Huntington disease is an autosomal dominant neurological disorder caused by mutation in the HTT gene. The disease typically manifests in adulthood and is characterized by progressive motor, cognitive and behavioural impairment. Although incurable, treatment is symptom-focused.

HTT encodes the protein huntingtin, the normal function of which is not fully understood but is known to be critical in the development of the nervous system. Huntington disease results when the CAG trinucleotide DNA sequence, which encodes a polyglutamine segment of the protein, is expanded. CAG repeat lengths of ≥40 units are disease-causing and highly penetrant. A strong body of evidence shows that the huntingtin protein is fragmented in affected individuals, through the activity of caspases, calpains and other proteases, but how these fragments cause toxicity is not wholly clear. The most studied fragment — called HTT exon1 — can take different conformations and can bind to various other proteins. Accordingly, determining how this fragment is involved in disease initiation and progression is extremely challenging. However, HTT exon1 is capable of forming amyloid fibril aggregates that might mediate toxicity, a feature that Huntington disease shares with other neurodegenerative conditions such as Alzheimer disease, Parkinson disease and amyotrophic lateral sclerosis.

A diagnosis of Huntington disease is made on the basis of family history, genetic testing for the CAG expansion in HTT and clinical evaluation.

Heritable increases or decreases of up to a few CAG repeats might reflect CAG repeat instability during spermatogenesis as these events occur during transmission from fathers.

Cognitive difficulties often occur before motor onset and are also progressive; inattention and emotion recognition deficits predominate.

Motor dysfunction in Huntington disease is predominantly chorea (involuntary muscle contractions).

Neuropsychiatric features are variable in patients but include apathy, irritability and depression.

The current management strategy for patients is centred around relieving symptoms and requires a multidisciplinary team to address all the facets of one's life that are affected by this condition: from physiotherapists and speech pathologists to nutritional experts and psychologists. Only one drug has gained FDA approval for patients with Huntington disease — tetrabenazine for the treatment of chorea. Other prescribed treatments are used off-label on the basis of efficacy in non-Huntington populations (for example, antidepressants). In late stages of the disease, patients often require specialist residential care.

Biomarker discovery is centred on finding tools to enable the precise measurement of prognosis, progression and treatment response. Cognitive and motor measures; biochemical species in cerebrospinal fluid, blood and urine samples; neuroimaging features; and pharmacodynamic markers are all being investigated. Drug development is exploring numerous targets (such as phosphodiesterases and histone deacetylases) and strategies (such as HTT RNA interference and antisense oligonucleotides) to reduce the production and activity of mutant huntingtin.