Success story

Statistical data analysis (OPLS) improves diagnosis of ALS and Parkinson's disease

An important mission for science today is to develop better diagnostics and better treatments of severe diseases such as amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD). Recently, a research group at Umeå University, Sweden, has shed new light on the possibility to improve the diagnosis of ALS and PD and better understand the disease progression.

ALS and PD are difficult to diagnose as they exhibit heterogeneous genetic causes as well as heterogeneous disease courses. They share etiology (together with other neurological diseases) of protein misfolding and aggregation, which lead to degeneration of different neurons in different areas of the central nervous system.

Study of metabolomics may aid in diagnosing ALS and PD

The last decade, metabolomics has become increasingly popular in investigating neurodegenerative disorders as it combines environmental, genetic, and physiological components. Metabolomics can be used for investigating perturbed metabolic pathways with the intention to better understand the underlying pathological mechanisms at onset and progression of the disease.

In their study, the research group analyzed mass spectrometry data of metabolomes from the cerebrospinal fluid (CSF) and plasma from patients with ALS and PD. The purpose of the study was to investigate if certain metabolites differentiate ALS and PD patients from their matched controls and if certain metabolites differentiate or overlap between ALS patients and matched PD patients.

Rigorously matched pairs of ALS, PD, and control group subjects

Metabolites can change due to a number of various factors such as the age and sex of the subject as well as nutrition. As these non-disease metabolic patterns can mask changes due to a disease, increasing the size of the cohort may not lead to more accurate study results. Instead, this study used rigorously matched pairs of subjects to limit potential bias due to non-disease metabolic patterns.

Only patients with a definite diagnosis were included in the study, 22 ALS patients and 22 PD patients matched for age, sex, and storage time of the samples (CSF and plasma collected at the same visit). In addition, a control group of 28 patients who had visited the same clinic with other neurological disorders were included, whereof 6 ALS and 6 PD patients were allotted two matched control individuals.

Identification of metabolites

CSF and plasma were analyzed using multi-platform mass spectrometry (gas chromatography and liquid chromatography mass spectrometry). Detected metabolites were identified using various public mass spectra libraries. Percentage relative standard deviation (%RSD) on the quality control samples was used to determine by which analysis the metabolite was detected most robustly – gas chromatography or liquid chromatography – and the measurement with the lowest %RSD, that is, the most certain identification of the metabolite, was used.

Data analysis

Both identified and non-identified metabolites were evaluated to discriminate between ALS, PD, and control. As a first step, the collected data were scaled to unit variance.

OPLS was then used to analyze the data. OPLS is a regression

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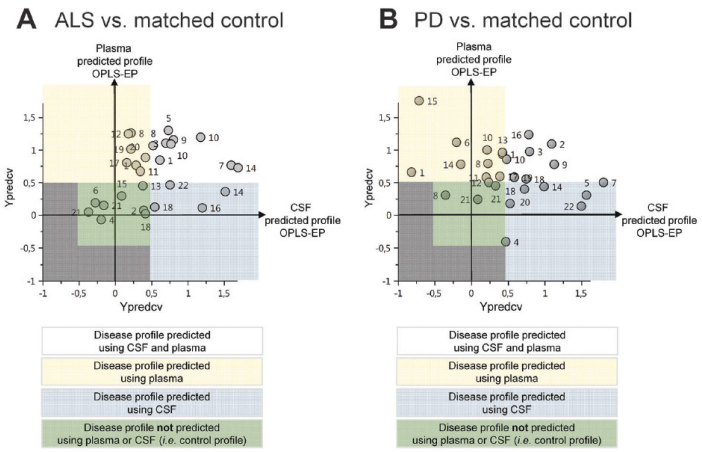
extension of the PCA method that can reveal latent structures and give a better understanding of the data. Of particular interest in this study was an extension to OPLS; OPLS-EP – orthogonal projection to latent structures-effect projections. It was used to investigate common variable patterns for each matched pair – a multivariate "paired" statistical test of latent variables. For each matched pair, a predicted response (Ypred) is calculated. If Ypred is >1 it will indicate a positive difference (the pair is less similar) and a value < 0 will indicate a negative difference (the pair is more similar). A visualization of the model is seen in the example picture, which illustrates the correlation of individual patients' predicted profiles with the optimized OPLS-EP cross-validated models (Ypredcv) for CSF metabolites (x-axis) versus the predicted profiles using plasma metabolites (y-axis).

Results

In CSF, 144 unique metabolites were found and in plasma 188. While none of the statistical models could completely distinguish all patients from their matched controls, certain metabolites were differentiating ALS and PD from matched controls and ALS from matched PD. For example, the OPLS-EP models revealed 12 identified metabolites that were significantly different in plasma for the two diseases and 6 in CSF. Similar to previous studies, this study suggests alterations in energy utilization pathways and that perturbed metabolites can be used for the diagnosis of ALS and PD.



The customer:

Multi-platform mass spectrometry analysis of the CSF and plasma metabolomes of rigorously matched amyotrophic lateral sclerosis, Parkinson's disease and control subjects, Molecular BioSystems, 2016, 12, 1287.

The challenge:

To improve diagnosis of ALS and PD patients.

The solution:

Using OPLS for analysis of mass spectrometry data of metabolomes from the CSF and plasma of rigorously matched pairs of patients with ALS, PD, and controls.

The result:

The study revealed metabolites that differentiate ALS and PD from matched controls and ALS from matched PD, providing additional information, which may lead to earlier diagnosis and guide proper treatment.

OPLS® is a statistical method for modeling data and is included in the SIMCA® software from the Umetrics® Suite of Data Analytics Solution.

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