Shining light on neurodegenerative pathway

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University of Adelaide researchers have identified a likely molecular pathway that causes a group of untreatable neurodegenerative diseases, including Huntington's disease and Lou Gehrig's disease.

The group of about 20 diseases, which show overlapping symptoms that typically include nerve cell death, share a similar genetic mutation mechanism ? but how this form of mutation causes these diseases has remained a mystery.

"Despite the genes for some of these diseases having been identified 20 years ago, we still haven't understood the underlying mechanisms that lead to people developing clinical symptoms," says Professor Robert Richards, Head of Genetics in the University's School of Molecular and Biomedical Sciences.

"By uncovering the molecular pathway for these diseases, we now expect to be able to define targets for intervention and so come up with potential therapies. Ultimately this will help sufferers to reduce the amount of nerve cell degeneration or slow its progression."

In an article published in *Frontiers in Molecular Neuroscience*, Professor Richards and colleagues describe their innovative theory and new evidence for the key role of RNA in the development of the diseases. RNA is a large molecule in the cell that copies genetic code from the cell's DNA and translates it into the proteins that drive biological functions.

People with these diseases all have expanded numbers of copies of particular sequences of the 'nucleotide bases' which make up DNA.

"In most cases people with these diseases have increased numbers of repeat sequences in their RNA," says Professor Richards. "The disease develops when people have too many copies of the repeat sequence. Above a certain threshold, the more copies they have the earlier the disease develops and the more severe the symptoms. The current gap in knowledge is why having these expanded repeat sequences of genes in the RNA translates into actual symptoms."

Professor Richards says evidence points towards a dysfunctional RNA and a pivotal role of the body's immune system in the development of the disease.

"Rather than recognising the 'expanded repeat RNA' as its own RNA, we believe the 'expanded repeat RNA' is being seen as foreign, like the RNA in a virus, and this activates the innate immune system, resulting in loss of function and ultimately the death of the cell," he says.

The University of Adelaide laboratory modelled and defined the expanded repeat RNA disease pathway using flies (Drosophila). Other laboratories have reported tell-tale, but previously inexplicable, signs characteristic of this pathway in studies of patients with Huntington's disease and Myotonic Dystrophy.

"This new understanding, once proven in each of the relevant human diseases, opens the way for potential treatments, and should give cause for hope to those with these devastating diseases," Professor Richards says.

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More information: www.frontiersin.org/Molecular_…
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