Lab method sheds light on how genetic mutations cause inherited Parkinson's disease

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Scientists have developed a new method of measuring the activity of disease-causing mutations in the LRRK2 gene, a major cause of inherited Parkinson's disease.

The team believes this breakthrough, which is published in the *Biochemical Journal*, could help pave the way for future development of a clinical test that could facilitate evaluation of drugs to target this form of the condition.

"It's important to better understand how disruption in LRRK2 biology causes Parkinson's disease and whether a drug that targeted the LRRK2 enzyme would offer therapeutic benefit," said lead study author Professor Dario Alessi from the University of Dundee.

Mutations in the LRRK2 gene are the most common cause of genetic Parkinson's disease (~1% total cases). The most common disease-causing mutation in this gene increases the activity of the LRRK2 protein (enzyme) three-fold, which implies that the increase in activity of the protein may contribute towards the symptoms of the disease in these patients. It also suggests that drugs that reduce the activity of the LRRK2 protein (LRRK2 inhibitors) may help treat patients with this form of inherited Parkinson's disease.

"Current drug treatments only deal with symptoms of the condition, such as tremors, but do not affect the progression of Parkinson's disease. An important question is whether a LRRK2 therapy might have potential to slow progression of the condition, which no other current therapy is able to do," commented Alessi.

When the LRRK2 protein is active, it stops another cellular protein called Rab10 from fulfilling its function in the body. There are many proteins in the Rab family, and a number of them have been shown to be low in number or deactivated in different forms of Parkinson's disease. The new method, which was developed using a mouse model, was established by a collaboration of researchers from the University of Dundee, The Michael J. Fox Foundation for Parkinson's Research, GSK and the University of Hong Kong. It analyses how much of the Rab10 protein has been deactivated - a process where phosphate groups are added to the Rab10 molecules by the LRRK2 protein - as a measure of heightened LRRK2 protein activity.

"The prediction is that elevation of LRRK2 activity leads to Parkinson's disease, and this is now testable using our assay," said Alessi. "The expectation is that if a sub-group of patients can be identified with elevated LRRK2 activity, these individuals might benefit most from LRRK2 inhibitors."

This new experimental assay is straightforward, only requires small amounts of sample material and is suitable for adapting to analyse large samples, in contrast to current mass spectrometry technology that is more complex and cumbersome and requires larger sample sizes.

While acknowledging that more work is needed, the researchers believe this breakthrough could help with future drug developments for patients with this form of Parkinson's disease.

"I am hopeful that the new technology elaborated on in our study will greatly aide future work on defining the role that LRRK2 plays in Parkinson's disease. I am also particularly excited about the potential of the methodology we have elaborated, especially if it could be exploited to assess LRRK2 activity in Parkinson's patients and accelerate

development and evaluation of LRRK2 drug candidates," Alessi explained.

The next steps for the researchers are to develop further tests to better detect and measure Rab protein deactivation and correlate elevated Rab10 deactivation with Parkinson's disease in samples from human patients. They believe that measuring the level of Rab10 deactivation, for example in human blood samples, could allow researchers to test the efficacy of new drug candidates.

"The identification earlier this year, by Alessi and colleagues, of Rab proteins as substrates of LRRK2 was a crucial step in unraveling the role of LRRK2 in the neurodegeneration underlying Parkinson's disease," commented Professor Aideen Sullivan from University College Cork, an expert in Parkinson's disease and Editor in Chief of the new Portland Press journal *Neuronal Signaling*.

"This new study has capitalized on their previous work by developing a method that can measure Rab10 deactivation in small samples, giving an indication of LRRK2 activity," she added. "If this method can be applied to human samples, it will be a significant step toward earlier and more definitive diagnosis of Parkinson's, a disease of steadily increasing prevalence that currently affects over 10 million people worldwide."

A commentary by Dr Patrick Eyers, University of Liverpool, accompanying the research paper will be published later this month also in the *Biochemical Journal*.

Commenting on the research Eyers said: "It is exciting to see how rapidly the LRRK2 field is developing. The methodology described in this paper expands the tools available to assess the effects of LRRK2-targeted drugs in Parkinson's disease models, and also potentially in samples derived from Parkinson's patients with activating mutations in LRRK2."

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