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Genes and Variants Underlying Human Congenital Lactic Acidosis—From Genetics to Personalized Treatment

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Abstract: Congenital lactic acidosis (CLA) is a rare condition in most instances due to a range of inborn errors of metabolism that result in defective mitochondrial function. Even though the implementation of next generation sequencing has been rapid, the diagnosis rate for this highly heterogeneous allelic condition remains low. The present work reports our group's experience of using a clinical/biochemical analysis system in conjunction with genetic findings that facilitates the taking of timely clinical decisions with minimum need for invasive procedures. The system's workflow combines different metabolomics datasets and phenotypic information with the results of clinical exome sequencing and/or RNA analysis. The system's use detected genetic variants in 64% of a cohort of 39 CLA-patients; these variants, 14 of which were novel, were found in 19 different nuclear and two mitochondrial genes. For patients with variants of unknown significance, the genetic analysis was combined with functional genetic and/or bioenergetics analyses in an attempt to detect pathogenicity. Our results warranted subsequent testing of antisense therapy to rescue the abnormal