Abstract

Up to 50% of pediatric end-stage renal failure are caused by the genetically heterogeneous group of congenital anomalies of the kidney and urinary tract (CAKUT). This proposal will focus on the identification of new genes associated with renal hypodysplasia (RHD), a term that refers to all congenital malformations involving the kidney parenchyma, including renal aplasia/agenesis, hypoplasia and dysplasia. RHD patients have a 40% five-year mortality and can be caused by variable genetic and genomic anomalies. Currently, RHD is identified in pre- or post-natal imaging studies demonstrating absent or small kidneys with or without additional urinary tract defects. RHD can be isolated or part of a syndrome, however, these imaging studies do not give information on its etiology or the presence of extra-urinary tract phenotypes.

Accurate diagnosis is one of the key components of modern medicine, without it, the capacity to adjust the care to the patient's needs is hampered. Using targeted sequencing, we showed that 10% of 73 children with RHD have a syndromic form of RHD due to a mutation in the *HNF1b* or *PAX2* genes. Advances in genomic technologies such as massively parallel genotyping and sequencing enable to analyze the entire genome and to precisely define the molecular etiology of more and more diseases, including kidney diseases. Using microarray, we showed that 10.5% of 522 RHD patients have a syndromic form of RHD due to a copy-number variation (CNV). Both types of diagnosis lead to significant changes in medical care. However, our data indicated that **more than 75% of cases remain unexplained**, motivating additional studies to identify novel genes that will clarify RHD's etiology.

Our hypothesis is that the combination of two whole-genome approaches with larger cohorts can reveal the genetic basis of more RHD cases and ultimately improve medical care. The innovative approach of this proposal include the integrated analysis of inherited and *de novo* variation combining both exome and CNV data, increasing therefore the power to detect new genes.

Patients will undergo microarray analysis for the detection of CNVs. In probands with negative microarray results, we will perform whole exome sequencing (WES) and identify mutations in genes known to cause renal malformations as well as variants in new genes. We already performed WES on more than 215 cases with RHD, enabling now the validation of the promising genes identified in previous studies. Specifically, we will analyze the variants in genes localized within CNV intervals identified in patients. We will also identify new candidate genes using gene-based burden tests and gene-set burden tests. Finally, by integrating our knowledge regarding renal development, we will prioritize the candidate genes and ultimately identify new causative genes using a large replication cohort of over 2000 cases of RHD.

Our long-term goal is to introduce genomic medicine as a standard of care for RHD patients. This study will increase the capacity to offer a genetic diagnosis, which can have significant implications for risk stratification and prediction of complications in RHD patients.