

A Journey Through Huntington's Disease: Exploring Genetics, Neurobiology, and Therapeutic Advances

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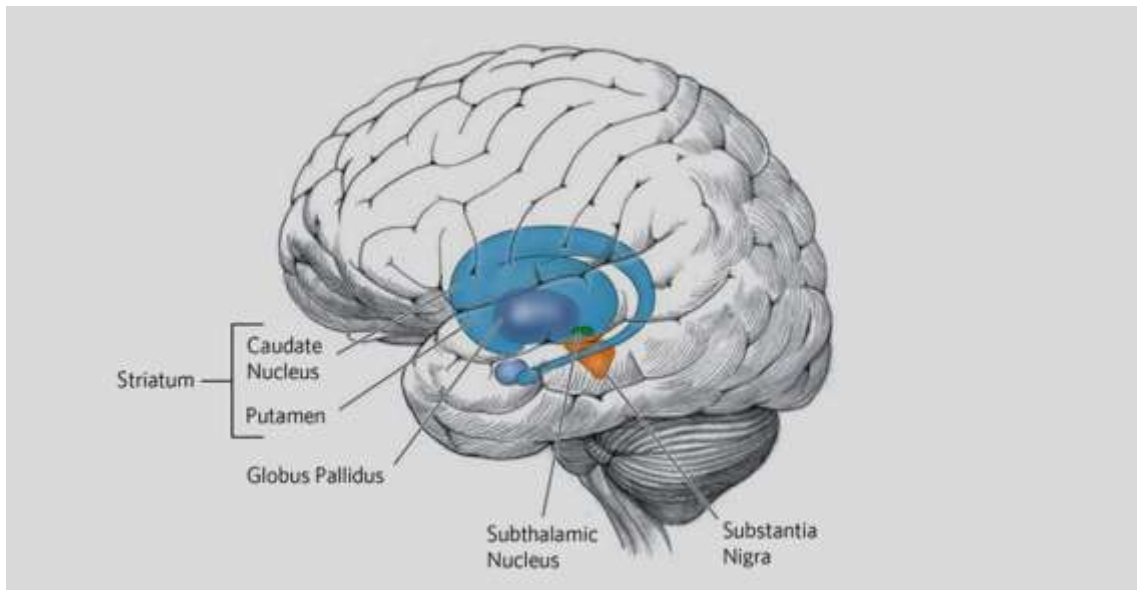
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Abstract

Huntington disease (HD) is a progressive neurodegenerative disease that is debilitating for families worldwide. Inherited in an autosomal dominant manner, HD results from a CAG expansion in the gene encoding the huntingtin protein. This mutation leads to a host of motor, cognitive, and psychiatric symptoms that generally appear in middle age. While spiny projection neurons in the striatum are the most vulnerable cell type in HD, notable atrophy occurs throughout the brain, including the white matter; for this reason, HD is now considered to be a brain-wide disease. The clinical features, ethics, and neurobiology of HD are discussed in this chapter. The chapter also reviews the exciting approaches being employed today to advance understanding of underlying mechanisms in an effort to develop therapies that would delay the onset and slow progression of this disease.

Introduction

Huntington's disease (HD) is a brain disease that is passed down in families from generation to generation. It is caused by a mistake in the DNA instructions that build our bodies and keep them running. DNA is made up of thousands of genes, and people with HD have a small error in one gene, called Huntington. Over time this error causes damage to the brain and leads to HD symptoms. HD causes deterioration in a person's physical, mental, and emotional abilities, usually during their prime working years, and currently has no cure. Most people start developing symptoms during adulthood, between the ages of 30 to 50, but HD can also occur in children and young adults (known as juvenile HD or JHD). HD is known as a family disease because every child of a parent with HD has a 50/50 chance of inheriting the faulty gene. Today, there are more than 200,000 at-risk of inheriting the disease. HD affects the whole brain, but certain areas are more vulnerable than others. Striatum – an area deep in the brain that plays a key role in movement, mood and behaviour control. The striatum is the part of the brain that is most affected by HD.



The symptoms of HD can vary a lot from person to person, but they usually include:

- Personality changes, mood swings & depression
- Forgetfulness & impaired judgement
- Unsteady gait & involuntary movements (chorea)
- Slurred speech, difficulty in swallowing & significant weight loss.

Most people with HD experience problems with thinking, behaviour, and movements. Symptoms usually worsen over the course of 10 to 25 years and affect the ability to reason, walk, and talk. Early on, a person with HD or their friends and family may notice difficulties with planning, remembering, and staying on task. They may develop mood changes like depression, anxiety, irritability, and anger. Most people with HD become “fidgety” and develop movements of the face and limbs known as chorea, which they are not able to control. Because of the uncontrolled movements (chorea), a person with HD may lose a lot of weight without intending to, and may have trouble walking, balancing, and moving around safely. They will eventually lose the ability to work, drive, and manage tasks at home, and may qualify for disability benefits. Over time, the individual will develop difficulty with speaking and swallowing, and their movements will become slow and stiff. People with advanced HD need full-time care to help with their day-to-day activities, and they ultimately succumb to pneumonia, heart failure or other complications. The symptoms of HD are sometimes described as having ALS, Parkinson’s and Alzheimer’s – simultaneously.

Importance of understanding the genetics, neurobiology and therapeutic advances in HD: The DNA error that causes HD is found in a gene called huntingtin. This gene was discovered in 1993. Everyone has the huntingtin gene, but only those that inherit the mistake, known as the HD mutation, will develop HD and risk passing it on to their children. Genes are made up of the nucleotide “letters” - A,G,C, and T, which form a code that is read in groups of three. HD is caused by a stretch of the letters C-A-G in the huntingtin gene which repeat over and over, too many times...CAG CAG CAG CAG CAG. This is known as a CAG repeat expansion. In the huntingtin gene, most people have around 20 CAG repeats, but people with HD have around 40 or more. Every person who has this CAG repeat expansion in the HD gene will eventually develop the disease, and each of their children has a 50% chance of developing HD. Our genes are like an instruction manual for making proteins, the machines that run everything in our bodies. The huntingtin gene (DNA) contains instructions that are copied into a biological message (RNA) which makes the huntingtin protein. The huntingtin protein is very large and seems to have many functions,

especially as the brain is developing before birth, but it is not fully understood. We know that the extra CAG repeats in people with HD cause the huntingtin protein to be extra-long and difficult to maintain, which makes it difficult for it to do its job. Over many years, this “mutant” huntingtin protein forms clumps in brain cells, and causes them to become damaged and die. The most vulnerable part of the brain in HD is called the striatum, and it controls movement, mood, and memory. Damage to the striatum over time is what causes the symptoms of HD. Also, we present a modern view on the molecular biology of HD as a representative of the group of polyglutamine diseases, with an emphasis on conformational changes of mutant huntingtin, disturbances in its cellular processing, and proteolytic stress in degenerating neurons. The main pathogenetic mechanisms of neurodegeneration in HD are discussed in detail, such as autophagy, impaired mitochondrial biogenesis, lysosomal dysfunction, organelle and protein transport, inflammation, oxidative stress, and transcription factor modulation. However, other unravelling mechanisms are still unknown. This practical and brief review summarises some of the currently known functions of the wild-type huntingtin protein and the recent findings related to the mechanisms involved in HD pathogenesis.

Cellular mechanisms implicated in HD pathogenesis: The major mechanisms associated with HD pathogenesis are depicted here. The schematic shows a presynaptic neuron and a postsynaptic neuron flanked by two astrocytes. Huntingtin gene (HTT) itself is depicted as a “solenoid,” based on the presumed folding due to its HEAT repeats. The mechanisms depicted are multimerization of mHtt-containing complexes, transcriptional modulation, ER-Golgi stress pathways, mitochondria and energy homeostasis, microtubular dynamics, endocytic and vesicular trafficking dynamics, autophagy, and synaptic signalling mechanisms. mHTT (mutant HTT protein). Traditionally, therapeutic approaches to HD have included compounds developed for psychiatric indications based on the affected neuronal circuitry: the frontal and motor corticostriatal circuits. None of these were initially developed for the treatment of HD. In this review we focus on the cellular and biological pathways affected by mutant HTT (mHTT) and the current status of associated drug discovery efforts. We also emphasise the need for further clinical research to validate existing hypotheses, which are mostly derived from animal studies and postmortem human tissues. It is generally accepted that most candidate therapeutics fail due to lack of efficacy in pivotal clinical studies. Leaving aside issues arising from inadequate clinical rating scales or trial design flaws, a simple explanation for this failure is that the pathogenic mechanistic hypotheses developed for a given indication, or the chosen intervention points within those mechanisms, the “targets”, are incorrect. The critical question for both the basic and clinical research communities is how we can work together more effectively to better define targets to maximise success. In this context, success is defined as developing therapies to slow the progression of HD, leading to significantly improved quality of life and extended functional lifespan. Although an ambitious goal, a disease such as HD represents a unique opportunity in which true disease modification should be attainable .

Aim and structure of the review: The review process includes the evaluation of the relevance and originality of the paper, ensuring that previous work in the field is taken into account, checking the methodology, statistics, and to verify whether the conclusions are supported by the experimental results.

Genetics of Huntington's Disease

Huntington's disease is inherited as an autosomal dominant trait, meaning that a single mutated copy of the responsible gene (called HTT) is sufficient to cause the disease. HD is typically inherited from an affected parent, who carries a mutation in the huntingtin gene (HTT). However, up to 10% of cases are

due to a new mutation. The huntingtin gene provides the genetic information for huntingtin protein (Htt). Expansion of CAG repeats of cytosine-adenine-guanine (known as a trinucleotide repeat expansion) in the gene coding for the huntingtin protein results in an abnormal mutant protein (mHtt), which gradually damages brain cells through a number of possible mechanisms. The mutant protein is dominant, so having one parent who is a carrier of the trait is sufficient to trigger the disease in their children

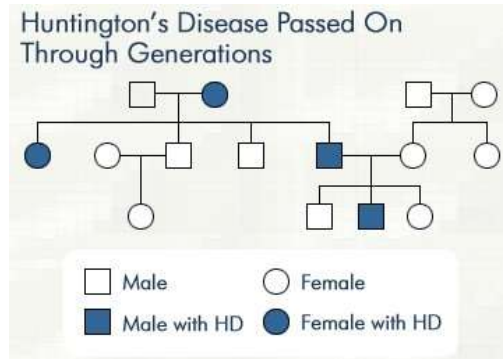
Description of the HTT gene and its mutation: Huntingtin (Htt) is the protein coded for in humans by the *HTT* gene, also known as the *IT15* ("interesting transcript 15") gene. The *HTT* gene provides instructions for making a protein called huntingtin. Although the exact function of this protein is unknown, it appears to play an important role in nerve cells (neurons) in the brain and is essential for normal development before birth. Huntingtin is found in many of the body's tissues, with the highest levels of activity in the brain. Within cells, this protein may be involved in chemical signalling, transporting materials, attaching (binding) to proteins and other structures, and protecting the cell from self-destruction (apoptosis). Some studies suggest it plays a role in repairing damaged DNA. Huntingtin upregulates the expression of brain-derived neurotrophic factor (BDNF) at the transcription level, but the mechanism by which huntingtin regulates gene expression has not been determined. From immunohistochemistry, electron microscopy, and subcellular fractionation studies of the molecule, it has been found that huntingtin is primarily associated with vesicles and microtubules. These appear to indicate a functional role in cytoskeletal anchoring or transport of mitochondria. The Htt protein is involved in vesicle trafficking as it interacts with HIP1, a clathrin-binding protein, to mediate endocytosis, the trafficking of materials into a cell. Huntingtin has also been shown to have a role in the establishment in epithelial polarity through its interaction with RAB11A. Mutation in the huntingtin gene causes Huntington's disease, a heritable and fatal neurodegenerative disease. The production of mutant huntingtin (HTT) protein is thought to be responsible for alterations of normal processes that ultimately result in the death of neurons. Thus, the mutation is considered a gain-of-function mutation. In its mutated form the HTT gene might acquire additional CAG trinucleotide repeats, resulting in the production of abnormal protein (Figure 2). This increase in the CAG repeats does not inhibit the protein production but results in protein accumulation. This accumulated protein over a period causes symptoms that are associated with Huntington's disease. The mutation of expanded CAG encodes the polyglutamine is the product for the mutant huntingtin protein, a key player in HD. Alteration of the huntingtin protein is a key factor in the induction of dysfunction or neurodegeneration, both of which lead to HD. It is not clear how the mutated huntingtin protein induces neuronal dysfunction and neuronal degeneration. There is a possibility that HD is caused by accumulation of the polyglutamine fragments in the cytoplasm and nucleus. Consequently, the neuropathology includes neuronal atrophy in the cerebral cortex and the striatum, forebrain regions that process a wide range of information for behavioural output. Mutant huntingtin protein can interact with other cellular proteins, leading to the progression of HD. The formation of neuronal intranuclear inclusions that contain mutant huntingtin protein causes neuronal degeneration in transgenic HD mouse models. The huntingtin protein itself is a cytoplasmic protein that interacts with vesicular and cytoskeletal proteins. Furthermore, studies demonstrated that huntingtin protein plays an important role in intracellular trafficking, including membrane recycling, clathrin-mediated endocytosis, neuronal transport and postsynaptic signalling. Thus, mutant huntingtin protein is likely to have an impact on a wide range of cellular functions. In addition, mutant huntingtin protein interacts with transcriptional regulatory proteins. Moreover, the expanded polyglutamine repeats facilitate the interactions of mutant huntingtin protein with huntingtin protein-associated proteins selectively expressed in the striatum and cortex. Among these

proteins are calmodulin, huntingtin protein-associated protein (HAP-1), huntingtin protein-interacting proteins (HIP-1 and 2) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH). The interactions of the mutant huntingtin protein with these proteins induce protein dysfunction and lead to toxicity characteristic of HD. Thus, the mutant huntingtin protein may trigger a cascade of several intracellular pathways that cause death of some neurons, including medium spiny neurons, although huntingtin protein is expressed in all types of cells.

Expansion of CAG repeats and its implications: The defect in the *HTT* gene responsible for Huntington's disease is known as a CAG trinucleotide repeat expansion. Like other genes, the *HTT* gene is comprised of four DNA bases — referred to as A, C, G, and T — that are “read” in groups of three, called codons, to produce a protein. The CAG trinucleotide repeat, as its name implies, is a small section of the *HTT* gene in which the bases “CAG” are repeated multiple times in a row. Normally, the *HTT* gene CAG trinucleotide repeat contains 10 to 35 repeats of this sequence. In people with Huntington's disease, however, it may be repeated from 36 to more than 120 times. People with 40 or more repeats almost always develop Huntington's, whereas for people with 36 to 39 repeats, the disease is incompletely penetrant — meaning an individual may or may not develop the disease. The reasons for this are still not completely understood. The number of repeats inversely correlates with the age of onset of the disease. That means that the more repeats there are, the earlier in life a person is likely to develop symptoms. In juvenile Huntington's disease, which affects children and young adults, the CAG trinucleotide is generally repeated more than 60 times. When there are more than 60 CAG repeats, the person develops a severe form of HD known as juvenile HD. Repeat size also influences the phenotype. High CAG repeats (>60 CAG) are associated with early onset and a phenotype characterised by bradykinesia, dystonia, severe psychiatric manifestations, and even developmental delay and epilepsy. The expanded CAG segment leads to the production of an abnormally long version of the huntingtin protein. The elongated protein is cut into smaller, toxic fragments that bind together and accumulate in neurons, disrupting the normal functions of these cells. It has also been suggested that loss of the huntingtin protein's DNA repair function may result in the accumulation of DNA damage in neurons, particularly as damaging molecules increase during ageing. Regions of the brain that help coordinate movement and control thinking and emotions (the striatum and cerebral cortex) are particularly affected. The dysfunction and eventual death of neurons in these areas of the brain underlie the signs and symptoms of Huntington's disease. As the altered *HTT* gene is passed from one generation to the next, the size of the CAG trinucleotide repeat often increases in size. This phenomenon is called anticipation. Trinucleotide repeat (TNR) instability varies between organs in a variety of neurodegenerative disorders which are caused by expansion of CAG repeats in a coding gene, with the greatest instability observed in the brain. In HD, striatum tissue shows the most severe neuropathology, followed by cortex. TNR sequences may form slipped strands during replication or repair, creating loops or hairpins, which protrude from the DNA duplex. However, the relationships among CAG expansions, death of specific cell types and molecular events associated with these processes are not established. Tissue-specific ongoing CAG repeat expansions of the mutant allele are a central feature of HD and other repeat expansion disorders. Expansion of the inherited *mHTT* allele to very long CAG tracts has been observed sporadically in various brain structures, including the caudate nucleus and putamen, but not in the cerebellum. A causal role for somatic expansions of the CAG repeat in HD pathogenesis is supported by findings from a genome-wide association study looking for genetic modifiers of HD motor symptom onset other than CAG tract length itself. Although analysis of individual cells captured from HD striatum and cortex by laser-microdissection capture has indicated that somatic

expansion occurs more frequently in neurons, it is not known whether CAG expansions occur in specific types of neuronal and glial cells in these regions. Therefore, it is unclear if CAG expansions are sufficient to explain selective cellular vulnerability in HD and what cell-specific factors in addition to somatically expanded *mHTT* CAG tract are required for toxicity.

Inheritance pattern and genetic counselling considerations:



Huntington's disease has autosomal dominant inheritance, meaning that an affected individual typically inherits one copy of the gene with an expanded trinucleotide repeat (the mutant allele) from an affected parent. Since the penetrance of the mutation is very high, those who have a mutated copy of the gene will have the disease. In this type of inheritance pattern, each offspring of an affected individual has a 50% risk of inheriting the mutant allele, so are affected with the disorder. This probability is sex-independent. Sex-dependent or sex-linked genes are traits that are found on the X or Y chromosomes.

Trinucleotide CAG repeats numbering over 28 are unstable during replication, and this instability increases with the number of repeats present. This usually leads to new expansions as generations pass (dynamic mutations) instead of reproducing an exact copy of the trinucleotide repeat. This causes the number of repeats to change in successive generations, such that an unaffected parent with an "intermediate" number of repeats (28–35), or "reduced penetrance" (36–40), may pass on a copy of the gene with an increase in the number of repeats that produces fully penetrant HD. The earlier age of onset and greater severity of disease in successive generations due to increases in the number of repeats is known as genetic anticipation. Instability is greater in spermatogenesis than oogenesis; maternally inherited alleles are usually of a similar repeat length, whereas paternally inherited ones have a higher chance of increasing in length. Rarely is Huntington's disease caused by a new mutation, where neither parent has over 36 CAG repeats. In the rare situations where both parents have an expanded HD gene, the risk increases to 75%, and when either parent has two expanded copies, the risk is 100% (all children will be affected). Individuals with both genes affected are rare. For some time, HD was thought to be the only disease for which possession of a second mutated gene did not affect symptoms and progression, but it has since been found that it can affect the phenotype and the rate of progression. Genetic testing for Huntington's disease (HD) is a process that involves much more than just getting the results of a blood test.

Many issues are at stake: financial, emotional, and social issues that involve not only the person seeking testing, but also his or her immediate family -- and often the extended family as well. Before giving a blood sample, the person seeking a test deserves an opportunity to examine these issues thoroughly with people who are experienced with genetic testing for HD. While the actual DNA test for the HD gene expansion is a fairly straightforward laboratory process, the implications and emotional aftermath of the results are usually anything but straightforward.

Since this is such a serious, degenerative brain disease and there is currently no cure for HD, the emotional

burden of the results can be very challenging. These are the reasons why genetic counselling has become an essential part of the HD testing process. Genetic counsellors are non-directive and non-judgmental. Their job is to help people become better informed and to support independent decision-making around these very emotional and personal testing decisions. By discussing the issues involved with caring professionals (often together with other family members), people who are thinking about getting tested have the best opportunity to make informed decisions about whether testing is right for them at this time in their lives.

Neurobiology of Huntington's Disease

Pathological mechanisms underlying HD (mutant huntingtin protein, neuronal dysfunction, and cell death):

Effects of mutant huntingtin protein in calcium homeostasis. Although the mechanism of action of mutant huntingtin protein is not clear, evidence has shown that it may induce mitochondrial dysfunction. There is an interrelationship between mitochondrial dysfunction and dysregulation of transcriptional factors in HD. Defects of mitochondrial respiratory chain activity have been shown in striatum of postmortem brains of patients suffering from HD and also in R6/2 HD mouse models. Isolated mitochondria from lymphoblasts of HD patients and from brains of the YAC72 transgenic HD mouse (yeast artificial chromosome, length of polyglutamine is 72) have shown deficit in intracellular Ca^{2+} . Moreover, mutant huntingtin protein induces impairment of Ca^{2+} homeostasis in cloned striatal cells. Cells expressing mutant huntingtin protein show a reduction in mitochondrial Ca^{2+} uptake compared to wild type cells. The mutant huntingtin protein-induced lower Ca^{2+} loads were attenuated in the presence of ADP; the decreases in the uptake of Ca^{2+} were abolished in the presence of permeability transition pore inhibitors. Moreover, a fragment of mutant huntingtin protein may be directly bound with mitochondria. This has been shown at the ultrastructural level in the brain of the YAC72 HD mouse model. Although the mechanism of action of mutant huntingtin protein in mitochondrial Ca^{2+} handling is still unknown, one possibility is that mutant huntingtin protein acts directly on the ion permeability of the mitochondrial membrane. Interestingly, several genes related to calcium signalling, including copine V, striatin, $SCN\beta 4$ and α -actinin2, are altered in the R6/1 transgenic HD mouse model. The highest level of gene expression is found in the subunit of the sodium channel, $SCN\beta 4$, with a decrease of its expression level in striatum of R6/1 HD mouse model compared to wild type. It has been suggested that sodium levels are directly dependent on intracellular Ca^{2+} levels through sodium-calcium exchanger. The reduction in $SCN\beta 4$ expression in R6/1 HD mice may have a dramatic effect on intracellular calcium accumulation. Decreases in Ca^{2+} signalling genes are found in HD mouse models. Interestingly, mutant huntingtin protein-induced alteration of calcium signalling was found to lead to apoptosis of medium spiny neurons in the YAC128 HD mouse model. Alteration of intracellular Ca^{2+} homeostasis may be a factor in the induction of apoptosis and consequent neurodegeneration in HD. Several lines of evidence suggest that stimulation of glutamatergic receptors such as ionotropic [N-methyl-D-aspartate receptors, NMDA receptors (subunits NR1/NR2R)] and metabotropic (mGluR5) glutamate receptors alter Ca^{2+} homeostasis in striatal medium spiny neurons in HD models. The overstimulation of these receptors, through application of excess glutamate, results in mitochondrial Ca^{2+} overload leading to apoptosis of medium spiny neurons. Excess glutamate might be associated with impaired glutamate transport, as it was demonstrated in HD animal models from studies performed by us and others. Alteration in glutamate uptake might be linked to a deficit in one of the major glutamate transporters, a glial glutamate transporter 1 (GLT1), as it was demonstrated in our recent study. GLT1 is one of the proteins that might be altered

by mutant huntingtin protein. Evidence indicates that perturbations of Ca²⁺ homeostasis may lead to excitotoxicity and, consequently, apoptosis. Activation of NR1/NR2B NMDA receptors induces a Ca²⁺ influx; activation of mGluR5 leads to production of InsP3 and Ca²⁺ release via InsP3R1. The mutant huntingtin protein alters the Ca²⁺ handling in medium spiny neurons of HD mouse model through NMDA and mGlutamate receptors. This results in an overload of cytosolic Ca²⁺ along with an excess of mitochondrial Ca²⁺ storage, which lead to cytochrome c release into the cytosol, inducing apoptosis through activation of the caspase cascade. The caspases convey the apoptotic signal in a proteolytic cascade, with caspases cleaving and activating other caspases that subsequently degrade cellular targets, leading to cell death. Upon mitochondrial stress through disruption of Ca²⁺ homeostasis, the release of cytochrome c may interact with Apaf-1, causing self-cleavage and activation of caspase-9. The effector of caspase cascade, such as caspase-3, -6 and -7, is downstream of the activator caspases and acts to cleave various cellular targets. Recent studies demonstrated that caspase-6 is a key factor in the cleavage of mutant huntingtin protein in HD. Thus, cleavage of mutant huntingtin protein by caspase-6 is an important event in mediating neuronal dysfunction and possibly neurodegeneration. Interestingly, the cleavage of mutant huntingtin protein is dependent on the brain region. The cleavage at two N-terminal sites (A and B) was predominant in the cortex, whereas cleavage occurred at one N-terminal (A) and a C-terminal site in the striatum. In addition, inhibition of digestion of mutant huntingtin protein by both caspase-3 and 6 inhibitors was found to reduce apoptosis *in vitro*, which suggests that caspase inhibitors may be a key factor in the prevention of HD. Inhibitors of the apoptotic cascade may be used as a tool for prevention of cell death in HD. Moreover, the depletion of huntingtin protein has been found to induce activation of caspase-3, and the overexpression of this protein caused a reverse action of caspase-3, its inhibition. Huntingtin protein was found to interact with active caspase-3 at high affinity, but mutant huntingtin protein binds to caspase-3 at lower affinity. These findings suggest a mechanism whereby caspase-mediated huntingtin protein depletion results in an amplification cascade leading to further caspase-3 activation, resulting in neuronal dysfunction and neuronal death.

Effects of mutant huntingtin protein in nucleus. Mutant huntingtin protein impairs gene transcription through either intranuclear aggregate formation or sequestration to transcription factors that play a key role in HD. Important transcriptional factors including p53, cAMP response-element binding protein (CREB)-binding protein (CBP), co-activator CA150, specificity protein 1 (SP1), co-activators TAFII130 and TFIID, and TATA-binding protein (TBP) can be recruited to intranuclear aggregates. There are interactions between these transcriptional factors and other associated proteins that may interact with SP1 in the regulation of gene expression. It has been demonstrated that huntingtin protein may strengthen the bridge between DNA-bound transcription factor SP1 and TFIID-associated proteins and consequently stimulate gene expression. The cAMP-responsive element (CRE) and CBP play a critical role in HD. Alteration of CRE-regulated genes has been found in HD mouse models and HD patients. The CBP and CRE-mediated transcription have been suggested to be affected by the coactivator TAFII130, which is also found in aggregates of CREB-dependent transcription. Additionally, mutant huntingtin protein may disrupt the interaction of SP1 and TAFII130 by formation of aggregates. Increased association of mutant huntingtin protein with SP1 has been found in brain extracts from HD patients. Consequently, the association of SP1 and TAFII130 was found to be reduced in brains of HD patients. Moreover, SP1 interacts with N-terminal huntingtin protein fragments in the nucleus of both transfected cells and in brains of HD mice. These findings suggest that shorter N-terminal huntingtin protein fragments, responsible for misfolding and aggregation, are more likely to bind SP1 and may inhibit its activity. Interestingly, this

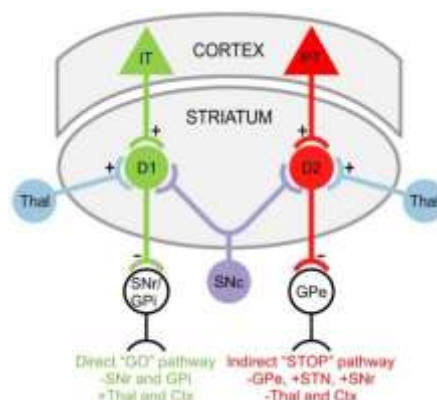
effect of huntingtin protein can be reversed by a molecular chaperone (Hsp40), which reduces the misfolding of mutant huntingtin protein. There are other transcriptional factors that may interact with normal or mutant huntingtin protein in the nucleus. Among them, CA150 transcriptional factor has been found to interact with normal and mutant huntingtin protein. CA150 protein levels have been found to be increased in HD brain samples. There are also nuclear repressors that have been shown to interact with huntingtin protein, including N-CoR and C-terminal binding protein (CtBP). The mechanism of the repression appears to occur through the formation of a complex of repressor proteins including the N-CoR, mSin3, histone deacetylases and CtBP. The relocalization of repressor proteins in HD brains may alter transcription, which plays a role in HD neuropathology.

Effects of mutant huntingtin protein in endocytosis and axonal vesicular transport: Mutant huntingtin protein has been found to be involved in clathrin-mediated endocytosis. Dysregulation of endocytosis occurs with the interactions of mutant huntingtin protein with proteins that play a role in clathrin-mediated endocytosis. Moreover, dysregulation of endocytosis is mediated through interactions of mutant huntingtin protein with its associated proteins, HIP1, HIP12, HIP14, PACSIN1 and SH3GL3, known as accessory factors in clathrin-dependent synaptic vesicle endocytosis. The interactions of mutant huntingtin protein with multiple accessory factors involve several steps that lead to dysregulation of clathrin-mediated endocytosis. Mutant huntingtin protein also is involved in vesicular transport processes in axons. In normal physiological situations, huntingtin protein and HAP1 are transported anterogradely and retrogradely along microtubules in axons. There is interaction of the complex huntingtin protein and HAP1 with dynactin, which influences the mobility of dynein in vesicular transport. Huntingtin protein and HAP1 stabilise the dynein-dynactin complex of vesicles and consequently enable transport along microtubules in endocytosis processes. However, if huntingtin protein is mutated, dysfunctional interaction occurs, which leads to impairment of the anterograde and retrograde transport. Neurotrophic factors may be involved in this transport. Alterations of the transport of neurotrophic may be critical in cell survival. There is little known about the role of glia in HD neuropathology. A previous study has shown that mutant huntingtin protein accumulates in nuclei of glial cells in the brain of HD mouse models. Interestingly, intranuclear mutant huntingtin protein in glial cells increases with age and was found to be correlated with disease progression in the R6/2 transgenic HD mouse model, which shows neuropathological symptoms around 6-8 weeks and often dies after 12 weeks of age.

Brain regions affected and their roles in motor, cognitive and psychiatric symptoms: Huntington disease is caused by gradual degeneration of parts of the basal ganglia called the caudate nucleus and putamen. The basal ganglia are collections of nerve cells located at the base of the cerebrum, deep within the brain. They help smooth out and coordinate movements. Neuropathological and imaging studies reinforce the view that brain abnormalities in HD develop well before evident symptoms, are progressive, and eventually involve the entire brain to a greater or lesser extent, resulting in about 25% brain weight loss in advanced HD. Nonetheless, the most prominent neuropathology in HD occurs within the striatal part of the basal ganglia, in which gross atrophy is accompanied by extensive neuronal loss and astrogliosis, both of which become more severe as the disease progresses, with the atrophy leading to great enlargement of the lateral ventricles. At least some of these dying neurons show nuclear fragmentation and marker expression characteristic of apoptotic cell death. Caudate atrophy as detected by MRI or CT has been shown to be correlated with CAG repeats and with a worsening of the UHDRS motor score. Marked neuronal loss and shrinkage is also seen in deep layers of the cerebral cortex. Other regions, including globus pallidus, hippocampus, amygdala, thalamus, subthalamic nucleus, substantia nigra, and

cerebellum, show varying degrees of atrophy and/or neuronal loss, depending on disease stage. Caudate volume loss, overall brain volume loss, and white matter disorganisation are manifest early in HD, and these HD brain abnormalities precede overt signs of disease. A system for grading HD neuropathological severity has been developed based on macroscopic and microscopic criteria related to striatal morphology. This system recognizes five Grades (0–4) designated in the ascending order of severity, with the grades correlating closely with the degree of clinical disability. There are no evident gross, and few microscopic abnormalities in premanifest HD striatum (Grade 0, also termed presymptomatic). The microscopic abnormalities that can be present involve increased abundance of oligodendrocytes and neurons with nuclear aggregates in the tail of the caudate, and some neuron loss in the head of the caudate. Grade 1 cases have abnormalities that can be detected microscopically in striatum (50% neuron loss in head of caudate) but gross atrophy is not evident, as the ventricular profile of the caudate maintains its normal convex appearance. The Grade 1 changes involve neuron loss and gliosis in the medial paraventricular portions of the caudate, in the tail of the caudate, and in the dorsal part of the putamen. In Grade 2, striatal atrophy is present, but the ventricular profile of the caudate remains convex, but less so than in normal brain. The lateral half of the striatum shows relative preservation in Grades 1–2. In Grade 3, striatal atrophy is more severe, and the ventricular profile of the caudate is flat. In Grade 4, 95% of caudate neurons are lost, striatal atrophy is severe, and the ventricular surface of the caudate is concave. Astrocytes are greatly increased above normal in HD Grades 2–4. This grading system has come to be widely used in neuropathological studies of HD that seek to describe changes as disease progresses.

Neurotransmitter dysregulation and its impact on disease progression: Dopamine (DA) plays an essential role in the control of coordinated movements. Alterations in DA balance in the striatum lead to pathological conditions such as Huntington's disease (HD). The principal pathology is the loss of striatal and cortical projection neurons. Changes in brain DA content and receptor number contribute to abnormal movements and cognitive deficits in HD. In particular, during the early hyperkinetic stage of HD, DA levels are increased whereas expression of DA receptors is reduced. Major symptoms of HD can be associated with biphasic changes in DA transmission and its modulatory role on glutamate (GLU) receptor function.



There is evidence from studies in HD patients that increased DA release induces chorea while a reduction in DA leads to akinesia. Thus giving rise to the biphasic movement symptoms of early and late HD. DA and GLU neurotransmission are intimately intertwined. During the early phase of HD, neuropathological studies have shown that discrete islands of neuronal loss and astrocytosis appear in the striosomes almost exclusively, whereas in the late phase, cell loss increasingly occurs in the matrix compartment. As MSNs from the striosomes project to the substantia nigra pars compacta, it may be that early degeneration of these inhibitory neurons produces hyperactivity of the DA pathway, contributing to chorea and other early

clinical manifestations of HD. Studies using positron emission tomography, autoradiography, and markers for pre- and postsynaptic neurons have observed reduced striatal D1 and D2 DA receptor density, even in asymptomatic HD patients, further indicating that DA signalling is disrupted early in HD. These observations have been confirmed by imaging studies, which reported reduced striatal D1 and D2 receptors in both HD patients and asymptomatic HD mutation carriers. There also is a progressive reduction of D1 and D2 receptor binding in the temporal and frontal cortices. Striatal and cortical loss of DA receptors in presymptomatic and early stage HD patients have been correlated with early cognitive decline, which may reflect altered synaptic plasticity and lead to deficits in cognitive processes such as attention, executive function, learning, and memory. In animal models of HD, biphasic changes in corticostriatal GLU transmission are characterised by initial increases in GLU synaptic activity followed by later decreases. Early increases in GLU are associated with cortical hyperexcitability and loss of D2 receptors contributes to increased synaptic activity. Stimulation of corticostriatal neurons has been shown to activate DA release in the striatum. In addition, DA neurons that modulate GLU release in the corticostriatal pathway are subject to afferent GLU regulation, which is suggested by the presence of GLU receptors on DA neurons. There is substantial evidence for a direct cortico-nigral projection and work in rodents demonstrates that this pathway both directly and indirectly regulates the firing pattern of DA neurons. Other studies indicate that stimulation of GLU receptors on DA neurons increases DA release in both the substantia nigra and in DA innervated areas. Thus, if DA neuron firing is regulated by frontal cortical neurons, the activity of which is upregulated in early HD, the biphasic trends of DA levels in early and late human HD may be correlated with the biphasic changes of GLU release by cortical afferents. This indicates biphasic changes in DA levels during early and late HD parallel changes occurring in GLU transmission. DA and GLU signalling pathways can synergistically enhance MSN sensitivity to huntingtin toxicity.

Clinical Manifestations

The nuclear symptoms and signs of Huntington's disease (HD) consist of motor, cognitive and psychiatric disturbances. Other less well-known, but prevalent and often debilitating features of HD include unintended weight loss, sleep- and circadian rhythm disturbances and autonomic nervous system dysfunction. The mean age at onset is between 30 and 50 years, with a range of 2 to 85 years. The mean duration of the disease is 17-20 years. The progression of the disease leads to more dependency in daily life and finally death. The most common cause of death is pneumonia, followed by suicide.

Motor symptoms: The characteristic motor changes are involuntary, unwanted movements. Initially, the movements often occur in the distal extremities such as fingers and toes, but also in small facial muscles. For bystanders these muscle twitches are often invisible or can be explained as nervousness. In daily life, walking becomes unstable and the person can look as if he/she is slightly drunk. Gradually the unwanted movements spread to all other muscles from distal to more proximal and axial. Choreatic movements are present all the time the patient is awake. No single pattern exists, but facial choreatic movements can lead to a continuous movement of facial muscles where for instance an eyebrow is lifted, an eye closed, the head is bent or turned while the tongue is protruded with the lips pouting. The most prominent are the extension movements of the long back muscles. Talking and swallowing gradually become more problematic leading to choking at any time in some patients. The ad hoc Committee on Classification of the World Federation of Neurology has defined chorea as "a state of excessive, spontaneous movements, irregularly timed, non-repetitive, randomly distributed and abrupt in character. These movements may

vary in severity from restlessness with mild intermittent exaggeration of gesture and expression, fidgeting movements of the hands, unstable dance-like gait to a continuous flow of disabling, violent movements. Patients with chorea exhibit motor impersistence (ie, they cannot maintain a sustained posture). When attempting to grip an object, they alternately squeeze and release ("milkmaid's grip"). When they attempt to protrude the tongue, the tongue often pops in and out ("harlequin's tongue"). Patients often drop objects involuntarily. Also common are attempts by patients to mask the chorea by voluntarily augmenting the choreiform movements with semi purposeful movements. Any discussion of chorea must also address the related terms athetosis, choreoathetosis, and ballism (also known as ballismus). The term athetosis comes from the Greek word *athetos* (not fixed). It is a slow form of chorea. Because of the slowness, the movements have a writhing (ie, squirming, twisting, or snakelike) appearance. Choreoathetosis is essentially an intermediate form (ie, a bit more rapid than the usual athetosis, slower than the usual chorea, or a mingling of chorea and athetosis within the same patient at different times or in different limbs). Given that the only difference between chorea, choreoathetosis, and athetosis is the speed of movement, some neurologists argue that the term athetosis is unnecessary and even confusing. They argue a simpler nomenclature would delineate fast, intermediate, and slow chorea. While the authors of this article understand the basis of that argument, they also believe that in some cases, the writhing movements are extremely prominent, even apart from the speed of the movement. Thus, the authors of this article advocate retaining this descriptive term. Ballism or ballismus is considered a very severe form of chorea in which the movements have a violent, flinging quality. In Greek, *ballismos* means "jumping about or dancing." Ballism has been defined as "continuous, violent, coordinated involuntary activity involving the axial and proximal appendicular musculature such that the limbs are flung about." This movement disorder most often involves only one side of the body (ie, hemiballism or hemiballismus). Occasionally, bilateral movements occur (ie, biballism or paraballism). Many patients with hemiballism have choreiform movements and vice versa, and hemiballismus often evolves into hemichorea. Currently, ballismus should be viewed as a severe form of chorea. In later stages the patient even becomes mute. Dysarthria and dysphagia become very prominent during the course of the disease. Dysarthria is a speech sound disorder resulting from neurological injury of the motor component of the motor–speech system and is characterised by poor articulation of phonemes, while Dysphagia refers to difficulty in swallowing. The motor speech disturbances of patients with HD are commonly referred to as hyperkinetic dysarthria. All patients develop hypokinesia, akinesia, and rigidity leading to a slower pace of all activities (bradykinesia: slowness of movement) and a severe hesitation in embarking on a movement (akinesia: difficulty in starting movements)). The balance between chorea and hypokinesia is determined individually. Orofacial dyskinesia is an intrinsic feature of Huntington's disease. While Huntington's disease is historically conceptualised as a disorder of choreiform *hyperkinesia*, particularly of the orofacial region, the clinical trajectory of motor dysfunction over the course of illness is characterised by transitions from dyskinesia to rigidity and other *hypokinetic* features; indeed, that *hypokinesia* as well as hyperkinesia can be present, especially in the early onset of variants and late in the course following more a typical onset, is one of the reasons underpinning contemporary preference for the term Huntington's disease rather than Huntington's chorea. The extremes are on one hand the younger patient with an overwhelming rigidity (Westphal variant) and on the other hand the very old patient severely affected in the last stage of the disease with a long duration of illness, bed-bound with rigidity and flexion contractures in the extremities. Dystonia is characterised by slower movements with an increased muscle tone leading to abnormal posture, for instance torticollis (also known as wry neck, is a painful, dystonic condition defined

by an abnormal, asymmetrical head or neck position), but also rotation of the trunk or limbs. Dystonia can be the first motor sign in Huntington's disease. Other unwanted movements include tics, comparable to the ones seen in Tourette syndrome, but these are fairly rare. Cerebellar signs can appear sporadically, similar to the presence of hypo- and hypermetria. The role of the cerebellum, a brain region involved in the coordination of movements, in HD neuropathology has been controversial. Studies utilise postmortem human brain tissue to investigate whether Purkinje cell degeneration in the neocerebellum is present in HD, and how this relates to disease symptom profiles. Although it is well established that the cerebellum has a major role in the coordination of movements, and HD patients commonly show movement coordination deficits, cerebellar involvement in HD neuropathology and symptomatology is controversial. The influence of motor disturbance on activities of daily life progresses over time. The presence of hyperkinesia and hypokinesia results in difficulties in walking and standing, and frequently leads to an ataxic gait and frequent falls. Distinguishing between choreatic and ataxic walking is very difficult. Pyramidal signs (Babinski sign) are present incidentally.

Cognitive symptoms: Cognitive decline is the other main sign of HD and can be present long before the first motor symptoms appear, but can also be very mild in far advanced stages of the disease. The cognitive changes are particularly in relation to executive functions. In normal conditions, cognitive and motor behaviour is goal-directed and planned. Normally individuals are able to distinguish what is relevant and what can be ignored, but patients with HD lose this capability. The patients are no longer able to organise their life or to plan things which in the past were simple. They lose flexibility of mind, and can no longer make mental adjustments. Misjudgements lead to complicated situations, with patients no longer reacting as they did in the past or in a way that the environment expects. Language is relatively spared. Memory certainly becomes impaired, although the semantic memory can be spared to a certain extent. All psychomotor processes become severely retarded .

Preserved Abilities: It is worth emphasising that many cognitive functions remain relatively unaffected in HD. For example, an affected person's long-term memory can remain relatively intact and they can therefore recount experiences from the past or still have a good general knowledge. Also, they are often able to remember well-learned skills and automatic actions or behaviours. Thus, if the individual has been working in a particular job for many years they will be able to continue to carry out the tasks required. However, this does become a problem if new skills are introduced and the person with HD is expected to learn new information. People with HD usually do not have trouble comprehending what you are saying to them, even until quite late in the illness, however they sometimes take a long time to respond. Their perceptual ability also remains relatively intact, for instance they are still able to recognise objects, shapes, letters, numbers, colours and persons.

Cognitive Decline in People with HD: Unfortunately, HD is characterised by specific cognitive deficits. Memory appears especially affected, with problems occurring for both verbal and non-verbal memory. For example, a person with HD may have trouble remembering what you have said to them, or storylines in TV programmes or movies. Similarly, they may have extreme difficulty interpreting maps or remembering places. They often have trouble finding their way around and frequently get lost in familiar places. Thus, they may have difficulties when transferred to a new environment, such as a nursing home and need time to adapt to their new surroundings. Because the disease affects the frontal lobes of the brain, planning ability, judgement and decision-making are affected. As a result, people with HD often have trouble monitoring their own behaviour and do not realise that they are making errors or mistakes. Another characteristic is that people with HD have trouble motivating themselves and others often mistake this as

stubbornness or laziness. Planning and problem solving become increasingly difficult and they may, for example, now have more trouble cooking a new recipe or fixing a fuse. Affected individuals often have difficulty changing from one idea or task to another and this is why they struggle when it comes to changing routines. They also tend to lose the ability to think in abstract terms and their thinking becomes more concrete and rigid. Consequently, their conversation becomes more simplistic and they are no longer able to discuss topics or understand complicated concepts. Verbal fluency is often impaired, so they have difficulty recalling words from memory and expressing them. Motor functions are of course also disrupted (involuntary movements), which interferes with speech and coordination. People with HD sometimes have trouble controlling their emotions and this can lead to inappropriate behaviour, which is often mistaken as a psychiatric disorder, particularly in the early stages when a diagnosis of HD has not been made. There are many emotional changes that occur in HD, which may be a psychological reaction to the illness or a result of physical changes in the brain, or a function of both these factors. Emotional changes include anxiety, depression, reduced motivation, apathy, irritability and rapid mood changes.

Psychiatric symptoms: Although psychiatric disorder is not an inevitable consequence of Huntington's disease, the prevalence of psychiatric symptoms is significantly higher than in the general population; therefore there is a need for awareness of psychiatric morbidity at primary and secondary care levels. History-taking should include a corroborative history from caregivers. The importance of early detection is exemplified by the case study, in which the patient presented with behavioural features and psychiatric symptoms of Huntington's disease years before diagnosis. By the time of diagnosis, she was estranged from her family, had given birth to a son (who has a 50% chance of inheriting the disease) and had endured distressing psychiatric symptoms for a significant period of time, without adequate treatment. The care of patients with Huntington's disease is predominantly multidisciplinary and should be conceptualised in a manner similar to that for any patient with a severe and enduring mental illness. Although psychiatric and cognitive symptoms may pre-date the motor symptoms, a broad consensus exists that a definite diagnosis of Huntington's disease cannot be made until the emergence of the specific motor disorder.

- Depression
- Suicide and self-harm
- Psychosis
- Mania

Description of prodromal and advanced stages of HD: The prodrome of HD is a phase that has arisen from detection and characterisation of certain cognitive and behavioural symptoms in at-risk persons who are years from appearance of the motor symptoms that are currently used for a clinical diagnosis of HD. Prodrome is defined as “clinical or physiological indicator that precedes onset of a particular disease”. Two central indicators of prodrome HD are CAG repeat length and current age. The course of the life of a person with one parent with Huntington's disease can be divided into an at-risk, a preclinical (A) and a clinical

(B) stage. The at-risk stage comes to an end when it is determined whether the person carries the increased CAG repeat on chromosome 4. If he does carry the gene, then he will go through the preclinical and clinical stages until the end.

1. PRECLINICAL STAGE

A1. At-risk stage (50%), one affected parent	Anxiousness Uncertainty about carriership Care for affected parent
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A2. Gene carrier, pre-manifest stage	Certainty about carriership Uncertainty about onset
A3. Transition phase	Changes in behaviour Changes in motor activity

A. CLINICAL STAGE

B1. Clinical stage I	First symptoms present; neurological, cognitive or psychiatric Most prominent: chorea Rare; death/suicide
B2. Clinical stage II	Motor disturbances Physical dependence Burden for family
B3. Clinical stage III	Deterioration Completely dependent on care Death

Diagnosis and Disease Monitoring

Clinical criteria for diagnosing HD: Huntington disease (HD) should be suspected in individuals with any of the following:

- Progressive motor disability featuring chorea. Voluntary movement may also be affected.
- Mental disturbances including cognitive decline, changes in personality, and/or depression
- Family history consistent with autosomal dominant inheritance

Objective assessment of clinical findings of patients with Huntington's disease (HD) is necessary for an evaluation of the individual progression of the disease and the effect of therapy, and it requires specific assessment scales. The Unified Huntington's Disease Rating Scale (UHDRS) is an overall scale to assess clinical performance and functional capacity. The Unified Huntington's Disease Rating Scale (UHDRS) was developed as a clinical rating scale to assess four domains of clinical performance and capacity in HD: motor function, cognitive function, behavioural abnormalities, and functional capacity. It is the only measure to be recommended by the Movement Disorders Society for the assessment of motor function in HD. The UHDRS, or specific sub-scales of the measure are used as both an endpoint for clinical research and as a screening tool for stratifying and selecting participants for inclusion in clinical trials. However, this clinician rated scale requires specialist training and is subject to potential inter-rate variability and changes in UHDRS score do not necessarily correlate with the degree of neurodegeneration in an individual.

The UHDRS(TM) has four parts with separate scoring for each part:

Part I: motor function. 31 items with 5-point ordinal scale ranging from 0-4 with the highest score indicating inability to perform the motor task.

Part II: cognitive function. 3 items with higher scores indicating better cognitive performance.

1. Verbal Fluency Test
2. Symbol Digit Modalities Test (SDMT)
3. Stroop Interference Test.

Part III: behavioural assessment. 10 items with a 5-point ordinal scale ranging from 0-4 with the highest score indicating severe behavioural symptoms; 4 items requiring the evaluator to answer yes/no questions about the overall clinical impression with respect to the participant showing clinical evidence of confusion, dementia, depression and requiring pharmacotherapy (1 point for yes)

Part IV: functional capacity. This domain is divided into three sections:

1. Huntington's Disease Functional Capacity Scale (HDFCS) is reported as the Total Functional Capacity Score (TFC) which has a total of 25 Yes/No questions assessing the total functional capacity of the individual. A score of 1 given to all yes replies.
2. Independence Scale rated from 10 to 100 with higher scores indicating better functioning than lower scores
3. Functional Capacity- 5 items with 4-point ordinal scale ranging from 0 to 3 with the highest score indicating higher functional capacity.

Role of genetic testing and predictive testing: The international guidelines of the Huntington Association and the World Federation of Neurology Research Group on Huntington's chorea of 1994 and the revised version of 2013 state that neurological examinations are considered important to establish a baseline evaluation of each person. The guidelines state that the examination should be done before predictive testing. Predictive DNA-testing for Huntington's disease has been available as a clinical service since 1987, initially by DNA linkage and since mid-1993 by direct mutation analysis. To understand the motives for requesting predictive testing and the consequences of a predictive test result, it is of the utmost importance to realise what it means psychologically to be at 50% risk for Huntington's disease. This risk influences the entire life of the at-risk individual. Although the risk to develop the disease decreases gradually with age, at-risk individuals are never entirely sure that they have escaped the disease. The variable age at onset is an additional source of uncertainty. It is very important to realise that the threat to get Huntington's disease does not only dramatically influence the life of those who will develop symptoms, but also of those individuals who will not have the disease. Predictive test protocols have been carefully established because the potential pitfalls and dangers were widely recognised before offering testing as a clinical service. Internationally agreed guidelines have been issued by the International Huntington Association and the World Federation of Neurology Research group on Huntington's disease. These guidelines aimed at protecting at-risk persons and at assisting "clinicians, geneticists, and ethical committees as well as lay organisations to resolve difficulties arising from the application of the test". Predictive genetic testing involves a simple blood test to detect whether or not the individual has the genetic mutation that causes the disease. Huntington's disease was the first disease for which predictive testing was offered. People over 18 years old who have a family member affected with Huntington's disease but do not yet have symptoms of the disease are eligible for testing. A neurological exam is also performed to look for early symptoms. Anyone considering predictive testing should meet with a genetic counsellor. There are four categories of testing for the HD gene:

1. Presymptomatic testing, for people at risk for HD but showing no symptoms.
2. Confirmatory testing determines whether a person showing possible HD symptoms actually has the HD gene.
3. Prenatal testing is used to determine whether a foetus has the HD gene. This can be done by amniocentesis or chorionic villus sampling (CVS).
4. Prenatal Genetic Diagnosis (utilising in vitro fertilisation).

Imaging modalities for disease monitoring (MRI, PET scans): Although all modalities capable of structural brain imaging will demonstrate morphological changes of Huntington disease, MRI has the greatest spatial and contrast resolution and is thus preferred.

MRI

The most striking and best-known feature is that of caudate head atrophy. There is also, however, prominent putaminal volume loss which is usually not as easily recognised on visual inspection but seen well on morphometry. This is particularly the case in younger patients. The combination results in enlargement of the frontal horns, often giving them a "box" like configuration.

This can be quantified by a number of measurements:

- frontal horn width to intercaudate distance ratio (FH/CC), which is reduced in Huntington disease
- intercaudate distance to inner table width ratio (CC/IT), which is increased in Huntington disease

In some cases, the basal ganglia may show decreased T2 signal and blooming on SWI in keeping with iron deposition. Generalised age-inappropriate cortical thinning and volume loss is also recognised. MR spectroscopy may demonstrate elevation of lactate, although this can be variably present in location (most often in the basal ganglia). There is also a decrease in NAA/creatine ratio, particularly in the basal ganglia, in-keeping with neuronal loss.

PET

PET demonstrates hypometabolism by decreased FDG uptake in basal ganglia and frontal cortex even before noticeable caudate nucleus volume loss. PET studies in humans have shown a decline of striatal postsynaptic D1, D2 and D3 receptors availability in manifest and premanifest HD individuals. The functional imaging techniques of positron emission tomography (PET) and single photon emission tomography (SPET) have been used to study regional brain function in Huntington's disease (HD) *in vivo*. Reduced striatal glucose metabolism and dopamine receptor binding are evident in all symptomatic HD patients and in

~50% of asymptomatic adult mutation carriers. These characteristics correlate with clinical measures of disease severity. Reduced cortical glucose metabolism and dopamine receptor binding, together with reduced striatal and cortical opioid receptor binding, have also been demonstrated in symptomatic patients with HD. Repeat PET measures of striatal function have been used to monitor the progression of this disease objectively.

Therapeutic Advances

Pharmacological interventions:

- **Medicines to control movement** include tetrabenazine (Xenazine), deutetrabenazine (Austedo) and valbenazine (Ingrezza). They have been approved by the Food and Drug Administration to suppress involuntary jerking and writhing movements, known as chorea. Chorea can happen as a result of Huntington's disease. These medicines don't affect how the disease progresses, however. Possible side effects include drowsiness, restlessness, and the risk of worsening or triggering depression or other psychiatric conditions.
- **Antipsychotic medicines** such as haloperidol and fluphenazine, olanzapine (Zyprexa) and aripiprazole (Abilify, Aristada) have a side effect of suppressing movements. Therefore, they may help to treat chorea. However, these medicines may worsen involuntary muscle contractions called dystonia and cause slowness of movements, resembling Parkinson's disease. They also may cause restlessness and drowsiness.
- **Antidepressants** include citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac) and sertraline (Zoloft). These medicines also may have some effect on obsessive-compulsive disorder symptoms. Side effects may include nausea, diarrhoea, drowsiness and low blood pressure.
- **Other medicines** that may help suppress chorea include amantadine (Gocovri), levetiracetam (Keppra,

Spritam) and clonazepam (Klonopin). However, mild effectiveness and side effects may limit their use.

Non-pharmacological interventions

- **Psychotherapy:** A psychotherapist — a psychiatrist, psychologist or clinical social worker — can provide talk therapy to help with behavioural symptoms. The psychotherapist can help you and your family develop coping strategies, manage expectations as the disease gets worse and help family members communicate.
- **Speech therapy:** Huntington's disease can affect the control of muscles of the mouth and throat that are essential for speech, eating and swallowing. A speech therapist can help improve your ability to speak clearly or teach you to use communication devices. A communication device might be as simple as a board covered with pictures of everyday items and activities. Speech therapists also can address trouble with eating and swallowing.
- **Physical therapy :** A physical therapist can teach you proper and safe exercises that enhance strength, flexibility, balance and coordination. These exercises can help maintain mobility as long as possible and may reduce the risk of falls. Instruction on posture and the use of supports to improve posture may help lessen some movement symptoms. When you need a walker or wheelchair, the physical therapist can advise on the proper use of the device and posture. Also, exercises can be adapted for your level of mobility.
- **Cognitive rehabilitation:** Family and caregivers can help create an environment that may help a person with Huntington's disease avoid things that cause stress. This can help manage cognitive and behavioural symptoms. These strategies include:
 1. Using calendars and schedules to help keep a regular routine.
 2. Starting tasks with reminders or assistance.
 3. Organising work or activities in order of importance.
 4. Breaking down tasks into manageable steps.
 5. Creating an environment that is as calm, simple and structured as possible.
 6. Looking for and steering away from stressors that can trigger outbursts, irritability, depression or other symptoms.
 7. For school-age children or teenagers, talking with school staff to develop an individual education plan.
 8. Providing chances for the person to maintain social interactions and friendships as much as possible.

Emerging therapies

- **Gene silencing:** Gene-silencing therapies that are currently being investigated in Huntington's disease work in a few different ways. Antisense oligonucleotides (ASOs) and RNA-interference (RNAi)-based therapies work by binding specifically to faulty RNA sequences that are made from mutated *HTT* gene codes. The CRISPR/CAS9 system, on the other hand, aims to directly modify the mutated *HTT* gene.

Antisense oligonucleotides:

An antisense oligonucleotide currently under clinical investigation for Huntington's disease is the investigative IONIS-HTTRx molecule (also called RG6042). It works by binding to and marking HTTmRNA for destruction. IONIS-HTTRx was initially developed by Ionis Pharmaceuticals and is now

licensed to Roche. Recent Phase 1/2a clinical trial results (NCT02519036) indicate this therapy may be successful in decreasing levels of abnormal HTT protein. An open-label extension trial (NCT03342053) to assess the long-term safety and efficacy of this compound is currently ongoing. Wave Life Sciences is also in the midst of producing two investigative antisense oligonucleotides, WVE-120101 and WVE-120102. Both compounds are currently being investigated in Phase 1/2 clinical trials.

RNAi-based therapies:

RNAi-based therapies differ from antisense oligonucleotides in that RNAi-compounds are usually delivered inside cells using a carrier, normally an inactivated virus. While ASOs are meant to bind directly to the specific mutated RNA sequence, RNAi-based compounds are first incorporated into naturally-occurring gene-silencing proteins present in the body before being able to target the mutated RNA sequence. Generally, the choice between ASOs or RNAi-based compounds depends on the location of cells that require gene silencing as well as on the type of disease. An RNAi-based therapy candidate called AMT-130 by uniQure is currently in preclinical stages of development. AMT-130 is carried inside nerve cells by a noninfectious adeno-associated virus. It then binds to and marks mutated HTT RNAs for degradation. VY-HTT01 is another RNAi-based investigative therapy. It is being developed by Voyager Therapeutics in collaboration with Sanofi-Genzyme and the CHDI Foundation.

CRISPR/Cas9 system

The CRISPR/Cas9 system is the latest in gene-silencing and altering technology. Discovered in 2015, it has been applied successfully in animal studies of several single-gene mutation disorders such as sickle cell anaemia, haemophilia, and cystic fibrosis. CRISPR/Cas9 works by “cutting out” specific gene sequences in the DNA. The cell’s repair mechanism then reattaches the cut ends. This may be particularly useful in the case of Huntington’s disease, as the gene defect causing the disease is a CAG repeat expansion, which means there are too many CAG repeats in patients’ DNA. Scientists have successfully used CRISPR/Cas9 to cut out CAG repeats in animal models of Huntington’s disease, with the animals demonstrating improved motor symptoms. Several animal studies have also shown that the CRISPR/Cas9 system is able to effectively remove the mutated *HTT* gene sequence without adversely affecting the rest of the DNA. The CRISPR/Cas9 system has the advantage of being cheaper and more accurate and effective compared to other gene-editing systems. But it has yet to be tested in clinical trials, and some scientists have concerns about its safety and gene editing ethical issues.

- **Stem cell therapy:** STEM cells are ideal for cell transplantation purposes in HD because they are relatively easy to obtain, and somatic stem cells, in particular, offer a means of eliminating immune rejection problems. Furthermore, stem cells can self renew continuously, produce progeny, and differentiate into many cell types. Several types of stem cells, such as, neural stem cells (NSCs), mesenchymal stem cells (MSCs) and adipose-derived stem cells (ASCs) have been isolated from specific adult human tissues. In addition, Takahashi and Yamanaka group recently induced pluripotent/ESC-like cells from somatic cells, named induced pluripotent stem cells (iPS cells). The current objectives of stem cell therapy in HD are: (I) to promote endogenous neurogenesis and improve self-repair in the brain; (II) to replace damaged or dying neurons; and (III) to protect neurons from disease progression using the factors released by stem cells.

- **Neuroprotective therapy:** Neuroprotection can be defined as a beneficial treatment effect on a biological process that contributes to neurodegeneration in HD and thus to clinical progression. Many possibilities for measuring such effects must be considered carefully when designing a clinical trial. In early-phase clinical trials, evidence for potential efficacy may be of secondary interest if examining

dosing, pharmacokinetics, pharmacodynamics, safety, and tolerability are the principal objectives. Preliminary evidence of potential neuroprotective efficacy from early-phase studies, however, can be vital for decision-making about whether to continue the development of the treatment into large and expensive phase III studies. A great need for HD has been clinical or other outcome measures that can provide that preliminary evidence. Indeed, without such signals it is also very difficult to stop development of a compound short of its failure in a large-scale study. Clinical measures, such as those contained in the Unified Huntington's Disease Rating Scale (UHDRS), can reveal an effect on HD symptoms, although symptomatic effects (whether better or worse) and neuroprotective effects cannot be considered to be synonymous. Global clinical measures that correspond to disease progression, such as the TFC or other indicators of functional decline, are insensitive measures in typical early-phase studies (involving anywhere from a few to 100 subjects, with durations measured in weeks to months). There are refined, often quantitative, clinical measures of motor and cognitive dysfunction that can be sensitively measured in HD subjects, including premanifest subjects. Some of these could be surrogates for measuring progression of the underlying disease and serve as indicators of the disease-modifying potential of a treatment. Because it is difficult to relate response magnitudes for such measures to clinically significant benefits, they are not yet usable as primary endpoints for assessing efficacy. Even more promising are biomarkers from neuroimaging or from biological samples or fluids ('wet' biomarkers) that could provide measures of disease activity or progression. To the extent that such biomarkers suggest a neuroprotective effect, they can be supportive of decisions about whether a compound should continue in development. Biomarkers are especially promising for this purpose, because neuroimaging showing slowed regional or whole-brain atrophy or 'wet' biomarkers showing a pharmacodynamic response are especially close to the biology of neurodegeneration can be revealing in pre manifest or manifest HD, and may have sufficient sensitivity in small sample size studies. Keep in mind also that brain volumes could be affected by a treatment without an accompanying effect on neurodegeneration, and that 'wet' biomarkers may capture only limited aspects of the entire biochemistry underlying neurodegeneration and thus may not be predictive of a significant clinical response later.

Challenges and Future Directions

Huntington's disease (HD) is a hereditary, progressive neurodegenerative disease clinically characterised by abnormal involuntary movements, behavioural disturbance, cognitive dysfunction, and psychiatric disease. The disease is caused by a CAG (glutamine) trinucleotide expansion in exon 1 of the huntingtin (htt) gene at the location. The normal function of htt is not known, but it may be involved in internal cell signalling, maintenance of cyclic adenosine monophosphate response element binding protein, and preventing neuronal toxicity. Early evidence suggests that the binding of the Ras homologue enriched in striatum protein to mutant htt (mhtt) may be necessary to cause cellular toxicity. However, why the protein causes cellular toxicity in adulthood is not well understood. There is evidence suggesting that the interaction of the group 1 metabotropic glutamate receptors and mhtt protein may be at the root of delayed onset. Although there is no established treatment to delay the onset or forestall the progression of HD, symptomatic treatment of chorea based on the neurochemical pathology known may be beneficial in some individuals, as it may have a favourable effect on motor function, quality of life, and safety. Clinicians may also consider treatment for dystonia, other movement disorders, and non-motor aspects of HD. Management of Huntington's disease (HD) is complex, requires multidisciplinary care and is based on pharmacological and non-pharmacological symptomatic treatments. As there are no treatments which can slow, halt or reverse disease progression. HD management aims to maximise function and optimise patients' quality of life. Over the past decade, major focus has been placed on the development of disease-modifying therapies (DMTs) for HD. One of the main therapeutic approaches

under investigation to slow or stop HD progression is the lowering of mutant huntingtin protein (mHTT) production. The most advanced DMTs in clinical development for HD are antisense oligonucleotides (ASOs). ASOs are generally too large to permeate the blood–brain barrier. Intrathecal (IT) administration of ASOs into the cerebrospinal fluid (CSF) via lumbar puncture allows distribution to the central nervous system. IT administration is a feasible and generally well-tolerated procedure, with established monitoring and management for side effects such as headache and CSF leakage. Practical considerations for performing the IT administration procedure in clinical settings include the availability of healthcare professionals (HCPs) with adequate expertise, the requirement for support staff, the monitoring of patients, and the availability of suitable facilities. For HD, experience of IT administration derives primarily from the global clinical development programme of the HTT-targeting ASO tominersen, including GENERATION HD1, the ongoing Phase III study of tominersen in patients with manifest HD as well as other ASO programmes that have not yet been published. Given that clinical guidelines for the IT administration of HD DMTs are not yet defined, the GENERATION HD1 clinical protocol currently provides the most relevant information on the procedure in the context of HD. Multi-source data collection was used to estimate the current and needed capacity for HD centres to manage patients in a future with intrathecally administered DMTs. Data were also gathered on the current resource availability of HD centres to perform follow-up consultations. Qualitative and quantitative data on HD centre capacity, local HD therapeutic environments and the IT administration procedure were gathered via interviews with therapy area experts (TAEs) including neurologists who had participated in HD clinical trials involving intrathecally administered DMTs, patient advocacy group (PAG) representatives and HCPs who were employed at HD centres. All interviews were anonymised, conducted in accordance with the local regulations of each country and used standardised discussion guides to ensure consistency of quantitative and qualitative data. All respondents were compensated at local Fair Market Value rates defined by F. Hoffmann-La Roche Ltd. Data modelling was used to generate quantitative data on the capacity gaps in HD centres for intrathecally administered HD DMTs. The steps and resources needed for the IT administration of HD DMTs were based on the protocol for GENERATION HD1. This study assumes a scenario whereby all patients fulfilling the GENERATION HD1 inclusion criteria will benefit from HD DMT treatment, rather than patients at a specific stage of HD. Twelve countries were selected for inclusion in the study based on consideration of HD prevalence, on seeking diversity of the structure (centralised or decentralised) and maturity of the healthcare system. This study aimed to recruit 40 HD centres in total, assessing at least one HD centre for each of the identified countries: Australia, Brazil, Canada, Colombia, Egypt, France, Germany, Italy, Mexico, Spain, Sweden and the United Kingdom. The United States did not participate in this assessment because they were included in a separate study. HD centres were defined as hospitals or academic institutions in which HD clinics are based. HD clinics were defined as the combination of resources currently dedicated to HD treatment within HD centres, e.g., one neurologist and one nurse dedicated to HD treatment 1 day per week, although resource combinations may vary between different HD clinics.

Addressing the heterogeneity of HD symptoms: The cellular basis of variable symptoms in Huntington disease (HD) is unclear. One important possibility is that degeneration of the interneurons in the cerebral cortex, which play a critical role in modulating cortical output to the basal ganglia, might play a significant role in the development of variable symptomatology in HD. This study aimed to examine whether symptom variability in HD is specifically associated with variable degeneration of cortical interneurons. A double-blind study was undertaken using stereological cell counting methods to quantify the 3

major types of γ -aminobutyric acidergic interneurons (calbindin-D28k, calretinin, parvalbumin) in 13 HD cases of variable motor/mood symptomatology and 15 matched control cases in the primary motor and anterior cingulate cortices. In the primary motor cortex, there was a significant loss (57% reduction) of only calbindin interneurons in HD cases dominated by motor symptoms, but no significant interneuron loss in cases with a dominant mood phenotype. In contrast, the anterior cingulate cortex showed a major significant loss in all 3 interneuron populations, with 71% loss of calbindin, 60% loss of calretinin, and 80% loss of parvalbumin interneurons in HD cases with major mood disorder, and no interneuron loss was observed in cases with major motor dysfunction. These findings suggest that region-specific degeneration of cortical interneurons is a key component in understanding the neural basis of symptom heterogeneity in HD

Future therapeutic development: During the past decade, attention has moved from targeting broad spectrum and downstream processes to targeting root causes for potential HD therapies, such as lowering mHTT. ASO therapies hold significant attention in potential HD therapeutics, with multiple ASOs currently in clinical trials. ASOs are single stranded oligonucleotide analogues. They bind to pre-mRNA or mRNA and can act through multiple mechanisms, including RNA degradation, blocking translation and splice modulation; these ultimately alter protein expression. ASOs can be allele-specific, indicating they specifically target mHTT, or allele non-specific, indicating they target both wild type HTT (wtHTT) and mHTT. There are 3 ASOs in clinical trials currently for HD – Tominersen (an allele non-specific ASO), WVE-120101 and WVE-120102 (allele-specific ASOs).

Tominersen (previously called IONIS Pharmaceuticals) is an ASO that binds to wild type HTT (wtHTT) and mHTT mRNA, inducing degradation. It is currently the most developed HD ASO therapeutic. Tominersen distributed well in mice and non-human primate brains during pre - clinical experiments. It lowered mHTT mRNA and mHTT protein in a dose-dependent, sustained fashion. Tominersen reversed the HD phenotype, improved survival and reduced brain atrophy in mice. These experiments informed the following phase 1b/2a clinical trial design. In the initial randomised, double blinded phase 1b/2a clinical trial, participants (n

= 46) were divided into 5 groups of ascending doses and a placebo group. Tominersen was given every 28 days in 4 doses, and participants were followed up after 4 months. No serious adverse events occurred, and minor adverse event incidence was similar for Tominersen and placebo groups. CSF mHTT was reduced by 40% on average at 90 mg and 120 mg doses and Tominersen showed dose dependency.

WVE-120101 and WVE-120102 are allele-specific, stereopure ASOs. They target single nucleotide polymorphisms (SNPs) specific to HD genotypes. Unpublished pre - clinical experiments showed they reduced mHTT mRNA without significantly altering wtHTT mRNA and protein in patient derived cell lines. This led to randomised, double blinded phase 1b/2a clinical trials which recruited participants with early manifest HD. Participants (n = 60 per trial) were divided into 6 groups – 2 mg, 4 mg, 8 mg, 16 mg or 32 mg WVE-120101/WVE-120102 doses or placebo (.9% NaCl). The parallel studies intended to measure adverse events, tolerability, pharmacokinetics and pharmacodynamics. Preliminary PRECISION-HD2 results showed WVE-120102 reduced CSF mHTT protein by 12.4% compared to placebo across all groups (n = 44). This was statistically significant in higher doses, and indicated dose dependency. Total HTT did not change between groups. There were no serious adverse events, and less minor and moderate adverse events for WVE-120102 (72%) than placebo (83%).

Psychosocial Impact and Caregiver Support

Impact of HD on patients and families: By assessing a group of adults who grew up in a household with a parent affected by Huntington's disease (HD), high rates of family dysfunction were reported. Adverse parenting in the form of parental and maternal overcontrol and paternal abuse were endorsed for both the HD-positive and HD-negative parent. These results illustrate the impact on all members of a family coping with HD. They are particularly stark, given the overall psychological health of the sample, and suggest that there is an urgent need to use a family perspective when assessing the need for psychosocial intervention in HD.

Ethical considerations in HD management: One major ethical issue that surrounds Huntington's disease concerns the genetic test that is used to diagnose the disease. This raises questions about how old a patient needs to be before they are considered mature enough to undergo testing, how confidentially the results are handled, and whether test results should be used to aid decisions on employment, insurance and other financial aspects. In 1910 Charles Davenport made a very controversial proposal that people with certain diseases including Huntington's disease should be subject to compulsory sterilisation and immigration control, as part of the eugenics movement. Another ethical issue in the debate over Huntington's disease is the use of embryonic stem cells in the research and development of therapies to cure the illness. The use of animal experiments and transgenic animal models that have been genetically engineered to develop symptoms of the disease is also a subject of ethical debate. The development of a genetic test that can diagnose Huntington's disease has led to several social, ethical and legal debates in terms of how such results should be accessed and used. For most testing procedures, strict guidelines for disclosure and confidentiality are in place that enable patients to decide when they are given their results as well as who the results are made available to.

Conclusion

Continuous improvement is the ongoing improvement of products, services or processes through incremental and breakthrough improvements. These efforts can seek "incremental" improvement over time or "breakthrough" improvement all at once. Among the most widely used tools is a four-step quality assurance method—the plan-do-check-act (PDCA) cycle:

- **Plan:** Identify an opportunity and plan for change.
- **Do:** Implement the change on a small scale.
- **Check:** Use data to analyse the results of the change and determine whether it made a difference.
- **Act:** If the change was successful, implement it on a wider scale and continuously assess your results.

If the change did not work, begin the cycle again.

Other widely used methods of continuous improvement, such as Six Sigma, lean, and total quality management, emphasise employee involvement and teamwork, work to measure and systematise processes, and reduce variation, defects, and cycle times. Huntington's disease (HD), a single-gene degenerative disorder of the striatum, has seen more than two decades of intense research, spurred by the identification of the gene in 1993. This research has led to a better understanding of the pathoetiology of the disease; however, there is much still to be studied, especially in the context of understanding the role of abnormal development. Over the past 20 years, there has been a significant improvement in both illness awareness and patient treatment. One often overlooks the many years spent in the at-risk and developmental phases, also known as the premanifest phase, prior to the manifestation of symptoms because the typical disease course is even more than 17 years. Both the sufferer as well as the household

are affected by HD for the rest of their lives. Articles have multiplied dramatically. Then what's the present viewpoint? Both pathogenesis, as well as the hunt for biomarkers, are the primary subjects of the fundamental investigations. New drug development disrupts the diseased mechanism and will undoubtedly result from a more profound knowledge of pathophysiology. The search is on for medications that can slow down, postpone, or halt the disease's onset. The second problem is the ongoing quest for accurate, easily identifiable, and clinically significant indicators indicating the beginning of the disease's terminal phase. The database research, which is the European Huntington Disease Network's flagship initiative, also intends to set the stage for more considerable investigations whenever medications are made accessible for testing on humans. The finest care for all sufferers and at-risk individuals at this moment is being sought after in tandem with the excellent road to identify treatments for this condition. The discoveries are encouraging; however, there is no doubt that there is a long way to go before a solution can be found. In addition, very little is known about the normal function of *HTT*, which is vital to brain development. Despite these areas of uncertainty, much progress has been made, particularly regarding the promise, and now reality, of new methods of treatment and potential prevention in the context of gene therapy approaches.

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