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Huntington's Disease: A Systematic Review and Overview of Treatments

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Huntington's Disease: A Systematic Review and Overview of Treatments

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Abstract

Huntington's Disease (HD) is a genetic neurodegenerative disease that is the result of a mutation of the huntingtin gene. The gene is passed in an autosomal dominant fashion and is the result of multiple Cystine, Adenine, and Guanine base repeats. HD symptoms manifest as motor, cognitive, and psychological symptoms that can range of chorea movements to depression or apathy. The disease progresses through various prodromal and clinical stages as the disease starts to manifest. The current technique to diagnose HD is the use of direct genetic testing, which counts the number of repeats. Due to the nature of HD, both the diagnosis and the symptoms of the disease themselves can cause psychological impacts for the individual impacted, the caregiver(s), and for those that are determined to be non-carriers. Currently, most of the HD treatments are focused on symptom management as there is no cure. These treatments can include prescription medications, non-medical forms of treatment, genetic-based treatments, and preventative measures. By providing an overview of HD, how it is diagnosed, the psychological aspects of the disease, and the overall treatments for the disease, it is the hope that awareness to HD can be increased to help improve general knowledge and to increase research efforts.

Table of Contents

I. Introduction

Words have different meanings to various people. Some people hear the word “dog” and are flooded with memories of joy while others are flooded with thoughts of terror or fear. When people hear “Huntington’s disease” something similar can happen. For some people they will have no clue what the disease is, or they may vaguely remember it from a class or television show. However, for others, they will know exactly what this disease is and what it entails. They will know the emotions that come with the disease, they will know what it is like to either have the disease themselves or to watch a family member with this disease. So, it can be seen how words, can evoke different emotions or knowledge depending on who is interpreting them.

The goal of this thesis is to introduce Huntington’s disease so that this word can have a more potent meaning to more people. Maybe these individuals will never experience or know anyone with the disease, however, maybe when they hear those words, they will have something come to mind. To achieve this goal an overview of Huntington’s disease will be discussed, including some current and future treatment options.

Many people do not know that Huntington’s Disease (HD) exists. Most people know what Alzheimer’s, Parkinson’s disease, and Lou-Gehrig’s disease are. They know that with each of these diseases comes problems with cognition, memory, and movement. What many do not know is that with HD, it can be similar to having the symptoms of all three diseases in one condition. With HD there is problems with cognition and processing, there are problems that develop with memory, and there are movement issues present as well. Thus, it is important to spread awareness about this disease so that more people are aware of it. Furthermore, if there is more awareness of the disease this can lead to greater opportunities for funding and research into the disease.

By providing an overview of HD, how it is diagnosed, the psychological aspects of the disease, and the overall treatments for the disease this purpose of bringing awareness can be achieved. For the general overview portion, the genetics of HD, the pathology of the disease, and the stages of disease progression will be examined. The diagnosis portion will examine the history of genetic testing, how a diagnosis is obtained, and syndromes or conditions that are similar to HD. The psychological aspects portion will look at how the disease and the diagnosis of the disease impacts the individual with the disease, the caregiver, and those who are non-carriers for the disease. The treatment portion will give an overview of treatments including prescription medications, non-medical forms of treatment, and genetic based treatments.

II. General Overview of Huntington's Disease

Huntington's Disease (HD) is a rare autosomal dominant disease that results in degeneration of the medium spiny neurons of the striatum (Jimenez-Sanchez et al., 2017). The striatum is a structure located within the basal ganglia and can be seen in Figure. In Figure 1, the striatum is the shaded area where the caudate nucleus is labeled (*Know Your Brain: Striatum*, n.d.; Gonzalez-Usigli, 2022). As a result of this degeneration, the disease is seen to have cognitive decline, decline in motor skills, and various psychiatric symptoms. As of 2017, the disease is thought to have a prevalence of "four to ten cases per 100,000 in populations of Western European origin." This prevalence may be slightly higher as there are likely many cases of undiagnosed HD (Jimenez-Sanchez et al., 2017, p. 1).

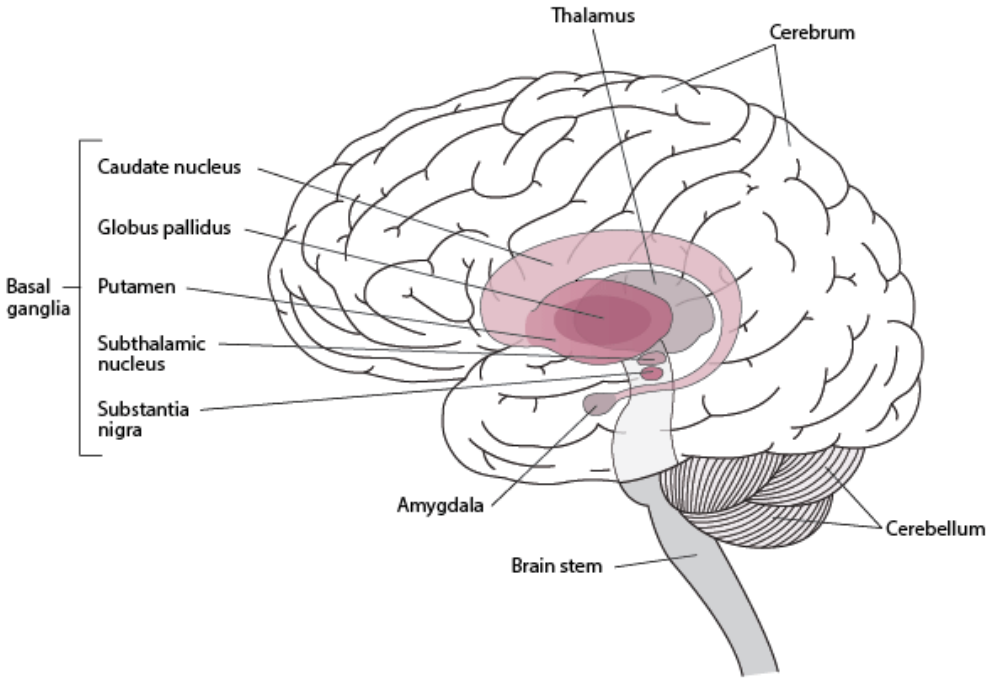

Figure 1. Image highlighting the area of the basal ganglia within the brain. Structures within the basal ganglia, the cerebrum, cerebellum, and the brainstem (Gonzalez-Usigli, 2022).

Genetics of Huntington's Disease

The gene associated with HD is the huntingtin gene (HTT gene). This gene is located on chromosome 4, specifically 4p16.3. The p designates that the gene is located on the short arm of the chromosome and the number 16.3 designates which specific band the gene is located on. The normal alleles for this gene are known as wildtype alleles (Zoghbi & Orr, 2022).

The HTT gene has a portion of it that is made up of CAG (Cystine, Adenine, and Guanine) base segments that repeat. For individuals with HD, the number of CAG repeats present, age of onset of the disease, and severity of symptoms will vary. For the normal HTT gene, known as the wild type gene, there can be between 6 and 26 of these repeats. However, more than 26 repeats can begin to result in issues. Individuals with 27 to 35 repeats are unlikely to develop HD but can potentially pass the disease on to future generations. Future generations are at risk to develop HD due to the expansion of the repeats as genetic information is being passed. The expansion of the gene is referring to the addition of additional CAG repeats to the gene. This increase in the number of repeats typically causes earlier onset and more intense progression. Individuals with 36 or more repeats typically develop HD, and individuals with greater than 40 repeats will have full penetrance of the disease. There is also a juvenile form of HD which is usually expressed when there are 60 or more repeats. Anticipation is seen within the transmission of HD. This means that as the unstable HTT gene becomes expanded as it passes from generation to generation. As this unstable region expands, onset of the disease occurs sooner and disease symptoms become more severe (Zoghbi & Orr, 2022).

Disease Pathology and Symptoms

In HD, when the normal amount of CAG repeats is present on the HTT gene, the wild type huntingtin protein is synthesized. While the functions of wild type huntingtin are not fully understood, it is known that the protein is necessary. Experiments showed that wild type

huntington is also involved in brain derived neurotrophic factor (BDNF) production and the transport of vesicles that carry the BDNF. Two other experiments also indicated that wild type HTT can have a role in inhibiting pro-caspase 9, which allows the wild type HTT protein to have a neuroprotective quality as well. Therefore, it is likely that wild type huntington does have some important roles in the body (Catteno et al., 2005).

HTT Protein and Disease Pathology

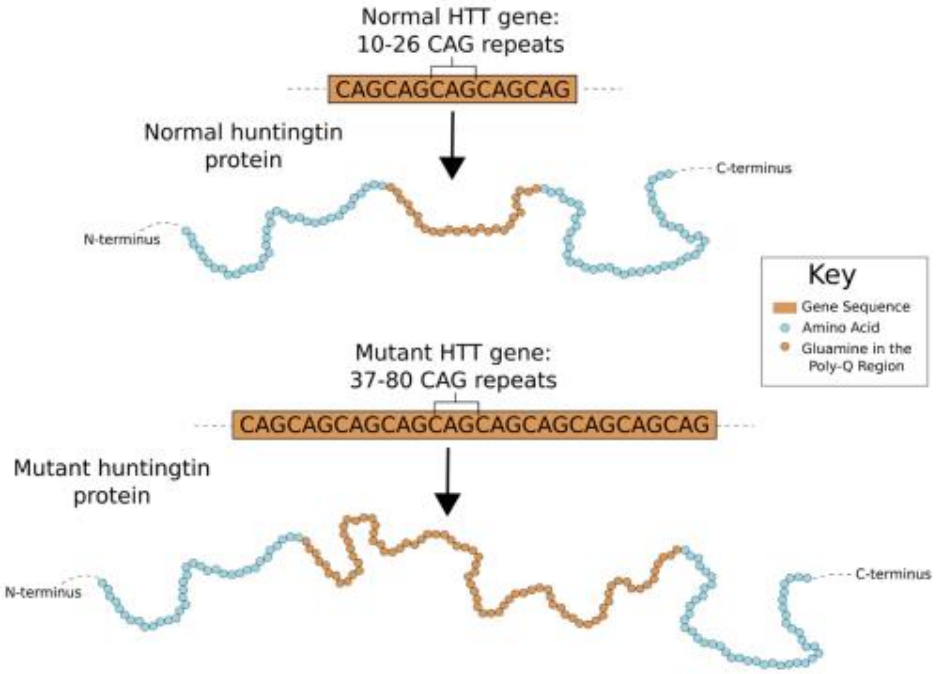

Figure 2. This image provides an example of a normal and mutant HTT gene and protein (*Detecting Huntington's Disease Experiment Objective - Edvo-Kit #1125*, n.d.).

However, some experimentation suggests that depending on where the aggregates are, they may have either a protective or toxic function. Typically, with HD, aggregates seem to form in the cytoplasm of cells. However, with the juvenile form of the disease, these aggregates are usually found more in the nucleus of the cell instead. This research noted that the cytoplasmic and nuclear aggregates do seem to be relatively harmless to the cell. However, some research

suggests that the aggregates that are classified as nuclear, may actually be around the nucleus (perinuclear) rather than actually being inside the nucleus. This research suggested that these perinuclear aggregates may be more toxic or harmful to the cell. These perinuclear aggregates cause harm as they seem to be involved in initiating the cell cycle process prematurely (Jimenez-Sanchez et al., 2017).

While information is still not fully certain on the role of aggregates in HD, it is known that the accumulation of fragments of the HTT protein is toxic and a characteristic of HD. These proteins have also been seen to accumulate more in the nucleus than in the cytoplasm. Their increased likelihood to accumulate and form aggregates in the nucleus may be linked to their toxicity. The origin of these N-terminal fragments are proteases, proteolyzing by caspases, and other mechanisms of the cell. There has been some research into therapeutic applications that could minimize the creation of these toxic fragments (Jimenez-Sanchez et al., 2017).

Another major way that mutant HTT may impacts cells is by altering gene expression. One way that mutant HTT alters gene expression is through the disruption of transcription. Mutant HTT influences the regulators of transcription as a result of HD's expanded polyglutamate region (this is the region that the CAG repeats code for) interacting with the glutamine areas of these regulators. Some examples of these regulators are cAMP response binding element, p35, and many others. It is thought that this impact in transcription is also responsible for the decrease in the amount of brain-derived neurotrophic factor (BDNF). BDNF is involved in ensuring and aiding in the survival of neurons in the striatum. Therefore, if its production is impaired, this can contribute to the neuronal death and symptoms that are developed in HD (Jimenez-Sanchez et al., 2017).

These examples are just a few that provide an idea of how the mutant HTT protein can lead to HD. The mutant protein can cause the disease as it disrupts various cellular processes. These disruptions can consist of prematurely starting the cell cycle, the production of toxic mutant HTT fragments, or changes in transcription or gene expression. Overall, these disruptions lead to problems within the cells and neurons, and these problems ultimately result in cell death (Jimenez-Sanchez et al, 2017).

Symptoms

Since the HD protein affects result in the deterioration of neurons, the diseases symptoms take the form of cognitive, motor, and psychological symptoms. The combination of these symptoms usually leads to problems in various aspects of life and in later stages of the disease, more assistance and care. The cognitive symptoms of the disease lead to problems in processing speed and flexibility of thinking. Some examples of cognitive symptoms are difficulty multitasking, difficulty with complex thoughts and tasks, attention deficits, problems recognizing emotions, and overall problems with memory and language. The motor symptoms of the disease affect the individual in a physical manner. Some examples of the motor symptoms are slow movements (bradykinesia), balance difficulties (walk or gait that is unsteady), and other movement issues that can limit the activities that the individual can engage in or lead to the individual falling. Another motor symptom, known as chorea is a major symptom of the disease and one of the most obvious symptoms. Chorea is when parts of the body undergo brief and irregular movements that are similar to the movements associated with Parkinson's disease. Chorea will usually start in the face muscles, hands, fingers, or legs, and progress throughout the body, including to the trunk. The psychological symptoms of the disease affect the behaviors and emotions of the affected individual. Some examples of the psychological symptoms of the

disease include depression, apathy, problems with decision making, and being impulsive. All of these symptoms can contribute to the daily to day difficulties faced by individuals with the disease (Babačić et al., 2019; *Huntington's disease symptoms*, n.d.).

Disease Progression

HD can be characterized by stages when examining the progression of the disease. There are a few stages of the disease that an individual can be characterized in prior to clinical diagnosis (motor diagnosis). The first stage is the "at risk" stage of the disease where the individual has no symptoms and is just at risk for developing the disease. These individuals are untested and have a biological parent who has a diagnosis of the disease. Once an individual undergoes genetic testing for the HTT gene and receives a positive result, they are considered to be in the "carrier" stage. At this stage, these individuals will still not have any symptoms of the disease onset yet. Once symptoms of the disease manifest, the affected individual is known to be in the "prodrome" stage of the disease (Paulsen et al., 2017).

Prodromal Stages of Huntington's Disease

There are several substages or degrees to the prodromal stage of HD. These stages are prodrome I, II, and III. Prodrome is characterized by the onset of symptoms. These symptoms can vary when examining these individuals. It is thought that the development of cognitive and psychological symptoms starts in this stage prior to the start of motor symptoms. However, these individuals are starting to lose brain volume, contributing to these symptoms and the onset of early motor symptoms (Paulsen et al., 2017).

In the prodrome I stage, the loss of brain volume in the basal ganglia is noted. The intensity of the motor symptoms that have resulted from this loss can also vary in this stage between individuals. The cognitive and psychological symptoms are also likely to start

presenting, but are not easily discerned in this stage. Most of these symptoms will be slower completion of tasks and impairments in thought processes. However, to observe this in most scenarios testing would need to be done to evaluate motor, cognitive, and psychological standing. Prodrome I is also synonymous with being farther from onset, with a prediction of onset being in thirteen years or longer. Since onset is predicted to be far in the future, this stage is also characterized by having a low probability of motor diagnosis within the near future (within five years) (Paulsen et al., 2017).

Prodrome II is the next stage of prodromal progression of HD. Prodrome II is considered to be more of a transitional stage of the disease. Many individuals tend to end up in different progressions of the disease, with some individuals progressing faster or slower than others. The faster progression is likely attributed to the disease progressing to the point where it becomes more aggressive and progresses rapidly. Thus, it is seen in this stage that symptoms continue to worsen in the individuals. Prodrome II is associated with individuals progressing to the stage where they are at the midpoint of the time until they receive a motor diagnosis (Paulsen et al., 2017).

The last stage of prodromal progression is Prodrome III. Prodrome III, is the stage that is associated with the greatest chance of receiving motor diagnosis within five years. During this stage, decline can be observed the easiest in tests and scans as decline is becoming more rapid (Paulsen et al., 2017).

Clinical Stages of Huntington's Disease

Once clinical diagnosis of motor symptoms occurs, the stages of the disease are the clinical stages of the disease. The Huntington's Disease Society of America (HDSA), separates the disease into early, middle, and late disease stages. In early stages of the disease, an affected

individual will still be able to function and take care of themselves. However, they will experience symptoms such as the beginnings of chorea, minor motor problems, problems with depression, and the beginnings of cognitive decline (*Huntington's Disease Stages*, n.d.).

Middle stage, according to the HDSA, this stage is where some individuals start to lose their ability to be independent. Their loss of independence is due to the loss of being able to work, manage finances, do chores, or drive. Despite this lack of independence, these individuals can still somewhat carry out personal hygiene and basic need tasks, though they may need assistance. Symptoms with this stage include more pronounced chorea, problems with motor functions, balance, and problems with complex thought (*Huntington's Disease Stages*, n.d.).

In the late stage of the disease, symptoms are more severe due to disease progression. In this stage the chorea is markedly more severe, the movement and balance issues are more pronounced, communication abilities are very hindered, etc. (*Huntington's Disease Stages*, n.d.).

III. Diagnosis of Huntington's Disease

While HD can be diagnosed by looking for the presence of clinical symptoms, genetic testing is a way to confirm genetically that HD is present before or after onset. Through genetic testing, individuals will be able to learn if they carry the mutant HTT allele that causes HD. Other testing can be used to diagnose HD clinically, this means to diagnose the onset of symptoms. Thus, the history of genetic testing for HD, how a diagnosis obtained, and conditions that can be misdiagnosed as HD will be explored.

History of Genetic Testing

Modern genetic testing for HD uses a process known as direct genetic testing in order to determine if the mutated allele is present. This type of genetic test involves counting the number of CAG repeats present. If the number of repeats surpasses the threshold number of CAG repeats, then it can be determined that the mutant allele is present and the development of HD will occur (*Huntington's Disease*, n.d.). Before getting a genetic test, individuals must speak with a genetic counselor and undergo genetic counseling before they can receive the test. This pre-test counseling is to assist the individual in making sure they want to know their genetic status, and to make sure they can and know how to cope with a positive diagnosis (*Pre-Symptomatic Testing*, n.d.).

While direct genetic testing is common in modern medicine, this was not always how HD was diagnosed. Prior to direct genetic testing, a method known as linkage analysis was used to diagnose individuals with HD. Linkage analysis use for genetic testing was first offered in 1986, as the genetic markers for HD were found in the 1980s (Crozier et al., 2014). Linkage analysis can be used to determine the location of a gene. This was based off the ideal that genes close to each other on the chromosome stay linked as they undergo meiosis. Linkage analysis can

identify short tandem repeat polymorphisms, such as dinucleotide, trinucleotide, etc. repeats. This makes diagnosis of diseases beneficial using linkage analysis. However, linkage analysis requires the use of samples from at least two family members with the disease (Pulst, 1999). Linkage analysis was found by tracking genetic markers through a family across multiple generations in both affected and unaffected individuals. Thus, it can be seen how the world of genetic testing for HD has evolved in the recent past to become opportunities that allow the genetic testing for conditions such as HD (Crozier et al., 2014).

Obtaining a Diagnosis

Diagnosis of HD consists of a genetic confirmation of the disease and a clinical diagnosis of disease onset. To become clinically diagnosed with Huntington's disease (HD) an individual must undergo some tests to confirm if they have the disease or not. These tests consist of a neurologic evaluation and a genetic test to test the HTT gene. One of these cognitive tests is the Unified Huntington Disease Rating Scale (UHDRS). This screening tests include the use of multiple cognitive tests such as the Stroop Color Word Test, Symbol Digit Modality Test, and the Verbal Fluency test. Even if symptoms are not detected through these cognitive screening tests, it is thought that cognitive and behavioral symptoms may start to show prior to clinical diagnosis. It is likely that these screening tests do not detect these changes as they are not sensitive enough to detect these prodromal changes (Paulsen, 2011).

As mentioned, genetic testing can be used to diagnose HD in those that are suspected of being a risk for having the mutated gene and for those that are showing clinical signs of the disease. In the case of prodromal individuals, genetic testing is done as a predictive measure of whether or not the individual will develop the disease. In the case of those manifesting symptoms

of the disease, this test is used more diagnostically to confirm if the individual has HD and not a similar condition (McColgan & Tabrizi, 2017).

Similar Conditions

For patients that are suspected of having HD who do not have a family history or their history is unknown, clinicians may want to ensure the patient does not have an HD-like conditions. Thus, Figure 3 illustrates a flow chart that could be used by clinicians to narrow down and determine which HD like disease is present. As seen by this figure, the location of the motor symptoms, the presence of ataxia, the presence of gait disorders, eye movement problems, seizures, the speed of disease progression, and cognitive or behavior problems can be used to differentiate these conditions and HD (Martino et al., 2013).

The location of motor symptoms can be used to differentiate between these HD and these similar syndromes. Some of these conditions tend to mimic the chorea movements seen in HD. These movements can affect the face, torso, neck, and the limbs as seen in HD. However, the presence of chorea or movement disorders within the facio-bucco-linguo-masticatory region can point clinicians towards these diseases that are like HD. Examples of these syndromes can include Mcleod syndrome, chorea-acanthocytosis, Wilson's disease, etc. With these diseases, these movement disorders can impact the neck or facial regions. There is also the presence of dystonia, which can impact the limbs, mouth etc. Each of these conditions has their own specific symptoms that when combined with the presence of dystonia or chorea can point to the diagnosis of one of these HD-like diseases (Martino et al., 2013).

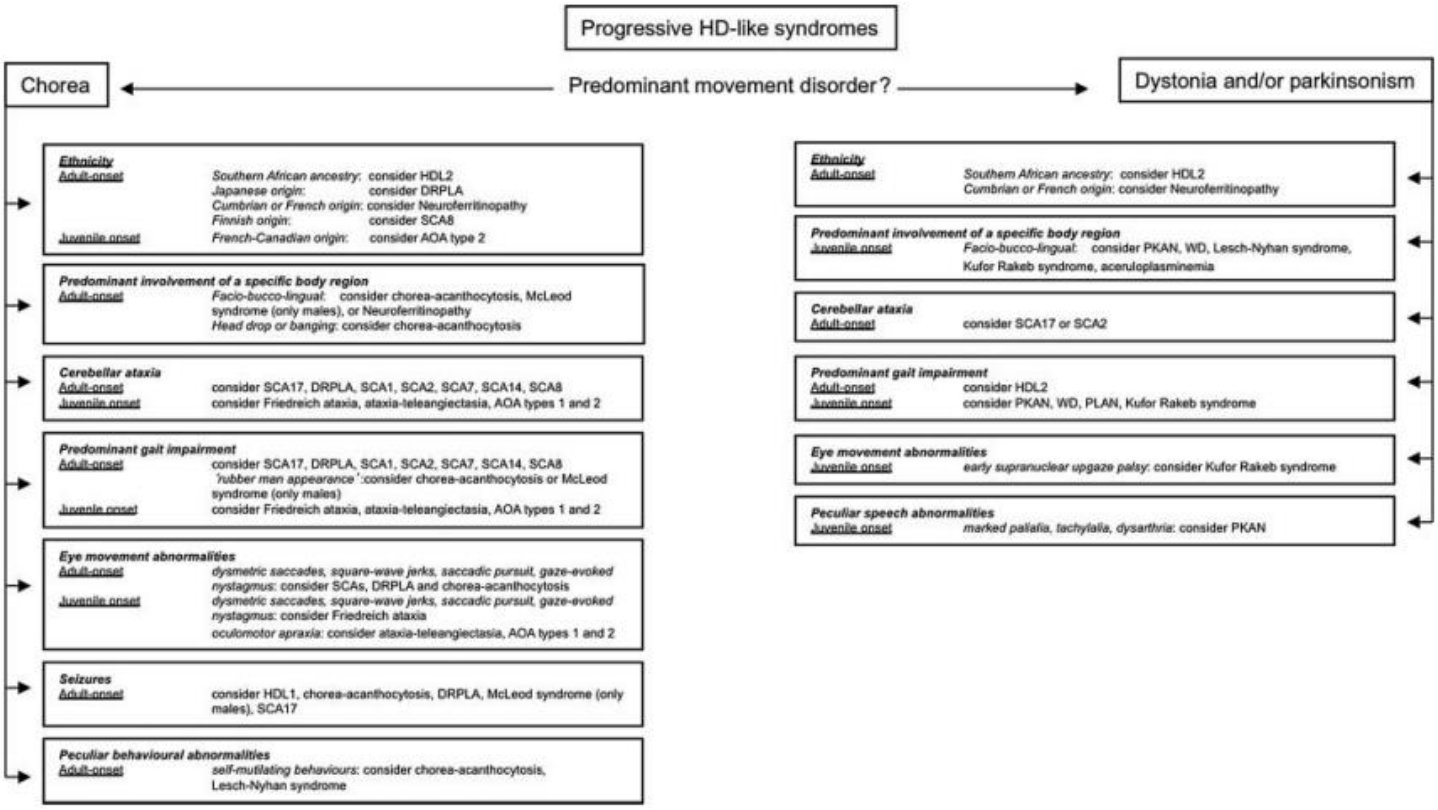

Figure 3. Flowchart summarizing the 'red flags' for the diagnosis of HD-like syndromes. The identification of acronyms is as follows: ataxia with oculomotor apraxia (AOA), denato-rubi-pallido-luysian atrophy (DRPLA), Huntington's disease (HD), pantothenate kinase-associated neurodegeneration (PKAN), PLA2G6-associated neurodegeneration (PLAN), spinocerebellar ataxia (SCA), and Wilson's disease (WD) (Martino et al., 2013).

The presence of cerebellar ataxia can also be used to point clinicians to an HD-like syndrome diagnosis. Typically with HD, the presence of cerebellar ataxia (or atrophy) is mild and is typically seen in the juvenile form of HD. Thus, if more severe forms of ataxia are present, it is likely that HD is not present. Some examples of these like conditions are spinocerebellar ataxia 17, ataxia-teleangiectasia, denato-rubi-pallido-lusian atrophy, and various other autosomal recessive ataxias. With many of these syndromes, chorea can still be present, but their symptoms, depending on the condition, can onset much earlier (prior to the 40s) than what is seen in HD. Thus, the presentation of severe ataxia in addition to an earlier onset can point to one of these

HD-like syndromes, especially when looking at the specific symptoms that are present along with the ataxia (Martino et al., 2013).

The examination of gait disorders, the location on the body where they are present, and the presence of other symptoms (such as ataxia) can also be used to help differentiate HD and a HD-like syndrome. Some examples of these diseases that could be potentially diagnosed this way is McLeod syndrome, Wilson's disease, pantothenate kinase-associated neurodegeneration, and some of the ataxia syndromes previously mentioned. With these conditions, not only is the unsteady gait observed (like in HD), but there is the presence of other symptoms. These other symptoms are dystonia and gait abnormalities that are the result of ataxia, neuropathy, or spams of the arms and trunk. Consequently, the presence of gait abnormalities and dystonia as a result of ataxia or neuropathy and the combination of the locations of the body they impact can help to direct clinicians to these HD-like syndromes (Martino et al., 2013).

Studying abnormalities in eye movements can also be beneficial in differentiating between HD and HD-like syndromes. In HD and these HD-like syndromes abnormalities of eye movements is present. These abnormalities impact saccade eye movements. These abnormalities of the saccades consist of eye movements being slowed and disfunctions in gaze fixation being present. With these syndromes, the eye movement abnormalities can be similar to what is developed in HD. However, these abnormalities can onset much sooner or present differently than what is seen in HD. This presentation can differ in that these abnormalities can consist of dysmetric saccades, fractionated saccades, square-wave jerks, etc. Clinicians can use the onset and specific type of eye movement abnormality in order to differentiate between HD and these like syndromes. Furthermore, the presence of seizures in a patient can also be used to as a method to differentiate these like syndromes. Seizures can be used to differentiate as seizures are

not typical in HD. However, in some of the HD-like syndromes, seizures are more common (Martino et al., 2013).

Overall, it can be seen how these HD-like syndromes differ and are similar to HD. While presentation of these symptoms can be very close, there are slight differences in these syndromes or the other symptoms present. Thus, these slight differences and combinations can serve to help clinicians identify these syndromes and separate them from HD. As mentioned, this ability to differentiate would be very helpful in cases where family history is unknown or unclear.

IV. Psychological Aspects of Huntington's Disease

With HD, there are psychological aspects that are seen with the disease. These aspects can correspond to the disease itself and its symptoms. However, these psychological implications can also be a result of the diagnosis of the disease. These physical implications definitely extend to the individual with the condition, but can also impact caregivers, and family. Thus, the psychological implications of the disease will be discussed in regards to the individual, caregiver, children, friends, and for non-carriers of the disease.

For the Individual

While HD does impact affected individuals in various aspects psychologically during the duration of the disease, it is worth looking at the psychological impacts of a positive diagnosis. Since a positive diagnosis results in the individual knowing with confidence that they will develop the disease within their lifetime, it leads to complicated psychological responses. On one hand, these individuals feel relief as they do not have to deal with the uncertainty of the genetic status and they may feel some appreciation for life. While on the other hand, they may experience more negative emotions or responses. These negative responses can be an increased feeling of stress, feeling hopeless, stress due to anticipating the onset of the disease, and even an increased feeling of being suicidal or having suicidal thoughts. In a review of current literature exploring the impact of genetic testing, researchers determined that those with the HD gene did have a higher level of stress and distress when compared to non-carriers of the gene. Some studies in this review noted that this distress and feelings of avoidance tended to decrease after a month but would "peak between one and three years post-test" (pp. 34-35). An increase in levels of depression was also noted for those that were expressing symptoms of HD. While other

feelings were reported, it seems that it is common for most individuals to have an increase in these more negative emotions such as distress and depression (Crozier et al., 2015).

In a study examining the effect of chorea, the researchers determined some common themes from the groups in the study. These themes were watching for the onset of chorea, its impacts on relationships and independence, and the stigma associated with chorea. Multiple individuals in the group mentioned how they were consistently watching for chorea. This constant watching would have likely caused great distress and uneasiness that over time would take its toll. Under the theme of the impacts of chorea on relationships and independence, it was mentioned how individuals with the disease could no longer do activities or do tasks for themselves. A woman in these groups shared how she could not drive herself anymore and losing the ability to "pop in [her] car" was hard. Individuals also mentioned how they had relationship issues due to the chorea as people were not used to the movements, did not understand them, or could not deal with them. Both the inability to be independent and to have trouble keeping relationships or having to depend on those relationships would be tiresome. This constant dependence, depending on the personality of the HD individual, could be the root of additional stress or fear due to not wanting to feel like a burden (Sherman et al., 2020).

In this group, there were some caregivers present and these caregivers also mentioned how the individuals with the condition would be left out of conversations or social situations due to the delay of responding within a conversation. This delay in response would be a result of the cognitive symptoms mentioned. The caregivers also noted how as a result of being left out of social situations and feeling isolated, these HD individuals would isolate themselves or push away others (Sherman et al., 2020).

When discussing the stigmas that are associated with the chorea, both affected individuals and caregivers noted the hardships resulting from these stigmas. Some examples mentioned had to do with people thinking affected individuals were drunk, individuals feeling watched or judged, or living in fear of upsetting others or losing a job due to the chorea. All of these examples and observations show how chorea has a major impact psychologically and socially. The review article states this best by saying how the "physical effects of chorea are most familiar, [but] the findings suggest that the interpersonal effects may be equally potent and impactful" (Sherman et al., 2020).

Thus far most of the discussion has been on the emotions and psychological implications of the disease in regards to the disease itself and diagnosis of the HD gene. However, it should also be discussed how during different stages of the disease certain emotions or psychological aspects of the disease could be present or elevated. In an article by Ho et al. (2011) explored where the researchers determined some common themes that were brought up in the focus groups containing individuals with all stages of the disease. Their findings are shown in Figure 4 where they show the average percentage the particular theme was mentioned within these groups (Ho et al., 2011).

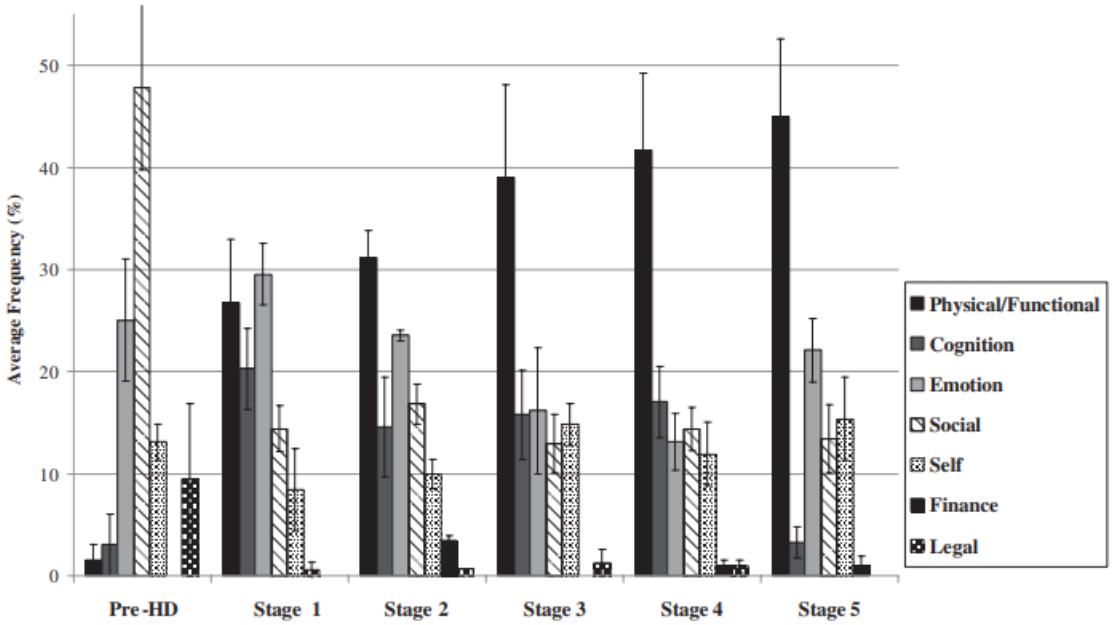

Figure 4. Average frequency (%) for each theme according to Huntington's disease stage (Ho et al., 2011)

As seen in Figure 4, the issues that fell into the physical theme increased as disease progression increased. This can likely be attributed to the worsening of physical symptoms that occurs as the disease progresses. The pre-HD stage would be the equivalent of the prodromal stage discussed in the general overview section. In the pre-HD stage, most of the issues fit in the social and emotional themes. Some issues that were raised in the social category had to do with lack of support, family dynamics, how HD is perceived and not well known, etc. Issues for the emotional category had to do with HD and how it impacts family as well as the emotional toll of symptoms emerging. These categories make sense for the pre-HD stage as this stage encompasses more emotional issues, social issues, and psychological distress due to a diagnosis of HD (Ho et al., 2011).

The researchers noted that once individuals reached stages 3 and 4 they seemed to enter a "period of stability" and this is why levels of issues other than physical issues stay relatively

consistent. Stages 3 and 4 would likely correspond to the middle stage of HD. It could also be inferred that the psychological impact of the disease in these stages is likely more focused on stresses to do with physical disease progression rather than the stresses seen in the pre-HD stage. Another psychological impact could be stress with declining cognition. However, as cognition declines, issues with cognition cannot be conveyed, which explains their decline in Figure 4. For stage 5, which would correspond to late stage HD, physical issues is the highest as this is the stage with the most physical decline. Thus, any psychological aspects or worries are going to be focused on lack of mobility and need for continual care or assistance (although this would likely depend on the cognitive state of the individual). Emotional issues are also higher in this stage, the researchers mentioned this was due to low mood being reported. This low mood makes sense as these individuals are in the most progressive and severe portion of the disease. Overall, it can be seen that over the stages of the disease, the issues or concerns of the disease can change. Not only do the issues change, but the psychological toll changes as well (Ho et al., 2011).

For the Caregiver

While HD does have a major impact on the individual with the disease, the disease also has a major impact on caregivers of the disease as well. Caregivers typically are either family members or spouses of the individual with HD. One major stress that occurs on caregivers, especially for spousal or family caregivers, is that "these behavioral problems, rather than the physical deterioration itself, cause greater difficulties for the individual with HD and their caregiver(s) as they try to come to terms with changes in personality, behavior, and character" (p. 1426). This change in personality can cause distress or stress in these caregivers. A major struggle that caregivers can face is trying to find access to and advocate for specialist services in order to help their loved one. This can lead to stress and anger as they feel like they have been let

down, especially if there is a lack of knowledge of the disease when talking to medical professionals (Aubeeluck et al., 2012).

Another major struggle is that many caregivers feel that they now have this weight upon them to take the role as caregiver. They feel that they must now take care of this individual and they feel responsible for all aspects of care. This pressure of becoming the caregiver also caused these individuals to neglect their own needs and wants, and at times to feel unsupported themselves. To deal with these feelings and to seek outlets to be able to talk about their feelings some caregivers would go to counseling or rely on their faith (Aubeeluck et al., 2012).

Caregivers also experienced stresses just from the actual caregiving itself. These stresses ranged from not having access to information and trying to find time to find it, trying to keep up with chores and caregiving tasks, having time to take care of themselves and their loved one, dealing with financial issues, etc. Caregivers also experienced feeling isolated, a loss of the connection with their loved one, and being surprised to find out about the disease itself. Not all emotions these caregivers experience are negative, some positive experiences of caregivers are feeling that the situation has brought their family closer. All in all, it can be seen how HD can have just as much of a psychological impact on caregivers as it does on the individuals with the disease itself (Aubeeluck et al., 2012).

Another study had many of the same conclusions previously mentioned, but also listed some more coping mechanisms of the caregivers. Some caregivers went on ahead and mourned the loss of their loved one, others focused on blessings, and some tried to set boundaries by setting aside time for themselves. Some caregivers have tried to continue activities they previously did with their loved ones, but modified due the disease. Along with mourning their loved ones, other caregivers would either cease to do shared daily activities together, or look at

the relationship as more of a parent-child relationship. This study also mentioned how these spousal caregivers also felt distress at the thought of their children being at risk. They felt guilty for having children or they were hyperaware of anything that could be construed as a symptom. To adapt to this, some caregivers have hoped for future cure that can cure their children or grandchildren, or they rely on their faith and that God will take care of the situation. Some caregivers also adapted to this situation by supporting their children's decision in regards to genetic testing (Williams et al., 2009).

For Non-Carriers

When looking at the psychological impacts of HD on someone's life, many people would focus on either the affected individual, their caregiver, or family. However, it is important to note that those who test negative for the disease also do experience some psychological impacts. Non-carriers can experience both positive and negative emotions when getting their result. In a study, it was found that non carriers experiences and emotions of receiving this negative result could fall into the categories of relief, a need for a new purpose, or an impact on family relationships. For the relief category, the participants talked about how they felt major relief at learning that they do not have to worry about developing the disease. For some of the participants they felt that they were not wasting limited time anymore while for others this relief was derived from feeling that they would not have to follow through with suicide (later in disease progression). For the feeling of a need for a new purpose category, many participants had a feeling of "a second chance at life." For some, this feeling resulted in feeling depressed or empty as their identity of potentially having the disease changed. One woman also talked about how she had to dismantle the "wall" she had built when she thought she was going to have the disease and that getting rid of this portion of her identity took time (Winnberg et al., 2018).

Some participants also felt pressure to make this new life meaningful and to make long term plans or choices. For others, this second chance made them feel that they had been given something wonderful and that this new life needed to be cherished. Furthermore, these results encourage some participants to make choices about their lives that removed them from unhealthy relationships, promoted their career, and in one interesting case, to revert from dangerous and reckless behavior. The category focused on impacts in family relationships it details how some participants were able to see improvements in these relationships. These improvements stemmed from the shared experiences and in the reduction of the weight of having to be taken care of. In the relationships where this weight of having to be taken care of was removed, one participant described these relationships becoming more "equal" with the other person (Winnberg et al., 2018).

However, in some family relationships, especially with siblings, more negative feelings were present. The participants felt guilt and the other siblings did not take the result well. Some siblings felt that their results would have a greater chance of being positive while other siblings felt that they had lost their shared experience and support of not knowing. Therefore, through this study it can be seen that a negative result does not have any less of a psychological impact than testing positive for the disease (Winnberg et al., 2018).

V. Overview of Huntington's Disease Treatments

Prescription Medications

Since HD has no cure, many prescription medications are used in order to treat and manage the symptoms of the disease. The medications can be used to treat chorea and mood disorders. The chorea movements come about due to the degeneration of the neurons in the basal ganglia region of the brain, specifically the striatum. Some examples of the medicines used to treat chorea are tetrabenazine and deutetrabenazine. Both of these medications work by inhibiting a cellular transporter known as the human vesicular monoamine transporter 2. A cellular transporter is a molecule that transports vesicles along the microtubules of the cell. Deutetrabenazine differs from tetrabenazine in that the deuterium atoms extend the half-life of the molecule. This extension of the half-life correlates to needing less frequent administration of the medication (Ferguson et al., 2022).

To aid in the treatment of mood disorders several medications can be mainly separated into antipsychotic, antidepressant, and mood stabilizing medications. Some common antipsychotic medications include olanzapine and risperidone. Both olanzapine and risperidone mainly target dopamine and serotonin receptors. Both of these antipsychotic receptors are also classified as atypical antipsychotics as they have a higher affinity towards the serotonin receptors over the dopamine receptors While these antipsychotics are mainly mood disorders, it is also thought that they may help to improve chorea (Ferguson et al., 2022).

Common antidepressants given with HD are fluoxetine, sertraline, and citalopram. These antidepressants, and other typical antidepressants given, are selective serotonin reuptake inhibitors (SSRIs). SSRIs work by inhibiting the reuptake of serotonin by the nerves of the brain. This leads to higher levels of serotonin, as it is not being accepted by its receptor. For HD

patients, these SSRIs are typically prescribed to help treat HD related depression. It was found that sertraline also seemed to improve symptoms of aggression and obsessive compulsive disorder (OCD) in HD patients (Ferguson et al., 2022).

Mood stabilizer medications are also another medication option for individuals with HD. Some examples of these medications are lamotrigine, sodium valproate, and carbamazepine. All of these specific medications are also considered to be anticonvulsants. Anticonvulsants aid in the prevention of synchronized neurons firing excessively. These medicines accomplish this by upregulating the number of inhibitory neurotransmitters, downregulating the number of excitatory neurotransmitters, and by influencing the voltage-gated ion channels. For most of the specific medications mentioned, they work within blocking sodium ion voltage channels. Typically, due to how these anticonvulsants can be used, they are usually employed in the treatment of seizures. However, for HD these medications have been found to help alleviate the severity of symptoms associated with aggression, OCD, and bipolar disorder. Depending on the anticonvulsant prescribed, various cellular mechanisms and chemical pathways are thought to be influenced. It is also thought that sodium valproate may also affect gene expression and induce changes that contribute to the long-term stabilization effects observed. Altogether, it can be seen that there are many medications that are available to help treat HD and its (Ferguson et al., 2022).

Non-Medicinal Forms of Treatment

While medications can be beneficial in trying to manage the symptoms of HD, there are some additional strategies that can be employed. These strategies consist of changes to the life of the individual with HD. These changes aim to make life easier for the individual and to make adaptations based on their specific symptoms and situation. For some symptoms, such as motor

symptoms, these adaptations may include physiological or occupational therapy. These therapies may either be aimed at improving balance and walking ability or they may be aimed at helping the individual to be able to complete daily tasks. For either scenario this would include the use of handrails, walking aids such as a walker, changes to bathroom set up, etc. If the individual has problems with speech or swallowing, specialists in those fields may also be consulted to provide assistance for these individuals. Since mental health problems are common with HD, seeing a psychologist can also help to alleviate these symptoms outside of medication. Therefore, it can be seen that there are multiple avenues through which these individuals can pursue treatments to help them that do not consist of medication or the associated side effects. However, much like the medications, these options can only help with the management of symptoms (Ferguson et al., 2022).

Genetic-Based Treatments

Antisense Oligonucleotide Based Therapies

While most treatments for HD consist of medications or therapies, there new research looking into using genetic-based treatments. Genetic based treatments are treatments that would be looking at either editing the DNA or RNA directly, or looking to manipulate them. This could include the use of proteins, pieces of RNA, etc. to edit or influence the desired genetic material. As of 2023, many of these treatments are in the experimental phase or they have reached human clinical trials. Thus, some of these treatments will be discussed to define what they are and their potential for individuals with HD (Ferguson et al., 2022).

One of these treatments is known as antisense oligonucleotide (ASO) therapies. ASO therapies work by binding to a sequence of the pre-mRNA for the HTT gene. As a result of binding to this sequence, RNAase H will degrade the sequence (McColgan & Tabrizi. 2017).

Along with RNA degradation, the blocking of translation and splice modulation can prevent the mutant form of the protein from being made from this sequence. Depending on the ASO used, the ASO can be used to target just the mutant form of the gene. The targeting of the mutant HTT gene would be referred to as allele specific. However, ASOs can also be used to target both the mutant and the wildtype (normal) HTT allele. This method would be known as non-allele specific (Ferguson et al., 2022).

There are current and past clinical trials that are looking at the use of ASOs for HD. Tominersen is an allele non-specific ASO that was being tested by Hoffman-LA Roche. This trial consisted of an initial randomized double-blind experiment with participants divided into five groups. These five groups were given Tominersen every 28 days until they had reached 4 doses of the medication. Each group had an ascending dose amount compared to each other. From this initial experiment the researchers did observe a decrease in mutant HTT, but also noted that there was a dosage dependency for effectiveness. Further trials were then conducted to continue the testing of Tominersen. There was a phase two open label trial and a double blinded phase three trial (GENERATION HD1). In the phase two trial, the participants were given 120 mg of Tominersen for fifteen months. In the phase three trial, the participants were divided into three groups where two of the groups were given the 120 mg of Tominersen at either 8 or 16 week intervals, and the third group was a placebo group. This phase three trial was the largest trial of the three discussed as it involved 109 participants rather than the same 46 used in the initial and phase two trial (Ferguson et al., 2022).

The phase three, GENERATION HD1, trial was halted a year early, in 2021, by an independent data board. The board halted the trial as they determined that the risk benefit ratio for long term periods was not favorable. Another phase three trial, GEN-EXTEND, was also halted due to the

halting of GENERATION HD1. GEN-EXTEND was a randomized open label trial where participants were given Tominersen either at 8 or 16 week intervals. The goal of this trial was to observe the long term tolerability or effects of Tominersen (Ferguson et al., 2022).

GEN-PEAK was another small, phase one trial with 20 participants. This trial was open label and wanted to look at the pharmacokinetics of Tominersen. Participants were given ascending doses every 28 days, for two doses and this trial was concluded in 2021 (Ferguson et al., 2022).

Trial Phase and Name (if applicable)	**National Clinical Trial Number**	**Trial Type**	**Number of Participants**	**Dosage Amount and Frequency**
Phase 1 (Initial trial)	NCT02519036	Randomized, double blind	46	1 dose every 28 days (4 total doses
Phase 2	NCT03342053	Open label	46	120 mg dose for 15 months at monthly or bimonthly intervals
Phase 3 (GENERATION HD1)	NCT03761849	Double blind	909	120 mg dose at 8 or 16 week intervals for a period of 25 months
Phase 3 (GEN-EXTEND)	NCT03842969	Randomized, open label	1100	Dose administered at 8 or 16 week intervals
Phase 1 (GEN-PEAK)	NCT04000594	Non-Randomized, open label	20	1 dose every 28 days (2 total doses)

Table 1. Summarization of ASO clinical trials in regards to their name, clinical trial number, trial type, number of participants, dosage amount, and dosage frequency.

While many ASO trials have been based on Tominersen, there are two other ASO clinical trials that involve allele specific ASOs. Allele specific ASOs may be more favorable as they can be used to only target the mutant form of the HTT gene rather than the wildtype version. By only targeting the mutant HTT, normal forms of HTT can be conserved, preventing the loss of HTT as a whole. These allele specific ASOs target particular single nucleotide polymorphisms (SNPs)

seen in HD. These are the WVE-120101 and WVE-120102 ASO trials. WVE-120101 is an ASO that targets SNP1 (rs362307) while WVE-120102 targets SNP2 (rs362331) (Ferguson et al., 2022).

Two clinical trials, both double blinded, were conducted to investigate the efficacy of both WVE-120101 and WVE-120102. These trials were known as PRECISION HD1 and PRECISION HD2. In these trials the patients were split into six groups where the groups outside of the placebo group received 2 mg, 4 mg, 8 mg, 16mg, or 32 mg of the ASOs. It was discovered that while mutant HTT levels did seem to decline by 12.4% (this was deemed statistically significant) in the PRECISION HD2 trial, the overall mutant HTT amount did not change when compared to the placebo for either trial. As a result of the lack of change both trials were ended. Additionally, further testing in an open labeled trials were conducted with the participants of these original trials. However, these trials saw inconsistent results of mutant HTT being lowered and researchers decided to end the trials. The researchers noted that WVE-12101 and WVE-120102 were not of clinical benefit as well. An application for another ASO trial clinical trial using WVE-003 was submitted in 2020. WVE-003 is an ASO that targets SNP3, but this SNP has not been completely discerned. In pre-clinical experiments, WVE-003 did seem to have positive results in lowering mutant HTT (Ferguson et al., 2022).

Overall, these are just a few examples of specific ASOs being examined in clinical trials. These trials illustrate how allele specific and allele non-specific ASOs are both being investigated as potential treatment options. It was further illustrated that some of these trials such as the PRECISON HD1 and HD2 trials resulted in data that suggested that these ASOs were not very beneficial in lowering mutant HTT. However, other ASOs such as WVE-003 showed promise based off their results in pre-clinical experiments and studies.

Clustered Regularly Spaced Palindromic Repeats (CRISPR) Based Therapies

CRISPR is another genetic based treatment that has promise to help treat HD by targeting the DNA itself. CRISPR is a complex made of a cas protein and single guide RNA (gRNA). It is also important to note that the CRISPR mechanism was originally found in bacteria. In the bacteria, CRISPR functioned as an immune system that the bacteria could use to fight off pathogens such as viruses. CRISPR fights viruses and pathogens by cleaving a portion of the pathogenic DNA and inserting it into the bacterial DNA. This pathogenic DNA is inserted into the bacterial DNA at the CRISPR locus. The CRISPR locus is made up of repeat and spacer sequences, and the spacer sequences correspond to the pathogenic fragments (Harrison et al., 2014)

CRISPR follows the following mechanism in order to induce edits on the DNA. To begin the CRISPR complex must be created itself. This creation is started by the transcription of the CRISPR repeats into short CRISPR RNAs (crRNAs). The crRNAs then combine with trans-acting RNA (tracr-RNA), the cas protein itself, and a single guide RNA (gRNA) sequence. This gRNA sequence identifies the sequence that will be targeted. The CRISPR protein complex is guided to its target sequence in the DNA through the use of the gRNA and the use of an RNA sequence known as the PAM sequence. Once the complex has located its target sequence, the DNA is cleaved on both strands through the help of the PAM sequence. The CRISPR complex then induces the desired edits into the DNA through either the addition or deletion of bases. Once the edits have taken place, cell DNA repair processes take over. DNA repair in the cell can undergo one of two pathways. One type of repair is non-homologous end joining and homology directed repair. Homology directed repair is preferred as this type of repair uses a template strand

to join the DNA strands back together. This process is less prone to causing mutations to occur on the DNA where this editing has taken place (Harrison et al., 2014).

While CRISPR is a major gene editing mechanism being studied in 2023, it is not the first gene editing mechanism to be used in research. Zinc finger nucleases (ZFNs) and transcriptional activator-like effector nucleases (TALENs) are examples of these earlier gene editors. ZFNs are gene editing mechanisms that recognize nucleotide triplets and cleave the DNA at these triplets. TALENs are "chimeric proteins" that cleave DNA and are made up of repeats, a DNA binding domain that is programmable, and a Fok1 nuclease. While these editors were being used prior to the discovery and success of CRISPR, they had downsides that make them less favorable for use today. These downsides included that these gene editors were labor intensive and time consuming to create. Thus, when CRISPR was discovered, it became the favorable gene editor to use as it was much easier to design and use (Harrison et al., 2014).

When using CRISPR to treat HD, it should not be used to completely edit out the whole portion of the HTT gene. Simply put, the HTT gene should not be knocked out using CRISPR. This was illustrated in an experiment using mice where it was the researcher's goal to knockout the HTT gene. However, in this experiment found that there was embryonic lethality that occurred. Since embryonic lethality occurred, this experiment did show that HTT does have essential functions. Therefore, it can be inferred that while the mutant HTT gene is not beneficial, having some wild type HTT would be beneficial (Jimenez-Sanchez et al., 2017). An experiment looking at partial elimination of the mutant protein or elimination of the entire mutant gene did have some success. Consequently, partial or whole elimination of the mutant allele may be the best course of action when using CRISPR or other gene editors to treat HD (Wild & Tabrizi, 2017). Additionally, as seen with ASOs, CRISPR may also be able to be used

to target SNPs. CRISPR may be able to do this for HD as these SNPs correlate to and identify different disease haplotypes (Fields et al., 2021).

While it has been established that using CRISPR as a potential treatment option for HD is viable, it should also be explored what version of CRISPR should be used to treat HD. There are different CRISPR mechanisms that use different cas proteins. Two examples of these proteins that will be explored is cas 9 and cas 12. Cas 9 is the typical protein that is a part of the CRISPR mechanism when most individuals are referring to CRISPR. Cas 12 has some advantages when compared to cas 9. For example, cas 12 is made up of a simpler mechanism, cas 12 induces a staggered double strand break to promote homology directed repair, and cas 12 typically has lower off target effects in some of the in vivo experiments conducted. This lower amount of off target effects can likely be attributed to the cas 12 mechanism having three components that act as checkpoints before editing occurs. These three components are the rec linker, lid, and rec finger checkpoints. One disadvantage of cas 12 that has been noted by researchers is that the mechanism has the tendency to start indiscriminately editing DNA similar to the crRNA. Indiscriminate editing has the potential to lead to harm depending on where it occurs and to the degree it occurs. Overall, while both of these cas proteins do have some differences, they are similar in specificity and mismatch tolerance (Paul & Montoya, 2020).

Prime Editors

There is also another type of gene editing mechanism that is known as a prime editor. A prime editor is a mechanism that works similarly to CRISPR. In prime editors, the cas 9 protein has been modified so that it is only cleaving one strand of DNA, rather than both strands as we see in CRISPR. In addition to the modified cas 9 protein, prime editors are also made up of a reverse transcriptase and a prime editing guide RNA (pegRNA) (Hampton, 2020). The pegRNA

is made up of a nicking single guide RNA, a primer binding site, and a reverse transcriptase template. The nicking single guide RNA contains the RNA sequence that is complementary to the DNA that will be targeted. The reverse transcriptase template contains sequence that includes the desired edits (Hong et al., 2022). When prime editors are compared to CRISPR, it has been found that their mechanism has more control, precision, and a reduction in off target effects as a result of the hybridization needed to engage the mechanism. However, different from CRISPR, prime editors cannot insert or delete large portions of the DNA (Hampton, 2020).

Disease Models

While a major focus of this section has been examining different approaches to treat or potentially cure HD, it is also important to mention how researchers determine the viability of these treatments. Researchers are able to determined the viability of treatments such as CRISPR and prime editors by studying these mechanisms in disease models. Two of the most common disease models are mice and the use of various types of cells (both human and mice) such as induced pluripotent stem cells. Less common disease model organisms include primates, sheep, and pigs. However, while disease model organisms can be very helpful in studying and understanding diseases like HD, there are some limitations. For example, there are differences in the complexity of an organism such as a mouse when compared to humans, This can be seen through the human brain being much more complex than the brain of the mouse. Another limitation, specifically to HD with these diseases models is that primates lack the mutant HTT protein. Hence, using these other organisms as disease models has limited benefit. Overall, these disease model organisms can help to study and determine viability of treatments to a certain point. Furthermore, the limitations seen for the use of these disease model organisms highlights

the need for the occurrence of human clinical trials in order to study these therapies in humans themselves (Babačić et al., 2019; Wild & Tabrizi, 2017).

VI. Conclusion

At this point an overview of HD and its treatments has been explored. This exploration included presenting information about HD in general, how HD is diagnosed, resources and care, the psychological aspects of the disease, and an overview of the treatments of the disease.

In the general overview of HD, it was discussed how HD is a rare autosomal dominant disease that results in neurodegeneration of the brain. Specifically in the striatum, which is found in the basal ganglia of the brain (Jimenez-Sanchez et al., 2017). It was discussed how HD is the result of a mutation in the HTT gene that codes for huntingtin. In this mutation there is the expansion of a CAG repeat portion of the gene. In the normal version of the gene, there is typically 6 to 26 CAG repeats. However, in the mutant version of the gene there is usually greater than 36 CAG repeats (Zoghbi and Orr, 2022). It is thought that the aggregation of the mutant protein, particularly when found around the nucleus (perinuclear), may contribute to the degeneration seen in HD. It is also thought that this degeneration may also be the result of alterations in gene expression due to the presence of the mutated HTT protein (Jimenez-Sanchez et al., 2017).

In the general overview of HD, the symptoms of the disease were also discussed. In HD, the neurodegeneration of the disease leads to the development of cognitive, motor, and psychological symptoms. Cognitive symptoms can consist of delays or issues in processing speed and the flexibility of thinking. Motor symptoms can consist of slow movements, chorea, etc. The psychological symptoms of the disease can consist of apathy, depression, etc (Babačić et al., 2019; *Huntington's disease symptoms*, n.d.). The three prodromal stages, the stages that occur between genetic diagnosis and clinical diagnosis, of HD were also discussed (Paulsen et al.,

2017). The three stages of the disease after clinical diagnosis were also mentioned (*Huntington's Disease Stages*, n.d.).

When discussing the diagnosis of HD, the history of genetic testing was discussed. The discovery of linkage analysis was made in 1986. (Crozier et al., 2014) It was mentioned how direct genetic testing differed from linkage analysis in that linkage analysis required the samples of at least two family members (Pulst, 1999). The process of getting an actual clinical diagnosis of HD was then explained. Getting a clinical diagnosis consists of undergoing various tests to detect symptoms. Some of these tests included the Stroop Color Word Test and Symbol Digit Modality Test (Paulsen, 2011). The differences between HD and HD-like syndromes were also examined. Various aspects such as motor symptoms, presence of ataxia, etc. were examined for both HD and these HD-like syndromes. Overall, with all of these aspects it could be seen that while HD and these like syndromes were similar, they did have some distinctions that separated them from a diagnostic standpoint. These differences could include different locations of the body being impacted, a different age of onset for a symptom, or the presence of multiple syndromes together at one time (Martino et al., 2013).

The psychological aspects of the disease and diagnosis of the disease was also examined. To start, the impact on the individual with the condition was examined. It was found that these individuals did experience some relief in knowing their genetic status, but they also experience a lot of stress and negative emotions as well (Crozier et al., 2015). It was also found that chorea also had a great psychological impact on the individuals with the disease as well (Sherman et al., 2020).

The impact of the disease on the caregiver was also assessed. It was noted that the disease added a lot of additional stress on the caregivers. This stress came from coping with the

personality and behavior changes brought on by the disease (Aubeeluck et al., 2012). This stress also came from the role of being caregiver itself and from a lack of addressing their own needs (Aubeeluck et al., 2012; Williams et al., 2009).

The psychological impact of a negative test result for the mutated HTT gene was also looked at for non-carriers. This research found that there was a lot of relief at knowing that HD could not develop. Many of these non-carriers felt like they were going to have another chance at life and to actually live it. However, it was also found that non-carriers also found guilt in that they did test negative for the mutant gene. This guilt did impact some family relationships as well (Winnberg et al., 2018).

The last section talked about an overview of the treatments of HD. The first treatments discussed were prescription medications. These medications were used to treat movement problems and mood disorders (mood stabilizers and antidepressants). Overall, with these prescription treatments, they could only be used to manage the symptoms of the disease rather than treat it. Non-medicinal options to help manage HD was to see a language pathologist, a physical/occupational therapist, etc. (Ferguson et all., 2022). Genetic based treatments such as ASOs, CRISPR, and prime editors were also explored. It was found that with ASOs there had been some mild success made (Ferguson et al., 2022). With CRISPR it was found that partial elimination of the diseased protein would be needed rather a complete deletion of the diseased protein. This was determined by the occurrence of embryonic lethality in mice where the entire gene was eliminated (Wild & Tabrizi, 2017; Jimenez-Sanchez et al., 2017).

It is the author's hope, when "Huntington's disease" is mentioned, there is now a hint knowledge upon hearing the words. Maybe now there is more understanding of the emotions of those who have the disease or those who have a loved one with this disease. Take this knowledge

and increase awareness to HD so that more people are aware of the disease and so that more research can be done in order to cure it. Many people are affected by the disease or by the diagnosis of a loved one. Thus, it is important the knowledge and awareness of the disease so that research can be conducted to improved and discover better treatments. By increasing awareness and knowledge of the disease, “Huntington’s disease” can become more than just a couple of words.

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