Precautions for study design and data interpretation of clinical metabolomics

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Metabolomics is increasingly used in clinical research such as mechanistic elucidation, biomarker discovery, and personalized and translational medicine. In a paper in PNAS by Teruya et al. (1) on whole-blood metabolomics in dementia patients, the authors report that they have discovered 33 blood metabolites that are linked to dementia. Unlike previous plasma metabolomics, this study includes metabolites typically enriched in red blood cells. These outcomes are noteworthy because they may lead to potential approaches in diagnosing and treating dementia. However, several points may influence the interpretation of the findings.

First, the sample size in this study (1) is relatively small, which might lead to a high chance of false discovery in clinical metabolomics. We roughly estimated the minimum sample size to obtain the true statistical differences of 33 discriminating features reported in the paper. A power analysis method described for high-dimensional metabolomics data (2) was used, and at least 17 subjects per group were required to achieve ≥80% statistical power. We understand that red blood cells are difficult to handle for large cohorts because they undergo rapid metabolic changes. Dried blood spots may then be considered as an alternative sample collection approach for whole-blood metabolomics (3).

Second, age matters for clinical metabolomics. We noted that the age was not balanced between the dementia group and the healthy elderly (HE) group, and patients with dementia were significantly older than the HE group (84.6 ± 4.3 y for dementia vs. 74.8 ± 4.1 y for the HE group, $P = 0.0014$, Mann–Whitney U test) (1). A Cohen's d effect size of 2.3 for age indicated that age differences might have a very large contribution to the metabolomic differences between two groups, as many metabolites were reported to show continuous changes after the age of 50 y for both men and women (4).

Third, medications and diet have significant influences on the metabolome and thus the interpretation of clinical metabolomics results. As described by the authors (1), subjects in the dementia group were taking a variety of drugs, while the healthy groups did not. It is known that these drugs can alter the metabolomic profiles (5). Even though the subjects underwent 8-h fasting before the blood draw, this is apparently not enough for washing out the drug effects. For example, memantine, taken by five out of eight patients in the study, has a half-life of about 60 h to 80 h. In addition, the authors highlight two dietary-derived compounds, ergothioneine and caffeine, as the biomarkers for differentiating dementia from the HE subjects. However, it is not clear whether the observations were caused by the differences in dietary intake.

The world's older population is growing substantially, and new technologies and diagnostic strategies that enable an increased understanding of age-related disorders are much needed. However, there are many factors to consider to ensure optimal results from a clinical metabolomic study, such as sample size, age, medications, and dietary effects. To avoid undue hype and false hopes, results should be interpreted with caution.

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