Tiny particles offer big clues toward predicting Alzheimer's decades in advance

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In a study published in the journal, *Cells*, a team of scientists describe using machine learning models to identify changes in RNA molecules of plasma extracellular vesicles (EVs) that may hold potential for

identifying Alzheimer's disease (AD) at its earliest stages.

EVs are tiny particles released by the body's cells found in all human biofluids, and they carry molecules that provide information about the health and disease status of the source tissue.

Scientists from the Translational Genomics Research Institute (TGen), part of City of Hope, in collaboration with physicians at the Shiley-Marcos Alzheimer's Disease Research Center at the University of California, San Diego, examined the contents of EVs from the plasma of over a hundred patients: a healthy control group alongside patients afflicted with AD or mild cognitive impairment (MCI).

The team used sequencing technology to analyze the spectrum of small RNA molecules that make up the EV cargo.

"Remarkably, we discovered that many of the changes we see in the EVs of our established AD patients are present in pre-symptomatic people who received a diagnosis five to 15 years later," said senior author Kendall Van Keuren-Jensen, Ph.D., a Professor in TGen's Neurogenomics Division and Deputy Director of Scientific Resources at TGen.

"Our models were able to predict disease development in roughly 80% of the participants, even a decade before symptom onset."

Alzheimer's disease (AD) affects millions globally and is not only devastating to the person that suffers from AD; the substantial physical, mental, societal, and financial toll AD inflicts extends to their loved ones and caregivers.

The disease unfolds in stages, starting with MCI that sometimes goes unnoticed, progressing into AD with notable deficits in memory and

cognition, and culminating in a devastating loss of identity, ability for self-care and social interaction, and eventual death.

"By comparing the RNA contents in EVs from our AD, MCI, and control participants, we found hundreds of different RNA transcripts," said study co-author and TGen computational scientist Eric Alsop, Ph.D. "We took advantage of those different transcripts to create machine learning models that can distinguish between our disease groups with high accuracy," Alsop added.

Neurodegenerative conditions, such as AD, may start many years before any noticeable symptoms emerge, often causing significant damage to the brain prior a diagnosis.

"This is one of the first studies to show changes in the RNA molecules of plasma EVs that precede the onset of symptoms," said study co-author and TGen Neurogenomics Division Staff Scientist Joanna Palade, Ph.D., "and provides evidence that some of the hidden pathology taking place early in the disease is reflected in plasma EVs, where it can be accessed in a minimally invasive manner and used for biomarker development."

Accurately identifying this extended development period could offer patients a chance to explore disease-modifying drugs or make lifestyle adjustments.

"The ability to reliably anticipate and monitor who will develop the disease and in what time frame provides immense value for the physicians seeing these patients in the clinic," said Timothy Whitsett, Ph.D., TGen Senior Director of Institutional Research Initiatives and study co-author.

More information: Joanna Palade et al, Small RNA Changes in Plasma Have Potential for Early Diagnosis of Alzheimer's Disease

before Symptom Onset, *Cells* (2024). DOI: 10.3390/cells13030207

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