

Undetected rare neurodegenerative disorder identified by Singapore researchers

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Neuronal intranuclear inclusion body disease (NIID), a neurodegenerative disease resembling Parkinson's disease, is caused by a mutation in the NOTCH2NLC gene



A joint study by the National Neuroscience Institute (NNI) and Singapore General Hospital (SGH) revealed that patients who have been diagnosed with Parkinson's disease might actually have NIID instead. The study findings were published online in *JAMA Neurology* on 24 August 2020.

NIID is a disabling neurodegenerative condition due to a gene mutation and has no effective treatment. Symptoms of NIID include dementia, Parkinsonism, poor balance, as well as numbness and weakness in the limbs. A patient with NIID may or may not experience symptoms, depending on age and stage of disease. The severe form of NIID is usually seen in older patients, where the disease has progressed to an advanced stage.

The team studied more than 2,000 study participants, comprising healthy individuals and those with Parkinson's disease (PD), over more than a decade. They were surprised to find NIID-causing mutations in those diagnosed with PD. Dr Ma Dongrui, Senior Medical Laboratory Scientist, Department of Neurology, SGH, and first author of the study explains, "To our knowledge, this is the first study reporting PD patients with NOTCH2NLC gene mutations as seen in NIID patients. Thankfully, they responded to PD medications better than most PD patients do. This suggests that there must be factors that can influence why some develop PD while many others develop the more severe form of NIID.

While analysing the NIID gene, the team found a group of healthy participants who had a "milder" form of mutation. Such

mutation in the NIID gene could indicate that they are at risk of developing NIID or PD.

Since NIID can go undetected, a high index of suspicion may be needed even in PD patients. Tracking early cognitive impairment or imaging evidence may suggest NIID in patients diagnosed with PD, along with tracing family members of PD patients who may show signs of NIID.

Considering the fact that neurodegenerative diseases overlap and may share a common etiology, the team plans to conduct more studies to better understand the mechanism behind NIID and identify new drugs for this condition. More research is needed to understand if the broad clinical phenotype of NIID is related to the subtle genetic differences at the NOTCH2NLC gene locus, race or other factors. Long-term follow-up of carriers of the gene mutation with PD phenotype may provide additional clues.