Researchers identify quadruplex structure in C9ORF72

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(Medical Xpress)—A Motor Neurone Disease (MND) Association funded research project at UCL has given new insights into the structure and function of an MND gene called C9ORF72. The work is published in the journal *Scientific Reports*.

Dr Pietro Fratta (UCL Institute of Neurology) is first author of the paper which successfully identifies the structure of the six-letter genetic mistake in C9ORF72.

Since the pivotal discovery in 2011 that genetic mistakes in C9ORF72 can cause up to 40 percent of cases of MND with a positive family history of the disease, researchers have been trying to unravel its role in the body, to determine how it could cause MND.

Understanding how C9ORF72 works, what it looks like and how mistakes in the gene may cause MND, could assist researchers in the future to identify potential treatments that target the disease.

Co-author Dr Adrian Isaacs (UCL Institute of Neurology) explains, "Nothing is currently known about how the mistake in C9ORF72 kills motor neurones. The mistake in C9ORF72 is similar to mistakes that cause some other neurological diseases. In these diseases the mistake leads to the formation of toxic aggregates of RNA – RNA is a copy of DNA that is made when a gene is switched on and is important for the generation of proteins.

"This is the first report in the MND field to work out the structure of the abnormal C9ORF72 RNA and therefore gives insight into how the mistake might be causing MND."

The UCL research group identified that a repetitive code in the C9ORF72 gene naturally forms a square tube-like structure when in its RNA copy form. This is called an 'RNA G-quadruplex'.

It is hoped that identifying this square, tube-like structure will give further clues about the C9ORF72 gene's specific role in the body. To date, quadruplexes have been identified as having a number of roles, including editing copies of genes to create functional proteins.

Dr Fratta explains how this structure could cause MND: "One possibility is that the RNA G-quadruplexes accumulate in motor neurones and then different proteins within the cell somehow bind to this structure and get stuck. As a result the motor neurones malfunction and perhaps even ultimately die.

"We have now determined the structure that this RNA forms. This will be important for understanding the effect of the C9ORF72 mistake in motor neurones and assist our approaches to trying to correct its effects."

MND Association's Director of Research Development Dr Dickie commented: "The UCL scientists have opened up an exciting new avenue of research. At the moment we know very little about whether, or how, these RNA structures may be linked to MND, but evidence from other diseases indicates that they are biologically active and therefore likely to be important to the function and health of nerve cells."

Following this finding, the next steps for researchers will be to determine the function of the G-quadruplex in nerve cells,and to identify drugs that can bind to the G-quadruplexes.

More information: Fratta P. et al. C9orf72 hexanucleotide repeat associated with amyotrophic lateral sclerosis and frontotemporal dementia forms RNA G-quadruplexes. *Scientific Reports*.

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