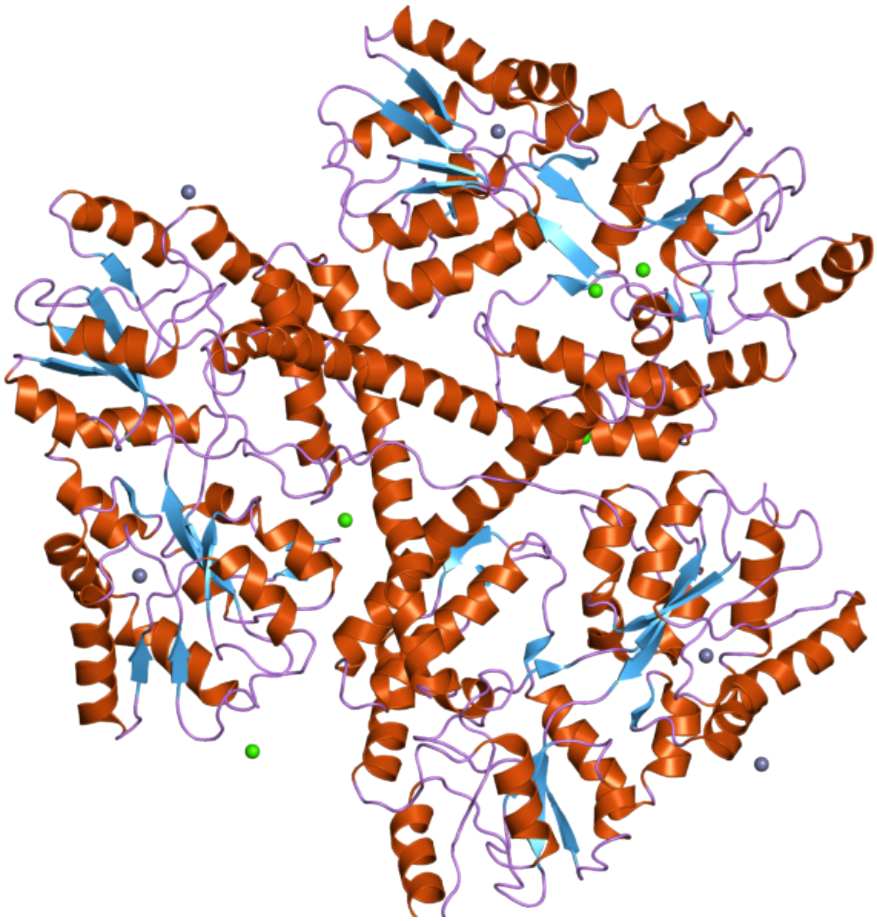
Study finds siRNA ineffective in reducing mutant huntingtin gene mRNA in nucleus

July 22 2024



Huntingtin. Crystallographic structure of the N-terminal region of the human Huntingtin protein with an artificially attached Maltose-Binding protein used for crystallographic purposes. Credit: Public domain

In Huntington's disease, the mutant huntingtin gene (HTT) mRNA is retained in the nucleus and forms insoluble clusters. A new study shows that short interfering RNA (siRNA), an oligonucleotide therapeutic strategy that reduces levels of huntingtin mRNA in the cytoplasm, does not lower mutant HTT mRNA expression in the nucleus of mouse brains.

The study is published in the journal *Nucleic Acid Therapeutics*.

Sarah Allen, from the University of Massachusetts Chan Medical School, and co-authors, state, "Mutant mRNA forms nuclear clusters that are resistant to RNAi, while both nuclear and cytoplasmic wild-type Htt mRNA can be silenced. This study is the first to report on the impact of structure of nuclear RNA impacting efficiency of RNAi-based silencing."

"Another key investigation from the laboratory of Anastasia Khvorova, to develop our understanding of the relationship between huntingtin RNA and protein levels where it matters functionally," says Executive Editor Graham C. Parker, Ph.D., Department of Pediatrics, Wayne State University School of Medicine, Detroit, MI.

More information: Sarah Allen et al, mRNA Nuclear Clustering Leads to a Difference in Mutant Huntingtin mRNA and Protein Silencing by siRNAs In Vivo, *Nucleic Acid Therapeutics* (2024). DOI: 10.1089/nat.2024.0027

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