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MetaboSeq: A clinical fatty acid oxidation disorders next-generation sequencing panel

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Abstract

Inherited defects in mitochondrial fatty acid oxidation (FAO) are an important class of metabolic disorders, comprised of at least 12 distinct enzyme or transporter deficiencies. Mutations in the genes of this pathway have serious clinical consequences including hypoglycemic seizures, rhabdomyolysis, cardiomyopathy, metabolic acidosis, and hepatic encephalopathy. Newborn screening for FAOD promises to identify many affected patients before the onset of symptoms by screening for the accumulation of specific biochemical markers such as acylcarnitine metabolites in blood and urinary dicarboxylic acids and acylglycines. Routinely, confirmatory testing requires enzymatic studies and DNA analysis. When an abnormal newborn screening result indicates a specific disorder, Sanger sequencing of the specific gene of interest can identify the underlying genetic cause of the disorder in many patients. However, biochemical screening results may show measurements that overlap with several conditions. Additionally, significant genetic heterogeneity has been reported for long-chain fatty acid oxidation disorders. These factors highlight the necessity, in some cases, of a comprehensive analysis of multiple genes involved in fatty acid oxidation; the MetaboSeq panel. We assessed the analytical sensitivity and specificity of this panel following microdroplet-based PCR target enrichment and next-generation sequencing (NGS). The NGS results were examined across several parameters, including sequencing metrics and genotype concordance with Sanger sequencing to assess the suitability of this panel for use in a diagnostic laboratory. MetaboSeq demonstrates the successful application of targeted enrichment and NGS to screen for mutations in hundreds of exons in diseases involved in multiple genes of a common pathway.

Biography

Dr. C. Alexander Valencia has developed and implemented, in a clinical laboratory setting, next-generation sequencing diagnostic tests for various inherited disorders. He completed his Ph.D. at Carleton University, Ottawa, Canada, and did his postdoctoral studies at the University of North Carolina School at Chapel Hill. He completed his clinical molecular genetics fellowship at the Emory University School of Medicine. He is an assistant director of the clinical Molecular Genetics Laboratory at Cincinnati Children's Medical Center and an assistant professor at the University of Cincinnati School Of Medicine. He has published more than 20 papers in reputed journals.