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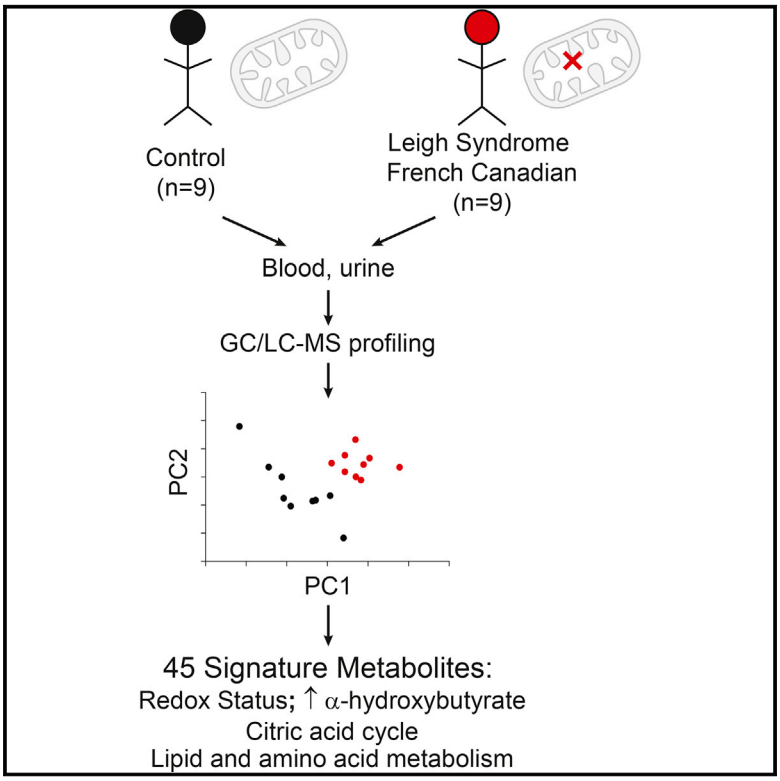
A Metabolic Signature of Mitochondrial Dysfunction Revealed through a Monogenic Form of Leigh Syndrome

Graphical Abstract



Highlights

- A metabolic signature is revealed in patients with a genetic mitochondrial disorder
- Profiling of 407 plasma/urine analytes identified 45 distinctive markers
- Markers reflect changes in cardiovascular risk as well as NAD^+ lipid and amine metabolism
- Markers also include metabolites linked to neurodegeneration

Authors

Julie Thompson Legault, Laura Strittmatter, Jessica Tardif, ..., John D. Rioux, Vamsi K. Mootha, Christine Des Rosiers

Correspondence

vamsi@hms.harvard.edu (V.K.M.), christine.des.rosiers@umontreal.ca (C.D.R.)

In Brief

In this prospective case-control study, Thompson Legault et al. applied comprehensive metabolic profiling in a genetically homogeneous form of Leigh syndrome to discover a robust signature of disrupted oxidative phosphorylation. The metabolic signature includes markers of mitochondrial disease, cardiometabolic risk, and disrupted NAD^+ as well as lipid and amino acid metabolism.

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A Metabolic Signature of Mitochondrial Dysfunction Revealed through a Monogenic Form of Leigh Syndrome

Julie Thompson Legault,[1,3] Laura Strittmatter,[5] Jessica Tardif,[6] Rohit Sharma,[5] Vanessa Tremblay-Vaillancourt,[6] Chantale Aubut,[6,7] Gabrielle Boucher,[3] Clary B. Clish,[8] Denis Cyr,[9] Caroline Daneault,[3] Paula J. Waters,[9] The LSFC Consortium, Luc Vachon,[10] Charles Morin,[7] Catherine Laprise,[6] John D. Rioux,[2,3] Vamsi K. Mootha,[4,5,8,*] and Christine Des Rosiers[1,3,*]

[1]Department of Nutrition, Université de Montréal, Montreal, QC H3C 3J7, Canada
[2]Department of Medicine, Université de Montréal, Montreal, QC H3C 3J7, Canada
[3]Research Centre, Montreal Heart Institute, Montreal, QC H1T 1C8, Canada
[4]Howard Hughes Medical Institute and Department of Molecular Biology, Massachusetts General Hospital, Boston, MA 02114, USA
[5]Department of Systems Biology, Harvard Medical School, Boston, MA 02445, USA
[6]Département des Sciences Fondamentales, Université du Québec à Chicoutimi, Chicoutimi, QC G7H 2B1, Canada
[7]Centre de Santé et de Services Sociaux de Chicoutimi, Chicoutimi, QC G7H 5H6, Canada
[8]Broad Institute, Cambridge, MA 02142, USA
[9]Medical Genetics Service, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC J1H 5N4, Canada
[10]The LSFC Consortium
*Correspondence: vamsi@hms.harvard.edu (V.K.M.), christine.des.rosiers@umontreal.ca (C.D.R.)
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SUMMARY

A decline in mitochondrial respiration represents the root cause of a large number of inborn errors of metabolism. It is also associated with common age-associated diseases and the aging process. To gain insight into the systemic, biochemical consequences of respiratory chain dysfunction, we performed a case-control, prospective metabolic profiling study in a genetically homogenous cohort of patients with Leigh syndrome French Canadian variant, a mitochondrial respiratory chain disease due to loss-of-function mutations in *LRPPRC*. We discovered 45 plasma and urinary analytes discriminating patients from controls, including classic markers of mitochondrial metabolic dysfunction (lactate and acylcarnitines), as well as unexpected markers of cardiometabolic risk (insulin and adiponectin), amino acid catabolism linked to NADH status (α-hydroxybutyrate), and NAD^+ biosynthesis (kynurenine and 3-hydroxyanthranilic acid). Our study identifies systemic, metabolic pathway derangements that can lie downstream of primary mitochondrial lesions, with implications for understanding how the organelle contributes to rare and common diseases.

INTRODUCTION

Mitochondrial dysfunction is increasingly being recognized as a hallmark of rare and common age-associated diseases. Among inherited metabolic diseases, those affecting mitochondria are the most prevalent worldwide (1:5,000), frequently manifest in early childhood, and are associated with high morbidity and mortality (DiMauro, 2004; Torraco et al., 2009; Vafai and Mootha, 2013). These disorders may be caused by genetic lesions in either nuclear or mtDNA, which may disrupt numerous metabolic pathways housed in the mitochondria but most prominently the oxidative phosphorylation (OXPHOS) system (Debray et al., 2008; Munnich and Rustin, 2001). These disorders can impact virtually any organ system as a whole or in a tissue-specific manner. A subtle decline in OXPHOS is associated with skeletal muscle atrophy, type 2 diabetes, neurodegeneration, and the aging process itself (Vafai and Mootha, 2012), though the molecular basis and biochemical consequences are currently not known. There is growing interest in rare mitochondrial disorders, and studying them may shed insight into the role of the organelle to more common, age-associated disease.

Recently, tremendous progress has been achieved in the genetic characterization of rare mitochondrial disorders, yet their management remains challenging because of the difficulty to track their progression and the absence of proven therapies (DiMauro and Mancuso, 2007; Orsucci et al., 2009; Pfeffer et al., 2013; Schapira, 2012). This is due in part to our lack of understanding of the metabolic consequences of OXPHOS defects beyond ATP and the commonly reported high blood lactate. In this regard, the recent emergence of metabolomics technologies offers a means to systematically measure thousands of low-molecular-weight compounds in order to provide a global view of alterations in metabolic pathways induced by a given perturbation, whether resulting from a gene mutation or disease onset. These methods have been applied to numerous diseases such as diabetes and cardiovascular disease (for reviews, see Roberts and Gerszten, 2013 and Shah et al., 2012). However, only few