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Blood transcriptomics for Parkinson disease?

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Abstract

Parkinson disease (PD) affects up to 10 million people worldwide and is clinically diagnosed. Molecular phenotyping of patient samples might help to corroborate diagnosis, and a new study suggests that blood-based gene expression profiling might distinguish between patients with PD and those without. However, experience suggests that additional replication is needed.

200 years after James Parkinson's description, the disease that bears his name is still diagnosed primarily on the basis of clinical pattern recognition. However, comparisons of the accuracy of clinical diagnosis relative to the ultimate neuropathological diagnosis, among patients who have had signs or symptoms of PD for <5 years and are deemed by fellowship-trained movement-disorder specialists to have probable PD, reveal a level of accuracy that is little better than chance[1]. Such findings suggest that ample room exists for confirmatory diagnostic tests to improve the accuracy of diagnosis in real-world situations where it is likely to make the greatest difference: early in the disease course.

> "transcriptomic profiling, as performed here, is by its very nature unbiased"

Shamir *et al.*[2] now report a blood-based transcriptomic profile based on 100 probes mapping to 87 genes that might differentiate patients with idiopathic PD from both individuals with no underlying neurological impairment and patients with other neurodegenerative diseases. Differentially expressed genes were identified using a training set consisting of whole-blood gene expression profiles of 140 patients with PD and 153 individuals without a neurological disease. The expression profile-based model was then fine tuned using expression data from an additional set of 35 patients with PD and 40 individuals without a neurological disease. This was followed by the ultimate evaluation of the performance characteristics of the classifier in a test set comprising samples from 30 patients with PD, 40 individuals with no neurological conditions and 48 patients with other neurodegenerative diseases. From this analysis, the authors developed a machine-learning classifier with an area under the receiver operating curve (AUC) of 0.74 in the final test set.

This reported effect size is encouraging, although clinicians and researchers should remember that we have been here before. Specifically, starting 10 years ago, multiple research groups have attempted to identify a blood-based gene expression signature that indicates the presence of PD, with little or no overlap in their findings[3–7]. The current study

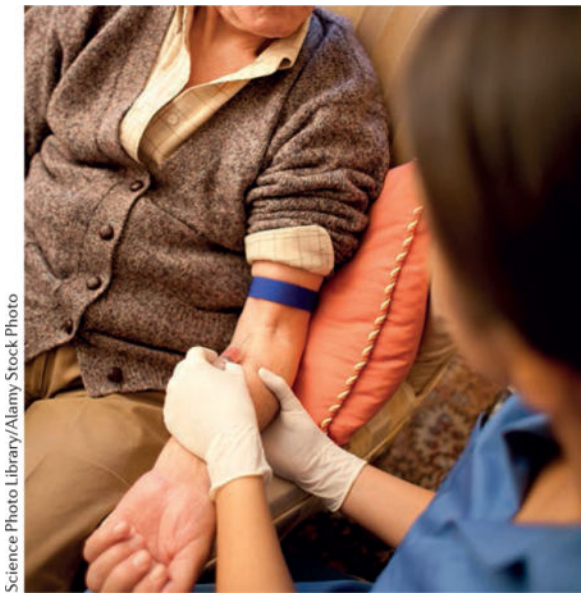
Competing interests

The author declares no competing interests.

improves upon previous work by tuning the classifier to an optimal number of probes, by investigating the influence of batch effects and, most importantly, by including multiple built-in replication cohorts. However, the main findings of the current study once again fail to overlap with those presented in most previous reports[3–7], and several aspects of the study design suggest that a good deal more work is needed before clinical implementation will become feasible.

First, all patients with PD in this study[2] received treatment with dopaminergic medications at the time of sampling. This creates an important potential confounder, as individuals without chronic illnesses or those with other neurodegenerative diseases are unlikely to be receiving similar treatments, and medication use can certainly affect gene expression. Second, an AUC of 0.74 indicates the ability to discriminate between patients with PD and those with no neurodegenerative disease. When the authors investigated the performance of their classifier in differentiating between patients with PD and those with other neurodegenerative diseases, the AUC fell considerably to <0.65 (REF. 2). In real-world situations, the difficulty is not usually in differentiating between those with PD and those without a neurological disease but in differentiating between those with PD and those with other neurological diseases that might have symptoms that mimic PD. Third, the diagnoses used to group individuals into the PD group, as opposed to other groups, were based solely on clinical diagnosis, thereby creating a tautological situation in which one cannot improve upon the thing upon which one might want to improve (clinical diagnosis).

This raises the question as to how we view these findings and their limitations. The utility of the research by Shamir *et al.*[2], as well as our understanding of the transcriptomic landscape of PD, could be improved in several ways. Some of these suggested improvements are easy to enact, whereas others require a cultural shift in terms of how translational research is conducted, communicated, and valued. One might argue, however, that now is the time to make such a cultural shift in the translational neurosciences if we are ever to garner genuine benefit for patients.



First, researchers need to know whether the results obtained with gene expression signatures are reproducible in other cohorts of patients with PD — and, in particular, among cohorts with ancillary information available that suggests that the diagnosis is correct (such as the dopamine-transporter imaging[8] available in the Michael J. Fox Foundation Parkinson disease Progression Marker Initiative (PPMI) cohort[9]) and in cohorts in which there is no ongoing dopaminergic medication use that might confound the conclusions. This approach might require RNA expression profiling in these additional cohorts, as well as the use of transparent methodology that enables true replication. Thus, second, researchers should aim to maximize transparency at each stage of the research and publication process. In the current report[2], the authors have deposited their gene expression data and analysis scripts publicly, for which they should be commended. However, this information is very hard to find, and no obvious reason exists for journals not to make information on how to access the data and analysis scripts easily available within the primary methods section. Third, although we are in a data-rich age, the availability of data is not synonymous with the true understanding of its meaning. In the case of a potential blood-based biomarker of PD, it should be considered how best to make findings accessible to scientists and clinicians who might not be able to parse an R-script, for example. Might there be a place, then, for a web-based tool that enables researchers to easily input datasets that will then automatically be processed in an identical way to those presented in the publication, resulting in output predictions of PD versus not PD? Finally, and this might be the most important point, researchers, clinicians and other stakeholders need to think hard, and collectively, about how to increase the incentive for replication and how best to create appropriate venues for the presentation and reporting of negative results.

Caveats and suggestions aside, two other important points about the current report[2] deserve further emphasis. First, transcriptomic profiling, as performed here, is by its very nature unbiased; every probe and gene has approximately the same chance of being incorporated into the eventual classifier as any other. Unbiased approaches were initially considered

heretical in the traditionally hypothesis-driven paradigm of the scientific process, although such approaches have led to major advances in other fields of medicine, such as oncology[10]. Second, in the current report, the authors attempted to phenotype patients and those with no neurodegenerative disease at the molecular level, using objective means. Similarly, the development of objective molecular phenotypes has greatly advanced the field of oncology (in which cancers are routinely defined by the presence or absence of molecular markers) as well as cardiovascular medicine (where vessel health and risk is routinely quantified using biomarkers such as circulating lipid levels). Given the clear need for better tools that improve the diagnosis, follow-up monitoring and phenotyping of patients with PD, the time is now ripe for the type of unbiased molecular phenotyping presented in this study report.

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