ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 09 | September - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

HUNTINGTON'S DISEASE:A REVIEW OF CURRENT UNDERSTANDING AND FUTURE DIRECTIONS

Neurology

Athira Premnath

ABSTRACT

Huntington's disease is a rare,autosomal dominant neurodegenerative disorder caused by an expanded CAG repeat in the Huntington gene which leads to progressive motor dysfunctions, cognitive decline and psychiatric symptoms. This review synthesizes current understanding of Huntington's disease pathophysiology, clinical features,diagnosis and symptomatic management strategies.Emerging therapeutic approaches targeting huntingtin protein like PTC518, LETI-101 and gene editing with Cas9 has been discussed in this review paper.

KEYWORDS

Huntingtin gene(HTT), CAG repeat expansion, chorea, genetic testing, targeting huntington protein, gene editing with CRISPR/Cas9

INTRODUCTION

Huntington's Disease was first observed by the American physician George Huntington in 1872. as These observations were found by him in the families of east hampton, long island and he published the paper on Chorea. In 1993 a group of investigators discovered the mutation in a gene located in chromosome 4.

The clinical trial of involuntary choreiform movements, cognitive impairments, and behavioral abnormalities characterizes this autosomal dominant neurodegenerative disease.

On the short arm of the chromosome 4p16.3 (HTT gene), repeats of the cytosine, adenine, and guanine (CAG) trinucleotide are typically the cause of Huntington's disease.(1)

The mutation causes an abnormally long polyglutamic expansion in the HTT protein's N-terminal fragments which leads to neurodegeneration and also causes HTT protein to be more prone to aggregation and accumulation which mitigates protein folding.

Etiology

- HD is an autosomal inherited neurodegenerative disorder caused if the elongation of CAG repeats of short arm of chromosome 4p16.3 in the HTT gene,this gene encodes for the HTT protein- plays a role in synaptic functions in the post embryonic period.
- CAG repeats larger than 60, are typically seen in juvenile onset illness.
- A repeat duration of no more than 26, is regarded as typical.
- Although they do not exhibit the illness phenotype, patients with alleles in the range of 27 to 35 are susceptible to instability and may spread into the disease-causing range with transmission.
- A repeat length of 36-39 leads to the development HD but not in all cases.
- Repeat lengths more than 40 are always associated with full penetrance and HD symptomatology.

Epidemiology

HD occurs in all human populations worldwide as its prevalence can vary between different ethnicities.

The relative incidence is high among those of Caucasian origin, ranging from 10.6 to 13.7 per 100,000 affected.

Longer life spans, the creation of an accurate genetic test, better care systems for HD patients that lead to longer illness survival, and a decline in the stigma attached to diagnosis are some of the reasons why HD has become more commonplace worldwide over the past 20 years. (2) The average CAG repeat length was 18.4–18.7 for people of European ancestry and 17.5–17.7 for people of East Asian origin.

Pathophysiology

- An increase in CAG (glutamine) trinucleotide repeats in Huntingtin gene (4p16.3), which leads to an autosomal dominant inheritance pattern, as it may further increase the number of inherited repeats with each subsequent generation.
- The age at which symptoms first appear is correlated with the amount of CAG repeats.(3)
- On the other hand as there is an excess glutamine repeats on Huntingtin protein, due to this there is an abnormal protein cleavage and intracellular aggregation which leads to the accumulation of intracellular toxic aggregates.

This Theory Gives Two Possibilities-

1) Neuronal abnormalities- it causes neuronal cell death from toxic aggregates and can lead to-(a) global central atrophy can cause dementia and personality changes. (b) Basal ganglia atrophy causes decrease in function of initiating, coordination and impaired motion due to which hypokinesia, dysarthria, dysphagia, dystonia, thalamic disinhibition occur.
2) Non-neuronal abnormalities- the death of cardiomyocytes causes ineffective myocardial contractions leads to systemic heart failure, can cause skeletal muscle atrophy and weight loss.

Signs And Symptoms

- Motor symptoms are the first ones to present,it may be accompanied by cognitive symptoms as the disease progresses.

a) Early stage- chorea, behavioural changes such as apathy, irritability, subtle loss of coordination, difficulty thinking through complex problems or social withdrawal.
b) Intermediate-dystonia,bradykinesia,rigidity ,postural instability, slowed cognition, impaired attention, visuospatial deficits and memory loss.
c) Late-akinetic-rigid syndrome with minimal or absent chorea, spasticity, clonus and extensor plantar responses,severe language difficulties and subcortical dementia and patients require assistance in all activities of daily life.(4)

- Neuropsychiatric symptoms can be presented at any stage like-Anxiety, irritability, depression, aggression, apathy, psychosis, obsessive-compulsive behaviours.
- In juvenile-onset HD (onset<20years), motor symptoms will differ from adult onset cases- Parkinsonism, dystonia, epilepsy, cognitive decline and mild or absent chorea.

Diagnosis

- Medical history of the patient.
- Physical and neurological examination- to evaluate any decline in the cognitive ability of the patient due to Huntington's disease.
- Psychiatric evaluation- to assess behavioural,mood and personality changes due to the disease.
- Brain imaging- MRI and CT scans to evaluate structural changes like shrinkage or ventricle enlargement,to monitor disease progression and to rule out any underlying disease causing the symptoms of Huntington disease.
- Genetic testing- to detect the expanded CAG repeat in huntington gene to confirm and determine the developing risk of the disease and passing it to the offspring.(5)

Presymptomatic genetic testing: to find out what proportion of Huntington's disease is inherited.

Treatment

There hasn't been a proven treatment to alter the course of Huntington disease.

However, symptomatic drugs can halt the progression of the illness.

- **Medications To Control Movement Disorders-** Tetrabenazine,

valbenazine and deutetrabenazine as it can suppress involuntary jerking and chorea like symptoms. (6) Side effects can include drowsiness, restlessness, triggering depression and other psychiatric conditions.

- **Medications For Mental Health Conditions-** Antidepressants-citalopram, escitalopram and sertraline. Low blood pressure, sleepiness, nausea, and diarrhea are among the adverse effects.(7)
- Psychotherapy can assist in creating coping mechanisms to control expectations as the illness worsens.

Newer Treatment Modalities-
Targeting Huntington Protein

PTC518- is an oral therapy which has shown to reduce huntingtin protein levels by 23% with a 5mg dose and 36% with a10mg dose over 12months, this plans to be accelerated approval with the FDA.(8)

LETI-101- it is an allele selective gene editing using CRISPR technology which aims to reduce huntingtin protein levels,this could be one time durable treatment.(9)

Gene editing with CRISPR/ Cas9- it has potential for treating Huntington's disease by targeting the mutant Huntington gene.(10)

Prognosis

Huntington's disease has a typically predictable course- as the symptoms worsen over time leading to increased disability,after the symptom onset life expectancy can be from 10-20 years,disease progression and symptoms can vary in individuals like age of onset and CAG repeat length. Patients will often require full time care in the end stage disease due severe motor,cognitive and psychiatric impairment. Disease progression can also depend on the CAG repeat length. Symptomatic management can only slow the progression of the disease but cannot cure the disease completely. Patients' quality of life can be enhanced by supportive care.

REFERENCES

1) Shiwal A, Nibrad D, Tadas M, Katariya R, Kale M, Wankhede N, Kotagale N, Umekar M, Taksande B. Polyamines signalling pathway: A key player in unveiling the molecular mechanisms underlying Huntington's disease. Neuroscience. 2025 Mar 27;570:213-224. doi: 10.1016/j.neuroscience.2025.02.042. Epub 2025 Feb 20. PMID: 39986431
2) Jiang A, Handley RR, Lehnert K, Snell RG. From Pathogenesis to Therapeutics: A Review of 150 Years of Huntington's Disease Research. Int J Mol Sci. 2023 Aug 21;24(16) doi: 10.3390/ijms241613021. PMID: 37629202; PMCID: PMC10455900.
3) The calgary guide to understanding diseasehttps://calgaryguide.ucalgary.ca/huntingtons-disease-pathogenesis-and-clinical-findings/
4) Huntington Disease Clinical Presentation-Updated:Jul 22,2025,Fredy J Revilla, MD, FAAN, FANA, Athira Premnath Nair: Jaime Grutzendler, MD, Travis R Larsh, Francisco Talavera, PharmD,Selim R Benbadis, MD https://emedicine.medscape.com/article/1150165-clinical#b1
5) Morbelli, S., Ferrarazzo, G. (2022). Case 12: Huntington's Disease with Atypical Onset. In: Varrone, A., Morbelli, S., Garibotto, V. (eds) Clinical Nuclear Medicine in Neurology. Springer, Cham. https://doi.org/10.1007/978-3-030-83598-9_12
6) Lucetti C, Gambaccini G, Bernardini S, Dell'Agnello G, Petrozzi L, Rossi G, Bonuccelli U. Amantadine in Huntington's disease: open-label video-blinded study. Neurol Sci. 2002 Sep;23 Suppl 2:S83-4. doi: 10.1007/s100720200081. PMID: 12548355.
7) Frank S. Treatment of Huntington's disease. Neurotherapeutics. 2014 Jan;11(1):153-60. doi: 10.1007/s13311-013-0244-z. PMID: 24366610; PMCID: PMC3899480.
8) Huntington Drug PTC518 Meets Primary End Point in Phase 2 Study-May 5, 2025,By Marco Meglio https://www.neurologylive.com/view/huntington-drug-ptc518-meets-primary-end-point-phase-2-study
9) Allele-selective gene editing: a breakthrough in Huntington's disease treatment-Posted: 8 May 2025 | Dr Amy Pooler (Senior Vice President of Research & Development at Life Edit) https://www.drugtargetreview.com/article/160421/allele-selective-gene-editing-a-breakthrough-in-huntingtons-disease-treatment/
10) Purohit, S., Nayak, A., Rani, V., Jain, C.K. (2025). CRISPR/Cas9 Technology and Its Advancements in Targeting Huntington's Disease: A Comprehensive Review. In: Rani, V., Jain, C.K., Gauba, P. (eds) Innovative Advancements in Biotechnology. Advances in Science, Technology & Innovation. Springer, Cham. https://doi.org/10.1007/978-3-031-80189-1_12