Scientists tackle Huntington's disease by targeting mutant gene

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Credit: AI-generated image (disclaimer)

Huntington's disease is an inherited, neurodegenerative disorder that usually appears in mid-adult life and leads to uncoordinated body movements and cognitive decline. The disease is due to multiple repetitions of a deoxyribonucleic acid (DNA) sequence (i.e. the nucleotides CAG) in the gene encoding the 'Huntingtin' protein. This

sequence is present more than 35 times in patients suffering from this disease, while it is repeated 10 to 29 times in healthy patients. In a recent study, published in the journal *PNAS*, researchers in Spain succeeded in reducing the chromosomal expression of the mutant gene, which could potentially hinder disease development.

Researchers say adult humans specifically need the Huntingtin protein, which is located in different tissues of the body, to ensure the development and survival of neurons. The presence of a mutant gene results in an abnormal form of the Huntingtin protein. When this happens, the body is affected by a number of symptoms, including involuntary movements, behavioural changes and dementia. Despite inroads made into this condition, no one has been able to find a cure for Huntington's disease. Patients are currently treated to ease their pain and discomfort, and most patients die around 15 years after their symptoms first appear.

Scientists know that one gene is responsible for Huntington's disease, which is not the case for other neurological disorders like Parkinson or Alzheimer. So they are hopeful that developing a therapy based on the inhibition of the mutant Huntingtin gene could lead to the development of a treatment for it. Current studies focus on the modification of proteins that are contained in all living beings, such as the Zinc Finger proteins (ZFP) that have the ability to recognise and bind to specific DNA sequences. Briefly, this process results in a regulated gene function.

Researchers from the CRG took their work one step further by reducing the chromosomal expression of the mutant gene, potentially hindering the development of the disease.

'We designed specific ZFP that recognize and specifically bind to more than 35 repetitions of CAG triplet, preventing the expression of the gene

containing these repeats and reducing the production of the mutant Huntingtin protein,' said lead author Mireia Garriga-Canut, a researcher from the Gene Network Engineering group at the CRG. 'When applying this treatment to a transgenic mouse model carrying the human mutant Huntingtin gene, we observed a delayed onset of the symptoms.'

Carmen Agustín Pavón, one of the authors of the study, said, 'The next step is to optimise the design for an effective and durable treatment for patients. This would pave the way to find a therapy for Huntington's disease.'

More information: Garriga-Canut, M., et al., 'Synthetic zinc finger repressors reduce mutant Huntingtin expression in the brain of R6/2 mice', *PNAS*, 2012. doi:10.1073/pnas.1206506109

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