Metabolomics and lipidomics as a research and diagnostic tool in inborn error of metabolism

Michel van Weeghel[1], Katharina Herzog[1], Mia L. Pras-Raves[1], Martin A. T. Vervaart[1], Angela C. M. Luyf[2], Antoine H. C. van Kampen[2,3], Riekelt H. Houtkooper[1], Ronald J. A. Wanders[1], Hans R. Waterham[1] and Frédéric M. Vaz[1]

[1]Amsterdam UMC, University of Amsterdam, Laboratory Genetic Metabolic Diseases, Amsterdam Gastroenterology & Metabolism, Meibergdreef 9, Amsterdam, The Netherlands

[2]Amsterdam UMC, University of Amsterdam, Bioinformatics Laboratory, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Meibergdreef 9, Amsterdam, The Netherlands

[3]Biosystems Data Analysis, Swammerdam Institute for Life Sciences, University of Amsterdam, The Netherlands

E-mail: m.vanweeghel@amc.nl

1. Introduction

Metabolomics and lipidomics are becoming increasingly important as analytical tools for biomarker discovery in research but have not frequently been applied to diagnostics. Inborn errors of metabolism (IEM) are routinely identified by targeted analysis of intermediary metabolites. The growing development of high-resolution mass spectrometric techniques, however, opens new avenues to perform semi-targeted metabolomics and lipidomics in complex matrices. These matrices include plasma, cells and/or tissues from patients who suffer from known or unknown inborn errors of metabolism.

2. Approach

In our study, we investigated the metabolome profiles from a set of 120 plasma samples from patients with the following 10 known inborn errors of peroxisomal metabolism: AMACR-, 3BHSD-, CTX-, DBP- and MVK-deficiency, NPC, RCDP, Refsum disease, SLO and ZSD. We used reversed-phase, normal-phase, and HILIC chromatography followed by full-scan orbitrap-MS on the Q Exactive plus in positive and negative ionization mode and annotated over 100 polar metabolites and over 1300 lipid species.

3. Results

Using partial least squares regression discriminant analysis (PLS-DA) some of the disorders were completely separated from the controls (data not shown). For example, compared to controls, Zellweger Spectrum Disorder (ZSD) patients had relatively increased phosphatidylcholine (PC) and Lyso PC (LPC) species containing very long-chain fatty acids (VLCFAs). PC ether phospholipid (PC(O), PC(P)) species, and sphingomyelin (SM) species were relatively decreased in these patients. This strong correlation was then visualized in a correlation matrix (data not shown). Furthermore, for some of these IEMs we identified new biomarkers. For example, in AMACR-deficiency, branched-chain LPC(19:0) and branched-chain LPC(20:0) appeared in plasma; in Refsum disease and ZSD only the branched-chain LPC(20:0) appeared when compared to control (figure 1).

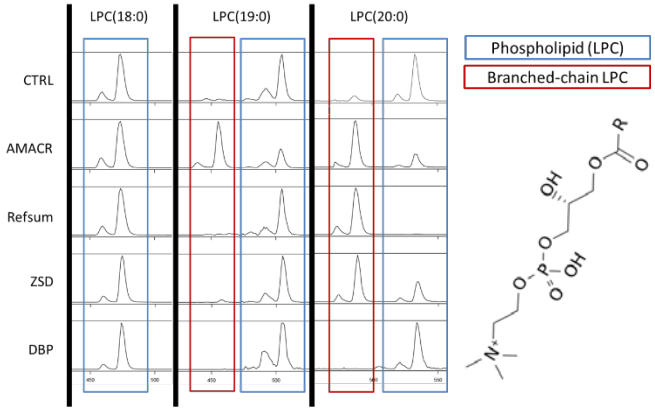

Figure 1. New biomarkers? Branched chain phospholipids.

Because this is a semi-targeted approach, identities of some of the newly found biomarkers remain to be characterized. The ultimate goal is to use this type of metabolomics and lipidomics analyses for first line screening of IEMs.

4. Highlights

- With our metabolomics and lipidomics approach we were able to annotate and identify over 1400 metabolites;
- We tested plasma of 10 known inborn errors of peroxisomal metabolism and identified the known specific biomarkers;
- New biomarkers were identified (branched-chain LPCs) for AMACR-deficiency, Refsum disease and ZSD;
- Our ultimate goal is to use metabolomics and lipidomics for first line screening of IEMs.

References

1. Katharina Herzog *et al.*, "Plasma lipidomics as a diagnostic tool for peroxisomal disorders". *J Inherit Metab Dis.* 41(3):489-498, 2018.