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# HUNTINGTON`S DISEASE

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## ABSTRACT

Huntington disease (HD) is a rare neurodegenerative disorder in the central nervous system characterized by the behavioral and psychiatric disturbances and dementia. The diagnoses include other causes of chorea including general iatrogenic disorders. The progression of the disease leads to a complete dependency in daily life, which results in patients requiring fulltime care, and finally death. The most common cause of death is pneumonia, followed by suicide. Typically, onset of symptoms is in middle age after affected individuals have had children, but the disorder can manifest at any time between infancy and senescence. The mutant protein in Huntington's disease having an expanded CAG repeat leading to a polyglutamine strand of variable length at the N-terminus. Evidence suggests that this tail confers a toxic gain of function. The precise pathophysiological mechanisms of Huntington's disease are poorly understood, but research in transgenic animal models of the disorder is providing insight into causative factors and potential treatments.

## INTRODUCTION

In 1872, the American physician George Huntington wrote about an illness that he called "an heirloom from generation's away back in the dim past." He was not the first to describe the disorder, which has been traced back to the middle Ages at least. One of its earliest names was chorea, which, as in "choreography," is the Greek word for dance. The term chorea describes how people affected with the disorder writhe, twist, and turn in a constant, uncontrollable dance-like motion. Later, other descriptive names evolved. "Hereditary chorea" emphasizes how the disease is passed from parent to child. "Chronic progressive chorea" stresses how symptoms of the disease worsen over time. Today, physicians commonly use the simple term Huntington's disease (HD) to describe this highly complex disorder that causes untold suffering for thousands of families. Until recently, scientists understood very little about Huntington's disease and could only watch as the disease continued to pass from generation to generation. Families saw the disease destroy their loved ones' ability to feel, think, and move. In the last several years, scientists working with support from the National Institute of Neurological Disorders and Stroke have made several breakthroughs in the area of Huntington's disease research. With these advances, our understanding of the disease continues to improve[1].

**Definition:** Huntington's disease, chorea, or disorder (HD), is a progressive neurodegenerative genetic disorder, which affects muscle coordination and leads to cognitive decline and dementia. It typically becomes noticeable in middle age. HD is the most common genetic cause of abnormal involuntary writhing movements called chorea and is much more common in people of Western European descent than in those from Asia or Africa. The disease is caused by an autonomic dominant mutation on either of an individual's two copies of a gene called Huntington, which means any child of an affected parent has a 50% risk of inheriting the disease[2].

**Symptoms and major effects of Huntington's disease:** Early signs of the disease vary greatly from person to person. A common observation is that the earlier the symptoms appear, the faster the disease progresses.

Depressive disorders

Progressive loss of mental abilities

Jerking uncontrollable moments

**Depressive disorders:** Family members may first notice that the individual experiences mood swings or becomes uncharacteristically irritable, apathetic, passive, depressed, or

angry. These symptoms may lessen as the disease progresses or, in some individuals, may continue and include hostile outbursts or deep bouts of depression.

**Progressive loss of mental abilities:** Huntington's disease may affect the individual's judgment, memory, and other cognitive functions. Early signs might include having trouble driving, learning new things, remembering a fact, answering a question, or making a decision. Some may even display changes in handwriting. As the disease progresses, concentration on intellectual tasks becomes increasingly difficult.

**Jerking uncontrollable moments:** In some individuals, the disease may begin with uncontrolled movements in the fingers, feet, face, or trunk. These movements which are signs of chorea often intensify when the person is anxious. Huntington's disease can also begin with mild clumsiness or problems with balance. Some people develop choreic movements later, after the disease has progressed. They may stumble or appear uncoordinated. Chorea often creates serious problems with walking, increasing the likelihood of falls. The disease can reach the point where speech is slurred and vital functions, such as swallowing, eating, speaking, and especially walking, continue to decline. Some individuals cannot recognize other family members. Many, however, remain aware of their environment and are able to express emotions. Some physicians have employed a recently developed Unified Huntington's Disease Rating Scale, or UHDRS, to assess the clinical features, stages, and course of Huntington's disease. In general, the duration of the illness ranges from 10 to 30 years. The most common causes of death are infection, injuries related to a fall, or other complications[3].

**Causes:** Huntington's disease results from genetically programmed degeneration of nerve cells, called neurons, in certain areas of the brain. This degeneration causes uncontrolled movements, loss of intellectual faculties, and emotional disturbance. Specifically affected are cells of the basal ganglia, structures deep within the brain that have many important functions, including coordinating movement. Within the basal ganglia, Huntington's disease especially targets neurons of the striatum, particularly those in the caudate nuclei and the pallidum. Also affected is the brain's outer surface, or cortex, which controls thought, perception, and memory[4].

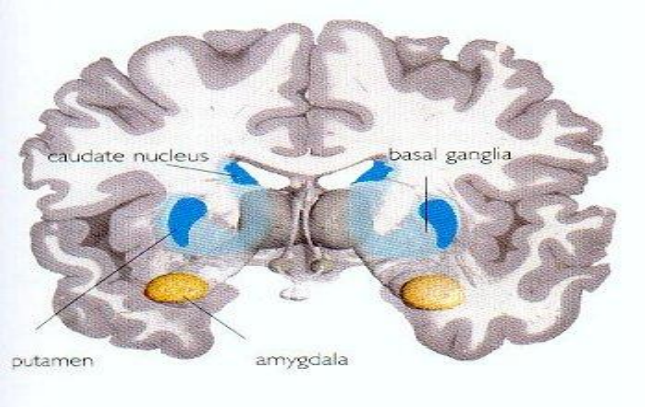


**Figure No: 1 Huntington's disease for genetically programmed degeneration of nerve cells.**

**Huntington's disease inherited:** Huntington's is a familial disease, passed from parent to child through a mutation or misspelling in the normal gene. A single abnormal gene, the basic biological unit of heredity, produces Huntington's disease. Genes are composed of deoxyribonucleic acid (DNA), a molecule shaped like a spiral ladder. Each rung of this ladder is composed of two paired chemicals called bases. There are four types of bases adenine, thymine, cytosine, and guanine each abbreviated by the first letter of its name: A, T, C, and G. Certain bases always "pair" together, and different combinations of base pairs join to form coded messages. These unique combinations determine the gene's function, much like letters join together to form words. Each person has about 30,000 genes a billion base pairs of DNA or bits of information repeated in the nuclei of human cells which determine individual characteristics or traits[5].

Genes are arranged in precise locations along 23 rod-like pairs of chromosomes. One chromosome from each pair comes from an individual's mother, the other from the father. Each half of a chromosome pair is similar to the other, except for one pair, which determines the sex of the individual. This pair has two X chromosomes in females and one X and one Y chromosome in males. The gene that produces Huntington's disease lies on chromosome 4, one of the 22 non-sex-linked, or "autosomal," pairs of chromosomes, placing men and women at equal risk of acquiring the disease.

Each parent has two copies of every chromosome but gives only one copy to each child. Each child of a Huntington's disease parent has a 50-50 chance of inheriting the Huntington's disease gene. If a child does not inherit the Huntington's disease gene, he or she will not develop the disease and cannot pass it to subsequent generations. A person who inherits the Huntington's disease gene, and survives long enough, will sooner or later develop the disease. In some families, all the children may inherit the Huntington's disease gene; in others, none

do. Whether one child inherits the gene has no bearing on whether others will or will not share the same fate. A small number of cases of Huntington's disease are sporadic, that is, they occur even though there is no family history of the disorder. These cases are thought to be caused by a new genetic mutation-an alteration in the gene that occurs during sperm development and that brings the number of CAG repeats into the range that causes disease[6].

**Huntington's disease appears at different ages:**

**In case of adults:** The rate of disease progression and the age at onset vary from person to person. Adult-onset Huntington's disease, with its disabling, uncontrolled movements, most often begins in middle age. There are, however, other variations of Huntington's disease distinguished not just by age at onset but by a distinct array of symptoms. For example, some persons develop the disease as adults, but without chorea.

**In case of Younger's (Before age 20 years):** Some individuals develop symptoms of Huntington's disease when they are very young before age 20. The terms "early-onset" or "juvenile" Huntington's disease are often used to describe Huntington's disease that appears in a young person. A common sign of Huntington's disease in a younger individual is a rapid decline in school performance. Symptoms can also include subtle changes in handwriting and slight problems with movement, such as slowness, rigidity, tremor, and rapid muscular twitching, called myoclonus. Several of these symptoms are similar to those seen in Parkinson's disease. People with juvenile Huntington's disease may also have seizures and mental disabilities. Individuals with juvenile Huntington's disease usually inherit the disease from their fathers. These individuals also tend to have the largest number of CAG repeats. The reason for this may be found in the process of sperm production. Unlike eggs, sperm are produced in the millions. Because DNA is copied millions of times during this process, there is an increased possibility for genetic mistakes to occur. To verify the link between the number of CAG repeats in the Huntington's disease gene and the age at onset of symptoms, scientists studied a boy who developed Huntington's disease symptoms at the age of two, one of the youngest and most severe cases ever recorded. They found that he had the largest number of CAG repeats of anyone studied so far nearly 100. The boy's case was central to the identification of the Huntington's disease gene and at the same time helped confirm that juveniles with Huntington's disease have the longest segments of CAG repeats, the only proven correlation between repeat length and age at onset[7].

**Mechanism of Huntington's disease:**

**The Huntington's disease mutation:** HD is caused by a mutation in the IT15 gene on the short arm of chromosome. This gene, which was subsequently renamed HD, consists of 67 exons that encode Htt, a 350-kD protein of 3,144 amino acids. The mutation is an expansion of the cytosine adenine guanine (CAG) tri nucleotide, which codes for a polyglutamine moiety in the Htt protein. Normal individuals have CAG repeat lengths of 7–34. The CAG repeat is expanded and unstable in HD patients, with repeat length inversely correlating with age of disease onset. Repeat lengths of more than 40 glutamines produce HD, and repeats of over 70 glutamines invariably cause juvenile onset[8].

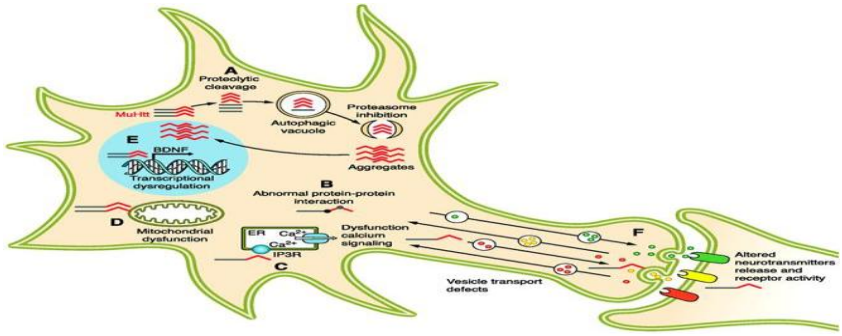


**Figure: 2 Mechanism of Huntington's disease:**

**Pathophysiology:**

HD is associated with progressive degeneration of neurons in certain regions of the brain and the presence of astrocytes that accumulate due to destruction of nearby neurons (gliosis). These neurodegenerative changes primarily occur within the caudate nuclei and the putamen, substructures of the basal ganglia that are collectively known as the striatum. HD is also characterized by associated neuronal degeneration within the temporal and frontal lobes of the cerebral cortex. This part of the brain is responsible for integrating higher mental functioning, movements, and sensations[9].

The degenerative changes in HD primarily affect certain nerve cells of the striatum known as medium-sized "spiny" neurons, which are named for their size and appearance and project into the globus pallidus and substantia nigra. These highly specialized "spiny" neurons secrete gamma-aminobutyric acid (GABA), a neurotransmitter that inhibits the release of neurotransmitters from other nerve cells. One theory suggests that selective loss of these specialized cells results in decreased inhibition (i.e., increased activity) of the thalamus. Therefore the thalamus increases its output to certain regions of the brain's cerebral cortex. This may lead to the disorganized, excessive (hyperkinetic) movement patterns of chorea[10].

In patients with HD, positron emission tomography (PET) scanning has shown decreased glucose and oxygen metabolism within the caudate nuclei early in the course of the disease. These findings occur in patients with other neurodegenerative diseases associated with chorea. This lends support to the theory that disturbances in the metabolism of certain neurotransmitters and heightened sensitivity of particular neuroreceptors may contribute to the symptoms associated with HD[11].

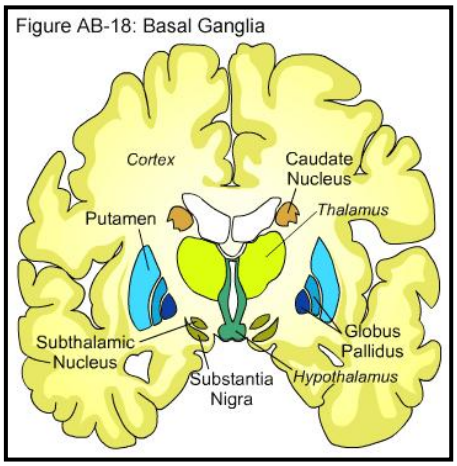


**Figure No. 3 Structure of Basal Ganglia**

**Mutant Huntington Protein and Intracellular Abnormalities**

The basic underlying defect in HD remains unclear. However, the disease processes associated with HD are thought to be caused by a toxic "gain of function," meaning that the mutated gene's protein (mutant Huntington) interferes with normal cellular functioning. For example, evidence suggests that abnormal Huntington may induce inappropriate, genetically programmed nerve cell death (apoptosis). In addition, investigators have demonstrated that caspase-1, an enzyme involved in controlling cellular death, is activated in the brain in patients with HD and a transgenic mouse model of the disease. Injection of a caspase inhibitor into the brains of transgenic mice was associated with delayed disease progression and prolonged life. In mice with genetically programmed reductions in caspase-1 activity, there were delays in nerve cell damage and in symptom onset, with extended survival. Such findings suggest the role caspase-1 may play in HD disease progression—and that blocking the action of caspase-1 may have implications for human disease[12].

**Diagnosis:** Medical diagnosis of the onset of HD can be made following the appearance of physical symptoms specific to the disease. Genetic testing can be used to confirm a physical diagnosis if there is no family history of HD. Even before the onset of symptoms, genetic testing can confirm if an individual or embryo carries an expanded copy of the trinucleotide

repeat in the HTT gene that causes the disease. Genetic counselling is available to provide advice and guidance throughout the testing procedure, and on the implications of a confirmed diagnosis. These implications include the impact on an individual's psychology, career, family planning decisions, relatives and relationships[13].

**Clinical:** Coronal section from a MR brain scan of a patient with HD showing atrophy of the heads of the caudate nuclei, enlargement of the frontal horns of the lateral ventricles, and generalised cortical atrophy. A physical examination, sometimes combined with a psychological examination, can determine whether the onset of the disease has begun. Excessive unintentional movements of any part of the body are often the reason for seeking medical consultation. If these are abrupt and have random timing and distribution, they suggest a diagnosis of HD. Cognitive or psychiatric symptoms are rarely the first diagnosed; they are usually only recognized in hindsight or when they develop further. How far the disease has progressed can be measured using the unified Huntington's disease rating scale which provides an overall rating system based on motor, behavioural, cognitive, and functional assessments. Medical imaging, such as computerized tomography (CT) and magnetic resonance imaging (MRI), only shows visible cerebral atrophy in the advanced stages of the disease. Functional neuroimaging techniques such as fMRI and PET can show changes in brain activity before the onset of physical symptoms[14].

**Treatments for Huntington's disease:**

**Medication:**

- Antipsychotics (hallucinations, delusions, violent outbursts): Haloperidol, chlorpromazine, olanzapine (contraindicated if patient has dystonia)
- Antidepressants (depression, obsessive-compulsive behavior): fluoxetine, sertraline hydrochloride, nortriptyline
- Tranquilizers (anxiety, chorea): benzodiazepines, paroxetine, venlafaxin, beta-blockers
- Mood-stabilizers (mania, bipolar disorder): lithium, valproate, carbamazepine
- Botulinum toxin (dystonia, jaw clenching)

**Prognosis:** The bedridden patient in the final stages of Huntington's disease often dies from complications such as heart failure or pneumonia. Juvenile Huntington's disease (16%) runs it course comparatively fast, with death typically occurring in about 10 years[15].

**Prevention of Huntington's disease:**

1. Understand that it is impossible to prevent Huntington's disease. The disease is an inherited neurological disease which, in all known cases, stems from an abnormal gene on either the male or female side.

2. Recognize the signs and symptoms of Huntington's disease. Since prevention of Huntington's disease is impossible, recognizing the various symptoms of the disease is the best method for easing progression. According to the Mayo Clinic, symptoms include: Dementia, balance issues, slurred speech, involuntary movement, and swallowing problems.

3. Understand that Huntington's disease is inherited. Come to terms with the fact that you did not cause yourself to get Huntington's disease, but rather inherited it from an abnormal gene in your mother or father's DNA. Learn as much as you can about the disease and then learn to adapt your lifestyle accordingly.

4. Learn the risk factors for Huntington's disease. According to the Mayo Clinic, "If one of your parents has Huntington's disease, you have a 50 percent chance of developing the disease." However, it is possible to develop Huntington's disease without a prior family history of the disorder.

5. Seek a formal diagnosis from a medical professional and begin treatment for the symptoms of Huntington's disease, if necessary. Medication will, often, decrease the severity of symptoms attached to Huntington's disease, but, according to the Mayo Clinic, the average lifespan after diagnosis is 10-30 years[16].

**CONCLUSION**

The Managing of many facets of Huntington's disease can be challenging and is the best served within multidisciplinary settings of the health. Huntington's disease could entail starting treatment in the asymptomatic phase of the disorder. In several observational studies of risk individuals, the feasibility of using the onset of the clinical. Within adequate funding for continued research, the discovery of meaningful treatment seems imminent. In parallel with the rational pathway to find solutions to treat this disorder, attention is being paid to finding the best care for all patients and at risk persons at this point in time.

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