Next generation metabolic screening – towards clinical application of X-omics

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1. Introduction

In clinical diagnostics of inborn errors of metabolism (IEM), currently a diverse spectrum of targeted biochemical assays is employed to analyze metabolite perturbations. We now present a single-platform, high-resolution LC-QTOF method, which we have termed 'next generation metabolic screening' (NGMS), which can be applied for holistic metabolic profiling in plasma of individual IEM-suspected patients.

2. Approach

Ultra-high pressure, reversed-phase liquid chromatography (UHPLC)-mass spectrometry was performed on an Agilent 1290 LC-QTOF 6545 system. Raw data was processed by Agilent MassHunter Qual software, and analyzed by XCMS software for retention time alignment, peak detection, and peak matching. The resulting features (i.e., ion signals with accurate mass (m/z), intensity and retention time) were uploaded to an in-house developed chemometric pipeline, which enables selection of features that are significantly different between patients and controls (t-test with Bonferroni-Holm correction), and automatically cross-references exact masses with the human metabolome database (HMDB) for putative metabolite annotation. To reduce data complexity and extract relevant information for diagnosis of IEMs, the automated pipeline included an initial targeted evaluation of ~350 known IEM-associated metabolites (IEM panel). As a subsequent step, the untargeted NGMS data is available for further evaluation of additional HMDB annotated- and/or unknown features.

3. Results

The NGMS 'IEM panel' methodology has been successfully validated for a broad spectrum of IEMs[1]. Diagnostic plasma samples for 46 individual IEMs were available for clinical validation, ranging from fatty acid oxidation disorders to organic acidurias and other amino acid metabolism disorders to disorders in purine/pyrimidine metabolism. Based on the composition of the IEM panel, we estimate that ~200 known IEMs should be detectable by NGMS.

4. Discussion

This proof-of-principle study demonstrates the feasibility of holistic metabolomics in clinical diagnostics for IEMs. Future challenges will lie in extracting diagnostic information from the untargeted metabolomics data, expanding the data evaluation to metabolites outside the IEM panel. Also the chemical identification of the many unknown metabolites that will be encountered will be challenging. We believe that further integration with other -omics applications (X-omics) will unlock the full clinical potential of metabolomics; the identification of a new IEM through the combination of metabolomics and genomics illustrates this potential[2].

References

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