

Huntington's disease

Huntington's disease is a progressive brain disorder caused by a single faulty gene on chromosome 4 — one of the 23 human chromosomes that carry a person's entire genetic code. This defect is “dominant,” meaning that anyone who inherits it from a parent with Huntington's will eventually develop the disease.

The defective gene codes the blueprint for a protein called huntingtin. This protein's normal function isn't yet known, but scientists have identified its defective form as the cause of Huntington's disease.

The disease is named for George Huntington, the physician who first described it in the late 1800s.

Prevalence

About 30,000 Americans — one in every 10,000 — have Huntington's. More than 200,000 individuals are known to be at risk because they have a parent with the disease.

Symptoms

The hallmark symptom of Huntington's disease is uncontrolled movement of the arms, legs, head, face and upper body. Huntington's also causes a decline in thinking and reasoning skills, including memory, concentration, judgment and ability to plan and organize.

In addition, Huntington's disease brain changes lead to changes in mood, especially depression, anxiety and uncharacteristic anger and irritability. Obsessive-compulsive behavior is also common, causing a person to repeat the same question or activity over and over.

Diagnosis

A diagnostic test can confirm if the defective gene for huntingtin protein is the cause of symptoms in people with suspected Huntington's disease. This test can also detect the defective gene in people who don't yet have symptoms but are at risk of developing Huntington's because a parent has the disease.

Research published in the March 15, 2021 issue of *Movement Disorders Clinical Practice* found that people with Huntington's disease who have had more formal education tend to be diagnosed earlier and have milder symptoms than those with less formal education.

Causes and risk factors

The defective gene, identified in 1993, causes virtually all cases of Huntington's disease. This gene codes a protein that scientists named "huntingtin" after linking it to the disease. The huntingtin protein gene, like all human genes, carries its biological blueprints in repetitions of simple chemical codes. This particular gene defect involves extra repeats of one specific chemical code in one small section of chromosome 4. The normal huntingtin gene includes 17 to 20 repetitions of this code among its total of more than 3,100 codes. The defect that causes Huntington's disease includes 40 or more repeats. Genetic tests for Huntington's disease measure the number of repeats present in an individual huntingtin protein gene.

Scientists don't yet understand the normal function of huntingtin protein or how a few dozen extra repeats in its genetic blueprint lead to the devastating symptoms of Huntington's disease. Researchers are eager to solve these mysteries, not only to find better understand Huntington's, but also because the answers may offer important insights into a wide range of other brain disorders, including Alzheimer's, Parkinson's disease and amyotrophic lateral sclerosis (ALS).

Every child of a parent with Huntington's disease has a 50% chance of inheriting the gene that causes the disease. If the child did not inherit the gene, he or she will never develop the disease and cannot pass it on to their children.

Huntington's disease does not discriminate — it affects both sexes as well as all races and ethnic groups around the world.

Outcomes

Huntington's is a progressive disease, meaning symptoms and brain changes gradually get worse. Symptoms usually develop between ages 30 and 50, but 10% may develop motor symptoms before age 20 (juvenile onset) and 10% after age 60. People with Huntington's survive an average of 15 to 25 years.

Treatment

There is currently no cure for Huntington's disease and no way to slow or stop the brain changes it causes. In July 2021, the U.S. Food and Drug Association granted orphan-drug designation (a status for drugs intended to treat a rare disease or condition) for VO659, an investigational antisense oligonucleotide (AON) therapy designed to lower the mutant protein levels causing neurodegenerative diseases, including Huntington's disease, and slow or halt disease progression. The first-in-human trials are expected to start in 2022.

Current treatments focus on managing symptoms. The following treatments are used as first-line strategies for three of the disorder's most troubling symptoms:

- **Chorea (involuntary movements):** The U.S. Food and Drug Administration (FDA) has approved tetrabenazine and deuterenazine to treat chorea associated with Huntington's. Antipsychotic drugs, such as olanzapine, may also be used to ease chorea.
- **Irritability:** For severe anger and threatening behavior, experts agree that an atypical antipsychotic drug is the preferred approach. For less severe, nonthreatening irritability, experts recommend first trying a selective serotonin reuptake inhibitor (SSRI), a type of antidepressant.
- **Obsessive-compulsive thoughts and actions:** Experts also recommend SSRIs as the standard treatment for these symptoms.

Other symptoms of Huntington's, such as anxiety, depression and insomnia, should also be treated. Due to the complexity of the disease, effective treatment of symptoms may be a lengthy process, and may include several approaches with different drugs and doses.

Research

The effort to combat Huntington's involves several lines of inquiry, each providing important information about the disease:

- **Basic neurobiology.** Investigators in the field of neurobiology, which examines the anatomy, physiology and biochemistry of the nervous system, continue to study the huntingtin gene to learn how it causes the disease.
- **Clinical research.** Neurologists, psychologists, psychiatrists and other investigators are improving our understanding of the symptoms and progression of the disease while attempting to develop new therapeutics. Researchers are also studying how environmental and lifestyle factors, such as education, influence the course of Huntington's.
- **Imaging.** Scientific investigations using positron emission tomography (PET) scans and other technologies are enabling scientists to see what the defective gene does to various structures in the brain and how it affects the body's chemistry and metabolism.
- **Animal models.** Laboratory animals, such as mice, are being bred with the hope of duplicating the clinical features of Huntington's disease to help scientists learn more about the symptoms and progression of the disease.
- **Fetal tissue research.** Investigators are implanting fetal tissue in rodents and nonhuman primates with the hope that success in this area will lead to

understanding, restoring or replacing functions typically lost by neuronal degeneration in individuals with Huntington's.

These areas of research are slowly converging and, in the process, are yielding important clues about the gene's relentless destruction of mind and body.

One global study — Enroll-HD — aims to make all other Huntington's research easier, speeding up the process of developing new drugs and other treatments. Enroll-HD is the world's largest observational study of Huntington's disease that hopes to add thousands of people with Huntington's disease to its registry, reaching a possible total of 30,000 over the next three years. The goals of the study are to better understand the disease as it happens in people, to give us insights into developing new drugs; improve design of clinical trials to give clear answers more quickly; and improve care for people with Huntington's by identifying best clinical practices around the world.

Additional resources

Huntington's Disease Society of America
hdsa.org
212.242.1968

Enroll-HD

enroll-hd.org

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