Dr. Simone Sanna-Cherchi

ABSTRACT

Congenital anomalies of the kidney and urinary tract (CAKUT) are responsible for 30-40% of pediatric end-stage renal failure with significant implications for cardiovascular morbidity and mortality. Despite strong evidence for a genetic determination of the disease, the genetic basis of human CAKUT remains unsolved in the majority of cases, motivating a comprehensive approach to identify novel genes.

This proposal is the natural continuation of the PI's AHA Scientist Development Grant. During the past years, we established a vast collaboration with major referral centers world-wide and recruited >2,200 patients and >50 multigenerational families with congenital kidney malformations. The DNA is available in the lab. By traditional linkage analysis we identified loci on chromosomes 1p32-33, 10q24-26 and 12p11-q13 in our largest families, and demonstrated high genetic heterogeneity for this trait. To overcome the difficulties in gene identification due to genetic heterogeneity and incomplete penetrance we developed a comprehensive strategy that implements novel technologies for the identification of rare structural variants by high-density chips genotyping and point mutations by next-generation sequencing. Preliminary data indicate that up to 20% of patients carry rare, genic deleterious copy number variations (CNVs). Moreover, using linkage analysis combined with exome capture followed by next-generation sequencing, we identified a novel gene for familial CAKUT. These data prompt us to perform a systematic screening of familial forms of CAKUT to identify novel susceptibility genes.

In this project we propose to analyze a cohort of 50 multigenerational CAKUT families. We will first assess the contribution of rare, segregating CNVs by genotyping 1 million markers across the genome and comparing to over 25,000 controls. We will next perform whole exome sequencing in the most informative 25 families in which there are no pathogenic CNVs, to identify deleterious segregating point mutations. After cross-annotation of CNV and exome data, the top candidate genes will be followed up for resequencing in 200 CAKUT patients to identify independent mutations and establish disease causation.