How mutations lead to neurodegenerative disease

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Scientists have discovered how mutations in DNA can cause neurodegenerative disease. The discovery is an important step towards better treatment to slow the progression or delay onset in a range of incurable diseases such as Huntington's and motor neurone disease – possibly through the use, in new ways, of existing anti-inflammatory drugs.

The team of scientists has shown experimentally, for the first time, how mutations ultimately set off an anti-viral like inflammatory response in cells that leads to cell death and, over time, progressive neurological damage.

Led by the University of Adelaide, the study published in *Human Molecular Genetics* is the culmination of over a decade of research with researchers at the Victor Chang Research Institute in Sydney, seeking to understand how DNA mutations result in neurological damage.

This study investigates the outcomes of a mutation linked to Huntington's disease and 20 other neurodegenerative diseases, including some forms of motor neurone disease. But it also may have implications for the progression of neurodegenerative diseases which aren't necessarily inherited, such as Alzheimer's and Parkinson's, which evidence suggests are caused by a similar inflammatory response to environmental triggers.

"Together these conditions affect millions of families worldwide, and there are no cures or effective treatments," says project leader Rob Richards, Professor of Genetics in the University of Adelaide's School of Biological Sciences.

"If the new mechanism we have discovered proves to be correct, it will transform the field, providing a different way of thinking about these diseases and offering new opportunities for medical intervention."

The so-called 'DNA repeat diseases' – named because of the repeat sequences found in the DNA of patients – share many common features in their symptoms, but the mechanisms by which symptoms arise have previously been thought to be different for each.

"We've known what mutations are involved for some years, and the set

of outcomes that result, but, until now, we've not known how one leads to the other. This new research shows us how each of these diseases can be caused by the same underlying cellular pathway."

The study results centre around RNA, the molecule in our cells which is the intermediate step between the DNA in chromosomes and the proteins that are the cells' main functional components.

The DNA provides a blueprint for producing RNA that is then normally 'bar-coded' to ensure cells recognise it as "self", distinguishing it from the RNA of a foreign invader, such as viruses. Using the experimental model fly Drosophila, Professor Richards and his team showed that the affected, 'double-stranded RNA' was instead recognised as foreign to the body, or "non-self".

"This elicits an anti-viral like, auto-inflammatory response that leads to neuronal destruction and death, in time causing progressive neurological damage," says Professor Richards. "The abnormal RNA is made from regions of repeated DNA sequences that are found in greater numbers in people affected with Huntington's and some other neurodegenerative diseases."

Professor Richards says there are existing drugs for other types of auto-inflammatory disease, which may prove to be effective in treating the symptoms of these diseases, by inhibiting the anti-viral inflammatory response.

More information: Clare L Eyk et al. 'Non-self' Mutation: Double-stranded RNA elicits antiviral pathogenic response in a Drosophila model of expanded CAG repeat neurodegenerative diseases, *Human Molecular Genetics* (2019). DOI: 10.1093/hmg/ddz096