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Abstract:

Glomerular disorders represent the third-most common cause of end-stage renal disease after diabetes and hypertension. IgA nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN) and minimal change disease (MCD) account for the majority of idiopathic glomerular diseases. Recent genetic studies have identified several genetic loci for these disorders and have begun to identify critical molecular pathways involved in their pathogenesis. However, well-designed and adequately powered genetic association studies are still missing for most glomerular disease types. Moreover, the field is faced with major challenges, including the need to validate the new loci across diverse patient cohorts, understand dysregulated pathways downstream of risk alleles and their consequences on clinical outcomes, define disease-specificity and interactions of risk alleles, and place their functional consequences within a coherent biological network. Such insights can then be translated into clinical benefits, including reliable biomarkers, effective strategies for screening and prevention, and rational selection of potential therapeutic targets. This proposal will address the above challenges by aiming to discover, validate, and fine-map known and novel genetic susceptibility loci by collaborative genetic studies. This will include a pioneering partnership with AstraZeneca and Columbia's Institute for Genomic Medicine to perform whole genome sequencing (WGS) of 4,000 cases of glomerular disease, including the entire CureGN study, the largest prospective cohort of patients with glomerular disorders. This will be followed by international meta-analyses and genetic validation studies in additional 26,000 cases of biopsy-confirmed primary glomerular disorders. Next, we will aim to discover precise pathogenic mechanisms underpinning each of the new genetic loci using systems genetics studies in the CureGN cohort. We will integrate the genetic data with blood transcriptomic studies and clinico-pathologic analyses to identify the key molecular disease drivers and their clinical and histopathologic consequences. Our studies will leverage the largest investment of NIDDK in glomerular diseases to refine the molecular pathogenesis and will be critical in defining targets for novel therapeutic interventions.