suggestive of HD diagnosis, or if the patient has a family history of HD, the final recommended test is genetic testing. There are some conditions that mimic the symptoms of HD, therefore genetic testing will confirm a HD diagnosis (Stoker et al., 2022). Although genetic testing is the most definitive way to diagnose HD, many patients struggle in deciding whether to get the test because of how the results could impact their lives. Patients may withhold having the test until they believe it is absolutely necessary. In this test, DNA from a blood sample is analyzed to determine the number of CAG repeats (National Human Genome Research Institute, 2011). Individuals who do not have HD will usually have 28 or fewer CAG repeats, while patients with HD will have 40 or more repeats. There are many pros and cons to a genetic test, some of which are subjective. Some people find that not knowing if they have HD is more stressful than knowing, while others find the reverse to be true (Stoker et al., 2022) Some at risk patients will get the test before they have children or before they get a new job. The results

of the test could potentially change their outlook on life and future plans, and cause fear and stress for the future. When a patient is deciding whether to receive a genetic test, genetic counseling is highly recommended so that the patients can make a well-informed decision.

Complications

By itself, HD is not fatal. However, the complications that arise from HD make it a fatal condition. Two of the most common complications in HD patients are pneumonia and heart disease (Huntington's Outreach Project for Education at Stanford, 2020). Additionally, HD patients have a higher incidence of choking (Jones et al., 2016). One of the hallmark symptoms of HD is the progressive loss of voluntary muscle control and increase of involuntary muscle movement, which includes the muscles responsible for swallowing (Jones et al., 2016). The epiglottis plays an important role in the swallowing process (Hamakawa et al., 2004). The epiglottis is a flap in the esophagus that prevents food from entering the trachea and allows the food to go down the esophagus and into the stomach. In HD, the epiglottis will often struggle to close off the trachea, which results in food traveling down the trachea instead of the esophagus (Hamakawa et al., 2004). This will increase the potential for choking and increases the potential of respiratory infections (Heemskerk & Roos, 2011; Huntington's Outreach Project for Education at Stanford, 2020).

Symptoms

Symptoms of HD vary between patients, and the most observed symptoms involve dysfunctions in movement, cognitive ability, and psychiatric state (Loi et al., 2018). The management of HD symptoms requires a comprehensive care team, comprised of physicians of varying specialties. While movement, cognitive, and psychiatric dysfunctions are the most

common groups of symptoms, HD patients are also affected by other medical issues, including weight loss, swallowing problems, sleep disturbances, and other complications (Loi et al., 2018).

Movement Disorders

The main movement disorder associated with HD is chorea, which is characterized by involuntary jerking or writhing movements (Ajitkumar & De Jesus, 2022). Other movement disorders include impaired posture, balance, and gait, as well as dystonia, which is characterized by problems with rigidity or muscle contracture (Ajitkumar & De Jesus, 2022). HD patients experience a progressive lack of muscle coordination and control. This increase in atypical involuntary movements and impairment of voluntary movements makes it difficult for HD patients to remain independent. As the disease progresses, HD patients lose the ability to work and perform normal daily activities and become increasingly dependent on the assistance of others (Mayo Clinic, 2020; Varela et al., 2022).

Involuntary movements begin in the extremities, like the hands and feet, and are relatively small (Ajitkumar & De Jesus, 2022). However, as HD proceeds through its course, the pathological movements grow in magnitude. The choreiform activities move from the distal extremities to the facial muscles, and then spread to more proximal and axial muscles. Patients are also affected with hypokinesia, or progressive rigidity of the body (Ajitkumar & De Jesus, 2022). The balance between chorea and hypokinesia varies between patients. HD patients lose control and coordination over muscles in the throat and mouth. This impairment may cause pulmonary complications including decreased respiratory muscle strength and irregular breathing patterns (Jones et al., 2016). As HD progresses, the characteristic dysfunctional movement

patterns also progress, eventually resulting in difficulty walking or standing (Ajitkumar & De Jesus, 2022).

Cognitive Disorders

Cognitive disorders are a major hallmark of HD and are sometimes extant prior to the onset of motor symptoms (Ajitkumar & De Jesus, 2022). These symptoms include difficulty organizing and focusing, slowness in processing thoughts, and lack of awareness, impulse control, and flexibility (Ajitkumar & De Jesus, 2022). Additionally, patients may have trouble with learning new information, and have outbursts and act without thinking (Mayo Clinic, 2020; Mörkl et al., 2016). The cognitive dysfunctions associated with HD often impact higher levels of thinking, therefore patients have problems with multitasking and planning. These cognitive symptoms may also progress into dementia (Ajitkumar & De Jesus, 2022). However, HD-induced dementia is not caused by a lack of memory, but rather as a lack of recall ability. One study indicated that HD patients experienced verbatim memory decline early in the disease but only partial decline of gist memory in late stage HD, meaning that patients could remember the essential meaning of situations throughout the disease, but lost their ability to remember precise situations early in the disease (Chen et al., 2017). Overall, patients with HD experience slowed cognitive functions, and eventually, neurodegeneration.

Psychiatric Disorders

HD patients suffer from psychiatric dysfunctions, the most common of which is depression. Depression in HD patients is usually a response to the news of the disease; however, some studies indicate that HD causes depression through impaired brain function (Ajitkumar & De Jesus, 2022; Bilal et al., 2022). Other psychiatric disturbances associated with HD include

social withdrawal, insomnia, fatigue, sadness, and irritability, among others (Gibson & Springer, 2022; Herzog-Krzywoszanska & Kryzwoszanski, 2019; Karagas et al., 2020). These symptoms are collectively indicative of major depressive disorder. Initially, HD patients become irritable, often resulting in outbursts of anger (Karagas et al., 2020). As the disease progresses, the irritability and outbursts subside in favor of fatigue, and sadness. Progressive apathy is also common in HD patients and often confused with depression (Loi et al., 2018). Many patients also experience a lack of awareness of all three types of symptoms (Ajitkumar & De Jesus, 2022).

Stages of HD Development

The progression of HD occurs in three stages. The *presymptomatic*, *prodromal*, and *manifest* classifications not only focus on symptom development, but also on genetic confirmation and recommended treatments and therapies for each stage (Ajitkumar & De Jesus, 2022). Once patients enter the manifest HD classification, their symptoms are used to categorize the disease as *early*, *middle*, or *late stage* (Huntington's Disease Society of America, 2022). These stages focus on the symptoms of HD, specifically the motor, cognitive, and psychiatric dysfunctions and how they develop throughout the progression of the disease.

Presymptomatic, Prodromal, and Manifest Stages of HD

The presymptomatic, prodromal, and manifest stages of HD describe a combination of genetic and symptomatic milestones, as well as potential treatment options. HD patients in the presymptomatic stage have either a genetic confirmation of the disease or are considered at risk for the disease (Ajitkumar & De Jesus, 2022). At this point, there are no signs or symptoms of motor or cognitive disorders, however there may be suggestive structural abnormalities in brain

imaging. Individuals in this stage may have the CAG expansion repeats but lack symptoms of the disease (Medina et al., 2022).

Following the presymptomatic stage of HD, patients enter the prodromal stage with either a genetic confirmation or the development of clinical symptoms (Ajitkumar and De Jesus, 2022). At this phase, patients begin to experience mild motor and cognitive symptoms. Psychiatric symptoms, specifically behavior changes, are more commonly observed in the prodromal stage. Additionally, brain structure abnormalities consistent with HD are present. Patients may begin treatment for symptoms; however, this treatment is dependent on the individual and severity of symptoms. Individuals in the prodromal stage have the CAG expansion repeats and clearly distinguishable motor and cognitive symptoms (Medina et al., 2022).

The final classification of HD is the manifest stage. Individuals in this stage either have the genetic confirmation of HD or meet the clinical criteria of the manifest stage without a genetic confirmation (Ajitkumar & De Jesus, 2022). At this point, if patients do not have a genetic test, they are highly recommended for genetic counseling and a genetic test, which would confirm the HD diagnosis. Patients at this point experience motor and cognitive dysfunction, which significantly impact their autonomy and ability to perform routine tasks (Medina et al., 2022). Once in the manifest stage, a patient's symptoms can be classified in early, middle, or late stages of HD.

Early, Middle, and Late Stages of HD

Classification as early, middle, or late stage HD hinges largely on the severity of clinical symptoms. The early stage of HD is characterized by minor involuntary movements, and subtle

cognitive symptoms (Huntington's Disease Society of America, 2022). However, early stage HD patients remain largely functional and independent.

As HD patients enter the middle stage, they may lose the ability to complete complex tasks and activities, however, patients are still able to care for themselves independently (Huntington's Disease Society of America, 2022). The characteristic choreiform movement of the patient, in addition to progressive muscular instability and decline in balance, becomes more severe. Cognitive symptoms also increase in severity, as patients find it more difficult to complete problem-solving tasks and have trouble with organization and prioritizing information.

HD patients in the late stage of the disease can no longer function independently. They require care and assistance for most tasks and become dependent on family or other caretakers (Huntington's Disease Society of America, 2022). Motor and cognitive symptoms continue to progress and psychiatric and behavioral dysfunctions become more prominent. However, it is harder to diagnose and treat psychiatric symptoms in the late stage because at that point, patients have trouble speaking and articulating other psychiatric symptoms, like depression, sadness, or irritability. Eventually, many patients become bedridden.

Normal Function

The normal huntingtin protein (HTT) also plays an important role in axonal transport (Vitet et al., 2020). Axonal transport is largely determined by the microtubule network surrounding the neurons. Kinesin motor proteins move molecules from the soma of the neuron to the synapses while dynein proteins move signals towards the soma (Gu et al., 2012). HTT is a large scaffolding protein that interacts with kinesin-1 and dynein motors (Vitet et al., 2020). Through these interactions, HTT allows for the transport of vesicles along axonal transport

microtubules by determining their direction of movement, thereby decreasing their pausing time by preventing directionality competition from different motor proteins (Vitet et al., 2020). Brain-derived neurotrophic factor (BDNF) is one cargo specifically associated with HTT (Vitet et al., 2020). BDNF is important for maintaining connections between cortical and striatal neurons, which is the primary degeneration site in HD (Vitet et al., 2020). HTT allows BDNF-containing vesicles to be released at the cortical-striatal synapse, where it will bind to its receptor and be transported back to striatal neurons and release a survival signal, maintaining neural function (Vitet et al., 2020).

Changes in the MRI between HD patients and normal patients are visible prior to the onset of symptoms (Ajitkumar & De Jesus, 2022). One study found that the brain of the HD patient showed a reduction in the size of the putamen and caudate nuclei, as well as dilation of the frontal horns of each lateral ventricle (Negi et al., 2014). The putamen is involved in learning and motor control, which involves speaking, language, and cognitive function (Ghandili & Munakomi, 2022). HD symptoms include a breakdown in motor control and coordination, as well as impaired speech and a decrease in cognitive function (Ghosh & Tabrizi, 2018). These symptoms may be attributed to a reduction in the size of the putamen in the brain. Additionally, HD patients experience a reduction in the caudate nuclei in the brain (Negi et al., 2014). The caudate nucleus plays a vital role in multiple higher neurological functions. This subcortical structure is responsible for motor activities, such as the planning of movements, memory, learning, and emotion (Driscoll et al., 2022). In later stages of HD, patients have trouble executing voluntary motor control and movements, and exhibit worsening psychiatric symptoms

(Mayo Clinic, 2020). A reduction in the size of the caudate nuclei is currently understood to be correlated with these symptoms (Driscoll et al., 2022).

The putamen and caudate nucleus together form the striatum (Driscoll et al., 2022). The striatum is the major input source for the basal ganglia, which includes three deep brain structures, the globus pallidus, subthalamic nucleus, and substantia nigra. Together these deep brain structures are responsible for controlling voluntary skeletal movement (Driscoll et al., 2022). The hallmark symptom of HD is chorea, or unintended movements (Ajitkumar & De Jesus, 2022). Atypical variations in size of the caudate nucleus have been associated with several neurologic and psychiatric pathologies. Thus, it is logical to postulate that the potential loss of the control of voluntary skeletal movement would result from these size variations (Driscoll et al., 2022). HTT is important in maintaining axonal transport of BDNF containing vesicles (Vitet et al., 2020). BDNF is crucial in promoting neuron survival and in maintaining communication between the cortical and striatal neurons, thus preventing neurodegeneration (Numakawa et al., 2010).

Pathogenesis

It is well-known that HD is caused by a mutation in the huntingtin gene. However, the pathogenesis of this disorder is complex, involving multiple different pathways and systems in the body. These studied pathways include glutamine aggregation, cerebellar degradation, ubiquitination, mitochondrial dysfunction, mitochondrial and oxidative stress, and DNA damage, among others (Illarioshkin et al., 2018).

Genetic Basis and Glutamine Aggregation

At its core, HD is a genetic disorder that affects the body in many ways. It is caused by an increased number of copies of a specific nucleotide sequence in the HTT gene, located on chromosome 4, which codes for the huntingtin protein (National Human Genome Research Institute, 2011). This trinucleotide repeat is CAG, which codes for the amino acid glutamine. Excessive repeats of CAG will lead to the production of excess glutamine; therefore, HD is considered a polyglutamine disease (Illarioshkin et al., 2018).

Similar to other polyglutamine diseases, HD includes a unique conformational characteristic at the protein level (Illarioshkin et al., 2018). Once the huntingtin protein contains 35 or more glutamine residues, its secondary structure gradually transforms from an α-helix to a β-sheet. These β-sheets cross-link to form antiparallel strands, which become the structural basis for complexes formed in the cell (Illarioshkin et al., 2018). These polyglutamine complexes have been found in the nucleus of degenerating neurons, indicating that polyglutamine aggregation in neurons plays a role in the pathogenesis of HD (Saudou & Humbert, 2016).

Additionally, glutamine aggregation is responsible for triggering the neurodegenerative cascade in HD. As HTT is processed, the N-terminal of the protein undergoes post-translational proteolysis, which produces truncated N-terminal fragments (Illarioshkin et al., 2018). These truncated fragments expose the polyglutamine repeats to the surrounding environment and substrates, which makes the mutant huntingtin protein (mHTT) aggressive (Illarioshkin et al., 2018). This triggered aggressive nature of the polyglutamine repeats allows them to aggregate in neurons (Illarioshkin et al., 2018). If these truncated N-terminal fragments are small enough, they will migrate across the nuclear membrane and into the nucleus. There, mHTT triggers the neurodegenerative cascade featured in HD (Saudou & Humbert, 2016).

Protein Degradation in HD

Ubiquitination is the process by which ubiquitin-proteins attach to substrate proteins and target them for degradation and is thus important for protein regulation. Ubiquitination also contributes to the pathology of HD. The mHTT-mediated conformational change into β-sheets causes the formation of spherical inclusions, which have been found in the nuclei of degenerating neurons and contain polyglutamine chains and ubiquitin (Illarioshkin et al., 2018). The presence of ubiquitin in these inclusions suggests that ubiquitination plays a role in mHTT degradation (Harding & Tong, 2018). In fact, the huntingtin protein has been found to directly interact with the ubiquitin-conjugating enzyme E2 (Harding & Tong, 2018). Additionally, the proteolytic 20S nucleus and the regulatory 19S subunit, both involved in the proteasomal complex, are also associated with these inclusions and mHTT (Illarioshkin et al., 2018).

Despite this, the efficiency of degrading mHTT via ubiquitination is low (Illarioshkin et al., 2018). The conformational change that occurs in mHTT allows it to form a more energetically stable molecule. In this more stable conformation, it cannot enter the proteolytic 20S subunit, and thus cannot be degraded (Illarioshkin et al., 2018). Instead, the inclusions that hold mHTT and E2 enzyme function as a place to contain the 20S subunit and 19S subunit, rendering them non-functional (Illarioshkin et al., 2018). Therefore, mHTT continues to aggregate in the nucleus of the neuron, thus contributing to the neurodegenerative cascade and cerebellar degradation.

When the ubiquitination process fails, the huntingtin protein may be phosphorylated by the inflammatory kinase, IKK (Thompson et al., 2009). When the protein is phosphorylated, its normal clearance by a proteasome and lysosome is enhanced. This process reduces the

aggregation of the protein, which helps stop the progression and pathogenesis of HD. Despite this pathway, it was also found that expansions of the trinucleotide CAG repeats reduce the ability of IKK to degrade mHTT (Thompson et al., 2009). Therefore, in some HD patients, degradation via IKK is not efficient and accumulation of mHTT may still occur (Thompson et al., 2009). Nevertheless, the IKK degradation mechanism is a more logical therapeutic target to attenuate the pathogenesis and progression of HD.

Mitochondrial Dysfunction, Oxidative Stress, and DNA Damage

Mitochondrial dysfunction, oxidative stress, and DNA damage are all associated with the pathogenesis of HD. Furthermore, mitochondrial dysfunction and oxidative stress are thought to be central to the underlying mechanism of mHTT toxicity (Tobore, 2019). HTT contributes to normal mitochondrial structure and function and plays an important role in axonal transport. mHTT decreases mitochondrial function and impairs protein movement across the inner mitochondrial membrane, which leads to neurological dysfunction by interrupting axonal transport to striatal neurons (Vitet et al., 2020). Medium spiny striatal neurons are neurons in the striatum considered to be the most susceptible to the effects of mHTT (Chih-Wei et al., 2021). Cortical and striatal neuronal synapses are important for maintaining the structure of medium spiny striatal neurons (Vitet et al., 2020). mHTT inhibits axonal transport and prevents the transport of BDNF and autophagosomes. These two molecules are important for neuronal health across the cortical-striatal synapse and may contribute to neurodegeneration. mHTT can also impact medium spiny striatal neurons because of their high energy demand due to their high mitochondrial content. (Costa & Scorrano, 2012). Therefore, the medium spiny neurons would be more susceptible to mitochondrial dysfunction and inhibition of cellular respiration. mHTT

heightens the vulnerability of the striatum, as the protein induces mitochondrial transcription defects and interferes with mitochondrial structures in striatal neurons (Tobore, 2019).

Oxidative stress contributes to the accumulation of mHTT in the nuclei of neurons because it causes proteasomal dysfunction in cells that express mHTT (Tobore, 2019). mHTT can aggregate in these cells and will not be broken down because the degradation machinery in the cells is nonfunctional (Ayala-Peña, 2013). Ku70 is a protein that is involved in DNA repair, specifically nonhomologous end joining of double stranded DNA breaks (Enokido et al., 2010). Ku70 does not repair DNA breaks independently, but rather forms a complex with Ku80 and DNA-protein kinases (Enokido et al., 2010). mHTT causes double-stranded breaks of genomic DNA. Following the DNA break, mHTT interacts with Ku70, which prevents it from repairing the break. Since mHTT is bound to Ku70, the repair complex with Ku80 and DNA-protein kinases cannot be formed (Enokido et al., 2010). The DNA remains damaged, which contributes to the accumulation of DNA damage in the neurons and neurodegeneration. Additionally, oxidative stress can lead to both nuclear and mitochondrial DNA damage. The accumulation of oxidative DNA lesions has been found to correlate with CAG expansion, which is directly related to the development of HD (Ayala-Peña, 2013). Other experiments have shown that the levels of oxidative nuclear DNA lesions are higher in the striatum and cerebral cortex of animal models of HD (Ayala-Peña, 2013).

Neurodegenerative Cascade

The neurodegenerative cascade featured in HD is the result of the aforementioned genetic and protein dysfunctions. The cerebellum is the brain structure that regulates and coordinates muscle activity (Mehrabi et al., 2016). The aggregation of mHTT in the nucleus of the neuron is

associated with initiating the neurodegenerative cascade, including the cerebellar degradation, that is responsible for many of the hallmark symptoms of HD. Some of these symptoms include chorea and the loss of involuntary muscle control and coordination. However, not everyone who presents these motor symptoms have the same cerebellar degradation. There is a strong association between symptom variability and neuronal loss in the cerebral cortex and basal ganglia (Singh-Baines et al., 2019). Variable degeneration of the medium spiny neurons in the matrix compartment of the striatum, which contains the putamen and caudate nucleus, is associated with the motor symptoms of HD (Mehrabi et al., 2016). Cortical and striatal synapses require brain-derived neurotrophic vesicles to release their contents to promote survival signals between the neurons (Vitet et al., 2020) However, mHTT inhibits axonal transport, which directly interferes with the passage and delivery of these vesicles containing survival signals, thus contributing to neurodegeneration. Pyramidal cells are the most common neurons in the cerebral cortex and project to the striatum (Mehrabi et al., 2016). In eight different regions of the cerebral cortex, the loss of these pyramidal cells correlates with different symptoms associated with HD (Mehrabi et al., 2016).

General Prognosis

Once diagnosed with HD, the general prognosis is poor. There is no cure for the disease, but rather a combination of drug treatments and physical therapies focusing on the treatment of symptoms. The course of the disease is around 15-20 years (Ajitkumar & De Jesus, 2022). This number depends on the length and stability of the trinucleotide CAG repeats. The number of CAG repeats is inversely related to the age of onset of the disease (Illarioshkin et al., 2018) and directly related to the rate of disease progression (Myers, 2004). Ultimately, the progression of

HD will result in complete dependency (Ajitkumar & De Jesus, 2022). At first, the patient will be able to function on his/her own, however as the disease continues to progress and symptoms worsen, patients rely on others and eventually need full-time care. The cause of death of most patients is not Huntington's disease itself, but the complications that arise because of the disease. One study indicated that HD patients are subject to suicide and suicidal ideations more than the general population (Wetzel et al., 2011). Another study discovered that 86.8% of HD patients died from aspiration pneumonia while 7.5% of HD patients died from cardiac disease (Heemskerk & Roos, 2012). Overall, the most common causes of death of HD patients are suicide, pneumonia, and heart disease (Ajitkumar & De Jesus, 2022).

Approved HD Drugs: Tetrabenazine and Deutetrabenazine

Despite abundant research and interest in HD, the FDA has only approved two drugs, tetrabenazine and deutetrabenazine, to specifically treat the symptoms associated with HD (Heo & Scott, 2017). Tetrabenazine was the first drug produced and approved by the FDA, followed by deutetrabenazine. Both tetrabenazine and deutetrabenazine are structurally similar, reversible inhibitors that bind to vesicular monoamine transporter type 2 (VMAT2) (Scorr & Factor, 2018). VMAT2 is expressed in monoaminergic cells in the central nervous system that functions to concentrate neurotransmitters and promote the rapid re-uptake of monoamines into neurons. Tetrabenazine and deutetrabenazine both function by depleting dopamine and other monoamines in the central nervous system (Chen et al., 2013). Dopamine plays a role in voluntary movement control and abnormally increased dopamine levels in the striatal synapse has been linked to HD (Chen et al., 2013). Therefore, depleting excess dopamine in these synapses is a potential treatment method (Chen et al., 2013).

In an efficacy comparison between the two drugs, motor scores and adverse effects were not significant, however patients experienced fewer depression symptoms when taking deutetrabenazine (Rodrigues et al., 2017). Compared to tetrabenazine, deutetrabenazine has a longer half-life, reduced metabolic variability, is required in lower doses and less frequently, and has improved tolerability, therefore leading to better patient compliance (Rodrigues et al., 2017). Furthermore, deutetrabenazine has been shown to be better tolerated as it causes fewer adverse effects, including depression, which is more appealing to HD patients (Rodrigues et al., 2017).

Other Medications and Therapies

While tetrabenazine and deutetrabenazine are helpful, they are not cures. Therefore, the majority of HD patients are treated with drugs and therapies that focus on palliative care (Ajitkumar & De Jesus, 2022). These drugs are used to manage chorea, muscle tremors, depression, anxiety, and cognitive dysfunction. Other supportive therapies may include speech therapy, physical therapy, occupational therapy, psychotherapy, as well as tailored at-home care regimens. There are also many new therapies. Several medications are in clinical trials. Other palliative drugs and gene therapy are also being evaluated (Ajitkumar & De Jesus, 2022).

Palliative HD Drugs

Palliative drugs are useful throughout the course of HD, especially near the end of life. Two antipsychotic drugs, haloperidol and fluphenazine, are given to HD patients to reduce chorea, however, the adverse effects from these drugs may worsen other HD symptoms (Mayo Clinic, 2020). Other antipsychotic drugs, quetiapine and olanzapine, are recommended to reduce violent outbursts and other mood disorders in patients, and these too, could trigger or exacerbate other movement disorders in HD patients (Ajitkumar & De Jesus, 2022). Additionally,

medications such as amantadine and levetiracetam may help suppress chorea, but the adverse side effects limit their use (Ajitkumar & De Jesus, 2022). Similar limitations are recorded for palliative drugs approved for psychiatric disorders common with HD, including the antidepressants Prozac (fluoxetine) and Zoloft (sertraline) (Ajitkumar & De Jesus, 2022). Overall, the benefits and side effects of each medication should be taken into heavy consideration before recommending them to a patient with HD.

Chlorzoxazone

A study performed in mouse models indicated that cerebral Purkinje cells would experience less activity in aging mice with HD, compared to mice without HD (Egorova et al., 2020). Markedly reduced activity in this region is associated with a loss of control of muscle movement and coordination (Egorova et al., 2020). The study evaluated chlorzoxazone, a muscle relaxer normally used to treat skeletal muscle conditions. Chlorzoxazone has already been in preclinical trials to treat episodic ataxia type 2 (Egorova et al., 2020). The results of this study indicated that chlorzoxazone alleviated muscle control and coordination symptoms related to HD, likely by alleviating the rapid firing of neurons and their impairment (Egorova et al., 2020). Specifically, chlorzoxazone restored the normal motor performance in the mice with HD (Egorova et al., 2020). Chlorzoxazone is a modulator of SK channels, which are important in the refractory period after an action potential in a neuron (Egorova et al., 2020). These impressive results indicate that chlorzoxazone should be used in more trials to determine its efficacy and safety in human models.

Azadiradione

In a study using mouse models, azadiradione, which is also used to treat infections and cancer, was found to restore protein quality control, and alleviate HD (Singh et al., 2018). Azadiradione helped enhance the folding of mHTT, helping it remain in physiological conformation, α-helices, instead of transforming into pathological β-sheets (Singh et al., 2018). The prevention of this conformational change has favorable effects regarding disease progression, as it prevents aggregation of mHTT in the nucleus of neurons. Furthermore, the study found that azadiradione treatment improved motor deficits and increased the lifespan in mice with HD (Singh et al., 2018). Overall, azadiradione is another promising drug that should be further evaluated for human application.

Regulatory Roles of microRNAs

One possible alternative therapy for HD involves the regulatory roles of microRNAs (miRNA). miRNA is a non-coding RNA strand that is responsible for gene regulation at the post-transcriptional level (Chih-Wei et al., 2021). One miRNA can target several different downstream genes and regulate multiple pathways simultaneously. In the context of HD, studies have shown that dysfunctions in miRNAs result in targeting proteins involved in ubiquitination and other degradation mechanisms, preventing the degradation of mHTT, and causing the accumulation of glutamine aggregates (Chih-Wei et al., 2021). Some studies have indicated that the use of artificial miRNAs can reduce the expression of mHTT and HTT. Although not selective, these artificial miRNAs will decrease the number of mHTT aggregates and help alleviate symptoms of HD (Chih-Wei et al., 2021). There is still much unknown about how exactly miRNAs can be employed for use in the treatment of HD, however since miRNAs are already closely related to the condition, this possible avenue for treatment is being considered.

Gene Therapy

Gene therapy is a novel approach to the treatment of HD. Through gene therapy, either all huntingtin genes could be silenced, or mHTT could be selectively silenced (Ajitkumar & De Jesus, 2022). Gene silencing would regulate and prevent the expression of either the normal huntingtin gene or the mutant huntingtin gene. If the gene expression was decreased, HD may be less severe. However, the use of this for HD is under consideration and being evaluated for study (Ajitkumar & De Jesus, 2022).

Speech, Physical, Occupational, and Psychotherapy

Speech therapy can be used to address the loss of control and coordination over the muscles in the mouth and throat that are necessary for speech, eating, and swallowing (Jones et al., 2016). A speech therapist can help the patient develop alternative ways to communicate. Commonly used strategies include voice therapy, reducing environmental distractions, and gestures (Ajitkumar & De Jesus, 2022). Physical therapy helps HD patients with coordination and balance (Ajitkumar & De Jesus, 2022). As the disease progresses, patients will eventually lose their strength, flexibility, and balance, and may become at higher risk for falls. A physical therapist can work with the patient throughout their treatment and can supply them with strategies and exercises needed to preserve their muscular health and independence for as long as they can (Mayo Clinic, 2020). Some strategies include assistive walking devices and the implementation of fall prevention programs (Ajitkumar & De Jesus, 2022). An occupational therapist can assist the patient and their family or caregivers with what they need to function at home. Home assistive devices include handrails, seats for baths, as well as adapted eating and drinking utensils (Ajitkumar & De Jesus, 2022). Finally, psychotherapy is used to help the

patient with behavioral issues and mental wellbeing. The psychotherapist can help the patient develop coping strategies and help the family understand and communicate with the patient (Jones et al., 2016). Overall, the management and treatment of HD is not an individual effort. Rather, it requires collaboration between the patient, his/her family, and those charged with the patient's medical care and therapy.

Conclusion

HD is a multifaceted, progressive, neurological disease that is characterized by motor, cognitive, and behavioral dysfunction. The disease is fatal with progressive severity of health decline (National Human Genome Research Institute, 2011). The pathology and cellular pathways that underlie the development of the disease is complex. Great strides have been made in research of the disease, as two drugs have been approved by the FDA for use to specifically treat symptoms of HD. These drugs, tetrabenazine and deutetrabenazine, although similar to one another, help alleviate chorea and other motor, cognitive, and psychiatric symptoms (Rodrigues et al., 2017). Despite these new and approved drugs, there is still a lack of research aimed at identifying novel therapeutics for HD. As research techniques continue to develop and additional discoveries about HD are made, new treatment options may become available to those who need them. Future research should focus specifically on selectively silencing mHTT via gene therapy or non-selectively decreasing mHTT and HTT expression via artificial miRNAs (Ajitkumar & De Jesus, 2022; Chih-Wei et al., 2021).

References

Ajitkumar, A., & De Jesus, O. (2022). *Huntington disease.* StatPearls Publishing LLC. https://www.ncbi.nlm.nih.gov/books/NBK559166/#_NBK559166_pubdet_

Ayala-Peña, S. (2012). Role of oxidative DNA damage in mitochondrial dysfunction and Huntington's disease pathogenesis. *Free Radical Biology and Medicine, 62,* 102-110. https://doi.org/10.1016/j.freeradbiomed.2013.04.017

Bhattacharyya, B.K. (2016). The story of George Huntington and his disease. *Annals of Indian Academy Neurology, 19*(1), 25-28. https://doi.org/10.4103%2F0972-2327.175425

Bilal, H., Warren, N., Dahanayake, P., Kelso, W., Farrand, S., & Stout, J.C. (2022). The lived experiences of depression in Huntington's disease: A qualitative study. *Journal of Huntington's Disease, 11*(3), 321-335. https://doi.org/10.3233/jhd-220537

Bruzelius, E., Scarpa J., Zhao, Y., Basu, S., Faghmous, J., & Baum, A. (2019). Huntington's disease in the United States: Variation by demographic and socioeconomic factors. *Movement Disorders, 34*(6), 858-865. https://doi.org/10.1002/mds.27653

Chen, I.W., Chen, C.M., Wu, Y.R., & Hua, M.S. (2017). Patterns of false memory in patients with Huntington's disease. *Archives of Clinical Neuropsychology, 32*(4), 391-400. https://doi.org/10.1093/arclin/acx022

Chen, J.Y., Wang, E.A., Cepeda, C., & Levine, M.S. (2013). Dopamine imbalance in Huntington's disease: A mechanism for the lack of behavioral flexibility. *Frontiers in Neuroscience, 7*(114). https://doi.org/10.3389%2Ffnins.2013.00114

Chih-Wei, T., Pin-Yu, H., Siew, C.C., Cheng, P.H., & Yang, S.H. (2021). The regulatory roles of microRNAs toward pathogenesis and treatments in Huntington's disease. *Journal of Biomedical Science, 28,* 1-11. http://dx.doi.org/10.1186/s12929-021-00755-1

Costa, V., & Scorrano, L. (2012). Shaping the role of mitochondria in the pathogenesis of Huntington's disease. *The EMBO Journal, 31*(8), 1853-1864. https://doi.org/10.1038%2Femboj.2012.65

Driscoll, M.E., Bollu, P.C., & Tadi, P. (2022). *Neuroanatomy, Nucleus Caudate.* StatPearls Publishing LLC. https://www.ncbi.nlm.nih.gov/books/NBK557407/#_NBK557407_pubdet_

Egorova, P.A., Gavvrilova, A.V., & Bezprozvanny, I.B. (2020). Ataxic symptoms in Huntington's disease transgenic mouse model are alleviated by chlorzoxazone. *Frontiers in Neuroscience*. http://dx.doi.org/10.3389/fnins.2020.00279

Enokido, Y., Tamura, T., Ito, H., Arumughan, A., Komuro, A., Shiwaku, H., Sone, M., Foulle, R., Sawada, H., Ishiguro, H., Ono, T., Murata, M., Kanazawa, I., Tomilin, N., Tagawa, K., Wanker, E.E., & Okazawa, H. (2010). Mutant huntingtin impairs Ku70-mediated DNA repair. *Journal of Cell Biology, 189*(3), 425-443. https://doi.org/10.1083/jcb.200905138

Ghandili, M., & Munakomi, S. (2022). *Neuroanatomy, Putamen.* StatPearls Publishing LLC. https://www.ncbi.nlm.nih.gov/books/NBK542170/#_NBK542170_pubdet_

Ghosh, R., & Tabrizi, S.J. (2018). Clinical features of Huntington's disease. *Advances in Experimental Medicine and Biology.* https://doi.org/10.1007/978-3-319-71779-1_1

Gibson, J.S., & Springer, K. (2022). Social withdrawal in Huntington's disease: A scoping review. *Journal of Huntington's Disease, 11*(1), 17-24. https://doi.org/10.3233/jhd-210519

Gu, Y., Sun W., Wang, G., Jeftinija, K., Jeftinija, S., & Fang, N. (2012). Rotational dynamics of cargos at pauses during axonal transport. *Nature Communications, 3.* https://doi.org/10.1038/ncomms2037

Hamakawa, S., Koda, C., Umeno, H., Yoshida, Y., Nakashima, T., Asaoka, K., & Shoji, H. (2004). Oropharyngeal dysphagia in a case of Huntington's disease. *Auris Nasus Larynx, 31*(2), 171-176. https://doi.org/10.1016/j.anl.2003.11.001

Harding, R.J., & Tong, Y.F. (2018). Proteostasis in Huntington's disease: Disease mechanisms and therapeutic opportunities. *Acta Pharmacologica Sinica, 39*, 754-769. https://doi.org/10.1038/aps.2018.11

Heemskerk, A.W., & Roos, R.A.C. (2011). Dysphagia in Huntington's disease: A review. *Dysphagia, 26*(1), 62-66. https://doi.org/10.1007/s00455-010-9302-4

Heemskerk, A.W., & Roos, R.A.C. (2012). Aspiration pneumonia and death in Huntington's disease. *PLoS Currents, 4.* https://doi.org/10.1371%2Fcurrents.RRN1293

Heo, Y., & Scott, L.J. (2017). Deutetrabenazine: A review in chorea associated with Huntington's disease. *Drugs, 77*(17), 1857-1864. http://dx.doi.org/10.1007/s40265-017-0831-0

Herzog-Krzywoszanska, R., & Krzywoszanski, L. (2019). Sleep disorders in Huntington's disease. *Frontiers in Psychiatry, 12*(10). https://doi.org/10.3389/fpsyt.2019.00221

Huntington's Disease Society of America. (2023). *History of Huntington's Disease*. https://hdsa.org/what-is-hd/history-and-genetics-of-huntingtons-disease/history-of-huntingtons-disease/

Huntington's Disease Society of America. (2022). *Huntington's disease stages.* https://hdsa.org/what-is-hd/huntingtons-disease-stages/

Huntington's Outreach Project for Education at Stanford. (2020). *Complications of Huntington's disease.* https://hopes.stanford.edu/complications-of-huntingtons-disease/#:~:text=Pneumonia%20and%20heart%20disease%20are,than%20the%20non%2DHD%20population.

Illarioshkin, S.N., Klyushnikov, S.A., Vigont, V.A., Seliverstov, Y.A., & Kaznacheyeva, E.V. (2018). Molecular pathogenesis in Huntington's disease. *Biochemistry*, *83*(9), 1030-1039. https://doi.org/10.1134/S0006297918090043

Jones, U., Busse, M., Enright, S., & Rosser, A.E. (2016). Respiratory decline is integral to disease progression in Huntington's disease. *European Respiratory Journal*, *48*(2), 585-588. https://doi.org/10.1183%2F13993003.02215-2015

Karagas, N.E., Rocha, N.P., & Stimming, E.F. (2020). Irritability in Huntington's disease. *Journal of Huntington's Disease, 9*(2), 107-113. https://doi.org/10.3233/jhd-200397

Loi, S.M., Walterfang, M., Velakoulis, D., & Looi, J.C.L. (2018). Huntington's disease: Managing neuropsychiatric symptoms in Huntington's disease. *Australasian Psychiatry*, *26*(4), 376-380. https://doi.org/10.1177/1039856218766120

Mayo Clinic. (2020, April 14). *Huntington's disease*. https://www.mayoclinic.org/diseases-conditions/huntingtons-disease/doctors-departments/ddc-20356125

Medina, A., Mahjoub, Y, Shaver, L., & Pringsheim, T. (2022). Prevalence and incidence of Huntington's disease: An updated systematic review and meta-analysis. *Movement Disorders, 37*(12), 2327-2335. https://doi.org/10.1002/mds.29228

Mehrabi, N.F., Waldvogel, H.J., Tippett, L.J., Hogg, V.M., Synek, B.J., & Faull, R.L.M. (2016). Symptom heterogeneity in Huntington's disease correlates with neuronal degermation in the cerebral cortex. *Neurobiology of Disease, 96*, 67-74. https://doi.org/10.1016/j.nbd.2016.08.015

Mörkl, S., Müller, N.J., Blesl, C., Wilkinson, L., Tmava, A., Wurm, W., Holl, A.K., & Painold, A. (2016). Problem solving, impulse control and planning in patients with early- and late-stage Huntington's disease. *European Archives of Psychiatry and Clinical Neuroscience, 266*(7), 663-671. https://doi.org/10.1007%2Fs00406-016-0707-4

Myers, R.H. (2004). Huntington's disease genetics. *NeuroRx, 1*(2), 255-262. https://doi.org/10.1602%2Fneurorx.1.2.255

National Human Genome Research Institute. (2011, November 17). *About Huntington's disease.* https://www.genome.gov/Genetic-Disorders/Huntingtons-Disease

Negi, R.S., Col, L., Manchanda, K.L., Col, & Sanga, S. (2014). Imaging of Huntington's disease. *Medical Journal Armed Forces India, 70*(4), 386-388. https://doi.org/10.1016%2Fj.mjafi.2012.08.002

Numakawa, T., Suzuki, S., Kumamaru, E., Adachi, N., Richards, M., & Kunugi, H. (2010). BDNF function and intracellular signaling in neurons. *Histology and Histopathology, 25*(2), 237-258. https://doi.org/10.14670/hh-25.237

Pinto, R.M., Arning, L., Giordano, J.V., Razghandi, P., Andrew, M.A., Gillia, T., Correia, K., Mysore, J.S., Grote Urtubey, D.M., Parwez, C.R., von Hein, S.M., Clark, H.B., Nguyen, H.P., Forster, E., Beller, A., Jayadaev, S., Keene, C.D., Bird, T.D., Lucente, D.,…Wheeler, V.C. (2020). Patterns of CAG repeat instability in the central nervous system and periphery in Huntington's disease and in spinocerebellar ataxia type 1. *Human Molecular Genetics, 29*(15), 2551-2567. https://doi.org/10.1093/hmg/ddaa139

Rodrigues, F.B., Duarte, G. S., Costa, J., Ferreira, J. J., & Wild, E. J. (2017). Tetrabenazine versus deutetrabenazine for Huntington's disease: Twins or distant cousins? *Movement Disorders Clinical Practice, 4*(4), 582-585. https://doi.org/10.1002/mdc3.12483

Saudou, F., & Humbert, S. (2016). The biology of huntingtin. *Neuron, 89*(5), 910-926. https://doi.org/10.1016/j.neuron.2016.02.003

Scorr, L.M., & Factor, S.A. (2018). VMAT2 inhibitors for the treatment of tardive dyskinesia. *Journal of the Neurological Sciences, 389,* 43-47. https://doi.org/10.1016/j.jns.2018.02.006

Singh, B.K., Vatsa, V.K., Kumar, V., & Kumar, S.S. (2018). Azadiradione restores protein quality control and ameliorates the disease pathogenesis in a mouse model of Huntington's disease. *Molecular Neurobiology, 55*(8), 6337-6346. http://dx.doi.org/10.1007/s12035-017-0853-3

Singh-Bains, M.K., Mehrabi, N.F., Sehji, T., Austria, M.D.R., Tan, A.Y.S., Tippett, L.J., Dragunow, M., Waldvogel, H.J., & Faull, R.L.M. (2019). Cerebellar degeneration correlates with motor symptoms in Huntington disease. *Annals of Neurology, 85*(3), 396-405. https://doi.org/10.1002/ana.25413

Stoker, T.B., Mason, S.L., Greenland, J.C., Holden, S.T., Santini, H., & Barker, R.A. (2022). Huntington's disease: Diagnosis and management. *Practical Neurology, 22*(1), 32-41. https://doi.org/10.1136/practneurol-2021-003074

Thompson, L.M., Aiken, C.T., Kaltenbach, L.S., Agrawal, N., Illes, K., Khoshnan, A., Martinez-Vincente, M., Arrasate, M., O'Rourke, J.G., Khashwii, H., Lukacsovich, T., Zhu, Y.Z., Lau, A.L., Massey, A., Hayden, M.R., Zeitlin, S.O., Finkbeiner, S., Green, K.N., LaFerla, F.M.,…Steffan, J.S. (2009). IKK phosphorylates Huntingtin and targets it for degradation by the proteasome and lysosome. *Journal of Cell Biology, 187*(7), 1083-1099. https://doi.org/10.1083/jcb.200909067

Tobore, T.O. (2019). Towards a comprehensive understanding of the contributions of mitochondrial dysfunction and oxidative stress in the pathogenesis and pathophysiology of Huntington's disease. *Journal of Neuroscience Research, 97*(11), 1455-1468. https://doi.org/10.1002/jnr.24492

Varela, L.E., Aria, M.M., Martorell-Poveda, M.A., Giraldo, C.V., & Estrada-Acuña, R.A. (2022). Beyond the clinical context: the process of losing oneself living with Huntington's disease. *Orphanet Journal of Rare Diseases, 17*(1). https://doi.org/10.1186%2Fs13023-022-02330-9

Vitet, H., Brandt, V., & Saudou, F. (2020). Traffic signaling: New functions of huntingtin and axonal transport in neurological disease. *Current Opinion in Neurobiology, 63*, 122-130. https://doi.org/10.1016/j.conb.2020.04.001

Wetzel, H.H., Gehl, C.R., Dellefave, L., Schiffman, J.F., Shannon, K.M., Paulsen, J.S. & Huntington Study Group. (2011). Suicidal ideation in Huntington disease: The role of

comorbidity. *Psychiatry Research, 188*(3), 372-376.

https://doi.org/10.1016%2Fj.psychres.2011.05.006