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Congenital anomalies of the kidney and urinary tract (CAKUT) account for up to 30-40% of pediatric end stage renal disease (ESRD) and for a significant proportion of adult nephropathy. Despite the knowledge of a genetic component in its determination, the genetic bases remain elusive, requiring efforts to recruit large cohorts of patients and families to conduct appropriate genetic studies to identify the causative gene(s).

Through an extended network of collaborators in United States and Europe, we collected a large cohort of patients with familial and sporadic forms of CAKUT suitable for genetic studies. Using linkage approaches, we identified several loci underlying these traits. These loci explain only a minor fraction of familial forms of CAKUT and likely also of sporadic disease, due to a very high degree of genetic heterogeneity, motivating efforts to use alternative approaches to identify novel genes. Newly developed technologies allow the assessment of the entire genome for sub-microsopic structural variants (copy number variations, CNVs) in single individuals. We performed a pilot CNV discovery study on 165 patients with syndromic and non-syndromic forms of kidney malformations and 3,060 controls using high-density SNP chips. Using a very stringent selection pipeline, we were able to identify the potential causal CNV in 38 patients, representing 23% of the entire cohort. Among those, 13 (8%) carried large structural variants including well known CNVs that cause disorders such as the Renal Cysts and Dysplasia Syndrome associated with TCF2 gene mutations. These data indicate that our selection algorithm has high potential for discovery of new pathogenic CNVs and their underlying genes. Our analytic approach integrates selection of CNVs absent in a large panel of controls, prioritization of structural variants of de novo occurrence and CNVs mapping to linkage signals from our linkage studies. Using these stringent criteria, we identified 38 high priority CNVs, which we are now validating and pursuing for replication in the entire cohort in order to identify the underlying genes.

The discovery of novel genes for kidney and urinary tract malformations will have tremendous impact on understanding urogenital development, on pathophysiology, diagnosis and treatment of kidney disease.