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REVIEW ARTICLE

A Review on Advances in Understanding and Therapeutic Strategies for Huntington's Disease

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Abstract: The trinucleotide repeat expansion of CAG in the huntingtin (HTT) gene is the underlying genetic abnormality responsible for Huntington's Disease (HD), an inherited neurodegenerative disorder characterized by severe cognitive impairment. HD manifests dominantly and is primarily attributed to the toxic gain-of-function effects of the mutant huntingtin protein. Degeneration of medium-spiny neurons within the caudate nucleus and putamen leads to motor, cognitive, and behavioral abnormalities in affected individuals. The estimated incidence of HD ranges from 1/10,000 to 1/20,000 in the Caucasian population, with symptoms typically emerging between the ages of 30 and 50. In addition to cognitive decline, HD can present with psychiatric disturbances and motor symptoms, notably chorea, which progressively affects muscle control and psychomotor skills. Juvenile Huntington's Disease (JHD) may manifest with behavioral issues and learning difficulties before the age of twenty. Given the lack of curative treatments for chorea, management focuses on symptomatic relief through medications targeting dopamine receptors. Multidisciplinary care is essential for optimizing quality of life, with interventions including home remedies and non-pharmacological approaches to address behavioral and psychological symptoms. As the disease progresses, individuals often require increasing levels of care, leading to significant caregiver burden. Tragically, suicide is a common cause of death among individuals with HD. Prognosis in HD is determined by the severity of clinical manifestations and confirmed genetic diagnosis. Effective management strategies aim to alleviate symptoms and enhance overall well-being, underscoring the importance of holistic care approaches in mitigating the impact of this devastating disease.

Keywords: Huntington's disease; Motor disorders; Neurogenetics; Chorea; Huntingtin gene.

1. Introduction

In 1872, Dr. George Huntington provided a seminal description of Huntington's Disease (HD), formerly known as Huntington's chorea, offering insights into its neurological manifestations that typically manifest in mid-life and exhibit familial inheritance patterns. HD presents with a spectrum of symptoms including dementia, involuntary choreatic movements, and behavioral and cognitive disturbances. [1] The pivotal discovery of a linkage on chromosome 4 in 1983, followed by the identification of the gene responsible for HD in 1993, marked significant milestones in the understanding of this debilitating disorder. These breakthroughs catalyzed a surge of interest in HD and neurogenetic disorders, prompting the development of precise genetic diagnostic tools based on the identification of a polyglutamine-coding repeat expansion within exon 1 of the huntingtin gene. [2] Notably, individuals harboring more than 39 CAG repeats demonstrate nearly complete disease penetrance. However, despite these advancements, therapeutic interventions in clinical practice primarily target symptom management rather than halting or preventing disease progression. Moreover, the underlying molecular mechanisms driving the extensive neuronal loss observed in HD remain incompletely elucidated, underscoring the need for further research to unravel the intricate pathophysiology of the condition [3]

2. Epidemiology

Huntington's disease is an uncommon neuropsychiatric condition caused by an autosomal dominant mutation in the huntingtin gene on chromosome 4. This mutation results in an abnormal polyglutamine repeat expansion in the huntingtin protein. The mutated huntingtin protein misfolds and accumulates in neurons, disrupting normal cellular processes. The prevalence varies across ethnic populations. In the Caucasian population, it affects approximately 5 to 10 people per 100,000. [4] However, there has been a significant decline in prevalence in Japan, estimated at about one-tenth of the Caucasian population. Some additional phenocopies

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of Huntington's, caused by different genetic mutations, have been reported recently, but their prevalence is much lower. Huntington's disease is a hereditary neurodegenerative disorder. Although categorized as late-onset, it can manifest at any age, but typically appears between 30 and 50 years old. The length of the CAG trinucleotide repeat expansion inversely correlates with the age of onset.[5]

Epidemiological data on Huntington's disease in the United States is limited. One study in a single US state in 1989–1990 estimated the incidence at 0.3 and prevalence at 1.9 per 100,000 person-years or persons. Another study focused on patients with commercial insurance calculated an incidence of 1.2 and prevalence of 6.5 per 100,000. However, these estimates may not accurately represent the current prevalence, especially among elderly individuals. Further study is necessary to establish up-to-date epidemiological data across different US populations [6]

3. Etiology

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an extended CAG trinucleotide repeat expansion in the huntingtin (HTT) gene located on the short arm of chromosome 4p16.3. The HTT gene encodes the huntingtin protein, which is crucial for proper embryonic development and synaptic function in the brain. The normal huntingtin protein is believed to possess anti-apoptotic properties and protect against the toxic effects of the mutant huntingtin protein. In individuals with HD, the HTT gene contains an abnormally long stretch of CAG repeats, typically between 36 and 55 repeats. The longer the CAG repeat sequence, the earlier the age of onset and the more severe the symptoms tend to be. Patients with juvenile-onset HD often have more than 60 CAG repeats in the HTT gene. In contrast, individuals with 27 to 35 CAG repeats do not exhibit symptoms of HD but are at an increased risk of unstable repeat expansions in subsequent generations, potentially leading to the disease. [7] The etiology of HD is illustrated in Figure 1.

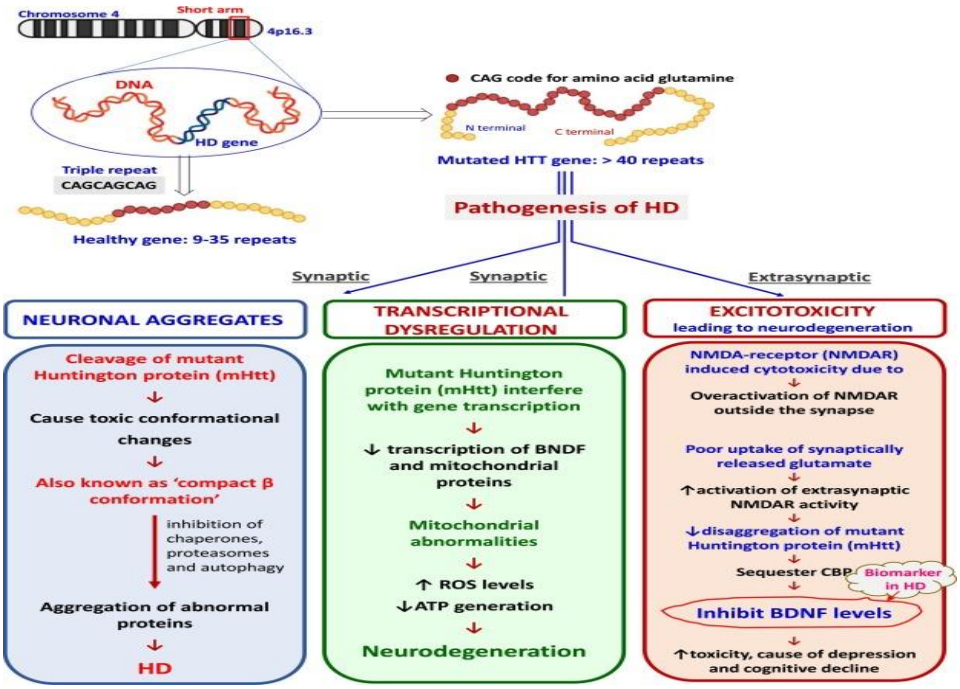

Figure 1. Etiology of HD

Approximately 5% of HD cases are classified as juvenile HD, occurring in individuals before the age of 20. Despite their younger age of onset, patients with juvenile HD exhibit several phenotypic features similar to those observed in adult-onset HD cases. These include stiffness (rigidity), akinesia (lack of movement), and bradykinesia (slowness of movement). However, chorea (involuntary jerking movements) is often less prominent in juvenile HD cases compared to adult-onset cases. Juvenile HD is frequently associated with progressive cognitive abnormalities, such as learning difficulties and intellectual disability, which can manifest at an early age. The primary risk factors contributing to the onset and severity of HD include the length of the CAG repeat expansion in the HTT gene, CAG repeat instability (the tendency for the repeat length to increase in subsequent generations), and genetic modifiers. Among these factors, the CAG repeat length is considered the most significant determinant, with longer repeat sequences strongly correlating with an earlier age of onset and more severe symptoms [8].

4. Underlying Genetics

The huntingtin gene (HTT) and its mutant form play a central role in the complex molecular mechanisms underlying Huntington's disease (HD). The huntingtin protein, both wild-type and mutant, can interact with and modulate the activity of various transcriptional regulators, including transcription factors, chromatin remodeling proteins, basal transcriptional machinery, and non-coding RNAs. These interactions can directly influence gene expression by binding to DNA at intronic, intergenic, or promoter regions. [9]

Transcriptional dysregulation caused by mutant huntingtin is not confined to specific brain regions; alterations in transcript patterns have been observed in non-neuronal organs such as the liver, muscle, and blood, suggesting that the pathogenic effects of mutant huntingtin are widespread throughout the body. Numerous studies, including microarray profiling, RNA-sequencing, and single-cell RNA-sequencing, have identified a wide range of genes that are differentially expressed between HD patients, HD cellular models, HD animal models, and healthy controls.

However, it is essential to recognize that not all changes in gene expression observed in HD are necessarily pathogenic. Some of these alterations may result from compensatory mechanisms activated to mitigate the harmful effects of mutant huntingtin or other cellular stress responses. Therefore, it is crucial to distinguish between primary transcriptional dysregulation caused by the direct interaction of mutant huntingtin with transcriptional machinery and secondary changes in gene expression that may represent adaptive or maladaptive cellular responses. [10]

Potential pathological molecular events in HD can involve various mechanisms, such as:

- Aberrant interactions between mutant huntingtin and transcriptional regulators, leading to dysregulation of gene expression patterns.
- Disruption of chromatin remodeling and histone modifications, altering the accessibility of DNA to transcriptional machinery.
- Sequestration or depletion of transcription factors and co-regulators by mutant huntingtin aggregates, impairing their normal function.
- Dysregulation of non-coding RNAs, including microRNAs and long non-coding RNAs, which can influence gene expression and RNA processing.
- Impairment of RNA processing, transport, and translation due to interactions between mutant huntingtin and RNA-binding proteins.

Potential therapeutic interventions in HD may target these pathological molecular events, such as using antisense oligonucleotides (ASOs) to modulate huntingtin expression, modulating the activity of histone deacetylases (HDACs) or histone acetyltransferases (HATs) to restore proper chromatin structure, or targeting specific transcriptional dysregulation pathways. It is crucial to continue investigating the complex interplay between mutant huntingtin and transcriptional regulation to elucidate the primary pathogenic mechanisms and develop effective therapeutic strategies for HD [11]

5. Signs and symptoms

5.1. Motor Signs

Chorea, characterized by involuntary jerking movements, is one of the most prominent early motor symptoms of HD. Tetrabenazine, an inhibitor of synaptic vesicular amine transport, is the only medication specifically approved to treat chorea in HD. A typical dose of 50-75 mg per day can provide long-lasting anti-choreic effects. However, side effects such as restlessness, anxiety, depression, and sleep disturbances may occur. [12]

Deutetrabenazine, a modified form of tetrabenazine containing deuterium molecules, has a longer half-life and less variability in metabolism. Clinical trials have shown that deutetrabenazine significantly reduces chorea compared to a placebo, and it is suggested that it may cause fewer side effects, such as depression and somnolence, compared to tetrabenazine, although no head-to-head studies have been conducted. In a randomized controlled trial (RCT), the neuroleptic drug sulpiride has also been found effective in treating chorea in HD. Other neuroleptics commonly used in clinical practice for HD include olanzapine, risperidone, and quetiapine, but they may cause side effects such as sleepiness and weight gain. Physiotherapy is often employed to manage other motor problems like irregular gait, poor balance, and falls. [13, 14]

5.2. Psychotic Signs

Due to limited evidence for treating psychiatric symptoms in HD, treatment decisions are often based on medical judgment and expert opinion. Non-pharmacological approaches like cognitive-behavioral therapy or psychodynamic therapy can be used to address depression, anxiety, obsessive-compulsive disorder, and irritability, although their applicability may be limited in cases of cognitive impairment. [15]

Pharmaceutical treatments include selective serotonin reuptake inhibitors (SSRIs) such as citalopram, fluoxetine, paroxetine, and sertraline, as well as noradrenergic and serotonergic antidepressants like mirtazapine and venlafaxine. Neuroleptics are useful in managing psychosis and aggressiveness. Various medications, including bupropion, atomoxetine, methylphenidate, amantadine, bromocriptine, and modafinil, have been used to treat apathy in HD, although no RCTs have been conducted to evaluate their efficacy. [16]

5.3. Cognitive Signs

Randomized controlled trials have evaluated the use of anticholinesterase inhibitors for cognitive impairment in HD, but the participant numbers have been limited, and the results have been inconsistent. Another RCT found that citalopram had no effect on cognitive performance in HD. Coping strategies for cognitive impairments can be helpful, such as requesting employers to modify the nature of work or the workspace, for example, switching to a task that requires less multitasking or working in a quieter environment [17]

6. Diagnosis

The diagnosis of Huntington's Disease (HD) typically involves a multifaceted approach. The Unified Huntington's Disease Rating Scale (UHDRS) general motor rating (TMS), along with clinical assessment of motor dysfunction, is utilized alongside established family history or confirmed genetic testing to ascertain the presence of HD. The TMS scores range from zero (indicating no motor abnormalities suggestive of HD) to four (suggestive of motor onset or "manifest" HD), with a score of four indicative of a high likelihood of HD involvement. Predictive testing for HD carries inherent risks, including psychological distress and, in extreme cases, suicidal ideation. Precautionary measures are implemented to mitigate these risks, such as informing patients of potential outcomes, providing access to counseling services, and ensuring confidentiality. While initial anxiety and stress may follow a positive test result, these symptoms typically subside over time. Regardless of test outcome, individuals may experience a reduction in overall distress and improved well-being over time. Those receiving negative results may sometimes encounter feelings of "survivor guilt" or anxiety, for which counseling is recommended. [18]

For individuals presenting with symptomatic manifestations suggestive of HD, positive genetic testing serves as a cost-effective means to confirm the diagnosis. Conversely, negative test results may indicate the presence of a syndrome akin to HD, warranting further investigation. Exclusionary testing is occasionally conducted on asymptomatic individuals of advanced age to alleviate concerns regarding potential transmission of the condition to offspring or subsequent generations. The experience garnered from Huntington's disease genetic testing serves as a model for testing methodologies in other late-onset disorders, shedding light on both the capabilities and challenges associated with genomic technologies [19]

6.1. Differential diagnosis

A phenocopy of HD encompasses chorea, cognitive impairment, and neuropsychiatric symptoms without the presence of a mutant HTT mutation. While several genetic disorders may manifest as HD phenocopies, definitive diagnoses are rare, occurring in only three percent of cases. Notable conditions resembling HD include C9orf72 and spinocerebellar ataxia (SCA) 17, prevalent within European populations. [20]

Additional features such as ataxia or peripheral neuropathy may indicate alternative diagnoses such as Friedrich's ataxia or SCA 1-3. Dentatorubral-pallidoluysian atrophy (DRPLA) should be considered in cases involving seizures. Aberrant MRI findings may suggest iron accumulation disorders like neuroferritinopathy or neurodegeneration with brain iron accumulation (NBIA). Peripheral blood film analysis for neuroacanthocytosis may reveal abnormal acanthocytes. Among African populations, Huntington's disease-like syndrome 2 (HDL2) is a frequent source of HD phenocopies. [21]

Acquired conditions including striatal pathology, pregnancy-related chorea, systemic lupus erythematosus/anti-phospholipid syndrome, thyrotoxicosis, post-infectious syndromes, polycythemia rubra vera, and medication-induced chorea can all mimic isolated choreic presentations [22]

7. Investigation

7.1. Genetic testing

Diagnostic or predictive genetic testing is available for the mutant huntingtin (mHTT) mutation associated with Huntington's Disease (HD). In cases where a patient presents with characteristic motor symptoms of HD, diagnostic testing may be initiated. However, it is crucial to provide comprehensive pre-test counseling to the patient, informing them about HD and its genetic basis, as a positive test result can have significant implications for both the individual and their family members.

Delivery of positive genetic test results should be conducted in person, preferably within a specialized HD management clinic. Predictive testing (PT) is recommended for asymptomatic adults who are at risk of inheriting the HTT mutation, enabling them to make informed decisions before the onset of symptoms. [23]

International guidelines, revised in 2013 following the discovery of the HTT gene in 1993, emphasize the importance of pre-test counseling as an integral component of the predictive testing process. This counseling provides candidates with information necessary to evaluate the benefits and risks associated with undergoing genetic testing. Subsequent to pre-test counseling, asymptomatic individuals undergo neurological examination to confirm their lack of symptoms. Positive test results are followed by psychiatric screening to identify individuals at heightened risk of suicidal ideation.

For individuals at risk of transmitting the HD mutation to their offspring, reproductive options include prenatal diagnosis (PND) with the possibility of pregnancy termination in cases where the fetus carries an expanded CAG repeat, or preimplantation genetic diagnosis (PGD) during in vitro fertilization (IVF), allowing for the selection and transfer of embryos without the expanded CAG repeat. Additionally, an exclusion test targeting the mutant HTT allele of the affected parent or grandparent enables individuals with uncertain genetic status to access these reproductive options [24]

8. Animal models

Numerous animal models have been developed for the study of Huntington's Disease (HD), with a primary focus on mouse models. These models encompass a range of genetic manipulations and toxin-induced approaches, including N-terminal huntingtin (HTT) models and early toxin-induced models such as quinolinic acid and 3-nitropropionic acid [25].

However, the utility of small animal models presents inherent limitations. One significant challenge is the discrepancy in the timescale of disease progression between humans and mice. HD is characterized by a protracted prodromal phase spanning several decades before clinical symptoms manifest in humans [26]. This extended latency period exceeds the natural lifespan of mice, thus restricting their utility for long-term studies and their ability to fully replicate the disease course observed in humans.

Furthermore, the translational relevance of murine models is hindered by inherent biological differences between mouse and human brains. Discrepancies in brain size, the absence of certain brain regions, and the lack of a complex gyrencephalic structure in mice limit their ability to faithfully recapitulate the pathophysiological features of human neurodegenerative diseases [13]. Despite these limitations, mouse models remain invaluable tools for investigating specific aspects of HD pathogenesis and evaluating potential therapeutic interventions. In addition to genetically engineered models expressing mutant HTT, wild-type HTT models have also been utilized to elucidate the normal physiological functions of huntingtin and its potential roles in disease pathology. These models, although imperfect, provide valuable insights into the molecular mechanisms underlying HD and serve as platforms for preclinical drug screening and mechanistic studies. The animal model mechanisms used for studying HD are illustrated in Figure 2.

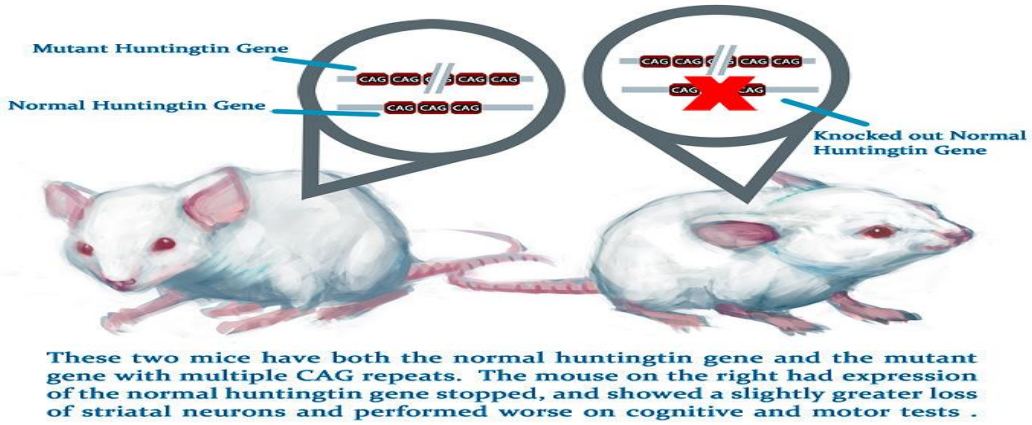

Figure 2. Animal models used in studying HD

9. Management

Effective management of Huntington's Disease (HD) necessitates a multidisciplinary approach involving various healthcare professionals, including physicians, nurses, physiotherapists, speech and language therapists, dieticians, and others. This collaborative team is essential for addressing the diverse and evolving needs of individuals with HD, with a primary focus on optimizing their quality of life throughout the course of the disease [27].

The management of HD typically involves a combination of non-pharmacological and pharmaceutical interventions tailored to individual patient needs. Non-pharmacological strategies may include physical therapy to maintain mobility and independence, speech and language therapy to address communication difficulties, and dietary interventions to ensure adequate nutrition and hydration. Additionally, psychological support and counseling play a crucial role in addressing the emotional and cognitive challenges associated with HD.

Pharmacological therapies are often employed to alleviate specific symptoms of HD, such as chorea, depression, or psychiatric disturbances. However, treatment decisions regarding pharmacotherapy are often guided by clinical expertise and judgment rather than robust evidence-based guidelines, highlighting the need for further research in this area [28].

Overall, the management of HD requires a holistic approach that addresses both the physical and psychological aspects of the disease. By integrating various therapeutic modalities and providing comprehensive support, healthcare professionals can strive to enhance the well-being and functional capacity of individuals living with HD

10. Conclusion

In conclusion, Huntington's Disease poses significant challenges for both patients and healthcare providers due to its complex and progressive nature. While advancements in understanding the pathophysiology of HD have led to the development of various therapeutic strategies, effective management remains elusive. A multidisciplinary approach that incorporates both non-pharmacological and pharmacological interventions is essential for addressing the diverse needs of individuals with HD and optimizing their quality of life. However, further research is warranted to elucidate the underlying mechanisms of the disease and to identify more effective treatment modalities. Through collaborative efforts and ongoing innovation, we can strive to improve outcomes and enhance the care of individuals affected by Huntington's Disease

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