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IgA Nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide and the leading cause of renal failure in East Asia. The affected individuals develop characteristic IgA1-containing antibody complexes that deposit in the kidney, producing progressive renal injury. The disease is associated with a specific pathogenic defect in the *O*-glycosylation of IgA1 that promotes formation of immune complexes. Similar to other immune-mediated disorders, IgAN has a complex genetic architecture. In a recent GWAS involving 20,574 individuals, we identified 15 genome-wide significant susceptibility loci for IgAN. Our new loci implicated both adaptive and innate immunity in the disease pathogenesis and defined the "Network of Intestinal IgA Production" as the key pathogenic disease pathway. Based on our results, we developed an original multi-hit pathogenesis model that describes sequential steps and molecular candidates involved in the development of the disease. In this application, we propose to further refine this model by defining additional genetic hits involved in the defective regulation of mucosal IgA response. We specifically aim to discover additional IgAN susceptibility loci by a quantitative GWAS for serum levels for IgA and galactose-deficient IgA1 (Gd-IgA1). The GWAS discovery phase will include a well-powered multi-ethnic population-based cohort of 9,707 individuals. New genome-wide significant loci will be replicated independently and annotated using existing datasets and public resources. Next, through integrative network-based analyses, we will dissect precise pathogenic mechanisms behind each of the GWAS risk alleles. We will use a systems genetics approach that integrates RNA-seq and SNP microarray data to reconstruct gene regulatory networks in IgA1 secreting cells. Based on our network analyses, we will define master regulators and key drivers of the disease process. Our network predictions will be validated using experimental, computational, and genetic approaches. These studies are expected to refine the disease pathogenesis model and will be critical in defining potential targets for novel therapeutic interventions in IgAN.