Integrative multi-omics approach in subjects affected by Glycogen storage disease type Ia

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Glycogen storage disease type Ia (GSDIa) is a genetic metabolic disorder caused by the deficiency of glucose-6-phosphatase-α that affects carbohydrate metabolism by impairing the final step of gluconeogenesis and glycogenolysis. The most common biochemical features include hypoglycemia, lactic acidosis, hypertriglyceridemia, hypercholesterolemia and hyperuricemia. Over time, patients with GSDIa accumulate glycogen and fat storage in the liver and kidneys, leading to hepatomegaly and kidney disease, respectively. Currently, there are no approved drug therapies for the treatment of GSDIa, but highly personalized diets to prevent hypoglycemia and secondary metabolic perturbations. Although GSDIa patients show a good compliance with the specific dietary treatments, over time they may develop long-term complications such as hepatocellular adenomas and carcinomas, as well as chronic kidney disease. To unravel the wide-ranging metabolic perturbations that occur in GSDIa and to elucidate the molecular basis of the known long-term complications, an integrative multi-omics approach was adopted including data from mass spectrometry-based serum proteomics, metabolomics and lipidomics in 12 GSDIa patients. Patients showed a unique multi-omics serum signature compared to age- and sex-matched healthy controls. Multi-omics data integration indicated liver injury and lipid metabolism dysfunction, highlighting the pivotal role of the liver in both early and late stages of the disease. In conclusion, our findings provided new insights into the field of GSDIa highlighting the primary role of the liver in the progression of the disease and the need for prognostic biomarkers discovery in GSDIa.