A functional genomics pipeline for genetic discovery in diabetic kidney disease

ABSTRACT

Diabetic kidney disease (DKD) is a devastating microvascular complication of both type 1 (T1D) and type 2 diabetes (T2D). It has been shown to have a heritable component, but prior searches for the genetic determinants of this condition have had limited success. In the Genetics of Nephropathy – an International Effort (GENIE) Consortium, a collaboration between Queen's University Belfast, University of Dublin, University of Helsinki, University of Michigan, University of Pennsylvania and the Broad Institute, we have leveraged an ongoing co-funding mechanism between Ireland, Northern Ireland and the US. This international genomics consortium enucleated a larger Diabetic Nephropathy Collaborative Research Initiative, which coalesced to assemble nearly 20,000 samples from participants with T1D, with and without kidney disease. We performed a genome-wide association study (GWAS) and discovered 16 new signals at genome-wide significance. The strongest signal centered on a protective missense coding variant at COL4A3, which encodes an integral component of the glomerular basement membrane, implicating this aspect of kidney biology in DKD. In this award, we propose to build on this established infrastructure to undertake the following Specific Aims: (1) to significantly expand our sample size by including ~150,000 samples with DKD in the context of T2D, thereby substantially increasing our power to discover shared and distinct risk factors for DKD in T1D and T2D, and to use computational tools to derive biological insights into DKD pathogenesis; (2) to generate a genome-wide epigenomic dataset in both peripheral blood and human kidney to inform the relevance of genetic findings, enable the construction of predictive tools, and infer causality via Mendelian randomization; and (3) to create an experimental pipeline centered on animal, cellular and organoid models of DKD to pursue functional validation of promising genetic findings. This ongoing close collaboration of multidisciplinary and synergistic research groups should advance our knowledge of the molecular determinants of DKD, identify potential molecular targets for therapeutics, and facilitate clinical prediction.

Public Health Relevance Statement

NARRATIVE Kidney disease is a common and devastating complication of diabetes, and represents a major public health problem worldwide. We have discovered inherited factors that influence risk of this complication in type 1 diabetes; in this cycle we propose to expand our approach to type 2 diabetes, increasing sample size seven-fold to augment the opportunities for genetic discovery. In addition, by combining and integrating data from several complementary approaches (genomics, epigenetics, gene expression analysis and functional studies in model systems) we hope to identify genes and biological processes that impact the development of diabetic kidney disease, and may help guide the development of improved treatments and preventive measures.