

Huntington's Disease

A microscopic image of neurons. The central neuron is highlighted in a bright orange color, while the surrounding neurons are in shades of blue and cyan. The neurons have a textured, almost crystalline appearance.

Hope Through Research

National Institute of Neurological Disorders
and Stroke
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What is Huntington's disease?

Huntington's disease is an inherited disease that causes the progressive dying off, or degeneration, of nerve cells in certain parts of the brain.

American physician George Huntington wrote the first thorough description of Huntington's disease (HD) in 1872, calling it "hereditary chorea" to underscore some of its key features. *Chorea*¹ is derived from the Greek word for dance and describes the uncontrollable dance-like movements seen in people with HD. The hereditary nature of HD helps distinguish it from other types of chorea with infectious, metabolic, or hormonal causes. Understanding the hereditary nature of HD eventually enabled modern researchers to pinpoint the cause of the disease—a *mutation* or misspelling in a single *gene*.

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More than 30,000 Americans have HD. Although the mutation 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 disease, which gets progressively worse, attacks motor control regions of the brain, as well as other areas. Chorea, abnormal body postures, and impaired coordination are among the most visible symptoms. But HD also causes changes in emotion and cognition (thinking) that can be devastating for people with the disorder and for their families.

¹ Words in italics appear in a Glossary found at the end of this document.

Although there is no cure for HD, treatments are available to help manage its symptoms and other potential treatments are under investigation to slow or stop its course. And there are now genetic tests available for HD, which gives people at risk for the disease the option to plan for their health and the health of future generations.

How does HD affect the brain?

The most severe loss of nerve cells (also called *neurons*) occurs in deep brain structures called the *basal ganglia*, especially in a part of the basal ganglia called the *striatum*. The basal ganglia have a variety of functions, including helping to control voluntary (intentional) movement. Subsections of the basal ganglia, called the caudate nuclei and putamen, are most severely affected. Another

strongly affected area is the brain's outer surface, or cerebral cortex, which has important roles in movement, as well as thought, perception, memory, and emotion. As HD progresses over time, neuronal degeneration becomes more widespread throughout the brain. In addition to metabolic changes, there is degeneration in areas of the brain that control hormones.



In HD, the most severe loss of neurons occurs in an area of the brain called the basal ganglia.

How is HD inherited?

HD is passed from parent to child through a mutation in a gene. Genes contain the blueprint for who we are, from our outer appearance to the composition and workings of our internal organs, including the brain. The gene responsible for HD lies on *chromosome 4*.

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. In some families, all the children may inherit the HD 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 person who inherits the HD mutation and survives long enough will develop the disease.

To understand the HD gene mutation, it helps to know a little more about what genes are and what they do. Genes contain the instructions for making the approximately one million proteins that run everything in our bodies. The HD gene makes an essential protein called *huntingtin*, whose function is largely unknown but may be necessary for early nerve cell development. Huntingtin is most active in the brain. Genes are composed of *deoxyribonucleic acid* (DNA), a long chain-like molecule. The links in a DNA chain are called bases, or nucleotides, and there are four varieties—adenine, thymine, cytosine, and guanine—typically abbreviated as A, T, C, and G. Within each gene, a unique combination of these nucleotides serves as a code that determines the gene's function; changes in the

code—such as through a mutation—can change a gene’s function.

The disease-causing mutation inside the HD gene consists of a three-base sequence repeated many times. This type of mutation, called a *triplet (or trinucleotide) repeat expansion*, is responsible for dozens of other neurological diseases, but in each case the three-base sequence, or triplet, resides within a different gene. The triplet sequences also vary; in HD, the triplet consists of the bases C-A-G. 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.

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Genes are composed of a long chain-like molecule called DNA. Within a DNA chain are four types of nucleotides abbreviated as A, T, C, and G.

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
36-39	Some, but not all, individuals in this range will develop HD; next generation is also at risk
> 40	Individual will develop HD

When HD occurs without a family history, it is called **sporadic HD**. These cases can occur when one parent has an intermediate range of CAG repeats, sometimes called a **premutation**. Prior to conception of a child, the number of repeats may expand into the disease-causing range. Most often, these expansions occur in the father's sperm cells, rather than in the mother's egg cells. Each time the father's DNA is copied to make new sperm, there is a possibility for the number of CAG repeats to expand. This increase in disease severity from one generation to the next—with a younger onset and faster progression—is called *anticipation*.

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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.** 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, thoughts of suicide, deep bouts of depression, and, rarely, psychosis. Social withdrawal is common.

- **Cognitive/judgment changes.** HD may affect a person's judgment, attention, and other cognitive functions. Early signs might include having trouble with driving, problem-solving or decision making, prioritizing tasks, and difficulty organizing, learning new things, remembering a fact, putting thoughts into words, or answering a question. Familiar tasks that were simple to complete when healthy now take longer or cannot be done at all. As the disease progresses, these cognitive problems worsen 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, however, remain aware of their environment and are able to express emotions. Some individuals cannot recognize other family members.
- **Uncontrolled and difficult movement.** Movement problems may begin with uncontrolled movement in the fingers, feet, face, or trunk. These movements, which are signs of chorea, often intensify when the person is anxious or distracted and become larger and more apparent over time. HD can also begin with mild clumsiness or problems with balance. Some people develop chorea-related movements. Chorea often creates serious problems with 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.** Speech becomes slurred and vital functions, such as swallowing, eating, speaking, and especially walking, continue to decline. Many people with HD lose weight as they encounter problems with feeding, swallowing, choking, and chest infections. Other symptoms may include insomnia, loss of energy, and fatigue. Some individuals with HD develop seizures. Eventually the person will be confined to a bed or wheelchair.

In general, the duration of the illness ranges from 10 to 30 years. The most common causes of death are infection (most often pneumonia) and injuries related to falls.

At what age does HD appear?

The rate of disease progression and the age at onset vary from person to person. As a general rule, having a higher number of CAG repeats is associated with an earlier onset and faster course of the disease. A common observation is that 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. Diagnosis in these people can be very difficult. The symptoms of HD may be masked by or confused with other health problems, or the person may not display the severity of symptoms seen in individuals with HD of earlier onset. These individuals may also show symptoms of depression rather than anger or irritability, or they may retain sharp control over their intellectual functions, such as memory, reasoning, and problem-solving.

There is also a related disorder called *senile chorea*. Some elderly individuals develop choreic movements, but do not become demented, have a normal HD gene, and lack a family history of the disorder. Some scientists believe that a different gene mutation may account for this small number of cases, but this has not been proven.

Juvenile HD

Some individuals develop symptoms of HD before age 20. This is called early-onset or juvenile HD. A common early sign of juvenile HD is a rapid decline in school performance. Movement problems soon become apparent, but they differ from the chorea typically seen in adult-onset HD. One common

Individuals with juvenile HD develop symptoms such as rapid decline in school performance before age 20.

motor symptom in juvenile HD is myoclonus, which involves rapid involuntary muscle twitches or jerks. Other motor symptoms typical in juvenile HD include slowness, rigidity

(in which the muscles remain constantly tense), and tremor. This constellation of symptoms can resemble Parkinson's disease, and is sometimes called "akinetic-rigid" HD or the Westphal variant of HD. People with juvenile HD may also have seizures and mental disabilities. The earlier the onset, the faster the disease seems to progress. 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 themselves. To verify the link between the number of CAG repeats in the HD gene and the age at onset of symptoms, scientists studied a boy who developed HD symptoms at the age of two, one of the youngest and most severe cases ever recorded. They found that he had nearly 100 repeats. The boy's case was central to the identification of the HD gene and at the same time helped confirm that juveniles with HD have the longest segments of CAG repeats. This correlation has been confirmed in other studies.

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How is HD diagnosed?

A diagnosis of Huntington's disease is generally based on findings from neurological, psychological, and genetic testing.

- **Neurological tests.** A neurologist will interview the individual intensively to obtain the medical history and rule out other conditions. Tests of neurological and physical functions may review

reflexes, balance, movement, muscle tone, hearing, walking, and mental status. A number of laboratory tests may be ordered as well, and individuals with HD may be referred to other health care professionals such as psychiatrists, genetic counselors, clinical neuropsychologists, or speech pathologists for specialized management and/or diagnostic clarification.

A tool used by physicians to diagnose HD is to take the family history, sometimes called a pedigree or genealogy. It is extremely important for family members to be candid and truthful with a professional who is taking a family history since another family member(s) may not have been accurately diagnosed with the disease but thought to have other issues.

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- **Genetic tests.** 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. A small percentage



In addition to a neurologist, individuals with HD may be referred to other healthcare professionals such as psychiatrists or genetic counselors for specialized management or to help clarify their diagnosis.

of individuals will have repeats in a borderline range. For such individuals, doctors may try to get a clearer picture of disease risk by asking other family members to come in for examination and genetic testing.

Prior to the availability of the direct genetic test, clinics used a method called *linkage testing*. This older method requires a sample of DNA from a closely related affected relative, preferably a parent, for the purpose of identifying *markers* close to the HD gene. A version of the linkage method is sometimes still used for prenatal testing.

- **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 of the striatum and parts of the cortex, and enlargement of fluid-filled cavities within the brain called ventricles. These changes do not necessarily indicate HD, however, because they can occur in other disorders. Conversely, a person can have early symptoms of HD and still have normal findings on a structural CT or MRI scan.

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What is predictive testing and how is it done?

A predictive or presymptomatic genetic test is an option for someone who has a family history of HD but shows no symptoms. Genetic testing makes it possible to predict with a higher degree of certainty whether or not the person will develop HD.

The decision to undergo presymptomatic testing is a highly personal and often difficult one to make. Common reasons that people choose to take the test include planning for marriage, children, education and career decisions, finances, stress, or simply to relieve uncertainty.



Prenatal exclusion testing indicates if a fetus has inherited a chromosome 4 mutation from an affected grandparent.

Centers across the U.S. offer genetic testing for HD, as well as pre- and post-test counseling. A list of such centers is available from the Huntington's Disease Society of America at 1-800-345-HDSA (<http://hdsa.org/about-hdsa/locate-resources/?i=genetic-testing>). With the participation of families with HD, researchers

and health professionals have developed guidelines for HD genetic testing. A team of specialists will help the at-risk person decide if testing is the right choice, and will carefully prepare the person for a negative, positive, or inconclusive test result. Whatever the results of genetic testing, the at-risk individual and family members can expect powerful and complex emotional responses. Because receiving test results may prove to be devastating, testing guidelines call for continued counseling even after the test is complete and the results are known.

In order to protect the interests of minors, including confidentiality, testing is not recommended for those under the age of 18 unless there is a compelling medical reason (for example, the child is exhibiting symptoms).

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. Before requesting a prenatal test, and even before pregnancy, it is a good idea to seek advice from a genetic counselor. Prenatal testing can be done using either the direct

method or the linkage method. As with adult testing, the direct method provides higher certainty.

However, in addition to revealing the HD gene status of the fetus, the direct method also reveals the status of the at-risk parent.

Hopeful parents who do want to know their own HD gene status may opt for the linkage method, which is also known as prenatal exclusion testing. This test does not look for the HD gene itself but instead indicates whether or not the fetus has inherited a chromosome 4 mutation from the affected grandparent. If the mutation is present, the parents then learn that the fetus's risk is the same as the at-risk parent (50 percent), but they learn nothing new about the parent's risk. If the test shows that the fetus has inherited a chromosome 4 mutation from the unaffected grandparent, then the fetus has not inherited HD.

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Another option for parents is *in vitro* fertilization (IVF) and preimplantation genetic diagnosis (PGD). Briefly, a woman is given fertility

drugs so that she produces many eggs at once, the eggs are fertilized by the man's sperm *in vitro* (literally, "in glass"), and embryos are screened at a very early stage to determine if they carry the HD mutation. Embryos free of the mutation are then implanted in the woman's uterus. Parents can choose not to know the exact results of genetic testing and thus are not forced to confront their own HD gene status. These procedures are available only at some specialized IVF clinics and require extensive counseling, preparation, and expense.

A person can have early signs of HD and still have normal findings on a CT or MRI scan.

What treatments are available for HD?

A number of 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. For many of these drugs, their mechanisms of action against HD are not fully understood.

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 alleviate choreic movements 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 dystonia (involuntary muscle contractions that can cause slow, repetitive movement or abnormal postures), and may in fact worsen the condition, causing stiffness and rigidity.



Medications may help control HD symptoms, however, there is no treatment to stop or reverse the course of the disease.

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 kind of care do individuals with HD need?

Cognitive problems are often the first changes that are noticed in HD. Evaluations conducted by clinical neuropsychologists, who specialize in cognitive assessment, can be helpful in clarifying an individual's cognitive strengths and weaknesses, making safety recommendations and monitoring cognitive changes over time. Education about cognitive symptoms is also helpful for individuals and families. As the disease progresses, it is important to maintain regular daily routines for the person and to provide an environment with minimal distractions. Care should be taken not to isolate individuals who have become slow to engage in conversation or respond to questions. Speech therapy and other communication techniques may improve an individual's ability to communicate and remain active in family and community life.



Daily exercise can help a person with HD feel better physically and mentally.

It is extremely important for a person with HD to maintain physical fitness as much as the course of the disease allows. Individuals who exercise and keep active tend to do better than those who do not. A daily regimen of exercise can help the person feel better physically and mentally. Although their coordination may be poor, individuals should continue walking, with assistance if necessary. Wearing special

padding may also help reduce injuries in the event of a fall. Wearing sturdy shoes that fit well can help too, especially shoes without laces that can be slipped on or off easily.

Impaired coordination may make it difficult for people with HD to feed themselves and to swallow. As the disease progresses, people with HD may even choke. In helping individuals to eat, caregivers should allow plenty of time for meals. While some foods may require the addition of thickeners, other foods may need to be thinned. Some individuals may benefit from swallowing therapy, which is especially helpful if started before serious problems arise. Suction cups for plates, special tableware designed for people with disabilities, and plastic cups with tops can help prevent spilling. The individual's physician can offer additional advice about diet and about how to handle swallowing difficulties or gastrointestinal problems that might arise, such as incontinence or constipation.

Proper nutrition is needed to ensure the individual with HD takes in enough calories to maintain body weight. Sometimes people with HD, who may burn as many as 5,000 calories a day through involuntary movements, require five meals a day to take in the necessary number of calories. Physicians may recommend vitamins or other nutritional supplements. When swallowing and nutritional problems become severe, some individuals and their families choose to use a feeding tube.

Individuals with HD are at special risk for dehydration and therefore require large quantities of fluids, especially during hot weather. Bendable straws can make drinking easier for the person. In some cases, water may have to be thickened with commercial additives to give it the consistency of syrup or honey.

What community resources are available?

Individuals and families affected by HD can take steps to ensure that they receive the best advice and care possible. Advocacy organizations including the Huntington's Disease Society of America (HDSA) and the Hereditary Disease Foundation are excellent resources with information specific to HD. Some organizations support scientific workshops and research and provide information that enables families, health professionals and investigators to exchange information, learn of available services and benefits, and work toward common goals. HD support groups exist in many states across the country. State and local health service agencies can provide information on community resources

and family support groups that may exist. Possible types of help include:

Legal and social aid. Since HD affects a person's capacity to reason, make judgments, and handle responsibilities, individuals may need help with legal affairs. Wills and other important documents should be drawn up early to avoid legal problems when the person with HD may no longer be able to represent his or her own interests. Family members should also seek out assistance if they face discrimination regarding insurance, employment, or other matters.

Home care services. Caring for a person with HD at home can be exhausting, but part-time assistance with household chores or physical care of the individual can ease this burden. Domestic help, meal programs, transportation programs, nursing assistance, occupational therapy, or other home services may be available from federal, state, or local health service agencies.

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Resources such as nursing assistance, meal programs, and occupational therapy can be used to help care for an individual with HD.

Recreation and work centers.

Many people with HD are eager and able to participate in activities outside the home. Therapeutic work and recreation centers give individuals an opportunity to pursue hobbies and interests and to meet new people.

Participation in these programs, including occupational, music, and recreational therapy, can reduce the person's dependence on family members and provides home caregivers with a temporary, much needed break.

Group housing. A few communities have group housing facilities that are supervised by a resident attendant and that provide meals, housekeeping services, social activities, and local transportation services for residents. These living arrangements are particularly suited to the needs of individuals who are alone and who, although still independent and capable, risk injury when they undertake routine chores like cooking and cleaning.

Institutional care. The individual's physical and emotional demands on the family may eventually become overwhelming. While many families may prefer to keep relatives with HD at home whenever possible, a long-term care facility may prove to be best. To hospitalize or place a family member in a care facility is a difficult decision that may require professional counseling.

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Finding the proper facility can itself prove difficult. Organizations such as the HDSA may have referrals to facilities that have had experience in the care of individuals with HD. Very few of these exist however, and even fewer have experience with individuals with juvenile or early-onset HD who require special care because of their age and symptoms.

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. The NINDS is a component of the National Institutes of Health (NIH), the



Researchers use animal models including the fruit fly to study the mechanisms of HD and to identify potential therapies.

leading supporter of biomedical research in the world. The NINDS conducts and supports research to better understand and diagnose Huntington's disease (HD), develop new treatments, and ultimately, prevent HD. The NINDS also supports training for the next generation of HD researchers and clinicians, and serves as an important source of information for people with HD and their families.

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. These findings have proven invaluable for diagnosis and research, and have enabled neuroscientists to create animal models of the disorder. Signs of HD have been reproduced in fruit flies, mice, and non-human primates by giving the animals one or more copies of the HD mutations found in people. These models are used to study mechanisms of the disease, to identify potential therapeutic strategies, and to move forward with those strategies most likely to work and least likely to cause harm for individuals. Just as important, the gene discovery enables neurologists to recruit individuals who carry the HD gene into clinical studies early—before they become ill.

The HD Gene

How do mutations in the HD gene lead to neuronal degeneration? The normal functions of the huntingtin (Htt) protein—the product of the HD gene—have

yet to be fully defined, but may include regulating the development of the embryo, transport of molecules and organelles inside nerve cells, and controlling factors that support neuronal health. However, there is very strong evidence that the mutant Htt protein gains one or more new and harmful functions. A major focus of research on HD is to understand the toxicity of mutant huntingtin protein and to develop potential drugs for counteracting it.

People with HD have an abnormal, repetitive, greatly expanded three-letter code, called a CAG repeat, in their DNA sequence. DNA uses a three-letter code (or triplet) to prescribe the order and identity of amino acids—a protein’s building blocks. The triplet “CAG” designates the amino acid glutamine. The repeated CAGs in the normal HD gene are translated into a string of glutamines, called *polyglutamine*. The mutant HD gene codes for an abnormal form of the Htt protein with much longer polyglutamine repeats that are toxic to neurons. Also, the abnormal polyglutamine sequence affects how the huntingtin protein interacts with other proteins. At least eight other inherited neurological disorders are caused by polyglutamine expansions, each in a different gene.

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RNA serves as an intermediate between DNA molecules and proteins; the genetic code within DNA is copied into RNA, which is then used as a template for making proteins. The mutant



People with HD have an abnormal repetitive CAG repeat in their DNA sequence.

huntingtin protein RNA may itself be toxic to cells; its numerous repeats can attract and bind essential cellular proteins which thus become unavailable to perform their critical function in processing other RNA molecules from other genes.

NINDS is funding cutting-edge research that aims to eliminate or reduce the production of toxic HD-RNA and huntingtin protein. One potential therapy, called RNA interference, involves designing small bits of synthetic RNA to match, target, and destroy specific RNA molecules inside cells. Researchers have designed interfering RNAs that target HD-RNA and block the production of mutant huntingtin protein, and they have found this approach to be beneficial in mouse models of HD. Such synthetic RNA molecules called antisense oligonucleotides are being developed to be delivered into the cerebrospinal fluid. Others are packaging the RNA into viruses to deliver into the brain. Pharmaceutical companies are now initiating ambitious trials to test whether this approach may help people with HD.

Mutant Huntingtin Protein

Aberrant regulation of genes in HD. The abnormal interactions between mutant huntingtin protein and other proteins can have many adverse consequences, including altered gene regulation. Humans have approximately 20,000 genes, about one-third of which are active (or expressed) in the brain at some point in life. Precisely when and where these genes are expressed is controlled by a complex machinery within cells—and mutant Htt can upset this system. For instance, DNA in the cells

of higher organisms is packed into chromatin—tight coils of DNA and small proteins called histones. Compounds that block gene expression and coil-tightening activity of certain histones have been shown to counteract HD in animal models, and are attractive candidates for drug development. Other alterations in chromatin not only keep some necessary genes shut off, but mutant Htt can also inappropriately turn on other genes, such as those driving excessive inflammation, which damages and kills nerve cells in the brain.

Mutant Htt aggregation. Besides sticking to other proteins, mutant Htt has a tendency to stick to copies of itself and accumulate in clumps known as *aggregates*. These aggregates can pull in and block the activity of other proteins, and grow to form inclusion bodies—protein deposits inside cells that may overburden the cell’s ability to handle and dispose of old or damaged proteins. Neurons from different brain regions may differ in their efficiency of waste disposal. Neurons in the striatum, the brain region most affected in HD, show the slowest mutant huntingtin clearance rates, perhaps explaining their

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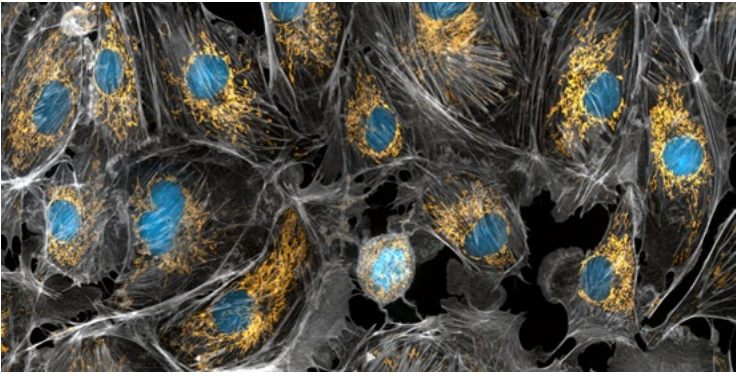


Neurons in an area of the brain called the striatum are most affected by HD.

heightened susceptibility to the disease. Compounds that activate cellular waste handling systems have been shown to reduce the toxicity of mutant Htt in animal models. Recent evidence suggests that mutant huntingtin may also move from cell to cell in a person's brain and induce aggregates and inclusions in neighboring cells, similar to what is seen in Alzheimer's and Parkinson's diseases.

Metabolism and mitochondria. Some studies suggest that mutant Htt interferes with the function of the tiny energy factories inside cells known as mitochondria. Others point to reduced efficiency of antioxidant pathways—protective pathways that scavenge harmful byproducts of brain activity that in normal conditions remain at innocuous levels. In HD some of these pathways are disrupted and the toxic byproducts accumulate to damaging levels. Drugs that inhibit the production of these harmful byproducts or accelerate their clearance have been designed and successfully tested in animal models. However, two NINDS-funded trials investigating any benefit of the metabolic supplements creatine and coenzyme Q10 in people with HD found no improvements in clinical symptoms at the doses tested.

Excitotoxicity, neural circuits, and survival factors. Researchers have yet to determine why Huntington's disease has its most severe effects on neurons in the striatum, specifically on a cell type called medium-sized spiny neurons. One culprit may be the brain chemical glutamate, which is produced by neurons in the cerebral cortex and transmits information by exciting (signaling them to turn on) medium spiny neurons in the striatum. Excessive glutamate



Mitochondria (shown in yellow) are tiny energy producers inside of cells. Research suggests mutant Htt interferes with mitochondrial function.

signaling between these cells may lead to over-excitation of medium spiny neurons in HD. Chronic over-excitation is toxic to neurons (called excitotoxicity). Several labs are investigating whether drugs that counteract excitotoxicity might help against HD.

Some of the clinical symptoms in neurodegenerative diseases may be caused by the ultimate malfunctioning of neuronal circuits rather than by the loss of individual cells. 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 such circuit defects in HD.

In addition to communications exchange, neurons may also provide each other with chemical signals (called trophic factors) that support the health and stability of neural circuits. Cortical neurons provide trophic support by releasing Brain Derived Neurotrophic Factor (BDNF), which supports the survival of medium spiny neurons in the striatum. Evidence suggests that mutant Htt suppresses the production of BDNF. Using animal models, researchers hope to restore BDNF-based trophic support to striatal cells and possibly prevent medium spiny neurons from dying.

Stem Cells

Stem cells are now a useful tool that helps us understand underlying molecular disease mechanisms.

Pluripotency—the ability of embryonic stem cells to become nerve, muscle, bone, and other cell types—depends on a unique genetic program that is typically shut off in adult cells. Scientists have discovered that it is possible to take adult blood or skin cells and, by activating this genetic program, return the cells to a pluripotent state (called induced pluripotent, or iPS, cells). Through an NINDS-funded consortium, individuals with HD have donated skin and blood samples for research, allowing the creation of iPS cell lines and iPS-derived neurons for studying HD. Researchers are using cultures of these cell lines to understand why neurons malfunction and die in HD, and to rapidly test potential new drugs. Their aim is increase the efficiency of turning a person's iPS cells into medium spiny neurons that reflect the human disease, and then to learn from these disease cells how the CAG-repeat expansion damages their function and viability.

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Investigators are studying the effects of transplanting nerve cells derived from embryonic or adult stem cells (immature cells that eventually give rise to all of the body's cell types) or fetal tissue. A number of small studies found no sustained improvement in transplanting fetus-derived cells into the striatum in people with HD.

In theory, induced pluripotent stem cells could be derived from a person with Huntington's disease and then implanted into the person's brain after

correcting the HD mutation. However, brain function is dependent upon the correct connections between neurons and currently it is not known how to generate cells to form connections appropriately in a disease such as HD.

An alternative to transplanting stem cells into the brain may be to mobilize stem cells that are already there and shown to move into damaged tissue. Research on rodent models of HD suggests it might be possible to reawaken these cells by delivering specific growth factors to the brain. It is not yet clear whether this strategy will work in humans, as those with HD seem to have significantly fewer and less potent brain stem cells than healthy people.

Biomarkers

The NINDS-funded PREDICT-HD study, as well as several international studies (such as REGISTRY, BIOHD, and Enroll-HD), seek to identify *biomarkers* for HD. Biomarkers are biological changes that can be used to predict, diagnose, or monitor a disease; for example, a sustained rise in blood sugar is a biomarker for diabetes. 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 biomarkers characteristic of prediagnostic HD; measurable changes in personality, mood, and cognition that typically precede the appearance motor symptoms of HD.

A large and related NINDS-supported study aims to identify additional genetic factors in people that influence the course of the disease. Individuals



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

with the same CAG expansions can differ widely in the age of disease onset and severity of symptoms. Researchers are trying to identify variations in the genomes of individuals with HD that account for those differences. Finding genetic variants that slow or accelerate the pace of disease progression promise to provide important new targets for disease intervention and therapy.

Clinical studies

Studies of cognition, emotional functioning, and movement. Studies of motor problems (abnormal eye movements, chorea, and dystonia), psychiatric symptoms (apathy, psychosis, depression, and irritability), and tests of cognitive skills (learning and memory, attention, concentration, and executive functioning such as multitasking, problem-solving, and planning) may serve to identify when the symptoms of HD appear, and help characterize their range and severity as the disease progresses over time.

Clinical trials of drugs. 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.

Imaging. Various imaging technologies allow investigators to view changes in the volume and structures of the brain, and to pinpoint when these changes occur in HD. Positron emission tomography (PET, which visualizes metabolic or chemical abnormalities in the brain) allows scientists to learn how HD affects the chemical systems of the brain. Investigators hope to learn if PET scans can reveal abnormalities that signal HD, as well as to characterize neurons that have died and chemicals that are depleted in parts of the brain of people with HD. Investigators are using functional MRI (fMRI), a form of magnetic resonance imaging that measures changes in the flow of blood-borne chemicals known to correlate with brain activity, to understand how HD affects the functioning of different regions of the brain.

Brain structure. 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 of the disease show measurable changes in the structure of their



Imaging technology allows researchers to see changes in the brain and determine when those changes occur.

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brain, even up to 20 years before onset of clinical diagnosis. It is not known when in life these changes become evident. One possibility is that the HD gene causes changes in early brain development that remain throughout life, and initially cause only subtle functional abnormalities.

In an effort to better understand how HD affects brain development, an NINDS-funded study is evaluating brain structure and function in children, adolescents, and young adults (ages 6-18) who are at risk for developing the disease because they have a parent or grandparent with HD. 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 go for more information?

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

BRAIN

P.O. Box 5801
Bethesda, MD 20824
301-496-5751
800-352-9424
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
www.hdfoundation.org

Huntington's Disease Society of America

505 Eighth Street, Suite 902
New York, NY 10018
212-242-1968
800-345-4372
www.hdsa.org

National Library of Medicine

Genetics Home Reference
National Institutes of Health
8600 Rockville Pike
Bethesda, MD 20894
301-594-5983
888-346-3656
www.nlm.nih.gov

Glossary

basal ganglia—a region located at the base of the brain composed of four clusters of neurons, or nerve cells. This area is responsible for body movement and coordination. The parts of the brain most prominently and consistently affected by HD are located here.

biomarkers—biological changes that can be used to predict, diagnose, or monitor a disease.

chorea—uncontrolled body movements. Chorea is derived from the Greek word for dance.

chromosomes—the structures in cells that contain genes. They are composed of deoxyribonucleic acid (DNA) and proteins and, under a microscope, appear as rod-like structures.

computed tomography (CT)—a technique used for diagnosing brain disorders. CT uses a computer to produce a high-quality image of brain structures.

deoxyribonucleic acid (DNA)—the substance of heredity containing the genetic information necessary for cells to divide and produce proteins. DNA carries the code for every inherited characteristic of an organism.

direct genetic test—a diagnostic test that counts the number of CAG repeats in the HD gene, using DNA taken from a blood sample.

gene—the basic unit of heredity, composed of a segment of DNA containing the code for a specific trait.

huntingtin (Htt)—the protein encoded by the gene that carries the HD defect. The repeated CAG sequence in the gene causes an abnormal form of huntingtin to be formed.

in vitro—a laboratory experiment that is conducted in an artificial environment, such as a glass dish or test tube.

linkage testing—an older form of testing for Huntington’s disease that uses a sample of DNA taken from a closely related affected relative, preferably a parent, for the purpose of identifying markers close to the HD gene.

magnetic resonance imaging (MRI)—an imaging technique that uses radiowaves, magnetic fields, and computer analysis to create a picture of body tissues and structures.

marker—a piece of DNA that lies on the chromosome so close to a gene that the two are inherited together. Like a signpost, markers are used during genetic testing and research to locate the nearby presence of a gene.

mutation—in genetics, any defect in a gene.

neuron—a nerve cell, the basic impulse-conducting unit of the nervous system. Nerve cells communicate with other cells through an electrochemical process called neurotransmission.

neurotransmitters—special chemicals that transmit nerve impulses from one cell to another.

polyglutamine—a string of the amino acid glutamate in a protein. This amino acid normally occurs in proteins but is abnormally repeated in individuals with HD. Polyglutamine stretches in other proteins have also been linked to several other neurodegenerative diseases.

senile chorea—a relatively mild and rare disorder found in elderly adults and characterized by choreic movements. It is believed by some scientists to be caused by a different gene mutation than that causing HD.

striatum—part of the basal ganglia of the brain that is severely affected by HD.

triplet (or trinucleotide) repeat expansion—a repeated chain of three of the four basic components of genetic material that determines a gene's function. In a normal gene, the repeat of the base materials cytosine, adenine, and guanine – abbreviated as CAG – appears less than 30 times; in Huntington's disease, the repeat occurs 40 or more times.



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