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Case Report

# Gene Therapy and Current Therapeutic Approaches for Huntington's Disease

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**Abstract**

Huntington's disease (HD) is a progressive neurodegenerative disorder. ASOs and RNAi have shown significant promise in both experimental and clinical studies for the treatment of this disease. Additionally, researchers are investigating the precise alteration of the genome using CRISPR/Cas9 and base editing techniques. Potential treatment targets include reducing the levels of mutant Huntington's protein and halting the neurobiological processes that contribute to the development of HD. These therapeutic approaches hold the potential to enhance the overall well-being of individuals affected by the disease. As new gene silencing and editing tools continue to be developed, further advancements in HD treatment are expected. This review provides an overview of the current research on treatment strategies for HD.

## Introduction

Huntington's disease (HD) is an inherited disorder characterized by the progressive development of cognitive, physical, and psychological symptoms. The disease is caused by an elongation of the CAG trinucleotide repeat in the Huntington's disease (HTT) gene, which results in the production of mutant Huntingtin protein (mHTT). The accumulation of mHTT in neurons leads to dysfunction and eventual cell death[1]. Currently, there is no proven treatment for HD, and the focus is on managing symptoms and improving quality of life. However, gene therapy has emerged as a promising approach to address the underlying cause of the disease. Gene therapy has shown success in altering gene expression or correcting genetic defects directly, which may slow or halt the progression of HD.[2].

Antisense oligonucleotides (ASOs) or RNA interference (RNAi) can achieve gene suppression in gene therapy for Huntington's disease (HD). The main goal of this method is to effectively reduce the synthesis of mutant HTT mRNA to establish or inhibit the appropriate expression of pathogenic mutant Huntingtin (mHTT) protein. Scientists have been studying various gene modification methods, focusing on CRISPR. CRISPR/Cas9 can precisely target mutations in the HTT gene. This can correct genetic abnormalities or stop the expansion of CAG repeat segments. Studies have shown good results using gene editing in the treatment of Huntington's disease.[3, 4].

Two important criteria must be met before gene therapy can be used to treat Huntington's disease (HD). The first goal is to target a specific mutant HTT gene, while the second goal is to find effective methods to deliver the drug. Adeno-associated viruses (AAVs) are frequently used as viral vectors due to their ability to infiltrate neurons [5]. The search for alternative vectors for gene therapy depends on further advances in science. Researchers have been conducted extensive studies on lipid- and polymer-based nanoparticles to increase the effectiveness and versatility of gene therapy.
Despite significant advances in the application of gene therapy for Huntington's disease, it has been requires further research. Many challenges must be addressed before disorders affecting the central nervous system can be effectively treated. Some of these factors include increasing the sensitivity and efficiency of gene transfer, prolonging the duration of therapeutic benefits, and reducing harmful consequences or immunological reactions. Scientists have been striving to present the latest research on gene therapy for Huntington's disease. In this review, we will examine various gene therapy techniques that involve gene editing and silencing. To effectively treat Huntington's disease, it is crucial to thoroughly investigate both the possible therapeutic benefits of these promising techniques and the problems that may be encountered. In light of this, possible treatment methods as well as difficulties that may be encountered will be comprehensively evaluated.

## Epidemiology and Clinical Manifestations Huntington’s Disease

Huntington's disease (HD) is a neurodegenerative disease characterized by the gradual deterioration of neurons [6]. Although Huntington's disease is rare in the population, it usually onset of diseases and gradually increases. Although symptoms usually appear between the ages of thirty and fifty, earlier and later ages of onset have been noted [6]. The disease is estimated to be common in 5 to 10 cases per 100,000 people, although this rate varies regionally [7]. This disease affects both men and women and usually occurs in adulthood, although there have been cases of it occurring earlier or later in life.A study conducted before the identification of the HTT gene found that there were 1.8 to 4.8 cases per 100,000 people in certain regions of Northern Italy [7].HD is significantly more common among European people, although this varies between countries and ethnic groups [8]. Additional studies have also supported these findings [9]. New findings suggest that cultural and genetic factors must be taken into account to assess the prevalence of HD and show previously unknown disparities between different ethnic groups. This highlights the importance of this disease and its many effects, including physical, emotional and cognitive problems. Although this information expands our understanding of the disease, it is important to remember that affected individuals may differ in terms of symptoms and progression of the disease[10]. HD consists of manual, mental, and cognitive symptoms. Patients may experience coordination and balance problems along with motor disorders such as involuntary movements, often known as chorea. Deficits in motor skills become more evident as the disease progresses [11-13]. Cognitive symptoms become more pronounced as the disease progresses. Some symptoms include memory loss, impaired cognitive skills, decreased mental processing speed, and difficulty making decisions. Mental symptoms, including obsessive behaviors and strong emotions such as grief, anxiety, and anger, may also occur during this period [11].

## Huntington Genes

HD is an autosomal dominant hereditary disease that progresses and causes neurodegeneration.It is characterized by chorea, loss of coordination, cognitive decline,

depression, and psychosis[14]. In 1872, George Huntington introduced hereditary chorea, which is now known as HD[15].

HD is a progressive neurodegenerative movement disorder. It is characterized by an increase in the trinucleotide repeat (CAG) of the IT15 gene, which worsens the severity of the disease[16]. According to the central dogma, the DNA genetic code determines the RNA to be copied as a complement to the DNA. This RNA is then translated into a protein with a specific function in the cells. The presence of CAG repeats in the gene results in the production of the Huntingtin (Htt) protein, which contains repeated glutamine stretches [17].This makes it susceptible to misfolding and subsequent aggregation, leading to the loss of the original function of the gene. The mutant protein is responsible for clinical symptoms including chorea, dystonia, incoordination, cognitive decline, and behavioral difficulties[18].

HD is the most prevalent monogenic neurodegenerative condition of the central nervous system. It is caused by a CAG repeat expansion in exon 1 of the huntingtin gene[19]. A reliable genetic test is available, and complete penetrance for CAG repeats above 39 ensures a reliable diagnosis in life. Individuals carrying the mutation can be identified in the presymptomatic phase[20]. Repeats longer than 36 glutamine repeats are predictive of HD while repeats shorter than 36 do not carry any HD risk. Additionally, the length of repeats on the mutant allele is inversely correlated with the age of onset of HD symptoms[21].

The HTT gene is located on chromosome 4p16.3 and spans 180 kb, containing 67 exons[22]. HTT protein consists of 3,144 amino acids and has a molecular weight of 348 kDa. The Huntingtin protein is expressed throughout the body, with varying levels depending on the cell type. The protein is ubiquitously distributed in both the nucleus and the cytoplasm and exhibits facile translocation between both compartments.[23].

When an abnormal conformation of the Htt protein occurs, it affects the central nervous system (CNS), acquiring toxic functions and causing large striatal neuron death in the brain. Up to 95% loss of γ-aminobutyric acid-releasing (GABAergic) neurons can occur, with selective preservation of some interneurons in the globus pallidus and substantia nigra, which are involved in motor control in the brain [18][24].

## Discussion

### Current Treatment Approaches

HD is a rare and highly complex neurodegenerative disorder. Currently, there are no approved gene-altering therapies for this disease. Currently, there is no disease-modifying therapy available for HD. However, ongoing trials are exploring potential therapies that target key viral and non-viral vectors[25]. These trials include various strategies to reduce mutant Huntingtin gene levels and target the DNA repair pathway. Due to the lack of curative treatment and the devastating neuropsychiatric symptoms, there is an urgent need for improved symptomatic treatments[26].Despite the complexity of HD, developments in the treatment are in progress[27]. Medications are intended to reduce and eliminate the symptoms of most of these treatments.

### Pharmacological Approaches

**1.1. Dopamine Depletion:** Tetrabenazine and deutetrabenazine are approved by the FDA to treat chorea, a common motor symptom associated with Huntington's disease, by reducing dopamine levels [28].

**1.2. Antipsychotics**: Anxiety disorders such as aggression and psychosis can be treated with two atypical antipsychotic drugs, namely olanzapine and quetiapine [29, 30].

**1.3. Antidepressants**Selective serotonin reuptake inhibitors (SSRIs) may be recommended for HD patients to effectively treat symptoms of sadness and anxiety [31].

**1.4. Cognitive Enhancers:** In people with HD, cholinesterase inhibitors such as donepezil can improve cognitive function [32, 33].

**Non Pharmacological Approaches**

**2.1. Physiotherapy**:Mobility and motor functions of HD patients can improve with exercise and physical therapy programs [34].

**2.2. Supportive Care**: Palliative care and symptomatic treatment can significantly improve the quality of life of individuals living with HD and their families [35, 36].

**Developing Treatment Methods**

**3.1. Gene Silencing:** The use of antisense oligonucleotides [37] and small interfering RNA (siRNA) can be used to reduce the production of mutant Huntingtion protein, as used in the treatment of SMA [38] [39, 40].

**3.2. Stem Cell Therapy:** Preclinical studies investigating the potential of stem cell transplantation for neuronal replacement and neuroprotection in HD are ongoing [41, 42].

**3.3. Neuroprotective and Disease Modifying Agents**: Various agents are being investigated to target specific pathways of HD such as inflammation and mitochondrial dysfunction [43, 44].

Experts are making steady advances as they examine both traditional and breakthrough treatments for HD. The main goal of this comprehensive research is to improve disease modification and optimize symptom management. Nevertheless, in order to do this, it is essential that the HD treatment plan include continuous examination, personalized therapeutic approaches, and a multidisciplinary healthcare team.

**Targeting Pathological Protein**

Huntington hastalığı (HD), mutant Huntingtin proteinini içeren atipik protein birikimlerinin varlığıyla ayırt edilir[13]. The priority in combating HD is to target the pathogenic protein that causes the disease. This therapeutic approach is becoming increasingly important in the treatment of HD. Ongoing research investigates various approaches to directly target the disease-causing protein mHTT. These methods are designed to reduce the formation of the mutant variant of the protein, increase its elimination from cells, and reduce its harmful effects.

**1.2. Transcriptional Regulation**: Abnormal transcriptional activity associated with HD can be reduced through epigenetic modifiers or transcriptional repressors (mHTT)[45, 46].

**2.1. Induction of Autophagy:** Promoting autophagy, an important cellular process involved in the degradation and elimination of misfolded proteins, is a promising approach in the treatment of mutant HD. Researchers continue to search for drugs and small molecules to induce autophagy [37].

**2.2. Chaperone Mediated Autophagy (CMA):** Targeting components of the CMA machinery involved in this process can facilitate mHTT selective degradation in neurons [47, 48].

**Modulation of toxic effects caused by mutant protein:**

**3.1. Protein Homeostasis:** The deleterious consequences of mutant Huntingtin protein (mHTT) accumulation can be mitigated by methods targeting the proper functioning of the proteostasis network and restoration of protein homeostasis[49].

**3.2. Mitochondrial Dysfunction:** Therapies used to correct mitochondrial dysfunction, such as promoting the formation of new mitochondria or reducing oxidative stress, can reduce the harmful effect of mHTT on cellular energy metabolism [50].

**3.3. Microglia activation and cytokine release:** Mutant Huntingtin protein (mHTT) [38] can reduce the negative effects of inflammation[51].

Possible ways to improve outcomes in HD are combination treatments, where more than one treatment is administered at the same time. Therefore, it is possible to use a combination of these treatments to target harmful proteins. These methods are used to silence genes. Therefore, focusing on disease-causing proteins, particularly mutated mHTT proteins, would be a very promising approach that could help people with HD. New treatments to slow or stop the progression of Huntington's disease (HD) have emerged in new techniques to turn off genes, control autophagy, and reduce the deleterious effects of mutant Huntington's (mHTT) gene accumulation. More research and extensive clinical studies are needed to prove that these methods are safe and effective.

**Cholinergic system modulation**

Extensive research is now underway to develop treatments for the cholinergic modulation system. Cholinesterase inhibitors (ChEI) are necessary to elevate acetylcholine (ACh) levels in the brain.This helps prevent the breakdown of acetylcholine (ACh). Extensive research has been conducted on this topic, particularly on the mental effects of acetylcholinesterase inhibitors (ChEI) such as Donepezil, Rivastigmine and Galantamine in people with HD[52].

It is crucial to achieve precise control over cholinergic signaling by selectively targeting specific receptors, such as muscarinic receptors. The use of specifically tailored agonists targeting muscarinic receptors in the treatment of HD has been studied. A number of studies have investigated the relationship between HD and mitochondrial dysfunction. A recent study investigated how dopamine receptors contribute to the adverse consequences of mutant Htt and found a strong link between HD and the control of neurotransmitter systems over mitochondrial function. In addition, researchers emphasize that it is possible to focus on the cholinergic system for HD treatment and suggested new approaches [53].

As a result, the cholinergic system is crucial in the development of neurodegenerative diseases such as HD. It controls synaptic activity and chemical transmission and can be used to treat many diseases. Modulation of cholinergic pathways only alleviates symptoms without altering disease progression. Consequently, ongoing research is necessary to better understand the role of the cholinergic system in HD and to investigate more precise therapeutic interventions for accompanying signs and symptoms.

**Gene therapy with Viral vectors and non viral vectors**

Currently, viral vectors are the preferred method for gene replacement in clinical trials. This is because viruses such as adeno-associated virus (AAV), lentivirus (LV), adenovirus (Adv), and retroviruses can express long genes and facilitate gene exchange. Viral vectors transform disease-causing viruses into a gene-carrier format by altering their genetic structure. Viruses have tropism for specific tissues and cell types, making them useful for developing targeted therapies[38].

AAV is the most commonly used viral vector in human gene therapy due to its lack of reported adverse effects. Adv is an icosahedral capsid virus with a size of 70 to 100 nm, and has been used as a vector for gene therapy due to its limited characteristics that restrict gene transfer. Adenoviruses (Advs) cannot integrate their genes into the host genome, which triggers only transient expression of transgenes. Moreover, Adv triggers an innate immune response in humans, which limits its therapeutic potential for CNS gene therapy[54].

In contrast, retroviruses and LVs can provide more stable and longer transgene expression by reverse transcription, allowing them to integrate their DNA into the host genome. However, retroviruses and LVs used in gene therapy can cause genotoxicity and mutagenesis by inserting into the genome [16]. Despite having an excellent safety profile, viral vectors have limitations such as broad tropism, limited loading capacity, difficulty in vector production, and host inflammatory responses. Therefore, the gene therapy sector is actively seeking new viral vectors. Non-viral vectors, such as nanoparticles, liposomes, and exosomes, have been suggested as a potential alternative to gene transfer, as they may help to address safety concerns[55].

Gene editing involves creating a double-strand break (DSB) in the targeted DNA sequence. Four main nuclease systems are used to induce DSBs: ZFNs, TALENs, meganucleases, and CRISPR/Cas9. Currently, CRISPR/Cas9 is the preferred treatment approach[55].

This technology can specifically target genes in a DNA region and make desired changes. The CRISPR/Cas9 mechanism is based on the defense mechanism that bacteria use to prevent viral attacks. It consists of the Cas9 protein and an RNA guide that targets a specific DNA sequence. The RNA guide enables Cas9 to bind to the targeted DNA region, where it cuts the double-stranded DNA and alters the genetic material [56].

Yang et al. carried out a mouse study in which they employed CRISPR technology to delete the mHTT polyQ domain in both wild-type (WT) and mutant mice. As a result of their investigation, four guide RNAs were meticulously designed to selectively target the DNA regions adjacent to the CAG repeat within exon 1 of HTT in human subjects. The reduction of mHTT expression appeared to attenuate the reactivity of astrocytes, without impacting the levels of other proteins examined within the realm of neurodegenerative disorders[57].

Clinical trials investigating miRNA therapy in Huntington's disease (HD) are already underway. One such study is the UniQure AMT-130 trial (NCT04120493), which aimed to assess the safety, tolerability, and efficacy of bilateral intrastriatal injection of AAV5-miHTT on cerebrospinal fluid (CSF) biomarkers in early-stage HD patients. The AAV5 viral vector was utilized for delivery in this study. Another AAV-based clinical trial in HD, sponsored by Spark Therapeutics, is currently being planned to evaluate the effectiveness of an anti-HTT miRNA delivered by AAV1. Promising results have been observed in non-human primates (NHPs). Voyager Therapeutics also has an ongoing program for AAV-mediated anti-HTT

RNAi therapy (VY-HTT01). However, the program is currently on hold pending the development of more efficient viral delivery methods[58, 59].

New oral drugs that target HTT expression are emerging as potential therapies for HD. The first of these drugs, branaplam, was identified in a phenotypic screen that targeted expression levels of the spinal motor neuron. Branaplam was shown to reduce the expression of both copies of the HTT protein through splicing modulation. The human HTT gene was spliced in

the region of exons 49-50 with or without branaplam, a small molecule splicing modulator. Branaplam recognizes a specific sequence in the intron between exons 49 and 50 and identifies it as an exon. This inclusion of a pseudoexon leads to down-regulation of HTT mRNA and protein due to the engagement of in-frame stop codons in the mature HTT transcript. Branaplam (LMI070 and NVS-SM1) is a pyridazine derivative developed to treat HD. However, the trial was terminated in 2023 due to harmful side effects[58, 60].

**Conclusion**

In conclusion, gene therapy research on Huntington's disease is promising. ASO and RNAi have shown positive results in clinical and experimental studies. Precise modification of the genome using new methods such as base editing and CRISPR/Cas9 is being investigated. Studies are ongoing to deliver these treatments to humans using both viral and non-viral carriers. Stopping the neurological processes that cause HD and reducing the amount of mHTT is one possible treatment target. This therapy intervention is appear to improve patients' overall well-being.As new gene silencing and editing techniques emerge, research in this field will continue.

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