INTEGRATIVE GENOMIC, EPIGENETIC AND FUNCTIONAL STUDIES IN DIABETIC KIDNEY DISEASE

Diabetic kidney disease (DKD) is a leading cause of kidney failure and end stage renal disease, and brings a substantial burden of early mortality and accompanying health care costs. Genetic factors contribute to the risk of DKD. If we could identify these genetic factors, we could better understand the mechanisms by which DKD occurs, and thereby accelerate the development of better therapies. We established the GENIE consortium, a collaboration between Queen's University Belfast, University of Dublin, University of Helsinki, and the Broad Institute. Together, we completed the largest genetic study to date of DKD, and successfully identified the first two robust genetic risk factors for DKD. In a separately funded genetic study, we are collaborating with additional groups to extend our efforts and encompass larger samples. To better understand the underlying biology and pathophysiology of DKD, we propose to complement and build on our past and ongoing genetic studies in several critical ways. We will leverage a co-funding mechanism between Ireland, Northern Ireland and the US to carry out a multidisciplinary investigation of DKD. We will assemble and jointly analyze all available genetic data pertinent to DKD, to begin the process of discovering rarer variants with stronger effects on DKD. We will also generate DNA methylation data in kidney and blood, and in patients with and without DKD, and also expression data in samples relevant to DKD. We use a novel and powerful method to integrate the genetic, epigenetic and genomic data to generate hypotheses about the biological causes of DKD, and test these hypotheses with further genetic studies (sequencing in a large follow-up sample) and with functional studies in models of DKD. This international, multidisciplinary collaboration will build on genetic discoveries to help decipher the underlying biology and pathophysiology of DKD and thereby guide the prevention and treatment of this important disease.

Kidney disease is a common and devastating complication of diabetes, and represents a major public health problem worldwide. The inherited, genetic factors that play a role in determining who will get this complication are beginning to be discovered, creating opportunities to understand the underlying biological basis of diabetic kidney disease, which will guide the development of improved treatments and preventive measures. We will combine and integrate data from several complementary approaches (genetics, epigenetics, gene expression analysis and studies in model systems) to identify genes and biological processes that influence the development of diabetic kidney disease.