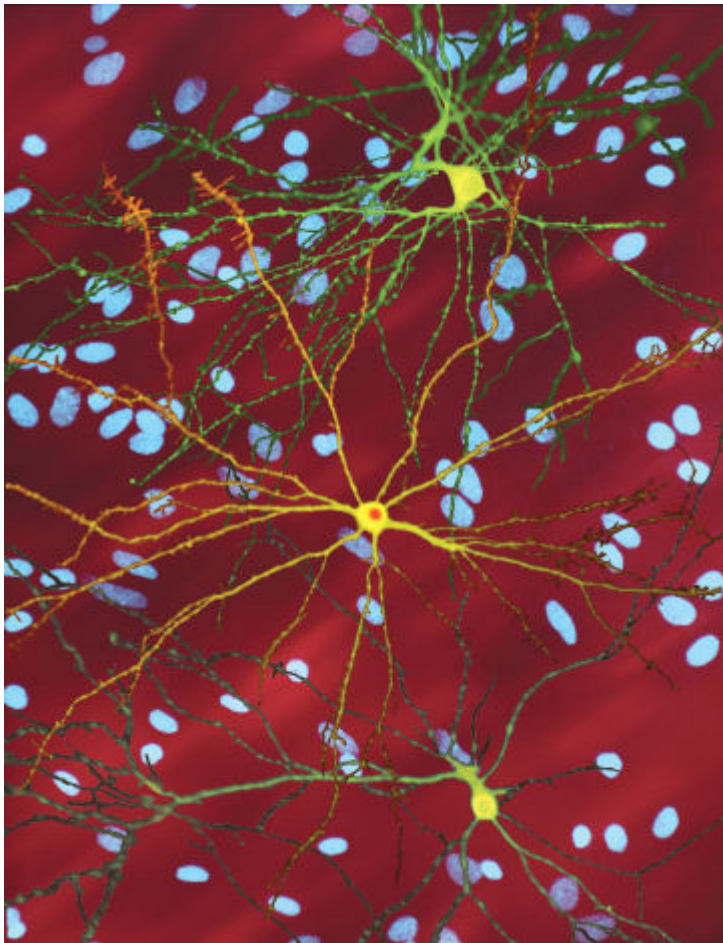


## Huntington's Disease (HD, Huntington's Chorea)—Genetics and Progression

[See online here](#)

**The clinical picture of Huntington's disease belongs to the category of movement disorders or extrapyramidal disorders and has an autosomal dominant inheritance. The disease is characterized by a progressing hyperkinetic syndrome, where an increase in motions or an akathisia occurs. The complete medical picture is characterized by a combined indication of choreatic hyperkinesia, dementia as well as weight loss (anorexia), which is caused by an increased basal metabolic rate.**

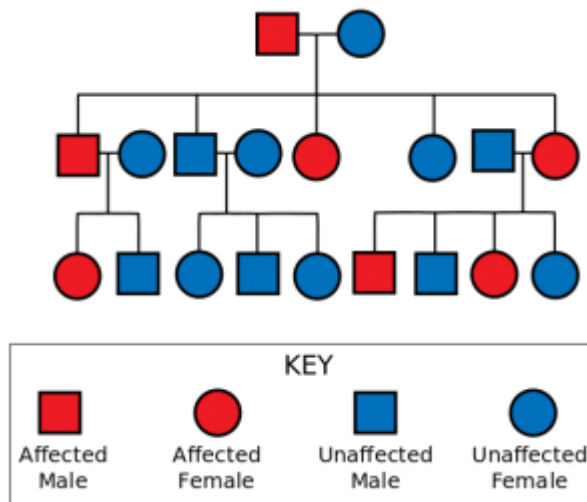


### Definition of Huntington's Disease

Huntington's disease is a hereditary disease

Huntington's disease, also known as St. Vitus' Dance, is a hyperkinetic disease inherited in an **autosomal dominant** manner with **full penetrance**, which means that those who

carry the mutant gene will manifest the disease at some point. The pathogenic gene is located on the short arm of **chromosome 4**.



*Image:* Autosomal Dominant Pedigree Chart. In Autosomal Dominance the chance of receiving and expressing a particular gene is 50% regardless of the sex of parent or child. By Jerome Walker, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Also known as **Chorea major**, it is synonymous with Huntington's disease. **Chorea major** is distinct from **Chorea minor (Sydenham's chorea)**, which is associated with different pathogenesis (see below).

## Epidemiology of Huntington's Disease

### Huntington's disease in the population

The **prevalence** of the disease is about 2–8 per 100,000. Often, the disease manifests clinically between the ages of 35 and 55 years, although the age of the disease onset varies widely.

**Note:** Huntington's disease is the most common hyperkinetic disorder of the basal ganglia.

Men and women are affected almost equally by the disease, which can be explained primarily by the autosomal dominant inheritance of the disease.

## Etiology of Huntington's Disease

### The genetics of Huntington's disease

Huntington's disease is one of the several **trinucleotide** repeat disorders containing multiple CAG triplet repeats. Medical diagnosis is based on the presence of at least 39 CAG triplet repeats. In fact, the higher the number of **triplet repeats**, the earlier is the onset of disease.

The severity of symptoms associated with Huntington's disease increases in successive generations or occurs at an earlier age of onset, a phenomenon known as anticipation. A gender-specific variation in DNA methylation known as **Genomic Imprinting** occurs during the course of gametogenesis, especially in children who inherit the mutation from

their father.

The Huntington gene is located on chromosome 4. The gene encodes a protein that is expressed predominantly in the brain but also detected in other types of tissue. The precise function of the protein has yet to be identified.

## Pathophysiology of Huntington's Disease

### Neuroanatomy of Huntington's disease

Huntington's disease is characterized by atrophy of the **corpus striatum**, resulting in **decreased concentrations of GABA** and a state of disequilibrium between **GABA** and **dopamine**.

**N.B.** The striatum is affected by irreversible destruction of GABAergic neurons.

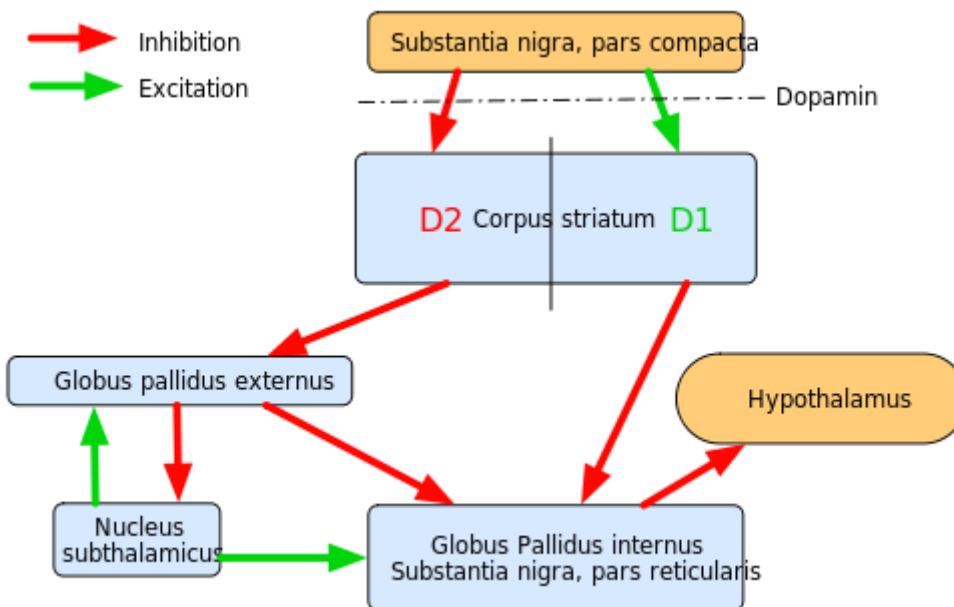


Image: Basalganglia. By Sigve, License: Public domain

Overall, dopamine has an excitatory effect on the direct pathway and an inhibitory effect on the indirect pathway of the **basal ganglia circuitry**, which results in increased activation of the **thalamus** and the **motor cortex**.

## Clinical Manifestations of Huntington's Disease

### Initial symptoms of Huntington's disease

Spontaneous movements caused by the increased activation of the **thalamus** primarily appear on the patient's face and limbs distally. **Orofacial hyperkinesia** occurs in the early stages of the disease and is also referred to as '**Grimacing**'.

Another facial sign that appears at an early stage involves the so-called '**chameleon tongue**', where the tongue is retracted immediately after it is stuck out.

Further in the course of the disease, limbs are affected by involuntary movements such as **chorea** and the back is often pulled back jerkily (**hyperlordosis**). Emotional stress

intensifies symptoms ('**choreatic movement attack**').

## Late symptoms of Huntington's disease

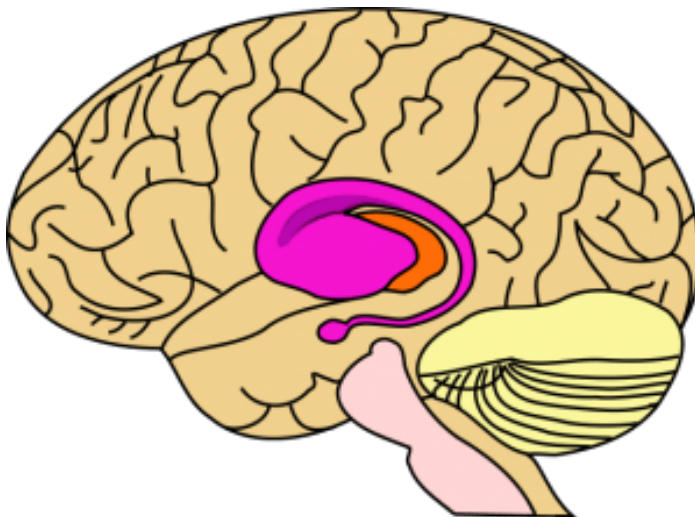
Overall, patients exhibit a significant increase in the rate of calorie consumption due to consistent abrupt movements and are often cachectic. Food intake is further hindered by damage to nerve tracts of the caudal cranial nerves and impaired chewing and tongue muscles.

## Mental symptoms of Huntington's disease

Frequently, **psychopathological changes** such as avolition, affective disorders as well as psychosis precede extrapyramidal movement disorders and partially occur 10-15 years before the onset of movement disorders.

Further, as the disease progresses, Huntington's disease generally leads to **dementia** with reduced cognitive capabilities and increased attention deficit disorders. This type of dementia is called **subcortical dementia**.

**N.B.** A definitive diagnosis of Huntington's disease is based on the triad of hyperkinesia, dementia, and anorexia.



[Image](#): Area of the brain most damaged in early Huntington's disease—striatum (shown in purple). By John Henkel, License: [Public Domain](#)

## Diagnosis of Huntington's Disease

### Genetic examination of Huntington's disease

In addition to using PCR for genetic analysis of mutations including the CAG triplet repeats, the medical diagnosis of Huntington's disease is established by the clinical presentation (see above) of the disease.

The patients undergo genetic testing of EDTA blood after qualifying under the standard guidelines for molecular genetic diagnostics such as those developed by Huntington's Disease Society of America, which recommend prior genetic counseling.

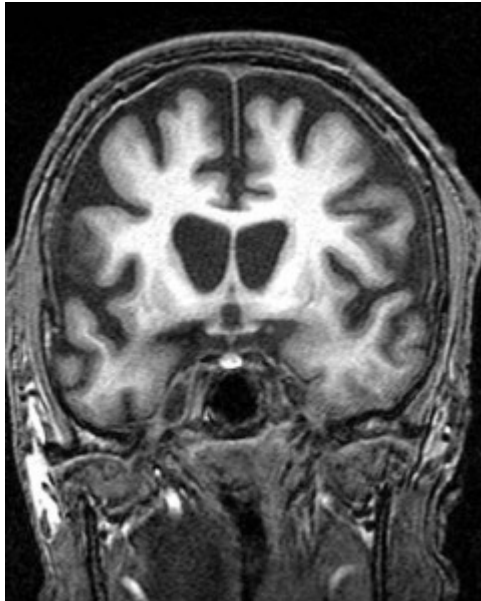
**N.B.** A positive family history is not always a prerequisite due to sporadic cases or cases

with a family history of deaths before disease onset.

## Imaging modalities for Huntington's disease screening

Occasionally, atrophy of the **nucleus caudatus** is visible in a CT or MRT scan of the head in patients with advanced disease.

Additionally, an **HMPAO-SPECT examination** may be indicated, which revealed reduced cerebral perfusion of the **striatum**. **FDG-PET** is optional and is used to detect hypometabolism of the striatum, even in the early phase of the disease.



**Image:** Coronal FSPGR through the brain at the level of the caudate nuclei demonstrating marked reduced volume in keeping with the patient's known diagnosis of Huntington disease. By Frank Gaillard, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

## Functional diagnosis of Huntington's disease

Additional diagnostic options are based on electrophysiology, including **somatosensory evoked potential (SEP)** as well as **electroneurography (ENG)**. **Median** or **tibial nerve SEP** can show the reduced amplitude of central potentials.

The ENG facilitates the visualization of a prolonged latency of saccades or a decelerated speed of saccades as well as possible **optokinetic nystagmus**.

Eventually, a differential diagnosis (see below) is needed. A **neuropsychological test** may also be required to determine the cognitive capabilities.

## Differential Diagnosis of Huntington's Disease

### Diseases similar to Huntington's disease

The most important differential diagnosis of Huntington's disease includes **chorea minor** and **extrapyramidal motor disorders** associated with hyperkinesia.

**Ballism, hemiballismus, dystonia, dyskinesia, or akathisia** (inability to sit still) are

considered as hyperkinetic diseases.

Medication-induced hyperkinesia is known as **dyskinesia**. **L-Dopa**, which is used in the treatment of Parkinson's disease, can trigger dyskinesia following long-term therapy.

Additional differential diagnoses include **hyperthyroidism**, **Wilson's disease**, and **hypoparathyroidism**. Inflammatory diseases such as **neuroacanthocytosis** must be ruled out using a spinal tap when indicated.

## Chorea minor as a differential diagnosis in Huntington's disease

Chorea minor (**Sydenham's chorea**) is a disorder attributed to a pathological immune reaction following infection with  $\beta$ -hemolytic **group A streptococci**. In approx. 50% of the cases, symptoms of rheumatic fever precede the choreatic movement disorders, including polyarthritides, carditis, erythema annulare and subcutaneous papules.

School-age children are particularly affected by chorea minor, and girls are affected more often than boys. **Choreatic hyperkinesia** is predominantly associated with **mimetic muscles**, **pharyngeal muscles**, tongue as well as the upper limbs **distally**.

Due to the accompanying psychic abnormalities including increased excitability, apathy and **labile affect**, the children's peculiar behavior is noticed at school.

Chorea minor is treated with medications consisting of penicillin G, which should be dosed at sufficiently high levels and administered for a prolonged period.

## Therapy of Huntington's Disease

### Treatment of Huntington's Disease

Huntington's disease has no cure. However, symptoms can be managed with **medications, physical and occupational therapy**. In addition, **high caloric nutrition** can counteract cachexia.

Drugs commonly used to treat hyperkinesia **such as sulpiride (atypical neuroleptic) and tiapride (classical neuroleptic)** are recommended upfront as the treatment of the 1st choice, whereas **haloperidol** is a drug of the 2nd choice (see literature for further information).

**N.B.** Neuroleptics can induce movement disorders and should only be used (with the lowest possible dose) in case of strong physical impairment caused by hyperkinesia. **Sulpiride** is also used to treat feelings of **depression**. Additional medications to treat depression include **alprazolam (benzodiazepine)**, **thioridazine (neuroleptic)**, and **tricyclic antidepressants**.

**N.B.** Tricyclic antidepressants can amplify hyperkinesia.

## Progression of Huntington's Disease

The disease is chronic and progressive. The earlier its onset, the faster is its progression: rapid progression when onset occurs < 20 years of age, and slower progression when onset occurs > 50 years of age. The average disease duration is about 20 years.

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