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CRISPR-Based Gene Editing in Monogenic Neurological Disorders: Opportunities and Limitations in Treating Huntington's Disease

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ABSTRACT: Huntington's disease (HD) is an inherited neurological disorder which progresses in a manner that causes the HTT gene to contain a pathogenic expanded CAG sequence. Current therapy simply controls the symptoms, but does not address the genetic defect. Thus, gene-editing techniques, based on CRISPR, have garnered widespread interest as disease-modifying strategies. The opportunities and limitations of strategies for the treatment of HD using CRISPR are critically discussed in this paper based on secondary academic literature. Immediate targets are mutant HTT allele-specific targeting; down regulation of the expression of the harmful huntingtin; CAG-repeat modification; and new precision-editing technologies like base editing. These strategies could offer people chances to intervene directly in the mechanisms of disease. But there are also some big obstacles to consider, such as accessing affected brain areas, off-target effects, unintended genomic changes, immune reactions and the long-term safety of these drugs. There are also ethical questions on irrevocable genetic modification and equitable access, which need to be taken into account. In conclusion, CRISPR shows significant promise but has not yet been tested for use in the clinic and needs more preclinical and clinical studies to be a viable treatment option for HD.

KEYWORDS: CRISPR-Cas9; Huntington's Disease; Gene Editing

I. INTRODUCTION

Huntington's disease (HD) is a hereditary, progressive neurologic disease that occurs when the CAG trinucleotide sequence is enlarged in the HTT gene on the chromosome 4. The expansion creates mutant huntingtin (mHTT) responsible for the progressive degeneration and dysfunction of the neurons, especially in the striatum and cerebral cortex. Since HD is predominantly a mutation in a single gene it is important to study this as a model for gene-based approaches to treatment. CRISPR-based gene editing is one of the most promising new technologies, as it can be designed to edit a set of specific sequences in the DNA. Selectively inactivating the mutant HTT allele, reducing the expression of HTT, removing the expanded CAG repeats, and newer precision editing tools, like base and prime editing (Shin et al., 2022), are among the proposed strategies in the context of HD research. Preliminary work in cellular and animal models has shown promising results, with genetic intervention found to have beneficial effects in lowering the pathological effects of mHTT. However, the translation to clinical treatments that are safe is a challenge. Key challenges are efficient delivery of editing systems to targeted regions of the brain, off-target effects, immune responses, and genomic instability, and the editing efficiency and requirement to maintain the normal function of healthy huntingtin. This paper, therefore, critically reviews the possibilities and constraints of using CRISPR-based genome editing as a therapeutic option for the treatment of HD.

II. RATIONALE AND OBJECTIVE

Rationale

Huntington's disease (HD) is an excellent disease model for studying gene editing due to its monogenic nature, which is attributable to a pathogenic CAG-repeat expansion in the HTT gene. In contrast with the conventional symptomatic treatments, CRISPR-based treatments can directly act at the genetic level by lowering the mutant huntingtin (mHTT), specifically targeting the disease-carrying allele, remove expanded repeats, or modify the disease-causing sequences (Shin et al., 2022). Promising results have been observed in cellular and animal models with preclinical studies showing decreases in mHTT and improvements in disease-related phenotypes. But CRISPR-based therapy is still in the experimental stage and there are key hurdles to its delivery to the central nervous system, its off-target activity,

genomic instability, immune responses, and the ability to maintain normal HTT function. In addition, recent studies on base editing and other precision editing tools further reinforce the need to explore the use of these methods as safer and more precise tools than traditional CRISPR nucleases.

Objectives

1. To examine the genetic and molecular basis of Huntington's disease and evaluate how CRISPR-based gene-editing technologies can target the HTT mutation.
2. To critically evaluate the potential therapeutic opportunities of CRISPR approaches, including mutant HTT silencing, allele-specific targeting, CAG-repeat modification and emerging precision-editing technologies.
3. To assess the major scientific, clinical, safety and ethical limitations that may affect the translation of CRISPR-based gene editing into effective treatments for Huntington's disease.

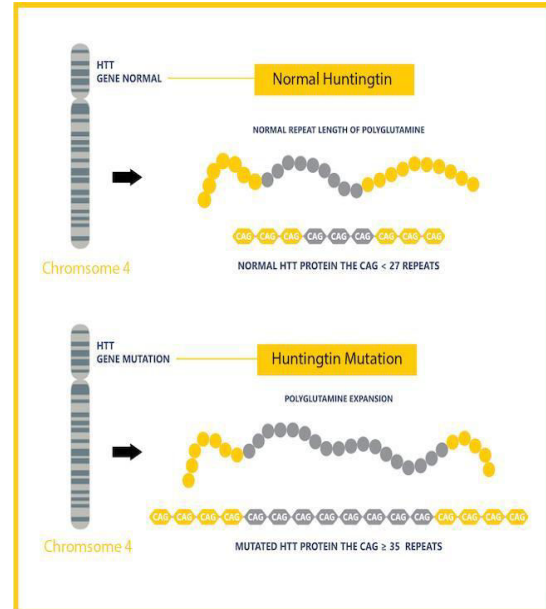
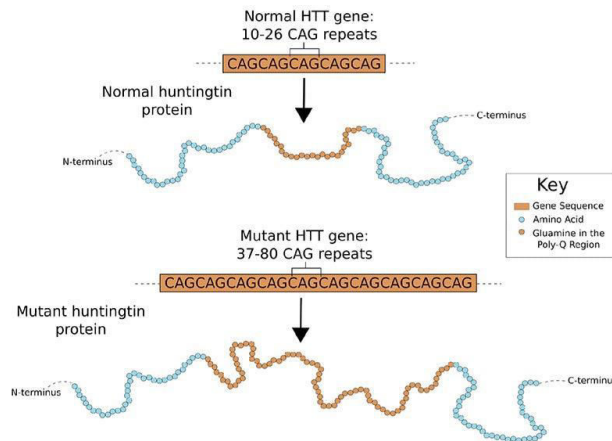
III. METHODOLOGY

This study will employ secondary research method, in which only academic literature found by using google scholar will be used. Studies in the relevant peer-reviewed journal articles, research papers and scholarly reviews on CRISPR-based gene editing, the HTT gene, HD, therapeutic applications, safety and ethical considerations will be analyzed. The literature will be thoroughly reviewed and analyzed to identify the consistent findings, contrasting views, gaps in research and new developments in CRISPR techniques. Care will be taken to ensure that published evidence is reliable and relevant, and conclusions will be drawn from scientific evidence rather than from unsubstantiated claims. The ethical issues will be discussed throughout the study. Issues of informed consent, patient autonomy, patient privacy, patient confidentiality, risk-benefit analysis and equitable access to the potential gene-editing treatments are key. Special attention will be paid to the difference between somatic and germline editing as the latter would impact generations beyond the first. The potential for the long-term effects of permanent changes to the genetic code and the possible unintended changes to the genetic code and the unequal access to cutting-edge treatments will also be taken into account. This study will not engage with human subjects, involve personal data collection, be clinical or involve laboratory experimentation. Thus, there will be no new biological samples or risks to participants posed by the research. The research will be conducted with integrity and will represent and not fabricate, plagiarize, or misinterpret published evidence.

IV. LITERATURE REVIEW

Theme 1: Genetic and Molecular Basis of Huntington's Disease

Huntington disease (HD) is a monogenic inherited, neurodegenerative disease with an abnormal (expanded) copy of the CAG trinucleotide repeat in the first exon of the gene for the protein huntingtin (HTT). This mutation results in the abnormal production of a huntingtin protein with an expanded polyglutamine tract that causes problems in the brain cells, leading to degeneration of the cells and gradual neurological problems. The disease is primarily known to affect the striatum and cerebral cortex, but other neuronal systems may also be affected (Shin et al., 2016). The length of the CAG repeat inherited is strongly associated with disease onset, and additional somatic expansion of the repeat in specific tissues (such as the brain) is now known to be an important factor in disease progression. Since HD is monogenic, it is an even more attractive target for gene-based intervention. The usual treatment of chorea and psychiatric disturbances and other complications are pharmacological, without attempting to correct the underlying genetic abnormality (Monteys et al., 2017). CRISPR technologies have the potential to offer a new therapeutic approach: either by altering the DNA or by controlling the expression of the pathogenic gene. For this reason, researchers have explored the possibility of selectively disrupting the mutant HTT allele through either transcriptionally suppressing or structurally modifying it.



CAG repeat expansion in *HTT*

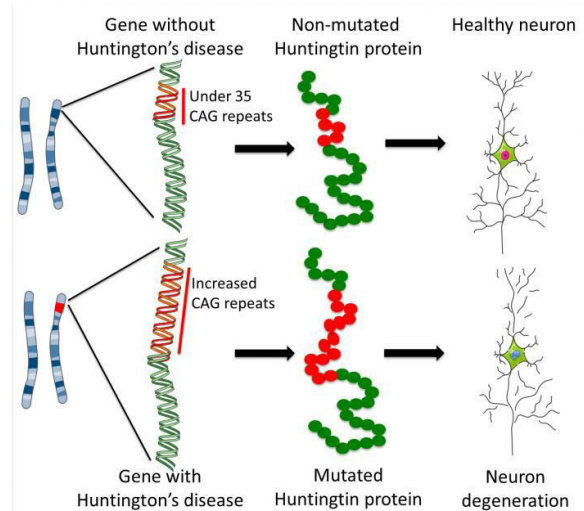
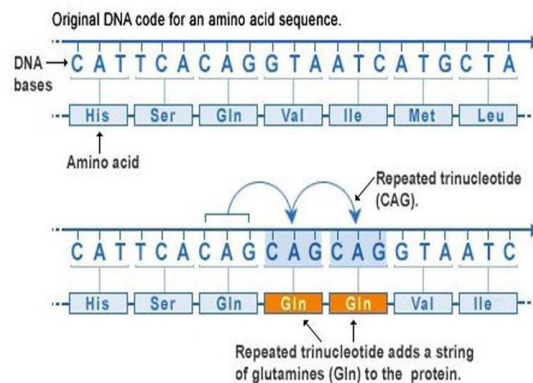


Figure 1: Genetic basis of Huntington's disease and CAG-repeat expansion in the *HTT* gene

Huntington's is a genetic defect in the brain that results in an abnormal accumulation of CAG in the *HTT* gene. There are also substantial challenges associated with the molecular characteristics of HD. Normal huntingtin protein has biological functions, so if both copies of the *HTT* gene are deleted, there are possible negative side effects. Thus, a strategy is focused on selectively reducing the expression of mutant huntingtin while keeping a sufficient level of normal huntingtin function (Oura et al., 2021). Three main categories of studies are identified in recent literature, namely, allele-specific editing, repeat excision, and transcriptional suppression and precision-editing approaches. Another factor to consider is somatic CAG-repeat instability. CRISPR-Cas9 research in the HD mouse has shed light on genes and pathways related to repeat expansion, which may offer potential avenues to discover biological mechanisms that could affect disease pathogenesis. This indicates that CRISPR can be useful for more than just as a therapeutics technology, it can also be used as a research tool to investigate the molecular mechanism behind HD (Huang et al., 2022)..

Theme 2: CRISPR-Based Therapeutic Opportunities for Huntington's Disease

The big advantage of CRISPR is its ability to directly interact with the genes themselves. In conventional CRISPR-Cas9, a guide RNA is used to guide a Cas nuclease to a specific DNA sequence where the enzyme can create a targeted break in the DNA. Genetic alterations can then occur at the target site as a result of cellular repair mechanisms (Yang et al., 2019). In HD, this idea has led to the exploration of approaches to modify or eliminate the mutant HTT gene or pathogenic repeat expansion. An important approach is the targeting of the mutant HTT allele and the preservation of the normal allele (allele-specific editing). This is important, potentially, because it is not desirable to have the loss of all huntingtin. To increase the specificity of CRISPR targeting, researchers have explored the sequence variations between mutant and normal alleles, as well as nearby genetic variants. This could potentially lower the amount of toxic mutant huntingtin produced while preserving the normal protein functions of healthy huntingtin (Swenson et al., 2021). A field review of the literature identifies allele specific editing of one of the most important therapeutic strategies currently being investigated.

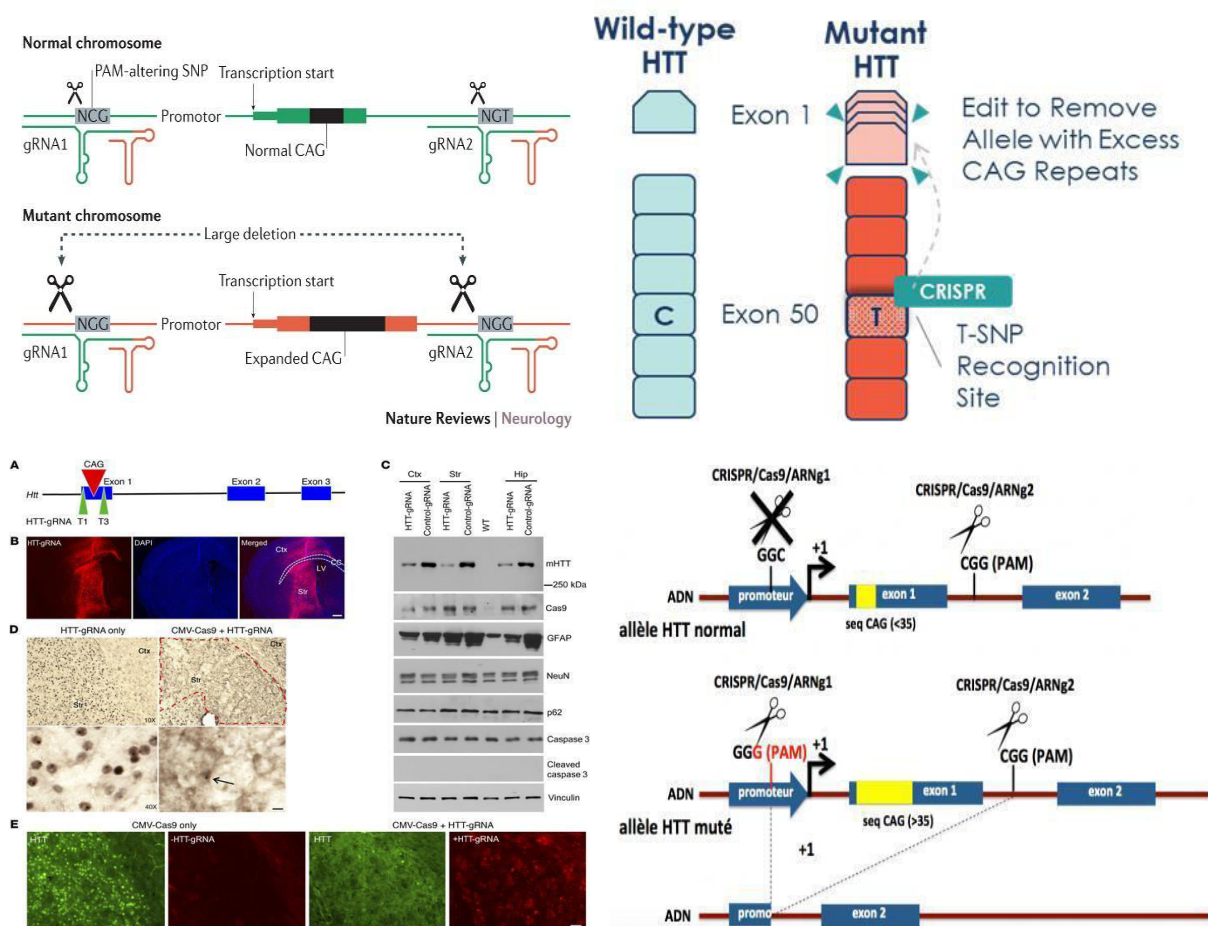


Figure 2: Allele-specific CRISPR-Cas9 targeting of the mutant HTT allele in Huntington's disease.

Targeting of the mutant HTT allele in HD using the allele-specific CRISPR-Cas9 system (allele-specific targeting). The second opportunity is for CAG-repeat excision. Because the expanded CAG sequence is the basic genetic defect associated with HD, theoretically, CRISPR systems could be engineered to eliminate or edit the expanded repeat. This is especially promising since it attempts to tackle the mutation itself rather than just the downstream expression of proteins. But the repetition of the sequence also poses technical challenges for precise and predictable editing (Friedman et al. 2023). The third strategy is transcription or epigenetic repression. Unlike CRISPR-based cutting, CRISPR-based systems can be engineered for regulation of gene expression. CRISPR interference and related methods might be used to selectively inhibit the transcription of mutant HTT, but without making permanent double-stranded

breaks in DNA (Shao et al., 2025). This can have benefits in situations where DNA cleavage is deemed to be undesirable. Emerging reviews thus refer to the conventional nuclease editing, along with transcriptional suppression, epigenome editing and the newer precision editing methods. The recent advances in base editing is another significant opportunity. In contrast to traditional Cas9 editing, the base editors do not require a traditional double-stranded break (DSB) in the DNA. An especially recent preclinical study created an HTT splice acceptor-targeted CRISPR base editor that can create an HTT gene with a pathogenic mutation. When applied to the striatum of an HD rodent model, it decreased the formation and aggregation of mutant huntingtin fragments, and was linked to improvement in functional deficits and brain atrophy (Miyake et al., 2019). The results are promising news for more targeted CRISPR strategies, but at this point they are only experimental and not proven to be effective or safe in people.

Theme 3: Delivery and Translational Opportunities

While there is significant therapeutic promise for CRISPR, the ability to treat HD will require the delivery of gene-editing components to the right cells in the central nervous system. Many biological molecules are unable to cross the blood-brain barrier (Yashooa et al., 2026), making the brain a particularly difficult therapeutic target. Moreover, entire neuronal populations are affected by HD, thus a clinically relevant intervention might require effective targeting of specific regions and adequate numbers of cells.

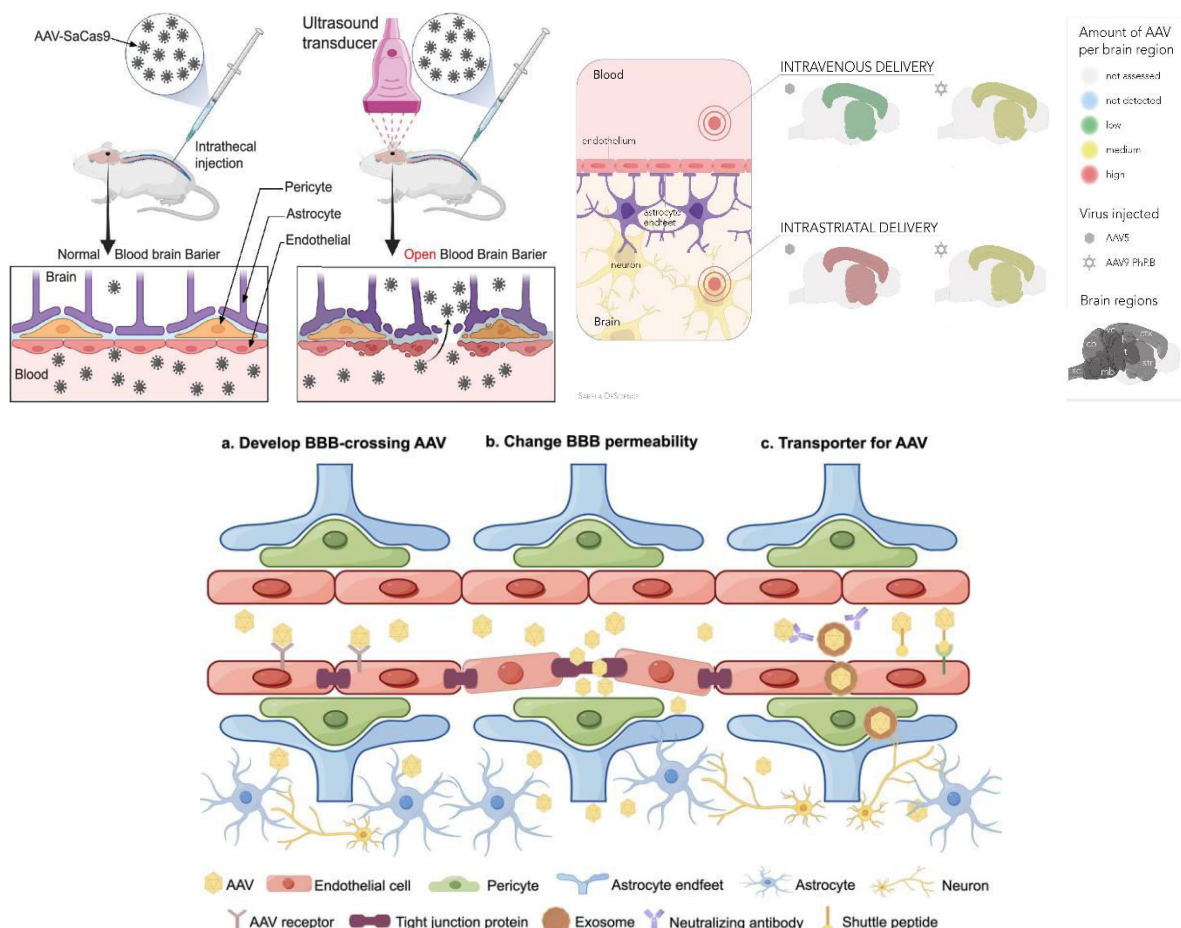


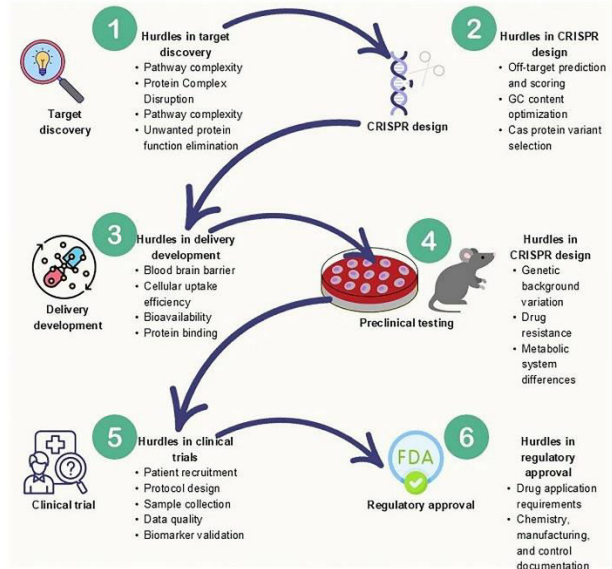
Figure 3: Potential delivery strategies for CRISPR/Cas9 systems to the central nervous system.

Viral vectors, especially adeno-associated viruses (AAVs), have been much in the spotlight due to their ability to deliver genetic material to neuronal cells. Their application is also limited by payload size, immune responses, delivery and the potential for long-term expression of the components of the gene editing system (Dhara et al., 2026). Thus, both viral and non-viral approaches are viewed as increasingly relevant for future research into the delivery of CRISPR into the brain to treat neurological diseases. Other options are emerging such as nanoparticles and virus-like particles that

offer increased flexibility and could overcome some of the drawbacks of current viral vectors. The delivery challenge is especially significant for permanent genome editing. Even with the editing machinery in cells, conventional CRISPR-Cas9 might still do their jobs, which could give more opportunities for unwanted activity. As a result, researchers are looking for ways to regulate the length and frequency of the editor's actions. Increased specificity and reduced unwanted genomic effects might be achievable through the development of high fidelity Cas variants, base editors, and the improved delivery vehicles. Another opportunity arises from more and more sophisticated experimental models. The human induced pluripotent stem cells, neuronal cell culture systems, animal models, and brain organoid systems can be used to test the efficiency of the editing and biological effects prior to human use. CRISPR is also a useful tool for research to discover genetic modifiers of HD. In vivo CRISPR screening has, for instance, been applied to study genetic elements that affect the somatic CAG-repet instability in HD knock-in mice (Chen et al., 2025). However, the difference between successful editing in laboratory models and effective treatment of patients is still quite large. There are anatomical, biological and regulatory issues in the CNS that can't be fully replicated in animal models. In contrast to other organs on which clinical development of CRISPR is further advanced, delivery is a significant challenge for the CNS, according to a review of the topic.

Theme 4: Safety, Technical Limitations and Clinical Challenges

The main problem with CRISPR therapy is that the edited genes need to be precise in order to not have unwanted side effects. One of the most heard of concerns is off-target editing. Cas enzymes may also have the potential to alter genomic positions that are similar to the intended target and thus may be considered as an off-target effect. These modifications could alter critical genes or regulatory regions and may have significant effects. Therefore, high-fidelity Cas variants, better design of guide-RNAs, and whole genome safety evaluation are current research priorities (Tan et al., 2026). An additional issue is on-target genomic instability. Although the CRISPR may edit the intended region of the genome, the process of DNA repair can lead to random insertions or deletions (or other changes) in the DNA. It is especially important for a therapeutic intervention that would ultimately lead to changes in the brain's genetic makeup of its neurons (Shin et al., 2022). Recent literature thus highlights the need to take both off-target activity and unintended effects at the site of intended editing into account for safety assessment.



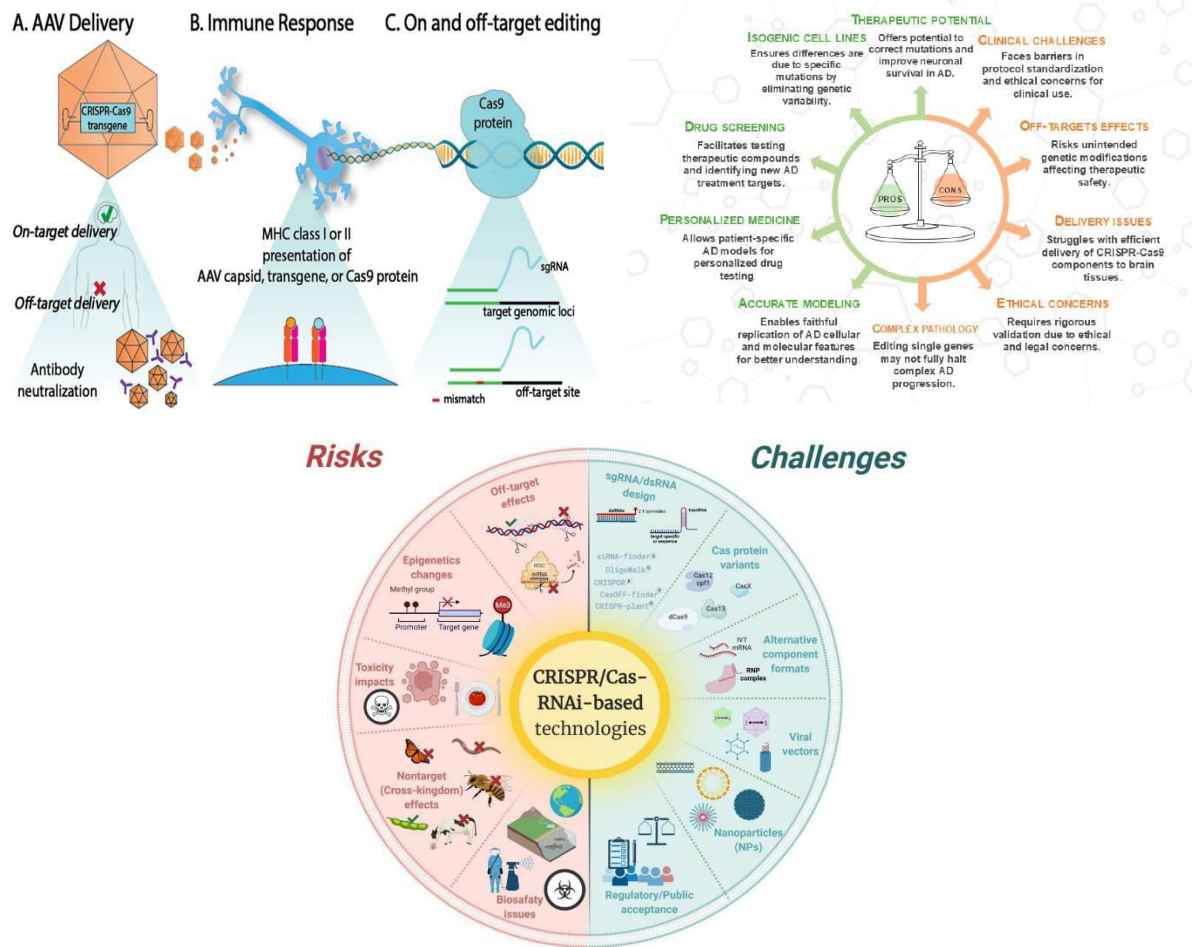


Figure 4: Major challenges associated with CRISPR/Cas-based therapies for neurological disorders.

The efficiency of editing is also an issue. A treatment might have a good effect on a percentage of cells, but be clinically ineffective if too few cells containing the disease are treated. Neuronal degeneration is a progressive process and involves multiple regions of the brain in HD (Shin et al., 2022). Additionally, it may not be possible to restore the neurons that have already died if significant damage has been done. So, when to treat may be a factor. Another limitation is the immune responses. Although the brain has distinctive immune characteristics, it is not completely immunologically isolated. Potential immune responses towards viral vectors or CRISPR-associated proteins may arise (Monteys et al., 2017). Some components may be delivered, and already have pre-existing immunity, which may make treatment more difficult. Current studies are thus aimed at finding delivery systems with high neuronal targeting efficiency and low toxicity and immune activation. Another drawback is that genome editing is a permanent change. When taking conventional symptomatic medication the drug can usually be stopped if it is having adverse effects, while a permanent change in the DNA can't just be taken away. This is a very challenging risk benefit analysis. If the disease is a progressive one that is presently incurable, the potential benefit could be significant, but there may be a lack of confidence in the benefits that may occur in decades of use, which is not easily resolved in short-term clinical trials. It is important to note that the evidence base currently is predominantly preclinical. Systematic and narrative reviews have recently reported potential benefits in cell and animal models, but this does not necessarily reflect clinical effectiveness of editing (Oura et al., 2021). There will be a need for evidence of safety, delivery, durability, effective dosing, patient selection, and patient outcomes in the transition to human treatment.

Theme 5: Ethical, Regulatory and Future Perspectives

The permanent and precise nature of genetic modification is strongly linked to the ethical considerations of CRISPR therapy for HD. While germline editing is different from somatic editing which is targeted for the treatment of an individual patient, as germline editing could be passed down through generations. The difference is especially significant in HD, which has a clear hereditary pattern due to the genetic mutation (Huang et al., 2022). Ethical discussions currently focus more on the potential harms of heritable genome editing, whereas somatic therapeutic procedures are considered more with regard to safety, consent and proportionality. The informed consent process is also complicated in HD due to the fact that the disease can slowly affect the mental and cognitive functions. Before giving an experimental genetic intervention, patients must be aware of the uncertainties and long-term risks as well as the potential benefits. Researchers and clinicians are thus challenged to provide informed consent that is not tainted by undue emphasis on the severity of the disease, or the lack of cure. The issues of justice and accessibility are also pertinent. Sophisticated infrastructure, specialist expertise and significant funds will likely be needed for advanced gene-editing therapies. The potential for successful CRISPR treatments that are not available or affordable would possibly exacerbate already present disparities in healthcare. Aside from the scientific effectiveness of a therapy, ethical development also ought to consider who is able to actually engage in the therapy. The prospects for CRISPRs for an HD cure are still bright, however. Research currently underway is moving beyond Cas9 cutting to allele-specific approaches, epigenetic approaches, base editing and prime editing. The goal of these methods is to lower the likelihood of unwanted genomic damage and raise the level of precision (Yang et al., 2019). Studies with HD models using base editing have provided recent evidence that can alter disease-associated molecular processes and enhance pathological outcomes, but much work is needed to bring this to fruition in existing human therapies. CRISPR is a potentially transformative approach to HD as it treats the underlying genetic cause of a monogenic neurologic condition, rather than just the symptoms. There are, however, significant hurdles to consider regarding the delivery, accuracy in editing, immune responses, long-term safety, and ethical responsibility/clinical translation of the therapeutic opportunity (Swenson et al., 2021). Thus, the most promising future avenue is likely to be the closer the editors get to the CNS and the better the delivery systems into the CNS, the more careful the clinical evaluation and the more stringent the preclinical testing.

V. CONCLUSION

CRISPR gene editing is an emerging technology that could be used to treat Huntington's Disease and has potential to treat the underlying genetic cause of the disease, rather than targeting symptoms. The HTT gene is a potential target for genetic intervention in HD, because the disease is monogenic. Several strategies have been investigated such as mutant HTT allele-specific targeting, reduction of HTT expression, modification of the CAG-repeats and newer precision-editing technologies including base editing. These methods offer avenues to create more focused and potentially disease-modifying therapies. But there are significant constraints which stop CRISPR being used as a proven therapy for HD at this time. Currently, delivery of the components of the gene-editing system to targeted regions of the brain is still a hurdle, and off-target effects, unintended changes in the genome and immune responses and low editing efficiency are all major safety concerns. Genetic modification is also permanent, which means long-term consequences are a concern, and they can be unpredictable. Moreover, the majority of the evidence is still derived from laboratory and animal research, and successful results in the lab do not necessarily reflect on the effectiveness of the research in humans. Overall, CRISPR shows great promise for therapeutic applications, however there is a need for further research to refine the accuracy of editing, delivery, and safety and durability of the edited cells. Before any potential intervention based on CRISPR can become a reliable treatment for HD, they must be clinically developed with great care and deeply supervised by clinical ethics, while also being carefully monitored over time.

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