GENOME-WIDE ASSOCIATION STUDIES OF DIABETIC NEPHROPATHY

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease worldwide. Although tight control of blood sugar can decrease the risk of diabetic kidney disease, many patients with adequate control develop nephropathy, while others remain complication-free despite poor glycemic control. Family studies point to a strong role for inherited factors in the development of nephropathy, but the relevant genetic variants remain unknown, limiting our understanding of this devastating complication. Our long term goal is to discover the genetic factors that influence the risk of diabetic nephropathy, with the hope that improved understanding of the disease will identify novel biological targets for therapeutic and preventive intervention. The search for causal genetic risk factors for multifactorial diseases such as diabetic nephropathy has until recently been quite difficult. In the past year, however, advances in genetics and genomics have enabled the completion of genome-wide association studies for an array of common diseases, which have successfully discovered common genetic variants with modest effects on disease risk. Critical to these successes has been careful and rigorous analysis of adequately powered samples. We hypothesize that the risk of diabetic nephropathy is influenced in part by common genetic variants of modest effect that can be identified by a well-powered genome-wide association study. We further hypothesize that genetic loci identified by this approach may harbor multiple variants (common or rare) that influence individual susceptibility to nephropathy. We propose a comprehensive search for these genetic risk factors, using a multistage genome-wide association study. We have established an international collaboration spanning investigative groups with complementary strengths, and assembled DNA samples from 898 patients with type 1 diabetes and nephropathy (cases) and 1,091 patients with long-standing type 1 diabetes and no nephropathy (controls). We propose to generate genome-wide genotype data at 900,000 single nucleotide polymorphisms (SNPs) in this sample and analyze these data in combination with recently released genome- wide data from the similarly ascertained GoKIND study (905 cases/890 controls). The combined association analysis will be further informed by gene expression data from a biobank of kidney biopsies. SNPs with the best signals of association will be tested in a validation panel of H2,500 additional patients. To search for additional common causal variants at validated loci, we will perform fine mapping studies; to search for rare variants with stronger effects we will resequence genes in patients with early-onset nephropathy and in patients with diabetes for 50 years but no complications. Identification of genetic risk factors for nephropathy would highlight biological pathways that are root causes of this disease, providing new insights that could help guide the development or application of improved treatments or preventive measures.

Kidney disease is a common and devastating complication of diabetes, and represents a major public health problem worldwide. Inherited, genetic factors play a role in determining who will get this complication, but these factors remain unknown, limiting our ability to develop improved treatments and preventive measures. We propose to use a new, powerful genetic approach (genome-wide association studies) to search for the genetic factors that influence the development of diabetic kidney disease.