

Simultaneous sequencing of 37 genes identified causative mutations in the majority of children with renal tubulopathies.

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Abstract

The clinical diagnosis of inherited renal tubulopathies can be challenging as they are rare and characterized by significant phenotypic variability. Advances in sequencing technologies facilitate the establishment of a molecular diagnosis. Therefore, we determined the diagnostic yield of a next generation sequencing panel assessing relevant disease genes in children followed through three national networks with a clinical diagnosis of a renal tubulopathy. DNA was amplified with a kit provided by the European Consortium for High-Throughput Research in Rare Kidney Diseases with nine multiplex PCR reactions. This kit produced 571 amplicons covering 37 genes associated with tubulopathies followed by massive parallel sequencing and bioinformatic interpretation. Identified mutations were confirmed by Sanger sequencing. Overall, 384 index patients and 16 siblings were assessed. Most common clinical diagnoses were 174 patients with Bartter/Gitelman syndrome and 76 with distal renal tubular acidosis. A total of 269 different variants were identified in 27 genes, of which 95 variants were considered likely, 136 definitely pathogenic and 100 had not been described at annotation. These mutations established a genetic diagnosis in 245 of the index patients. Genetic testing changed the clinical diagnosis in 16 cases and provided insights into the phenotypic spectrum of the respective disorders. Our results demonstrate a high diagnostic yield of genetic testing in children with a clinical diagnosis of a renal tubulopathy, consistent with a predominantly genetic etiology in known disease genes. Thus, genetic testing helped establish a definitive diagnosis in almost two-thirds of patients thereby informing prognosis, management and genetic counseling.