Smelling Parkinson’s Disease: New Metabolomic Biomarker for PD

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A “super-smeller” helps identify a skin sebum odor as a noninvasive biomarker for Parkinson’s disease.

Parkinson’s disease (PD) is the second most common neurodegenerative disease after Alzheimer’s disease (AD) with an estimated 6 million people affected worldwide. Numbers are expected to double over the next generation, motivating research in the development of biomarkers for early detection, like that reported by Barran and co-workers. PD is characterized by a combination of classical motor abnormalities, including a characteristic bilateral or asymmetric rest tremor (most commonly affecting the upper limbs initially), combined with muscular rigidity and a peculiar type of loss of speed and amplitude of voluntary movements. These motor abnormalities are accompanied by a variety of nonmotor symptoms in a majority of patients. These nonmotor symptoms include a decreased sense of smell, constipation, disorders of the sleep–wake-cycle (rapid eye movement sleep behavior disorder, RBD, being the most characteristic for PD), anxiety, depression, and cognitive dysfunction.

Although diagnosing PD can be a straightforward exercise for expert neurologists solely by using classical clinical skills of history taking and clinical examination, there are significant error rates of up to 30% in early disease diagnosis even in the best of hands. This is due to overlapping features and symptoms between PD and other types of parkinsonism, particularly in early disease stages. Additionally, it has become clear that, similar to other chronic neurodegenerative diseases like Alzheimer’s disease, the pathological processes underlying this illness begin much earlier—maybe even by decades—before patients present with specific symptoms and signs (Figure 1). This prediagnostic phase of PD is conceptually divided into a preclinical stage, where pathology is present in the nervous system, but does not produce any clinical symptoms, and a prodromal stage where symptoms are present that have been associated with varying degrees of risk for future PD. These include hyposmia, RBD, and many others.

Research criteria for a diagnosis of prodromal PD have recently been developed, and testing their performance at the population level has found high specificity but limited sensitivity and suboptimal predictive values of less than 70% for the development of PD over 5 years. These challenges highlight the critical need for biomarkers in PD, necessary to enhance diagnostic accuracy in early disease and to improve sensitivity and predictivity of current criteria for prodromal PD. Moreover, PD-specific biomarkers are the only way by which one could diagnose preclinical PD and are also necessary to characterize disease-subtypes with different prognostic trajectories. PD-specific biomarkers in PD, which could be detected by a noninvasive test such as sniffing a sample, have been identified in a recent study. This study evaluated a skin sebum odor as a noninvasive biomarker for Parkinson’s disease.

Figure 1. Schematic illustration of the time course of neurodegeneration in PD. A long preclinical period with ongoing neuronal cell loss (example of the nigro-striatal dopamine system in this graph) precedes the occurrence of diagnostic clinical features. Current unmet needs for PD biomarkers include detection of preclinical and prodromal disease stages as well as enhanced accuracy of clinical diagnosis, identification of disease subtypes, and assessment of disease progression. The upper panel depicts the Braak stages of spread of pathology in the PD brain. The upper panel was adapted by permission from Springer Nature: Journal of Neurology, ref 3, Copyright 2002.
biomarkers will also permit a means to measure disease progression in a more objective and sensitive way than currently possible by using clinical rating scales. Although recent years have seen progress in the definition of PD biomarkers, many candidates suffer from limited sensitivity, specificity, or dependence on invasive or costly procedures and tests (Table 1).

Table 1. PD Biomarkers

| category         | markers                                                                 |
|------------------|-------------------------------------------------------------------------|
| prodromal markers| REM sleep behavior disorder (RBD)                                       |
|                  | hyposmia                                                                |
|                  | constipation                                                            |
|                  | imaging abnormalities (DAT-SPECT)                                       |
|                  | depression                                                              |
|                  | autonomic dysfunction                                                   |
| diagnostic markers| imaging abnormalities (DAT-SPECT, MRI)                                  |
|                  | genetic mutations                                                       |
|                  | biofluid markers (e.g., alpha-synuclein, CSF metabolomics)              |
|                  | gut microbiome composition                                              |
|                  | tissue biopsies for pathological alpha-synuclein species                |

In this issue of *ACS Central Science*, Barran and colleagues present an intriguing novel approach to defining metabolomic PD biomarkers based on clinical analysis of sebum obtained through simple noninvasive gaze swabs from the neck region of Parkinson’s patients. The starting point of their research was the serendipitous encounter of the wife of a PD patient who reported to be able to detect PD by a peculiar smell. The research teams were able to verify the extraordinary smell identification capability of this “super-smeller” by a series of intelligent experiments that eventually led to sebum as the likely source of the “PD odor”.

Barran and colleagues present an intriguing novel approach to defining metabolomic PD biomarkers based on clinical analysis of sebum obtained through simple noninvasive gaze swabs from the neck region of Parkinson’s patients.

In this work, Trivedi et al. set out to analyze the composition of sebum samples obtained from patients with Parkinson’s disease and healthy controls using thermal desorption gas chromatography mass spectrometry (TD-GC-MS). Starting from 17 compounds with differential expression in PD sebum versus controls in their discovery cohort, the authors identified four compounds that were either significantly different in their levels between patients and controls or trended to be increased in Parkinson’s disease. Using this set of four to statistically model ROC (receiver operating characteristic) curves yielded an overall area under the curve for the four compounds of 77%. This is in the range of ROC curves for other PD biomarkers and distinguishes this method as a highly promising prospect of obtaining a metabolomic signature of Parkinson’s disease through a simple noninvasive approach involving little more than moving a gaze swab across the neck region of a patient. Intriguingly, three of the four discriminant compounds had GC-MS retention times overlapping with those where the “super-smeller” described a strong PD smell via an odor port linked to the GC-MS system.

The mechanisms responsible for the differential composition of sebum in PD—a condition classically associated with increased sebum production (seborrhea)—remain elusive. Next to skin punch biopsies, which reveal pathological aggregates of alpha-synuclein in autonomic dermal nerve fibers in Parkinson’s disease, the current findings introduce a new skin-related PD biomarker, which can be obtained noninvasively and potentially on a large-scale basis. Future research will have to show whether this new metabolomic marker could even enter the arena of screening scenarios for prodromal or preclinical PD.

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