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Huntington's disease – I. Symptomatology, Etiology, and action Mechanisms

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Abstract

Huntington's disease is a rare inherited, progressive, incurable, and fatal neurodegenerative disorder of the central nervous system. It is caused by a defective gene characterized by an excessive number of trinucleotide repeat expansions. The defective gene produces a protein of unknown function named Huntingtin, which is involved in the functioning of the nerve cells in the brain (neurons). The protein is toxic and causes selective loss of neurons in the striatum. The disease affects primarily the brain with a profound effect on the ability of the affected individual to communicate. This article will review and analyze the symptomatology, etiology, and mechanisms of action of the disease. It will also analyze the underlying genetics.

Abbreviations

AD: Alzheimer's disease; ADI: Autosomal dominant inheritance; ATD: Acetyltransferase domain; BPD: Bipolar disorder; CAG: Cystosine-Adenine-Guanine; DM: Dynamic mutation; GA: Genetic anticipation; HD: Huntington's disease; HTT: Huntington gene; Htt: Huntingtin protein; mHtt: mutant Htt; JHD: Juvenile HD; OCD: Obsessive–compulsive disorder; OS: Oxidative stress; PD: Parkinson's disease; RGHC: Research Group on Huntington's Chorea; ROS: Reactive oxygen species; TRE: Trinucleotide repeat expansion.

Keywords

Autosomal dominant inheritance; CAG repeats; Caspase activation; Chorea; Free radical toxicity; Huntington gene; Huntingtin protein; Motor symptoms; Cognitive symptoms; Glutamate excitotoxicity; Psychiatric symptoms; Transcriptional dysregulation; Trinucleotide repeat expansion.

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Huntington's disease (HD) is a rare inherited,

progressive, incurable, and fatal neurodegenerative disorder of the central nervous system. Every child of a parent with HD has a 50/50 chance of inheriting it. If not inherited, the child will never develop the disease and will not pass it on to future generations. HD affects muscle function and further leads to cognitive decline and dementia. It is caused by a defective gene characterized by an excessive number of CAG (Cystosine-Adenine-Guanine) trinucleotide repeats - a part of the DNA code. The defective gene produces a protein of unknown function named Huntingtin, which is involved in the functioning of the nerve cells in the brain (neurons). When defective, the gene produces an abnormal (or mutated) Huntingtin protein that is toxic and causes selective loss of neurons in the striatum - an area of the brain that controls movement, balance and walking - and other areas of the brain as well. The disease affects primarily the brain with a profound effect on the ability of the affected individual to communicate.

Introduction

HD was long considered solely a brain disorder associated with brain pathology and mitochondrial abnormalities but, contrary to that earlier thinking, it has ben found that it is also associated with abnormalities in peripheral tissues, impaired muscle energy metabolism, and impaired energy metabolism through mitochondrial dysfunction. The pathogenesis remains, however, largely unclear so that the exact cause of neuronal death is unknown. Recent studies implicate caspase activation, glutamate excitotoxicity, and free radical toxicity as possible causes of the disease. The leading hypothesis is that of excitotoxicity and apoptosis induced by a defect in energy metabolism that may be caused by oxidative stress. If these processes were confirmed, pharmacological agents that block their pathways may be therapeutic.

The disease can present at any time in people during their life span. Symptoms may vary from person to person; they usually appear in people who are in their 30s or 40s but also earlier in life (juvenile HD) and even in children younger than 10 years old (infantile HD). Since each patient may have a unique combination of symptoms, there is no standardized treatment and only medications are prescribed on a case-by-case basis. There is an extensive range of medications and non-drug treatments that are used to treat each of the unique symptoms. Regretfully, notwithstanding such approved therapies for specific disease symptoms, there is currently no cure and there are no approved drugs that delay the onset or slow disease progression. Current approved drugs address the range of symptoms that arise as a consequence of the disease, but they do not address the disease at its origin. They can be categorized by the symptom they treat and include: chorea medication, antipsychotics, antidepressants, mood-stabilizing medication as well as non-drug therapies. Side effects from medications can also affect each patient differently. Fortunately, there are also many new therapeutics currently undergoing clinical trials that target the disease at its origin by lowering the levels of the mutant Huntingtin protein. In this series of articles, I will discuss the disease at length in all its several facets and address the issue of prevention and prognosis.

Signs and symptoms

Signs and symptoms of HD most commonly become noticeable between the ages of 30 and 50 years, but they can begin at any age. When developed in an early stage, the condition is known as juvenile Huntington's disease (JHD). The symptoms vary widely between people; even people in the same family may be affected differently. They may also change in severity throughout the course of the disease. The first symptoms vary greatly from person to person, some of them appearing to be worse or have a greater effect on functional ability. Most symptoms can be classified

under motor, behavioral, or cognitive categories. Atypical symptoms can also occasionally be observed.

Below are just a few of the possible symptoms - some people experience them and others may experience different ones. There are many people living with HD who have greatly improved their quality of life by getting the right help and support and the right interventions at the right time. There are many different kinds of support and help that people with HD can try to manage their symptoms and live as well as possible. Their carer and family members may also need additional support, practically and emotionally. In the later stages of the disease more care and support will be needed.

Motor symptoms (chorea)

These are the most obvious changes patients display, affecting some people more than others. People may have involuntary movements while at the same time having more difficulty with the movements they want to make. These movement disorders are collectively called "chorea". People with HD also may not be able to control voluntary movements. This can have a greater impact than the involuntary movements caused by the disease. Having trouble with voluntary movements can affect a person's ability to work, perform daily activities, communicate, and remain independent.

Motor symptoms may include:

• Involuntary jerking or writhing, random, and uncontrollable movements. Many people are not aware of such movements or impeded by them.

• Muscle rigidity or muscle contracture.

• Slow or unusual eye movements.

• Trouble walking or keeping posture and balance.

• Trouble with speech or swallowing.

Chorea may be initially exhibited as general restlessness, small unintentionally initiated or uncompleted motions, lack of coordination, or slowed saccadic eye movements. These minor motor abnormalities usually precede more obvious signs of motor dysfunction by at least three years. The clear appearance of symptoms such as rigidity, writhing motions, or abnormal posturing appear as the disorder progresses. These signs indicate that the system in the brain that is responsible for movement has been affected.

Psychomotor functions become increasingly impaired such that any action that requires muscle control is affected. When muscle control is affected such as rigidity or muscle contracture, this is known as "dystonia". Dystonia is a neurological hyperkinetic movement disorder that results in twisting or repetitive movements, that may resemble a tremor. Common consequences are physical instability, abnormal facial expression, and difficulties chewing, swallowing, and speaking. Sleep disturbances and weight loss are also associated symptoms. Eating difficulties commonly cause weight loss and may lead to malnutrition. Weight loss is common in people with HD and progresses with the disease.

Cognitive symptoms

HD often causes trouble with cognitive skills. These symptoms may include:

• Trouble organizing, prioritizing or focusing on tasks.
• Lack of flexibility or getting stuck on a thought, behavior or action, known as perseveration.
• Lack of impulse control that can result in outbursts, acting without thinking, and sexual promiscuity.
• Lack of awareness of one's own behaviors and abilities.
• Slowness in processing thoughts or finding words.
• Trouble learning new information.

The symptoms affect people most in daily life, tasks may take longer or become harder, and concentration is a struggle with increased forgetfulness. It becomes more difficult to learn new things and make important decisions.

Cognitive abilities are progressively impaired and tend to generally decline into dementia. Especially affected are executive functions, which include planning, cognitive flexibility, abstract thinking, rule acquisition, initiation of appropriate actions, and inhibition of inappropriate actions.

Different cognitive impairments include difficulty focusing on tasks; lack of flexibility, impulse, and awareness of one's own behaviors and abilities; and difficulty learning or processing new information. As the disease progresses, memory deficits tend to appear. Reported impairments range from short-term memory deficits to long-term memory difficulties, including deficits in episodic (memory of one's life), procedural (memory of the body of how to perform an activity), and working memory. (Refer to my book on Memory, 2023.)

Psychiatric symptoms

These symptoms are the most difficult for the person and for family members. The person may feel and behave differently, which can cause them to become more frustrated, irritable or angry. In 50% of cases, the psychiatric symptoms appear first. Their progression is often described in early stages, middle stages, and late stages (see Section below) with an earlier prodromal phase. In the early stages, subtle personality changes, problems in cognition and physical skills, irritability, and mood swings occur, all of which may go unnoticed, and usually precede the motor symptoms. Almost everyone with HD eventually exhibits similar physical symptoms, but the onset, progression, and extent of cognitive and behavioral symptoms vary significantly between individuals.

Reported neuropsychiatric signs are anxiety, depression, a reduced display of emotions, egocentrism, aggression, compulsive behavior, hallucination, and delusion. Other common psychiatric disorders could include obsessive–compulsive disorder (OCD), mania, insomnia, and bipolar disorder (BPD). Difficulties in recognizing other people's negative expressions have also been observed.

The prevalence of these symptoms is highly variable between studies, with estimated rates for lifetime prevalence of psychiatric disorders between 33% and 76%. For many with the disease, and their families, these symptoms are among the most distressing aspects of the disease, often affecting daily functioning and constituting reason for institutionalization. Early behavioral changes in HD result in an increased risk of suicide. Often, individuals have reduced awareness of chorea, cognitive, and emotional impairments.

Mental health conditions

The most common mental health condition associated with HD is depression. This is not simply a reaction to receiving a diagnosis of HD. Instead, depression appears to occur because of damage to the brain and changes in brain function.

Symptoms may include:

• Irritability, sadness or apathy.
• Social withdrawal.
• Trouble sleeping.
• Fatigue and loss of energy.
• Thoughts of death, dying or suicide.

Other common mental health conditions include:

• Obsessive-compulsive disorder (OCD), a condition marked by intrusive thoughts that keep coming back and by behaviors repeated over and over.
• Mania, which can cause elevated mood, overactivity, impulsive behavior and inflated self-esteem.

• Bipolar disorder, a condition with alternating episodes of depression and mania.

Atypical symptoms

Occasionally, an individual may be strongly suspected of having HD despite atypical symptoms. This might apply to individuals with prominent psychiatric symptoms, atypical dementia disorders, and unusual movement disorders, and to any child suspected of having HD. Physicians must carefully consider the value and potential implications of establishing the presence of the HD gene, recalling that its presence may not explain the individual's symptoms. It may be appropriate in some circumstances to evaluate an individual with atypical symptoms several times over the course of a year to monitor whether the condition is static, improving, or progressing in a manner consistent with HD, prior to obtaining a gene test. This is particularly important for children, in whom the presence of symptomatic HD is rare and different from adult symptoms, and for whom the premature detection of the HD gene may have greater negative psychological and social impacts.

Symptoms of juvenile Huntington's disease

Juvenile HD generally begins and progresses slightly differently than it does in adults. It proceeds at a faster rate with greater cognitive decline and chorea is exhibited briefly, if at all. The Westphal variant of slowness of movement, rigidity, and tremors is more typical in juvenile HD, as are seizures.

Symptoms that may appear early in the course of the disease include:

- **Physical changes**

• Contracted and rigid muscles that affect walking, especially in young children.
• Slight movements known as tremors that cannot be controlled.
• Frequent falls or clumsiness.
• Seizures.

- **Behavioral changes**

• Trouble paying attention.
• Sudden drop in overall school performance.
• Behavioral issues, such as being aggressive or disruptive.

Stages

HD is staged depending on the time scale of appearance of the symptoms. Stages are characterized as early, middle, and later.

- **Early stages**

• Early symptoms may include slight, uncontrollable muscular movements; stumbling and clumsiness; lack of concentration and short-term memory lapses; depression and changes of mood and personality.
• Making uncontrollable movements (chorea) while, at the same time, it can become harder to make the movements such as doing up buttons or turning the pages of a book
• Difficulty with organizing and planning.
• Behaving differently - becoming angry, irritable or frustrated.
• Activities take longer or are hard to finish.
• Finding it harder to deal with new situations.
• Becoming more forgetful.

- **Middle stages**

Symptoms of the middle stage of the illness often revolve around changes in muscles and movement, although changes in behavior may also become more significant and challenging too.

• Muscles are likely to start making involuntary

contractions and become stiff and rigid.

• Movements will slow down and arms and legs may become clumsy.

• Changes in how they speak as forming words becomes more tricky.

• Swallow and eating becomes difficult.

• Behavior may change as feelings of anger, frustration or depression become quite intense. While this does not happen to everyone, it is more likely in the younger persons.

➢ **Later stages**

The nature of the disease means that over a period of many years, the disease progresses until the end of life. Later on, people with HD experience difficulties with:

• Weight loss and nutrition.

• Speech and swallowing.

• Movement and stiffness.

• Communication.

Genetics and etiology

HD is caused by a difference in a single gene that is passed down from a parent. It follows an autosomal dominant inheritance (ADI) pattern, meaning that a person needs only one copy of the nontypical gene to develop the disorder. With the exception of genes on the sex chromosomes, a person inherits two copies of every gene — one copy from each parent. A parent with a non-typical gene could pass along the non-typical copy of the gene or the healthy copy. Each child in the family, therefore, has a 50% chance of inheriting the gene that causes the genetic condition.

History and basic lesion identification

Reports on the neuropathology of chorea in adults appeared as early as the 1870s, with researchers generally agreeing that the basic lesion was located in the basal ganglia (red area in Figure 1).

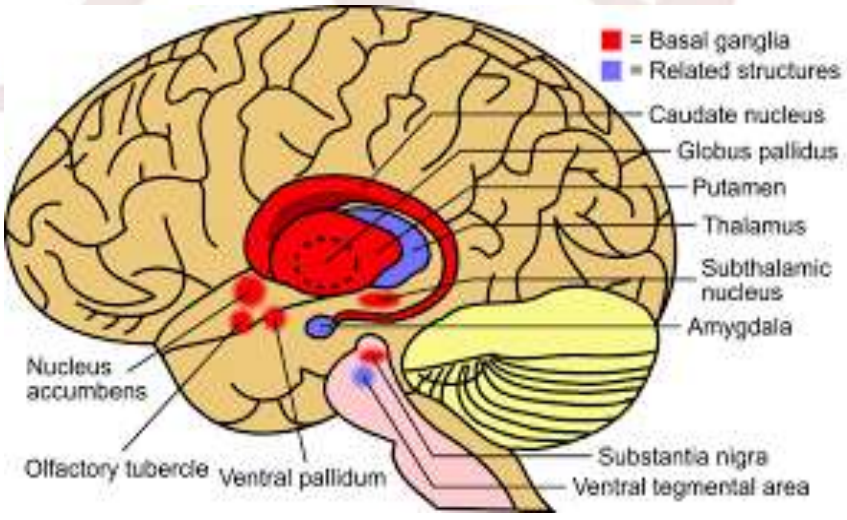


Figure 1: The basal ganglia and related structures of the brain

However, there was little agreement on its cause and relatively little progress for decades. The confluence of several developments in the 1960s radically transformed this bleak research landscape. First, the discovery of the drug Levodopa (L-Dopa) and its benefits for patients with Parkinson's disease (PD) spurred an international gathering of neurologists in 1967 to organize a Research Group on Huntington's Chorea (RGHC). Second, the rise of social movements in the 1960s challenged the legacy of eugenics and encouraged members of families with HD to become active on their own behalf, spearheading efforts to improve care as well as to interest scientists in research. With revolutionary advances in molecular genetics and neuroscience, biomedical interest in HD expanded. New technologies of gene mapping opened up new possibilities for identifying — and perhaps disabling — the aberrant gene. In addition, new modes of imaging offered possibilities for understanding — and potentially intervening in — the sequence of pathological changes in the brain.

HD affects the whole brain, but certain areas are more vulnerable than others. Pictured in Figure 2 is the striatum – an area deep in the brain that is the most vulnerable part in HD. It controls movement, mood, and memory. Damage to the striatum over time is what causes the symptoms of HD.

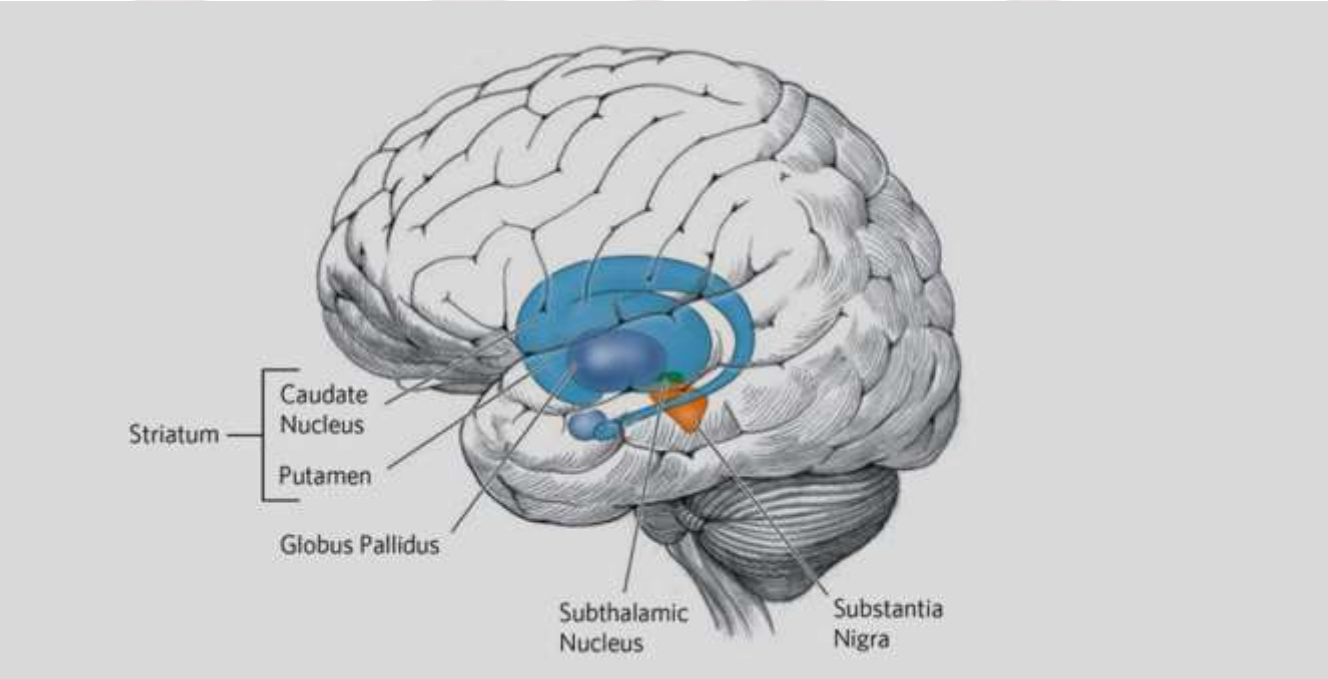


Figure 2: The striatum region of the brain

Genetics of HD

Everyone has two copies of the Huntington gene (HTT, also called ITI5)), which codes for the Huntingtin protein (Htt) - an important protein needed by nerve cells in the brain (neurons) and for the body's development before birth. When HTT is faulty, the huntingtin protein it produces repeats of the genetic sequences CAG discussed below, which in turn appear to damage neurons in certain areas of the brain - although how and why this happens is not yet fully understood.

➢ The Huntingtin gene protein

The DNA error that causes HD is found in HTT. Discovered in 1993, this gene is present in everyone but only those who inherit the mistake, known as the HD mutation, will develop HD and risk passing it on to their progeny.

Now, genes are made up of the nucleotide "letters" A,G,C, and T, which form a code that is read in groups of three ("codons"). HD is caused by a stretch of the letters C-A-G in HTT repeating itself over and over, too many times…CAGCAGCAGCAGCAG.... This is known as the "CAG repeat expansion". 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 likewise developing it.

Our genes are like an instruction manual for making proteins, the machines that run everything in our bodies. The Huntington gene contains instructions that are copied into a biological message (RNA) which makes the huntingtin protein. The huntingtin protein is very large and, while not fully understood, seems to have many functions, especially as the brain is developing before birth. We know that the extra CAG repeats in people with HD cause the huntingtin protein to be extra-long and difficult to maintain, making it difficult for it to do its job. Over many years, this "mutant" huntingtin protein forms clumps in brain cells, causes them to become damaged, and eventually die.

➢ Trinucleotide repeat expansion

Part of the Hungtinton gene is a repeated section called a trinucleotide repeat expansion (TRE) – a short repeat, which varies in length between individuals, and may change length between generations. CAG is part of the DNA code. DNA (deoxyribonucleic acid) is a self-replicating material that is present in nearly all living organisms. It is the carrier of genetic information. The four chemicals that make up DNA are A (Adenine), T (Thymine), C (Cystosine) and G (Guanine). The code for the Huntington's gene contains three of these chemicals C, A and G, which are repeated over and over again in a particular sequence.

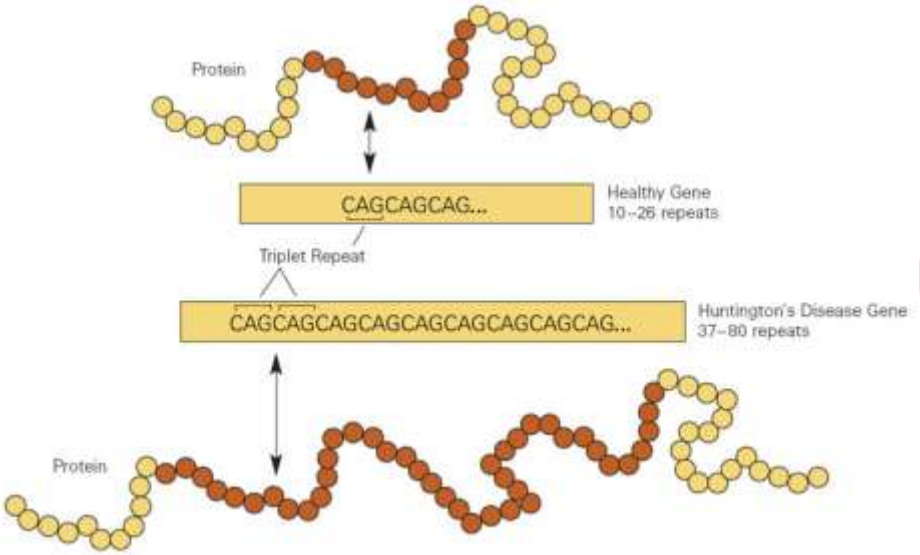


Figure 3: Illustration of the trinucleotide repeat expansion

Figures 3 and 4 illustrate the trinucleotide CAG repeat expansion. The graphics show the correspondence between the CAG repeat length and the corresponding Huntington's status, specifically the unaffected case (normal or intermediate allele) and the affected case (reduced or full penetrance). A normal CAG repeat is between 10 and 26 times. Usually one of the CAG repeats will be in this region (unless inherited from both parents, although this is very rare). If the number of CAG repeats is over 40, this means that the bearer will go on to develop HD at some stage.

If the repeat is present in a healthy gene, a dynamic mutation may increase the repeat count and result in a defective gene. When the length of this repeated section reaches a certain threshold, it produces an altered form of the protein, called mutant huntingtin protein (mHtt). The differing functions of the proteins (Htt and mHtt) are the cause of pathological changes, which in turn cause the disease symptoms. Where it gets a little more complicated is the intermediate allele and the reduced penetrance.

The HD mutation is genetically dominant and almost fully penetrant. The mutation of either of a person's HTT alleles causes the disease. It is not inherited according to sex, but by the length of the repeated section of the gene. However, its severity can be influenced by the sex of the affected parent.

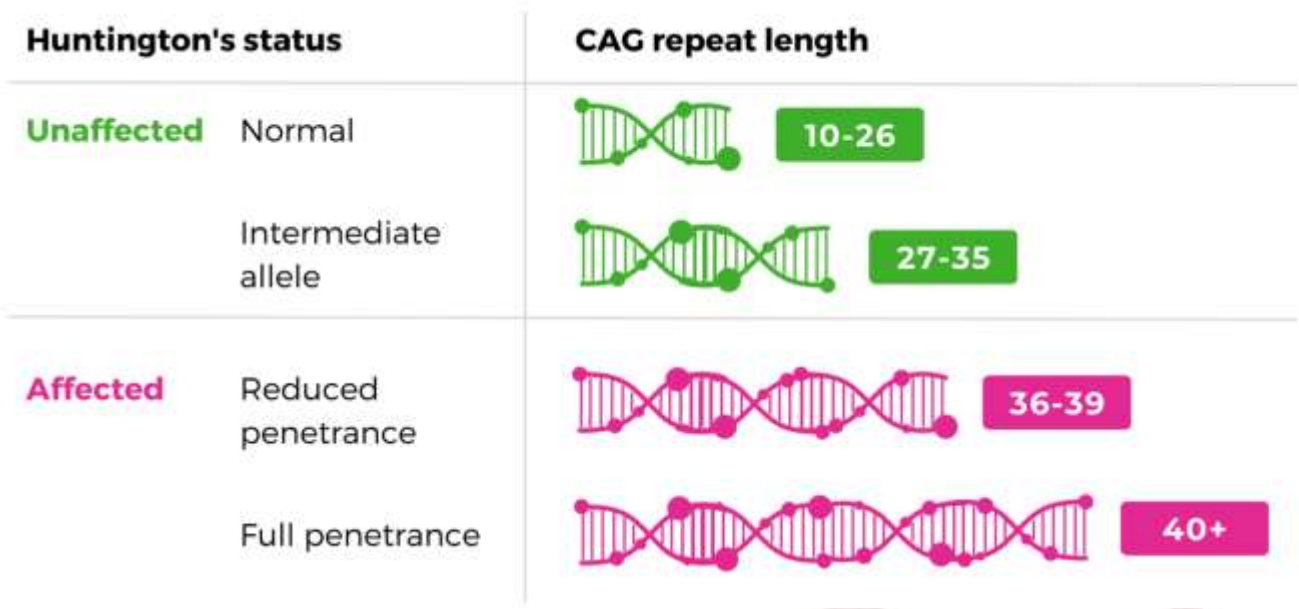


Figure 4: CAG repeated length and Huntington's status

Classification of trinucleotide repeats and resulting disease status

Worldwide, experience suggests the interpretations for the results of HD genetic testing according to Table 1 (Nance, Paulsen, Rosenblatt, and Wheelock, 2011):

Repeat count	Classification	Disease status	Risk to offspring
< /=26	Normal	Will not be affected	None
27-35	Intermediate	Will not be affected	Elevated, but <50%
36-39	Reduced penetrance	May or may not be affected	50%
40+	Full penetrance	Will be affected	50%

Table 1: Repeat count and disease status with associated disease classification and risk to offspring

Generally, people have fewer than 36 repeated glutamines in the polyQ region, which results in the production of the cytoplasmic protein huntingtin. 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 [so-called "dynamic mutations" (DM)] instead of reproducing an exact copy of the trinucleotide repeat. It also 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 a fully penetrant HD.

To clarify this table further, for repeat lengths:

• **Less than or equal to 26:** This is considered normal. Within this range, the size of the CAG repeat segment also appears to be stable, i.e., does not appear as prone to expansion.

• **Within the range of 27-35:** These are also normal and they are not associated with symptoms of HD. However, the CAG repeat length tends to be more unstable in this range and can increase, so that a parent with a repeat number in this range can have a child whose repeat number is in the HD range. However:

• **36 or more glutamines:** It results in the production of a protein with different characteristics. This altered form, called mutant huntingtin (mHtt), increases the decay rate of certain types of neurons.

• **Within the range of 36-39:** Whether or when HD symptoms will develop cannot be predicted with certainty. It results in a reduced-penetrance form of the disease, with a much later onset and slower progression of symptoms. In some cases, the onset may be so late that symptoms are never noticed.Within this range, some individuals have been found to have classical symptoms of HD, while others have lived to be very old without developing the symptoms of HD. The gene is unstable in this range and may expand, so that a child may have a number of CAG repeats that is clearly within the HD range.

• **Length of 40 or greater:** This is virtually always associated with the development of the symptoms of HD at some time during a normal life span.

• **Very large, more than 60:** HD's onset can occur below the age of 20 (juvenile HD or JHD). JHD is typically of the Westphal variant that is characterized by slowness of movement, rigidity, and tremors. This accounts for about 7% of HD carriers.

Large increases in CAG repeat length are more likely to occur when the HD gene is passed on to a child by an affected father (Hendricks et al., 2009). While CAG repeat length is a significant factor in determining the age of onset of HD symptoms, it is not the only factor. The CAG repeat length does not predict with any accuracy when a particular individual's symptom onset will be or the clinical course that the disease may take. Two individuals with similar CAG repeat lengths may have different ages of onset and different symptomatology.

Regions of the brain have differing amounts and reliance on these types of neurons and are affected accordingly. Generally, the number of CAG repeats is the onset of symptoms. The remaining variation is attributed to the environment and other genes that modify the mechanism of HD.

The earlier age of onset and greater severity of the disease in successive generations due to increases in the number of repeats is known as "genetic anticipation" (GA). 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 HD 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 mutation

HD is one of several TRNs that are caused by the length of a repeated section of a gene exceeding a normal range. The HTT gene is located on the short arm of chromosome 4 at 4p16.3. As already indicated, it contains a sequence of three DNA bases—cytosine-adenine-guanine (CAG)—repeated multiple times (i.e. ... CAGCAGCAG …). CAG is the three-letter

related to how much this process is affected, and accounts for about 60% of the variation of the age of

genetic code (codon) for the amino acid glutamine, so a series of them results in the production of a chain of glutamine known as a polyglutamine tract (or polyQ tract), and the repeated part of the gene, the polyQ region.

Mutant huntingtin is expressed throughout the body and associated with abnormalities in peripheral tissues that are directly caused by such expression outside the brain. These abnormalities include muscle atrophy, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, and testicular atrophy.

Inheritance

HD has autosomal dominant inheritance (ADI). In an ADI disorder, the changed gene is the dominant gene. It is located on one of the non-sex chromosomes, called "autosomes". Only one changed gene is needed for someone to be affected by this type of condition.

A person with an ADI condition — in the example of Figure 5, this is the father — has a 50% chance of having an affected child with one changed gene and a 50% chance of having an unaffected child, 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 is affected with the disorder. This probability is sex-independent.

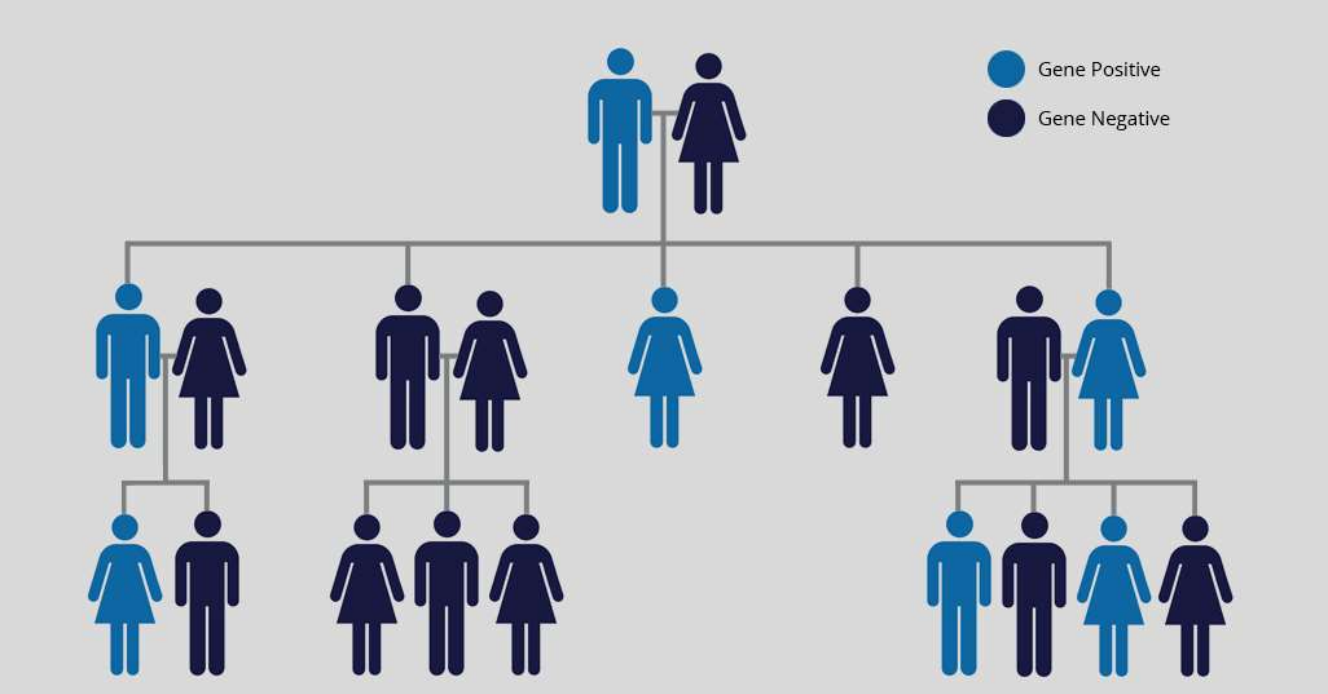


Figure 5: Autosomal dominant inheritance pattern of the HD gene

Mechanisms of action

The Huntingtin protein (Htt) interacts with over 100 other proteins, and appears to have multiple functions. The behavior of the mutated protein (mHtt) is not completely understood, but it is toxic to certain cell types, particularly brain cells.

Early damage is most evident in the subcortical basal ganglia (Figure 1), initially in the striatum (Figure 2), but as the disease progresses, other areas of the brain are also affected, including regions of the cerebral cortex.

Early symptoms are attributable to functions of the striatum and its cortical connections—namely control over movement, mood, and higher cognitive function. DNA methylation also appears to be changed in HD.

Huntingtin function

Htt is expressed in all cells, with the highest concentrations found in the brain and testes, and moderate amounts in the liver, heart, and lungs. Its functions are unclear, but it does interact with proteins involved in transcription, cell signaling, and intracellular transporting. In animals genetically modified to exhibit HD, several functions of Htt have been identified. In these animals, Htt is important for embryonic development, as its absence is related to embryonic death.

Caspase, an enzyme which plays a role in catalyzing apoptosis, is thought to be activated by the mutated Huntington gene (mHTT) through damaging the ubiquitin-protease system. It also acts as an anti-apoptotic agent preventing programmed cell death. It also controls the production of brain-derived neurotrophic factor, a protein that protects neurons and regulates their creation during neurogenesis.

Htt also facilitates synaptic vesicular transport and synaptic transmission, and controls neuronal gene transcription. If the expression of Htt is increased, brain cell survival is improved and the effects of mHtt are reduced, whereas when the expression of Htt is reduced, the resulting characteristics are more as seen in the presence of mHtt. Accordingly, the disease is thought not to be caused by inadequate production of Htt, but by a toxic gain-of-function of mHtt in the body.

Cellular changes

The toxic action of mHtt may manifest and produce the HD pathology through multiple cellular changes. In its mutant (polyglutamine-expanded) form, the protein is more prone to cleavage that creates shorter fragments containing the polyglutamine expansion. These protein fragments have a propensity to undergo misfolding and aggregation, yielding fibrillar aggregates in which non-native polyglutamine β-strands from multiple proteins are bonded together by hydrogen bonds. These aggregates share the same fundamental cross-beta amyloid architecture seen in other protein deposition diseases (for example, Alzheimer's disease, AD).

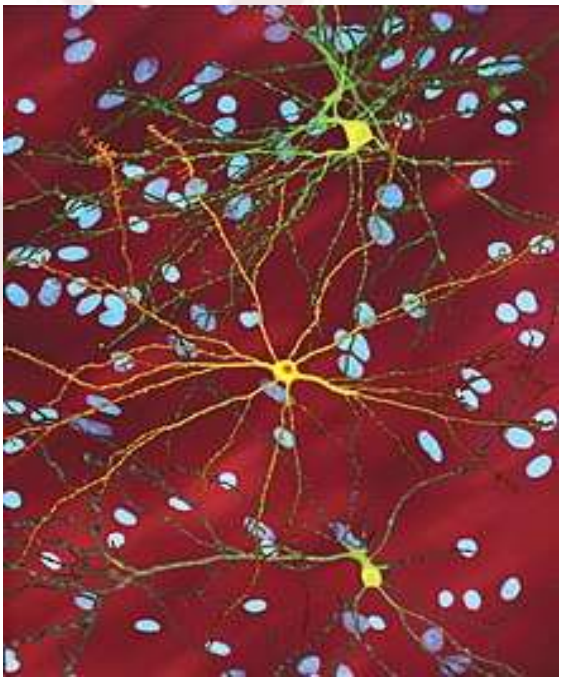
Over time, the aggregates accumulate to form inclusion bodies within cells, ultimately interfering with neuronal function. Inclusion bodies have been found in both the cell nucleus and the cytoplasm. They are one of the earliest pathological changes in brain cells. Some experiments have found that they can be toxic for the cell, but other experiments have shown that they may form as part of the body's defense mechanism and help protect cells. Figure 6 shows a microscope image of a neuron with an inclusion body caused by HD.

Several pathways by which mHtt may cause cell death have been identified. These include:

• Effects on chaperone proteins: They help fold proteins and remove misfolded ones;
• Interactions with caspases: They play a role in the process of removing cells;
• Toxic effects of glutamine on nerve cells;
• Impairment of energy production within cells; and
• Effects on the expression of genes.

Mutant huntingtin protein has been found to play a key role in mitochondrial dysfunction.The impairment of mitochondrial electron transport can result in higher levels of oxidative stress (OS) and release of reactive oxygen species (ROS).

Glutamine is known to be excitotoxic when present in large amounts and can cause damage to numerous cellular structures. Excessive glutamine is not found in HD, but the interactions of the altered huntingtin protein with numerous proteins in neurons lead to an increased vulnerability to glutamine. The increased vulnerability is thought to result in excitotoxic effects from normal glutamine levels.



Inclusion body in orange Image width 250 µm

Figure 6: Microscope image of a neuron with an inclusion body caused by HD

Macroscopic changes

Initially, damage to the brain is regionally specific with the dorsal striatum in the subcortical basal ganglia being primarily affected, followed later by cortical involvement in all areas. Other areas of the basal ganglia affected include:

• The substantia nigra;
• Cortical involvement: It includes cortical layers 3, 5, and 6;
• Involvement of the hippocampus;
• Purkinje cells in the cerebellum; and
• Hypothalamus and parts of the thalamus: The lateral tuberal nuclei.

These areas are affected according to their structure and the types of neurons they contain, reducing in size as they lose cells.

Striatal medium spiny neurons are the most vulnerable, particularly the ones with projections towards the external globus pallidus, with inter-neurons and spiny cells projecting to the internal globus pallidus being less affected.

HD also causes an abnormal increase in astrocytes and activation of the brain's immune cells – the microglia.

The basal ganglia play a key role in movement and behavior control. Their functions are not fully understood, but theories propose that they are part of the cognitive executive system and the motor circuit. The basal ganglia ordinarily inhibit a large number of circuits that generate specific movements.

To initiate a particular movement, the cerebral cortex sends a signal to the basal ganglia that causes the inhibition to be released. Damage to the basal ganglia can cause the release or reinstatement of the inhibitions to be erratic and uncontrolled, which results in an awkward start to the motion(s) to be unintentionally initiated or in a motion to be halted before or beyond its intended completion. The accumulating damage to this area causes the characteristic erratic movements associated with HD known as chorea, a dyskinesia. Because of the basal ganglia's inability to inhibit movements, individuals affected by it inevitably experience a reduced ability to produce speech and swallow foods and liquids (dysphagia).

Transcriptional dysregulation

CREB-binding protein (CBP), a transcriptional co-regulator, is essential for cell function because, as a co-activator at a significant number of promoters, it activates the transcription of genes for survival pathways. It contains an acetyltransferase domain (ATD) to which HTT binds through its polyglutamine-containing domain.

Autopsied brains of those who had HD also have been found to have incredibly reduced amounts of CBP. In addition, when CBP is over-expressed, polyglutamine-induced death is diminished, further demonstrating that CBP plays an important role in HD and neurons in general.

Conclusions

- Every child of a parent with Huntington's disease (HD) has a 50/50 chance of inheriting the expanded gene that causes the disease. The symptoms vary widely between people. Even people in the same family may be affected differently.
- Signs and symptoms of HD most commonly become noticeable between the ages of 30 and 50 years, but they can begin at any age and present as a triad of motor, cognitive, and psychiatric symptoms. When developed in an early stage, it is known as juvenile Huntington's disease (JHD).

- Motor symptoms (chorea) are the most obvious changes patients display. They affect some people more than others. These movement disorders are collectively called chorea.
- Cognitive symptoms often cause trouble with cognitive skills. Cognitive abilities are progressively impaired and tend to generally decline into dementia.
- Psychiatric symptoms are the most difficult for the person and for family members. The person may feel and behave differently, which can cause them to become more frustrated, irritable or angry. The most common mental health condition associated with HD is depression, which appears to occur because of damage to the brain and changes in brain function.
- JHD symptoms include behavioral changes and physical changes. They generally progress at a faster rate with greater cognitive decline, and chorea is exhibited briefly, if at all. The Westphal variant of slowness of movement, rigidity, and tremors is more typical in juvenile HD, as are seizures.
- There are three stages of HD: Early, middle, and later stages.
- The scope of the disease and its worldwide prevalence have been summarized.
- HD is caused by a difference in a single gene that is passed down from a parent. It follows an autosomal dominant inheritance.
- Researchers generally agree that the basic HD lesion is located in the basal ganglia. Helpful revolutionary advances have taken place in molecular genetics and neuroscience; new technologies of gene mapping; identification of the aberrant gene; and sequencing of pathological changes in the brain.
- While HD affects the whole brain, the striatum is that part of the brain that is most affected and plays a key role in movement, mood, and behavior control.
- Everyone has two copies of the Huntington gene (HTT, also called IT15), which codes for the huntingtin protein (Htt) - an important protein, which is needed by nerve cells in the brain (neurons) and for the body′s development before birth.
- Part of the Hungtinton gene is a repeated section called a trinucleotide repeat expansion – a short repeat, which varies in length between individuals, and may change length between generations.
- The code for the Huntington gene contains three of the DNA chemicals CAG (C: Cystosine; A: Adenine; G: Guanine), which are repeated over and over again in a particular sequence. If the repeat is present in a healthy gene, a dynamic mutation may increase the repeat count and result in a defective gene. When the length of this repeated section reaches a certain threshold, it produces an altered form of the protein, called mutant huntingtin protein (mHtt).
- The differing functions of the proteins (Htt and mHtt) are the cause of pathological changes, which in turn cause the disease symptoms. The HD mutation is genetically dominant and almost fully penetrant.
- The mutation of either of a person's HTT alleles causes the disease. It is not inherited according to sex, but by the length of the repeated section of the gene. However, its severity can be influenced by the sex of the affected parent.
- When the Huntington gene is faulty, the huntingtin protein it produces repeats certain genetic sequences known as CAG (cytosine-adenine-guanine) too many times. This in turn appears to damage neurons in certain areas of the brain - although how and why this happens

is not yet fully understood.

- The trinucleic repeats and the resulting disease status, including the disease classification and the associated risk to offspring have ben tabulated.
- Mutant huntingtin is expressed throughout the body and associated with abnormalities in peripheral tissues that are directly caused by such expression outside the brain.
- HD has autosomal dominant inheritance in which the changed gene is the dominant gene. It is located on one of the non-sex chromosomes (autosomes).
- The Huntingtin protein interacts with over 100 other proteins, and appears to have multiple functions. The behavior of its mutated form is not completely understood, but it is toxic to certain cell types, particularly brain cells. Early damage is most evident in the subcortical basal ganglia, initially in the striatum. As the disease progresses, other areas of the brain are also affected, including regions of the cerebral cortex.
- HD is thought not to be caused by inadequate production of the huntingtin protein, but by a toxic gain-of-function of it in the body.
- Over time, aggregates accumulate to form inclusion bodies within cells, ultimately interfering with neuronal function. These inclusion bodies have been found in both the cell nucleus and the cytoplasm. In the case of brain cells, they are one of the earliest pathological changes.
- Several pathways by which the mutated huntingtin protein may cause cell death have been identified, including: Effects on chaperone proteins, interactions with caspases, toxic effects of glutamine on nerve cells, impairment of energy production within cells, and effects on the expression of genes.
- Mutant huntingtin protein has also been found to play a key role in mitochondrial dysfunction. It can result in higher levels of oxidative stress and release of reactive oxygen species.

Sidebar - The scope of HD

HD affects both sexes and all races and ethnic groups around the world. The devastating effects of the disease touch many more. Within a family, multiple generations may have inherited the disease. Those at-risk may experience tremendous stress from the uncertainty and sense of responsibility. In the community, lack of knowledge about HD may keep friends and neighbors from offering social and emotional support to the family, fostering unnecessary isolation. The Huntington's Disease Society of America (HDSA) has a nationwide network that provides support and referrals for individuals with HD and their families.

Prevalence

The HD's average prevalence across the world is summarized in Table 2. The worldwide prevalence varies greatly geographically as a result of ethnicity, local migration, and past immigration patterns. Prevalence is similar for men and women. The rate of occurrence is highest in peoples of Western European descent and lower for people of Asian and African descent. Additionally, some localized areas have a much higher prevalence than their regional average. One of the highest incidences is in the isolated populations of the Lake Maracaibo region of Venezuela, Other areas of high localization have been found in Tasmania and specific regions of Scotland, Wales and Sweden. Increased prevalence in some cases occurs due to a local "founder effect", a historical migration of carriers into an area of geographic isolation. Some of these carriers have been traced back hundreds of years using genealogical studies. Genetic haplotypes can also give clues for the geographic variations of prevalence. Iceland, on the contrary, has a rather low prevalence

despite the fact that Icelanders as a people are Scandinavia, which also gave rise to the Swedes; all cases with the exception of one going back nearly two centuries having derived from the offspring of a couple living early in the 19th century. Finland, as well, has a low incidence.

Until the discovery of a genetic test, statistics could only include clinical diagnosis based on physical symptoms and a family history of HD, excluding those who died of other causes before diagnosis. These cases can now be included in statistics and, as the test becomes more widely available, estimates of the prevalence and incidence of the disorder are likely to increase.

descended from the early Germanic tribes of

Region/Country	Average prevalence per 100,000
Worldwide	5-10
People of Western European descent	7
People of Asian and African descent	0.1
U.S.A.	12.0
U.K. (1990-2010)	12.3
Venezuela, Lac Maracaibo	700
Iceland	1
Finland	2.2

Table 2: Average worldwide prevalence of HD cases

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