

Huntington's Disease



National Institute of Neurological Disorders
and Stroke
National Institutes of Health

Hope Through Research

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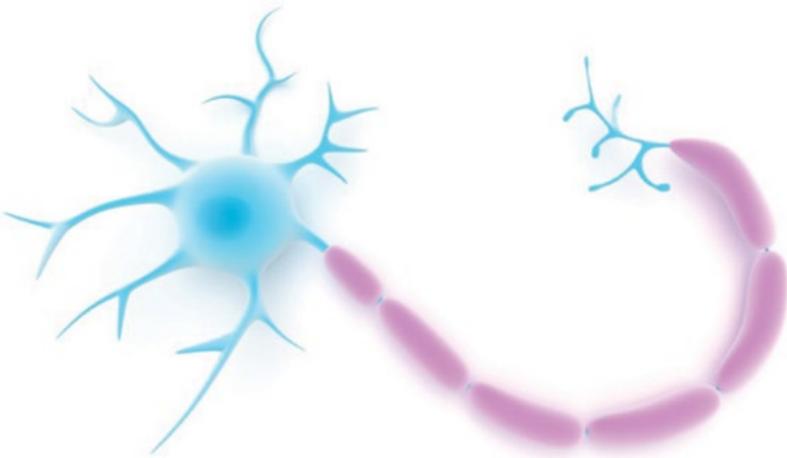
What is Huntington's disease?

Huntington's disease (HD) is an inherited disorder that causes nerve cells (called neurons) in parts of the brain to gradually break down and die. The disease, which gets worse over time, attacks motor control regions of the brain (those involved with movement), as well as other areas. People with HD develop problems with behavior, emotion, thinking, and personality, along with uncontrollable dance-like movements (called chorea) and abnormal body postures.

The gene mutation that causes HD is present from birth. Symptoms of HD typically appear in middle age (adult HD), and in rare cases they appear in children (juvenile HD).

The duration of the illness generally ranges from 10 to 30 years. HD is not fatal. The most common causes of death are infection (most often pneumonia) and injuries related to falls.

There is no cure for HD, but treatments are available to help manage its symptoms.



Huntington's disease causes nerve cells in parts of the brain to break down and die.

What are the major effects of the disease?

Early signs of the disease vary greatly from person to person, but typically include cognitive or psychiatric symptoms, difficulties with movement, and behavioral changes. Symptoms of Huntington's disease include:

Behavioral changes such as mood swings, irritability, apathy, inactivity, depression, or anger. These symptoms may lessen as the disease progresses or, in some individuals, may continue and include hostile outbursts, thoughts of suicide, deep bouts of depression, and psychosis. People with HD also may avoid social interaction.

Cognitive/judgment changes may include issues with judgment, attention, other cognitive functions, problem-solving, or decision making. Other affects may include trouble with driving, prioritizing tasks, and difficulty organizing, learning new things, remembering a fact, putting thoughts into words, or answering a question.

These cognitive problems worsen as the disease progresses and affected individuals are no longer able to work, drive, or care for themselves. When the level of cognitive impairment is significant enough to impair daily functioning, it is described as dementia. Many people with HD, however, remain aware of their environment and can express emotions.

Uncontrolled and difficult movement in the fingers, feet, face, or torso. These movements, which are signs of chorea, often intensify when the person is anxious or distracted and become more pronounced and apparent over time. HD can also begin with mild clumsiness or problems with balance.



As the disease progresses, individuals are no longer able to care for themselves.

Some people develop chorea-related movements such as problems walking, increasing the likelihood of falls. Some individuals with HD do not develop chorea; instead, they may become rigid and move very little, or not at all, a condition called akinesia. Others may start out with chorea but become rigid as the disease progresses. In addition to chorea, some individuals have unusual fixed postures, called dystonia. The two movement disorders can blend or alternate. Other symptoms may include tremor (unintentional rhythmic muscle movement in a back-and-forth manner) and abnormal eye movements that often occur early.

Physical changes may include slurred speech and continued decline in vital functions, such as swallowing, eating, speaking, and especially walking. Weight loss may occur due to problems with feeding, swallowing, choking, and chest infections. Other symptoms may include insomnia, loss of energy, fatigue, and seizures. Eventually the person will be confined to a bed or wheelchair.

How is HD inherited?

HD is passed from parent to child through a mutation in a gene. The gene responsible for HD lies on chromosome 4. (A chromosome contains all or part of the genetic material that makes up a person or organism.)

When a parent has HD, each child has a 50 percent chance of inheriting the copy of chromosome 4 that carries the HD mutation. If a child does not inherit the HD mutation, he or she will not develop the disease and cannot pass it to subsequent generations.

People with HD have an abnormal, repetitive, greatly expanded three-letter code (or triplet) in the DNA sequence that is found in genes. DNA uses a triplet to prescribe the order and identity of amino acids—a protein's building blocks. This three-base repeat—called a triplet repeat expansion—causes dozens of other neurological diseases, but in HD the triplet involves the excessive repeat of cytosine, adenine, and guanine (called CAG).

Most people have fewer than 27 CAG repeats in the HD gene and are not at risk for the disease. Individuals with the disease may have 36 or more repeats. People who have repeats in the intermediate range (27-35) are unlikely to develop the disease, but they could pass it on to future generations.

When HD occurs without a family history, it is called sporadic HD.

Number of CAG repeats	Outcome
< 26	Normal range; individual will not develop HD
27-35	Individual will not develop HD but the next generation is at risk
35-39	Some, but not all, individuals in this range will develop HD; next generation is also at risk
> 40	Individual will develop HD

At what age does HD appear?

The rate of disease progression and the age at onset vary from person to person. Having a higher number of CAG repeats is associated with an earlier onset and faster course of the disease. Generally, the earlier the symptoms appear, the faster the disease progresses.

Adult HD

Adult-onset HD most often begins between ages 30-50. A few individuals develop HD after age 55.

There is also a related disorder called **senile chorea**. Some elderly individuals develop the unintended, uncontrolled movements, but do not develop dementia, have a normal HD gene, and lack a family history of the disorder.

Juvenile HD

Some individuals develop symptoms of HD before age 20. This is called early-onset or juvenile HD. Symptoms of people with juvenile HD may include:

- a rapid decline in school performance
- myoclonus (rapid involuntary muscle twitches or jerks)
- slowness
- rigidity (in which the muscles remain constantly tense)
- tremor
- seizures
- cognitive disabilities

The disease progresses most rapidly in individuals with juvenile or early-onset HD, and death often follows within 10 years.

Individuals with juvenile HD usually inherit the disease from their fathers, who typically have a later onset form of HD.

How is HD diagnosed?

A diagnosis of HD is generally based on findings from neurological, psychological, and genetic testing.

Neurological exam and patient history. A neurologist will conduct an in-depth interview to obtain the medical history (including any family history, called a pedigree or genealogy) to rule out other conditions. Neurological and physical exams may review reflexes, balance, movement, muscle tone, hearing, walking, and mental status. Laboratory tests may also be ordered, and individuals with HD may be referred to specialists such as psychiatrists, genetic counselors, clinical neuropsychologists, or speech pathologists for specialized management and/or diagnostic clarification.

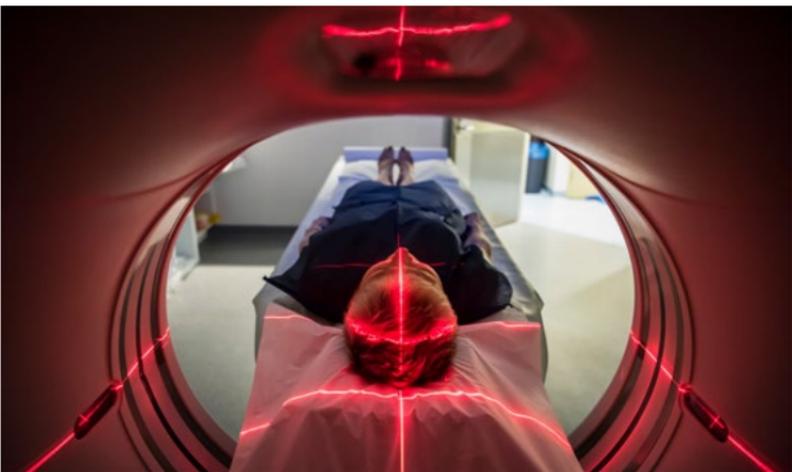
Diagnostic imaging. In some cases, especially if a person's family history and genetic testing are inconclusive, the physician may recommend brain imaging, such as computed tomography (CT) or, more likely, magnetic resonance imaging (MRI). As the disease progresses, these scans typically reveal shrinkage in parts of the brain and enlargement of fluid-filled cavities within the brain called ventricles. These changes do not necessarily indicate HD, because they can occur in other disorders. A person can have early symptoms of HD and still have normal findings on a structural CT or MRI scan.

Genetic tests. Genetic testing can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder. Genetic testing makes it possible to predict with a higher degree of certainty if someone will develop HD.

- The most effective and accurate method of testing for HD—called the **direct genetic test**—counts the number of CAG repeats in the HD gene, using DNA taken from a blood sample. The presence of 36 or more repeats supports a diagnosis of HD. A test result of 26 or fewer repeats rules out HD.
- An older genetic test, called **linkage testing** (also called prenatal exclusion testing) requires a sample of DNA from a closely related affected relative, preferably a parent, to identify markers close to the HD gene and to determine if a fetus has inherited a chromosome 4 mutation from an affected grandparent. A version of the linkage method is sometimes used for prenatal testing.

Prenatal testing is an option for people who have a family history of HD and are concerned about passing the disease to a child. Prenatal testing can be done using either the direct method or the linkage method. As with adult testing, the direct method provides higher certainty.

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When family history and genetic testing are inconclusive, brain imaging like CT or MRI may be used to help diagnose HD.

What treatments are available for HD?

Medications may be prescribed to help control emotional and movement problems associated with HD. It is important to remember however, that while medicines may help keep these clinical symptoms under control, there is no treatment to stop or reverse the course of the disease.

Most of the medications available for HD symptoms work by modulating neurotransmitters—the chemical messages that shuttle between neurons.

Tetrabenazine, which causes depletion of the neurotransmitter dopamine, is prescribed for treating Huntington's-associated involuntary movements, as is deutetrabenazine.

Antipsychotic drugs, such as risperidone, olanzapine, or haloperidol, or other drugs such as clonazepam, may help to lessen chorea and may also be used to help control hallucinations, delusions, and violent outbursts. Antipsychotic drugs, however, typically do not help with the muscle contractions associated with involuntary muscle contractions and may in fact worsen the condition, causing stiffness and rigidity.

For depression, physicians may prescribe citalopram, fluoxetine, sertraline, nortriptyline, or other compounds. Tranquilizers can help control anxiety and lithium may be prescribed to combat pathological excitement and severe mood swings.

Drugs used to treat the symptoms of HD may have side effects such as fatigue, sedation, decreased concentration, restlessness, or hyperexcitability, and should be only used when symptoms create problems for the individual. For those on medication, it may be difficult to tell if a particular symptom, such as apathy or memory loss, is a sign of the disease or a drug reaction.

What research is being done?

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. NINDS is a component of the National Institutes of Health (NIH), the leading supporter of biomedical research in the world. NINDS-funded research has played a key role in our understanding of HD—helping to localize the HD-causing gene to chromosome 4 and identifying the mutation that causes HD.

HD strikes individuals at different ages and it is hard to predict the age of disease onset. Researchers are focusing on discovering and studying factors that hasten or delay the disease onset, which would provide clues for strategies to slow or stop progression of the disease before symptoms even begin.

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Understanding Huntington's disease mechanisms

NINDS-funded researchers are trying to better understand the cellular and molecular mechanisms involved in the neurodegenerative processes of HD by investigating, for instance, how the mutant Huntingtin protein affects cell signaling and how its altered structure can contribute to disease. Among research efforts:

- A new avenue of NINDS-supported research is asking whether additional changes to the mutant Huntington gene during development and in adulthood impact disease onset and severity, and whether the mutant Huntington gene affects the brain's overall ability to maintain healthy, undamaged DNA.

This work is a promising area for identifying new modifiers of HD onset and progression that may be attractive drug targets.

- Excessive chemical signaling between cells in the brain may lead to chronic overexcitation (overactivation of neurons to turn on), which is toxic to neurons. Several labs are investigating whether drugs that counteract excitotoxicity might help against HD.
- Cutting-edge methods such as optogenetics (where neurons are activated or silenced in the brains of living animals using light beams) are being used to probe the cause and progression of cell circuit defects in HD.

Biomarkers

The NINDS-funded PREDICT-HD study and several international studies seek to identify and validate biomarkers for HD. Biomarkers are biological changes that can be used to predict, diagnose, or monitor a disease. One goal of PREDICT-HD is to determine if the progression of the disease correlates with changes in brain scan images, or with chemical changes in blood, urine, or cerebrospinal fluid. Another goal is to find measurable changes in personality, mood, and cognition that typically precede the appearance of motor symptoms of HD. A third phase of PredictHD is ongoing.

A related NINDS-supported study aims to identify additional human genetic factors that influence the course of the disease. Finding genetic variants that slow or accelerate the pace of disease progression promise to provide important new targets for disease intervention and therapy.



One goal of the PREDICT-HD study is to discover biomarkers that precede the appearance of HD motor symptoms.

Stem cells

Scientists can take adult blood or skin cells and return them to a pluripotent state (called iPS, cells), where they can become most cells of the body.

Through a NINDS-funded consortium, researchers are using cultures of these cell lines (created from people with HD who have donated skin and blood samples for research) to understand why neurons malfunction and die in HD, and to rapidly test potential new drugs. Another approach may be to mobilize stem cells that are already there and can move into damaged tissue

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Turning research into treatment

Testing investigational drugs may lead to new treatments and at the same time improve our understanding of the disease process in HD. Classes of drugs being tested include those that control symptoms, slow the rate of progression of HD, block the effects of excitotoxins, provide support factors that improve neuronal health, or suppress metabolic defects that contribute to the development and progression of HD.



Some scientists are using gene-editing to reduce or eliminate Htt production.

Several groups of scientists are using gene-editing or specific molecules that can interfere with the production of Htt in cells or animals to reduce or eliminate the production of Htt.

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Imaging

Scientists are using imaging technology to learn how HD affects the chemical systems of the brain, characterize neurons that have died, view changes in the volume and structures of the brain in people with HD, and to understand how HD affects the functioning of different brain regions.

Brain Development

Altered brain development may play an important role in HD. Huntingtin is expressed during embryonic development and throughout life. Studies in animals have shown that the normal HD gene is vital for brain development. Adults who carry the mutant HD gene but have not yet displayed symptoms show measurable changes in the structure of their brain, even up to 20 years before clinical diagnosis.

A NINDS-funded study is evaluating brain structure and function in children, adolescents, and young adults up to age 30 who are at risk for developing the disease because they have a parent or grandparent with HD. This study hopes to capture potential HD effects during the late stages of brain development. Participants who carry the expanded gene will be compared to individuals who carry the gene but have CAG repeats of 39 or less, as well as to individuals who do not have a history of HD in their family. Changes in brain structure and/or function in the gene-expanded group may point to a developmental component in HD.

Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN

P.O. Box 5801
Bethesda, MD 20824
800-352-9424
<http://www.ninds.nih.gov>

Additional information on Huntington's disease is available by contacting:

Hereditary Disease Foundation

3960 Broadway, 6th Floor
New York, NY 10032
212-928-2121
<http://www.hdfoundation.org>

Huntington's Disease Society of America

505 Eighth Avenue, Suite 902

New York, NY 10018

212-242-1968; 800-345-4372

<http://hdsa.org>

National Library of Medicine

Genetics Home Reference

National Institutes of Health

8600 Rockville Pike

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