APPLICATION NOTE

OMICs Hub
Metabolomics

Inter-individual heterogeneity in clinical metabolomics studies:
Assessment of inter-individual NMR/MS metabolic signatures variability in plasma of a heterogeneous group of healthy volunteers – impact for biomarkers discovery.

In a study on critically ill patients*, we performed metabolomics on a group of healthy volunteers (HV) vs. patients with different pathologies (P1, P2 and P3). The HV group (74 individuals) was designed from a wide demographic population (sex, age), thus reinforcing the potential metabolic heterogeneity. In this context, we addressed the question of the variability of metabolites in plasma, with a NMR/MS untargeted metabolomics approach, and evaluated the potential impact for biomarkers discovery.
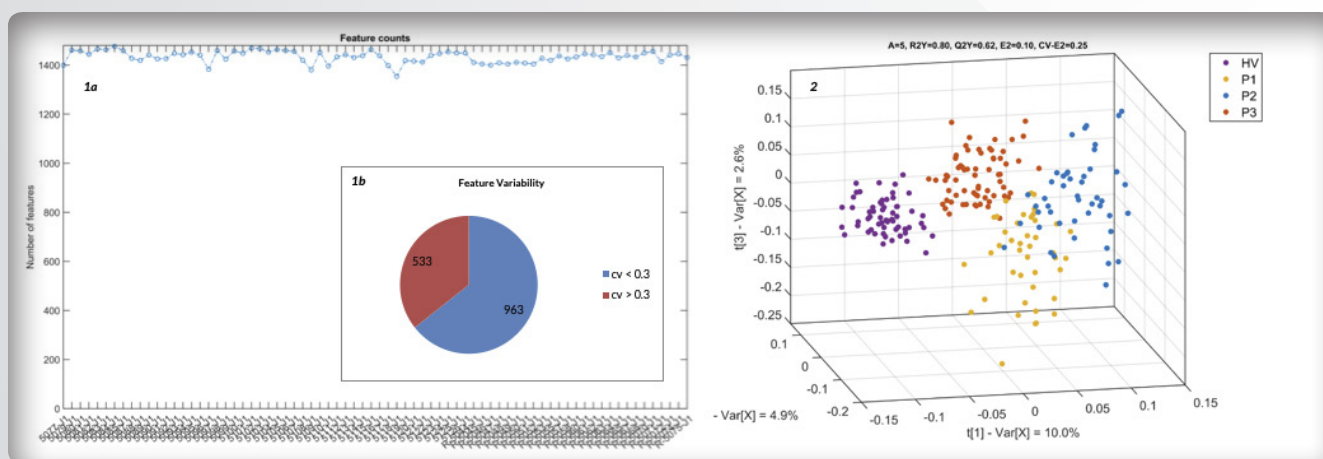

Figure 1: a) Feature count plot of the metabolites observed in each HV sample. b) The pie chart shows the proportion of features having a cv < 0.3 and cv > 0.3 (in blue and red, respectively).
Figure 2: PLS of the data after preprocessing showing the separation of the group of HV (in purple) and the three groups of pathology P1, P2 and P3.

PRINCIPLE

- We put in place a standardized workflow for sample collection at the clinical site and automated sample preparation;
- We integrated two technologies to assess the metabolomics profiles in plasma samples: 1H NMR for the polar metabolites and LC-HRMS for lipidomics;
- The preprocessing of data used an OpenMS workflow for feature extraction and alignment and MIMOSA, an in-house software, for filtration, batch correction and feature grouping.

KEY RESULTS

- After the processing of the data (quality control, filtration) we obtained **1496 relevant features** (potential metabolites) **(Figure 1a)**;
- In order, to assess the robustness of these features, we calculated the coefficient of variation (cv) for each feature among the samples. A cv < 0.3 means that the feature is stable and robust across all the samples for metabolomics. In our study, **963 features** (64.4%) *are stable* between samples **(Figure 1b)**;
- In our metabolomics workflow, we apply advanced statistics and in particular a supervised approach (PLS, partial least squares) to separate the groups and to identify the most relevant features **(Figure 2)**. This analysis minimizes the variability between individuals of the healthy group HV and maximize the variance between the sick individuals with different pathology (P1, P2 and P3), allowing to identify biomarkers or signatures.

ACHIEVEMENTS

In this study, specifically designed for metabolomics, we established a NMR/MS/bioinformatics workflow allowing to obtain ~1000 stable putative metabolites in plasma of a group of healthy volunteers. This high quality data set is therefore relevant for biomarker discovery in a clinical context.

*Clinical data were collected, analysed and transfered to BIOASTER in compliance with applicable law and regulations (clinicaltrials.gov ref. NCT02638779)

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