UCSF Memory and Aging Center
Weill Institute for Neurosciences

Huntington's Disease

Huntington's disease (HD) results from degeneration of neurons of structures deep within the brain, the *basal ganglia,* which are responsible for movement and coordination. It is a progressive, neurodegenerative disorder typically characterized by involuntary movements (chorea), behavioral and personality changes and cognitive decline (dementia). It is caused by a dominantly inherited gene mutation that can be passed down from generation to generation, but there is great variability in the expression of HD, even within the same family.

What Causes HD?

Identification and location of the HD gene *(HTT)* have made it possible to determine who will develop the disease through DNA mutation analysis of a blood sample. An accurate family history is essential, as the test is specific to HD. Brain imaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI) may show atrophy of the affected parts of the brain, especially the caudate nuclei and putamen (parts of basal ganglia), as well as

generalized brain atrophy. DNA mutation analysis may be of value to confirm a diagnosis suspected by symptoms, predict HD in an at-risk individual or make a prenatal diagnosis in an at-risk pregnancy.

Autosomal dominant pattern of inheritance implies that only one copy of the mutated gene, from either parent, causes the disease. A parent with the HD gene mutation has a 50% chance at each pregnancy of passing the gene to their offspring. Males and females are equally affected. The *HTT* gene is located on the short arm of chromosome 4 (4p16.3). It synthesizes the production of the protein huntingtin, which accumulates and is toxic in the brains of HD patients. The mutation in HD consists of an expansion in the repeated sequence of a trinucleotide codon (CAG). How exactly huntingtin protein causes harm in HD is not yet completely understood.

The HD gene mutation is known to be dynamic, meaning that it can change from one generation to another. If the CAG sequence expands from the previous generation to the offspring, the affected offspring may develop an earlier and more severe course. This phenomenon is known as "anticipation." Anticipation most often occurs through transmission from an affected father.

Very rarely, an individual can develop HD who has no known family history of the disorder. Situations like this are thought to occur due to spontaneous mutations or from a missed or incorrect diagnosis in the previous generation.

How is Age Related to HD?

In the United States, the overall prevalence of HD is about 1 in every 10,000–20,000 persons. The disease typically begins in mid-adulthood, i.e. 30–55 years. However, juvenile onset HD (JHD) occurs in about 10% of families, nearly always inherited from a father with the HD gene mutation.

What Happens in HD?

The characteristic triad includes

1. **physical symptoms** (e.g., involuntary movements, restlessness, fidgety, loss of balance, awkward gait, poor coordination, dysarthria)
2. **cognitive changes** (e.g., memory loss, inability to multitask, poor calculations, disorganization)
3. **emotional and behavioral disturbances** (e.g., depression, apathy, paranoia, anger, withdrawal, anxiety)

Early symptoms may include personality changes, such as mood swings, irritability, apathy, depression, anger or aggression. Early in the disease, cognitive decline may manifest as memory and learning difficulties, judgment impairment, and trouble with driving, answering questions or making decisions. As the disease progresses, concentration and focus on intellectual tasks become increasingly difficult. Weight loss, not due to decreased caloric intake, is a common feature of patients with HD.

Manifestations of chorea may appear at various stages of the disease and may begin as uncontrolled movements of the extremities, face, or trunk that become progressively worse. Fidgety movements, restlessness, clumsiness or imbalance may precede chorea. The movement component of HD is extremely variable, with some affected individuals experiencing only mild involuntary movements and others suffering from movements that interfere with daily function.

The disease can progress to the point where speech is slow and slurred (dysarthria) and vital functions, such as walking, self-care, eating and eventually swallowing may continue to decline. Affected individuals require increasing levels of care with disease progression, but many patients remain close to their family and friends, continue to be aware of their environment and able to express emotions.

Are There Medicines to Treat HD?

Currently, there is no cure for HD or treatment that is able to slow or stop the progression. However, there are treatments available to help manage some of the symptoms. Antipsychotic drugs may help to alleviate involuntary movements, hallucinations, delusions, and violent outbursts. Antipsychotic drugs, however, can have severe side effects, including stiffness and sedation, and for that reason are used in the lowest possible doses. Antidepressants are used for depression and tranquilizers can help with severe mood swings. Studies are underway to determine if antioxidants and several other agents may provide neuroprotection, and therefore prevent degeneration in HD.

Making healthy life choices clearly contributes to general well-being, such as nutritious diet, safe exercise and maintaining connections with friends, family and community. Special devices to assist in activities of daily living (ADLs), special diet to aid in swallowing, and increasing calories to counteract weight loss may eventually require consideration.

Resources

- The National Institute of Neurological Disorders and Stroke (NINDS) Huntington’s Disease Information Page

- Huntington’s disease support groups
- HD Lighthouse Families
- Huntington’s Disease Society of America (HDSA)
- Huntington’s Outreach Project for Education (HOPES) at Stanford
- Family Caregiver Alliance
- Adult Huntington’s disease on the Social Security Administration's Compassionate Allowances Program

Participate in Research

To refer a patient for HD or ataxia research, please contact our HD research coordinator, Divya Krishnakumar, at 415.476.2909 or Divya.Krishnakumar@ucsf.edu.

- Huntington’s Disease Trial of Laquinimod (LEGATO-HD)
- Huntington Disease Observational Research (Enroll-HD)
- HD Trial Finder
- Clinical trials at UCSF