A New Biomarker for Parkinson's Disease?

Locascio JJ, Eberly S, Liao Z, et al. Association between alpha-synuclein blood transcripts and early, neuroimaging-supported Parkinson's disease. *Brain* 2015;138(Pt 9):2659-2671.

Despite the best efforts of researchers worldwide, a clinically useful, well-validated biomarker for Parkinson's disease (PD) still remains elusive. The most useful diagnostic marker to date is dopamine transporter imaging, but this is expensive and laborious and cannot distinguish PD from other causes of presynaptic dopaminergic degeneration.[1] Cerebrospinal fluid (CSF) markers (in particular, amyloid β1-42) consistently predict cognitive decline in PD,[2] but there is considerable overlap with other conditions and controls, and there are issues of accessibility of CSF, particularly in older patients. Blood-based biomarkers represent a more attractive option: potential candidates, including urate[3] and epidermal growth factor EGF,[4] may be helpful in disease prognostication, but need to be well validated in larger cohorts. A novel blood-based biomarker candidate has now emerged in the form of alpha-synuclein (SNCA) transcripts in peripheral blood cells, as recently reported in this article by Locascio and colleagues in *Brain*.[5] The major strength of the study is that the results were replicated in three independent cohorts comprising 500 cases in total (one cohort being de novo and unmedicated), and using different gene expression platforms, thus the findings are very robust. The marker is appealing because of the ease of sample collection (venous whole blood in PAXgene tubes) and because of the obvious significance of the protein in PD. However, the direction of the observed relationship is somewhat surprising, with *lower* SNCA transcripts being associated with both disease status (odds ratio for PD 2.45 in lowest vs. highest quartile) and higher rate of cognitive decline over up to 5 years of follow-up. The interpretation of this is a matter of debate, but a mechanism whereby intracellular accumulation of SNCA leads to downregulation of transcription in a feedback loop is proposed by the researchers and constitutes an interesting hypothesis for further study.

It is important to point out that SNCA transcript level does not show great promise as a diagnostic marker, with significant overlap between patient and control groups. Furthermore, this initial study measured SNCA transcript levels at only a single time point, thus their ability to monitor changes in the disease over time is unknown. However, the observed relationship with subsequent longitudinal cognitive decline indicates a possible role for this marker in stratification of dementia risk in PD, which is of such importance for future clinical trials in this area. Given the genetic, clinical, and pathological heterogeneity of the disease, it makes sense that we are now moving away from the concept of a single laboratory-based biomarker for PD and toward the goal of building a panel of well-validated markers for different phenotypic characteristics of the disease. Blood SNCA transcripts may earn a place in such a panel. ■

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