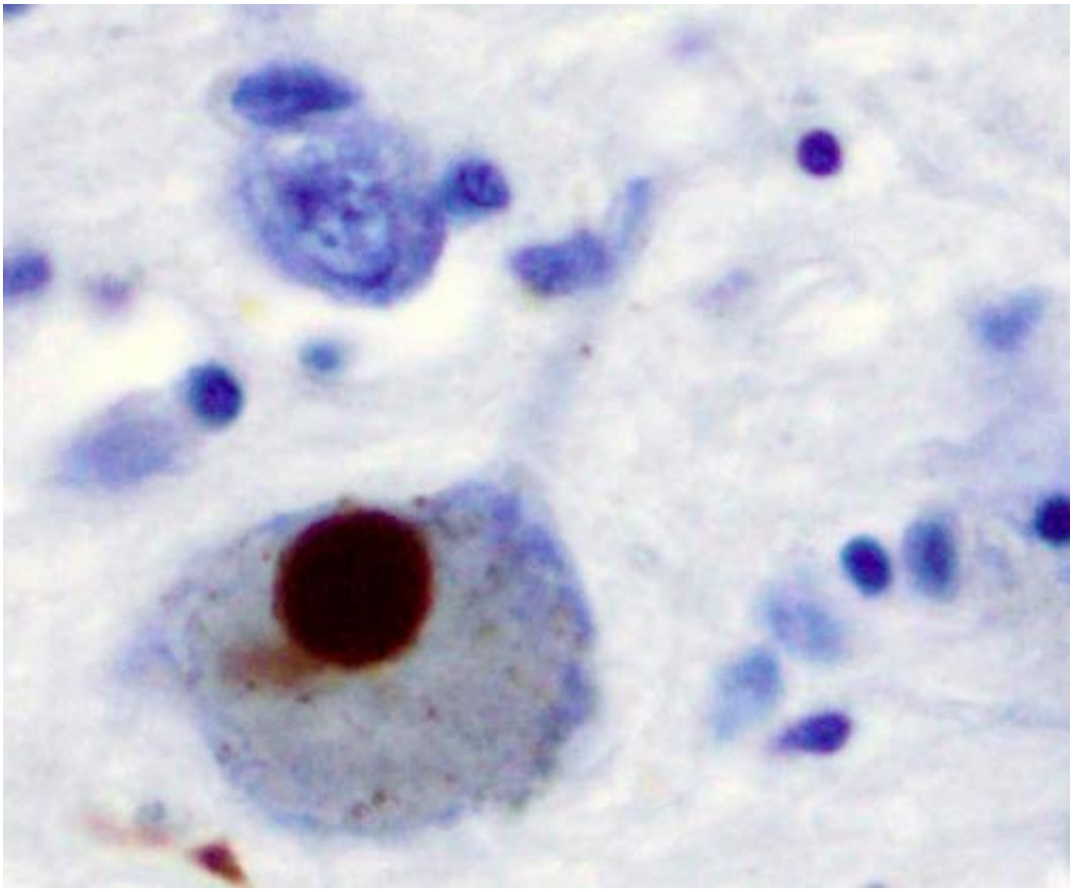
Identifying 'hallmark' Parkinson's disease protein buildup could aid early detection, improved diagnosis and treatment

April 12 2023



Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

A technique that identifies the build-up of abnormal protein deposits linked to Parkinson's disease could aid in early detection and play a key role in the disease's clinical diagnosis and characterization, according to research published in *The Lancet Neurology* journal.

Findings from the study confirm that the technique—known as α-synuclein seed amplification assay (αSyn-SAA)—can accurately detect people with the neurodegenerative disease and suggest it can identify at-risk individuals and those with early, non-motor symptoms prior to diagnosis. The presence of misfolded α-synuclein protein aggregates in the brain is the pathological hallmark of Parkinson's disease.

Co-lead author Professor Andrew Siderowf, of the University of Pennsylvania Perelman School of Medicine (U.S.) and Parkinson Progression Marker Initiative (PPMI) investigator, says, "Recognizing heterogeneity in underlying pathology among patients with Parkinson's disease has been a major challenge. Identifying an effective biomarker for Parkinson's disease pathology could have profound implications for the way we treat the condition, potentially making it possible to diagnose people earlier, identify the best treatments for different subsets of patients, and speed up clinical trials."

"Our findings suggest that the αSyn-SAA technique is highly accurate at detecting the biomarker for Parkinson's disease regardless of the clinical features, making it possible to accurately diagnose the disease in patients at early stages. Moreover, our results indicate that misfolded α-synuclein is detectable before dopaminergic damage in the brain is about to be observed by imaging, suggesting ubiquitous spread of these misfolded proteins before substantial neuronal damage has occurred," adds study co-lead author Luis Concha, director of research and development at Amprion (U.S.).

The new study is the largest analysis of the diagnostic performance of

αSyn-SAA for Parkinson's disease. While previous research has shown αSyn-SAA can distinguish clearly between individuals with Parkinson's disease and people without the condition, no large-scale studies including such a broad range of carefully described participants have been conducted until now.

The authors assessed the usefulness of αSyn-SAA for identifying underlying heterogeneity in people with Parkinson's disease, and its ability to detect early signs of the condition, using data from the Parkinson's Progression Markers Initiative (PPMI) cohort. Among the 1,123 participants in the analysis were individuals with a diagnosis of Parkinson's disease and at-risk people with gene variants (GBA and LRRK2) linked to the condition.

So-called prodromal participants were also included. These people had non-motor symptoms—sleep disturbance or loss of smell—that can be early signs of Parkinson's disease, but they had not been diagnosed with the disease and had none of the typical motor symptoms, such as tremors or muscle stiffness, which come later in the disease's development. The reason to include prodromal participants was to determine whether αSyn-SAA might predict the onset of Parkinson's as well as help diagnose people with established symptoms.

Samples of cerebrospinal fluid that surrounds the brain and spinal cord—from each participant were analyzed using αSyn-SAA. This breakthrough technique amplifies very small amounts of misfolded aggregates of α-synuclein in samples from people with Parkinson's disease to the point that they can be detected using standard laboratory techniques.

Findings of the analyses confirm that αSyn-SAA identifies people with Parkinson's disease with high accuracy, with positive results in 88% of all participants with a diagnosis (combining sporadic and genetic cases).

In sporadic cases—those with no known genetic cause—93% of individuals had a positive αSyn-SAA result. However, results varied for people with genetic forms of Parkinson's disease, with 96% of those with the GBA variant having a positive αSyn-SAA, compared with 68% of those with LRRK2.

Most prodromal participants had positive αSyn-SAA results, indicating they had α-synuclein aggregates despite not yet being diagnosed with Parkinson's disease. Among those recruited based on their loss of smell, 89% (16/18 participants) had positive αSyn-SAA results. Similarly, in people with REM sleep behavior disorder, a sleep disturbance that is known to be a precursor to Parkinson's disease, positive αSyn-SAA results were present in 85% (28/33) of cases. No other clinical features were associated with a positive αSyn-SAA result.

In participants who carried LRRK2 or GBA variants but had no Parkinson's disease diagnosis or prodromal symptoms—known as non-manifesting carriers (NMCs)—9% (14/159) and 7% (11/151), respectively, had positive αSyn-SAA results.

Importantly, most prodromal participants and NMCs with positive αSyn-SAA had brain scans that did not show a decline in the expected number of dopamine-producing nerve cells—a biomarker signature that is present even before diagnosis. This result suggests build-up of α-synuclein aggregates may be a very early indicator of disease onset.

The clinical feature that most strongly predicted a positive αSyn-SAA result was loss of smell—one of the most common symptoms in prodromal people and those with a Parkinson's disease diagnosis. Among all participants with Parkinson's disease who had loss of smell, 97% had positive αSyn-SAA compared to 63% of those whose sense of smell was unchanged.

"While loss of smell appears to be a strong predictor of Parkinson's disease, it's important to note that this study identified individuals with positive αSyn-SAA results, but who had not yet lost their sense of smell, indicating that α-synuclein pathology may be present even before there is a measurable loss of sense of smell. Our study looked at patients a fixed point in time only, and further research is needed to find out how patients' sense of smell may change over time, and how this relates to the build-up of a-synuclein aggregates in the brain," says study author Dr. Tanya Simuni of Northwestern University (U.S.).

Some differences in αSyn-SAA results were also seen based on age and sex, particularly among people with a mutation in LRRK2. While 55% of female Parkinson's disease participants with an LRRK2 variant had a positive αSyn-SAA result, the figure for males was 79%. People with an LRRK2 variant and negative αSyn-SAA results also tended to be older (69 years vs. 62 years) than those with positive αSyn-SAA results. Among males and females with sporadic or GBA-associated Parkinson's disease, the results did not differ.

Autopsy data for 15 participants, all with a Parkinson's disease diagnosis in life, showed 14 had typical pathology and were αSyn-SAA positive. The one αSyn-SAA negative case was an individual whose sense of smell was unchanged in life and who also carried the LRRK2 variant.

The authors acknowledge some limitations to their study. Greater numbers of samples would improve analyses by helping to overcome issues posed by factors including skewed data and low sample numbers for some participant groups. The analyses presented are all cross-sectional, but the availability of PPMI samples collected over time would enable future studies to assess changes over specific time periods. Longer-term studies are also needed to further investigate differences in αSyn-SAA results between people with different genetic forms of Parkinson's disease.

Writing in a linked Comment, Professors Daniela Berg and Christine Klein, of University Hospital Schleswig-Holstein, Germany, who were not involved in the study, highlighted the significance of the finding that αSyn-SAA could spot early signs of disease: "Siderowf and colleagues showed that people with prodromal Parkinson's disease and non-manifesting mutation carriers had abnormal α-synuclein aggregation before any other detectable clinical or biomarker changes, a finding that lays the foundation for a biological diagnosis of Parkinson's disease.…"

To harness the full potential of αSyn-SAA, Berg and Klein say blood tests will need to be developed: "Although the blood-based method needs to be further elaborated for scalability, αSyn-SAA is a game-changer in Parkinson's disease diagnostics, research, and treatment trials."

More information: Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study, *The Lancet Neurology* (2023). DOI: 10.1016/S1474-4422(23)00109-6 , www.thelancet.com/journals/lan … (23)00109-6/fulltext

Daniela Berg et al, α-synuclein seed amplification and its uses in Parkinson's disease, *The Lancet Neurology* (2023). DOI: 10.1016/S1474-4422(23)00124-2 , www.thelancet.com/journals/lan … (23)00124-2/fulltext

Provided by Lancet