Huntington's disease:

Where are we and where should we be?

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Dedication

Writing a scholarly project takes many hours of dedicated and uninterrupted time. There is no way that I would have been able to complete such a paper without the help and support of my husband, Brian. He is my inspiration and motivation. There were times when I wasn't sure I could finish my project, but he never let me give up. He did everything in his power to keep me stress free and confident. It is because of his kindness and understanding that I dedicate my scholarly project to Brian. Thank you.

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Introduction

Huntington's disease (HD) is a progressive, neurodegenerative disorder with an autosomal-dominant (see Figure 3a) pattern of inheritance. Anyone carrying the mutation responsible for the pathogenesis of HD will ultimately develop the disease. This disease is generally late-onset and characterized by psychiatric, cognitive, and motor disturbances due to progressive neurodegeneration in the cerebral cortex and basal ganglia (Landles & Bates, 2004). As the disease progresses, the individual becomes bed or wheelchair bound. This functional decline is followed by death anywhere between 10 to 25 years after the onset of disease. Death has been known to result from various possible sequelae due to the effects of disease process such as malnutrition, aspiration pneumonia, cardiac complications, and many others.

Worldwide incidence is estimated to be between 4 and 5 per million, but is more prevalent in certain countries (Brown & Ropper, 2005). Malta and Norway have rates that are higher than others while countries like Finland and Japan have a decreased prevalence (Harper, 1992). Specifically in Finland, the prevalence falls to 5 per million being affected (Palo, Somer, Ikonen, Karila, & Peltonen, 1987). Venezuela is another area with increased prevalence of HD (Wexler, 2004). With so many lives affected by HD, it is important to gain better understanding of the disorder. This paper discusses characteristics and hereditability of HD, pathogenesis, predictive and prenatal testing, as well as current treatment options and ideas for future research. With increase in knowledge comes the higher likelihood of discovering a cure.

Genetic Transmission

Symptoms of Huntington's disease can be nonspecific and include a wide range of personality or mood changes, dementia, and the hallmark choreiform movements. Irritability, depression, aggressive tendencies, and impulsive actions can all be a part of the personality changes associated with HD (Gusella & Macdonald, 2006). Chorea involves involuntary jerky movements of the whole body. The disease symptoms occur because of a mutation that causes more than 36 CAG (glutamate) trinucleotide repeats to occur on a portion of the IT15 gene located on chromosome 4p16.3 (Kremer et al., 1994; Landles & Bates, 2004). The expanded sequence causes a polyglutamine tail to be added to the huntingtin protein (htt) when the mRNA from the altered gene is translated (Landles & Bates, 2004). The polyglutamine tail is located on the 5' end of the htt protein (Gusella & Macdonald, 2006). A conformational change in the protein's structure occurs that appears to be directly related to the change in its function (Landles & Bates, 2004). The length of the trinucleotide repeat and age at the time of onset are inversely related (Gusella & Macdonald, 2006). As the mutation is passed from one generation to the next, alterations in the length of the CAG repeat may occur (Gusella & MacDonald, 1994). This may either increase or decrease the age of onset observed for individuals in that generation.

Most cases of Huntington's disease involve onset in middle age. However, there is also the possibility that onset can occur much sooner in life. The actual age range for HD onset is anywhere from as young as 2 years to as old as 85 years. While CAG repeat length may influence the timing of onset, it seems to have very little, if anything, to do with the timeline of progression for the disease symptoms (Gusella & Macdonald, 2006). The symptoms that a patient presents with seem to differ depending on his or her age at the time. In order to be diagnosed with Juvenile Huntington's Disease (JHD), onset of symptoms must begin before the

age of 20 (Ribai et al., 2007). The symptoms that a juvenile onset patient may present with commonly include slowed speech and awkward gait (Kirkwood, Su, Conneally, & Foroud, 2001). Patients with JHD tend to have increased severity in symptoms such as bradykinesia, abnormal eye movements, and dystonia (Louis, Anderson, Moskowitz, Thorne, & Marder, 2000). Epileptic seizures and rigidity have also been associated with earlier age of onset, whereas the late onset forms of the disease have been associated more with choreiform movements (Siesling, Vegter-van der Vlis, & Roos, 1997). Rigidity may be the most distinguishing feature of an individual with JHD (Van Dijk, Van der Velde, Roos, & Bruyn, 1986).

A significant correlation has been established between onset of disease and paternal inheritance. If an allele is inherited from the father, age of onset is typically significantly younger (Gusella & Macdonald, 2006). This could in part be due to the fact that sperm undergo a greater number of cellular divisions than the female's ovum. This provides a greater opportunity for possible genetic mutations. In general, cases of juvenile onset HD involve a greater number of CAG trinucleotide repeats than the adult onset form (Panov et al., 2002).

Nationality and ethnic background have not been found to play a significant role in the pathogenesis of HD. In 1994, a study of over 1,000 patients from more than 40 ethnic groups showed that the number of CAG repeats was similar across cultures (Kremer et al., 1994). The same study also found an average of around 44 trinucleotide repeats. The range was 36 to 121 repeats.

In 2004, there were approximately 30,000 individuals, or approximately one in every 5,000, thought to be carrying the mutation that results in the development of Huntington's disease (Moutou, Gardes, & Viville, 2004). HD has the highest prevalence of the nine inherited

neurodegenerative disorders (Landles & Bates, 2004). Most individuals affected by the mutation have only one copy of the allele, or are heterozygous (see Figure 2a). However, there are rare instances in which an individual can be homozygous (see Figure 2b) for the mutation resulting in two copies of the allele (Gusella & Macdonald, 2006). To be homozygous, an individual would have to inherit the dominant allele from two affected parents. This means that even if he or she married an unaffected individual, his or her offspring would still have a 100% chance of carrying the mutation, and a 50% chance of transmitting it their children (see Figure 3b). Interestingly, the course of the disease is not worsened in individuals who are homozygous for the allele when compared to the heterozygous inheritance (Kremer et al., 1994).

A study conducted over a 3 year period in Canada revealed the average age of onset for a total of 282 people with HD to be 48.4 years and ranged anywhere from 6 to 81 years of age. This seems to be consistent with most other predictions that state age of onset to fall mostly between the ages of 30 to 50. The age of onset appears to be significantly elevated in individuals who have no family history of the disease; an average of 54.5 vs. 46.6 in those with a family history. Those without a family history of HD may be confused as to how they acquired the disease. The individual may be carrying a new genetic mutation, may have lost his or her affected parent before the onset of any clinical symptoms, or the diagnosis may have simply been missed in his or her parent and his or her neurologic symptoms attributed to another genetic disorder (Creighton et al., 2003).

A discussion of our current knowledge of HD would not be complete without mentioning the work and research being done in Lake Maracaibo, Venezuela by Nancy Wexler and many others. Nancy Wexler is a well known pioneer in the Huntington's world. Her mother passed away due to HD, and she herself is at risk for the disease. She has spent most of her life

dedicated to finding a cure for the disease. Her quest began in 1979 and has continued to the present, spilling over the Venezuelan borders to include several different countries. Nancy Wexler and the U.S.-Venezuela Collaborative Research Project have worked with information from over 18,000 individuals, across ten generations, within what is known as the Venezuelan HD Kindred. Residents of Lake Maracaibo are a part of what is known as the founder effect, meaning that there were a limited number of founders of the community and one or more of them had the mutation for HD. Their research has confirmed that age of onset does, in fact, correlate negatively with length of CAG repeat. Repeat lengths between 40 and 60 have shown to have the greatest amount of onset age variation. The age of onset according to information gained from the participants ranges from 2 to 84 years. The cooperation of the people of Lake Maracaibo, Venezuela has led to valuable research that will continue in the future (Wexler, 2004).

Pathophysiology

The neurodegeneration seen in HD has been shown to be specific for the GABA (Gamma-aminobutyric acid) releasing medium-sized spiny neurons (MSN) of the striatum (Gusella & Macdonald, 2006; Landles & Bates, 2004). This region of the brain includes the globus pallidus, caudate nucleus, and putamen (see Figure 1). These are all a part of the basal ganglia that are in part responsible for receiving and sending information to and from the cerebral cortex. The location of the MSN helps explain why there are motor complications associated with neurodegeneration that is seen in Huntington's disease. Around 20-30% of neurons within the caudate may already be lost prior to the onset of any motor related symptoms of the disease (Gusella & Macdonald, 2006).

GABA is the major inhibitory neurotransmitter in the brain. Glutamate is the major excitatory neurotransmitter. As the neurons in the striatum degenerate there is either an increased or decreased release of these neurotransmitters which initiates a cascade of neurologic events. This decreased release causes a diminished inhibitory signal from the putamen's GABAergic neurons to be transmitted to the external globus pallidus (EGP). Due to the decreased inhibition, the EGP increases its release of inhibitory neurotransmitters to the subthalamic nuclei (STN). The chain reaction continues as the STN, now overly inhibited, decreases its own release of the neurotransmitter glutamate that would ordinarily produce an excitatory response in the internal globus pallidus (IGP). The normal action of the IGP is thus reduced, causing its GABAergic inhibitory role in regulation of the thalamus to be interrupted. This in turn causes the activity of the thalamus to increase causing greater stimulation of the motor cortex. The result is the inability to control voluntary movements, or what is known clinically as chorea.

The neurodegeneration in Huntington's disease eventually results in atrophy of the brain. Atrophy causes a decreased brain volume within the skull. Over time, cerebrospinal fluid (CSF) begins to fill the vacant areas. This results in what is know as hydrocephalus ex vacuo or "water-head." The increase in CSF can cause an increase in pressure on the brain tissue. This can lead to further brain damage and neurodegeneration. The most advanced stages of the disease are correlated with the largest increase in CSF. The individual may complain of nausea, headache or visual changes. Later on there may also be personality changes that may be dismissed as part of HD progression. Time before initiation of treatment affects the prognosis of the patient. Placement of a ventriculoperitoneal shunt can help move the CSF into the abdominal cavity where it can be absorbed. This relief of intracranial pressure may be a possible option for therapeutic treatment in HD patients that show symptoms related to increased CSF, although not widely used at this time (Ciarmiello et al., 2006).

The huntingtin protein serves several different functions throughout the body. Htt can be found in several types of cells, such as skeletal muscle cells, platelets, fibroblasts, and lymphoblasts. However, it seems that most affected cells can compensate for the mutation in a way that MSN in the striatum can not. This discrimination presents a possible area for future research. If the exact mechanism of striatal cell selectivity can be pinpointed, it may provide an opportunity for potential treatment or cure. Although the entire list of htt functions has not yet been fully described, the lack of the htt protein was proven to be lethal in both animal embryos and adult human cells. The structure of the huntingtin protein is mostly made up of HEAT repeats (huntingtin, elongation factor 3, regulatory A subunit of protein phosphatase 2A and TOR1 [target of rapamycin 1]) which are helical in nature, suggesting a possible role in the cytoskeleton of a cell (Gusella & Macdonald, 2006).

Mutated htt creates problems with normal calcium homeostasis in the mitochondria of cells. Mitochondria depolarize at lower levels of calcium and retain less calcium than mitochondria that have not been exposed to mutant htt. Mitochondria in patients with Huntington's disease require less calcium in order to be depolarized. This lowered threshold allows for overstimulation which results in subsequent excitotoxicity. The excitotoxicity leads to mitochondrial dysfunction and is ultimately damaging to a neuronal cell (Panov et al., 2002). .

Another suggested function of htt deals with transcriptional regulation. This contributes to HD because of the bulkiness of the polyglutamine end on mutant htt protein, which causes alteration of the protein's physical properties; this can lead to the formation of aggregations (Gusella & Macdonald, 2006). Aggregations can sequester important transcription factors such as CREB-binding protein (CBP), an acetyltransferase enzyme, and specificity protein 1 (Sp1), which binds to a variety of gene promotors involved in the transcription of DNA as well as the dopamine-D2-receptor gene (Landles & Bates, 2004). The reduced function of CBP and Sp1 cause a decrease in the transcription of normal genes required for proper cell functioning.

The reason that aggregations can damage neuronal cells is that they cannot be eliminated quickly enough. These misfolded proteins overwhelm the chaperones of the cell that would normally clear out troublesome aggregates. Chaperones are proteins that assist in the folding and unfolding, as well as the assembly and disassembly, of macromolecular structures in a cell. In the same way that transcription factors can be sequestered into aggregations, chaperones can also become tangled in the web of misfolded proteins. This further potentiates the creation of additional protein aggregates and decreases the number of the already overstressed remaining available chaperones (Landles & Bates, 2004).

Due to the many proposed functions of the huntingtin protein, pathogenesis of HD has the possibility of including many different processes. These include, but are not limited to, problems with the formation and breakdown of various proteins, transcriptional regulation, intracellular vesicle transport, cytoskeletal components of cells, neuronal communication, and mitochondrial functioning (Landles & Bates, 2004). There may be one that predominates as the major factor in development of the disease, or it could be a combination of mechanisms. The latter appears to be more probable.

Much of the current research involving Huntington's disease utilizes murine (rodent) experiments and data collected from individuals who have died of HD. One such article, by Weydt et al. (2006), discusses the possible role of PGC-1α (Peroxisome proliferator-activated receptor ɣ coactivator 1α) in linking the mitochondrial and transcriptional aspects of Huntington's. PGC-1α is an essential intermediary in the regulation of thermogenesis. When transcription of PGC-1α was disrupted, possibly by the polyglutamine sequence on the htt, HD mice displayed marked hypothermia due to decreased energy metabolism. This result may explain why the extremely active striatal neurons appear to be more susceptible to the consequent neurodegeneration seen in the brains of HD patients and mice.

Of the 26 genes examined in this study that rely on PGC1- α for coactivation, 92% had greatly reduced activity in Huntington's disease patients. Analysis of RNA from the striatum of HD patients also showed a decrease number of genes associated with PGC1- α (Weydt et al., 2006). These results, together with the results of the murine studies, strongly suggest that obstruction of PGC1- α transcription plays a significant part in the pathogenesis of Huntington's disease.

Predictive Testing

Due to the hereditability and prevalence of Huntington's disease, genetic testing is an issue that warrants discussion. Huntington's disease is unique among genetic disorders in that a single mutation is responsible for almost all cases of the disease (Harper, Lim, & Craufurd, 2000). HD was the very first late onset, autosomal dominant neurologic disorder for which predictive testing was available to aid in diagnosis (Creighton et al., 2003). Due to the lack of available treatment options, it can be questioned whether or not pursuing prenatal or presymptomatic genetic testing carries any benefit at all.

There are several reasons why an individual may choose to find out his or her predicted level of risk through genetic testing. A study from 2002 found that 81% of those choosing to undergo screening did so in order to alleviate the feeling of uncertainty (Evers-Kiebooms et al., 2002). Other reasons may include career or family planning, as well as other long term issues such as establishing advance care directives, a living will, and naming a durable power of attorney. Genetic testing also offers answers to those individuals who previously would have been misdiagnosed or undiagnosed (Creighton et al., 2003). Patients who present atypically are starting to be identified appropriately. Those who may appear to be developing symptoms related to the disease can have a definitive answer regarding their diagnosis. Out of 626 diagnostic tests performed in fifteen genetic centers throughout Canada, 31.5% of patients that came in displaying symptoms commonly seen in HD were found to be negative for the mutation (Creighton et al., 2003). So a typical presentation can result in an unexpected diagnosis. Another reason an individual may undergo a genetic screening test is for the benefit of his or her children who may or may not have already begun having children of their own. The parent may

feel as though it is his or her duty to inform his or her children of the possibility that a mutation may be transmitted before they make the decision to start a family.

Linkage analysis, exclusion testing, and definitive testing are the three types of genetic screening tools currently available. Linkage analysis was available even before the exact location of the mutation for HD had been discovered (Creighton et al., 2003). This method of testing requires prior knowledge of other family members' status in regards to the disease. Exclusion testing is a newer more accurate method that is most commonly used now in both prenatal and presymptomatic testing. Interestingly, one study showed that when given the option, only 9 out of 426 individuals that previously underwent linkage analysis chose to come back and have exclusion testing performed as confirmation (Harper et al., 2000). Definitive testing offers a more concrete answer regarding the risk status of a fetus. However, it requires more information regarding the individual's family in order for it to be accurate.

Linkage analysis involves identifying two genetic markers on either side of the region in which the disease gene is believed to be located. The genetic markers are then used to approximate the location of the sequence of DNA that causes the disease. This is accomplished by studying the recombination that takes place along an allele. If recombination has not occurred between two DNA sequences they tend to be located closer to one another. Recombination that occurs between two DNA sequences suggests that they are farther apart on an allele. Using this information can then provide the necessary details regarding the location of the gene associated with the disease in question. A pedigree of the individual being tested is used to establish the occurrence of the disease gene and apply it to determining which allele is normal and which carries the DNA sequence for the causative mutation (Botstein, White, Skolnick, & Davis, 1980).

Exclusion testing is a form of genetic testing that does not require the status of the parent to be known. It checks for the presence of the HD region on chromosome 4 that could have been transmitted via the affected grandparent (Creighton et al., 2003). Using linkage analysis, the existence of a mutation can be excluded. This type of testing is used with parents who are at a 50% risk of carrying the mutation (see Figure 2a), meaning that one of his or her parents was diagnosed with HD and had the dominant allele (Adam et al., 1993). The fetus of a 50% risk parent carries a 25% risk of receiving the chromosome containing the disease. Exclusion testing can further clarify the status of quantifying the fetal risk as either very low or the same as the parent if the mutation cannot be excluded (Adam et al., 1993). This gives the parents the information they need to decide whether to continue or terminate the pregnancy. However, it is important to realize that 50% of the time they may be aborting a normal fetus. This type of testing is a great resource to those who were not planning to get pregnant due to their own risk, but now have a chance to try until their fetus tests negative for the mutation (Maricle, 1993).

Definitive testing can only be done if the status of the parent is known (Croyle & Lerman, 1995). This can be done through chorionic villus sampling or amniocentesis. According to the Huntington's Disease Society of America guidelines, chorionic villus sampling usually takes place around the 8^{th} to 10^{th} week of gestation (Rosenblatt, Ranen, Nance, & Paulsen, 1999). Amniocentesis is usually performed closer to 16 weeks of gestation. Either method will offer a conclusive result giving the fetus as low as a 3% risk or as high as a 96% risk. In some instances, exclusion testing and definitive testing can both be used. If exclusion testing reveals the fetus to be at 50% risk, definitive testing can then be performed to confirm or rule out increased risk before termination of the pregnancy is considered (Adam et al., 1993).

Knowing the types of genetic tests available and where to go to have them completed (see Table 1) is an important first step in the decision making process involved in determining risk stratification. Scully, Porz, and Rehmann-Sutter (2007) conducted multiple interviews which have helped to clarify this issue. Drawing conclusions from their interactions, they report two ways that individuals seem to approach the decision of whether or not to undergo genetic testing for themselves or their children. The first was a stepwise pattern of decisions leading to the final decision, and the second involved the individual focusing specifically on the present and refraining from considering the implications for the future. Huntington's disease patients were one of the three groups of individuals who were interviewed. The decision dealt with either future reproductive concerns or plausible health conditions later in life. The number of participants interviewed was small; however, the information addressed seems to be applicable to many individuals dealing with the choice of genetic testing.

Small gradual steps may be the best way for many individuals to make a decision whether or not to pursue genetic testing. It is the responsibility of a health care professional to allow any amount of time that the patient needs. Recommendations could be made on the first visit, and the patient could take home some information regarding the testing options and his or her potential diagnosis. Health care professionals need to encourage the individual to search on his or her own for different sources of information. Table 2 lists several different organizations that offer various types of information. This allows them to proceed on their own terms and according to their own time frame. Due to the late onset of Huntington's disease, patients are not as pressured by time to make a decision (Scully, Porz, & Rehmann-Sutter, 2007). Patients could then schedule a second appointment where they discuss any questions they may have regarding

the material they have reviewed. At this point, if the patient wishes to make their decision, they do so well-informed. If they prefer not to make a decision at that time, there is no pressure.

Many factors influence the decision regarding testing for Huntington's disease. Individuals who are a part of a religious organization are less likely to pursue screening. Those who already had other children are also at a significantly decreased percentage of prenatal genetic tests performed. Many also refrain from testing because termination of pregnancy is not seen as an option (Adam et al., 1993). Other reasons that individuals decline genetic testing include the lack of available treatment options, the cost of the screening test, fear of increased risk to their children, and fear of dealing with the reality of the result (Creighton et al., 2003). Some individuals feel that they would be unable to cope with a negative result. There is also a concern for any person at risk regarding future employment or insurance coverage (Evers-Kiebooms et al., 2002). Some refuse to risk jeopardizing a career or possibly increasing their insurance premiums. Due to the inability to change the diagnosis, others simply prefer not to know and to go on with their lives.

Along the pathway to deciding whether or not to undergo genetic testing (either presymptomatic or prenatal) there are a variety of issues, originating from multiple viewpoints that must be addressed. The individual being tested, his or her spouse, parents, grandparents, and children all need to considered and perhaps actively involved in the decision making process. The argument can be made that it is only the preferences of the specific person that matter. He or she is trying to figure out his or her own risk level. However, it cannot be ignored that when a risk level is determined and results disclosed, this not only divulges the status of the tested individual but also may reveal the status of parents and grandparents, as well as the possible risk to his or her children.

Being tested for any genetic mutation can lead to peace of mind or an ominous diagnosis of a late-onset, slowly progressive disease. Every individual has to determine the personal value of testing, as his or her life will be directly affected by the result. The individual will have to deal with and adjust to the outcome. The results of a genetic test impact each person differently. One case study discussed a test candidate who underwent additional counseling due to depression as well as other psychological stress. It took about one year before she began to adjust to all that accompanied her positive test result (Benjamin & Lashwood, 2000). A study that took place over a ten year period found that the incidence of more severe psychiatric disorders including attempted suicide were very rare shortly after learning of the diagnosis (Harper et al., 2000). Long term effects of receiving a negative result had not yet been assessed.

It is important for healthcare professionals and genetic counselors to remind those that have received a positive test result that they have options. This is especially true for individuals who want to start a family, but feel as though they cannot in good conscience do so knowing that they are at an increased risk for the mutation. A study published in 2002 examined a few ways that couples could address the issue of reproduction. There is always the option to forego having children and adopt. This would ensure that the mutation would not be passed on to the next generation. The individual could choose to proceed with having a child and hope that the child will not receive the allele from the affected parent. Only 14% of individuals enrolled in a collaborative study who were found to be at high risk chose to become pregnant (Evers-Kiebooms et al., 2002). Another option would be utilization of prenatal diagnosis with subsequent termination of an affected pregnancy. Artificial insemination and in vitro fertilization are also different ways that transmission of HD can possibly be avoided. However, both of these methods would require the use of either a donor sperm or egg to avoid passing the

allele to the child. Preimplantation genetic diagnosis (discussed later) is also something to be considered.

Significantly more females request genetic testing than males (Creighton et al., 2003). In one study, 58% of the participants were female. This discrepancy may be due to the greater focus of females on reproductive decision making. Females more closely examine the possible impact that genetic disorders may have on their future family. Women also are thought to have an increased willingness to deal with difficult choices when compared to men (Harper et al., 2000).

If adult children are tested for the presence of the htt mutation and find that they are positive for the CAG expansion, this could possibly divulge the status of the parents. The parents may not wish to know their status, or may not want others to know. The parents who are now finding out their status by proxy may not have had adequate access to counseling prior to receiving the news (Harper et al., 2000). This puts them at an increased risk for negative psychosocial complications. In a study that took place in the United Kingdom, 56% of the family members felt that they had been given unsought information. When asked, 35.7% of the parents did not want the individual to undergo testing. This difference in opinion may easily create tension among families, especially if an individual proceeds regardless of his or her parents' wishes. Interestingly, a little less than a third of genetic testing centers in the UK were hesitant or refused to test an individual if his or her parents expressed feelings to the counter (Benjamin & Lashwood, 2000). However, it can still be argued that it is the right of the child, who is in fact an autonomous adult (age 18 or older), to know his or her own risk level for developing the disease.

The issue gets more ethically challenging when considering genetic testing in children who are not yet autonomous. Performing genetic testing early in a child's life can be viewed as allowing the child to have the time he or she needs to adjust to the diagnosis and its future consequences. The child can then plan accordingly to account for changes that will occur later in the disease process. Knowing a child's risk level prior to the onset of any clinical symptoms may also bring a family closer together as they rally to support the child as he or she grows older. Once the diagnosis or lack of diagnosis has been established, other family members may want to undergo testing themselves. Lastly, if a parent knew prior to having a child that they were at a 50% risk of carrying the mutation, it may offer them peace of mind to know the status of the child. He or she would not be constantly wondering whether or not they had passed on the mutation. However, it may not be wise to alleviate the anxieties of a parent at the expense of ignoring analysis of benefit to the child in question (Clarke & Working party of the Clinical Genetics Society, 1994).

Just as there are benefits, there are also shortcomings associated with child genetic testing. Confidentiality between a patient and the genetic specialist who is available to an adult is denied to a child. Also, the knowledge of having a late onset disease may cause the individual to have difficulty with self-esteem, discrimination at work or school, as well as hindering the ability to form relationships throughout life. The diagnosis could also affect how the family perceives the child from that point on. Certain expectations that the parent might have held regarding reproductive capabilities of the child may be greatly disappointed. When adults are offered predictive testing, several counsel sessions are usually available to them long before and then again after they receive the test results. Children who are tested do not have the same opportunity for counseling. He or she would then have to learn to cope with the knowledge of

having a disease for which there is not effective treatment or cure. From that point on, any oddity or change in health may falsely be considered early onset of the disease resulting in unnecessary anxiety. It may be best to forego testing until the child has reached the appropriate age and is able to understand not only the genetic aspects, but also the possible social and emotional repercussions associated with testing (Clarke & Working party of the Clinical Genetics Society, 1994). Then he or she could make an informed decision on his or her own terms of whether or not to be tested for the disorder.

Another question arises when it involves a child who has been placed up for adoption. Caution and careful consideration should be used when deciding what option will best benefit the child. It could be considered of benefit to the individuals adopting an "at risk" child to know the likelihood of the child actually acquiring the disease prior to bringing him or her into their home (Clarke & Working party of the Clinical Genetics Society, 1994). Also, it is the responsibility of the adopting agency to know and divulge any information related to the health of a child (Clarke & Working party of the Clinical Genetics Society). Knowing that a child is positive for a mutation that leads to an illness, whether adult onset or not, may affect that child's chances of finding home. Ideally, a family will adopt the child regardless of the outcome of genetic testing for the diagnosis of HD. Unfortunately, most individuals want a "healthy baby" and the stigma resulting from an early diagnosis of Huntington's disease may dramatically decrease a couple's willingness to adopt the child.

While there may never be agreement on the proper course of action, the rights of the child should always be taken into account. The fact that the disease is late in onset suggests that it may be warranted to postpone the genetic testing until the child is at a proper comprehension level to fully understand the gravity of the situation. There is still a lack of consensus between

geneticists, physicians, hematologists, and adoption agencies regarding the concept of child genetic testing (Clarke & Working party of the Clinical Genetics Society, 1994). With so many unique viewpoints, backgrounds, and belief systems, there may never be a consensus opinion on this issue.

When a member of a family is diagnosed with a disease, the entire family is affected in different ways. Knowing the results of a genetic test has the potential to bring challenges of emotional, social, and economic origin to everyone involved. Family members may be glad that they were told and wish to be tested as well. Others may wish that they had not found out that they could be at an increased risk. There is a possibility for a great deal of emotional stress surrounding the future of the recently diagnosed individual. Knowing that they may need to coordinate medical care for him or her in the future may add a considerable burden upon relatives. There may also be fear of the unknown regarding the status of other members of the family and what will happen next. A family must come to the decision of whether it is better not to know and be forced to deal with uncertainty, or to know and be forced to deal with the fact that a member of their family has HD (Clarke & Working party of the Clinical Genetics Society, 1994).

A positive test result also affects the children of the recently diagnosed person. They must cope first with the fact that their parent has HD. In addition to that, they now find themselves at increased risk for that same late onset disease. Whether or not they develop the disorder, the thought of the possibility will be in the back of their minds until they either get tested or begin to develop symptoms of the disease. They may be burdened with caring for that parent and struggle with watching him or her decline as the disease slowly progresses. The child in turn will recognize that if he or she has children they may have to endure the same situation.

Children may also view the knowledge of their parent's positive test result as a good thing. This may give them an opportunity to learn more about HD and how to care for their loved one prior to onset of symptoms associated with the later stages. This may allow them to feel prepared to handle the tough times ahead. It may also give them the time they need to sit down and discuss end of life care with their parent before severe cognitive impairment occurs. Then decisions and arrangements could be made to bring both parent and child one step closer to having peace of mind about a difficult situation.

Prenatal Testing

Prenatal testing is also a concern whenever genetic disorders are discussed. The prenatal decision regarding genetic testing occurs under a much more pressured time frame than that of an adult (Scully et al., 2007). The pressure is on both the parents and the counselor who has only a certain amount of time to work through the process with them. The parent(s) whose fetus may be at risk for the genetic mutation have to make the decision whether or not to go through with testing knowing that their future, and that of their child, may be greatly altered by that decision. Many individuals who now know they carry the mutation choose to undergo prenatal testing so that their child will not have to bear the weight of a high risk result in the way that they did (Simpson & Harper, 2001).

One issue that inevitably arises is that of possible abortion if the fetus tests positive for the genetic defect in question. In a study of data for several genetic testing centers published in 2003, eleven of twelve mothers who received an increased-risk result following linkage analysis or mutation analysis underwent abortion (Creighton et al., 2003). A study completed in 1993 showed that six of seven pregnancies proven to be at an increased risk for the mutation were terminated (Adam et al., 1993). This study also mentioned an individual, who had been diagnosed with HD, who kept trying until she conceived a fetus that was at decreased risk. The previous conception that had been found to be at an elevated risk of carrying the mutation was terminated shortly after the result was presented. Other studies have also shown high rates of termination rates for high risk pregnancies. Out of 66 unfavorable results in a study done from 1994-1998 61, or 92% were aborted (Simpson & Harper, 2001). Lastly, there was a study that took place across several European countries in which each of the twelve affected pregnancies were terminated (Evers-Kiebooms et al., 2002).

With so many individuals choosing to abort a high risk fetus, the question of the unborn child's right to live can not go unaddressed. Should women be allowed to repeatedly abort babies until they become pregnant with one testing at a reduced risk? Genetic testing then becomes not unlike a conveyor belt where the products of fertilization are analyzed and the "defective" discarded. Is the fetus that is [possibly] carrying the mutation a defective product, or an unborn life? Some may see this as an overly dramatic illustration, but it is a relevant one. When the decision is made to procreate, it is from that point on a commitment between three individuals: father, mother, and child. The choice to terminate is ultimately the mother's. However, it can be argued that they have already made the commitment and must follow through to whatever end. Others may argue that it was irresponsible of the parents not to undergo genetic testing prior to conceiving a child. If this had been done, pregnancy and resultant termination of pregnancy could have been avoided.

It is important to view the issue from multiple perspectives. After all, the parents will have the responsibility to raise the child. They may not want to bring a child into this world knowing that, in time, that child with develop a slowly progressive and ultimately fatal disease. Depending on the time of onset, the parents may also be burdened with medical bills associated with the disease. Many could view allowing an increased risk pregnancy to progress to full term as an irresponsible action. They could have prevented greater strain on an already taxed medical system and chose not to do so. Also, it can be argued that it may be seen as unfair to allow the child to live knowing what their fate may be. He or she would live each day knowing that the many debilitating effects of HD lie ahead. To show them life and then take it away prematurely may seem almost cruel. So the question remains whether or not that choice belongs to the parent or the unborn child; that is the core of the prenatal testing debate.

Even though prenatal testing has been available for several years, the percentage of individuals deciding to utilize the available screening tests is not as high as expected. In Canada, over approximately a thirteen year span, only 18% of those eligible to receive prenatal genetic testing did so (Adam et al., 1993; Creighton et al., 2003). Another study showed that only 9-15% of people were tested after 56-80% of them had previously stated that they would if it were made available to them (Simpson & Harper, 2001).

Preimplantation genetic diagnosis (PGD) is newer alternate form of prenatal testing. PGD allows for the transfer of only those embryos for which the mutation has been ruled out (Moutou et al., 2004). All other embryos are discarded; even those that still have a 50/50 chance of being healthy. This is another moral dilemma. An embryo is a fertilized egg that has already begun its early stages of development. The question is whether or not an embryo is a life at that point. Some may argue that because it is not yet a fetus and will not be until the eighth week of gestation that it is not yet a "baby," or life. It is only a product of conception at this point and could not be viable outside the womb. Others may say that once an embryo is formed, it is a life due to the fact that if allowed to progress it will become an infant. Whether discarded before or after it is termed a fetus, it is simply a different stage of development for the same life and timing of termination is irrelevant.

There is also the issue to consider if "leftover" embryos could be used instead of discarded. It may be beneficial to use the embryos in various types of research. An embryo could also be bought by a barren couple incapable of producing their own offspring. While both of these options are valid, there are also some problems. Using an embryo for research purposes may again violate the idea that the embryo is already a life. Some may equate it to performing an experiment on someone's five year old child, seeing no difference between the two. The view

that the possibility of saving lives through ground breaking discoveries in research outweighs the loss of a possible life must also be considered. An undeveloped product of conception may seem insignificant when compared to saving an individual who has been loved by family for decades. Using an embryo in a couple unable to conceive may at first glance seem noble and compassionate. It could also be viewed as irresponsible as the embryo is still at a 50% risk for developing Huntington's disease.

Even if a couple undergoes PGD, it is important to mention that a diagnosis cannot always be made for an embryo, and there is no guarantee that the implantation will be successful (Moutou et al., 2004). In a study published in 2004, a diagnosis was made for 75 out of 94 embryos in the first group that were analyzed, and 34 of the 41 embryos for the second group (Moutou et al.). This is about 80% and 83% respectively. That particular study produced a pregnancy rate of about 19% between the two groups.

PGD may be a good option for individuals who know they are positive for the mutation. If a pregnancy can be started earlier in life, the parent will have more time with the child before his or her own symptoms begin to have an impact on daily function. Whether or not this is fair to the child is open to discussion for reasons that have been stated previously. The use of preimplantation genetic testing instead of using prenatal testing after conception has already taken place relieves the parent of the decision to terminate a pregnancy (Moutou et al., 2004). Unwillingness to terminate a pregnancy is one of the main reasons that individuals choose not to undergo genetic testing in the first place (Creighton et al., 2003). Preimplantation genetic diagnosis offers a unique new way of addressing a possibly positive genetic result and avoiding termination of pregnancy, but it is not without its drawbacks that every couple must consider.

Prenatal testing is a difficult topic that can be best addressed by the scientific community learning as much as possible about the pathogenesis of HD. This may allow a more promising prognosis to be established for this terminal disease. The acquired knowledge will then hopefully change the purpose of genetic testing from determining the outcome of pregnancy, to detecting the diagnosis early so that a treatment plan can be implemented soon after birth. In a five year study done in 1993, 82% of individuals who did not choose to undergo prenatal testing made that decision because they hoped for a cure within their unborn child's lifetime prior to the onset of disease (Adam et al.). Another study revealed a similar response with 80% of those choosing to refrain from testing stating that they were hoping for a cure (Evers-Kiebooms et al., 2002). It is the responsibility of the scientific community to make this hope a reality. Many lives, both unborn and already in existence depend on it.

Where We Are

Much information is known regarding Huntington's disease, especially when the knowledge base is compared to only twenty years ago. However, present research still suffers from various limitations and gaps that must be resolved and overcome before a cure can be found. For the most part, Huntington's disease remains a medical mystery.

Current treatment options are focused on symptomatic relief rather than a curative solution. Unfortunately, most of the symptomatic treatments available have limited efficacy. Bonelli, Wenning, and Kapfhammer (2004) took a detailed look at 24 studies and concluded that the current available pharmaceutical treatment options are not beneficial clinically. Some of the studies even showed a worsening of symptoms. Even though the outlook appears poor at this time, continuing research and experimental trials will hopefully present new and exciting options for the symptomatic treatment of HD.

Congo red is just one of many compounds that have been tested for efficacy in Huntington's disease. Following injection of Congo red into mice expressing the HD mutation, there were no significant observable improvements in motor function, memory, or overall health (Wood, Pallier, Wanderer, & Morton, 2007). Even though Congo red had been shown to bind to aggregates, its therapeutic benefits were found to be limited at best.

Minocycline, a second generation tetracycline, has been shown to cause a significant decrease in the motor portion of the Unified Huntington's Disease Rating Scale (UHDRS) scores (see Table 3) (Festoff et al., 2006). However, other areas of the UHDRS, such as psychiatric symptoms, were not improved. This study was limited by small sample size and the possibility that changes observed may have been due to placebo effect. A similar vague outcome was also seen in a study involving creatine therapy in HD patients. Based on a previous successful

murine trial, creatine was administered to thirteen patients for a period of twelve months. There was no significant therapeutic effect seen from creatine therapy (Tabrizi et al., 2003). Another study of creatine therapy involving 41 patients also showed a lack of clinical benefit or improvement in any symptoms (Verbessem et al., 2003). No toxicity was noted in either the minocycline or creatine trials.

Riluzole is a medication that showed significant benefits in mice (Schiefer et al., 2002). Striatal aggregate size decreased, hyperactivity decreased, weight loss reduced, and there was an overall increase in survival time in treated versus control mice. However, no significant motor function changes were observed. The effects seen during the treatment with riluzole may be in part due to its effects on the N-methyl-D-aspartate receptors in the brain. An antagonist at these receptors, riluzole is thought to block glutamate induced excitotoxicity and therefore alleviate some symptoms of HD (Schiefer et al., 2002).

Dichloroacetate increases the activity of pyruvate dehydrogenase complex (PDHC) thus increasing oxidative phosphorylation in mitochondria of neurons. HD mice given dichloroacetate in their drinking water displayed increased longevity, decreased weight loss, delay of diabetes onset, improvement in motor capabilities, and maintenance of PDHC concentration. Aggregates, however, were unaffected by the drug (Andreassen et al., 2001). This study presents another possible treatment option that needs to be explored in humans for possible alleviation of disease symptoms.

Current therapies are being also being aimed at slowing progression of the disease. A study published in 2002 showed that benzothiazoles could be utilized in vitro' to slow down the development of protein aggregates that are thought to be a contributor to neuronal cell death (Heiser et al.). This drug therapy was unfortunately found to be toxic when tested in vivo. So

while this demonstrates that there are compounds that could be used to slow the disease process, it also demonstrates how frustrating research on HD can be.

The use of creatine before brain injury may prove to be considerably more effective than beginning creatine therapy following onset of symptoms. A creatine-enriched diet was shown to decrease the amount of cortical damage seen in rats. Mitochondrial membrane potentials also showed a greater level of stability than those of control rats (Sullivan, Geiger, Mattson, & Scheff, 2000). It may then be that treatment with creatine early on in the disease process and prior to onset of symptoms may be neuroprotective.

Another option for neuroprotection and symptomatic improvement may be the use of rapamycin. Normal function of the kinase mTOR (mammalian target of rapamycin) is disrupted when it is sequestered into the aggregates associated with HD. Rapamycin has been demonstrated to decrease the amount of aggregates being formed and therefore decrease the amount of mTOR sequestered. Rapamycin may present a way to stop neuronal cell death before it begins (Ravikumar & Rubinsztein, 2006).

Leventhal et al. published a study in 2000 that used cyclosporine A to treat areas of decreased neurons. Cyclosporin A prevents a disruption in the maintainence of mitochondrial membrane potential and other forms of mitochondrial damage. These neuroprotective effects were seen in vitro and in vivo. Higher doses were needed in order to obtain positive results in vivo. Partial disruption of the blood brain barrier showed to increase efficacy of the cyslosporin A. This represents both a hope and a challenge. Disruption of the blood brain barrier may be necessary for better drug absorption into the brain, but it could also make the brain more susceptible to infection and effect of other chemicals (Leventhal et al., 2000).

A 1997 study presented a treatment option that allowed for the blood brain barrier to remain intact with positive results still being obtained. Epidermal growth factor (EGF)-responsive neural stem cells were used as grafts that after differentiating secreted human nerve growth factor (hNGF). The hNGF then provided a neuroprotective role in the striatum. Rats that had received the implants of the EGF stem cells showed little to no decrease in neurons upon injection of quinolinic acid when compared to the control rats ($P = 0.001$). Several different types of neurons were spared in the striatum. This included GABA-ergic cells which represent a majority of the neurons present in the striatum (Kordower et al., 1997).

Ciliary neurotrophic factor (CNTF) is one of many factors present in the brain that work to ensure repair and regrowth of damaged neurons (Jones & Redpath, 1998). Direct application of a capsule containing CNTF into the lateral ventricle of patients is another more invasive treatment option currently being researched (Bloch et al., 2004). This phase I trial included six patients who had a total of four capsules placed, one every six months. Though no toxicities were noted, either locally or systemically in relation to the release of CNTF into the CSF, they did have difficulty controlling the amount that was circulated. Less than half of the capsules were still secreting the CNTF in a measurable amount upon removal. While there were some electrophysiologic changes observed, none of the patients exhibited significant improvements clinically. If the rate of secretion could be controlled, the number of necessary surgeries minimized, and best location for implantation specified, CNTF administration may prove to be a potentially disease altering therapeutic option (Bloch et al., 2004).

A 2005 study showed that small interfering RNAs (siRNAs) present a new and efficient way that the disease may one day be treated in childhood or maybe even infancy in order to delay onset. siRNAs were administered to the neurons inside HD affected, newborn mice, and

the result was effective HD gene suppression. This resulted in delayed weight loss, increased longevity, and overall increase in age of onset of the disorder. Knowing that htt is important in normal neuronal cell function, finding a balance between suppression and partial expression warrants further investigation as a treatment option for HD (Wang et al., 2005).

Neural stem cells have been used in experiments in an attempt to moderate and possibly improve the progressive neurodegeneration. When grafts of neural stem cells were placed in areas of lesion created by injection of quinolinic acid, significant improvements were seen in rat striatum. The neural stem cells were shown to successfully differentiate into striatal neurons as well as astrocytes and the rats previously exhibited motor deficiencies were much improved. The largest amount of functional recovery was seen when the stem cells were pretreated with ciliary-derived neurotrophic factor (CNTF). This factor added in cellular differentiation. Newly differentiated cells not only improved the motor capabilities of the rats, but also added in support and protection of the remaining surrounding neurons (McBride et al., 2004).

The research experiments mentioned above are only a few of the many. Those that have been mentioned have served to illustrate two important points. The road to finding a cure for HD has so far been slow and long, and there are areas of possible therapies that show great promise. While vague results and failed experiments may be difficult to accept when the world wants a cure, they are all being used as stepping stones to reach an answer for that which at this time remains unexplained.

Where We Are Going

There are many possible treatment options currently being explored. These include but are not limited to, gene therapy, aggregation inhibitors, proteolysis inhibitors, excitotoxicity inhibitors, mitochondrial enhancers, and transplantation of embryonic stem cells. Many of these options show great promise in symptomatic relief, but it will take a scienitfic breakthrough for a cure to be developed.

Gene therapy is one way that the defective allele in HD may be corrected. A gene not affected by the mutation could be placed inside the genome in hopes of replacing the defective gene. A process called homologous recombination is also a possibility. Smithies et al. (1985) conducted a series of studies in which they found that they could modify a specific gene without interrupting the rest of the genome. Their experiments showed limited success rates, but that the homologous recombination can be done. The process involves the utilization of the process of cross over and recombination that occurs naturally within a cell. This is one way that a normal DNA sequence could be introduced into a gene. A plasmid DNA with the new sequence is inserted into a human cell where it recombines with a specific target locus and replaces the affected region (Smithies, Gregg, Boggs, Koralewski, & Kucherlapati, 1985). Other studies since then have also utilized the same mechanism to repair DNA in murine models with a known genetic disorder. After the cells have been inserted with the modified DNA sequence, they are allowed to differentiate and are then transplanted into the host organism (Rideout III, Hochedlinger, Kyba, Daley, & Jaenisch, 2002). The hope is that there may also be a way of altering the regulation of the gene involved in HD. One of the challenges related to gene therapy is how to safely introduce progenitor cells into the central nervous system. The use of various

types of viruses, such as adenoviruses or retroviruses may prove a useful method of delivering normal genetic information into a cell affected by HD.

Aggregation blockers may decrease the amount of damage being done to the striatal neurons and thus postpone the progression of the disease. The mammalian target of rapamycin (mTOR) has been found to induce autophagy once it has been sequestered by a protein aggregate. Cellular toxicity is then reduced by their clearance. This has been shown in both murine and human brains and offers a very promising avenue for a future treatment modality (Ravikumar & Rubinsztein, 2006).

The idea of protecting mitochondria found in neuronal cells may prove to be one of the most promising areas for future research. Restoring function to the power house of the cells may decrease the effects of neurodegeneration seen in HD. ADP and cyclosporine A were both found to increase the ability for mitochondria to retain calcium and to delay the rapid depolarization that was taking place within them (Panov et al., 2002). This may be useful if were able to be utilized in increasing the mitochodria's ability to fulfill their role within a cell that has been damaged by the mutant htt.

Reducing the amount of oxidative stress on neurons by decreasing the amount of excitotoxic exposure would be an avenue through which neuronal mitochondria may be protected. Keeping the concentration of reactive oxygen species low within a cell is essential to proper function. If the level of PGC-1α in a cell is kept at an adequate concentration it serves to decrease ROS levels and stimulate activity of the mitochondria in nerve cells. This allows for a neuroprotective effect that may offer a revolutionary treatment option for HD sufferers. If a pharmaceutical agent could be found that specifically increases the amount of the PGC-1α protein being made, this could possibly act to halt the neurodegeneration. If those at risk

underwent predictive testing at a young age, medication like this could be started early on, before the onset of symptoms, and possibly delay or permanently suppress the disease (St-Pierre et al., 2006).

It would also be of interest to see if individuals with a positive predictive test result would benefit from early initiation of creatine therapy (Sullivan et al., 2000). Early prophylactic treatment and prevention of oxidative damages may delay onset of HD. Testing this type of drug efficacy would require several years of observation and brain imaging. While the process would be long and would require the involvement of many patients, the benefits may in the end outweigh the difficulties.

Neuroprotection is a common theme for possible treatments in HD. However, if neurons could be replaced altogether, then the issue of degeneration would be resolved. Embryonic stem cell transplantation offers a hope not only to HD patients, but also to all affected by neurodegenerative disorders. The amazing ability for the stem cells to differentiate makes them a wonderful research opportunity. Anytime the use of embryonic stem cells arises in medical or clinical conversation, there are multiple conflicting viewpoints. McBride et al. (2004) used cells from tissue obtained from terminated pregnancies to conduct their testing. This presents an ethical dilemma. Even if a pregnancy is deemed to be genetically abnormal, should it be terminated? If it is terminated, should we then be comfortable using the discarded tissue of the fetus to do experiments? As previously discussed, there are benefits and consequences to either way.

The answer may lie in the use of cord blood in order to avoid the use of products of termination. Cord blood is the blood remaining in the umbilical cord after it has been clamped off and must be collected in the first few minutes after birth. It contains hematopoietic stem cells

(HSC) which are able to differentiate in to many different cell types (Bhatia, 2007). However, the success rates for the use of HSC from cord blood have been much higher in children. There are also risks and benefits to the use of these stem cells. Cord blood is relatively easy to procure, not harmful to the donor to do so, and has a low chance of transmitting disease. However, there is still a small risk for development of disease further down the road, and the collection of the blood is a one time occurrence which makes future treatment a dilemma (de Lima & Shpall, 2006). Despite the possible problems, cord blood banks are in place around the country and offer an effective alternative to a questionable practice.

The application of various neurotrophic factors may also aid in stifling the damage done by the mutant htt and aid in replacing lost striatal neurons. The regeneration of neurons is an excellent area for future research. It is important to consider the possibility that regrowth will not occur properly or exactly as desired. There is no guarantee that the neurons, if stimulated to regenerate, will do so back to the appropriate target cells. While connections may be formed, it may not recreate the original and intended circuitry. So even though the host generally tolerates grafts into the CNS well, there is still much to refine in this type of experimental procedure (Jones & Redpath, 1998).

Mechanism and modality of delivery is also an issue needing remediation with neurotrophic factors such as CNTF. Bloch et al. (2004) discussed the difficulties with controlling the amount released from implanted capsules. If murine trials can be conducted whose goal would be to work out the technical details with rate of capsule CNTF release, this could then be trialed again with patients. The study in 2004 contained a total of six subjects. Increasing the sample size and utilizing a better mode of transmission could lead to the discovery of a safe and effective treatment for neurodegeneration.

Preimplantation diagnosis with in vitro and in vivo fertilization, as previously discussed, is another promising alternative. While this does not offer a cure to the individual carrying the mutation, it does halt the transmission of the disease across generations. This could be used to decrease the incidence of Huntington's disease dramatically worldwide. However, low pregnancy rate and costs of the process certainly represent a large challenge.

Stopping a disease that is already progressing is definitely an area that warrants further investigation. However, it may also be beneficial to attempt to prevent the onset of disease by decreasing the mutant htt protein concentration rather than attacking each and every problem it causes (Ravikumar & Rubinsztein, 2006). EGF-responsive stem cells that secrete hNGF present one such opportunity (Kordower et al., 1997). Predictive testing could identify individuals positive for the HD mutation and administration of these stem cell implants could be initiated soon after. This treatment modality is in need of long term study, but shows great possible preventative capabilities.

The use of siRNAs prior to the development of neuronal intranuclear inclusions and neural stem cell grafts after the disease progression begins presents an amazing avenue for future treatment. This is just one way that treatment options may be combined in an attempt to achieve greater efficacy. As various methods of treatment or prophylaxis are proven to be effective, it may be of benefit to conduct trials involving a combination of therapies. Each new modality found to be effective could become a part of a greater treatment plan. In time, researchers may find a way to delay onset, slow progression, and treat symptoms, thus improving the quality of life and dramatically extending longevity.

Unfortunately, until the pathogenesis is clarified, finding a cure remains a difficult task. "Understanding the pathways that are responsible for repeat instability in patients with HD could

ultimately provide the possibility of therapeutic strategies aimed at preventing CAG repeat expansion..." (Wheeler et al., 2007). With continued research and clinical trials perhaps more can be discovered regarding Huntington's disease within the near future. There are many men and women like Nancy Wexler and her family who have dedicated their lives to finding a cure. With the determination of individuals and the support of organizations, it may only be a matter of time before Huntington's disease is a thing of the past.

Conclusion

Huntington's disease is a neurodegenerative disorder without remission. It is caused by an increase in CAG repeats on the htt protein and selectively affects the medium spiny neurons of the striatum. The motor, cognitive, and other symptoms of the disease progressively worsen over a time period of usually fifteen to twenty years; eventually, the disease will take the life of the patient. Affected individuals have a 50% chance of passing the disease to their offspring. The use of genetic testing is one way in which transmission of the disease can be stifled, but it is not without repercussions and negative sequlae. The decision whether or not to undergo genetic testing involves consideration of more than just the individual being tested. The fact that there are currently no effective treatments for the disorder also makes the decision more difficult. While new areas of research such as neural stem cell transplant are being explored, there are still many others needing research to advance HD treatment modalities. However, gene therapy, neuronal replacement and regeneration, and several other more current concepts are promising areas of future research in HD.

Finding a cure for Huntington's disease would open a door to future research and cures for other debilitating neurologic diseases. The impact on the health of our society as a whole would be incredible. There needs to be a renewed fervor for genetic research that could quite possibly change the face of medicine as we know it and revolutionize the treatment of genetic disorders.

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Tables

Table 1. *Genetic Testing Centers in the United States of America (from www.hdsa.org).*

State	Genetic Testing Center	Contact Information
Alabama	HDSA Center of Excellence at the University of Alabama at Birmingham Huntington's Disease Testing Center Laboratory of Medical Genetics Presymptomatic	Phone: (205) 934-4983 Fax: (205) 975-6389
Arizona	Arizona Health Sciences Center Section of Medical and Molecular Genetics	Phone: (520) 626-5175 Fax: (520) 626-8056
California	Huntington's Disease Clinic: The College of Medicine at UC Irvine Gottschalk Center	Phone: (714) 456-7239
	HDSA Center of Excellence at UCLA Medical Center Huntington's Disease Testing Center Neurogenetics Clinic	Phone: (310) 206-6581 Fax: (310) 206-8616
	University of California, San Francisco Huntington Disease Clinic: Genetic Counseling and Evaluation	Phone: (415) 476-9320 Fax: (415) 476-9305
	HDSA Center of Excellence at University of California Huntington's Disease Testing Center	Phone: (858) 622-5854
	Kaiser Permanente of Southern California Department of Medical Genetics	Phone: (818) 375-2073 Fax: (818) 375-3108
	Kaiser Permanente Hospital	Phone: (408) 972-3300 Fax: (408) 972-3298
	HDSA Center of Excellence at University of California, Davis Huntington's Disease Testing Center	Phone: (916) 734-3588 Fax: (916) 452-2739
Colorado	University of Colorado Neurology HD Testing Program	Phone: (720) 848-2080 Fax: (720) 848-2106
	HDSA Center of Excellence at Colorado Neurological Institute Huntington's Disease Testing Center Movement Disorders Center	Phone: (303) 357-5455 Fax: (303) 357-5459
Connecticut	Yale University School of Medicine Department of Genetics	Phone: (203) 785-2661 Fax: (203) 785-7673
	University of Connecticut Health Center Huntington's Disease Program	Phone: (860) 679-4441
Florida	HDSA Center of Excellence at the University of South Florida Huntington's Disease Testing Center Regional Genetics Program	Phone: (813) 974-6022
	University of Miami: Department of Neurology	Phone: (305) 243-5757
Georgia	HDSA Center of Excellence at Emory University	Phone: (404) 728-6364

	Huntington's Disease Testing Center Neurobehavior Program	Fax: (404) 728-6685
Hawaii	Kaiser Permanente Medical Group	Phone: (808) 597-2481 Fax: (808) 597-2498
Illinois	HDSA Center of Excellence at Rush-Presbyterian-St. Luke's Medical Center Huntington's Disease Testing Center	Phone: (312) 563-2900
	Advocate Medical Group Lutheran General Prenatal Center	Phone: (847) 723-7705
Indiana	Indiana University HDSA Center of Excellence Medical Center Huntington's Disease Testing Center	Phone: (866) 488-0008
Iowa	HDSA Center of Excellence at University of Iowa Hospitals and Clinics Regional Genetic Consultation Service	Phone: (319) 353-4307 Fax: (319) 356-3347
Kansas	University of Kansas Medical Center	Phone: (913) 588-6983
	Hereditary Neurological Disease Center	Phone: (888) 232-4632 or (316) 721-9250 Fax: (316) 722-2710
Maryland	HDSA Center of Excellence at Johns Hopkins Huntington's Disease Testing Center	Phone: (410) 955-2398 Fax: (410) 955-8233
	University of Maryland Department of Genetics	Phone: (410) 328-3335 Fax: (410) 328-5484
Massachusetts	Boston University School of Medicine Neurogenetics Laboratory Department of Neurology	Phone: (617) 638-5393 Fax: (617) 638-8076
	New England HDSA Center of Excellence Huntington's Disease Testing Center Massachusetts General Hospital	Phone: (617) 726-5532 Fax: (617) 724-1227
Michigan	University of Michigan Molecular Medicine and Genetics Clinic	Phone: (734) 763-2532 Fax: (734) 763-7672
	Butterworth Genetic Services	Phone: (616) 391-8664
	Michigan State University Pediatrics and Human Development	Phone: (517) 353-3003 Fax: (517) 353-8464
	Wayne State University School of Medicine Department of Neurology	Phone: (313) 577-8317
Minnesota	HDSA Center of Excellence at Hennepin County Medical Center Huntington's Disease Clinic	Phone: (612) 873-2595 Fax: (612) 904-4270
	University of Minnesota, Fairview	Phone: (612) 624-8948 Fax: (612) 624-6645
Missouri	HDSA Center of Excellence at Washington University Huntington's Disease Clinic	Phone: (314) 362-3471
Montana	Shodair Hospital Department of Genetics	Phone: (800) 447-6614 Fax: (406) 444-7536

New Jersey	Samuel L. Baily Huntington's Disease Family Service Center University of Medicine and Dentistry of New Jersey	Phone: (732) 235-5730
New Mexico	University of New Mexico Medical Center, Division of Genetics	Phone: (505) 272-6631
New York	Albany Medical Center Department of Clinical Genetics	Phone: (518) 262-5120 Fax: (518) 262-5924
	HDSA Center of Excellence at University of Rochester Huntington's Disease Clinic Movement Disorders Unit	Phone: (585) 273-4147 Fax: (585) 341-7510
	State University of New York Health Science Center College of Medicine: Division of Genetics	Phone: (315) 464-7610 Fax: (315) 646-7564
	HDSA Center of Excellence at Columbia Presbyterian Medical Center Testing Center Huntington's Disease Clinic	Phone: (212) 305-4655 Fax: (212) 305-2426
	George C. Powell HDSA Center of Excellence at North Shore University Hospital Huntington's Disease Clinic	Phone: (516) 570-4477
	Women and Children's Hospital of Buffalo Division of Genetics	Phone: (716) 888-1378 Fax: (716) 888-1368
North Carolina	University of North Carolina at Chapel Hill Division of Genetics and Metabolism	Phone: (919) 966-4202
Ohio	University Hospitals of Cleveland	Phone: (216) 844-3936 Fax: (216) 844-7497
	MetroHealth Medical Center Genetics Department	Phone: (216) 778-4323 Fax: (216) 778-8840
	Children's Hospital Medical Center Human Genetics Division	Phone: (513) 636-4760
	HDSA Center of Excellence at Ohio State University Huntington's Disease Clinic	Phone: (614) 688-8672 Fax: (614) 688-4060
Oregon	Oregon Health Sciences University CDRC Genetics	Phone: (503) 494-8307
South Carolina	Huntington's Disease Test and Clinical Services Center W.S. Hall Psychiatric Institute	Phone: (803) 898-2343 or (803) 898-2344 FAX: (803) 898-1170
Tennessee	Vanderbilt University Medical Center Division of Genetics	Phone: (615) 322-7601 Fax: (615) 343-9951
Texas	Children's Medical Center of Dallas Department of Genetic and Metabolism	Phone: (214) 456-2357 Fax: (214) 456-6233
	HDSA Center of Excellence at Baylor College of Medicine Presymptomatic HD Testing Program	Phone: (832) 822-4295 Fax: (832) 825-4294
	Southwest Genetics	Phone: (210) 615-8237
Utah	University of Utah Medical Center	Phone: (801) 581-8943

Virginia	HDSA Center of Excellence at University of Virginia Division of Medical Genetics	Phone: (434) 924-2665 Fax: (434) 924-1797
Washington	HDSA Center of Excellence at University of Washington Huntington's Disease Clinic	Phone: (206) 598-4030 Fax: (206) 616-2414
West Virginia	West Virginia University Department of Pediatric/Genetics	Phone: (304) 293-7332 Fax: (304) 293-4337
Wisconsin	Marshfield Clinic	Phone: (800) 782-8581

Table 2. *Available resources including various organizations for learning more about Huntington's disease.*

Organization	Mission Statement/Goals	Contact Information
Huntington's Disease Society of America	"The Society is a National, voluntary health organization dedicated to improving the lives of people with Huntington's Disease and their families. To promote and support research and medical efforts to eradicate Huntington's Disease. To assist people and families affected by Huntington's Disease to cope with the problems presented by the disease. To educate the public and health professionals about Huntington's disease."	Go to: http://www.hdsa.org Or Email: hdsainfo@hdsa.org Tel: 212-242-1968 800-345-HDSA (4372) Fax: 212-239-3430
Huntington's Disease Association	"The HDA exists to support people affected by the disease and to provide information and advice to professionals whose task it is to support Huntington's disease families. The HDA is financed through the generosity of trusts, foundations, the statutory and corporate sectors, branches of the HDA, members and friends."	Go to: http://www.hda.org.uk/index.html Or Email: info@hda.org.uk
International Huntington Association	"IHA is a federation of national voluntary health agencies that share common concern for individuals with Huntington's Disease and their families. Each agency promotes lay and professional education, individual and family support, psycho-social, clinical and biomedical research, and ethical and legal considerations related to Huntington's Disease in its respective country."	Go to: http://www.huntington-assoc.com/ Or Email: iha@huntington-assoc.com
Hereditary Disease Foundation	"The HDF aims to cure genetic illness by supporting basic biomedical research. The Foundation uses a variety of strategies - workshops, grants, fellowships, and targeted research contracts - to solve the mysteries of genetic disease and develop new treatments and cures."	Go to: http://www.hdfoundation.org Or Email: cures@hdfoundation.org Tel: 212-928-2121 Fax: 212-928-2172
Huntington's Society of Canada	"The Huntington Society of Canada aspires to a world free from Huntington disease. The Society maximizes the quality of life of people living with HD by: Delivering services; Enabling others to understand the disease and; Furthering research to slow and to prevent Huntington disease."	Go to: http://www.huntingtonsociety.ca/english/index.asp Or Email: info@hsc-ca.org Tel: (519) 749-7063 Fax (519) 749-8965

The Huntington Study Group	"The HSG aims to advance knowledge about the cause(s), disease progression and treatment of HD and related disorders. The HSG is committed to: open communication within the scientific community; full disclosure of research results in scientific journals after independent expert review; revealing all potential conflicts of interest of the group and each HSG member and; democratic governance of its organizations and activities."	Go to: http://www.huntington-study-group.org/
National Institute of Neurological Disorders and Stroke	"The mission of NINDS is to reduce the burden of neurological disease - a burden borne by every age group, by every segment of society, by people all over the world."	Go to: http://www.ninds.nih.gov/index.htm Tel: (800) 352-9424 or (301) 496-5751

Table 3. *Unified Huntington's Disease Rating Scale (UHDRS) Motor Section from the Huntington Study Group.*.

Ocular Pursuit (horizontal)	0-complete 1-jerky 2-interrupted/full range 3-incomplete range 4-cannot pursue
Ocular Pursuit (vertical)	0-complete 1-jerky 2-interrupted/full range 3-incomplete range 4-cannot pursue
Saccade Initiation (horizontal)	0-normal 1-increased latency 2-suppressible blinks/head movements to initiate 3-unsuppressible head movements 4-cannot initiate
Saccade Initiation (vertical)	0-normal 1-increased latency 2-suppressible blinks/head movements to initiate 3-unsuppressible head movements 4-cannot initiate
Saccade Velocity (horizontal)	0-normal 1-mild slowing 2-moderate slowing 3-severely slow, full range 4-incomplete range
Saccade Velocity (vertical)	0-normal 1-mild slowing 2-moderate slowing 3-severely slow, full range 4-incomplete range
Dysarthria	0-normal 1-unclear, no need to repeat 2-must repeat 3-mostly incomprehensible 4-mute
Tongue Protrusion	0-normal 1-<10 seconds 2-<5 seconds 3-cannot fully protrude 4-cannot beyond lips
Finger Taps (right)	0-normal (15/5sec) 1-mild slowing or reduction in amp. 2-moderately impaired. may have occasional

	arrests (7- 10/15sec) 3-severely impaired. Frequent hesitations and arrests 4-can barely perform
Finger Taps (left)	0-normal (15/5sec) 1-mild slowing or reduction in amp. 2-moderately impaired. may have occasional arrests (7- 10/15sec) 3-severely impaired. Frequent hesitations and arrests 4-can barely perform
Pronate/Supinate (right)	0-normal 1-mild slowing/irregular 2-moderate slowing and irregular 3-severe slowing and irregular 4-cannot perform
Pronate/Supinate (left)	0-normal 1-mild slowing/irregular 2-moderate slowing and irregular 3-severe slowing and irregular 4-cannot perform
Fist-Hand-Palm Sequence	0->4 in 10 seconds without cues 1-<4 in 10 sec. without cues 2->4 in 10 sec. with cues 3-<4 in 10 sec. with cues 4-cannot perform
Rigidity-arms (right)	0-absent 1-slight or only with activation 2-mild/moderate 3-severe, full range of motion 4-severe with limited range
Rigidity-arms (left)	0-absent 1-slight or only with activation 2-mild/moderate 3-severe, full range of motion 4-severe with limited range
Bradykinesia	0-normal 1-minimally slow 2-mildly but clearly slow 3-moderately slow 4-marked slowing, long delays in initiation
Maximal Dystonia(trunk)	0-absent 1-slight/intermittent 2-mild/common or moderate/intermittent

	3-moderate/common 4-marked/prolonged
Maximal Dystonia(RUE)	0-absent 1-slight/intermittent 2-mild/common or moderate/intermittent 3-moderate/common 4-marked/prolonged
Maximal Dystonia(LUE)	0-absent 1-slight/intermittent 2-mild/common or moderate/intermittent 3-moderate/common 4-marked/prolonged
Maximal Dystonia(RLE)	0-absent 1-slight/intermittent 2-mild/common or moderate/intermittent 3-moderate/common 4-marked/prolonged
Maximal Dystonia(LLE)	0-absent 1-slight/intermittent 2-mild/common or moderate/intermittent 3-moderate/common 4-marked/prolonged
Maximal Chorea (Face)	0-absent 1-slight/intermittent 2-mild/common or moderate/intermittent 3-moderate/common 4-marked/prolonged
Maximal Chorea (BOL)	0-absent 1-slight/intermittent 2-mild/common or moderate/intermittent 3-moderate/common 4-marked/prolonged
Maximal Chorea (Trunk)	0-absent 1-slight/intermittent 2-mild/common or moderate/intermittent 3-moderate/common 4-marked/prolonged
Maximal Chorea (RUE)	0-absent 1-slight/intermittent 2-mild/common or moderate/intermittent 3-moderate/common 4-marked/prolonged
Maximal Chorea (LUE)	0-absent 1-slight/intermittent

	2-mild/common or moderate/intermittent 3-moderate/common 4-marked/prolonged
Maximal Chorea (LLE)	0-absent 1-slight/intermittent 2-mild/common or moderate/intermittent 3-moderate/common 4-marked/prolonged
Maximal Chorea (RLE)	0-absent 1-slight/intermittent 2-mild/common or moderate/intermittent 3-moderate/common 4-marked/prolonged
Gait	0-normal narrow base 1-wide base, and/or slow 2-wide base, walks with difficulty 3-walks with assistance 4-cannot attempt
Tandem Walking	0-normal for 10 steps 1-1-3 deviations 2->3 deviations 3-cannot complete 4-cannot attempt
Retropulsion	0-normal 1-recovers spontaneously 2-would fall if not caught 3-falls spontaneously 4-cannot stand

Permission was obtained from the Huntington's Study Group to cite this scale on October 24, 2008.

Figures

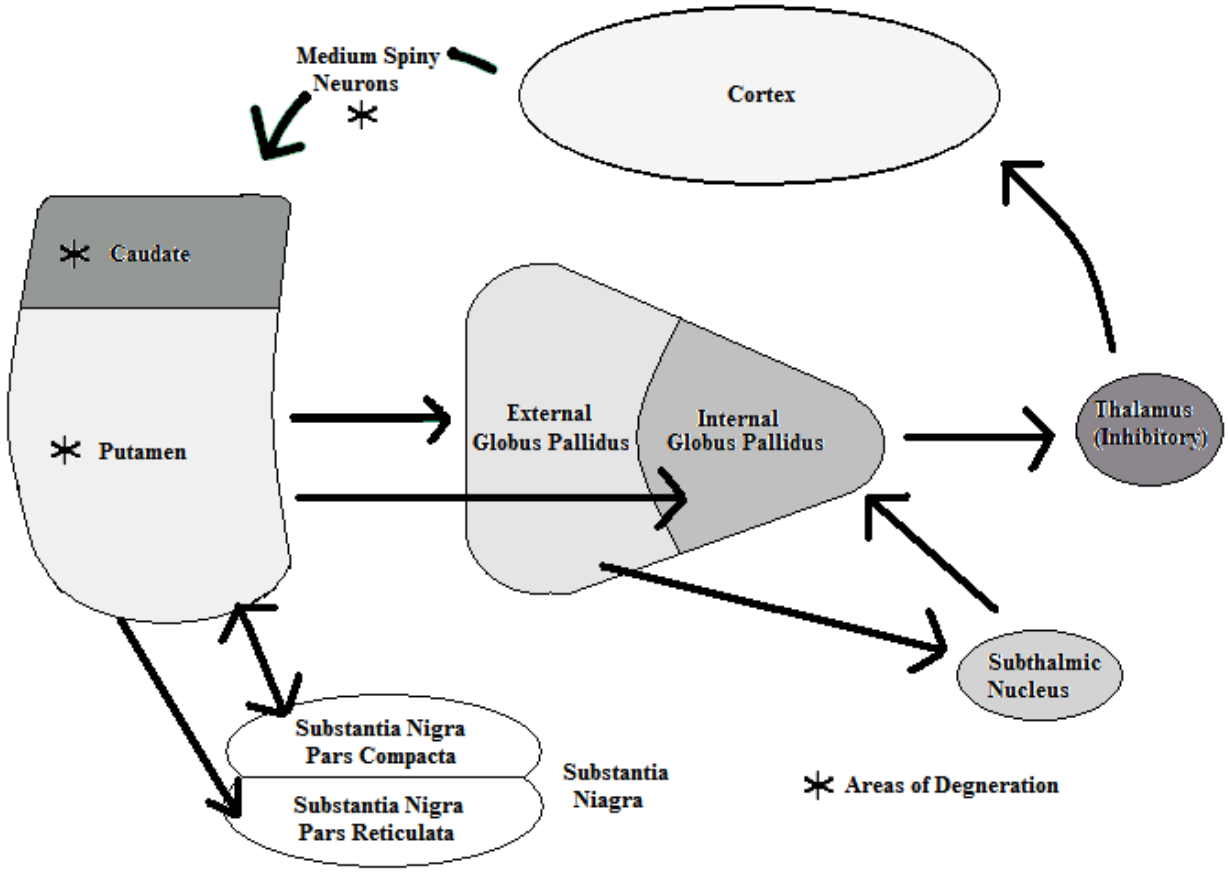

Figure 1. Areas of degeneration along the brain pathway involved in the pathogenesis of Huntington's disease. The caudate, putamen, globus pallidus, substantia nigra, and subthalamic nucleus together make up a majority of the basal ganglia. The striatum consists of the caudate and putamen portions.

	h	h
H	Hh	Hh
h	hh	hh

Figure 2a. A Mendelian punnett square depicting possible outcomes of a cross between an unaffected individual (hh) and an affected individual (Hh) carrying the allele for Huntington's disease. Each child has a 50% chance of inheriting the allele.

	h	h
H	Hh	Hh
H	Hh	Hh

Figure 2b. A Mendelian punnett square depicting possible outcomes of a cross between an unaffected individual (hh) and an affected individual (HH) carrying two mutated alleles for Huntington's disease meaning that both parents were affected. Each child has a 100% chance of inheriting the allele.

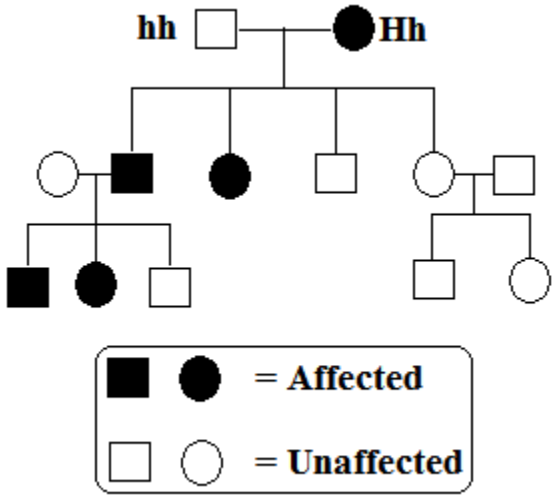

Figure 3a. A pedigree showing one possible pattern of inheritance of the Huntington's mutation (H). Autosomal dominant diseases affect both sexes equally and if present it will be expressed. Huntington's disease does not skip generations.

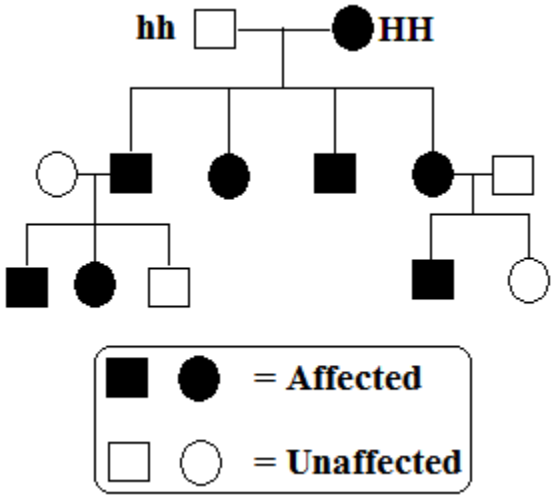

Figure 3b. A pedigree showing a possible pattern of inheritance for an individual that is homozygous for the mutation. 100% of the offspring will carry the mutation and develop the disease. 50% of the second generation's offspring will inherit the mutation from their parent.

Abstract

Objective: Huntington's disease (HD) is a late onset neurodegenerative disorder without remission or cure. The purpose of this paper was to explore issues surrounding genetic testing and future treatments for HD.

Method: A review of the literature was preformed using multiple online databases including MEDLINE, PubMed, and the Cochrane Library. Search terms included "Huntington's disease," "huntingtin," "treatment," "genetic testing," "genetics," "ethics," "pathogenesis," "gene," and "hereditary."

Results: HD pathology, genetic transmission, predictive and prenatal testing, and treatment options were reviewed. There are currently no effective treatments for HD making the decision whether to undergo genetic testing difficult.

Conclusion: Neural stem cell transplant and gene therapy are some of the promising areas of future research in HD. This summary of current knowledge will help to advance the dialog regarding this complex neurodegenerative genetic disorder.