SIGNIFICANCE STATEMENT

Research in diabetic kidney disease (DKD) has been hindered by the lack of animal models that recapitulate human disease progression to renal failure. This manuscript describes a novel approach to accelerate DKD by establishing persistent hypertension with ReninAAV in diverse strains of diabetic mice, identifying strains that exhibited progression to advanced renal failure. ReninAAV in *db/db* mice provided a progressive DKD model that closely mimics several features of the human disease with robust proteinuria, decline in renal function, pathologic changes, and similar gene expression profiles. This approach provides an efficient alternative to transgene-dependent hypertension and should facilitate the study of therapeutics for diabetic nephropathy.