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Mass spectrometry approach for novel Fabry disease biomarker detection

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Abstract

Fabry disease is an X-linked lysosomal storage disorder due to alpha-galactosidase A deficiency. It leads to the accumulation of glycosphingolipids, mainly globotriaosylceramide (Gb3) and globotriaosylphingosine (lyso-Gb3) in biological fluids, and different organs. The objectives of this research project were to discover novel biomarkers related to Gb3 and lyso-Gb3, to elucidate their chemical structure, and to quantify the biomarkers of interest by tandem mass spectrometry (UPLC-MS/MS). Urine and plasma samples from untreated Fabry patients and healthy controls were collected. Biomarker discovery was performed using time of flight mass spectrometry (Waters Corporation). The results generated were processed for multivariate analysis. Eight novel lyso-Gb3 and 18 Gb3 biomarkers were specifically detected in urine and plasma. An internal standard was synthesized for relative urinary quantification of lyso-Gb3-related analogues using UPLC-MS/MS. Fabry patient urine specimens presented analogues which were excreted in larger quantities than the lyso-Gb3 biomarker itself, whereas, plasma levels of lyso-Gb3 were found to be in higher quantities than the rest of the analogues. This suggests a possible metabolic process between plasma and urine. No significant quantities of lyso-Gb3 urinary analogues were found in normal healthy controls. One male Fabry patient with a cardiac variant mutation (N215S) had a normal urinary Gb3/creatinine level, but he presented abnormal levels of urinary and plasma lyso-Gb3, as well as urinary lyso-Gb3 analogues.

Conclusion: These metabolomic studies using a time of flight mass spectrometry approach allowed the detection of 26 novel Fabry disease biomarkers, some of which were found specifically in patients having Fabry cardiac variant mutations.

Biography

Christiane Auray-Blais is the Director of the Quebec Provincial Mass Urinary Screening Program for hereditary metabolic disorders. She holds a Ph.D. in radiobiology from the Faculty of Medicine and Health Sciences, at the Université de Sherbrooke, and postdoctoral studies from Duke University Medical Center. She has a masters degree in Health Law from the Faculty of Law at the Université de Sherbrooke. She is the author of 175 publications, abstracts and articles. She is a professor at the Université de Sherbrooke and Clinical Research Centre Étienne-LeBel. She is the Scientific Director for the Waters-CHUS Expertise Centre in Clinical Mass Spectrometry.