Genome-Wide Association Study of Diabetic Kidney Disease Highlights Biology Involved in Glomerular Basement Membrane Collagen


Due to the number of contributing authors, the affiliations are listed at the end of this article.

ABSTRACT

Background Although diabetic kidney disease demonstrates both familial clustering and single nucleotide polymorphism heritability, the specific genetic factors influencing risk remain largely unknown.

Methods To identify genetic variants predisposing to diabetic kidney disease, we performed genome-wide association study (GWAS) analyses. Through collaboration with the Diabetes Nephropathy Collaborative Research Initiative, we assembled a large collection of type 1 diabetes cohorts with harmonized diabetic kidney disease phenotypes. We used a spectrum of ten diabetic kidney disease definitions based on albuminuria and renal function.

Results Our GWAS meta-analysis included association results for up to 19,406 individuals of European descent with type 1 diabetes. We identified 16 genome-wide significant risk loci. The variant with the strongest association (rs55703767) is a common missense mutation in the collagen type IV alpha 3 chain (COL4A3) gene, which encodes a major structural component of the glomerular basement membrane (GBM). Mutations in COL4A3 are implicated in heritable nephropathies, including the progressive inherited nephropathy Alport syndrome. The rs55703767 minor allele (Asp326Tyr) is protective against several definitions of diabetic kidney disease, including albuminuria and ESKD, and demonstrated a significant
association with GBM width; protective allele carriers had thinner GBM before any signs of kidney disease, and its effect was dependent on glycemia. Three other loci are in or near genes with known or suggestive involvement in this condition (BMP7) or renal biology (COLECI11 and DDR1).

Conclusions The 16 diabetic kidney disease-associated loci may provide novel insights into the pathogenesis of this condition and help identify potential biologic targets for prevention and treatment.


The devastating diabetic complication of diabetic kidney disease (DKD) is the major cause of worldwide.1,2 Current treatment strategies at best slow the progression of DKD, and do not halt or reverse the disease. Although improved glycemic control influences the rate of diabetic complications, a large portion of the variation in DKD susceptibility remains unexplained: one third of people with type 1 diabetes (T1D) develop DKD despite adequate glycemic control, whereas others maintain normal renal function despite long-term severe chronic hyperglycemia.3

Though DKD demonstrates both familial clustering4–6 and single nucleotide polymorphism (SNP) heritability,7 the specific genetic factors influencing DKD risk remain largely unknown. Recent genome-wide association studies (GWAS) have only identified a handful of loci for DKD, albuminuria, or eGFR in individuals with diabetes.7–13 Potential reasons for the limited success include small sample sizes, modest genetic effects, and lack of consistency of phenotype definitions and statistical analyses across studies. Through collaboration within the JDRF Diabetes Nephropathy Collaborative Research Initiative, we adopted three approaches to improve our ability to find new genetic risk factors for DKD: (1) assembling a large collection of T1D cohorts with harmonized DKD phenotypes, (2) creating a comprehensive set of detailed DKD definitions, and (3) augmenting genotype data with low frequency and exome array variants.

Significance Statement

Although studies show that diabetic kidney disease has a heritable component, searches for the genetic determinants of this complication of diabetes have had limited success. In this study, a new international genomics consortium, the JDRF-funded Diabetic Nephropathy Collaborative Research Initiative, assembled nearly 20,000 samples from participants with type 1 diabetes, with and without kidney disease. The authors found 16 new diabetic kidney disease-associated loci at genome-wide significance. The strongest signal centers on a protective missense coding variant at COL4A3, a gene that encodes a component of the glomerular basement membrane that, when mutated, causes the progressive inherited nephropathy Alport syndrome. These GWAS-identified risk loci may provide insights into the pathogenesis of diabetic kidney disease and help identify potential biologic targets for prevention and treatment.

Committees from participating institutions. We defined a total of ten different case-control outcomes to cover the different aspects of renal complications, using both albuminuria and eGFR (Figure 1). Five comparisons (“All versus control (ctrl),” “Micro,” “diabetic nephropathy [DN],” “Macro,” and “ESKD versus macro”) were on the basis of albuminuria, measured by albumin excretion rate (AER) from overnight or 24-hour urine collection, or by albumin-to-creatinine ratio. Two out of three consecutive collections were required (when available) to classify the renal status of patients as either normalalbuminuria, microalbuminuria, macroalbuminuria, or ESKD; for detailed thresholds, see Figure 1. Controls with normal AER were required to have a minimum diabetes duration of 15 years; participants with microalbuminuria/macroalbuminuria/ESKD were required to have minimum diabetes duration of 5, 10, and 10 years, respectively, to exclude renal complications of nondiabetic origins. Two comparisons (“ESKD versus ctrl” and “ESKD versus non-ESKD”) were on the basis of presence of ESKD as defined by eGFR<15 ml/min or dialysis or renal transplant. Two phenotypes (“CKD” and “CKD extreme”) were defined on the basis of eGFR estimated by the CKD Epidemiology Collaboration formula: controls had eGFR≥60 ml/min per 1.73 m² for both phenotypes, and ≥15 years of diabetes duration; cases had eGFR<60 ml/min per 1.73 m² for the CKD phenotype, and eGFR<15 ml/min per 1.73 m² or dialysis or renal transplant for the CKD extreme phenotype, and ≥10 years of diabetes duration. For the “CKD-DN” phenotype that combined both albuminuria and eGFR data, controls were required to have both eGFR≥60 ml/min per 1.73 m² and

METHODS

Cohorts and Phenotype Definitions

The GWAS meta-analysis included up to 19,406 patients with T1D of European origin from 17 cohorts (for study list and details see Supplemental Table 1). All participants gave informed consent and all studies were approved by ethics committees from participating institutions. We defined a total of ten different case-control outcomes to cover the different aspects of renal complications, using both albuminuria and eGFR (Figure 1). Five comparisons (“All versus control (ctrl),” “Micro,” “diabetic nephropathy [DN],” “Macro,” and “ESKD versus macro”) were on the basis of albuminuria, measured by albumin excretion rate (AER) from overnight or 24-hour urine collection, or by albumin-to-creatinine ratio. Two out of three consecutive collections were required (when available) to classify the renal status of patients as either normalalbuminuria, microalbuminuria, macroalbuminuria, or ESKD; for detailed thresholds, see Figure 1. Controls with normal AER were required to have a minimum diabetes duration of 15 years; participants with microalbuminuria/macroalbuminuria/ESKD were required to have minimum diabetes duration of 5, 10, and 10 years, respectively, to exclude renal complications of nondiabetic origins. Two comparisons (“ESKD versus ctrl” and “ESKD versus non-ESKD”) were on the basis of presence of ESKD as defined by eGFR<15 ml/min or dialysis or renal transplant. Two phenotypes (“CKD” and “CKD extreme”) were defined on the basis of eGFR estimated by the CKD Epidemiology Collaboration formula: controls had eGFR≥60 ml/min per 1.73 m² for both phenotypes, and ≥15 years of diabetes duration; cases had eGFR<60 ml/min per 1.73 m² for the CKD phenotype, and eGFR<15 ml/min per 1.73 m² or dialysis or renal transplant for the CKD extreme phenotype, and ≥10 years of diabetes duration. For the “CKD-DN” phenotype that combined both albuminuria and eGFR data, controls were required to have both eGFR≥60 ml/min per 1.73 m² and

Received March 1, 2019. Accepted July 8, 2019.
Published online ahead of print. Publication date available at www.jasn.org.
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normoalbuminuria; cases had both eGFR<45 ml/min per 1.73 m² and micro- or macroalbuminuria, or ESKD.

**GWAS Genotyping, Quality Control, and Imputation**

All study samples underwent genotyping, quality control (QC), and imputation centrally at the University of Virginia. In brief, samples were genotyped on the HumanCore BeadChip array (Illumina, San Diego, CA), which contains approximately 250,000 genome-wide tag SNPs and >200,000 exome-focused variants. All samples were passed through a stringent QC protocol. Following initial genotype calling with Illumina software, all samples were recalled with zCall, a calling algorithm specifically designed for rare SNPs from arrays. Variant orientation and position were aligned to hg19 (Genome Reference Consortium Human Build 37, GRCh37). Variant names were updated using 1000 Genomes as a reference. The data were then filtered for low-quality variants (e.g., call rates <95% and excessive deviation from Hardy–Weinberg equilibrium) and samples (e.g., call rates <98%, sex mismatch, extreme heterozygosity). Principal component analysis was performed separately for each cohort to empirically detect and exclude outliers with evidence of non-European ancestry (see Supplemental Material for full QC details, and Supplemental Figure 1 for trait-specific Manhattan and QQ plots). Genotypes were expanded to a total of approximately 49 million by imputation, using the minimac imputation tool and 1000 Genomes Project (phase 3v5) as a reference.

**GWAS Analysis**

A genome-wide association analysis was performed for each of the case-control definitions under an additive genetic model, adjusting for age, sex, diabetes duration, study site (where applicable), and principal components. We conducted a second set of analyses, adjusting for body mass index and glycated hemoglobin (HbA1c), which we refer to as our fully adjusted covariate model. Allele dosages were used to account for imputation uncertainty. Inverse-variance fixed effects meta-analysis was performed using METAL and the following filters: INFO score >0.3, minor allele count ≥10 in both cases and controls, and presence of variant in at least two cohorts (Manhattan and QQ plots each trait and covariate model presented in Supplemental Figure 1). The X chromosome was similarly analyzed for men and women both separately and

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**Figure 1.** Phenotypic analysis of DKD. Schematic diagram of outcomes analyzed in this study. Numbers indicate the total number of cases (darker gray) and controls (lighter gray) included in the meta-analyses for each phenotype. ESKD defined as eGFR<15 ml/min per 1.73 m² or undergoing dialysis or having renal transplant.
in a combined analysis, with the exception of using hard call genotypes in place of allele dosages.\textsuperscript{16} We estimated the percentage of variance explained for all genome-wide significant SNPs across all disease definitions using the McKelvey and Zavoina\textsuperscript{17} pseudo-$R^2$ statistic predicting continuous latent variables underlying binary outcomes.

**Glomerular Basement Membrane Measurement in Renin-Angiotensin System Study**

In brief, the renin-angiotensin system study (RASS) was a double-blind, placebo-controlled, randomized trial of enalapril and losartan on renal pathology among 285 normoalbuminuric, normotensive participants with T1D and normal or increased measured GFR (>90 ml/min per 1.73 m$^2$).\textsuperscript{18} Participants were followed for 5 years with percutaneous kidney biopsy completed prior to randomization and at 5 years. Structural parameters measured by electron microscopy on biopsy included glomerular basement membrane (GBM) width, measured by the electron microscopic orthogonal intercept method.\textsuperscript{18} All RASS participants contributed DNA for genotyping.

**In Silico Replication in SUMMIT Consortium**

The Surrogate Markers for Micro- and Macro-vascular Hard Endpoints for Innovative Diabetes Tools (SUMMIT) consortium included up to 5193 European Ancestry participants with type 2 diabetes (T2D), with and without kidney disease. In silico replication was performed on previously published GWAS on DKD with harmonized trait definitions for seven of our primary T1D analyses: “DN,” “Micro,” “Macro,” “ESKD,” “ESKD versus non-ESKD,” “CKD,” and “CKD-DN” under an additive model, adjusting for age, sex, and duration of diabetes.\textsuperscript{13}

**RNA-Sequencing and Microarray Profiling of Human Kidney Samples from the Pima Cohort**

Kidney biopsy samples from the Pima Indian cohort were manually microdissected into 119 glomerular and 100 tubule-interstitial tissues to generate gene expression profiles.\textsuperscript{19} Expression profiling in the Pima Indian cohort kidney biopsies was carried out using Affymetrix GeneChip Human Genome U133 Array and U133Plus2 Array, as reported previously, and Affymetrix Human Gene ST GeneChip 2.1,\textsuperscript{20,21} and on RNA-seq (Illumina). The libraries were prepared using the ClonTech SMARTSeq v4 Ultra Low Input polyA selection kit. Samples were sequenced on a HiSeq4000 using single-end, 75 bp reads. Mapping to human reference genome GRCh38.7 was performed with STAR 2.5.2b (https://github.com/alexdobin/STAR). For annotation and quantification of mapping results we used cufflinks, cuffquant, and cuffnorm in version 2.2.1 (https://cole-trapnell-lab.github.io/cufflinks/). After mapping and quantification, principal component analysis and hierarchical clustering was used to identify outliers and reiterated until no more outliers could be identified.

**RNA-Sequencing and cis Expression Quantitative Trait Loci Analysis in Human Kidney Samples from University of Pennsylvania Cohort**

Human kidney samples were obtained from surgical nephrectomies for a total of 455 participants with pathologic data and were manually microdissected under a microscope in RNA later for glomerular and tubular compartments (433 tubule and 335 glomerulus samples). The local renal pathologist performed an unbiased review of the tissue section by scoring multiple parameters, and RNA were prepared using RNeasy mini columns (Qiagen, Valencia, CA) according to manufacturer’s instructions.

Whole kidney,\textsuperscript{22} tubularm and glomerular\textsuperscript{23} expression quantitative trait loci (eQTL) analyses have been described previously. Tubular and glomerular eQTL data sets were generated by 121 samples of tubules and 119 samples of glomeruli, respectively.\textsuperscript{23} The cis window was defined as 1 Mb up- and downstream of the transcriptional start site (±1 Mb). The whole kidney cis-eQTL (further referred to as just eQTL) data set was generated from 96 human samples obtained from The Cancer Genome Atlas (TCGA) through the TCGA Data portal.\textsuperscript{22}

**Mouse Kidney Single-Cell RNA-Sequencing**

Kidneys were harvested from 4- to 8-week-old male mice with C57BL/6 background and dissociated into single-cell suspension as described in our previous study.\textsuperscript{24} The single-cell sequencing libraries were sequenced on an Illumina HiSeq with 2×150 paired-end kit. The sequencing reads were demultiplexed, aligned to the mouse genome (mm10) and processed to generate gene-cell data matrix using Cell Ranger 1.3 (http://10xgenomics.com).\textsuperscript{24}

**Genomic Features of Human Kidney**

Human kidney-specific chromatin immunoprecipitation sequencing data can be found at Gene Expression Omnibus under accession numbers GSM621634, GSM670025, GSM621648, GSM772811, GSM621651, GSM1112806, and GSM621638. Different histone markers were combined into chromatin states using ChromHMM.\textsuperscript{25}

**Gene and Gene Set Analysis**

PASCAL and MAGMA (v1.06) gene and pathway scores were conducted on all 20 sets of GWAS summary statistics using default pathway libraries from BioCarta, REACTOME, and KEGG. MAGENTA (v5, July 2011) pathway analysis included 4725 pathways with a minimum of five genes within the gene set for the ten standard adjustment models. We conducted DEPICT individually on all 20 sets of GWAS summary statistics with $P < 10^{-5}$ and additional pooled analyses using genome-wide minimum $P$ values from all 20 analyses (ten phenotypes and two covariate models) and 16 analyses of the eight most related phenotypes, which excluded ESKD versus Macro and Micro.
Transcriptome-Wide Association Study

A transcriptome-wide association study (TWAS) of kidney glomeruli and tubules was performed using MetaXcan with default parameters,26 on the basis of eQTL data for human glomerular and tubular cells.23

RESULTS

Phenotypic Comparisons

We investigated a broad spectrum of DKD definitions on the basis of albuminuria and renal function criteria, defining a total of ten different case-control comparisons to cover the different aspects of disease progression (Figure 1). Seven comparisons were on the basis of albuminuria and/or ESKD (including DN, defined as either macroalbuminuria or ESKD), two were defined on the basis of eGFR (used to classify severity of CKD), and one combined both albuminuria and eGFR data (CKD-DN). Each phenotypic definition was analyzed separately in GWAS; to account for the ten definitions each analyzed under two covariate adjustment models, we estimated16 the total effectively independent tests as 7.4, allowing us to compute a more conservative study-wide significance threshold ($P<6.76 \times 10^{-9}$), on the basis of genome-wide significance ($P<5 \times 10^{-8}$) and Bonferroni correction for 7.4 effective tests.

Top Genome-Wide Association Results Highlight COL4A3

GWAS meta-analysis included association results for up to 19,406 individuals with T1D of European descent from 17 cohorts for the ten case-control definitions (Supplemental Table 1). We identified 16 novel independent loci that achieved genome-wide significance ($P<5 \times 10^{-8}$) in either the minimal or fully adjusted models, in which four lead SNPs also surpassed our more conservative study-wide significance threshold (Figure 2, Manhattan plot; Table 1; Supplemental Figure 2, A–P, regional association and forest plots). None of the loci reaching genome-wide significance have been previously identified in GWAS or candidate gene studies for DKD or closely related traits. All SNPs with minor allele frequency (MAF) >1% explain 2.5% and 3.0% of the total variance (McKelvey and Zavoina17 pseudo-$R^2$) of DN after adjusting for covariates in the minimal and full covariate models, respectively (Supplemental Table 2).

The strongest signal was rs55703767 (MAF=0.21), a common missense variant (G>T; Asp326Tyr) in exon 17 of...
Table 1. Loci associated with DKD at study-wide (P<6.76×10⁻⁵, see bolding) and genome-wide (P<5×10⁻⁸) significance

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr:pos</th>
<th>Effect Allele</th>
<th>Other Allele</th>
<th>EAF</th>
<th>Notable Gene(s)</th>
<th>Phenotype</th>
<th>ORmin</th>
<th>P Value min</th>
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<td>rs55703767</td>
<td>2:228121101</td>
<td>T</td>
<td>G</td>
<td>0.026</td>
<td>COL4A3(M,B,N)</td>
<td>DN</td>
<td>0.79</td>
<td>5.34×10⁻¹²</td>
<td>0.78</td>
<td>8.19×10⁻¹¹</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>All versus ctrl</td>
<td>0.83</td>
<td>3.88×10⁻¹⁰</td>
<td>0.84</td>
<td>9.66×10⁻⁹</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CKD+DN</td>
<td>0.77</td>
<td>5.30×10⁻⁹</td>
<td>0.76</td>
<td>3.77×10⁻⁸</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Macro</td>
<td>0.78</td>
<td>9.28×10⁻⁹</td>
<td>0.77</td>
<td>9.38×10⁻⁹</td>
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<td></td>
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<td></td>
<td></td>
<td>CKD</td>
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<td>9.43×10⁻⁹</td>
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<td>1.60×10⁻⁷</td>
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<td>G</td>
<td>A</td>
<td>0.133</td>
<td>COLEC11(B)</td>
<td>ALLC(N,G)</td>
<td></td>
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<tr>
<td>rs142823282</td>
<td>3:11910635</td>
<td>G</td>
<td>A</td>
<td>0.011</td>
<td>TAMM41(N,B)</td>
<td>Micro</td>
<td>6.73</td>
<td>8.32×10⁻¹⁰</td>
<td>9.18</td>
<td>1.13×10⁻¹¹</td>
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<td>A</td>
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<td>(N,G,B)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Micro</td>
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<td>C</td>
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<td>CA</td>
<td>C</td>
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<td>PRRCN1(N)</td>
<td>ESKD versus macro</td>
<td>1.70</td>
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<td>C</td>
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<td>Micro</td>
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<td>C</td>
<td>0.011</td>
<td>BMP7(N,G,B)</td>
<td>Micro</td>
<td>6.78</td>
<td>2.67×10⁻⁹</td>
<td>6.66</td>
<td>4.65×10⁻⁹</td>
</tr>
</tbody>
</table>

Common variants and/or genes with relevant kidney biology are reported in the top half of the table. Uncommon variants (MAF<2%) with no known relevant kidney biology are reported in the bottom half of the table. Genes are annotated as follows: missense variant in the indicated gene (M); intronic, synonymous, or noncoding variant in the indicated gene (G); gene nearest to lead variant (N); gene has relevant kidney (B). Chr, chromosome; pos, position; EAF, effect allele frequency; min, minimally adjusted covariate model; full, fully adjusted covariate model.

**COL4A3.** This SNP was associated with protection from DN (odds ratio [OR], 0.79; 95% Confidence Interval [95% CI], 0.73 to 0.84; P=5.34×10⁻¹²), any albuminuria (OR, 0.83; 95% CI, 0.79 to 0.88; P=3.88×10⁻¹⁰), the combined CKD-DN phenotype (OR, 0.77; 95% CI, 0.71 to 0.84; P=5.30×10⁻⁹), and macroalbuminuria (OR, 0.78; 95% CI, 0.72 to 0.85; P=9.28×10⁻⁹). Interestingly, we found that rs55703767 in **COL4A3** was more strongly associated in men (OR, 0.73; 95% CI, 0.66 to 0.80; P=1.29×10⁻¹¹) than in women (OR, 0.85; 95% CI, 0.76 to 0.94; P=1.39×10⁻³; R²het=1.58×10⁻²). **COL4A3** encodes the α3 chain of collagen type IV, a major structural component of the GBM. In persons with TID and normoalbuminuria, GBM width predicts progression to proteinuria and ESKD independently of glycated hemoglobin (HbA1c). We examined the influence of the **COL4A3** variant on GBM width in 253 RASS18 participants with TID and normal AER, eGFR (>90 ml/min per 1.73 m²), and BP, who had biopsy and genetic data (Supplemental Table 3). The DKD-protective minor T allele was associated with 19.7 nm lower GBM width (SEM 8.2 nm; P=0.02), with the lowest mean GBM width (4.60×10⁻⁸) in men (OR, 0.73; 95% CI, 0.66 to 0.80; P=1.29×10⁻¹¹). **COL4A3** expression was negatively correlated with the GBM surface density (filtration surface density) (β=−0.27; P=0.02), which is associated with eGFR in DKD in both T1D and T2D. Furthermore, in 335 microdissected human glomerulus samples, expression of **COL4A3** was negatively correlated with glomerulosclerosis, potentially reflecting podocyte depletion in sclerotic glomeruli.
COL4A3 expression in glomeruli, but not in tubules, was also nominally correlated with eGFR (correlation=0.108; \( P = 0.05 \); Supplemental Figure 3).

**Evidence for Hyperglycemia Specificity**

Hyperglycemia promotes the development of diabetic complications. If a genetic variant exerts a stronger effect in the setting of hyperglycemia, (1) it might not be detected in general CKD, (2) it may be detected whether hyperglycemia is conferred by T1D or T2D, (3) its effect may be stronger at higher glycemic strata, and (4) interventions that reduce glycemia may attenuate the association signal. COL4A3 rs55703767 was not associated with eGFR in a general population sample of 110,517 mainly nondiabetic participants of European ancestry\(^3\) (Supplemental Table 5). However, in a smaller cohort of 5190 participants with T2D and DKD phenotypes in the SUMMIT consortium, we detected a directionally consistent suggestive association of COL4A3 rs55703767 with DN (two-tailed \( P = 0.08 \); Supplemental Table 6).

We further stratified the association analyses by HbA1c in the Finnish Diabetic Nephropathy (FinnDiane) Study, a T1D cohort study with extensive longitudinal phenotypic data\(^3\). On the basis of the time-weighted mean of all available HbA1c measurements for each individual, 1344 individuals had mean HbA1c \(< 7.5\%\) (58 mmol/mol), and 2977 with mean HbA1c \(\geq 7.5\%\). COL4A3 rs55703767 was nominally significant \((P<0.05)\) only in individuals with HbA1c \(\geq 7.5\%\) (Figure 4, Supplemental Figure 4, Supplemental Table 7). However, the interaction between HbA1c and COL4A3 rs55703767 was not significant \((P=0.83)\). Upon further examination, the genetic effect was diminished also in the highest HbA1c quartile.
>9.3%), as the environmental effect of HbA1c seems to overwhelm any potential genetic effects of COL4A3 (test of heterogeneity nonsignificant). In a similar setting of individuals with T2D from the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) study (n=3226),13,33 no difference was observed for COL4A3 rs55703767 between HbA1c strata below or above 7.5% (Supplemental Figure 5). We performed a similar HbA1c stratified analysis in the Diabetes Control and Complications Trial (DCCT), whose participants, all with T1D, continue to be followed in the Epidemiology of Diabetes Interventions and Complications (EDIC),34,35 In DCCT-EDIC the effect of COL4A3 rs55703767 was stronger among those recruited in the secondary cohort (mild retinopathy and longer diabetes duration at baseline) who were originally randomized to conventional treatment and therefore had higher HbA1c than the intensive treatment group (Supplemental Table 8). Taken together, these independent lines of evidence strongly suggest that the COL4A3 variant effect on DKD risk is amplified by poor glycemic control.

Other Association Signals

A comprehensive list of all loci that achieved genome-wide significance from either the minimal or the fully adjusted covariate models is reported in Table 1. The fewer covariates required for the minimal model results in improved statistical power because of fewer participants with missing data, whereas the fully adjusted model allows the identification of associations potentially mediated by covariates. Comparison of the adjustment models revealed strong consistency between the two models (Supplemental Figure 6). Table 1 is stratified into two sets of loci: common and/or known kidney biology loci (top half, n=7) and uncommon and no known kidney biology loci (bottom half, n=9). We focus on loci in the top half of the table, common and/or in/near genes with relevant kidney biology.

Two other genome-wide significant signals were near genes encoding proteins related to collagen. Variant rs12615970 (MAF=0.13), located 53 kb downstream of COLEC11, was associated with CKD (OR, 1.31; 95% CI, 1.19 to 1.45; P=4.40×10⁻⁸), and rs116772905 (MAF=0.011) in exon 14 of DDR1 was associated with microalbuminuria (OR, 3.78; 95% CI, 2.35 to 6.11; P=4.40×10⁻⁸). rs116772905 is in perfect linkage disequilibrium with rs118124843, the lead association with microalbuminuria (full model OR, 0.78; 95% CI, 0.71 to 0.85; P=3.06×10⁻⁸). The remaining eight variants associated with features of DKD had lower allele frequencies (four with 0.01≤MAF≤0.05 and four with MAF<0.01) and did not achieve study-wide significance.

As we had done for COL4A3 rs55703767, we tested whether the associations of the 15 other variants were amplified by hyperglycemia. None of the 15 variants were significantly associated with eGFR in the general population (Supplemental Table 5). In the smaller SUMMIT T2D cohort13 we were able to interrogate seven loci with comparable trait definitions. The ORs were directionally consistent in six of them (binomial sign test: P=0.06; Supplemental Table 6). In FinnDiane seven of the remaining 15 loci were observed with sufficient frequency (minor allele counts >10) to allow subgroup analysis. Two additional SNPs (rs149641852 in SNAIP and rs12615970 near COLEC11) were nominally significant (P<0.05) only in individuals with HbA1c ≥7.5%; however, the genotype-by-HbA1c interaction term was nonsignificant (Supplemental Figure 4, Supplemental Table 7).

Variants Previously Associated with DKD

We investigated the effect of variants previously associated at genome-wide significance with renal complications in individuals with diabetes.8–13,39 Across the ten subphenotypes in our meta-analysis, we found evidence of association for seven of nine examined loci (P<0.05; Supplemental Figure 7): We replicated two loci that were previously discovered without overlapping individuals with the current study: SCAF8/CNKS3 rs12523822, originally associated with DKD (P=6.8×10⁻⁴ for “All versus ctrl”); and UMOD rs77924615, originally associated with eGFR in both individuals with and without diabetes (P=5.2×10⁻⁸ for “CKD”).31 Associations at the AFF3, RGMAC-MCTP2, and ERBB4 loci, identified in the Genetics of Nephropathy–an International Effort consortium12 comprising a subset of studies included in this current effort, remained associated with DKD, although the associations were attenuated in this larger dataset (RGMAC-MCTP2 rs12437854 P=2.97×10⁻⁵; AFF3 rs7583877 P=5.97×10⁻⁴; ERBB4 rs7588550 P=3.53×10⁻⁵; Supplemental Figure 8). Associations were also observed at the CDCA7/SP3 (rs4972593,
Gene and Gene Set Analysis

We conducted gene-level analyses by using two methods that aggregate SNP summary statistics over a gene region while accounting for linkage disequilibrium: MAGMA and PASCAL. \(^{40,41}\) MAGMA identified five genes at a Bonferroni-corrected threshold \((P<0.05/18,222 \text{ genes tested }= 2.74 \times 10^{-6})\): the collagen gene \(COL20A1\) associated with “CKD extreme” (full model \(P=5.77 \times 10^{-7}\)) and “ESKD versus non-ESKD” (full model \(P=9.53 \times 10^{-7}\)), SLC46A2 associated with “All versus control” \((P=7.38 \times 10^{-7}\)), SFXN4 associated with “Macro” (full model \(P=1.65 \times 10^{-7}\)), GLT5D1 associated with “ESKD versus macro” \((P=1.49 \times 10^{-6}\)), and SNX30 associated with “All versus control” \((P=2.49 \times 10^{-6}\)) (Supplemental Table 9). Although PASCAL did not identify any significant gene-level associations, the five MAGMA-identified genes had \(P<5.0 \times 10^{-4}\) in PASCAL (Supplemental Table 10). Both \(SFXN4\) and \(CBX8\) have been reported to be differentially methylated in patients with diabetes with and without nephropathy. \(^{42,43}\)

Additionally, we used MAGMA, PASCAL, DEPICT, and MAGENTA to conduct gene-set analysis in our GWAS dataset. The four methods identified 12 significantly enriched gene sets (Supplemental Table 11). One gene set, “negative regulators of RIG-I MDA5 signaling” was identified in two different pathway analyses (MAGMA and PASCAL) of our fully adjusted GWAS of ESKD versus Macro. Several additional related and overlapping gene sets were identified, including “RIGI MDA5 mediated induction of IFN alpha beta pathways,” “TRAF3 dependent IRF activation pathway,” and “TRAF6 mediated IRF activation” (PASCAL) and “activated TLR4 signaling” (MAGENTA). RIG-I, MDA5 and the toll-like receptor TLR4 are members of the innate immune response system that respond to both cellular injury and infection \(^{44,45}\) and transduce highly intertwined signaling cascades. These include the signaling molecules TRAF3 and TRAF6, which induce expression of type 1 IFN and proinflammatory cytokines implicated in the progression of DKD. \(^{46,47}\)

Specifically, the TLR4 receptor and several of its ligands and downstream cytokines display differential levels of expression in DKD renal tubules versus normal kidneys and versus non-DKD controls. \(^{48}\) and TLR4 knockout mice are protected from DKD and display marked reductions in interstitial collagen deposition in the kidney. \(^{49}\)

Other pathways of interest include “other lipid, fatty acid and steroid metabolism,” “nitric oxide signaling in the cardiovascular system,” and “TNF family member,” with both nitric oxide and TNF-α implicated in DKD. \(^{50,51,52}\)

Expression and Epigenetic Analyses

We interrogated gene expression datasets in relevant tissues to determine whether our top signals underlie eQTL. We first analyzed genotype and RNA-sequencing gene expression data from 96 whole human kidney cortical samples \(^{22}\) and micro-dissected human kidney samples (121 tubule and 119 medullary samples) \(^{23}\) from participants of European descent without any evidence of renal disease (Supplemental Figure 9).

No findings in this data set achieved significance after correction for multiple testing. In the GTEx and eQTLgen datasets, \(COLAA3\) rs55703767 had a significant eQTL \((P=5.63 \times 10^{-3}\) with the MFF gene in blood, but is most likely due to modest LD with other nearby strong eQTLs in the region. \(rs118124843\) near \(DDR1\) and \(VARS2\) had multiple significant eQTLs in blood besides \(VARS2\) \((P=1.71 \times 10^{-5}\); Supplemental Table 12). Interestingly, \(rs142823282\) near \(TAMM41\) was a cis-eQTL for \(PPARG\) \((P=4.60 \times 10^{-7})\), a transcription factor regulating adipocyte development and glucose and lipid metabolism; PPARγ agonists have been suggested to prevent DKD. \(^{53}\)

To ascertain the potential functional role of our top non-coding signals, we mined chromatin immunoprecipitation sequencing data derived from healthy adult human kidney samples. \(^{25}\) SNP \(rs142823282\) near \(TAMM41\) was located close to kidney histone marks \(H3K27ac, H3K9ac, H3K4me1,\) and \(H3K4me3\), suggesting that this is an active regulator of \(TAMM41\) or another nearby gene (Supplemental Figure 11). Interestingly, in recent work we have shown that DNA methylation profiles in participants with T1D with/without kidney disease show the greatest differences in methylation sites near \(TAMM41\). \(^{54}\)

To establish whether the expression of our top genes shows enrichment in a specific kidney cell type, we queried an expression dataset of approximately 50,000 single cells obtained from mouse kidneys. \(^{24}\) Expression was detected for six genes in the mouse kidney atlas: three \((COLAA3, SNCAIP, BAMP7)\) were almost exclusively expressed in podocytes (Figure 5), supporting the significant role for podocytes in DKD.

Gene expression levels in kidneys in cases versus controls were predicted with TWAS on the basis of the GWAS summary statistics and eQTL data of kidney glomeruli and tubuli. \(^{23}\) While none of the genes survived correction for multiple testing, analysis suggested 18 genes with differential expression in cases and controls with \(P<1 \times 10^{-4}\), including the \(NPNT, PRRC2C,\) and \(VPS33B\) genes (Supplemental Table 13). \(NPNT\) encodes for nephronectin, an extracellular matrix protein on GBM. Knocking out \(NPNT\) or decreasing \(NPNT\) expression levels have been shown to induce podocyte injury related to GBM. \(^{55}\) On the contrary, TWAS predicted higher \(NPNT\) expression within DN cases versus normal AER. In line with our TWAS finding, \(NPNT\) is significantly upregulated in glomeruli of DN mouse model versus nondiabetic mouse \((P=6.4 \times 10^{-4}; \text{fold change } 1.3, \text{ in top } 2\%, \text{ accessed through www.neproseq.org})\). \(^{56}\) Furthermore, a variant near \(PRRC2C\) was recently associated with albuminuria in the UK Biobank, \(^{57}\) and rare mutations in \(VPS33B\) gene cause arthrogryposis, renal
dysfunction, and cholestasis-1 syndrome involving proximal-tubular dysfunction and usually death by 1 year of age.58

DISCUSSION

Our genome-wide analysis of 19,406 participants with T1D identified 16 genome-wide significant loci associated with DKD, four of which remained significant after a conservative correction for multiple testing. Four of the 16 genome-wide significant signals are in or near genes with known or suggestive biology related to renal function/collagen (COL4A3, BMP7, COLEC11, and DDR1), but this is the first time that naturally occurring variation (MAF >1%) in these loci has been associated with DKD. Our most significant signal was a protective missense variant in COL4A3, rs55703767, reaching both genome-wide and study-wide significance with multiple definitions of DKD. Moreover, this variant demonstrated a significant association with GBM width such that protective allele carriers had thinner GBM before any signs of kidney disease, and its effect was dependent on glycemia.

COL4A3, with COL4A4 and COL4A5, make up the so-called “novel chains” of type IV collagen,59 which together play both structural and signaling roles in the GBM. Specifically, COL4A3 is known to bind a number of molecules including integrins, heparin, and heparin sulfate proteoglycans, and other components of the GBM, such as laminin and nidogen. These interactions mediate the contact between cells and the underlying collagen IV basement membrane, and regulate various processes essential to embryonic development and normal physiology, including cell adhesion, proliferation, survival, and differentiation. Dysregulation of these interactions has been implicated in several pathologic conditions, including CKD.60

Mutations in COL4A3 are responsible for the autosomal recessive form of Alport syndrome, a progressive inherited nephropathy, as well as benign familial hematuria, characterized by thin (or variable width) GBM, and thought to be a milder form of Alport syndrome.61 Furthermore, mutations in COL4A3 have also been identified in patients with FSGS, often leading to proteinuria and renal failure. Some of these patients with FSGS presented with segmental GBM thinning.62 Of note, the common rs55703767 (COL4A3 Asp326Tyr) variant, protecting from DKD, was also associated with thinner GBM in individuals with diabetes but without renal complications, a feature that seems to be beneficial in the context of diabetes. The rs55703767 SNP is predicted to alter the third amino acid of the canonical triple-helical domain sequence of Glycine (G)-X-Y (where X and Y are often proline [P] and hydroxyproline [Y], respectively) from G-E-D (D=Aspartic) to G-E-Y,63 potentially affecting the structure of the collagen complex. In addition, a recent study64 of
candidate genes involved in renal structure reported rs34505188 in COL4A3 (not in linkage disequilibrium with rs55703767, r²<0.01) to be associated with ESKD in black Americans with T2D (MAF=2%; OR, 1.55; 95% CI, 1.22 to 1.97; P=5×10⁻⁴). Together with the trend toward association we have seen in SUMMIT and the glycemic interaction we have reported here, these findings suggest variation in COL4A3 may be associated with DKD in T2D as well.

Given its association as a protective SNP, we can speculate that the rs55703767 variant may confer tensile strength or flexibility to the GBM, which may be of particular relevance in the glomerular hypertension associated with DKD. Alternatively, COL4A3 may regulate the rates of production and/or turnover of other GBM components, affecting GBM width changes in diabetes. How these effects might confer protection in a manner dependent on ambient glucose concentrations is unknown. Future mechanistic studies will be required to determine the precise role of this variant in DKD; elucidation of its interaction with glycemia in providing protection might be relevant to other molecules implicated in diabetic complications.

In keeping with the collagen pathway, the synonymous exonic variant rs118124843, which reached genome-wide significance for the “Micro” phenotype, is located near DDR1, the gene encoding the discoidin domain-containing receptor 1. On the basis of chromatin conformation interaction data from Capture HiP Plotter,⁶⁵ the rs118124843 containing fragment interacts with six gene promoter regions, including DDR1, suggesting that the variant regulates DDR1 expression across multiple tissues (Supplemental Table 12). DDR1 is a collagen receptor⁶⁶ shown to bind type IV collagen,⁶⁷ and is highly expressed in kidneys, particularly upon renal injury.⁶⁸ Upon renal injury, Ddr1-deficient mice display lower levels of collagen,⁶⁹ decreased proteinuria, and an increased survival rate compared with wild-type controls,⁷⁰ with Ddr1/Col4a3 double-knockout mice displaying protection from progressive renal fibrosis and prolonged lifespan compared with Col4a3 knockout mice alone.⁶⁹ Thus, through its role in collagen binding, DDR1 has been suggested as a possible therapeutic target for kidney disease.⁶⁹

The association of rs12615970, an intronic variant on chromosome 2 near the COLEC11 gene, met genome-wide significance for the KD phenotype, as well as nominal significance for multiple albuminuria-based traits. The rs12615970 containing fragment was found to interact with COLEC11, ALLC, and ADI1 transcription start sites in chromatin conformation data on GM12878 cell line (Supplemental Table 12).⁶⁵,⁷¹ Collectin-11 is an innate immune factor synthesized by multiple cell types, including renal epithelial cells with a role in pattern recognition and host defense against invasive pathogens, through binding to fructose and mannose sugar moieties.⁷²,⁷³ Mice with kidney-specific deficiency of COLEC11 are protected against ischemia-induced tubule injury because of their reduced complement deposition,⁷⁴ and mutations in COLEC11 have been identified in families with 3MC syndrome, a series of rare autosomal recessive disorders resulting in birth defects and abnormal development, including kidney abnormalities.⁷⁵

The intronic variant rs144434404, associated at study-wide significance with the microalbuminuria phenotype, resides within the bone morphogenetic protein 7 (BMP7) gene. BMP7 encodes a secreted ligand of the TGF-β superfamily of proteins. Developmental processes are regulated by the BMP family of glycosylated extracellular matrix molecules via serine/threonine kinase receptors and canonical Smad pathway signaling. Coordinated regulation of both BMP and BMP-antagonist expression is essential for developing tissues, and changes in the levels of either BMP or BMP-antagonists can contribute to disease progression such as fibrosis and cancer.⁷⁶ BMP7 is required for renal morphogenesis, and Bmp7 knockout mice die soon after birth, because of reduced ureteric bud branching.⁷⁷,⁷⁸ Maintenance of Bmp7 expression in glomerular podocytes and proximal tubules of diabetic mice prevents podocyte loss and reduces overall diabetic renal injury.³⁸ More recently, we have identified a mechanism through which BMP7 orchestrates renal protection through Akt inhibition, and highlights Akt inhibitors as potential antifibrotic therapeutics.⁸⁰ It is also noteworthy that the BMP7 antagonist gremlin-1 is implicated in DKD,⁸¹–⁸³ and gremlin has been implicated as a biomarker of kidney disease.⁸⁴

Strengths of this analysis include the large sample size, triple that of the previous largest GWAS; the uniform genotyping and QC procedures; standardized imputation for all studies (1000 Genomes reference panel); the inclusion of exome array content; the exploration of multiple standardized phenotype definitions of DKD; and supportive data from various sources of human kidney samples. Several of the loci identified have known correlations with kidney biology, suggesting that these are likely true associations with DKD. However, we acknowledge a number of limitations. First, nine variants have low MAF and were driven by only two cohorts, indicating that further validation will be required to increase confidence in these associations. Second, seven variants were significantly associated with microalbuminuria only, a trait shown to be less heritable in previous studies. We included these loci to maximize comprehensiveness in reporting novel DKD associations. Replication in independent samples and functional confirmation is required to validate all of these loci. Although the gene-level, gene set, and pathway analyses had limited power, these analyses identified several additional potential DKD loci and pathways, some with relevance to kidney biology, that require further follow-up. Finally, although we included only controls with a minimum diabetes duration of 15 years, we cannot fully rule out that some of the controls would progress to DKD in the future, as the improvements in diabetes treatment in the past decades have postponed the onset of complications. We also excluded cases with short diabetes duration to avoid renal complications that might be due to other causes. These phenotypic definitions were meant to overcome the limitation that in clinical practice kidney biopsy specimens are rarely taken from individuals with diabetes to verify the
Diabetic complications are unquestionably driven by hyperglycemia and partially prevented by improved glycemic control in both T1D and T2D, but there has been doubt over what contribution, if any, inherited factors contribute to disease risk. In line with previous genetic studies, this study with a marked expanded sample size identified several loci strongly associated with DKD risk. These findings suggest that larger studies, aided by novel analyses and including T2D, will continue to enhance our understanding of the complex pathogenesis of DKD, paving the way for molecularly targeted preventive or therapeutic interventions.

ACKNOWLEDGMENTS

Conceptualization: Godson, Maxwell, Groop, Hirschhorn, and Florez; Formal analysis: Salem, Cole, Sandholm, Valo, Di Liao, Cao, Pezzolesi, Smiles, Qiu, Nair, Park, Liu, Menon, Kang, R. Klein, B.E. Klein, Canty, Paterson, Chen, van Zuydam, and Onengut-Gumuscu; Investigation: Pezzolesi, Smiles, Skupien Qiu, Nair, Haukka, McKnight, Snell-Beigeon, Maahs, Maxwell, Paterson, Forsblom, Ahlvist, Ahluwalia, Lajer, Boustany-Kari, Kang, Macaestroni, Tregouet, Gyorgy, Bull, Palmer, Stechemesser, Paulweber, Weitgasser, Rovite, Pirägs, Prakapiene, Radzeviciene, Verkauskiene, Panduru, Groop, McCarthy, Gu, Möllsten, Falhammar, Brismar, Rossing, Costacou, Zerbini, Marre, Hadjadji, Forsblom, Chen, and Onengut-Gumuscu; Resources: Smiles, Harjutsalo, McKnight, Nelson, Caramori, Maurer, Gao, Snell-Beigeon, Maahs, Guo, Miller, Maxwell, Paterson, Chen, and Onengut-Gumuscu; Data curation: Hiraki, Di Liao, Cao, Smiles, Harjutsalo, Skupien, McKnight, R. Klein, B.E. Klein, Lee, Gao, Maurer, Caramori, Snell-Beigeon, Maahs, Guo, Miller, Maxwell, Chen, and Onengut-Gumuscu; Writing, original draft: Salem, Todd, Sandholm, Cole, Brennan, Andrews, Doyle, Hughes, Hiraki, Paterson, and Godson; Writing, review and editing: Salem, Todd, Sandholm, Cole, Brennan, Andrews, Doyle, Hughes, Hiraki, Paterson, Godson, Qiu, Park, Skupien, Maurer, Caramori, de Boer, Martin, McKnight, McKay, Maxwell, Susztak, McCarthy, Groop, Rich, Forsblom, Hirschhorn, and Florez; Visualization: Salem, Todd, Sandholm, Cole, Pezzolesi, Qiu, Di Liao, Cao, Park, Skupien, R. Klein, B.E. Klein, Lee, McKnight, McKay, Maxwell, and Paterson; Project administration: Todd; Supervision: Paterson, Krolevski, Groop, Godson, Maxwell, Colhoun, Rich, Kretzler, Susztak, Hirschhorn, and Florez; Funding acquisition: Paterson, Krolevski, Florez, and Hirschhorn. All authors approved the final version of the manuscript.

AusDiane acknowledges Dr. Bernhard Baumgartner from Department of Medicine, Diakonissen-Wehrle Hospital, Salzburg, Austria. LatDiane acknowledges the following doctors and researchers: A. Bogdanova, D. Grikmame, I. Care, A. Fjodorova, R. Graudipa, A. Valterva, D. Teterovska, I. Dziviite-Krișane, I. Kiriłova, U. Lauga-Turiqa, K. Geldner, D. Seissma, N. Fokina, S. Steina, L. Jaunozola, I. Balcerse, U. Gališa, E. Menise, S. Broka, L. Akmane, N. Kapla, I. Nagaiceva, A. Petersons, A. Lejinieks, I. Konrade, I. Salna, A. Dekante, A. Grämatniece, A. Salina, A. Šilda, V. Mšečko, V. Mijejeva, K. Kudrijeva, I. Markska, M. Čirse, D. Zerme, S. Kalva-Vivavde, J. Klovig, L. Nikolitina-Załe, S. Skrebinska, Z. Dźerve, and R. Mallons. LitDiane acknowledges Drs. Jurate Lasiene, Prof. Dzilda Velickiene, Dr. Vladimiras Petenkos and nurses from the Department of Endocrinology, Hospital of Lithuanian University of Health Sciences. RomDiane acknowledges the following doctors and researchers: M. Anghel, DM Cheta, BA Cimpoca, D. Cimponeri, CN Czoza, N. Dandum, D. Dobrin, I Dutu, AM Frentescu, C. Ionescu-Tirgoviste, R. Ionica, R. Lichiardopol, AL Oprea, NM Panduru, A. Pop, G. Pop, R. Radescu, S. Radu, M. Robu, C. Serafinicenu, M. Stavarchi, O Tudose from the N.C. Paulescu National Institute for Diabetes Nutrition and Metabolic Diseases from Bucharest; and M. Bacu, D. Clenciu, C. Graunteanu, M. Ioana, E. Mota, and M. Mota from Craiova Emergency County Hospital. SDR: Thanks to Maria Sterner and Malin Neptin for GWAS genotyping in the Scania Diabetes Registry. The FinnDiane study thanks M. Parkkonen, A. Sandelin, A-R. Salonen, T. Soppela, and J. Tuomikangas for skilful laboratory assistance in the FinnDiane study. We also thank all the participants of the FinnDiane study and gratefully acknowledge all the physicians and nurses at each centre involved in the recruitment of participants (Supplemental Table 14). GoDARTS: We are grateful to all the participants in this study, the general practitioners, the Scottish School of Primary Care for their help in recruiting the participants, and to the whole team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses. The study complies with the Declaration of Helsinki. We acknowledge the support of the Health Informatics Centre, University of Dundee for managing and supplying the anonymised data and NHS Tayside, the original data owner. For a full list of SUMMIT consortium members, see Supplemental Table 15.

The views expressed in this article are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

Data and Software Availability

GWAS summary statistics for all ten DKD phenotypes and two adjustment models are available for download at the AMP-Type 2 Diabetes Knowledge Portal (http://www.type2diabetesgenetics.org informational/data), under “JDRF Diabetic Nephropathy Collaborative Research Initiative GWAS” datasets. Individual-level genotype data cannot be shared for all cohorts because of restrictions set by study consents and by European Union and national regulations regarding individual genotype data.

DISCLOSURES

We acknowledge the following conflicts of interest: Groop has received investigator-initiated research grants from Eli Lilly and Roche, is an advisory board member for AbbVie, AstraZeneca, Boehringer Ingelheim, Cebix, Eli Lilly, Janssen, Medscape, Merck Sharp & Dohme, Novartis, Novo Nordisk
and Sanofi, and has received lecture fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Elow Water, Genzyme, Merck Sharp & Dohme, Medescape, Novo Nordisk and Sanofi. McCarthy is a Wellcome Investigator and an NIH Senior Investigator. He serves on advisory panels for Pfizer, NovoNordisk, and Zoe Global, has received honoraria from Merck, Pfizer, NovoNordisk and Eli Lilly, has stock options in Zoe Global, and has received research funding from Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, NovoNordisk, Pfizer, Roche, Sanofi Aventis, Servier and Takeda. Rossing has received consultancy and/or speaking fees (to his institution) from Abbvie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, MSD, Novo Nordisk and Sanofi Aventis and research grants from AstraZeneca and Novo Nordisk, and shares in Novo Nordisk.

Dr. Onenget-Gumucu reports grants from JDRF, during the conduct of the study. Dr. Caramori reports grants from Bayer Pharmaceuticals, personal fees from Elcelix, outside the submitted work. Dr. de Boer reports personal fees from Boehringer-Ingelheim, personal fees from Ironwood, non-financial support from Medtronic, non-financial support from Abbott, outside the submitted work. Dr. Snell-Bezorge reports grants from NIH, grants from JDRF, during the conduct of the study; other from GlaxoSmithKline, outside the submitted work. Dr. Weitgasser reports personal fees from Abbott, personal fees from Astra Zeneca, personal fees from Boehringer-Ingelheim, grants and personal fees from Eli Lilly, personal fees from MSD, grants and personal fees from NovoNordisk, personal fees from Dexcom, personal fees from Roche, grants and personal fees from Sanofi, personal fees from Servier, personal fees from Takeda, personal fees from Spar, outside the submitted work. Dr. McCarthy reports grants, personal fees and other from Pfizer, grants, personal fees and other from Merck, grants, personal fees and other from Novo Nordisk, grants from Takeda, grants from Servier, grants from Sanofi Aventis, grants from Boehringer Ingelheim, grants from Astra Zeneca, grants from Janssen, grants, personal fees and other from Eli Lilly, grants from Abbvie, grants from Roche, during the conduct of the study; grants, personal fees and other from Pfizer, grants, personal fees and other from Eli Lilly, grants, personal fees and other from Merck, other from Zoe Global, other from Gentech (wef June 2019), outside the submitted work. Dr. Costacou reports grants from National Institutes of Health (NIH), during the conduct of the study. Dr. McKnight reports grants from Northern Ireland Public Health Agency (Research and Development Division) and Medical Research Council as part of the USA-Ireland-Northern Ireland research partnership and Department for the Economy NI 15/IA/3152 during the conduct of the study. Dr. Kretzler reports grants from NIH, non-financial support from University of Michigan, during the conduct of the study; grants from JDRF, grants from AstraZeneca, grants from NovoNordic, grants from Eli Lilly, grants from Gilead, grants from Goldfinch Bio, grants from Merck, grants from Janssen, grants from Boehringer-Ingelheim, grants from Elpidera, grants from European Union Innovative Medicine Initiatiive, outside the submitted work; In addition, Dr. Kretzler has a patent Biomarkers for CKD progression issued. Dr. Suznik reports grants from GSK, Regeneron, Boehringer, Gilead, Bayer, Lilly, Merck, outside the submitted work. Dr. Colhoun reports grants from AstraZeneca, Pfizer, other from Bayer, grants and other from Eli Lilly and Company, other from Novartis Pharmaceuticals, grants and other from Regeneron, grants from Pfizer Inc., other from Roche Pharmaceuticals, grants and other from Sanofi Aventis, grants and personal fees from Novo Nordisk, outside the submitted work. Dr. Groop reports personal fees from Abbvie, personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Eli Lilly, personal fees from Elow Water, personal fees from Janssen, personal fees from Medscape, personal fees from Mundipharma, personal fees from MSD, personal fees from Novartis, personal fees from Novo Nordisk, personal fees from Sanofi, outside the submitted work. Dr. Marre reports personal fees from Novo-Nordisk, personal fees from Servier, personal fees from Merck, outside the submitted work; and Marre is president of the Fondation Francophone pour la Recherche sur le Diabete, a French, non for profit institution. This institution is supported financially by the following companies: Novo-Nordisk, Merck, Sanofi, Eli Lilly, Astra-Zeneca, Roche, Abbott. Dr. Hirschhorn reports other from Camp4 Therapeutics, outside the submitted work. Dr. Florez reports personal fees from Janssen, outside the submitted work. Dr. Hiraki reports grants from Juvenile Diabetes Research Foundation (JDRF), during the conduct of the study; Dr. Rossing reports grants and other from Astra Zeneca, other from Boehringer Ingelheim, other from Bayer, grants and other from Novo Nordisk, other from MSD, other from Eli Lilly, other from astellas, other from Abbvie, other from Mundipharma, other from Sanofi, other from Gilead, outside the submitted work.

FUNDING

This study was supported by a grant from the JDRF (17-2013-7) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grants R01 DK081923 and R01 DK105154. Salem was supported in part by JDRF grant 3-APF-2014-111-A-N, and National Heart, Lung and Blood Institute grant R00 HL122515. Todd was supported by NIDDK grant K12-DK094721. Sandholm received funds from the European Foundation for the Study of Diabetes (EFSF) Young Investigator Research Award funds and Academy of Finland (299200). Godson, Andrews, Brennan, Martin, Hughes, and Doyle are supported by Science Foundation Ireland - Health Research Board (SFI-HRB) US Ireland Research Partnership SFI15/US/B3310. Nelson was supported in part by the Intramural Research Program of the NIDDK. The FinnDiane study was funded by JDRF (17-2013-7), Folkhalsan Research Foundation, the Wilhelm and Else Stockmann Foundation, the Liv och Hälsa Foundation, Helsinki University Central Hospital Research Funds (EVO), the Novo Nordisk Foundation (NNF OCO013659), and Academy of Finland (275614 and 316664). The Pittsburgh Epidemiology of Diabetes Complications Study (EDC) study was supported by NIDDK grant DK34818 and by the Rossi Memorial Fund. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) study was funded by National Eye Institute grant EY016379. The Sweden study was supported by Family Eirling-Perssion (Brismar) and Stig and Gunborg Westman foundations (Gu). SUMMIT Consortium: this work was supported by Innovative Medicines Initiative (IMI) (SUMMIT 115006); Wellcome Trust grants 098381, 090532, and 106310; National Institutes of Health grant R01-MH101814; and JDRF grant 2-SRA-2014-276-Q-R; and other grants from Swedish Research Council, European Research Council Advanced (ERC-Adv) research grant 269045-GENE TARGET T2D, Academy of Finland grants 263401 and 267882, and Sigrid Juselius Foundation. The George M. O’Brien Michigan Kidney Translational Core Center, funded by NIH/NIDDK grant 2P30-DK-081943 for the bioinformatics support. The Wellcome Trust United Kingdom Type 2 Diabetes Case Control Collection (GoDARTS) was funded by the Wellcome Trust (072960/Z/03/Z, 084726/Z/08/Z, 084727/Z/08/Z, 085475/Z/08/Z, 085475/B/08/Z) and as part of the European Union’s IMI-SUMMIT program.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl?doi:10.1681/ASN.2019030218/-/DCSupplemental.

Supplemental Table 1. Cohorts contributing to analyses.

Supplemental Table 2. Pseudo-$R^2$ of all SNPs across all GWAS as calculated by the McKelvey and Zavoina method.

Supplemental Table 3. Characteristics of RASS participants. Categorical variables display counts and percentage. Continuous values are mean ± SD.

Supplemental Table 4. Multivariate analysis of association between rs55703767 and GBM width.

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Supplemental Table 6. Look-up of the lead loci in GWAS in the SUMMIT consortium (van Zuydam et al.13).
Supplemental Table 7. Association at lead loci stratified by HbA1c <7.5%.

Supplemental Table 8. Association of rs55703767 with DN in DCCT/EDIC subgroups.

Supplemental Table 9. Significant (P<0.05/18,222 genes tested =2.74×10−6) gene level associations with DKD in MAGMA.

Supplemental Table 10. Top nominally significant gene-level associations (P<1.0×10−5) with DKD in PASCAL.

Supplemental Table 11. Significant gene set and pathway analysis results.

Supplemental Table 12. eQTL associations and chromatin conformation interactions for the lead SNPs.

Supplemental Table 13. TWAS results with P<1×10−4.

Supplemental Table 14. Physicians and nurses at health care centers participating in the collection of FinnDiane patients.

Supplemental Table 15. Members of the SUMMIT consortium.

Supplemental Figure 1. Manhattan and QQ plots for each case-control definition and covariate model (minimal and full).

Supplemental Figure 2. Regional chromosomal location plots and forest plots by cohort of newly discovered DKD associations.

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Supplemental Figure 4 (S3). Genotype-phenotype associations at the lead loci when stratified by mean HbA1c <7.5% in the FinnDiane study.

Supplemental Figure 5 (S4): Genotype-phenotype associations at the lead rs55703767 (COL4A3) locus when stratified by mean HbA1c <7.5% in up to 3226 individuals with T2D from the GoDARTS.

Supplemental Figure 6 (S6). Fishplots comparing significance and directionality between minimal and fully adjusted models for each of the ten phenotype definitions.

Supplemental Figure 7 (S5). Association at previously reported loci (P<5×10−8) for renal complications in individuals with diabetes.

Supplemental Figure 8 (S7). Forest plots of the associations at the previously reported lead locus from the GENIE consortium with largely overlapping studies.

Supplemental Figure 9 (S7). Meta-analysis results for the loci that have previously been associated with DKD, or with eGFR or AER in the general population.

Supplemental Figure 10 (S8). eQTL analysis in microdissected tubule samples.

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Supplemental Appendix 1. Cohort descriptions and references.

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SUPPLEMENTAL METHODS.

**Cohorts in GWAS.** The GWAS meta-analysis included up to 19,406 patients with type 1 diabetes and of European origin from 17 cohorts: The Austrian Diabetic Nephropathy Study (AusDiane); The Coronary Artery Calcification in Type 1 Diabetes (CACTI)\(^1\); the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC)\(^2,3\); Pittsburgh Epidemiology of Diabetes Complications Study (EDC)\(^4\); The Finnish Diabetic Nephropathy (FinnDiane) Study\(^5,6\); French and Belgian subjects from the Genetics of Diabetic Nephropathy (GENEDIAB)\(^7\) and Genesis\(^8\) studies; Genetics of Kidneys in Diabetes US Study (GoKinD) from George Washington University (GWU-GoKinD)\(^9\); patients from the Joslin Kidney Study\(^9,10\); individuals with T1D from Italy\(^5\); The Latvian Diabetic Nephropathy Study (LatDiane)\(^11\); The Lithuanian Diabetic Nephropathy Study (LitDiane) [Reference pending, submitted]; The Romanian Diabetic Nephropathy Study (RomDiane)\(^12\); The Scottish Diabetes Research Network Type 1 Bioresource (SDRNT1BIO)\(^13,14\); individuals with T1D from Steno Diabetes Center\(^15\); individuals with T1D from Uppsala, Sweden\(^16,17\); UK GoKinD, Warren 3 and All Ireland (UK-ROI) study\(^18\); and The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)\(^19\). All participants gave informed consent and all studies were approved by ethics committees from all participating institutions.

**GWAS Genotyping.** Samples were genotyped on the HumanCore BeadChip (Illumina, San Diego, CA, USA), which contains 250,000 genome-wide tag SNPs (and other variants) and over 200,000 exome-focused variants. All samples were passed through a stringent quality control protocol. Following initial genotype calling with Illumina software, all samples were re-called with zCall, a calling algorithm specifically designed for rare SNPs from arrays. Once calling was completed for all cohorts, our pipeline updated variant orientation and position aligned to hg19.
GWAS of DKD Supplement

Variant names were updated using 1000 Genomes as a reference. The data were then filtered for low quality variants (e.g. call rates <95% or excessive deviation from Hardy-Weinberg equilibrium) or samples (e.g. call rates <98%, gender mismatch, extreme heterozygosity). Principal Component Analysis (PCA) was performed separately for each cohort in order to empirically detect and exclude outliers with evidence of non-European ancestry. Genotypes were expanded to a total of approximately 49 million by imputation, using 1,000 Genomes Project (phase 3 version 5) as a reference.

GWAS Phenotype definitions. Participant renal status was evaluated on the basis of both albuminuria and eGFR. We defined a total of 10 different case-control outcomes to cover the different aspects of renal complications (Figure 1). Five comparisons (“All vs. ctrl”, “Micro”, “DN”, “Macro”, and “ESRD vs. macro”) were based on albuminuria, measured by albumin excretion rate (AER) from overnight or 24-h urine collection, or by albumin creatinine ratio (ACR). Two out of three consecutive collections were required (when available) to classify the renal status of subjects as either normoalbuminuria, microalbuminuria, macroalbuminuria, or ESRD; for detailed thresholds, see Table S9. Controls with normal AER were required to have a minimum diabetes duration of 15 years; subjects with microalbuminuria/ macroalbuminuria/ ESRD were required to have minimum diabetes duration of 5/ 10/ 10 years, respectively, in order to exclude renal complications of non-diabetic origins. Two comparisons (“ESRD vs. ctrl” and “ESRD vs. non-ESRD”) were based on presence of end-stage renal disease as defined by eGFR< 15 mL/min or dialysis or renal transplant. Two phenotypes (“CKD” and “CKD extreme”) were defined based on estimated glomerular filtration rate (eGFR; evaluated with the CKD-EPI formula): Controls had eGFR ≥ 60ml/min/1.73m² for both phenotypes, and minimum of 15 years of diabetes duration; cases had eGFR <60ml/min/1.73m² for the “CKD” phenotype, and eGFR <15 ml/min/1.73m² or dialysis or renal transplant for the “CKD extreme” phenotype, and
minimum of 10 years of diabetes duration. For the “CKD-DN” phenotype that combined both albuminuria and eGFR data, controls were required to have both eGFR ≥60ml/min/1.73m² and normoalbuminuria; cases had both eGFR <45ml/min/1.73m² and micro- or macroalbuminuria, or ESRD.

**GWAS Statistical Analysis.** A genome-wide association analysis of each of the case-control definitions was performed using logistic regression under an additive genetic model, adjusting for age, sex, diabetes duration, study site (where applicable) and principal components. As disease onset and progression is also closely related to BMI and HbA1c levels, we conducted a second set of analyses adjusting for BMI and HbA1c which we refer to as our fully adjusted covariate model. Allele dosages were used to account for imputation uncertainty. Inverse-variance fixed effects meta-analysis was performed using METAL and the following filters: INFO score >0.3, minor allele count >10, and presence of variant in at least two cohorts. The X chromosome was similarly analyzed for males and females both separately and in a combined analysis, with the exception of using hard call genotypes in place of allele dosages. The study-wide significance threshold (P<6.76×10⁻⁹) was calculated by applying a Bonferroni correction to the traditional GWAS threshold (P<5.00×10⁻⁸), based on the number of effectively independent tests, using methods previously described on the eigenvalues of the GWAS summary statistics correlation matrix²¹.

**Glomerular basement membrane measurement in Renin-Angiotensin System Study (RASS).** RASS was a double-blind placebo-controlled randomized trial of the angiotensin converting enzyme inhibitor (ACEi) enalapril and the angiotensin II receptor blocker (ARB) losartan on renal pathology among 285 normoalbuminuric, normotensive subjects with T1D and had normal or increased measured glomerular filtration rate (>90 ml/min/1.73m²)²². Beginning in
2005, participants were recruited from three centers: University of Minnesota (Minneapolis, Minnesota), McGill University (Montreal, Canada) and University of Toronto (Toronto, Canada) and included those with 2 to 20 years of diabetes and excluded those on any antihypertensive medications. Written informed consent was obtained from each participant and the study was approved by the relevant institutional review boards. RASS study participants were followed for 5 years with percutaneous kidney biopsy completed prior to randomization and at 5 years. Structural parameters measured by electron microscopy on biopsy included GBM width, measured by the electron microscopic orthogonal intercept method\textsuperscript{22}.

RASS study participants were followed for 5 years with percutaneous kidney biopsy completed prior to randomization and at 5 years. Structural parameters measured by electron microscopy on biopsy included GBM width, measured by the electron microscopic orthogonal intercept method\textsuperscript{22}.

**RASS genotyping:** All RASS participants contributed DNA for genotyping on the Illumina HumanOmni1-Quad and HumanCoreExome beadchip arrays. Genotypes were called using BeadStudio/Genomestudio software (Illumina®). Quality control (QC) measures included removing duplicate samples, samples with evidence of contamination (heterozygosity range 0.25-0.32) and those with cryptic relatedness identity-by-state (IBS) (n=24). Principal component analyses were completed and 7 non-European outliers were removed. Of those genotyped, 1 participant was missing kidney biopsy data.

**RASS GBM width analysis:** We completed linear regression of the COL4A3 variant (rs55703767) and within person mean GBM width (nm) from both baseline and 5 year measures, in additive and genotypic genetic models. Both univariate and multivariate analyses were run including sex, baseline age and diabetes duration, within person mean HbA1c over 5 years, indicators for treatment group assignment and treatment center. A two-sided significance threshold of alpha <0.05 was applied.
In silico replication in SUMMIT consortium. The SUMMIT consortium included up to 5193 subjects with type 2 diabetes, with and without kidney disease, of European ancestry. All studies were approved by ethics committees from relevant institutions and all participants gave informed consent. Complete list of SUMMIT Consortium members provided in Table S13.

SUMMIT genotyping and statistical analysis: SUMMIT Cohorts were genotyped on the Affymetrix SNP 6.0, the Illumina Omni express and the Illumina 610Quad arrays. QC measures included filtering out low frequency (<1% MAF) variants, filtering out low quality variants or samples, removal of duplicate samples, and removal of non-European samples based on principal component analysis. Genome-wide association analyses were performed for DKD trait definitions harmonized with seven of our primary T1D analyses: “DN”, “Micro”, “Macro”, “ESRD”, “ESRD vs. non-ESRD”, “CKD”, and “CKD-DN” under an additive model, adjusting for age, gender and duration of diabetes.

RNA-sequencing and cis-eQTL analysis in human kidney samples from University of Pennsylvania cohort. Human kidney tissue collection was approved by the University of Pennsylvania Institutional Review Board. Kidney samples were obtained from surgical nephrectomies. Nephrectomies were de-identified, and the corresponding clinical information was collected through an honest broker; therefore, no consent was obtained from the subjects. Tubular and glomerular eQTL data sets were generated by 121 samples of tubules and 119 samples of glomeruli, respectively. The cis window was defined as 1 megabase up- and downstream of the transcriptional start site (±1Mb). Whole kidney cis-eQTL (further just referred to as eQTL) data set was generated from 96 human samples were obtained from The Cancer Genome Atlas (TCGA) through the TCGA Data portal.
**RNA-sequencing of human kidney samples in the University of Pennsylvania cohort:** Human kidney tissue was manually microdissected under a microscope in RNAlater for glomerular and tubular compartments. The local renal pathologist performed an unbiased review of the tissue section by scoring multiple parameters, and RNA were prepared using RNAeasy mini columns (Qiagen, Valencia, CA) according to manufacturer's instructions. RNA quality was assessed with the Agilent Bioanalyzer 2100 and RNA integrity number scores above 7 were used for cDNA production. The library was prepared in the DNA Sequencing Core at University of Texas Southwestern Medical Center. One microgram total RNA was used to isolate poly(A) purified mRNA using the Illumina TruSeq RNA Preparation Kit. We sequenced samples for single-end 100bp, and the annotated RNA counts (fastq) were calculated by Illumina’s CASAVA 1.8.2. Illumina sequence quality was surveyed with FastQC. Adaptor and lower-quality bases were trimmed with Trim-galore. Trimmed reads were aligned to the Gencode human genome (GRCh37) with STAR-2.4.1d. The readcount of each sample was obtained using HTSeq-0.6.1 (htseq-count) and then normalized fragments per kilobase million values were used to perform association analysis with fibrosis and sclerosis using linear regression.

**Human kidney cis-eQTL analysis.** Nominal p-values were calculated for each SNP-gene pair with FastQTL using linear regression with an additive effects model, and adjusted by six genotype PCs.

**RNA-sequencing of human kidney samples.** Normalized fragment per kilobase million values were used to perform association analysis with fibrosis and sclerosis using linear regression.

**RNAseq and microarray profiling of human kidney samples from the Pima cohort.** Kidney biopsy samples from the Pima Indian cohort were manually micro-dissected into 119 glomerular and 100 tubule-interstitial tissues to generate gene expression profiles. Expression profiling in the Pima Indian cohort kidney biopsies was carried out using Affymetrix GeneChip Human
 Genome U133 Array and U133Plus2 Array, as reported previously, and Affymetrix Human Gene ST Genechip 2.1,26,27, and on RNA-seq (Illumina). The libraries were prepared using the ClonTech SMARTSeq v4 Ultra Low Input polyA selection kit. Samples were sequenced on a HiSeq 4000, single end, 75bp. Mapping to human reference genome GRCh38.7 was performed with STAR 2.5.2b (https://github.com/alexdobin/STAR). For annotation and quantification of mapping results we used cufflinks, cuffquant and cuffnorm in version 2.2.1 (https://cole-trapnell-lab.github.io/cufflinks/). After mapping and quantification, PCA and Hierarchical Clustering was used to identify outliers and reiterated until no more outliers could be identified.

**eQTL analysis.** Analysis was performed with Robust Multi-array Average quantile normalization28 after removing probes overlapping with variants identified by WGS. Batch effects between platforms were corrected using ComBat29 and unknown batch effects were also adjusted using singular value decomposition with first four eigenvectors. eQTL mapping was performed using EPACTS (https://genome.sph.umich.edu/wiki/EPACTS) software tool using linear mixed model accounting for hidden familial relatedness, after inverse Gaussian transformation of expression levels, adjusting for age and sex.

**Mouse kidney single cell RNA-sequencing.** Animal studies were approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania. We mated Cdh16Cre mice (Jackson Lab, 012237), Nphs2Cre mice (Jackson Lab, 008205) and SclCre mice (MGI number is 3579158) with Tomato-GFP (mT/mG) mice (Jackson Lab, 007576) to generate Cdh16Cre:mT/mG, SclCre:mT/mG and Nphs2cre:mT/mG mice30.

**Mouse kidney single cell RNA-sequencing:** Kidneys were harvested from 4 to 8-week-old male mice with C57BL/6 background and dissociated into single cell suspension as described in our previous study31. The single cell sequencing libraries were sequenced on an Illumina HiSeq with 2x150 paired-end kit. The sequencing reads were demultiplexed, aligned to the mouse.
genome (mm10) and processed to generate gene-cell data matrix using Cell Ranger 1.3 (http://10xgenomics.com)\textsuperscript{31}.

To calculate the average expression level for each cluster, a z-score of normalized expression value was first obtained for every single cell. Then, we calculated the mean z-scores for individual cells in the same cluster, resulting in 16 values for each gene.

**Genomic features of human kidney.** Human kidney-specific chromatin immunoprecipitation followed by sequencing (ChIP-seq) data can be found at GEO: GSM621634, GSM670025, GSM621648, GSM772811, GSM621651, GSM1112806, GSM621638. Different histone markers were combined into chromatin states using ChromHMM\textsuperscript{32}.

**Gene and gene set analysis.** PASCAL gene and pathway scores were conducted on all 20 sets of GWAS summary statistics (10 outcomes and 2 covariate models). Gene scores were derived using the sum option, averaging association signal across each gene using the default 50kb window size. Pathway scores were then computed from pathway member gene scores where membership was defined using default pathway libraries from BioCarta, REACTOME, and KEGG. Using a similar approach, MAGMA (v1.06) gene and pathway scores were conducted on all GWAS summary statistics using both the default gene region defined by the transcription start and stop sites and a 5kb window definition. MAGMA pathway analysis included all 1077 of the PASCAL reported libraries plus an additional 252 pathways included in MSigDB canonical pathway set. MAGENTA (vs2, July 2011) pathway analysis included 4725 pathways with a minimum of five genes within the gene set. Gene sets were obtained with the MAGENTA distribution and included Gene ontology terms, PANTHER sets (biological processes, molecular functions, metabolic and signaling pathways), KEGG pathways, and
Ingenuity pathways. DEPICT gene set enrichment uses a more comprehensive collection of gene sets that allows genes to have a continuous probability for gene set membership. We conducted DEPICT individually on all 20 sets of GWAS summary statistics with $P < 1.0 \times 10^{-5}$. We conducted two additional pooled analyses using genome-wide minimum $P$-values from: 1) All 20 analyses (10 phenotypes and 2 covariate models) and 2) Sixteen analyses of the 8 most related phenotypes (8 phenotypes and 2 covariate models) which excluded ESRD vs Macro and Micro.

**Data and Software Availability**

All cohorts can share genome-wide meta-analysis summary statistics. Individual level genotype data: due to restrictions set by study consents and by EU and national regulations, individual genotype data cannot be shared for all cohorts.
**Table S1. Cohorts contributing to analyses.**

This table can be found in a separate excel sheet, Supplemental_table_S1.xlsx

**Table S2. Characteristics of RASS participants.** Categorical variables display counts and percentage. Continuous values are mean ± standard deviation.

<table>
<thead>
<tr>
<th>Variables (Total N = 253)</th>
<th>Freq(%)/Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex - Female</td>
<td>134 (53%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30 ± 10</td>
</tr>
<tr>
<td>T1D duration (years)</td>
<td>11 ± 5</td>
</tr>
<tr>
<td>Within-person mean HbA1c (%) (mmol/mol)</td>
<td>8.6 ± 1.4 70 ± 15</td>
</tr>
<tr>
<td>Mean GBMW (nm)</td>
<td>480 ± 88</td>
</tr>
<tr>
<td>rs55703767 – GG</td>
<td>163 (64%)</td>
</tr>
<tr>
<td>GT</td>
<td>80 (32%)</td>
</tr>
<tr>
<td>TT</td>
<td>10 (4%)</td>
</tr>
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Table S3. Multivariate analysis of association between rs55703767 and GBM width

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted model</th>
<th>Fully adjusted model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effect (SE)</td>
<td>P</td>
</tr>
<tr>
<td>rs55703767 (T allele)</td>
<td>-22.8 (8.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Females (vs males)</td>
<td>-48.4 (9.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age at baseline (yrs)</td>
<td>-2.4 (0.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diabetes duration (yrs)</td>
<td>3.8 (1.0)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Mean HbA1c (%)</td>
<td>27.2 (3.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
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</tr>
<tr>
<td>Minnesota</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Fully adjusted model also included 3 principal components for population structure within Europeans.
† SNP genotypes modelled as additive genetic effects.
Table S4: Look-up of the lead loci in GWAS on eGFR in the general population (Gorski et al., 2017)\textsuperscript{33}

<table>
<thead>
<tr>
<th>Nearest Gene</th>
<th>SNP</th>
<th>Meta-analysis results</th>
<th>GWAS on eGFR (Gorski 2017)</th>
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<tr>
<td></td>
<td></td>
<td>EA</td>
<td>NEA</td>
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<tr>
<td>COL4A3</td>
<td>rs55703767</td>
<td>T</td>
<td>G</td>
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<td>COL4A3</td>
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<td>C</td>
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<td>COLEC11</td>
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<td>LINC01266</td>
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<td>A</td>
<td>T</td>
</tr>
<tr>
<td>SNCAIP</td>
<td>rs149641852</td>
<td>T</td>
<td>G</td>
</tr>
<tr>
<td>PAPLN</td>
<td>rs113554206</td>
<td>A</td>
<td>G</td>
</tr>
<tr>
<td>STAC</td>
<td>rs116216059</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>HAN2-AS1</td>
<td>rs145681168</td>
<td>A</td>
<td>G</td>
</tr>
<tr>
<td>TAMM41</td>
<td>rs142823282</td>
<td>A</td>
<td>G</td>
</tr>
<tr>
<td>VARS2</td>
<td>rs118124843</td>
<td>T</td>
<td>C</td>
</tr>
<tr>
<td>MUC7</td>
<td>rs191449639</td>
<td>A</td>
<td>T</td>
</tr>
<tr>
<td>MBLC1</td>
<td>rs77273076</td>
<td>T</td>
<td>C</td>
</tr>
<tr>
<td>BMP7</td>
<td>rs144434404</td>
<td>T</td>
<td>C</td>
</tr>
<tr>
<td>PLEKHA7</td>
<td>rs183937294</td>
<td>T</td>
<td>G</td>
</tr>
<tr>
<td></td>
<td>rs185299109</td>
<td>T</td>
<td>C</td>
</tr>
</tbody>
</table>

EA: Effect allele. Positive odds ratio indicates that EA is associated with higher risk; positive beta indicates that EA is associated with higher eGFR, i.e. lower renal risk.
Table S5: Look-up of the lead loci in GWAS in the SUMMIT consortium (van Zuydam et al., 2018).23

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr:pos</th>
<th>EA</th>
<th>NEA</th>
<th>EAF</th>
<th>Notable gene(s)</th>
<th>Phenotype</th>
<th>N</th>
<th>OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs55703767</td>
<td>2:228121101</td>
<td>T</td>
<td>G</td>
<td>0.211</td>
<td>COL4A3</td>
<td>DN</td>
<td>5190</td>
<td>0.911</td>
<td>0.08</td>
</tr>
<tr>
<td>rs145681168</td>
<td>4:174500806</td>
<td>G</td>
<td>A</td>
<td>0.017</td>
<td>HAND2-AS1</td>
<td>Micro</td>
<td>3477</td>
<td>1.034</td>
<td>0.97</td>
</tr>
<tr>
<td>rs149641852</td>
<td>5:121774582</td>
<td>T</td>
<td>G</td>
<td>0.018</td>
<td>SNCAIP</td>
<td>CKD</td>
<td>4676</td>
<td>1.032</td>
<td>0.30</td>
</tr>
<tr>
<td>rs118124843</td>
<td>6:30887465</td>
<td>T</td>
<td>C</td>
<td>0.018</td>
<td>DDR1, VARS2</td>
<td>Micro</td>
<td>2439</td>
<td>1.137</td>
<td>0.63</td>
</tr>
<tr>
<td>rs77273076</td>
<td>7:99728546</td>
<td>T</td>
<td>C</td>
<td>0.014</td>
<td>MBLAC1</td>
<td>Micro</td>
<td>3252</td>
<td>0.866</td>
<td>0.48</td>
</tr>
<tr>
<td>rs61983410</td>
<td>14:26004712</td>
<td>T</td>
<td>C</td>
<td>0.184</td>
<td>STXB6</td>
<td>Micro</td>
<td>3760</td>
<td>0.990</td>
<td>0.58</td>
</tr>
<tr>
<td>rs144434404</td>
<td>20:55837263</td>
<td>T</td>
<td>C</td>
<td>0.011</td>
<td>BMP7</td>
<td>Micro</td>
<td>2439</td>
<td>1.100</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Chr, chromosome; pos, position; EA: Effect allele; EAF, effect allele frequency; OR, odds ratio.
### Table S6: Association at lead loci stratified by HbA1c <7.5%.

<table>
<thead>
<tr>
<th>Locus</th>
<th>SNP</th>
<th>Pheno</th>
<th>EA</th>
<th>NEA</th>
<th>ALL</th>
<th>HbA1c &lt; 7.5%</th>
<th>HbA1c &gt;= 7.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N (MAF)</td>
<td>P</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N (case/ctrl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>COL4A3</strong></td>
<td>rs55703767</td>
<td>MACROESRD</td>
<td>G</td>
<td>T</td>
<td>3611 0.19 2.16E-03 1.00</td>
<td>1165 (499/666)</td>
<td>0.659</td>
</tr>
<tr>
<td><strong>COL4A3</strong></td>
<td>rs55703767</td>
<td>MACRO</td>
<td>G</td>
<td>T</td>
<td>2803 0.19 0.06 1.00</td>
<td>837 (164/673)</td>
<td>0.663</td>
</tr>
<tr>
<td><strong>COL4A3</strong></td>
<td>rs55703767</td>
<td>ALLvCTRL</td>
<td>G</td>
<td>T</td>
<td>4271 0.19 7.04E-03 1.00</td>
<td>1344 (692/652)</td>
<td>0.870</td>
</tr>
<tr>
<td><strong>COL4A3</strong></td>
<td>rs55703767</td>
<td>CKDDN</td>
<td>G</td>
<td>T</td>
<td>3059 0.19 1.17E-02 1.00</td>
<td>984 (379/605)</td>
<td>0.973</td>
</tr>
<tr>
<td><strong>PRNCR1</strong></td>
<td>rs551191707</td>
<td>ESRdMACRO</td>
<td>C</td>
<td>A</td>
<td>1371 0.14 2.50E-03 0.81</td>
<td>498 (340/158)</td>
<td>1.92E-02</td>
</tr>
<tr>
<td><strong>STXB6</strong></td>
<td>rs61983410</td>
<td>MICRO</td>
<td>T</td>
<td>C</td>
<td>2976 0.23 3.75E-03 0.93</td>
<td>863 (195/668)</td>
<td>1.34E-02</td>
</tr>
<tr>
<td><strong>COLEC11</strong></td>
<td>rs12615970</td>
<td>CKD</td>
<td>A</td>
<td>G</td>
<td>4264 0.14 3.13E-03 0.82</td>
<td>1432 (531/901)</td>
<td>0.086</td>
</tr>
<tr>
<td><strong>LINC01266</strong></td>
<td>rs115061173</td>
<td>ESRD</td>
<td>T</td>
<td>A</td>
<td>3119 0.00 1.89E-02 0.36</td>
<td>1012 (340/672)</td>
<td>0.284</td>
</tr>
<tr>
<td><strong>SNCAIP</strong></td>
<td>rs149641852</td>
<td>CKDEXTREMES</td>
<td>G</td>
<td>T</td>
<td>3907 0.01 3.04E-03 0.33</td>
<td>1323 (415/908)</td>
<td>0.559</td>
</tr>
<tr>
<td><strong>PAPLN</strong></td>
<td>rs113554206</td>
<td>MACRO</td>
<td>G</td>
<td>A</td>
<td>2803 0.00 0.32 0.34</td>
<td>837 (164/673)</td>
<td>0.793</td>
</tr>
<tr>
<td><strong>STAC</strong></td>
<td>rs116216059</td>
<td>ESRdALL</td>
<td>C</td>
<td>A</td>
<td>4272 0.01 0.48 0.67</td>
<td>1340 (340/1000)</td>
<td>0.867</td>
</tr>
<tr>
<td><strong>HAND2-AS1</strong></td>
<td>rs145681168</td>
<td>MICRO</td>
<td>A</td>
<td>G</td>
<td>2976 0.01 0.50 0.48</td>
<td>863 (195/668)</td>
<td>0.509</td>
</tr>
<tr>
<td><strong>TAMM41</strong></td>
<td>rs142823282</td>
<td>MICRO</td>
<td>A</td>
<td>G</td>
<td>2976 0.00 0.93 0.15</td>
<td>863 (195/668)</td>
<td>0.533</td>
</tr>
<tr>
<td><strong>VARS2</strong></td>
<td>rs118124843</td>
<td>MICRO</td>
<td>C</td>
<td>T</td>
<td>2976 0.01 0.93 1.00</td>
<td>863 (195/668)</td>
<td>0.533</td>
</tr>
<tr>
<td><strong>MUC7</strong></td>
<td>rs191449639</td>
<td>MACROESRD</td>
<td>T</td>
<td>A</td>
<td>3611 0.00 0.09 0.28</td>
<td>1165 (499/666)</td>
<td>0.487</td>
</tr>
<tr>
<td><strong>MBLAC1</strong></td>
<td>rs77273076</td>
<td>MICRO</td>
<td>C</td>
<td>T</td>
<td>2976 0.01 1.36E-04 0.37</td>
<td>863 (195/668)</td>
<td>3.98E-03</td>
</tr>
<tr>
<td><strong>BMP7</strong></td>
<td>rs144434404</td>
<td>MICRO</td>
<td>C</td>
<td>T</td>
<td>2976 0.01 0.57 0.67</td>
<td>863 (195/668)</td>
<td>0.407</td>
</tr>
<tr>
<td><strong>PLEKHA7</strong></td>
<td>rs183937294</td>
<td>MICRO</td>
<td>T</td>
<td>G</td>
<td>2976 0.00 0.22 0.26</td>
<td>863 (195/668)</td>
<td>0.407</td>
</tr>
<tr>
<td><strong>18p11.32</strong></td>
<td>rs185299109</td>
<td>CKD</td>
<td>C</td>
<td>T</td>
<td>4264 0.00 0.68 0.32</td>
<td>1432 (531/901)</td>
<td>0.147</td>
</tr>
</tbody>
</table>

Association stratified by HbA1c in the FinnDiane study. P-values <0.05 are given with scientific notation and bold. Lines with gray text had minor allele count (MAC)<10 in cases and/or controls and did not contribute to the meta-analysis.
### Table S7. Association of rs55703767 with DN in DCCT/EDIC subgroups.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Treatment Group</th>
<th>DN %</th>
<th>MAF</th>
<th>Last measure</th>
<th>Time to Event</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR (95%CI)</td>
<td>P value</td>
<td>HR (95%CI)</td>
</tr>
<tr>
<td>Primary Prevention (diabetes dur 1-5 yrs)</td>
<td>Intensive</td>
<td>3%</td>
<td>0.22</td>
<td>2.86 (0.4-22)</td>
<td>0.32</td>
<td>0.91 (0.2-4.0)</td>
</tr>
<tr>
<td></td>
<td>Conventional</td>
<td>10%</td>
<td>0.21</td>
<td>0.67 (0.3-1.4)</td>
<td>0.31</td>
<td>0.66 (0.32-1.33)</td>
</tr>
<tr>
<td>Secondary Intervention (diabetes dur 1-15 yrs)</td>
<td>Intensive</td>
<td>5%</td>
<td>0.20</td>
<td>0.86 (0.3-2.6)</td>
<td>0.79</td>
<td>0.65 (0.22-1.9)</td>
</tr>
<tr>
<td></td>
<td>Conventional</td>
<td>13%</td>
<td>0.22</td>
<td>0.18 (0.1-0.5)</td>
<td>0.003</td>
<td>0.30 (0.13-0.68)</td>
</tr>
</tbody>
</table>

OR=Odds Ratio for last measure, HR=Hazard Ratio for time to event phenotype.
Table S8. Significant ($P<0.05/18,222$ genes tested = $2.74 \times 10^{-6}$) gene level associations with diabetic kidney disease in MAGMA.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype</th>
<th>Model</th>
<th>Window</th>
<th>Number of SNPs</th>
<th>Total Sample Size</th>
<th>MAGMA P-value</th>
<th>PASCAL P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC46A2</td>
<td>All vs. ctrl</td>
<td>Min</td>
<td>nowindow</td>
<td>66</td>
<td>17817</td>
<td>$6.74 \times 10^{-7}$</td>
<td>$1.57 \times 10^{-5}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skbwindow</td>
<td>93</td>
<td>17832</td>
<td>$7.38 \times 10^{-7}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Full</td>
<td>64</td>
<td>16821</td>
<td>$8.13 \times 10^{-7}$</td>
<td>$6.93 \times 10^{-5}$</td>
</tr>
<tr>
<td>SFXN4</td>
<td>Macro</td>
<td>Full</td>
<td>nowindow</td>
<td>69</td>
<td>11953</td>
<td>$3.98 \times 10^{-7}$</td>
<td>$1.45 \times 10^{-4}$</td>
</tr>
<tr>
<td>COL20A1</td>
<td>Ckdextreme</td>
<td>Min</td>
<td>nowindow</td>
<td>111</td>
<td>11165</td>
<td>$2.47 \times 10^{-6}$</td>
<td>$7.88 \times 10^{-5}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skbwindow</td>
<td>137</td>
<td>11603</td>
<td>$2.01 \times 10^{-6}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Full</td>
<td>110</td>
<td>8533</td>
<td>$6.65 \times 10^{-7}$</td>
<td>$4.47 \times 10^{-5}$</td>
</tr>
<tr>
<td>ESRD vs. All</td>
<td>Min</td>
<td>nowindow</td>
<td>111</td>
<td>12063</td>
<td>$1.34 \times 10^{-6}$</td>
<td>$3.76 \times 10^{-5}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skbwindow</td>
<td>137</td>
<td>12362</td>
<td>$1.04 \times 10^{-6}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Full</td>
<td>110</td>
<td>8638</td>
<td>$1.12 \times 10^{-6}$</td>
<td>$5.81 \times 10^{-5}$</td>
</tr>
<tr>
<td>GLT6D1</td>
<td>ESRD vs. Macro</td>
<td>min</td>
<td>Skbwindow</td>
<td>96</td>
<td>4248</td>
<td>$1.49 \times 10^{-6}$</td>
<td>$2.15 \times 10^{-5}$</td>
</tr>
<tr>
<td>SNX30</td>
<td>All vs. ctrl</td>
<td>min</td>
<td>Skbwindow</td>
<td>434</td>
<td>18249</td>
<td>$2.49 \times 10^{-6}$</td>
<td>$1.05 \times 10^{-5}$</td>
</tr>
</tbody>
</table>

Table S9. Top nominally significant gene level associations ($P<1.0 \times 10^{-5}$) with diabetic kidney disease in PASCAL.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype</th>
<th>Model</th>
<th>Number of SNPs</th>
<th>PASCAL P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INIP</td>
<td>All vs. ctrl</td>
<td>Min</td>
<td>248</td>
<td>$1.99 \times 10^{-6}$</td>
</tr>
<tr>
<td></td>
<td>Full</td>
<td></td>
<td>248</td>
<td>$5.54 \times 10^{-6}$</td>
</tr>
<tr>
<td>LCN9</td>
<td>ESRD vs. macro</td>
<td>Min</td>
<td>301</td>
<td>$5.25 \times 10^{-6}$</td>
</tr>
<tr>
<td>CBX8</td>
<td>DN</td>
<td>Min</td>
<td>119</td>
<td>$8.47 \times 10^{-6}$</td>
</tr>
</tbody>
</table>
**Table S10: Significant gene set and pathway analysis results.** Significantly enriched gene sets identified from at least one of the following methods: MAGENTA (FDR < 0.05, MAGMA (P<0.05 empirical permutation multiple testing correction), PASCAL (P<0.05/1,078 gene sets tested = 4.64 × 10^{-5}), and DEPICT (FDR < 0.01).

<table>
<thead>
<tr>
<th>Gene set</th>
<th>Gene set database</th>
<th>Phenotype</th>
<th>Model</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative regulators of RIG I MDA5 signaling</td>
<td>REACTOME</td>
<td>ESRD vs. Macro</td>
<td>Full</td>
<td>MAGMA</td>
</tr>
<tr>
<td>Platelet aggregation plug formation</td>
<td>REACTOME</td>
<td>Micro</td>
<td>Min</td>
<td>MAGMA</td>
</tr>
<tr>
<td>negative regulators of RIG I MDA5 signaling</td>
<td>REACTOME</td>
<td>ESRD vs. Macro</td>
<td>Full</td>
<td>PASCAL</td>
</tr>
<tr>
<td>RIG I MDA5 mediated induction of IFN alpha beta pathways</td>
<td>REACTOME</td>
<td>ESRD vs. Macro</td>
<td>Full</td>
<td>PASCAL</td>
</tr>
<tr>
<td>TRAF3 dependent IRF activation pathway</td>
<td>REACTOME</td>
<td>ESRD vs. Macro</td>
<td>Full</td>
<td>PASCAL</td>
</tr>
<tr>
<td>TRAF6 mediated IRF activation</td>
<td>REACTOME</td>
<td>ESRD vs. Macro</td>
<td>Full</td>
<td>PASCAL</td>
</tr>
<tr>
<td>Nitric Oxide Signaling in the Cardiovascular System</td>
<td>Ingenuity</td>
<td>ESRD vs. ctrl</td>
<td>Min</td>
<td>MAGENTA</td>
</tr>
<tr>
<td>Nicotinic acetylcholine receptor signaling pathway</td>
<td>Panther</td>
<td>ESRD vs. non-ESRD</td>
<td>Min</td>
<td>MAGENTA</td>
</tr>
<tr>
<td>ACTIVATED TLR4 SIGNALLING</td>
<td>REACTOME</td>
<td>All vs. ctrl</td>
<td>Min</td>
<td>MAGENTA</td>
</tr>
<tr>
<td>Other lipid, fatty acid and steroid metabolism</td>
<td>PANTHER BIOLOGICAL PROCESS</td>
<td>CKD</td>
<td>Min</td>
<td>MAGENTA</td>
</tr>
<tr>
<td>DNA degradation</td>
<td>PANTHER BIOLOGICAL PROCESS</td>
<td>CKD</td>
<td>Min</td>
<td>MAGENTA</td>
</tr>
<tr>
<td>Tumor necrosis factor family member</td>
<td>PANTHER MOLECULAR FUNCTION</td>
<td>CKD-extreme</td>
<td>Min</td>
<td>MAGENTA</td>
</tr>
<tr>
<td>TUFM (Tu Translation Elongation Factor, Mitochondrial) PPI subnetwork</td>
<td>InWeb protein-protein interaction database</td>
<td>DN</td>
<td>Min</td>
<td>DEPICT</td>
</tr>
</tbody>
</table>
Table S11. eQTL associations and chromatin conformation interactions for the lead SNPs.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr:pos</th>
<th>EA</th>
<th>NEA</th>
<th>EAF</th>
<th>Notable gene(s)</th>
<th>eQTL</th>
<th>PC-HiC</th>
<th>Gene</th>
<th>Score (Tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs12615970</td>
<td>2:3745215</td>
<td>G</td>
<td>A</td>
<td>0.133</td>
<td>COLEC11 (B); ALLC (G)</td>
<td></td>
<td></td>
<td>ALLC</td>
<td>10.42 (GM12878);</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MFF 5.63×10⁻³⁶ T blood</td>
<td></td>
<td>COLEC11, AC010907.2</td>
<td>9.67 (GM12878);</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MFF 9.0×10⁻⁸ T Cells - Transformed fibroblasts</td>
<td></td>
<td>ADI1, AC142528.1</td>
<td>8.75 (GM12878);</td>
</tr>
<tr>
<td></td>
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**Notable genes:**
- **DNAL1, RNU6-240P**
  - 11.07 (GM12878);
- **PSEN1**
  - 10.96 (Endothelial precursors);
  - 10.96 (Endothelial precursors);
  - 10.56 (CD34);
- **PNMA1**
  - 10.9 (GM12878);
- **RP3-414A15.2**
  - 10.64 (GM12878);
  - 10.64 (GM12878);
  - 7.24 (Monocytes);
  - 5.99 (Neutrophils);
- **ZFYVE1**
  - 10.53 (GM12878);
- **PTGR2, Y RNA, RP5-1021I20.4**
  - 10.42 (CD34);
  - 10.42 (CD34);
  - 10.16 (GM12878);
- **RP4-693M11.3**
  - 10.33 (GM12878);
- **RP4-687K1.2**
  - 9.96 (GM12878);
- **HEATR4, C14orf169, AC005280.1**
  - 9.52 (GM12878);
  - 9.52 (GM12878);
  - 5.35 (Pancreatic islets);
- **RBM25**
  - 9.34 (GM12878);
- **RP3-414A15.10**
  - 9.32 (GM12878);
- **ELMSAN1**
  - 9.12 (GM12878);
- **CCDC176**
  - 8.85 (GM12878);
- **RBM25, RP11-109N23.5**
  - 8.74 (GM12878);
- **ACOT6**
  - 8.74 (GM12878);
- **DNAL1**
  - 8.7 (GM12878);
- **FAM161B, RP5-1021I20.5**
  - 5.58 (Total CD8);
### Notable Genes: based on genetic findings (G), (B), (N), (M); eQTL associations were searched from GTEx and eQTLgen (cis-eQTL) data sets. HIGH A: allele associated with higher gene expression levels. Promoter Capture Hi-C (PChi-C) data: searched from www.chicp.org (date accessed: 1.12.2018; Schofield EC, Carver T, Achuthan P, Freire-Pritchett P, Spivakov M, Todd JA, Burren OS. CHiCP: a web-based tool for the integrative and interactive visualization of promoter capture Hi-C datasets. Bioinformatics. (2016) 15:32(16):2511-3), including 16 primary blood cell types and foetal thymocytes (Javierre et al.), CD34 and GM12878 cell line (Mifsud et al.), pancreatic isles (Miguel-Escalada et al.), and hESC derived cardiomyocytes (Choy et al.). Score: CHICAGO score, values >5 were considered significant and listed. Protein coding genes are highlighted with bold typing.

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Table S12: Transcriptome-wide association analysis (TWAS) results with p<1×10^{-4}

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Tissue: glomeruli (glomer) or tubuli (tub); Z-core, Effect and P-value: MetaXcan's association results for the gene. Var_G: variance of the gene expression, calculated as W' * G * W (where W is the vector of SNP weights in a gene's model, W is its transpose, and G is the covariance matrix). Prediction performance r2, P-value and Q-value: r2, p-value and q-value of tissue model's correlation to gene's measured transcriptome (prediction performance). N SNPs ... used: number of snps from GWAS that got used in MetaXcan analysis; ... in cov: number of snps in the covariance matrix; ... in model: number of snps in the model
Table S13: Pseudo-R2 of all SNPs across all GWAS as calculated by the McKelvey and Zavoina method. Total variance explained is the sum of pseudo-R2 across all SNPs with minor allele frequency (MAF) greater than 5% or 1%, noting that effect size and therefore variance explained tend to be overestimated with rare variants. Missing values indicate SNPs that did not pass our GWAS filters for those disease definitions as described in the methods section.

Minimally Adjusted Model

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<th>CKD-DN</th>
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Variance explained (MAF>5%): 0.75% 0.48% 0.89% 1.47% 1.49% 1.50% 1.26% 1.92% 0.73% 0.65%

Variance explained (MAF>1%): 2.46% 2.34% 2.17% 5.44% 10.26% 9.36% 9.53% 1.92% 2.68% 10.21%
### Fully Adjusted Model

<table>
<thead>
<tr>
<th>SNP</th>
<th>Minor allele frequency</th>
<th>DN</th>
<th>All vs. ctrl</th>
<th>CKD</th>
<th>CKD-DN</th>
<th>CKD extreme</th>
<th>ESRD vs. ctrl</th>
<th>ESRD vs. non-ESRD</th>
<th>ESRD vs. macro</th>
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<td>0.01%</td>
<td>0.04%</td>
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<td>0.02%</td>
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<td>0.22%</td>
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<td>variance explained (MAF&gt;1%)</td>
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<td>2.86%</td>
<td>2.30%</td>
<td>6.62%</td>
<td>3.23%</td>
<td>4.23%</td>
<td>2.63%</td>
<td>2.20%</td>
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Table S14. Physicians and nurses at health care centers participating in the collection of FinnDiane patients.

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<th>FinnDiane Study Centers</th>
<th>Physicians and nurses</th>
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<tbody>
<tr>
<td>Anjalankoski Health Centre</td>
<td>S. Koivula, T. Uggeldahl</td>
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<tr>
<td>FinnDiane Study Centers</td>
<td>Physicians and nurses</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Central Hospital of Åland Islands, Mariehamn</td>
<td>M. Forsen, H. Granlund, A-C. Jonsson, B. Nyroos</td>
</tr>
<tr>
<td>Central Hospital of Kanta-Häme, Hämeenlinna</td>
<td>P. Kinnunen, A. Orvola, T. Salonen, A. Vähänen</td>
</tr>
<tr>
<td>Central Hospital of Länsi-Pohja, Kemi</td>
<td>H. Laukkkanen, P. Nyländen, A. Sademies</td>
</tr>
<tr>
<td>Central Ostrabothnian Hospital District, Kokkola</td>
<td>S. Anderson, B. Asplund, U. Byskata, P. Liedes, M. Kuusela, T. Virkkala</td>
</tr>
<tr>
<td>City of Espoo Health Centre</td>
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<tr>
<td>Espoonlahti</td>
<td>A. Nikkola, E. Ritola</td>
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<tr>
<td>Tapiola</td>
<td>M. Niska, H. Saarinen</td>
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<tr>
<td>Samaria</td>
<td>E. Oukko-Ruponen, T. Virtanen</td>
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<tr>
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<td>A. Lyytinen</td>
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<tr>
<td>Puistola</td>
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<tr>
<td>Suutarila</td>
<td>A. Kaprio, J. Kärkkäinen, B. Rantaeskola</td>
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<tr>
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<td>P. Kääriäinen, J. Haaga, A-L. Pietiläinen</td>
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<tr>
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<td>A. Ahola, J. Fagerudd, M. Feodoroff, D. Gordin, O. Heikkilä, K Hietala, L. Kylönén, J. Kytö, S. Lindh, K. Pettersson-Fernholm, M. Rosengård-Bärlund, M. Rönnback, A. Sandelin, A-R Salonen, L. Salovaara, L. Thorn, J. Tuomikangas, T. Vesisenaho, J. Wadén</td>
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<td>E. Toivanen</td>
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<tr>
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<tr>
<td>-----------------------------------------</td>
<td>------------------------------------------------------------</td>
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<td>Mera Tilley</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theresa Tuthill</td>
<td>Imaging specialist</td>
<td></td>
</tr>
<tr>
<td>Ciara Vangjeli</td>
<td>Cardiovascular genetic epidemiologist, Pfizer Europe</td>
<td></td>
</tr>
<tr>
<td>Daniel Ziemek</td>
<td>Computational biologist</td>
<td></td>
</tr>
</tbody>
</table>
Figure S1. Manhattan and QQ Plots for each case-control definition and covariate model (minimal and full)

DN - minimal

$\lambda = 1.011$
DN - full

\[ \lambda = 1.009 \]
macro - min

$\lambda = 1.010$

Manhattan Plot - PHENO2_macro
macro - full

$\lambda = 1.012$
ESRD vs. ctrl- min

$\lambda = 1.025$
ESRD vs. ctrl - full  \( \lambda = 1.019 \)
ESRD vs. non-ESRD - \( \lambda = 1.032 \)
ESRD vs. non-ESRD -

\[ \lambda = 1.021 \]
ESRD vs. macro - full

\[ \lambda = 1.014 \]
All vs. ctrl - min

\[ \lambda = 1.019 \]
All vs. ctrl - full

\( \lambda = 1.013 \)
Micro - full

\[ \lambda = 1.010 \]
CKD - full

\[ \lambda = 1.017 \]
CKD extreme - min

$\lambda = 1.027$
CKD-DN - full

$\lambda = 1.017$
Figure S2. Regional chromosomal location plots and forest plots by cohort of newly discovered DKD associations
GWAS of DKD Supplement

rs12615970 – CKD min

<table>
<thead>
<tr>
<th>Cohort</th>
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<tbody>
<tr>
<td>CACTI</td>
<td>.126699</td>
<td>0.90 (0.40, 2.06)</td>
</tr>
<tr>
<td>EDC</td>
<td>.114606</td>
<td>0.61 (0.34, 1.10)</td>
</tr>
<tr>
<td>EDIC</td>
<td>.126419</td>
<td>0.89 (0.48, 1.66)</td>
</tr>
<tr>
<td>FD</td>
<td>.1387</td>
<td>0.80 (0.68, 0.93)</td>
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<td>France</td>
<td>.137077</td>
<td>0.83 (0.59, 1.17)</td>
</tr>
<tr>
<td>GWU_GOKIND</td>
<td>.132239</td>
<td>1.00 (0.61, 1.65)</td>
</tr>
<tr>
<td>Italy</td>
<td>.122767</td>
<td>0.84 (0.40, 1.77)</td>
</tr>
<tr>
<td>Joslin</td>
<td>.134103</td>
<td>0.67 (0.52, 0.88)</td>
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<tr>
<td>RomDiane</td>
<td>.127016</td>
<td>0.85 (0.38, 1.92)</td>
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<tr>
<td>Scotland</td>
<td>.11494</td>
<td>0.71 (0.54, 0.94)</td>
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<tr>
<td>Steno</td>
<td>.141644</td>
<td>0.64 (0.44, 0.93)</td>
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<tr>
<td>UK-ROI</td>
<td>.133887</td>
<td>0.83 (0.60, 1.14)</td>
</tr>
<tr>
<td>WESDR</td>
<td>.123773</td>
<td>0.67 (0.44, 1.04)</td>
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<tr>
<td>Overall</td>
<td>(I-squared = 0.0%, p = 0.942)</td>
<td>0.76 (0.69, 0.84)</td>
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rs115061173 – ESRD vs ctrl min

<table>
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<th>ES (95% CI)</th>
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<tbody>
<tr>
<td>FinnDiane</td>
<td>.004891</td>
<td>6.03 (1.46, 25.00)</td>
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<tr>
<td>France</td>
<td>.017945</td>
<td>17.39 (4.12, 73.42)</td>
</tr>
<tr>
<td>UK-ROI</td>
<td>.018004</td>
<td>6.04 (2.06, 31.37)</td>
</tr>
<tr>
<td>Overall</td>
<td>(I-squared = 0.0%, p = 0.570)</td>
<td>9.36 (4.15, 21.08)</td>
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</table>

chr2:3745215 – rs12615970 – COLEC11 – CKD min

chr3:926345 – rs115061173 – LINC01266 – ESRD vs ctrl min
GWAS of DKD Supplement

**chr2:228121101 – rs55703767 – COL4A3 – DN min**

**chr3:11910635 – rs142823282 – TAMM41 – Micro full**

**rs55703767 – DN min**

<table>
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<th>ES (95% CI)</th>
</tr>
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<td>EDC</td>
<td>.23</td>
<td>0.82 (0.55, 1.21)</td>
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<tr>
<td>EDIC</td>
<td>.21</td>
<td>0.63 (0.42, 0.92)</td>
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<tr>
<td>FD</td>
<td>.19</td>
<td>0.81 (0.71, 0.93)</td>
</tr>
<tr>
<td>FRANCE2 Marged</td>
<td>.22</td>
<td>0.77 (0.61, 0.98)</td>
</tr>
<tr>
<td>GWJ-GOKINOD</td>
<td>.22</td>
<td>0.94 (0.67, 1.31)</td>
</tr>
<tr>
<td>ITALY</td>
<td>.25</td>
<td>1.17 (0.78, 1.77)</td>
</tr>
<tr>
<td>JOSLIN</td>
<td>.2</td>
<td>0.73 (0.61, 0.87)</td>
</tr>
<tr>
<td>LATDIANE</td>
<td>.25</td>
<td>1.01 (0.67, 1.73)</td>
</tr>
<tr>
<td>LITDIANE</td>
<td>.24</td>
<td>1.73 (0.61, 4.99)</td>
</tr>
<tr>
<td>ROMDIANE</td>
<td>.22</td>
<td>0.81 (0.63, 1.05)</td>
</tr>
<tr>
<td>SCOTLAND</td>
<td>.21</td>
<td>0.76 (0.60, 0.97)</td>
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<tr>
<td>SINDROMO</td>
<td>.2</td>
<td>0.85 (0.59, 1.48)</td>
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<tr>
<td>UK-ROI</td>
<td>.19</td>
<td>0.70 (0.58, 0.86)</td>
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<td>WEDS</td>
<td>.24</td>
<td>0.83 (0.60, 1.13)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.79 (0.73, 0.84)</td>
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**rs142823282 – Micro full**

<table>
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<th>ES (95% CI)</th>
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<tbody>
<tr>
<td>Justin</td>
<td>.015969</td>
<td>1.40 (0.57, 3.46)</td>
</tr>
<tr>
<td>Scotland</td>
<td>.017362</td>
<td>24.97 (10.94, 56.99)</td>
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<tr>
<td>Overall (I-squared = 95.3%, p = 0.000)</td>
<td></td>
<td>6.74 (3.66, 12.38)</td>
</tr>
</tbody>
</table>

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GWAS of DKD Supplement

**chr4:71358776 – rs191449639 – MUC7 – DN min**

- **rs191449639**
- **Chr4:71358776 – 8776**
- **MUC7**
- **DN min**

**chr5:121774582 – rs149641852 – SNCAIP – CKD extreme min**

- **rs149641852**
- **Chr5:121774582 – 121774582**
- **SNCAIP**
- **CKD extreme min**

**rs191449639 – DN min**

<table>
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<th>ES (95% CI)</th>
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<tbody>
<tr>
<td>Fireworks</td>
<td>0.03102</td>
<td>2.57 (0.58, 11.31)</td>
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<tr>
<td>Scotland</td>
<td>0.07543</td>
<td>3989.23 (504.37, 29682.47)</td>
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<tr>
<td>Overall  (I-squared = 94.9%, p = 0.006)</td>
<td>32.42 (9.77, 107.58)</td>
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**rs149641852 – CKD extreme min**

<table>
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<tr>
<td>FD</td>
<td>0.008086</td>
<td>5.26 (1.77, 15.63)</td>
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<tr>
<td>France</td>
<td>0.015511</td>
<td>63.97 (11.33, 361.07)</td>
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<tr>
<td>UK-ROI</td>
<td>0.016152</td>
<td>6.29 (1.65, 23.97)</td>
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<td>Overall  (I-squared = 67.4%, p = 0.046)</td>
<td>9.01 (4.22, 19.25)</td>
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GWAS of DKD Supplement

chr7:99728546 – rs77273076 – MBLAC1 – Micro min

rs77273076 – Micro full

<table>
<thead>
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<th>Cohort</th>
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<th>ES (95% CI)</th>
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<tr>
<td>FinDiane</td>
<td>.05779</td>
<td>11.84 (3.12, 45.00)</td>
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<tr>
<td>Scotland</td>
<td>.00896</td>
<td>8.11 (3.23, 20.37)</td>
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<tr>
<td>Overall</td>
<td>(I-squared = 0.0%, p = 0.647)</td>
<td>9.16 (4.29, 19.56)</td>
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chr11:16937846 – rs183937294 – PLEKHA7 – Micro min

rs183937294 – Micro min

<table>
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<tbody>
<tr>
<td>Joslin</td>
<td>.006562</td>
<td>11.13 (2.39, 51.74)</td>
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<tr>
<td>Scotland</td>
<td>.008037</td>
<td>23.43 (6.45, 85.11)</td>
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<tr>
<td>Overall</td>
<td>(I-squared = 0.0%, p = 0.467)</td>
<td>17.22 (6.41, 46.26)</td>
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GWAS of DKD Supplement

**chr14:26004712 – rs61983410 – STXBP6 – Micro full**

![Plot showing SNPs and linkage disequilibrium](image1)

**chr18:1811108 – rs185299109 – 18p11 – CKD min**

![Plot showing SNPs and linkage disequilibrium](image2)

**rs61983410 – Micro full**

<table>
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<td>0.64 (0.37, 1.11)</td>
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<td>EDC</td>
<td>20.5985</td>
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<tr>
<td>EDIC</td>
<td>21.6586</td>
<td>0.84 (0.63, 1.12)</td>
</tr>
<tr>
<td>FD</td>
<td>22.3647</td>
<td>0.77 (0.66, 0.91)</td>
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<tr>
<td>France</td>
<td>22.7868</td>
<td>1.08 (0.74, 1.56)</td>
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<tr>
<td>Joslin</td>
<td>21.0581</td>
<td>0.65 (0.53, 0.81)</td>
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<tr>
<td>LatDiane</td>
<td>24.8255</td>
<td>0.40 (0.16, 0.99)</td>
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<td>LiDiane</td>
<td>27.5833</td>
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<td>24.2876</td>
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<td>Scotland</td>
<td>16.7599</td>
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<td>21.7363</td>
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<td>21.9411</td>
<td>1.04 (0.49, 2.23)</td>
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<td>Overall</td>
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<td>0.78 (0.71, 0.85)</td>
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**rs185299109 – CKD full**

<table>
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<tbody>
<tr>
<td>Joslin</td>
<td>0.08203</td>
<td>6.68 (1.65, 27.07)</td>
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<tr>
<td>Scotland</td>
<td>0.05833</td>
<td>86.71 (18.01, 417.98)</td>
</tr>
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<td>Overall</td>
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<td>20.75 (7.30, 58.99)</td>
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rs113554206 – Macro full

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<td>France</td>
<td>.015411</td>
<td>9.42 (2.81, 31.58)</td>
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<td>Joslin</td>
<td>.010394</td>
<td>11.27 (3.90, 32.57)</td>
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<td>Overall</td>
<td>(I-squared = 0.0%, p = 0.826)</td>
<td>10.42 (4.69, 23.15)</td>
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rs144434404 – Micro min

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<td>Joslin</td>
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<td>6.29 (1.69, 23.37)</td>
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<tr>
<td>Scotland</td>
<td>.012241</td>
<td>6.94 (3.38, 14.24)</td>
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<tr>
<td>Overall</td>
<td>(I-squared = 0.0%, p = 0.897)</td>
<td>6.78 (3.61, 12.74)</td>
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Figure S3. Correlation of expression of \textit{COL4A3} with degree of fibrosis and eGFR in microdissected kidney samples.
Figure S4. Genotype – phenotype associations at the lead loci when stratified by mean HbA$_1c$ <7.5% in the FinnDiane study. Only loci with a minor allele count ≥10 in each stratum are shown.
Figure S5. Genotype – phenotype associations at the lead rs55703767 (COL4A3) locus when stratified by mean HbA1c <7.5% in up to 3226 individuals with type 2 diabetes (T2D) from the GoDARTS.

For All vs. ctrl phenotype, 1632 individuals (848 cases, 784 controls) had HbA1c<7.5%, and 1572 individuals (874 cases, 698 controls) had HbA1c>=7.5%.

<table>
<thead>
<tr>
<th>Pheno</th>
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<th>P HbA1c&lt;7.5</th>
<th>P HbA1c&gt;7.5</th>
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<tr>
<td>All vs. ctrl</td>
<td>0.003</td>
<td>0.02</td>
<td>0.07</td>
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<tr>
<td>DN</td>
<td>0.028</td>
<td>0.03</td>
<td>0.26</td>
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<tr>
<td>Macro vs. ctrl</td>
<td>0.058</td>
<td>0.01</td>
<td>0.55</td>
</tr>
<tr>
<td>CKD-DN</td>
<td>0.851</td>
<td>0.57</td>
<td>0.77</td>
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</table>

0.90  0.95  1.0  1.05
OR (95% CI)
Figure S6. Fishplots comparing significance and directionality between minimal and fully adjusted models for each of the 10 phenotype definitions. Fishplots comparing the significance and directionality between the minimal and fully adjusted models for each of the 10 phenotype definitions. P-values are signed according to consistency in the direction of effect between the two GWAS under comparison, such that the $-\log(P)$ of SNPs with effect sizes in the same direction are plotted on quadrant 1 (the head and body of the fish), and the $-\log(P)$ of SNPs with effect sizes in opposite directions are plotted in quadrant 3 (the tail of the fish).
Figure S7: Association at previously reported loci (p<5×10^{-8}) for renal complications in individuals with diabetes. AFF3 and RGMA-MCTP2 were originally reported for ESRD (T1D) (Sandholm et al., 2012); CDCA7/SP3 for ESRD in women (T1D) (Sandholm et al., 2013); ERBB4 for DN (T1D) (Sandholm et al., 2012); GABRR1 for microalbuminuria (T2D)(Van Zuydam et al., 2018); GLRA3 for albuminuria (T1D) (Sandholm et al., 2014); PRKAG2 and UMOD for eGFR (Pattaro et al., 2016; Van Zuydam et al., 2018); and SCAF8/CNKSR3 for DN (T2D) (Iyengar et al., 2015).
Figure S8: Forest plots of the associations at the previously reported lead loci from the GENIE consortium with largely overlapping studies. A: \textit{RGMA-MCTP2} rs12437854. B: \textit{AFF3} rs7583877. C: \textit{ERBB4} rs7588550. Meta-analysis results for \textit{RGMA-MCTP2}:

Previous $P = 2.0 \times 10^{-9}$, OR = 1.80 (95% confidence interval 1.48, 2.17), Current $P = 7.4 \times 10^{-4}$, OR = 1.31 (1.12, 1.54); Meta-analysis results for \textit{AFF3}:

Previous $p = 1.20 \times 10^{-8}$, OR = 1.29 (1.18, 1.40), Current $p = 5.97 \times 10^{-4}$, OR = 1.15 (1.06, 1.24). Meta-analysis results for \textit{ERBB4}:

Previous $P = 2.1 \times 10^{-7}$, OR = 0.66 (0.56, 0.77), Current $P = 3.5 \times 10^{-5}$, OR = 0.76 (0.67, 0.87).
Figure S9: Meta-analysis results for the loci that have previously been associated with DKD, or with eGFR or AER in the general population. Figure shows OR [95% CI] for the 25 loci with \( p < 0.05 \) for at least one sub-phenotype; associations with \( p < 0.05 \) are indicated with black confidence intervals. Results are plotted so that odds ratio (OR) > 1 indicates association in the same direction with the original report (for eGFR, this means that the allele associated with higher risk of DN is associated with lower eGFR). A total of 69 loci were evaluated, including loci for DKD (5 loci: AFF3, RGMA-MCTP2, ERBB4 (Sandholm 2012), CDCA7/SP3 (Sandholm2014), SCAF8/CNKSR3 (Iyengar 2015)), for albuminuria in individuals with diabetes (GLRA3 (Sandholm 2013), 3 suggestive loci CUBN, HST6ST1 and RAB38 (Teumer 2016)), for eGFR in individuals with diabetes (UMOD, Pattaro et al. 2016 and Van Zuydam et al. 2018, PRKAG2 Van Zuydam et al. 2018) or without diabetes (61 loci, Gorski 2017). Associations at AFF3, RGMA-MCTP2, ERBB4, SCAF8/CNKSR3, and UMOD remained significant after correction for 69 tested loci \( (p < 7 \times 10^{-4}) \).
Figure S10. Expression of quantitative trait loci (eQTL) analysis in microdissected tubule samples. Boxplots showing normalized gene expression by stratified by homozygous common (red), heterozygous (green), and homozygous rare (blue) genotype. We identified nominal associations for rs55703767 in tubule samples with IRS1 (a) and in glomerular samples with RP11-395N3.2 and AGFG1 (b). We also found nominal associations of rs61983410 with the gene encoding Cathepsin G, CTSG, in both eQTL analysis of whole kidney samples (c) and microdissected tubule samples (d).
Figure S11. Functional annotation of *TAMM41*. ChIP-seq data derived from healthy adult human kidney samples (Bernstein et al., 2010) shows that variants associated with microalbuminuria are located close to H3K27ac, H3K9ac, H3K4me1, and H3K4me3 signals, suggesting that this locus is an active regulator of *TAMM41*. 
Supplemental Methods: Cohort descriptions

**CACTI:** The Coronary Artery Calcification in Type 1 Diabetes (CACTI) study enrolled 656 subjects with diabetes diagnosed before age 30 years, treated with insulin within 1 year of diagnosis, and diabetes duration of at least 10 years on enrollment.¹

**DCCT/EDIC:** The Diabetes Control and Complications Trial (DCCT) was a multi-center randomized clinical trial to compare intensive and conventional insulin therapy on the development and progression of early vascular and neurological complications of type 1 diabetes (T1D). Renal outcomes were defined as time in years from DCCT baseline until the event. AERs were measured annually in DCCT and every other year in the post-study Epidemiology of Diabetes Interventions and Complications (EDIC) cohort. Persistent microalbuminuria was defined as the time to two consecutive AER >30 mg/24 hours (>20.8 μg/min); severe nephropathy was the time to AER >300 mg/24 hours (>208 μg/min) with prior persistent microalbuminuria, or ESRD. 22% developed persistent microalbuminuria during follow-up (268 events, 976 censored), while 10% developed severe nephropathy (132 events, 1,172 censored).² ³⁵

**EDC:** The Pittsburgh Epidemiology of Diabetes Complications (EDC) is a historical cohort study based on incident cases of childhood onset (prior to age 17 years) T1D, diagnosed or seen within one year of diagnosis (1950-80) at Children’s Hospital of Pittsburgh.⁴ The cohort, which has been shown to be epidemiologically representative of the Allegheny County, Pennsylvania, T1D population, ³⁶ was first assessed for the EDC study between 1986 and 1988 (mean participant age and diabetes duration were 28 and 19 years, respectively). Subsequently, biennial examinations were conducted for 10 years, with a further detailed examination at 18 and 25 years from enrollment. All EDC study participants provided informed consent, and all study procedures were approved by the University of Pittsburgh Institutional Review Board (IRB). Microalbuminuria was defined as albumin excretion rate (AER) 20-200 μg/min (30-300 mg/24 hours), overt nephropathy as AER >200 μg/min (>300 mg/24 hours) and albuminuria as >20 μg/min (>30 mg/24 hours) in at least two of three validated timed urine collections. End-stage renal disease was defined as receiving dialysis or renal transplantation.
**FinnDiane: Finnish Diabetic Nephropathy Study (FinnDiane)** is an ongoing nationwide Finnish multicenter study of adult participants with T1D described previously. The participants were invited to the study by their attending physician who filled a questionnaire on the medical status of the patient and performed a clinical examination. A subset of the patients participated at one or more follow-up visits with a similar setting. Additional health-related information was obtained from Finnish hospital discharge registry and from the patients’ medical records. Further patients were included to the FinnDiane study through collaboration with the Finnish National Institute for Health and Welfare; for these participants, health-related data was obtained from the hospital discharge registry and from the medical records. For this study, participants were limited to those with T1D diagnosed prior to age 40 years and with insulin treatment begun within 2 calendar years from diabetes onset. Disease status was defined by urine albumin excretion rate (AER) or urine albumin to creatinine ratio (ACR) in at least two out of three consecutive urine collections at local centers: microalbuminuria was defined as AER 20-200 µg/min or 30-300 mg/24h or an ACR of 2.5-25 mg/mmol for men and 3.5-35 mg/mmol for women in overnight, 24-hour or spot urine collections, respectively. Similarly, the limit for macroalbuminuria was AER >200 µg/min or >300 mg/24h or ACR > 25 mg/mmol for men and >35 mg/mmol for women. ESRD was defined as ongoing dialysis treatment or receipt of transplanted kidney. Control patients with normal AER were required to have T1D duration of at least 15 years.

**France-Belgium:** The GENEDIAB (‘Génétique de la Néphropathie Diabétique, Genetics of Diabetic Nephropathy) and Genesis subjects were recruited in France, and in France-Belgium, respectively. Patients with T1D were selected on the following criteria: 1) age at diabetes onset before age 35 years, and 2) definitive insulin use within one year after diagnosis. Diabetic nephropathy was classified according to the highest three AER measurements within the last 5 years. Categories included: 1) controls (normoalbuminuria), 2) incipient nephropathy (microalbuminuria), 3) established nephropathy (proteinuria), and 4) advanced nephropathy (serum creatinine >150 mol/L and/or renal replacement therapy).
GoKinD US: Genetics of Kidneys in Diabetes US Study (GoKinD): The GoKinD study consists of a DKD case-control cohort of individuals diagnosed with T1D prior to 31 years of age who began insulin treatment within 1 year of T1D diagnosis. Controls were 18-59 years of age, with T1D for at least 15 years but without DKD. DKD definition includes individuals with end-state renal disease (ESRD), dialysis or kidney transplant and persistent macroalbuminuria (at least 2 out of 3 tests positive for albuminuria by dipstick ≥1+, or ACR >300 µg albumin/mg of urine creatinine). Cases were defined as people 18-54 years of age, with T1D for at least 10 years and DKD. Individuals were recruited at two study centers, George Washington University and the Joslin Diabetes Center using differing methods. The Joslin GoKinD subjects were analyzed jointly with subjects from the Joslin Microalbuminuria and 50-years medalists (see below).

The InterDiane Consortium: The International Diabetic Nephropathy Consortium (InterDiane) was initiated in 2010 based on the protocol of the FinnDiane Study. The aim of the study is to identify risk factors for diabetic nephropathy and other chronic complications in patients with T1D. The participating studies follow the main protocol of the FinnDiane Study and use the same standardized questionnaires for data acquisition. T1D was defined as diabetes onset <40 years with insulin treatment initiated within one year of diagnosis. The main renal phenotype information has been collected at a baseline visit but in some countries prospective patient visits have been performed and additional phenotype information has been gathered. The last available phenotype information has been used in the analyses. Patients included fulfil the harmonized case and control criteria of the present study. InterDiane centers included in this study come from Romania, Austria, Latvia and Lithuania.

- AusDiane: The Austrian Diabetic Nephropathy Study (AusDiane) was initiated in 2012 in the state of Salzburg in Austria, and is part of the InterDiane Consortium (please see also the InterDiane cohort description). The patients have been studied during a regular visit at two hospitals (Department of Internal Medicine 1, Paracelsus Medical University Hospital Salzburg and Diakonissen-Wehrle Hospital Salzburg). Recruitment was done consecutively in the outpatient departments of these two hospitals. Clinical data were collected mainly as part of
the Type 1 diabetes Registry of the state of Salzburg. Patients have been studied repeatedly every 1 to 1.5 years to improve the phenotype. The last available phenotype is used for the analysis. This study comprises 71 patients with normal AER and diabetes duration ≥15 years, 13 with microalbuminuria, 4 with macroalbuminuria and 2 with ESRD and with GWAS data available and passing the inclusion criteria. Renal status was assessed by morning urine samples at least once every year. The study received ethical approval from the local ethics committee (Ethikkommission Salzburg). Written consent was obtained prior to participation in the study.

- The Latvian Diabetic Nephropathy Study (LatDiane) was initiated in 2012 and is part of the InterDiane Consortium (please see also the InterDiane cohort description). Recruitment of patients took place in Pauls Stradins University Hospital (Riga). The patients were recruited from the Endocrinology department of Pauls Stradins University Hospital and from out-patient clinics of Riga and Riga district (cities Jelgava, Jurmala, Ogre, Salaspils ect). The study comprises 80 patients with normal AER and diabetes duration ≥15 years, 33 with microalbuminuria, 18 with macroalbuminuria and 7 with ESRD and with GWAS data available and passing the inclusion criteria. Patients from out-patients clinics of Riga and Riga district were invited for a separate recruitment visit following the invitation of their endocrinologist. Patients undergoing treatment or correction of therapy in Endocrinology department of Pauls Stradins University Hospital were recruited in the department. Renal status was assessed based on available data of albuminuria (albumin content in 24-hour urine or albumin/creatinine in morning spot urine). In addition, during the recruitment visit, morning spot urine was collected from all patients, and sent for albumin/creatinine measurement. For patients without available data on measurements of albuminuria before recruitment to the LatDiane Study, albumin/creatinine determination in morning spot urine was repeated also several weeks after recruitment. Follow-up visits are planned for 2018. The study received ethical approval from the Latvian Central Ethics Committee. Written consent was obtained prior to participation in the study.11
- **The Lithuanian Diabetic Nephropathy Study (LitDiane)** was initiated in 2013 and is part of the InterDiane Consortium (please see also the InterDiane cohort description). Patients with T1D have been collected in a single center at the Hospital of Lithuanian University of Health Sciences (HLUHS) in Kaunas. Patients were included in the study from out-patient and inpatient departments of Endocrinology clinic of HLUHS during separate study visit. Medical records were reviewed for each patient and prospective visits are performed once a year. Renal status was classified based on the urinary albumin excretion rate (AER) in at least two out of three consecutive urine collections as: normal AER (<30mg/24h in a 24-hour urine collection), incipient diabetic nephropathy (microalbuminuria; AER ≥30 and <300mg/24h) or overt diabetic nephropathy (macroalbuminuria; AER ≥300mg/24h). Patients on dialysis or with a kidney transplant were considered to have end-stage renal disease (ESRD). As a measure of renal function estimated GFR (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. At the time of analysis, the study comprised 39 patients with normal AER, 32 with microalbuminuria, 9 with macroalbuminuria and 10 with ESRD and with GWAS data available and passing the inclusion criteria. The study received ethical approval from the Kaunas Regional Biomedical Research Ethics Committee (No. BE-2-16, 13-March-2013). Written consent was obtained prior to participation in the study.

- **The Romanian Diabetic Nephropathy Study (RomDiane)** was initiated in 2010 in Romania as the pilot study of the InterDiane Consortium. Patients have been studied in a cross-sectional manner in two centers in Bucharest and one in Craiova between 2010 and 2012. Renal status was assessed based on the AER or ACR in two out of three consecutive urine collections at local centers. This study comprises 89 patients with normal AER and diabetes duration ≥15 years, 48 with microalbuminuria, 70 with macroalbuminuria and 28 with ESRD, and with GWAS data available and passing the inclusion criteria. The study received ethical approval from the local ethics committee. Written consent was obtained prior to participation in the study.\(^{12}\)
Italy: Subjects with T1D were recruited at the Complications of Diabetes Unit of the San Raffaele Scientific Institute, Milan, Italy. Diabetic nephropathy was defined as a median AER >200 µg min-1 in three overnight collections of sterile urine in patients with T1D for at least 10 years, concomitant diabetic retinopathy and absence of clinical or laboratory evidence of cardiac failure or other renal or urinary tract disease. Patients without nephropathy had a median AER <20 µg/min.5

Joslin Cohort: There were 2,271 Joslin patients with T1D included in this study. These patients were derived from three cohorts included in the ongoing Joslin Kidney Study.10 Recruitment of 1,600 patients into the 1st Joslin Kidney Study on Natural History of Microalbuminuria in T1D took place between 1991 and 1993, and the cohort was followed through 2004. Recruitment of 1,108 patients into the 2nd Joslin Kidney Study on Natural History of Early Renal Decline in T1D took place between 2003 and 2012 and the follow-up of this cohort is still ongoing. The Joslin Proteinuria Cohort that included 630 patients was assembled from among those who developed proteinuria while attending the Joslin Clinic between 1991 and 2004. The follow-up of this cohort is still ongoing. In the analysis of data for this study, the kidney phenotypes of patients at the enrollment into the Joslin Kidney Study were considered. Genotyping data were available for 244 patients with ESRD, 475 patients with proteinuria, 470 patients with microalbuminuria and 1,189 patients with normoalbuminuria.

SDRN1B1O: The Scottish Diabetes Research Network Type 1 Bioresource is a prospective cohort study of 6,127 individuals from across Scotland. Participants aged 16 years and over with a clinical diagnosis of T1D and insulin use within a year of onset were recruited from primary and secondary care across Scotland between 2010 and 2013. Serum, plasma, whole blood and urine samples were collected at study day allowing eGFR and albuminuria status to be obtained. Further retrospective and prospective biochemistry, co-morbidity and lifestyle data were linked from routine electronic health care records, providing serial estimates of renal status.13

Steno: Patients with T1D attending the outpatient clinic at Steno Diabetes Center were invited to participate in a study of genetic risk factors for diabetes complications. T1D was
considered present if the age at onset of diabetes was ≤35 years and time to definite insulin therapy ≤1 year. DKD was defined by persistent albuminuria (>300 mg/24 h) in two out of three consecutive measurements, presence of retinopathy, and absence of other kidney or urinary tract disease. Absence of DKD (controls) was defined as persistent normoalbuminuria (<30 mg/24 h) after more than 15 years of T1D in patients not treated with ACE inhibitors or angiotensin-II receptor blockers. ESRD was defined as chronic dialysis or kidney transplantation.\textsuperscript{15}

**Sweden:** All patients with T1D were Swedish and diagnosed before 30 years of age. The patients with macroalbuminuria (urinary AER ≥ 200 µg min\(^{-1}\) in at least two consecutive overnight samples) were defined as case. The patients with AER <20 µg min\(^{-1}\) were considered as control.\textsuperscript{16}

**UK-ROI:** In the United Kingdom (UK) GoKinD, Warren 3 and All Ireland (UK-ROI) study, data were collected under a parallel protocol to that of the GoKinD study in the United States (see above). Briefly, all individuals are white with parents and grandparents born in the UK or Ireland and who had T1D diagnosed before 31 years of age. Cases have DKD diagnosed by the onset of proteinuria (>0.5 g/24 hr) >10 years since diagnosis of diabetes; controls are diabetic individuals without evidence of proteinuria (or microalbuminuria) >15 years after onset of diabetes.\textsuperscript{18}

**WESDR:** The Wisconsin Epidemiologic Study of Diabetic Retinopathy was an epidemiologic study of subjects with diabetes diagnosed before 30 years of age and taking insulin. Outcomes collected included proteinuria on a urine dipstick test.\textsuperscript{19}
References


GWAS of DKD Supplement


PMCID:PMC4800984


