

Researchers develop a blood test to identify individuals at risk of developing Parkinson's disease

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Research carried out at Oxford's Nuffield Department of Clinical Neurosciences has led to the development of a new blood-based test to

identify the pathology that triggers Parkinson's disease before the main symptoms occur. This could allow clinicians to screen for those individuals at high risk of developing the disease and facilitate the timely introduction of precision therapies that are currently at clinical trial stage.

Parkinson's disease is the second most common neurodegenerative disease affecting seven million people worldwide with a projected doubling in cases by 2040. A major bottleneck in conducting [clinical trials](#) for disease modification is the identification of patients at the earliest stages of disease development (pathogenesis) and the exclusion of other diseases with similar symptoms (mimics).

Parkinson's disease starts more than ten years before patients come to the clinic with symptoms because their [brain cells](#) fail to handle a small protein called [alpha-synuclein](#). This leads to the formation of abnormal clumps of alpha-synuclein which damage vulnerable nerve cells, causing the familiar movement disorder and often dementia. By the time people are diagnosed with Parkinson's disease, most of these vulnerable nerve cells have already died and alpha-synuclein clumps have formed in many brain regions.

It would be useful if there was a way to predict whether the pathways that handle alpha-synuclein are impaired before the onset of Parkinson's symptoms. This could help clinicians to identify people most likely to benefit from disease-modifying therapies when they become available.

In the paper, "Neuronally Derived Extracellular Vesicle α -Synuclein as a Serum Biomarker for Individuals at Risk of Developing Parkinson Disease" in [JAMA Neurology](#), Shijun Yan and colleagues in the Tofaris lab revealed the promise of measuring a subtype of extracellular vesicles to identify changes in alpha-synuclein in people who are likely to develop Parkinson's disease. Extracellular vesicles are nanoparticles that

are released by all [cell types](#) and circulate in biofluids including blood, transporting molecular signals between cells.

Using an improved antibody-based assay developed by the research group, the test involves isolating those extracellular vesicles originating from nerve cells from blood, and then measuring their alpha-synuclein content. Professor George Tofaris explains, "A robust assay is crucial because neuronally-derived extracellular vesicles constitute less than 10% of all circulating vesicles, and ~99% of alpha-synuclein in blood is released from peripheral cells, mostly red blood cells."

In the first study of its kind, the team looked at 365 at-risk individuals from four clinical cohorts (Oxford Discovery, Marburg, Cologne and the US-based Parkinson's Progression Markers Initiative), 282 healthy controls and 71 people with genetic or sporadic Parkinson's disease.

They found that those with the highest risk of developing Parkinson's (more than 80% probability based on research criteria) had a two-fold increase in alpha-synuclein levels in neuronal extracellular vesicles and the test could accurately differentiate them from those with low risk (less than 5% probability) or healthy controls. Overall, the test could distinguish an individual with high risk of developing Parkinson's from a healthy control with 90% probability.

These findings indicate that the blood test, together with a limited clinical assessment, could be used to screen and identify people who are at high risk of getting the disease. In further analysis, the test could also identify those who had evidence of neurodegeneration detected by imaging, or pathology detected by a spinal fluid assay, but had not yet developed a movement disorder or dementia.

In a small subgroup of 40 people who went on to develop Parkinson's and related dementia, the [blood test](#) was positive in more than 80% of

cases up to as much as seven years before the diagnosis.

In this group, there was a trend for higher levels of alpha-synuclein in neuronal extracellular vesicles in the blood to be associated with lower alpha-synuclein in the spinal fluid, and a longer interval before the onset of the main symptoms of Parkinson's disease. This suggests that the nerve cells may protect themselves by packaging excess alpha-synuclein in extracellular vesicles which are then released in the blood.

The research builds on earlier findings by the Tofaris lab, also confirmed in the current study, showing that the biomarker is increased in patients with Parkinson's disease but not in other Parkinson's-like conditions.

The Tofaris lab, which is part of the Nuffield Department of Clinical Neurosciences and based in the Kavli Institute for Nanoscience Discovery, previously delineated the pathway which targets alpha-synuclein for destruction inside nerve cells. This pathway may also direct alpha-synuclein outside cells in [extracellular vesicles](#), when intracellular protein turnover is inefficient in conditions such as aging and Parkinson's disease.

Professor Tofaris said, "Collectively our studies demonstrate how fundamental investigations in alpha-synuclein biology can be translated into a biomarker for clinical application, in this case for the identification and stratification of Parkinson's risk. A screening test that could be implemented at scale to identify the disease process early is imperative for the eventual instigation of targeted therapies as is currently done with screening programs for common types of cancer."

More information: Shijun Yan et al, Neuronally Derived Extracellular Vesicle α -Synuclein as a Serum Biomarker for Individuals at Risk of Developing Parkinson Disease, *JAMA Neurology* (2023). [DOI: 10.1001/jamaneurol.2023.4398](https://doi.org/10.1001/jamaneurol.2023.4398)

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