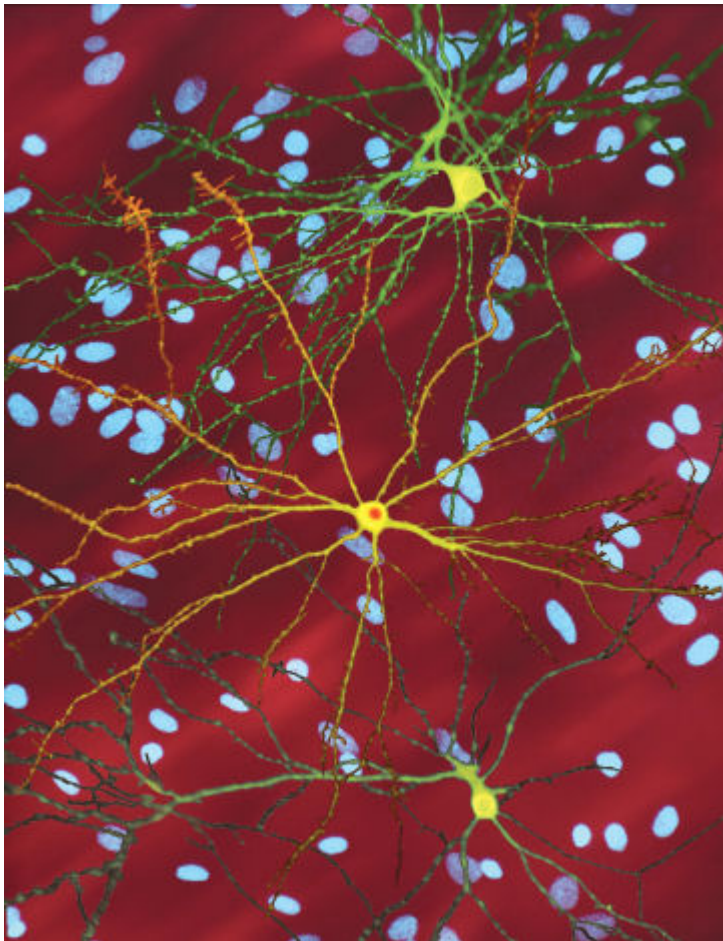


Huntington's Disease (HD, Huntington's Chorea) — Genetics and Progression

[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 of

autosomal dominant inheritance which manifests in **full penetrance**, which means that those who have the mutated gene will become diseased at some point. The pathogenic gene is located on the short arm of **chromosome 4**.

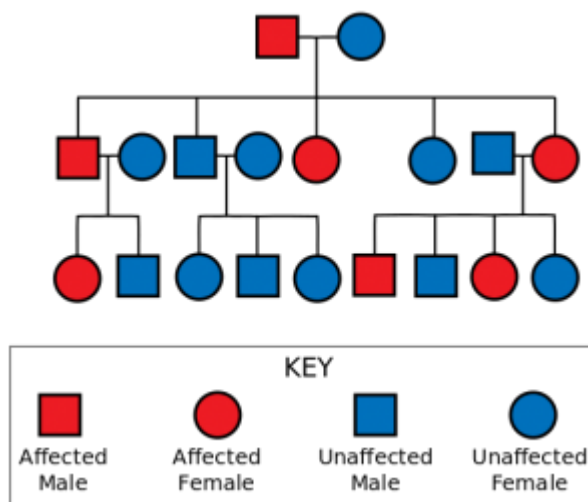


Image: "Autosomal Dominant Pedigree Chart. In Autosomal Dominance the chance of receiving and expressing a particular gene is 50% regardless of the sex of parent or child." by Jerome Walker. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Synonymous with Huntington's disease is the name **Chorea major**. Chorea major must be strictly distinguished from Chorea minor (**Sydenham's chorea**), which has different pathogenesis (see below).

Epidemiology of Huntington's Disease

Huntington's disease in the population

The **prevalence** of the disease is about 2 - 8 / 100,000. Often, the disease clinically manifests between the ages of 35 and 55, although there is a wide range in age of the disease's onset.

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

Men and women are affected almost equally by the disease. This can be explained by the autosomal dominant inheritance of the disease, among other things.

Etiology of Huntington's Disease

Huntington's disease at the genetic level

Huntington's disease is one of several **trinucleotide** repeat disorders containing multiple CAG triplet repeats. Medical diagnosis is made if a repetition of CAG-triplets of at least 39 times is present. As a matter of fact, the more the count of **triplet-repeats**, the earlier the disease's onset.

The fact that the severity of symptoms of Huntington's disease increases in successive generations or manifests at an earlier age of onset, is called anticipation. In correlation to a gender-specific varying DNA-methylation in the course of gametogenesis, especially in

children who inherit the mutation from their father, are affected by the consequence of anticipation. This is referred to as **Genomic Imprinting**.

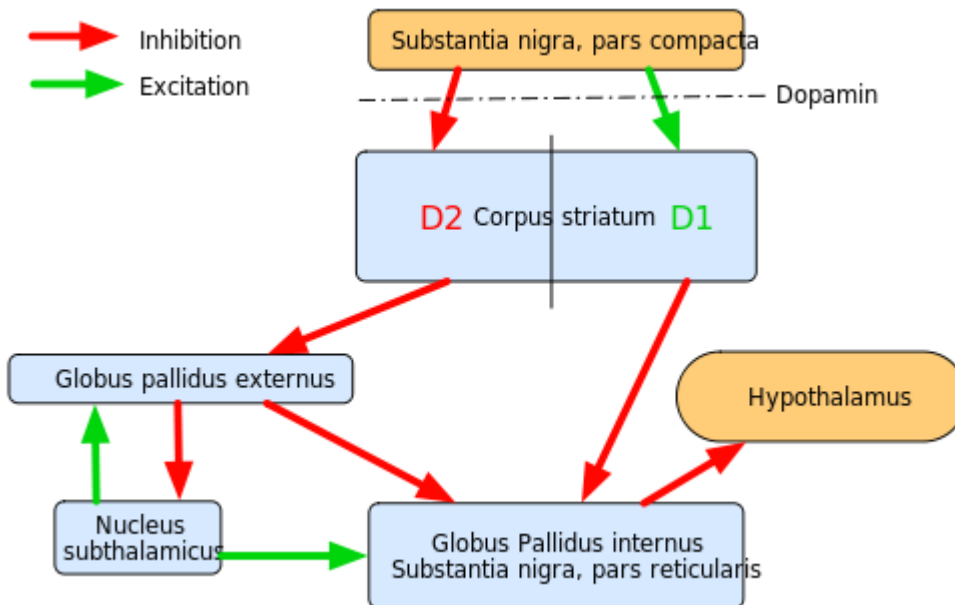
The location of the repeats on chromosome 4 is also called 'Huntingtin-gene'. This gene provides the genetic information to a protein that is found mostly in the brain, but also present in other types of tissue. The precise function of the protein has not been identified yet.

Pathophysiology of Huntington's Disease

Huntington's disease on a neuroanatomical level

Huntington's disease is characterized by atrophy of the **Corpus striatum**. Consequently, GABA-concentration decreases and a state of disequilibrium between **GABA** and **dopamine** is induced.

Note: The striatum is affected by irreversible destruction of GABA neurons.



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

Clinic 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 in distal parts of the limbs. **Orofacial hyperkinesia** of the face can occur in the early stages of the disease and is also referred to as '**Grimacing**'.

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

Further in the course of the disease, limbs are affected by involuntary arrhythmical

movements and the back is often pulled back jerkily (**hyperlordosis**). During times of emotional stress, symptoms can intensify (**'choreatic movement attack'**).

Late symptoms of Huntington's disease

Altogether, patients exhibit a significantly increased calorie consumption rate caused by consistent abrupt movements and are often cachectic. Food intake is even more hindered if nerve tracts of the caudal cranial nerves are also damaged and if the chewing and tongue muscles are also impaired.

Mental symptoms of Huntington's disease

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

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

Note: The definite clinical picture of Huntington's disease is characterized by the triad of hyperkinesia, dementia, and anorexia.

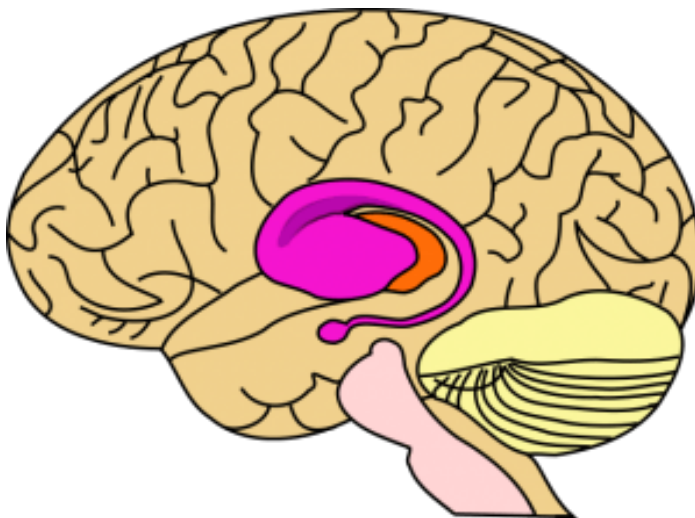


Image: "Area of the brain most damaged in early Huntington's disease—striatum (shown in purple)" by John Henkel. License: [Public Domain](#)

Diagnosis of Huntington's Disease

Genetic examinations in Huntington's disease

Besides using PCR for genetic analysis of gene mutations including a CAG-triplet-repeat, the medical diagnosis of Huntington's disease is made by looking at the clinical picture (see above) of the disease.

EDTA-blood is used for genetic testing. However, prior to that, the guidelines for molecular genetic diagnostics of the Huntington-self-help group must be fulfilled. This includes prior human genetic counseling conducted by the correspondent institute.

Note: Family history does not always have to be positive since there are also i.e. sporadic cases or cases where family members have died before the disease's onset.

Imaging techniques in Huntington's disease

Moreover, in some cases, atrophies of the **Nucleus caudatus** can be visible in a CT or MRT scan of the head when the disease is in its advanced stage.

Additionally, an **HMPAO-SPECT-examination** can be performed if necessary, in which reduced cerebral perfusion of the **striatum** appears. Another optional examination is the **¹⁸FDG-PET** (positron emission tomography), whereby a hypometabolism of the striatum can be detected, possibly even in the early phase of the disease.

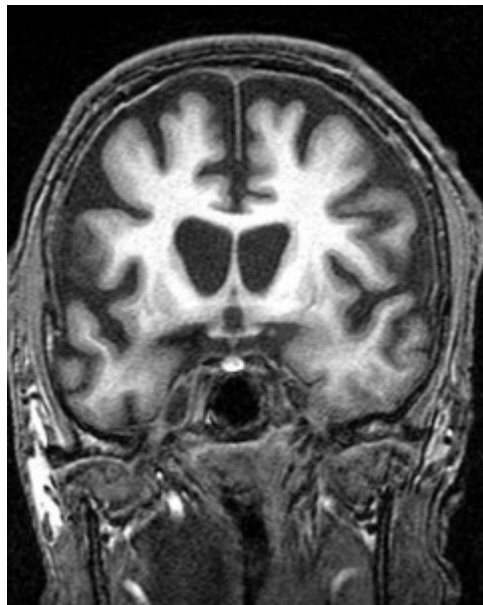


Image: "Coronal FSPGR through the brain at the level of the caudate nuclei demonstrating marked reduced volume in keeping with the patient's known diagnosis of Huntington Disease" by Frank Gaillard.
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Functional diagnostics in Huntington's disease

More possibilities of diagnostics lie in the field of electrophysiology, comprising a SEP (**somatosensory evoked potential**) as well as ENG (**electroneurography**). The **Medianus-** or **Tibialis-SEP** can show a reduction of the amplitude of central potentials.

The ENG is able to visualize a prolonged latency of saccades or a decelerated speed of saccades as well as possible **optokinetic nystagmus**.

Eventually, within the diagnostic setting, possible differential diagnosis (see below) needs to be ruled out. Furthermore, a **neuropsychological test** to record cognitive capabilities may be performed.

Differential Diagnosis of Huntington's Disease

Diseases similar to Huntington's disease

Among the most important differential diagnoses of Huntington's disease is on one hand **Chorea minor** and on the other hand **extrapyramidal motoric disorders** with hyperkinesia.

Ballism, hemiballismus, dystonia, dyskinesia, or **akathisia** (inability to sit still) are considered to be among hyperkinetic diseases.

Medication-induced hyperkinesia is called **dyskinesia**. A possible drug that can trigger dyskinesia is **L-Dopa**, which is used in the treatment of Parkinson's disease. In this case, dyskinesia usually occurs during the course of long-term therapy.

More possible differential diagnoses from the field of internal medicine are **hyperthyreosis, Wilson's disease**, as well as **hypoparathyroidism**. Within the field of neurology, inflammatory diseases like a **neuroacanthocytosis** must be ruled out using a spinal tap when indicated.

Chorea minor as a differential diagnosis to Huntington's disease

Chorea minor (**Sydenham's chorea**) is a disorder resulting from a pathological immune reaction subsequent to infection with β -haemolytic **group A streptococcus**. In about 50 % of the cases, symptoms of rheumatic fever precede the choreatic movement disorders, including polyarthritis, carditis, erythema annulare and subcutaneous papules.

School-age children are particularly affected by this. In this age group, girls are more often affected than boys. **Choreatic hyperkinesia** predominantly appears in the areas of **mimetic muscles, pharyngeal muscles**, the tongue, as well as **distal parts** of the upper limbs.

Due to the accompanying psychic abnormalities like increased excitability, apathy and **labile affect**, the children's peculiar behavior often becomes noticeable at school.

Therapy of chorea minor consists of medication consisting of penicillin G, which should be dosed at sufficiently high amounts and administered for an adequately long period.

Therapy of Huntington's Disease

Treatment of Huntington's Disease

The course of the disease cannot be changed using any treatment, which means that there is no cure. However, symptoms can be managed with **medications, physical and occupational therapy**. In addition, **high caloric nutrition** can counteract cachexia.

Drugs commonly used for treating hyperkinesia are **sulpiride (atypical neuroleptic)** or **tiapride (classical neuroleptic)**. Both these drugs are given first choice, whereas **haloperidol** is a drug of second choice (see literature for further information).

Note: Neuroleptics can induce movement disorders and should only be used if there is a strong physical impairment caused by hyperkinesia. If its use is justified, the lowest possible dose should be administered.

The above-mentioned **sulpiride** is also used for treating feelings of **depressions**. In this context, further medications for treating depression are **alprazolam (benzodiazepine)**,

thioridazine (neuroleptic) and tricyclic antidepressants.

Note: Tricyclic antidepressants can amplify hyperkinesia.

Progression of Huntington's Disease

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

Review Questions

The correct answers are below the list of references.

1. Which statement about the etiology of Huntington's disease is incorrect?

1. It is a disease of autosomal dominant inheritance.
2. Penetrance adds up to 100 %.
3. It is a trinucleotide repeat disorder.
4. The more the count of triplet repeats, the earlier the onset of the disease.
5. The phenomenon of genomic imprinting exists in a maternal inheritance.

2. Which statement about the symptoms of Huntington's disease is incorrect?

1. During the early stage of the disease, orofacial hyperkinesia which can be described as 'grimacing' occurs regularly.
2. Dysarthrophonia can occur.
3. Dementia only develops in extremely rare cases in the later course of the disease.
4. A pseudobulbar palsy can occur.
5. During times of emotional stress, symptoms can intensify.

3. Which statement about the diagnostics of Huntington's disease is correct?

1. The gene mutation can be detected using PCR.
2. An MRT of the head can regularly visualize atrophy of the nucleus ruber in the later stages of the disease.
3. The HMPAO-SPECT-examination detects increased perfusion of the striatum.
4. The PET-examination reveals a hypometabolism in the striatum, which only occurs during later stages of the disease.
5. In the ENG an increased speed of the optokinetic nystagmus is conspicuous.

References

DiDonato, S. (1988). *Molecular genetics of neurological and neuromuscular disease*. New York: Raven Press.

Harper, P. S. (1996). *Huntington's disease*. London: W.B. Saunders.

Huntington's Chorea (Huntington's disease, HD). (2008). *Encyclopedia of Genetics, Genomics, Proteomics and Informatics*, 927-928. doi:10.1007/978-1-4020-6754-9_7945

Huntington's Disease (HD). (n.d.). *SpringerReference*. doi:10.1007/springerreference_115820

Management, P. (2012). *21st Century Huntington's Disease (HD) Sourcebook: Clinical*

Data for Patients, Families, and Physicians–Hereditary Chorea, Diagnosis, Symptoms, Genetics, Medications, Clinical Trials.

Correct answers: 1E, 2C, 3A

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Notes