The goals of this project are to apply genetic approaches to resolve the biology of kidney malformations. Kidney and urinary tract malformations account for up to 50% of pediatric end-stage kidney failure worldwide. They are highly heterogeneous in manifestation and outcome, and the biological basis of these disorders is poorly understood, limiting the development of optimal diagnostic and prognostic tools to improve clinical management. During the last funding cycle, we achieved considerable progress in resolving the genetic architecture and biology of kidney malformations. We found that pathogenic copy number variants (CNVs) are a common (10.5% of the cohort) and overlooked cause of kidney malformations. Applying exome sequencing, we defined a new syndrome caused by mutations in Dual Serine-threonine and Tyrosine Kinase (DSTYK) in 2.3% of children with urinary tract malformations. Altogether, our studies suggest that point mutations or CNV disorders can explain 25-30% of congenital kidney defects and provide many novel opportunities for clinical and basic investigations.

Here, we now propose to extend these studies in a large cohort of patients with kidney malformations. In aim 1, we will develop a comprehensive map of genomic structural variants contributing to kidney malformations and define candidate genes. In aim 2, we will define additional candidate genes for kidney malformations via analysis of exome data from 100 index cases from multiplex families and 50 trios derived from sporadic cases. In subsequent aims, we will comprehensively model variants in zebrafish and confirm novel genes for kidney malformation by screening for independent mutations in the full cohort by targeted resequencing. Finally we will perform genotype/phenotype correlations to aid in the characterization and workup for patients with kidney malformations.