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Opinion Article

Role of HTT Gene Mutations in Huntington's Disease Pathogenesis and Therapy Development

Mateus Rocha*

Department of Clinical Laboratory, University of São Paulo, São Paulo, Brazil

DESCRIPTION

Huntington's Disease (HD) is a progressive, autosomal dominant neurodegenerative disorder characterized by motor dysfunction, cognitive decline, and psychiatric disturbances. It typically manifests in mid-adulthood, although juvenile cases are known. The disorder is caused by mutations in the *HTT* gene, which encodes the huntingtin protein. Over the years, research has unraveled the complex molecular mechanisms linking *HTT* gene mutations to the pathology of Hd, paving the way for novel therapeutic approaches.

The *HTT* gene, located on chromosome 4p16.3, contains a polymorphic CAG trinucleotide repeat in its coding region. In normal individuals, this repeat ranges from 10 to 35 copies. However, in patients with Hd, the CAG repeat expands beyond 36 copies, leading to the production of mutant huntingtin protein with an abnormally long polyglutamine tract. This expanded polyglutamine sequence confers toxic gain-of-function properties to the protein, initiating a cascade of cellular dysfunction and neuronal death, particularly in the striatum and cerebral cortex. The pathogenic mechanisms triggered by mutant huntingtin are multifaceted. The abnormal protein tends to misfold and aggregate, forming intracellular inclusions that disrupt normal cellular functions. These aggregates interfere with proteostasis, impair mitochondrial function, and induce oxidative stress. Additionally, mutant huntingtin alters transcriptional regulation by interacting with various transcription factors, thereby affecting the expression of critical neuronal survival genes. The disruption of axonal transport, synaptic transmission, and calcium homeostasis further exacerbates neuronal dysfunction.

An important pathological hallmark of Hd is the selective vulnerability of medium spiny neurons in the striatum. The reasons for this selective neurodegeneration are not fully understood but may relate to differences in neuronal metabolism, receptor expression, and intrinsic susceptibility to toxic insults. This selective loss underpins the characteristic motor symptoms of Hd, including chorea, dystonia, and impaired voluntary movement.

Genetic testing for expansions in the *HTT* gene is the gold standard for confirming the diagnosis of Hd. This test allows for predictive testing in at-risk individuals and informs clinical management. Furthermore, the size of the CAG repeats correlates inversely with the age of onset and disease severity, with longer repeats leading to earlier onset and more aggressive progression. This genotype-phenotype correlation has been crucial in understanding disease dynamics and counseling patients.

Therapeutic strategies for Hd have traditionally focused on symptomatic management, including medications to control chorea and psychiatric symptoms. However, recent advances in molecular genetics have opened avenues for disease-modifying therapies targeting the *HTT* gene or its mutant protein product. One promising approach involves the use of Antisense oligonucleotides (Aso) designed to selectively reduce mutant *HTT* mRNA levels, thereby decreasing the production of toxic huntingtin protein. Clinical trials investigating Aso therapies have shown encouraging results in lowering mutant huntingtin in cerebrospinal fluid and improving clinical outcomes.

Other gene-based therapies include RNA interference (Rnai), which also aims to silence mutant *HTT* expression, and genome editing technologies such as CRISPR-Cas9 that hold potential for directly correcting pathogenic CAG expansions. Although these approaches are in experimental stages, they represent a significant shift toward precision medicine in Hd. In addition to gene-targeting therapies, research is focusing on modulating downstream pathogenic pathways. Enhancing autophagy to clear protein aggregates, stabilizing mitochondrial function, and reducing neuroinflammation are areas of active investigation. Neuroprotective agents aiming to preserve neuronal function and delay disease progression are also being explored.

Despite these advances, several challenges remain in translating gene-based therapies into clinical practice. Ensuring specificity to mutant *HTT* while sparing the normal protein, achieving efficient delivery to affected brain regions, and managing immune responses are critical hurdles. Moreover, the timing of intervention may be essential, as early treatment before extensive neurodegeneration may yield better outcomes.

Correspondence to: Mateus Rocha, Department of Clinical Laboratory, University of São Paulo, São Paulo, Brazil, E-mail: mateus.rocha@novela-br.org

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CONCLUSION

Mutations in the *HTT* gene underlie the complex pathogenesis of Huntington's disease, linking genetic abnormality to progressive neuronal dysfunction and clinical manifestations. The expanding knowledge of molecular mechanisms has fueled the development of innovative therapeutic strategies targeting the root cause of Hd. As gene-based therapies continue to evolve, there is hope for more effective treatments that can alter the disease course and improve quality of life for affected individuals.