CRISPR in Huntington's Disease Treatment

Shrinidhi Sridhar

Millions of people around the world suffer from genetic disorders, which diminish their quality of life and present significant challenges for them and their families. One such condition is Huntington's Disease (HD), a genetic neurodegenerative disorder that progressively impacts one's motor control, cognitive function, and mental health over time (Huntington's Disease - NORD, 2015). Individuals diagnosed with HD experience a range of symptoms such as involuntary movements, emotional instability, and memory loss, all of which are life changing (Cleveland Clinic, 2017). Currently, available treatments are focused on symptom management and there is no cure. However, advancements in gene therapy, especially CRISPR-Cas9, offer a chance to address the root cause of Huntington's Disease. This paper provides an overview of Huntington's Disease and examines how CRISPR-Cas9 could lead to new treatment options for this condition.

Huntington's disease is caused by a mutation in the HTT gene, which contains the huntingtin protein. This mutation occurs due to an expansion of CAG nucleotide repeats, which produces a misfolded Huntington protein that accumulates in the brain's neurons leading to cellular toxicity (National Institute of Neurological Disorders and Stroke, 2022). Over time, this toxic buildup leads to neurodegeneration in the brain, affecting a patient's motor function and cognitive abilities. As a neurodegenerative disorder, HD significantly impacts patients due to its progressive nature and associated mental health issues. Individuals with HD often experience increased levels of depression, anxiety, and irritability as the disease advances, which is compounded by physical challenges such as involuntary movements and poor coordination (Johnson et al., n.d.).

Unlike many genetic disorders that require both parents to carry a mutated gene, Huntington's follows an autosomal dominant pattern, which means that a single mutated copy of the HTT gene can cause the disease (Mayo Clinic, 2020). As a result, each child of an affected parent has a 50% chance of inheriting the disease, increasing its prevalence within families (National Institute of Neurological Disorders and Stroke, 2022). Currently, HD affects 3 to 7 per 100,000 individuals in the European population, with lower rates among other ethnic groups (Medline Plus, 2020). While the disease usually manifests in adulthood, there have been appearances of early-onset cases in younger people, which often result in more severe symptoms and a faster progression of the disease.

Currently, there is no cure for Huntington's disease. Available treatment options mainly focus on symptom management rather than addressing the cause of the genetic mutation (Ferguson et al., 2022). There are medications that can help control involuntary movements and antidepressants to help alleviate psychiatric symptoms (Ferguson et al., 2022). Additionally, physical therapy and counseling can improve the quality of life for those who are affected. However, these options do not target the root cause of the disease. As a result, there is still an urgent need for treatments that can directly target the HTT mutation to stop or even reverse the progression of the disease.

The emergence of gene editing technologies, specifically CRISPR CAS 9, has opened up new ways to treat genetic disorders such as Huntington's by targeting the mutation at its source. CRISPR-Cas9 uses a guide RNA sequence to direct the Cas9 protein to the precise location on the genome, where it can make targeted cuts to modify specific genes (Redman et al., 2016). In the case of Huntington's disease, CRISPR Cas9 could be used to target and modify the expanded CAG repeats in the HTT gene, preventing the formation of the toxic Huntington protein responsible for neurodegeneration (Alkanli et al., 2022). By focusing on targeting the underlying genetic mutation, CRISPR-Cas9 presents a potential pathway for addressing the root cause of the disease, rather than alleviating symptoms temporarily. However, using CRISPR-CAS9 to treat HD doesn't come without its challenges. One major concern is the risk of off-target edits, where the Cas9 protein may make unintended cuts at similar DNA sequences elsewhere in the genome (Mengstie et al., 2024). Such off-target edits like these could disrupt other essential genes and lead to harmful side effects (Mengstie et al., 2024). Another challenge is ensuring that the gene editing components are effectively delivered to the affected brain cells. Various delivery systems, including viral vectors or nanoparticles, are in the process of being tested for their efficiency in reaching brain tissue (Sioson et al., 2021). However, each method has its own risks and complications, some of which are still poorly understood. Additionally, HD is a complex disease with variability in its progression among affected individuals (Mühlau et al., 2012). This variability could impact how different patients respond to CRISPR Cas9 treatment, creating the need for personalized approaches to gene therapy and ongoing monitoring of patient outcomes. The application of CRISPR CAS9 in treating HD also raises ethical concerns, specifically regarding germline editing - the modification of reproductive cells- which could prevent the spread of HD to future generations (Schleidgen et al., 2020). This area is especially controversial due to the undiscovered long term implications and ethical debates surrounding human genetic alteration (Schleidgen et al., 2020).

In conclusion, Huntington's Disease is a challenging genetic disorder with significant impacts on affected individuals and their families. Current treatments only provide temporary relief without targeting the underlying genetic cause. However, gene-editing technologies like CRISPR-Cas9 have the potential to be a more comprehensive solution. By directly targeting the HTT mutation, CRISPR-Cas9 could potentially stop or even reverse the neurodegenerative effects of HD, marking a significant advancement in the treatment of Huntington's and similar genetic disorders. Research into CRISPR-Cas 9's use in HD is still in its initial stages, and there are still major clinical and ethical issues that must be addressed to ensure its safety and effectiveness- a process which will take time. However, as research progresses, CRISPR-Cas9 could expand the realm of treatment possibilities for Huntington's, providing a new sense of hope to both patients and their families .

Works Cited

Cleveland Clinic. (2017). *Huntington's Disease | Cleveland Clinic*. Cleveland Clinic; Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/14369-huntingtons-disease

NORD. (2015). *Huntington's Disease - NORD (National Organization for Rare Disorders)*. NORD (National Organization for Rare Disorders); NORD. https://rarediseases.org/rare-diseases/huntingtons-disease/

National Institute of Neurological Disorders and Stroke. (2022). *Huntington's Disease*. National Institute of Neurological Disorders and Stroke. https://www.ninds.nih.gov/health-information/disorders/huntingtons-disease

Johnson, A., Paulsen, J., Lovecky, D., & Tarapata, K. (n.d.). *Understanding Behavior In Huntington's Disease: A Guide For Professionals*. https://hdsa.org/wp-content/uploads/2015/03/Understanding-Behavior.pdf

Mayo Clinic. (2020, April 14). *Huntington's disease - Symptoms and causes*. Mayo Clinic; Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/huntingtons-disease/symptoms-causes/syc-20356117
Medline Plus. "Huntington's Disease: MedlinePlus Genetics." *Medlineplus.gov*, 2020, medlineplus.gov/genetics/condition/huntingtons-disease/.

Ferguson, M. W., Kennedy, C. J., Palpagama, T. H., Waldvogel, H. J., Faull, R. L. M., & Kwakowsky, A. (2022). Current and Possible Future Therapeutic Options for Huntington's Disease. *Journal of Central Nervous System Disease*, *14*(35615642), 117957352210925. https://doi.org/10.1177/11795735221092517

Redman, Melody, et al. "What Is CRISPR/Cas9?" *Archives of Disease in Childhood - Education & Practice Edition*, vol. 101, no. 4, 2016, pp. 213–215, www.ncbi.nlm.nih.gov/pmc/articles/PMC4975809/, https://doi.org/10.1136/archdischild-2016-310459.

Alkanli, S. S., Alkanli, N., Ay, A., & Albeniz, I. (2022). CRISPR/Cas9 Mediated Therapeutic Approach in Huntington's Disease. *Molecular Neurobiology*, *60*(3). https://doi.org/10.1007/s12035-022-03150-5

Mengstie, M. A., Azezew, M. T., Dejenie, T. A., Teshome, A. A., Admasu, F. T., Teklemariam, A. B., Mulu, A. T., Agidew, M. M., Adugna, D. G., Geremew, H., & Abebe, E. C. (2024). Recent Advancements in Reducing the Off-Target Effect of CRISPR-Cas9

Genome Editing. *Biologics: Targets and Therapy*, *18*(1), 21–28. https://doi.org/10.2147/BTT.S429411

Schleidgen, S., Dederer, H.-G., Sgodda, S., Cravcisin, S., Lüneburg, L., Cantz, T., & Heinemann, T. (2020). Human germline editing in the era of CRISPR-Cas: risk and uncertainty, intergenerational responsibility, therapeutic legitimacy. *BMC Medical Ethics*, *21*(1). https://doi.org/10.1186/s12910-020-00487-1

Mühlau, M., Winkelmann, J., Rujescu, D., Giegling, I., Koutsouleris, N., Gaser, C., Arsic, M., Weindl, A., Reiser, M., & Meisenzahl, E. M. (2012). Variation within the Huntington's Disease Gene Influences Normal Brain Structure. *PLoS ONE*, *7*(1), e29809. https://doi.org/10.1371/journal.pone.0029809

Sioson, V. A., Kim, M., & Joo, J. (2021). Challenges in delivery systems for CRISPR-based genome editing and opportunities of nanomedicine. *Biomedical Engineering Letters*, *11*(3), 217–233. https://doi.org/10.1007/s13534-021-00199-4