Integration of Metabolite CSF Measurements, Magnetic Resonance Imaging and Protein Measurments to Enable Early Diagnosis of Secondary Progressive Multiple Sclerosis

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1. Introduction

Molecular networks in neurological diseases are complex. Despite this fact, contemporary biomarkers are in most cases interpreted in isolation, leading to a significant loss of information and power. We present an analytical approach to scrutinize and combine information from biomarkers originating from multiple sources with the aim to discover a condensed set of biomarkers that in combination could distinguish the progressive degenerative phenotype of multiple sclerosis (SPMS) from the relapse-remitting phenotype (RRMS).

2. Approach

The cerebrospinal fluid (CSF) metabolome was recorded using liquid chromatography-mass spectrometry and analyzed using methods developed in the PhenoMeNal consortium (1,2). Clinical and magnetic resonance imaging (MRI) data were integrated with data from protein and metabolite measurements of CSF and a method was developed to sift through all the variables to establish a small set of highly informative measurements.

3. Results

We have developed an architecture which uses components for data analysis encapsulated as microservices connected into operating computational workflows including more than 200 tools, for use in analysis of metabolomics data (1,2). Using selected tools to analyse the CSF metabolome, SPMS patients could be moderately (AUROC: 0.83) distinguished from RRMS patients, showing alterations in the arginine and proline metabolism. However, by combining only eleven variables we were able to distinguish SPMS from RRMS patients with high confidence ($p=8.5\times10^{-9}$), superior to any single measurement (3) (Figure 1). The identified variables consisted of three MRI variables, six proteins and two metabolites. The proteins myelin basic protein (MBP) and macrophage-derived chemokine (MDC), as well as the metabolites 20β-DHF and 5,6-dihydroxyprostaglandin F1a (5,6-DH-PGF_1) were in addition identified as potential biomarkers of disability progression.

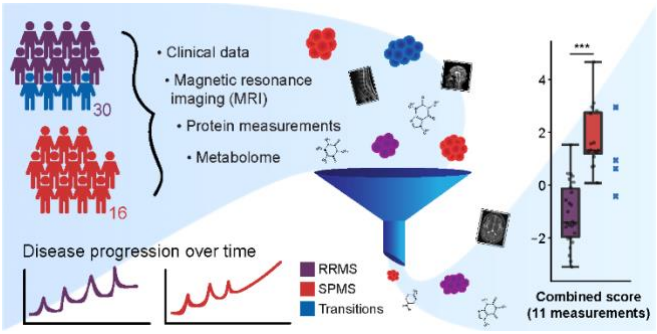

Figure 1. By a combination of eleven variables we were able to distinguish SPMS from RRMS patients with high confidence superior to any single measurement.

4. Discussion

A few metabolomics studies on CSF from MS patients have previously been performed, e.g. suggesting alterations in energy and phospholipid metabolism compared to non-MS. We have here shown that a model-based approach integrating metabolite measurements with clinical data, radiological and protein measurements could be used for early diagnosis of SPMS patients. Using a linear combination of only eleven variables, the identification of SPMS patients could be improved. We also identified four biomarkers that were associated with a worse prognosis in patients with SPMS that potentially could be used to evaluate the disease course of these patients.

References

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