A Plasma Metabolomic Signature Involving Purine Metabolism in Human Optic Atrophy 1 (OPA1)-Related Disorders

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Résumé en anglais	Purpose: Dominant optic atrophy (DOA; MIM [Mendelian Inheritance in Man] 165500), resulting in retinal ganglion cell degeneration, is mainly caused by mutations in the optic atrophy 1 (OPA1) gene, which encodes a dynamin guanosine triphosphate (GTP)ase involved in mitochondrial membrane processing. This work aimed at determining whether plasma from OPA1 pathogenic variant carriers displays a specific metabolic signature. Methods: We applied a nontargeted clinical metabolomics pipeline based on ultra-high-pressure liquid chromatography coupled to high-resolution mass spectrometry (UHPLC-HRMS) allowing the exploration of 500 polar metabolites in plasma. We compared the plasma metabolic profiles of 25 patients with various OPA1 pathogenic variants and phenotypes to those of 20 healthy controls. Statistical analyses were performed using univariate and multivariate (principal component analysis [PCA], orthogonal partial least-squares discriminant analysis [OPLS-DA]) methods and a machine learning approach, the Biosigner algorithm. Results: A robust and relevant predictive model characterizing OPA1 individuals was obtained, based on a complex panel of metabolites with altered concentrations. An impairment of the purine metabolism, including significant differences in xanthine, hypoxanthine, and inosine concentrations, was at the foreground of this signature. In addition, the signature was characterized by differences in urocanate, choline, phosphocholine, glycerate, 1-oleoyl-rac-glycerol, rac-glycerol-1-myristate, aspartate, glutamate, and cystine concentrations. Conclusions: This first metabolic signature reported in the plasma of patient carrying OPA1 pathogenic variants highlights the unexpected involvement of purine metabolism in the pathophysiology of DOA.
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