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Summary:
Immunoglobulin A Nephropathy is a major cause of kidney failure worldwide. It is the most common cause of kidney failure among Asian populations, and the most common form of primary glomerulonephritis among Caucasians. We recently completed a genome-wide association study (GWAS) of IgAN, with discovery in 1,194 cases and 902 controls of Chinese Han ancestry, and targeted follow-up in Chinese cohorts and European cohorts (1,950 cases and 1,920 controls). We identified three independent loci in the major histocompatibility complex (MHC) on Chr. 6p21, a common deletion of CFHR1 and CFHR3 at Chr. 1q32 and a locus at Chr. 22q12 that each surpassed genome-wide significance (p-values for association between 1.6 x 10-26 and 4.8 x 10-9 and minor allele odds ratios of 0.63-0.80). These five loci explain 4-7% of the disease variance and up to a 10-fold variation in interindividual risk.

In this study, we propose to follow-up recent genome-wide association study (GWAS) for IgAN, which identified five new susceptibility loci. We propose to refine the five newly discovered risk loci using the Immunochip, targeted genotyping and MPLA to identify underlying functional variants. We will next examine the impact of these loci on immunological and clinical parameters.

Our initial GWAS also suggested that there are yet-undiscovered risk loci in Europeans. In addition, we have tripled our sample size, totaling 7,203 biopsy documented IgAN cases and 8,069 healthy controls of Asian and European ancestry. We will therefore perform a second GWAS with discovery in a European population (1440 cases, 1217 controls) and replication in the remaining samples to identify new IgAN loci and further define molecular pathways underlying disease. Finally, we will refine and validate a genetic risk score model for IgAN in the full cohort

These studies will provide insight into the pathogenesis of IgAN, providing novel opportunities for development of diagnostic and therapeutic tools for this major cause of kidney failure.
