Blood-based biomarkers may lead to earlier diagnosis of Parkinson's disease

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Parkinson's disease (PD) is a progressive neurological condition. At present, it is usually diagnosed only when motor features are present. Hence, there is a need to develop objective and measurable biomarkers to improve PD diagnostics during its earlier stage, prior to its motor onset. In this pilot study, researchers identified and tested the first blood-based circulating microRNA (miRNA) biomarkers for PD. Their results are published in the latest issue of *Journal of Parkinson's Disease.*

PD is the second most common neurodegenerative disorder in the United States, affecting approximately one million Americans and five million people worldwide. Its prevalence is projected to double by 2030. The most obvious symptoms are movement-related, such as involuntary shaking and muscle stiffness; later, cognitive and behavioral problems may develop along with additional peripheral symptoms such as gastrointestinal dysfunction. There is currently no cure, although the drug levodopa can relieve the symptoms. The differential diagnosis of PD is based primarily on subjective clinical rating scales associated with motor functions. As these scales can only be used when motor features are present, 60-70% of a patient's dopaminergic neurons are already lost by the time of diagnosis.

"The ideal biomarker should be minimally-invasive, cost efficient, quantifiable, reproducible, specific, and sensitive," explains lead investigator Sok Kean Khoo, PhD, of the Center for Neurodegenerative Science and Genomic Microarray Core Facility at the Van Andel Institute, Grand Rapids, Michigan. "Biofluids such as plasma could

provide an ideal resource for development of such desirable biomarkers. However, clinical diagnostic tests based on biochemical analysis of biofluids from PD patients have yet to be established," she continues.

Investigators hypothesized that specific miRNAs related to PD can be detected in plasma. It is known that miRNAs detected in various cells and tissues can also be found in biofluids such as blood plasma and serum. A preliminary study using miRNA microarrays showed that approximately 4% (35/866) of miRNAs from healthy brain tissues could also be detected in the plasma of healthy controls.

In an initial study they obtained the global miRNA expressions in plasma of an initial discovery set of 32 PD patients and 32 normal controls and identified nine pairs of PD-predictive classifiers and 13 most-differentially expressed miRNAs as potential biomarkers to discriminate PD patients from normal controls. They then used a quantitative real-time Polymerase Chain Reaction technique (qRT-PCR) to validate and evaluate the performance of these biomarkers in a new replication set of 42 PD patients and 30 controls from the same clinical site.

They then identified a combination of biomarkers that achieved the highest predictive performance and applied this panel of biomarkers to a new, independent validation set of samples from 30 PD patients from a different clinical site, which showed lower biomarker performance.

The investigators acknowledge that there are still challenges to be overcome in validating biomarker candidates due to clinical and sample variability and factors that influence miRNA expression such as comorbidities and other medication the patient is taking. However, explains Dr Khoo, "This is a proof-of-concept study to demonstrate the feasibility of using plasma-based circulating miRNAs, and the hypothesis that miRNA expression changes are associated with the neurodegenerative disease process, either directly or as part of positive

feedback loops, is emerging rapidly. This study opens new opportunities to the exploration of circulating miRNAs for diagnostic, prognostic, and therapeutic interventions for PD and possibly other neurodegenerative diseases."

"A diagnostic test to determine the status of a patient's disease onset would provide crucial data for more timely, efficient, and successful therapeutic interventions," said Patrik Brundin, MD, PhD, Director of Van Andel Institute's Center for Neurodegenerative Science. "There is an urgent need to develop objective, measureable biomarkers to improve PD diagnostics and help define its subtypes, and Dr. Khoo's interesting study is an important step in that direction."

More information: Khoo, S. et al. Plasma-Based Circulating MicroRNA Biomarkers for Parkinson's Disease, *Journal of Parkinson's Disease*, Volume 2/Issue 4 (December 2012). DOI: 10.3233/JPD-012144

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