The Genetic Landscape of Renal Complications in Type 1 Diabetes

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~~Systematic Dissection of the~~ The Genetic Landscape of Renal Complications in Type 1 Diabetes

Running title: Genome-wide dissection of diabetic kidney disease

Niina Sandholm[1,2,3], Natalie Van Zuydam[4,5,6], Emma Ahlqvist[7], Thorhildur Juliusdottir[4], Harshal A. Deshmukh[8], N. William Rayner[4,5,9], Barbara Di Camillo[10], Carol Forsblom[1,2,3], Joao Fadista[7], Daniel Ziemek[11], Rany M. Salem[12,13,14], Linda T. Hiraki[15], Marcus Pezzolesi[16], David Trégouët[17,18], Emma Dahlström[1,2,3], Erkka Valo[1,2,3], Nikolay Oskolkov[7], Claes Ladenvall[7], M. Loredana Marcovecchio[19], Jason Cooper[20], Francesco Sambo[10], Alberto Malovini[21,22], Marco Manfrini[10], Amy Jayne McKnight[23], Maria Lajer[24], Valma Harjutsalo[1,2,3,25], Daniel Gordin[1,2,3], Maija Parkkonen[1,2,3], Jaakko Tuomilehto[25,26,27,28], Valeriya Lyssenko[7,24], Paul M. McKeigue[29], Stephen S. Rich[30], Mary Julia Brosnan[31], Eric Fauman[32], Riccardo Bellazzi[21], Peter Rossing[24,33,34], Samy Hadjadj[35,36,37], Andrzej Krolewski[16], Andrew D. Paterson[15], Jose C. Florez[38,39,40], Joel N. Hirschhorn[12,13,14], Alexander P. Maxwell[23,41], David Dunger[19], The DCCT/EDIC Study Group^, GENIE Consortium^, The FinnDiane Study Group^, Claudio Cobelli[10], Helen M. Colhoun[8], Leif Groop[7], Mark I McCarthy[4,5,42], Per-Henrik Groop[1,2,3,43], on behalf of The SUMMIT Consortium^

1. Folkhälsan Institute of Genetics, Folkhälsan Research Center, 00290, Helsinki, Finland
2. Abdominal Center, Nephrology, University of Helsinki and Helsinki University Hospital, 00290, Helsinki, Finland
3. Research Programs Unit, Diabetes and Obesity, University of Helsinki, 00290, Helsinki, Finland
4. Wellcome Trust Centre for Human Genetics, University of Oxford, OX3 7BN, Oxford, UK
5. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, OX3 7LE, Oxford, UK
6. Medical Research Institute, University of Dundee, UK
7. Department of Clinical Sciences, Diabetes and Endocrinology, Skåne University Hospital, Lund University, 20502, Malmö, Sweden
8. Division of Population Health Sciences, University of Dundee, DD1 9SY, Dundee, UK
9. Wellcome Trust Sanger Institute, Hinxton, CB10 1SA, UK
10. Department of Information Engineering, University of Padova, 35131, Padova, Italy
11. Computational Sciences, Pfizer Worldwide Research and Development, 10785, Berlin, Germany
12. Department of Genetics, Harvard Medical School, Boston, MA 02115, USA
13. Broad Institute of the Massachusetts Institute of Technology and Harvard University, Cambridge, MA 02142, USA
14. Divisions of Endocrinology and Genetics, Boston Children's Hospital, Boston, MA 02115, USA
15. Genetics and Genome Biology Program, Hospital for Sick Children, Toronto, ON M5G 0A4, Canada
16. Joslin Diabetes Center, Boston, MA 02215, USA
17. UMR_S 1166, Team Genomics & Pathophysiology of Cardiovascular Diseases, Sorbonne Universités, UPMC Univ. Paris 06, INSERM, 75013, Paris, France
18. ICAN Institute for Cardiometabolism and Nutrition, 75013, Paris, France
19. Department of Paediatrics, Institute of Metabolic Science, University of Cambridge, CB2 0QQ, Cambridge, UK
20. Department of Chemical Engineering and Biotechnology, University of Cambridge, CB2 3RA, Cambridge, UK
21. Department of Electrical, Computer and Biomedical Engineering, University of Pavia, 27100, Pavia, Italy
22. IRCCS Fondazione Salvatore Maugeri, 27100, Pavia, Italy
23. Nephrology Research, Centre for Public Health, Queen's University of Belfast, BT7 1NN, Belfast, UK
24. Steno Diabetes Center, 2820, Gentofte, Denmark
25. The Chronic Disease Prevention Unit, National Institute for Health and Welfare, 00271, Helsinki, Finland

26. Centre for Vascular Prevention, Danube-University Krems, 3500, Krems, Austria
27. Diabetes Research Group, King Abdulaziz University, 80200, Jeddah, Saudi Arabia
28. Dasman Diabetes Institute, Dasman, Kuwait
29. Centre for Population Health Sciences, University of Edinburgh, EH8 9AG, Edinburgh, UK
30. Center for Public Health Genomics, University of Virginia, Charlottesville, VA 22908, USA
31. CV and Metabolic Diseases (CVMET) Research Unit, Pfizer Worldwide Research and Development, Cambridge, MA 02139, USA
32. Computational Sciences, Pfizer Worldwide Research and Development, Cambridge, MA 02139, USA
33. Health, Aarhus University, 8000, Aarhus, Denmark
34. Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, 2200, Copenhagen, Denmark
35. UFR Médecine Pharmacie, Centre d'Investigation clinique, Université de Poitiers, 86021, Poitiers, France
36. Service d'Endocrinologie-Diabetologie and Centre d'Investigation clinique, CHU de Poitiers, 86021, Poitiers, France
37. CIC1402 and U1082, Inserm, 86021, Poitiers, France
38. Programs in Metabolism and Medical & Population Genetics, Broad Institute, Cambridge, MA 02142, USA
39. Department of Medicine, Harvard Medical School, Boston, MA 02115, USA
40. Diabetes Unit and Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA 02114, USA
41. Regional Nephrology Unit, Belfast City Hospital, BT9 7AB, Belfast, UK
42. Oxford NIHR Biomedical Research Centre, University of Oxford, OX3 7LE, Oxford UK
43. Baker IDI Heart & Diabetes Institute, Melbourne, VIC 3004, Australia

The authors of this manuscript are those listed above. Membership of the listed consortia is provided in supplementary material, but those members who are NOT listed on page 1 do not meet the criteria for authorship.
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Corresponding author:
Per-Henrik GROOP, MD DMSc FRCPE
Professor, Chief Physician
Abdominal Center Nephrology
University of Helsinki and Helsinki University Hospital
Biomedicum Helsinki (C318b)
Haartmaninkatu 8

FIN-00290 Helsinki
FINLAND
Tel: +358-500-430 436 or +358-2941-25459 (office)
Email: per-henrik.groop@helsinki.fi

Abstract

Diabetes is the leading cause of end stage renal disease. Despite evidence for a substantial heritability of diabetic kidney disease, efforts to identify genetic susceptibility variants have had limited success. We extended previous efforts in three dimensions, examining a more comprehensive set of genetic variants in larger numbers of subjects with type 1 diabetes characterized for a wider range of cross-sectional diabetic kidney disease phenotypes. In 2,843 subjects, we estimated that the heritability of diabetic kidney disease was 35% (p=6x10^{-3}). Genome-wide association analysis and replication in 12,540 individuals identified no single variants reaching stringent levels of significance and, despite excellent power, provided little independent confirmation of previously published associated variants. Whole exome sequencing in 997 subjects failed to identify any large-effect coding alleles of lower frequency influencing the risk of diabetic kidney disease. However, sets of alleles increasing body mass index (p=2.2×10^{-5}) and the risk of type 2 diabetes (p=6.1x10^{-4}) were associated with the risk of diabetic kidney disease. We also found genome-wide genetic correlation between diabetic kidney disease and failure at smoking cessation (p=1.1×10^{-4}). Pathway analysis implicated ascorbate and aldarate metabolism (p=9×10^{-6}), and pentose and glucuronate interconversions (p=3×10^{-6}) in pathogenesis of diabetic kidney disease.

These data provide further evidence for the role of genetic factors influencing diabetic kidney disease in those with type 1 diabetes and highlight some key pathways that may be responsible. Altogether these results reveal important biology behind the major cause of kidney disease.

Introduction

Diabetes is the leading cause of end stage renal disease (ESRD).[1] Among the patients with type 1 diabetes (T1D), as many as one third develop serious renal complications,[2] characterized by increasing urinary albumin excretion rates (AER) and decreasing kidney function, measured by estimated glomerular filtration rate (eGFR), with 10%-20% of the subjects progressing to ESRD.[3,4] In the vast majority of patients with T1D, renal complications reflect the condition of diabetic nephropathy,[5] though we use the term diabetic kidney disease (DKD) here to reflect the fact that not all have histological evidence of DN. While DKD is associated with high risk of cardiovascular disease[6] and premature mortality,[7] those who manage to avoid DKD have much better prognosis with survival rates comparable to subjects without diabetes.[7] The treatment of DKD, primarily relying on the control of blood glucose levels and on the use of anti-hypertensive medication, can only retard disease progression rather than restore kidney function or efficiently prevent ESRD. This highlights the need for a better mechanistic understanding of DKD which would provide improved therapeutic targets and biomarkers of progression, both of which are expected to lead to improved personalization of care.

Family studies have shown familial clustering of DKD with a 2.1 – 2.3 fold increased risk of DKD in T1D siblings of probands with DKD.[8-10] There is also evidence for shared genetic background between DKD and other diseases: the parents of the subjects with T1D and DKD have more type 2 diabetes (T2D) and cardiovascular disease[11-13]. Despite evidence for genetic predisposition, few compelling signals have been identified for DKD. Positive reports of association with a range of candidate genes have generally failed to find support in larger analyses of independent samples,[14] and only a few loci have been identified with genome-wide association studies (GWAS)[15-17]. In contrast, there have been a number of a robust, replicated associations described for chronic kidney disease (CKD) in the general population[18-20]. However, evidence that these variants influence predisposition to CKD in diabetes is mixed[15,20].

The limited success of GWAS on DKD thus far may be due to multiple factors: relatively small sample sizes (in the thousands at the discovery stage); imprecise and variable diagnostics or phenotypic heterogeneity; and a focus on common variants (minor allele frequency [MAF] ≥5%), that neglects the possible contribution of lower frequency variants to DKD predisposition. In other complex traits, such as schizophrenia, initial challenges in identifying robust association signals have been overcome as sample sizes have increased[21,22].

To overcome the limitations of previous studies in DKD, in this study we: increased sample size through GWAS meta-analysis; analysed a range of phenotypic comparisons that encompass different stages and severity of DKD in subjects with T1D; and extended the genome-wide association screen from common variants to lower frequency coding variants through whole exome sequencing (WES).

Results

DKD traits are heritable

Since no comprehensive evaluation of heritability exists for the various stages of DKD, we estimated the narrow-sense, "chip" heritability (i.e. the proportion of phenotypic variance explained by genome-wide SNPs; h^2) for the seven applied DKD phenotypic comparisons (Figure 1) in the context of T1D using data from the largest included GWAS study, the Finnish Diabetic Nephropathy (FinnDiane) Study[23]. Heritability estimates varied greatly across the comparisons (Figure 2): For the primary, 'combined DKD' phenotypic comparison (micro- or macroalbuminuria or ESRD versus normal AER), h^2 was 35% (p=6x10^{-3}; Supplemental Table 1). The highest value, h^2 =59%, was obtained for 'CKD+DKD' (those with both CKD and DKD assigned as cases, and those with no CKD and no DKD as controls; p=1x10^{-3}). Other late stage phenotype definitions also yielded high estimates of heritability, e.g. 47% for 'ESRD versus no DKD' (p=3x10^{-3}). When we included gender, diabetes duration, and age at diabetes diagnosis as covariates, the proportion of the remaining phenotypic variance explained by the genotyped SNPs increased for each phenotypic comparison, e.g. from 35 % to 50% for

'combined DKD' (p=2.5×10^{-4}). The estimates represent lower limits for the total heritability of DKD traits, as the method considers only those causal variants captured by the variants genotyped on the array.

GWAS

The GWAS discovery stage included 3,135-5,156 subjects with T1D, depending on phenotypic comparison (Supplemental Figure 1), from four studies: FinnDiane[23], the EURODIAB Family Study[24], the Scania Diabetes Registry (SDR)[25], and the UK Nephropathy Family Study and Oxford Regional Prospective Study (NFS-ORPS/ Cambridge)[26,27] (Table 1, Supplemental Tables 2 and 3).

With 2,563 T1D DKD cases and 2,593 T1D non-DKD controls for the 'combined DKD' phenotype in the discovery cohorts, we estimated >80% statistical power to detect variants with MAF≥10% and allelic odds ratios (OR) ≥1.55 at genome-wide significance (p<5×10^{-8}; Supplemental Table 4). Results from meta-analyses were well calibrated (genomic control [λ_{GC}] 1.01-1.05; Supplemental Figure 2) but showed little deviation from the null with no SNP reaching p<5×10^{-8} (no adjustment for multiple phenotypes). Across seven DKD case-control comparisons, a total of 101 regional lead SNPs reached a suggestive p-value of <5×10^{-6} in at least one analysis (Supplemental Table 5). These 101 associations were tested for all DKD phenotypes available in the various stage 2 samples (Supplemental Tables 2 and 3), though meta-analysis results were only compiled across data for equivalent phenotypes. The two-stage design provided ≥80% power for the primary 'combined DKD' comparison to reach p<5×10^{-8} for variants with an OR≥1.47 and MAF≥10% (Supplemental Table 6).

In the joint meta-analysis of stage 1 and 2 samples, no SNP reached p<5×10^{-8}, while three achieved p<1×10^{-6}, all for the ESRD based case definitions: rs1989248 near *CNTNAP2*, rs61277444 in *PTPN13*, and rs7562121 in *AFF3* (Supplemental Figure 3, Supplemental Table 5). We also identified rs72809865 near *NRG3* for further replication based on nominal replication (p=0.047) for 'combined DKD' in stage 2. These four SNPs were examined in 1,087 additional subjects using *de novo* genotyping (Stage 3), though direct genotyping was

unsuccessful for rs1989248 (near *CNTNAP2*). After the joint analysis of stage 1-3 results, the association at rs7562121 in *AFF3* remained suggestive ($p<1\times10^{-6}$; Table 2).

Rs7562121 in *AFF3* is in moderate linkage disequilibrium (LD) with rs7583877 ($r^2=0.67$, D'= 0.94), the variant previously associated with ESRD in T1D[15]. Conditional analysis showed that both SNPs represent the same signal (Supplemental Table 7). However, the present study cannot be considered replication of previous reports because of substantial overlap of study samples. Analysis in non-overlapping samples (222 ESRD cases, 1,640 non-ESRD controls) provided no independent corroboration of the *AFF3* association (OR=1.02, p=0.82).

The substantial heritability captured by SNPs on the genotyping array, and the failure to detect genome-wide significant signals, suggest that the causal variants are beyond detection in the present study, due to more modest effect size (e.g. OR<1.47 for MAF≥10%) and/or imperfect capture by common variant-focused GWAS analyses.

Re-evaluation of previous DKD associations

The enlarged sample size provided an opportunity to investigate the previous, often contradictory reports of SNP associations.[28] We selected signals from three sources: a literature-based meta-analysis of candidate gene associations;[28] GWASs on DKD in subjects with either T1D[15,17,29-31] or T2D[32,33]; and GWASs on CKD irrespective of underlying pathology[20]. Many of these previous studies included subjects overlapping with those in the present analysis.

We estimate >80% statistical power to detect associations with allelic OR≥1.25 and MAF≥10% at nominal significance (α=0.05; Supplemental Table 8) for the 'late DKD' phenotype, which was most commonly used in previous publications. We observed only a modest deviation from the null p-value distribution for the set of previously-associated variants, suggesting that many of these have been false positive findings (Supplemental Figure 4). Nevertheless, in addition to the *AFF3* SNP associations described above, the associations between

rs2838302 (in *SIK1*) and 'ESRD vs. non-ESRD', and between rs17709344 (*RGMA–MCTP2*) and 'CKD+DKD' were directionally consistent and significant ($p<1.1\times10^{-3}$ to correct for 46 loci). The association between rs2838302 (*SIK1*) and 'ESRD vs. no DKD' remained nominally significant ($p=0.04$) even after exclusion of the substantial overlap of the subjects (Supplemental Table 9).

We observed directionally consistent associations (less stringent $p<0.05$) for variants near *WNT4-ZBTB40*, *SEMA6D-SLC24A5*, *ELMO1*, *ERBB4*, 4p15.1 and 13q regions (Supplemental Figure 5). However, at four of these loci, the modest evidence of association was lost when overlapping samples were removed. Independent replication of previously reported signals (directionally consistent p<0.05) was therefore restricted to the signals at *ELMO1*, 13q and *SIK1* (Supplemental Table 9).

DKD shows shared genetic background with obesity, T2D, and smoking cessation

BMI, systolic blood pressure, serum lipids, and smoking have been associated with DKD in epidemiological studies[24,34-36] while T2D, obesity, hypertension, and lipid disorders have been reported to cluster in families with DKD[11,12,37], suggesting a shared genetic background or a close correlation amongst these phenotypes. We constructed weighted genetic risk scores (GRS) for 19 diabetes,[38-45] obesity,[46-48] hypertension,[49] or lipid-related[50] intermediate phenotypes based on 10 to 96 established SNPs ($p<5\times10^{-8}$) for each phenotype from previously published GWAS. The GRS for increasing BMI[46] was associated ($p<2.6\times10^{-3}$ to correct for 19 traits) with multiple DKD traits ($p=2.2\times10^{-5}$ for 'late DKD'; Figure 3; Supplemental Table 10), implicating a causal role of BMI for DKD. While observational studies have shown contradictory results,[51,52] these findings are consistent with those from a recent Mendelian Randomization study including FinnDiane subjects.[53] The GRS predisposing to T2D was associated with increased risk of multiple DKD traits (e.g. $p=1.9\times10^{-3}$ for 'combined DKD' excluding pleiotropic lipid and glycemic SNPs; $p=6.1\times10^{-4}$ for 'combined DKD' including pleiotropic lipid SNPs) in line with previous reports of parental T2D being associated with DKD in subjects with T1D.[12] These data support a causal, mechanistic link between metabolic syndrome and DKD in T1D.[23]

We also applied the LD score regression method to estimate the genetic correlation between traits. In contrast to the GRS approach which uses only the most associated variants, this method examines the allelic effects of all SNPs in the meta-analysis.[54,55] As expected, the seven DKD phenotypes were highly correlated with each other, at least in part due to overlapping phenotypic definitions, with the exception of 'early DKD' (Supplemental Figure 6). Smoking cessation was inversely correlated with 'CKD' (p=1.1×10^{-4}) and other DKD traits (Figure 4). This is in line with a previous epidemiological study showing higher risk of DKD for smokers, whereby ex-smokers had similar risk of developing DKD as non-smokers.[36]

Gene set enrichment analyses suggest glucuronidation and other pathways affecting DKD

We performed gene set enrichment analyses (GSEA) of the GWAS results to identify biological pathways and processes enriched among the most significant GWAS signals. The ascorbate and aldarate metabolism, and pentose and glucuronate interconversions pathways showed significant enrichment (p<1.6×10^{-5} to correct for multiple tested pathways). Literature linking ascorbate metabolism to DKD is sparse, but cell studies have suggested a reduced uptake rate of ascorbic acid (vitamin C) in DKD,[56] and vitamin C plus E supplementation was reported to improve glomerular function in T2D.[57] In the latter pathway, the flagged genes overlapped especially the glucuronate sub-pathway (Supplemental Figure 7). Negatively charged glucuronic acid units on heparan sulfate side chains participate in the maintenance of the negative charge selectivity of the glomerular basement membrane in the kidneys, and their cleavage by heparanase (endo-ß-D-glucuronidase) has been suggested as an underlying cause for DKD.[58] While knock-out of the *HSPE* (heparanase) gene protects mice from DKD,[59] no specific genetic variants in or near *HSPE* have been associated with DKD. Other gene sets with less marked enrichment (false discovery rate (FDR)<0.05; Supplemental Table 11) included the cholesterol biosynthesis pathway (p=8.0×10^{-4}) flagging among others the *HMGCR* gene (lowest p=0.023 for rs11726245 for 'CKD'), which encodes the main target of statins, commonly used for prevention of diabetic macrovascular

complications. Cholesterol levels are reported to be related to eGFR decline in T1D, while statin use improved eGFR in subjects with T2D in some[60] but not all studies.[61]

Single-marker association tests of whole exome sequencing show suggestive associations for ESRD

To identify low frequency (1% ≤ MAF <5%) and rare (MAF<1%) coding variants contributing to DKD, we performed WES of 997 subjects with T1D from the FinnDiane, SDR and Steno Diabetes Center. To maximize power, subjects were ascertained from the tails of the liability distribution: we selected cases with onset of macroalbuminuria or ESRD relatively soon after diagnosis of T1D, and controls with normal AER despite prolonged duration of T1D (Supplemental Table 12). This setting allowed us to study the 'late DKD' and 'ESRD vs. no DKD' case–control contrasts (Figure 1).

No associations were observed at exome-wide significance ($p<5\times10^{-7}$; Supplemental Figure 8). Variants in five loci reached a p-value of $<1\times10^{-5}$ for association with 'ESRD vs. no DKD' (Supplemental Tables 13 and 14) with the strongest associations obtained for an intronic SNP rs188427269 within *NVL* (MAF 0.2%, $p=3.3\times10^{-7}$) and for rs13003941 in the 3'UTR of *ERBB4* (MAF 35%, $p=3.5\times10^{-6}$). Other variants in *ERBB4* (not in LD with rs13003941) were previously suggestively associated with DKD,[15] and ErbB4 was shown important for the development of kidneys in mouse models.[62]

Gene aggregate tests of WES

To improve power to detect low frequency and rare variant associations, we performed gene-level aggregate tests using three complementary approaches: a variable threshold (VT) burden test,[63] a dispersion test (SKAT),[64] and a hybrid test (SKAT-O)[65]. No gene achieved exome-wide significance ($p<2.5\times10^{-6}$, adjusted for 20,000 genes; Supplemental Figures 9 and 10). For the 'late DKD' phenotype, the lowest p-value was for *GGA1* ($p=3.1\times10^{-5}$; Supplemental Figure 11), showing rare (MAF≤0.13%)[66] missense alleles in seven cases but no

controls across five variant sites (Supplemental Tables 15-17). For the 'ESRD vs. no DKD' phenotype, the strongest associations were found at *CCDC77* (p=2.1x10^{-5}), *THADA* (p=8.3x10^{-5}) and *CHPT1* (p=1.9x10^{-5}; Supplemental Figure 12, Supplemental Tables 18-20).

While it has been hypothesized that common disease diagnoses are partially comprised of rare monogenic forms of the disease, we did not see enrichment in genes causing rare human glomerular diseases in our WES results (Supplemental Table 21). In addition, there was no enrichment between the WES signals and those arising from our GWAS studies. Thus, the variants and genes generating suggestive evidence for association in WES seem independent of rare variants identified for monogenic forms of kidney disease, and of the common variant contribution to DKD in subjects with T1D.

Bivariate analysis of GWAS and WES data

As some genetic factors may affect disease outcome only in the presence of interacting genetic factors, we complemented the GWAS and WES analyses using a multivariate variant selection method (ABACUS)[67] applied to both GWAS and WES data. Although no variant reached simulation p-value (p_S<5×10^{-8}), suggestive evidence of association was obtained for variants in *OSGIN1* in two different data sets (p_S<5×10^{-6} for 'ESRD vs. no DKD' in EURODIAB GWAS and in Steno WES; Supplemental Tables 22 and 23). Functional clustering of the results pointed at processes previously linked with DKD such as cholesterol and sucrose/glucose metabolism and inflammatory response pathway (Supplemental Tables 24 and 25).

Discussion

This study represents a systematic evaluation of common genetic risk factors and rare coding variants for a broad range of kidney complication phenotypes in T1D. To complement the association analyses, we

performed various enrichment and correlation analyses considering the genome-wide content to obtain insight of the genetic architecture, biological background, and correlation with other traits.

This study confirmed that renal complications in T1D are highly heritable, as a substantial proportion of the phenotypic variation can be captured by common variants on the GWAS chip, with the strongest heritability estimates observed for the most extreme phenotypic comparisons. This captured heritability could consist of common variants with modest effects, and/or variants of lower frequency, some of them imperfectly tagged by common SNPs. The limited evidence for linkage to DKD[68] and general experience regarding the architecture of other common complex traits, suggest that it is unlikely that DKD risk is dominated by rare variants of large effect, though ultimately sequence based studies will be required for definitive evaluation.

We found suggestive common variant signals for DKD in or near *AFF3*, *CNTNAP2*, *NRG3*, and *PTPN13* genes, but additional data sets will be needed to confirm (or refute) these signals and to increase power to detect others. For example, the effective sample size required to implicate a risk allele of MAF 20% and allelic OR 1.2 at genome wide significance is ~15.000. We demonstrated that many previously claimed DKD associations signals are likely to be false positives, although modest, independent evidence was found for associations near *ELMO1*, 13q and *SIK1* (p<0.05). While the three-stage analysis of this study brings together the largest studies with the largest number of participants with T1D for GWAS on DKD, the total sample size remains modest. Future efforts to identify novel genetic risk factors for DKD will require investment in additional sample ascertainment and genotyping.

Different genetic factors may affect the various stages of DKD progression. To address the phenotypic heterogeneity within DKD, we applied selection of sub-phenotypes for the evaluation of renal complications. As various phenotypic comparisons yielded significant findings for different tests, these comparisons may address diverse aspects of the disease progression. Future studies would likely benefit from improved phenotyping and, in particular from the detailed longitudinal follow-up of research participants.

Even though this study concentrated on patients with T1D, some of the results may be extended to DKD in T2D as well. However, as the pathology behind renal complications in T2D is more heterogenous,[5] with ageing, atherosclerosis and hypertension contributing appreciably to the renal function, the genetic background of DKD in T2D may have more features of the kidney disease in the general population.

Although no novel susceptibility loci were identified in this study, some signals are starting to appear when we aggregated genetic data as in pathway analysis, genetic risk score and LD score regression analysis. The pathway analyses, for example, highlighted involvement of glucuronate interconversions pathway and supported the role of cholesterol metabolism in DKD. Analysis of genetic risk scores suggested that high BMI, as well as the genetic risk factors behind T2D, causally increase the risk of DKD in T1D. Finally, the LD score regression identified genetic correlation between smoking cessation and reduced risk of DKD in subjects with T1D, supporting the previous research of smoking as a risk factor for DKD[36]. Altogether, these results may provide valuable clues to the biological processes relevant to the pathogenesis of DKD.

Concise Methods

Subjects with T1D in GWAS and WES

The GWAS discovery stage included subjects with T1D from the FinnDiane Study,[23] the EURODIAB Family Study[24], SDR[25], and NFS-ORPS[26,27]. WES included subjects from FinnDiane, SDR, and Steno Diabetes Center (characterized in Supplemental Table 12). All studies were approved by the local ethics committees and conducted according to the principles of the Declaration of Helsinki. Written consent was obtained from the participants in FinnDiane, EURODIAB, SDR and Steno Studies. In the NFS-ORPS study, written consent was obtained from parents, and verbal assent was obtained from children.

Phenotype definitions: All subjects had T1D as diagnosed by their attending physician, with age at diabetes onset ≤40 years and insulin treatment initiated within one year of diagnosis. The kidney status was classified based on AER and eGFR (please see Complete Methods and Supplemental Table 26). Patients receiving dialysis treatment, with a kidney transplant, or with an eGFR ≤15 ml/min/1.73m^2 were defined to have ESRD. Based on these definitions, we analysed seven different case – control phenotypes (Figure 1).

Patient selection for WES: Patients were selected from the extreme ends of the liability distribution of DKD from each participating study. Cases had rapid onset of macroalbuminuria (within 20/25 years of diabetes onset in FinnDiane and Steno, respectively; no threshold in SDR) or ESRD (onset within 25 years of diabetes onset in FinnDiane and Steno). Controls were subjects with normal AER despite prolonged duration of T1D (≥ 32, 30, or 27 years in FinnDiane, Steno, and SDR, respectively). In addition, the FinnDiane controls were enriched for higher HbA_{1C} values (excluding subjects with HbA_{1C} < 6.5 %).

Genotypes

Genome-wide genotyping and imputation of the discovery cohorts: The genome-wide genotyping of the subjects in the SDR, NFS-ORPS, and EURODIAB was performed with the Illumina OmniExpress assays (Illumina, San Diego, CA, USA). In quality control, samples with a call rate <98%, gender discrepancy, extremely high or low heterozygosity, or excess of estimated relatedness, were removed. Common SNPs (MAF≥5%) with genotyping rate <95% or not in Hardy-Weinberg equilibrium (HWE; $p \leq 5.7\times10^{-7}$) were removed. For low-frequency SNPs (MAF 1% – 5%), the thresholds were 99% and $p<10^{-4}$, respectively. In the FinnDiane Study, genotyping was performed with the Illumina 610Quad assay and the quality control was similar to the other studies, as described previously in detail.[15] Principal component analysis was performed in all cohorts with Eigensoft.[69] Imputation was performed with IMPUTE2[70] using the 1000 Genomes project (phase 1 v.3, released March 2012) as the imputation reference panel.[71] Variants were filtered post-imputation to those with MAF ≥ 1%, minor allele count ≥10 in both cases and controls, and SNPtest INFO estimate of imputation quality ≥0.4.

Whole exome sequencing and variant calling: Samples were sequenced at two centres. Sequencing was performed on an Illumina HiSeq2000. We required an average 20x target capture above 80% coverage, otherwise additional DNA was requested to 'top up' the sample. This resulted in mean sequencing depth of 54.97 (FinnDiane) and 42.23 (SDR and Steno) bases per position. After additional sequencing 497 samples were included from FinnDiane and 500 from SDR and Steno. Samples were mapped with Burrows-Wheeler aligner v7.4. Genome analysis toolkit v2.1 (GATK) was used to refine and recalibrate the sequences and to call variants. Polymorphic variants (MAF>0) with a mapping quality < 250, HWE *p*-value $>1\times10^{-10}$ and call rate ≥75% were retained in the analysis. Samples with ≥10% missingness or extreme heterozygosity were excluded. Population outliers, duplicates and related samples were removed. Variants were annotated using CHAos (http://www.well.ox.ac.uk/~kgaulton/chaos.shtml), snpEff[72] and VEP[73] for functional class and transcript.

With 530,565 variants (491,553 SNPs and 39,012 indels) across 479 controls and 481 cases after the quality control, each individual carried a mean of 7,566 synonymous, 6,452 missense and 103 protein truncating variants. The lower number of total variant sites compared to other, more outbred populations[74] is in line with fewer variable sites seen in founder populations such as the Finns.[75]

Statistical methods

Heritability estimates: The narrow-sense heritability of the kidney phenotypes was estimated as the proportion of the phenotypic variance explained by the additive effects of the genotyped SNPs based on the FinnDiane GWAS data using the GCTA v. 0.93.9, excluding samples with estimated relatedness ≥ 0.025.[76] The observed variance explained was transformed to the underlying population scale based on rough prevalence estimates as given in Supplemental Table 1. The heritability was estimated without covariates, and adjusting for sex, duration of T1D and age at T1D onset.

GWAS analysis: The genome-wide association analyses in stage 1 studies were performed with two methods in parallel. To obtain stable effect size estimates, we performed additive test for association using SNPtest with the score method adjusted for sex, diabetes duration, age at diabetes onset, and the two first principal components. *P*-values were obtained with a variance component based mixed model method, EMMAX, which accounts for the sample structure, allowing to include relatives in the analysis.[77] Models were adjusted for sex, diabetes duration and age at diabetes onset and the kinship matrix was calculated with EMMAX. EMMAX algorithm was implemented with the EPACTS software (www.sph.umich.edu/csg/kang/epacts/). Meta-analyses of the effect sizes were performed with the fixed-effect inverse variance method (GWAMA[78] and METAL[79]), while *p*-values were combined based on the study-wise *p*-values, sample sizes and effect directions (METAL[79]). Meta-analysis results were further filtered to those with valid results from at least two studies. P-values below 5×10^{-8} were considered genome-wide significant, not correcting for multiple testing due to seven phenotypic comparisons, as the case and control groups were overlapping and the traits were correlated with each other.

Power calculations were performed with the genetic power calculator (pngu.mgh.harvard.edu/~purcell/gpc/) for simple case-control setting,[80] and with Power Calculator for Two Stage Association Studies (CaTS; http://csg.sph.umich.edu//abecasis/cats/).[81]

Replication: Independent variants with $p<5\times10^{-6}$ were selected for *in silico* replication in six additional studies: the All Ireland – Warren 3 – Genetics of Kidneys in Diabetes UK collection (UK-ROI)[15] and the Genetics of Kidneys in Diabetes US Study (GoKinD US)[15] from the GENIE Consortium, the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study[82,83], 1,073 subjects from the Joslin Diabetes Center T1D nephropathy collection, and the French, Belgian and Danish subjects (the Steno Diabetes Center) from the French-Danish Effort[84] (Supplemental Tables 2 and 3). After *in silico* replication, variants that replicated with a $p<0.05$ or had a combined *p*-value $< 1\times10^{-7}$ after meta-analysis were selected for *de novo* genotyping with TaqMan in 1,095 additional FinnDiane patients, not part of the GWAS (Supplemental Table 2). rs1989248 was not successfully genotyped. Association testing was performed

with logistic regression (implemented in PLINK or SNPtest, depending on the study), adjusted for sex, duration of diabetes, age at diabetes onset, and study specific covariates.

Genetic risk score analysis: SNPs associated ($p<5\times10^{-8}$) in previous studies with Waist-Hip-ratio (adjusted for BMI)[47], BMI (untransformed[48] and z-transformed[46]), systolic blood pressure (SBP),[49] low-density lipoprotein cholesterol (LDL-C), triglycerides, high-density lipoprotein cholesterol (HDL-C)[50], T1D[39], T2D[38] (including all SNPs, and without any other effects other than on T2D or lipids[50] and T2D or glycemic traits[41,85]), 2-hr glucose (adjusted for BMI),[40] fasting glucose (adjusted for BMI),[41] glycated haemoglobin (HbA1c),[42] fasting insulin (natural log transformed and adjusted for BMI),[41] fasting pro-insulin (adjusted for BMI and fasting glucose),[43] HOMA-B, HOMA-IR,[44] and insulin resistance[45] were included in a genetic risk score (GRS) for each trait respectively. The GRS was weighted by the allelic effect of each variant on the DKD risk factor and associated with the DKD phenotypes using the stage 1 GWAS meta-analysis data.[49] The lipid GRS were restricted to variants that predicted that specific trait and removed those that had effects on other lipid traits. We did not include a GRS for smoking behaviours as there were too few genome-wide significant associations to form a sufficient instrument.

LD score regression to estimate genetic correlation: To estimate the genetic correlation between the GWAS stage 1 meta-analysis results for DKD phenotypes, and the related traits, we assembled the genome-wide summary statistics from all the studies used to calculate GRS except for systolic blood pressure and T1D as the full summary statistics were not available. We additionally computed genetic correlation with smoking behaviour phenotypes (cigarettes per day, smoking addiction, smoking cessation and age at smoking onset).[86]

Gene set enrichment analyses: gene set enrichment analysis was performed in the GWAS stage 1 meta-analysis results with the MAGENTA(vs.2)[87] applied on 10,992 partially overlapping gene sets from GO, PANTHER, INGENUITY, KEGG, REACTOME, and BIOCARTA data bases; 3,126 gene sets with ≥10 genes were analysed. The 95 percentile cut-off for the gene scores was employed to define the significant results.

Correction for multiple testing: The significance threshold for the results of the evaluation of previous loci, GRS, LD score regression, and pathway enrichment analyses were Bonferroni corrected for multiple testing with α=0.05 significance level, accounting for the number of tested loci, traits, or pathways. The results were not corrected for the seven phenotypic comparisons due to a considerable overlap of the case and control groups.

WES single variant analysis: Single variants were tested for association with DKD (cases N=481, controls N=479) and ESRD (cases N=168, controls N=479) using the logistic score test[88] implemented in Epacts, with sex and two principal components as covariates. Related individuals, monomorphic SNPs and those with standard error greater than 10 were excluded from the analysis. While the study setting provided low statistical power to detect rare variants (MAF<1%) with exome-wide significance ($p<9\times10^{-8}$ to correct for 530,776 tested variants) in line with previous reports on the statistical power to detect rare variants,[89] we had sufficient power (80%) to detect a low frequency variant (MAF=5%) with a large OR of 5.65 (Supplemental Figure 13).

WES gene-based analysis: We applied three series of gene based tests: a burden test (VT) [63] that assumes the direction of effect of grouped variants is the same, a dispersion test (SKAT) [64] that performs well when the direction of variant effect differs, and a hybrid (SKAT-O) [65] that uses multiple methods in a single test. Analyses were adjusted for sex and principal components. For all three tests we grouped variants into four categories: protein truncating variants (PTV; e.g. nonsense, frameshift, essential splice site), deleterious protein altering variants sub-divided into "strict" and "broad" grouping if predicted deleterious by all five/ at least one annotation algorithm, and any protein altering variants (e.g. missense, in-frame indel, non-essential splice-site. These four groups are referred to as 1) PTV-only, 2) PTV+strict, 3) PTV+broad, and 4) PTV+missense, from the strictest to the most permissive class. A MAF threshold of 1% was applied to the more permissive masks PTV+missense and PTV+broad to exclude common variants from the WES analysis.

WES gene set enrichment analysis: A total of 43 gene sets were created, based on top findings from the GWAS analyses, kidney-related functional terms in public databases, text mining approaches and kidney gene

expression (Supplemental Table 21). These gene sets were analysed for enrichment in 'Late DKD' WES association results (SKAT-O, all four masks) using the GSEA method with SKAT-O's p-value as the ranking statistic[90]. To guard against potential miscalibration of GSEA's reported p-values we conducted 100 permutations of case/control status and subsequently re-ran burden tests and GSEA analysis for each permutation. Significance of enrichment was validated with permutation. For validation of enrichment of GWAS result, the samples in WES were removed from the GWAS data and the analyses were repeated.

Bivariate analysis of GWAS and WES data: We applied ABACUS[67] to the individual GWAS discovery cohorts on each of the seven different case-control phenotypes. In addition, ABACUS was applied to the WES cohorts (FinnDiane, Steno and SDR) on the two phenotypic comparisons. SNP-sets were defined based on REACTOME, KEGG and GO Biological Processes. To analyse non-annotated and intergenic SNPs, we also defined SNP-sets of continuous 3,000 SNPs. Functional clustering of the ABACUS results was performed with DAVID software[91,92].

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A complete list of participants in the DCCT/EDIC research group can be found in New England Journal of Medicine, 2011;365:2366-2376 [82].

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Presentation of results prior publication

Parts of this study have been presented in abstract form at the 49th European Association for the Study of Diabetes (EASD) Annual Meeting 2013 in Barcelona, Spain; at the 74th American Diabetes Association (ADA) Scientific Session 2014 in San Francisco, CA, USA; at the 75th ADA Scientific Session 2015 in Boston, MA, USA; and at the 51st EASD Annual Meeting 2015 in Stockholm, Sweden.

Statement of competing financial interests

P-HG has received lecture honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Genzyme, MSD, Novartis, Novo Nordisk, and Sanofi, and research grants from Eli Lilly and Roche. P-HG is also an advisory board member for AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, MSD, Novartis and Sanofi.

HMC has acted as consultant / advisory panel for Pfizer, Sanofi Aventis, Regeneron and Eli Lilly, Data safety panel for Novartis,; has received research support from Roche, Pfizer, Eli Lilly, Boehringer Ingelheim, AstraZeneca, Sanofi; has participated in a lecture/speaker‘s bureau and received honorarium from Pfizer; and is a shareholder in Roche.

JT has acted as consultant / advisory panel for Bayer Health Care, Sanofi Aventis, Eli Lilly, Roche, Impeto Medical and Novo Nordisk, and has received research support from Roche, Pfizer, Eli Lilly, Boehringer Ingelheim, AstraZeneca, Sanofi; and is a shareholder in Orion Pharma.

PR has acted as consultant /advisory panel for Eli Lilly, Novo Nordisk, AbbVie, Boehringer Ingelheim, Astra Zeneca, Janssen, Astellas, BMS and MSD (all honoraria to institution). Has received research grants from Novo Nordisk, Astra Zeneca and Novartis. Has shares in Novo Nordisk AS.

JCF has acted as consultant for Sanofi.

DZ, MJB, and EF are employees and stockholders of Pfizer.

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Figure legends

Figure 1: Schematic picture of the DKD phenotypic comparisons based on measured AER and eGFR, encompassing different stages and severity of DKD. 'Combined DKD' and 'Late DKD' (conventionally used in many previous genetic studies of DKD) are expected to capture genetic factors affecting DKD in general; 'Early DKD' comparison targets the genetic factors affecting the initiation of DKD, or with milder effect on the phenotype, whereas the two ESRD-based case definitions are expected to capture factors related to the late progression of DKD such as fibrotic processes, or genetic factors with particularly strong effect on the phenotype. While the 'CKD' phenotype may reveal genetic factors for reduced renal function irrespective of the presence of albuminuria, the 'CKD+DKD' phenotype is an extreme phenotype that requires that controls have no signs of renal complications (neither AER or eGFR based). AER thresholds are given in μg/min, eGFR thresholds in ml/min per 1.73 m^2. Normo: Normal AER; miA: microalbuminuria; maA: macroalbuminuria. Number of samples per sub-phenotype: Normo: 2,593; miA: 800; maA: 944; ESRD: 813; no CKD: 2,909; CKD: 1,255; no CKD, no DKD: 2,018; CKD+DKD: 1,117.

Figure 2: The proportion of phenotypic variance explained by genotypes (V(G)/V(p_L)), i.e. the narrow-sense heritability, of the seven studied DKD phenotypic comparisons indicate high heritability especially for the more extreme phenotype definitions. Error bars represent the standard error.

Figure 3: The genetic risk scores (GRS) for body mass index (BMI) and type 2 diabetes (T2D) were associated with diabetic kidney disease (DKD) phenotypes in subjects with type 1 diabetes. A GRS for body mass index (BMI; z-transformed) was associated ($p<2.6\times10^{-3}$ to account for multiple testing, 19 GRS traits) with combined and late DKD, and CKD phenotypes; GRS for T2D was associated with late DKD.

Figure 4: Genome-wide comparison of DKD traits and other phenotypes, evaluated with LD score regression, shows negative correlation between DKD traits, and smoking cessation. Significant correlations (p<0.0029 to account for multiple testing, 17 related phenotypes) are indicated with *. Bars represent 95% confidence intervals.

TABLES

Table 1: Clinical characteristics of the subjects, divided into cases and controls based on the 'combined DKD' phenotype definition

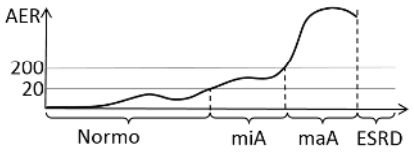
	FinnDiane (N=3,415)		EURODIAB (N=789)		SDR (N=558)		Cambridge (N=396)	
Cohort (N)	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
N	1,802	1,613	298	491	266	292	197	199
N Males (%)	1,067 (59)	669 (41)	170 (57.2)	222 (45.3)	150 (56)	160 (55)	109 (54)	93 (47)
Age of onset of diabetes [year][a]	13.4 (8.4)	15.6 (8.8)	16.7 (8.3)	17.9 (8.1)	15.9 (9.4)	17.1 (9.5)	9.1 (4.0)	7.6 (6.0)
Age [year][a]	45.1 (11.1)	43.6 (11.7)	40.3 (10.3)	42.9 (10.2)	48.2 (14.5)	48.7 (13.2)	17.0 (5.7)	23.4 (10.2)
Duration of diabetes [year][a]	31.7 (9.9)	27.9 (9.6)	23.7 (9.07)	25.0 (7.7)	32.3 (14.0)	31.5 (12.3)	7.9 (5.4)	15.8 (6.8)
BMI [kg/m^2][a]	25.7 (4.1)	25.3 (3.5)	24.6 (3.7)	25.1 (3.42)	24.6 (3.3)	24.4 (3.2)	-	-
HbA_{1C} [%][a]	8.7 (1.6)	8.1 (1.2)	8.3 (1.9)	7.7 (1.6)	7.9 (1.1)	7.1 (0.9)	10.5 (2.3)	8.7 (1.6)
HbA_{1C} [mmol/mol][a]	72 (17)	65 (13)	68 (21)	61 (18)	63 (12)	54 (10)	91 (25)	72 (18)

[a]mean (sd)

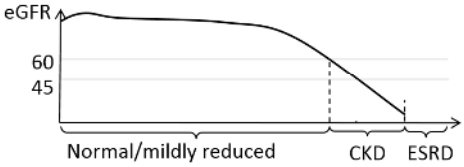
Table 2: Association analysis results for the top SNPs from the GWAS discovery + *in silico* replication analysis, selected for additional *de novo* replication.

	SNP	rs61277444*		rs7562121	rs1989248		rs72809865
	CHR	4		2	7		10
	Gene**	in *PTPN13*		in *AFF3*	23kb to *CNTNAP2*		350kb to *NRG3*
	Pheno	[a,b] ESRD vs. non-ESRD	[b] ESRD vs. no DKD	[a,b] ESRD vs. non-ESRD	[b] CKD+DKD	[a] ESRD vs. no DKD	[a] Combined DKD
Stage I	N	813/3,995	813/2,394	813/3,995	1,117/2,018	813/2,394	2,563/2,593
	EAF	0.09	0.09	0.23	0.28	0.28	0.16
	OR	1.55	1.58	1.46	1.28	1.40	1.30
	95% CI	1.26–1.91	1.26–1.97	1.28–1.66	1.12–1.47	1.21–1.62	1.16–1.46
	P	4.3×10^{-6}	8.7×10^{-6}	8.9×10^{-8}	1.8×10^{-4}	4.0×10^{-6}	5.0×10^{-6}
Stage II	N	964/4,806	964/3,187	964/4,806	1,104/1,981	964/3,187	2,659/3,842
	P	2×10^{-3}	3×10^{-3}	0.037	1×10^{-3}	0.021	0.047
Stage III	N	94/993	94/627	67/822			367/516
	P	0.19	0.14	0.59			0.54
All	N	1,871/9,794	1,871/6,208	1,844/9,623	2,221/3,999	1,777/5,581	5,589/6,951
	N total	11,665	8,079	11,467	6,220	7,358	12,540
	OR	1.41	1.42	1.27	1.26	1.29	1.17
	95% CI	1.21–1.65	1.20–1.67	1.17–1.39	1.15–1.38	1.17–1.43	1.09–1.26
	P	1.9×10^{-6}	6.0×10^{-6}	3.5×10^{-7}	6.0×10^{-7}	1.8×10^{-6}	7.4×10^{-6}

N: number of cases/ controls. EAF: Effect allele frequency. Selection criteria for *de novo* replication: [a] *p*-value < 10^{-6} for discovery + stage two meta-analysis. [b] *p*-value < 0.05 in the *in silico* replication for the phenotype selected for replication; *Due to moderate imputation quality at the discovery stage, rs61277444 was directly genotyped in 2,913/3,415 FinnDiane subjects. The association in FinnDiane was moderately attenuated from OR=1.49 (95% CI 1.19 - 1.86, $p=4.5\times10^{-4}$; ESRD vs. non-ESRD) and OR=1.50 (95% CI 1.18 - 1.91, $p=1\times10^{-3}$; ESRD vs. no DKD) with the imputed data to OR=1.36 (95% CI 1.11 - 1.66, $p=3.0\times10^{-3}$; ESRD vs. non-ESRD) and OR=1.40 (95% CI 1.11 - 1.75, $p=3.9\times10^{-3}$; ESRD vs. no DKD) using directly genotyped data. ** The closest gene/genes.



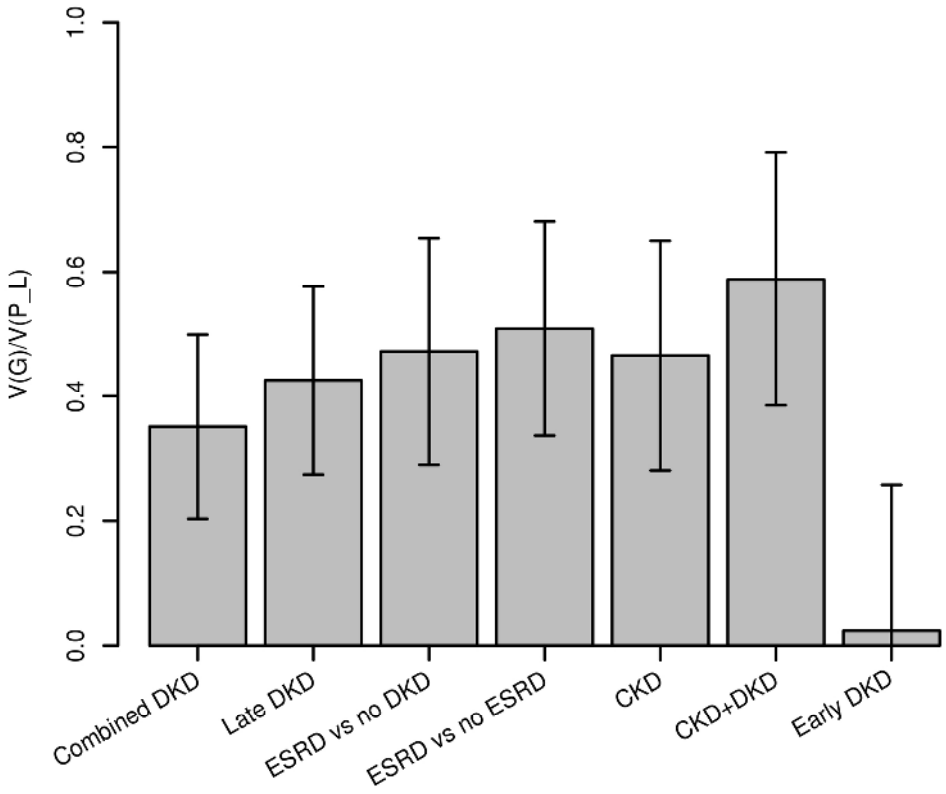
Pheno	Normo	miA	maA	ESRD*
Combined DKD	CTRL	CASE	CASE	CASE
Early DKD	CTRL	CASE		
Late DKD	CTRL		CASE	CASE
ESRD vs. no DKD	CTRL			CASE
ESRD vs. non-ESRD	CTRL	CTRL	CTRL	CASE



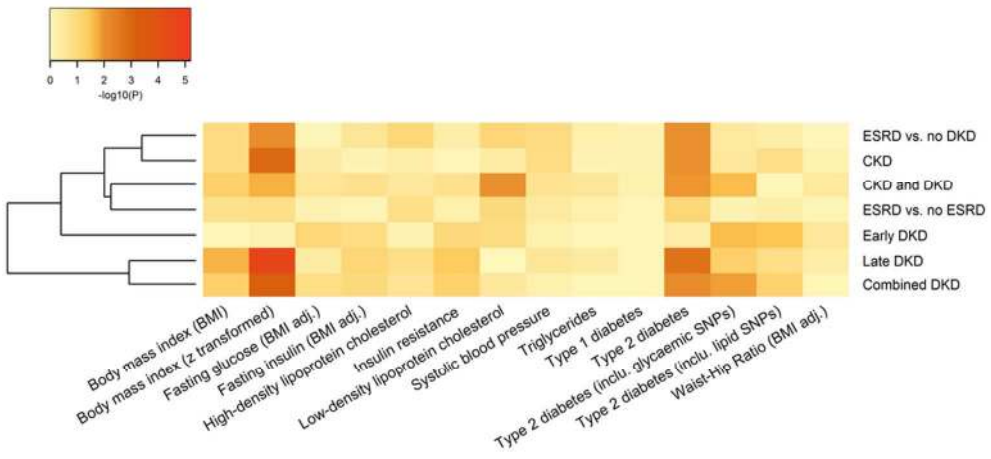
Pheno	≥60	(45,60]	<45**
CKD	CTRL	CASE	CASE
CKD+DKD	CTRL if normo		CASE if miA/ maA/ ESRD

*ESRD: Dialysis/ transplant/ eGFR<15
**eGFR<45 or ESRD

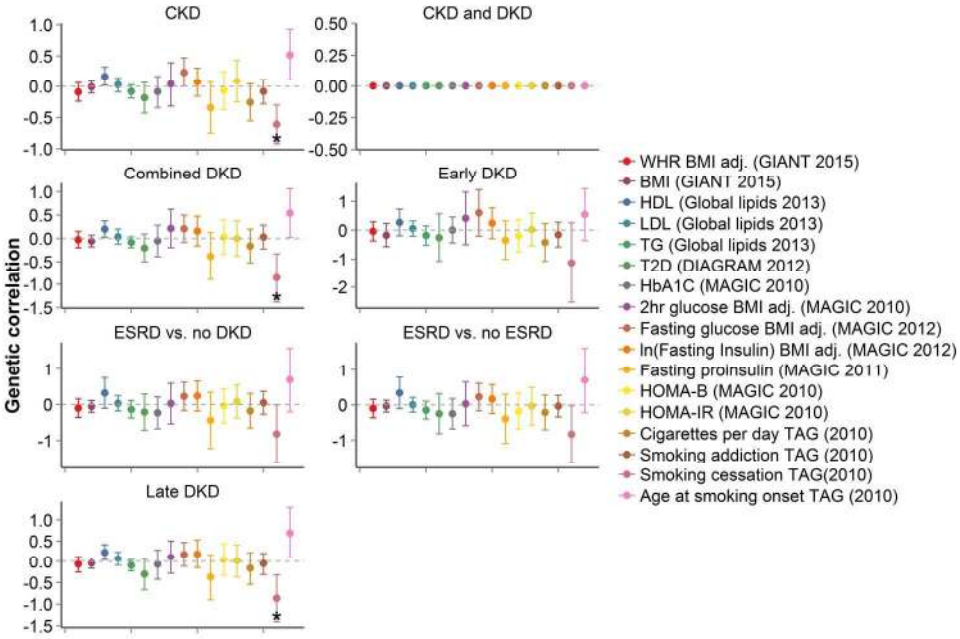
254x96mm (150 x 150 DPI)



76x65mm (600 x 600 DPI)



93x43mm (300 x 300 DPI)



194x129mm (300 x 300 DPI)

The Genetic Landscape of Renal Complications in Type 1 Diabetes

SUPPLEMENTAL INFORMATION

Niina Sandholm, Natalie Van Zuydam, Emma Ahlqvist, Thorhildur Juliusdottir, Harshal A. Deshmukh, N. William Rayner, Barbara Di Camillo, Carol Forsblom, Joao Fadista, Daniel Ziemek, Rany M. Salem, Linda T. Hiraki, Marcus Pezzolesi, David Trégouët, Emma Dahlström, Erkka Valo, Nikolay Oskolkov, Claes Ladenvall, M. Loredana Marcovecchio, Jason Cooper, Francesco Sambo, Alberto Malovini, Marco Manfrini, Amy Jayne McKnight, Maria Lajer, Valma Harjutsalo, Daniel Gordin, Maija Parkkonen, Jaakko Tuomilehto, Valeriya Lyssenko, Paul M. McKeigue, Stephen S. Rich, Mary Julia Brosnan, Eric Fauman, Riccardo Bellazzi, Peter Rossing, Samy Hadjadj, Andrzej Krolewski, Andrew D. Paterson, Jose C. Florez, Joel N. Hirschhorn, Alexander P. Maxwell, David Dunger, The DCCT/EDIC Study Group, GENIE Consortium, The FinnDiane Study Group, Claudio Cobelli, Helen M. Colhoun, Leif Groop, Mark I. McCarthy, Per-Henrik Groop, on behalf of The SUMMIT Consortium

COMPLETE METHODS

Subjects with Type 1 diabetes (T1D)

Subjects in the GWAS discovery studies: The GWAS discovery stage included subjects with T1D from four studies: The Finnish Diabetic Nephropathy (FinnDiane) Study[1,2], the EURODIAB Family Study[3], the Scania Diabetes Registry (SDR)[4], and the UK Nephropathy Family Study and Oxford Regional Prospective Study (NFS-ORPS/ Cambridge)[5,6]. All studies were approved by the local ethics committees and conducted according to the principles of the Declaration of Helsinki. Written consent was obtained from the participants in FinnDiane, Eurodiab, SDR and Steno Studies. In the NFS-ORPS study, written consent was obtained from parents, and verbal assent was obtained from children.

The Finnish Diabetic Nephropathy (FinnDiane) Study[1,2]: FinnDiane is a Finnish nationwide prospective multicenter study, with the aim to identify genetic, clinical, biochemical and environmental risk factors for diabetic complications. The study includes patients from all five Finnish University Central Hospitals, all 16 central hospitals, and 56 regional hospitals and health care centers. The study protocol and patient recruitment criteria have been previously described [1]. In short, patients with type 1 diabetes (T1D) were recruited at their own health care center by their attending physician, who completes the main questionnaire. Blood and urine samples are sent to the central laboratory of the FinnDiane Study. The patients have been followed up in prospective follow-up visits roughly 5-7 years after the baseline visit. In addition, FinnDiane Study includes patients with type 1 diabetes recruited by the Finnish National Institute of Health and Welfare across Finland. Retrospective data has been retrieved from medical records. Furthermore, information on major clinical events, such as the onset of ESRD, can be retrieved from the Finnish Hospital Discharge Registry (HILMO).

The EURODIAB Family Study[3]: The Eurodiab Insulin Dependent Diabetes (IDDM) Complications Study was a cross-sectional investigation of a stratified random sample of IDDM patients attending 31 clinics in 16 European countries that were carried out in 1989/91. These subjects were then followed up around 6-8 years later in the EURODIAB Prospective Complications Study. T1D was defined as diabetes onset <35 years with insulin within one year of diagnosis. This collection was supplemented by additional T1D cases with nephropathy at those EURODIAB

participating centres even if the patient hadn't participated in the original EURODIAB IDDM Complications study. We also recruited several additional centres (UK, Austria & Poland) to focus specifically on late stage and dialysis patients. The current GWAS study comprised cases with micro- or macroalbuminuria, ESRD, or elevated serum creatinine (>200 µmol/lit) consistent with ESRD. Cases were captured from several sources (EURODIAB at baseline, EURODIAB at follow up, additional cases from these centres not in the original cohort study and renal failure cases from several new non-EURODIAB centres). Non-DKD controls were only recruited from the original Eurodiab IDDM Complications Study cohort. They had at least 15 years of T1D duration and remained normoalbuminuric for the follow-up period. In addition to local MICRAL strip testing, the controls had normoalbuminuria confirmed by the central EURODIAB on two overnight collections at follow up and on one collection at baseline.

Scania Diabetes Registry (SDR)[4]: Patients in SDR were randomly collected from the Department of Endocrinology, Malmö Sweden and surrounding clinics in Skåne (Scania) Sweden. Patients of known non-Scandinavian origin were excluded from the analysis. Diabetes classification was done based on presence of GAD antibodies and low c-peptide levels, or in case of incomplete information, based on the diagnosis given by the treating physician. All patients with T1D were diagnosed before 35 years of age.

The UK Nephropathy Family Study and Oxford Regional Prospective Study (NFS-ORPS/ Cambridge)[5,6]: ORPS is a population-based inception cohort of childhood-onset T1D, established between 1986 and 1997, with the aim of assessing the natural history of microalbuminuria [5]. Children diagnosed with T1D under the age of 16 years, in the defined geographic region of the Oxford Health Authority, were recruited within 3 months of diagnosis of Type 1 diabetes to receive annual assessments. Ninety-one percent of eligible children were recruited at a mean age of 8.8 years and were followed annually thereafter. The overall dropout rate for the ORPS cohort has been 9.6%.

The NFS is a prospective study started in the year 2000 with the aim of assessing factors influencing changes in albumin excretion during adolescence in young people with T1D [6]. Between 2000 and 2005, adolescents (aged 10–18 years), diagnosed with T1D before the age of 16 years, were recruited throughout England. Cases of secondary diabetes treated with insulin or maturity-onset diabetes of the young were identified by clinical histories and

examination of case records, and were excluded. Similarly, children with chronic renal disease or other chronic diseases likely to affect renal function were excluded.

Both cohorts were monitored with annual centralized assessments of ACR, based on three consecutive early morning urine samples.

The studies received ethical approval from district ethics committees. Written consent was obtained from parents, and verbal assent was obtained from children.

Phenotype definitions: All subjects had T1D as diagnosed by their attending physician. In addition, subjects were limited to those with the age at diabetes onset ≤40 years and insulin treatment initiated within one year of diagnosis. The kidney status was classified based on the urinary albumin excretion rate (AER) and on the estimated glomerular filtration rate (eGFR). The subjects were classified as normal AER, microalbuminuria or macroalbuminuria based on two out of three consecutive urine samples surpassing the required threshold (Supplemental Table 26). Patients receiving dialysis treatment, with a kidney transplant, or with an eGFR ≤15 ml/min/1.73m^2 were defined to have ESRD. eGFR was calculated either with the MDRD4 [7] or the CKD-EPI [8] formula depending on the study. In addition, subjects were classified to CKD classes: No CKD was defined as eGFR ≥60ml/min/1.73m^2 (i.e. CKD classes 1 and 2), and CKD as eGFR <60 ml/min/1.73m^2 (i.e. CKD classes 3-5). Based on these definitions, we analysed seven different case – control phenotypes: i) cases with DKD (microalbuminuria or worse) versus controls with normal AER; ii) cases with macroalbuminuria or ESRD versus normal AER; iii) cases with ESRD versus controls with normal AER; iv) cases with ESRD versus everyone else; v) cases with microalbuminuria versus controls with normal AER; vi) cases with CKD versus controls without CKD; vii) cases with severe CKD (eGFR ≤45 ml/min/1.73m^2) and microalbuminuria or worse versus controls with normal AER and no CKD. The number of subjects in the four discovery studies is specified for the different phenotype definitions in Supplemental Table 3.

Patient selection for WES: WES included subjects from FinnDiane, SDR, and Steno Diabetes Center (Supplemental Table 12). Whilst we adopted broadly similar schemes for ascertaining the extremes in each of three contributing

studies, there were some differences. Patients were selected from the extreme ends of the liability distribution of DKD from each participating study (FinnDiane, SDR, and Steno). Cases were defined as subjects with rapid onset of macroalbuminuria (within 20/25 years of diabetes onset in FinnDiane and Steno, respectively; no threshold in SDR) or ESRD (onset within 25 years of diabetes onset in FinnDiane and Steno). Controls were subjects with normal AER despite prolonged duration of T1D (≥ 32, 30, or 27 years in FinnDiane, Steno, and SDR, respectively). In addition, the FinnDiane controls were enriched for higher HbA_{1c} values (excluding subjects with HbA_{1c} < 6.5 %), and a half of the controls were selected to have proliferative diabetic retinopathy or retinal laser treatment.

Genotypes

Genome-wide genotyping and imputation of the discovery cohorts: The genome-wide genotyping of the subjects in the SDR, NFS-ORPS, and EURODIAB (a sub-study of the EURODIAB PCS) was performed within the SUMMIT project with the Illumina OmniExpress assays (Illumina, San Diego, CA, USA). Samples with a call rate <98% or gender discrepancy were removed in the first step of quality control. Subsequently, common single nucleotide polymorphisms (SNPs; i.e. minor allele frequency (MAF) ≥0.05) with low genotyping rate (<95%) or not in Hardy-Weinberg equilibrium (HWE; p-value≤5.7×10^{-7}) were removed. For non-common SNPs (MAF 0.01 – 0.05), the thresholds were 99% and p-value <10^{-4}, respectively. Samples with extremely high or low heterozygosity or excess of estimated relatedness were removed due to suspected sample contamination or issues in the sample processing, based on study specific distributions. In the FinnDiane Study, genotyping was performed with the Illumina 610Quad assay and the quality control was similar to the other studies, as described previously in detail [2]. Principal component analysis was performed in all cohorts with the Eigenstrat software (Eigensoft v. 3.0, [9]).

After the quality control, the SNP positions were converted to human genome build 37, and genome-wide imputation was performed with IMPUTE2 (https://mathgen.stats.ox.ac.uk/impute/impute_v2.html [10]) using 1,092 samples from the 1000 Genomes project (http://www.1000genomes.org, phase 1 v.3, released March 2012) as the imputation reference panel [11]. The pre-phasing and imputation were performed with the default parameters and the effective

sample size of 20,000 as suggested in the IMPUTE2 tutorial. Variants were filtered post-imputation to those with MAF ≥ 0.01, minor allele count ≥10 in both cases and controls, and SNPtest INFO estimate of imputation quality ≥0.4.

Whole exome sequencing and variant calling: Samples were sequenced at two centres. The samples were prepared using the Illumina TruSeq™ DNA LT Sample Prep Kit, pooled into multiplexes of five and were captured using the Illumina TruSeq™ Exome Enrichment Kit. The concentration of each library was determined by real-time qPCR using Agilent qPCR Library Quantification Kit and a MX3005P instrument (Agilent). Sequencing was performed on an Illumina HiSeq2000, using 100bp paired end reads and with an anticipated minimum yield of 30 Gb per lane. Five exomes of 63Mb were run per lane (single lane for most), aiming for approximately 100x read depth. We required an average 20x target capture above 80% coverage, otherwise additional DNA was requested to 'top up' the sample. This resulted in mean sequencing depth of 54.97 (FinnDiane) and 42.23 (SDR and Steno) bases per position. After additional sequencing 497 samples were included from FinnDiane and 500 from SDR and Steno.

Samples were mapped with Burrows-Wheeler aligner v7.4 (BWA), refined by removing duplicates and realigning around known insertions and deletions (INDELs), and recalibrated using genome analysis toolkit v2.1 (GATK). GATK's UnifiedGenotyper was applied to call variants, followed by recalibration of SNVs using VQSR and hard filtering of INDELs.

Polymorphic variants (MAF>0) with a mapping quality < 250, HWE *p*-value >1×10^{-10} and call rate ≥75% were retained in the analysis. Samples with ≥10% missingness or heterozygosity rate greater or less than 3 standard deviations from the sample mean were excluded. Population outliers (based on visual inspection of the four first principal components), duplicates and related samples were removed. Variants were annotated using CHAos (http://www.well.ox.ac.uk/~kgaulton/chaos.shtml), snpEff (http://snpeff.sourceforge.net/ [12]) and VEP (http://www.ensembl.org/info/docs/tools/vep/ [13]) for functional class and transcript.

With 530,565 variants (491,553 SNPs and 39,012 indels) across 479 controls and 481 cases after the quality control, each individual carried a mean of 7,566 synonymous, 6,452 missense and 103 protein truncating variants. The lower number of total variant sites compared to other, more outbred populations [14] is in line with fewer variable sites seen in founder populations such as the Finns [15].

Statistical methods

Heritability estimates: The narrow-sense heritability of the kidney phenotypes was estimated as the proportion of the phenotypic variance explained by the additive effects of the genotyped SNPs based on the FinnDiane GWAS data using the GCTA v. 0.93.9, excluding samples with estimated relatedness ≥ 0.025 [16]. The observed variance explained was transformed to the underlying population scale based on rough prevalence estimates as given in Supplemental Table 1. The heritability was estimated without covariates, and adjusting for sex, duration of T1D and age at T1D onset.

GWAS analysis: The genome-wide association analysis was performed with two methods in parallel. To obtain stable effect size estimates, we performed additive test for association using SNPtest with the score method and adjusted for sex, diabetes duration and age at diabetes onset [17], and the two first principal components calculated with the Eigenstrat software (Eigensoft v. 3.0, [9]). Close relatives were not included in the analysis. *P*-values were obtained with a variance component based mixed model method, EMMAX, which accounts for the sample structure, allowing to include close relatives in the analysis [18]. Models were adjusted for sex, diabetes duration and age at diabetes onset and the kinship matrix was calculated with EMMAX. EMMAX algorithm was implemented with the EPACTS software (www.sph.umich.edu/csg/kang/epacts/).

Meta-analyses of the effect sizes were performed with the fixed-effect inverse variance method implemented in GWAMA [19]). *P*-values were combined with METAL software based on the study-wise *p*-values, sample sizes and effect directions [20]. Meta-analysis results were further filtered to those with valid results from at least two studies. P-values below 5×10^{-8} were considered genome-wide significant, not correcting for multiple testing due to seven phenotypic comparisons, as the case and control groups were overlapping and the traits were correlated with each other.

Power calculations were performed with the genetic power calculator (pngu.mgh.harvard.edu/~purcell/gpc/) for simple case-control setting,[21] and with Power Calculator for Two Stage Association Studies (CaTS; http://csg.sph.umich.edu//abecasis/cats/).[22]

***In silico* Replication:** Independent variants with a *p*-value < 5×10^{-6} were selected for *in silico* replication. Variants were defined independent if they were at least 100 kilo base pair (kbp) away from each other. The selection was performed separately for each phenotype, and therefore, multiple variants were selected for some loci with different lead variants for different phenotypes. Replication consisted of six additional studies: the All Ireland – Warren 3 – Genetics of Kidneys in Diabetes UK collection (UK-ROI) [2] and the Genetics of Kidneys in Diabetes US Study (GoKinD US) [2] from the GENIE Consortium, the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study [23,24], 1,073 subjects from the Joslin Diabetes Center T1D nephropathy collection, and the French, Belgian and Danish subjects (the Steno Diabetes Center) from the French-Danish Effort [25]. The number of subjects in each study is given in Supplemental Table 3. Association testing was performed with PLINK or SNPtest depending on the study, using the same covariates as in the discovery stage.

***De novo* replication and genotyping:** After *in silico* replication, variants replicated with a *p*<0.05 or a combined *p*-value < 1×10^{-7} after meta-analysis were selected for *de novo* replication. A total of 1,095 additional FinnDiane patients, not part of the GWAS, were genotyped for stage 3 analysis with TaqMan (Supplemental Table 2). Additionally, subjects with T1D from the Diabetes in Region of Vaasa (DIREVA) study, a follow-up study from Finland with >5,000 subjects with diabetes, were genotyped together with DIREVA subjects with T2D using either Taqman (rs72809865) or Sequenom (the rest). rs1989248 was not successfully genotyped in either *de novo* replication study. Additionally, genotyping of rs72809865 was unsuccessful in DIREVA, and only four cases with T1D and ESRD were identified in DIREVA after removing subjects that were included in the FinnDiane discovery study. Thus, no SNPs remained for analysis from DIREVA. Association analysis was performed in the FinnDiane replication cohort similarly to *in silico* replication using logistic regression and adjusted for sex, duration of diabetes, and age at diabetes onset. As one of the lead SNPs, rs61277444 was imputed with only moderate quality, that SNP was *de novo* genotyped also in 2,913 FinnDiane subjects from the discovery study. Concordant to the imputation quality INFO score of 0.83 in FinnDiane, the *de novo* genotyping agreed with the imputed genotypes (converted to most likely genotypes with genotype likelihood threshold of 0.9) for 73% of the samples.

Genetic risk score analysis: SNPs associated with Waist-Hip-ratio (adjusted for BMI, N_{SNPs}=54)[26], BMI (untransformed, N_{SNPs}=96 [27] and z-transformed, N_{SNPs}=24 [28]), systolic blood pressure (SBP, N_{SNPs}=22)[29], low-density lipoprotein cholesterol (LDL-C, N_{SNPs}=24), triglycerides (TRIG, N_{SNPs}=20), high-density lipoprotein cholesterol (HDL-C, N_{SNPs}=26)[30], T1D (N_{SNPs}=51) [31], T2D [32] (including all SNPs (N_{SNPs}=70), and without any other effects other than on T2D or lipids (N_{SNPs}=56)[30] and T2D or glycemic traits (N_{SNPs}=62)[33,34]), 2-hr glucose (adjusted for BMI, N_{SNPs}=15)[35], fasting glucose (FG, adjusted for BMI, N_{SNPs}=21) [34], glycated haemoglobin (HbA1c, N_{SNPs}=15)[36], fasting insulin (natural log transformed and adjusted for BMI, N_{SNPs}=13)[34], fasting pro-insulin (adjusted for BMI and FG, N_{SNPs}=10)[37], HOMA-B (N_{SNPs}=15), HOMA-IR (N_{SNPs}=15)[38] and insulin resistance [39] at genome-wide significance were included in a genetic risk score (GRS) for each trait respectively. The GRS was weighted by the allelic effect of each variant on the DKD risk factor and associated with the DKD phenotypes using meta-analysis data [29]. The lipid GRS were restricted to variants that predicted that specific trait and removed those that had effects on other lipid traits. We did not include a GRS for smoking behaviours as there were too few genome-wide significant associations to form a sufficient instrument.

LD score regression to estimate genetic correlation: Genetic correlation was estimated between the GWAS stage 1 meta-analysis results of the seven binary DKD phenotypes, and related traits. We assembled the summary statistics from all the studies used to calculate genetic risk scores except for systolic blood pressure and T1D as the full summary statistics were not available. We restricted the GRS and LD score regression analyses to reports from full genome-wide SNP data as LDScore regression takes the effect of all SNPs into account. We additionally computed genetic correlation with smoking behaviour phenotypes (cigarettes per day, smoking addiction, smoking cessation and age at smoking onset).[40]

Gene set enrichment analyses: MAGENTA gene set enrichment analysis was performed in the GWAS stage 1 meta-analysis results with the MAGENTA (vs.2) software, [41] applied on 10,992 partially overlapping gene sets from GO, PANTHER, INGENUITY, KEGG, REACTOME, and BIOCARTA data bases; 3,126 gene sets with ≥10 genes were analysed. Gene boundaries used for mapping SNPs onto genes were 110kb upstream to most extreme gene transcript start position, and 40kb downstream to most extreme gene transcript end position. The 95 percentile cut-off for the gene scores was employed to define the significant results.

Correction for multiple testing: The significance threshold for the results of the evaluation of previous loci, GRS, LD score regression, and pathway enrichment analyses were Bonferroni corrected for multiple testing with α=0.05 significance level, accounting for the number of performed tests. The results were not corrected for the seven phenotypic comparisons due to a considerable overlap of the case and control groups.

WES single variant analysis: Single variants were tested for association with DKD (N cases=481, N controls=479) and ESRD (N cases=168, N controls=479) using the logistic score test [42] implemented in Epacts, with sex and two principal components as covariates. Related individuals, monomorphic SNPs and those with standard error greater than 10 were excluded from the analysis. While the study setting provided low statistical power to detect rare variants with exome-wide significance ($p<9\times10^{-8}$ to correct for 530,776 tested variants) in line with previous reports on the statistical power to detect rare variants [43], we had sufficient power (80%) to detect a low frequency variant (MAF=0.05) with a large OR of 5.65 (Supplemental Figure 13).

WES gene-based analysis: We applied three series of gene based tests: a burden test (VT) [44] that assumes the direction of effect of grouped variants is the same, a dispersion test (SKAT) [45] that performs well when the direction of variant effect differs, and a hybrid (SKAT-O) [46] that uses multiple methods in a single test. Only unrelated individuals were included in the analysis and sex and principal components were used as covariates to adjust for population structure. For all three tests we grouped variants into four categories using the same procedure as described in Mahajan *et al.* [47], were variants were categorized as either protein truncating (PTV; e.g. nonsense, frameshift, essential splice site), deleterious protein altering variants (e.g. missense, in-frame indel, and non-essential splice-site variants predicted to be deleterious, further sub-divided into "strict" and "broad" grouping if predicted deleterious by all five/ at least one annotation algorithm (Polyphen2-HumDiv, PolyPhen2-HumVar, LRT, MutationTaster and SIFT), respectively, as described by Purcell *et al.* [48], and any protein altering variants (e.g. missense, in-frame indel, non-essential splice-site) if predicted to be so by at least one of three annotation algorithms (snpEff, CHAos and VEP). These four groups are referred to as 1) PTV-only, 2) PTV+strict, 3) PTV+broad, and 4) PTV+missense, from the strictest to the most permissive class. A MAF threshold of 1% was applied to the more permissive masks PTV+missense and PTV+broad to exclude common variants from the WES analysis.

WES gene set enrichment analysis: We were interested in seeing whether we could find any signals in common with GWAS and WES association data, as well as detect enrichment for specific gene-sets. A total of 43 gene sets were created, based on top findings from the GWAS analyses, kidney-related functional terms in public databases, text mining approaches and kidney gene expression. These gene sets were analysed for enrichment in WES association results (obtained with SKAT-O using the four different masks described above) using the GSEA method with SKAT-O's p-value as the ranking statistic[49]. We applied permutations to the enriched gene sets to verify whether this enrichment was greater than expected by chance, by randomly assigning case/control status to the samples prior to re-analysing them with SKAT-O (using the same parameter settings as applied to the real data). This was repeated 100 times for each of the enriched gene sets, noting the number of times the top finding in the permuted data had a better enrichment score than the candidate geneset in the real data. Since both of the enriched gene sets were derived from GWAS data, which included some of the WES samples, we removed overlapping samples and re-created the gene-sets and repeated the GSEA analysis.

Bivariate analysis of GWAS and WES data: We applied ABACUS[50] to the individual GWAS discovery cohorts (FinnDiane, EURODIAB, SDR, NFS-ORPS) on each of the seven different case-control phenotypes. In addition, ABACUS was applied to the WES cohorts (FinnDiane, Steno and SDR) on the 'Late DKD' and 'ESRD vs. no DKD' phenotypic comparisons as in the main WES analysis. For the SNP-sets definition we used REACTOME, KEGG and GO Biological Process, as defined in MSigDB database (sets c2 and c5) after mapping SNPs to genes according to the Illumina HumanOmniExpress.12v1_J gene annotation file. In order to analyse non-annotated SNPs/genes, we also defined SNP-sets of continuous 3,000 SNPs within each chromosome. Functional clustering of the ABACUS results was performed with DAVID software[51,52].

SUPPLEMENTAL TABLES

Supplemental Table 1: Proportion of phenotypic variance explained by the GWAS genotypes in FinnDiane, estimated with GCTA

Phenotype	Prevalence	N	Adj	V(G)/V(p)	SE V(G)/V(p)	V(G)/V(p_L)	SE V(G)/V(p_L)	P
Combined DKD	0.3	2,843	no	0.24	0.10	0.35	0.15	6.4E-03
Combined DKD	0.3	2,843	yes	0.34	0.10	0.50	0.15	2.5E-04
Late DKD	0.2	2,495	no	0.32	0.11	0.43	0.15	1.3E-03
Late DKD	0.2	2,495	yes	0.51	0.12	0.67	0.15	2.0E-06
ESRD vs. no DKD	0.1	1,985	no	0.38	0.14	0.47	0.18	3.4E-03
ESRD vs. no DKD	0.1	1,985	yes	0.54	0.15	0.68	0.18	7.5E-05
ESRD vs. non-ESRD	0.1	2,843	no	0.31	0.10	0.51	0.17	1.2E-03
ESRD vs. non-ESRD	0.1	2,843	yes	0.34	0.10	0.57	0.17	4.7E-04
CKD	0.3	2,595	no	0.28	0.11	0.47	0.18	4.2E-03
CKD	0.3	2,595	yes	0.39	0.11	0.65	0.19	1.5E-04
CKD+DN	0.2	1,949	no	0.42	0.14	0.59	0.20	1.1E-03
CKD+DN	0.2	1,949	yes	0.59	0.15	0.84	0.20	9.8E-06
Early DKD	0.1	1,820	no	0.02	0.16	0.02	0.24	0.46
Early DKD	0.1	1,820	yes	0.03	0.16	0.04	0.24	0.43

Prevalence: Estimated prevalence of the cases in the T1D, employed for transforming the results for the underlying T1D population. Adj: no, model unadjusted; yes: model adjusted for sex, diabetes duration, and age at diabetes onset. V(G)/V(p) proportion of phenotypic variance explained by the genotypes, i.e. heritability, as observed in the study population. SE: standard error. V(G)/V(p_L): proportion of phenotypic variance explained by the genotypes, i.e. heritability, transformed for the underlying population scale.

Prevalences were estimated as a combination of the following data:

Microalbuminuria or worse: Cumulative incidence of persistent micro-albuminuria was 33,6% (95% confidence interval 27.2% to 40.0%; median follow-up 18-years) in Hovind P. *et al*., *BMJ* 2004 [53]

Macroalbuminuria or worse: Cumulative incidence of persistent macroalbuminuria was 14.6% (8.9% to 20.3%; Median follow-up 18 years) in Hovind P. *et al*., *BMJ* 2004 [53]

ESRD: 40-year Cumulative risk of ESRD was 23.0% in Harjutsalo V. *et al., Diabetologia* 2011 [54]

CKD (eGFR≤60 ml/min/1.73m^2): The 16-year cumulative incidence of CKD was 31.7 percent in Shankar A et al., *Exp Clin Endocrinol Diabetes* 2007 [55]

CKDDN: All patients with ESRD, plus patients with macroalbuminuria and eGFR<45 ml/min/1.73m^2.

Supplemental Table 2: Information on genotyping, and clinical characteristics of the discovery and replication patients divided based on the seven case – control definitions

Supplemental Table 2 can be found on the Supplemental Excel sheet.

Supplemental Table 3: Number of subjects included in the analysis in the discovery and *in silico* replication cohorts

Phenotype criteria	Cohort	Stage 1: Discovery GWAS					Stage 2: *In silico* replication						Total Stages 1+2
		FinnDiane	EURODIAB	SDR	NFS-ORPS	Total	UK-ROI	GoKinD US	French/Danish	DCCT/EDIC	Joslin	Total	
	N total	3,415	789	556	396	5,156	1,726	1,595	1,415	1,271	1,073	7,095	12,251
Combined DKD	total	3,415	789	556	396	5,156	1,726	1,595	1,430	1,271	1,073	7,095	12,251
miA/maA/ESRD	case	1,802	298	266	197	2,563	823	774	691	551	349	3,188	5,751
noA	control	1,613	491	290	199	2,593	903	821	739	720	724	3,907	6,500
Early DKD	total	2,076	586	382	349	3,393	–	–	931	1,130	–	2,061	5,454
miA	case	463	95	92	150	800	–	–	192	410	–	602	1,402
noA	control	1,613	491	290	199	2,593	–	–	739	720	–	1,459	4,052
Late DKD	total	2,952	694	458	246	4,350	1,726	1,595	1,188	861	1,073	6,443	6,878
maA/ESRD	case	1,339	203	168	47	1,757	823	774	449	141	349	2,536	4,293
noA	control	1,613	491	290	199	2,593	903	821	739	720	724	3,907	6,500
ESRD vs. no DKD	total	2,267	575	365	–	3,207	1,149	1,329	811	–	862	4,151	7,358
ESRD	case	654	84	75	–	813	246	508	72	–	138	964	1,777
noA	control	1,613	491	290	–	2,394	903	821	739	–	724	3,187	5,581
ESRD vs. non-ESRD	total	3,415	789	604	–	4,808	1,687	1,595	1,415	–	1,073	5,770	5,385
ESRD	case	654	84	75	–	813	246	508	72	–	138	964	1,777
noA/miA/maA	control	2,761	705	529	–	3,995	1,441	1,087	1,343	–	935	4,806	8,801
CKD	total	3,056	580	528	–	4,164	1,274	1,586	1,421	1,266	1,048	6,595	10,759
eGFR<60	case	979	113	163	–	1,255	668	710	391	79	198	2,046	3,301
eGFR>60	control	2,077	467	365	–	2,909	606	876	1,030	1,187	850	4,549	7,458
CKD+DKD	total	2,211	567	357	–	3,135	839	1,419	836	–	827	3,921	7,056
eGFR<45 AND miA/maA/ESRD	case	789	210	118	–	1,117	316	635	162	–	153	1,266	2,383
eGFR>60 AND noA	control	1,422	357	239	–	2,018	523	784	674	–	674	2,655	4,673

miA: microalbuminuria. maA: Macroalbuminuria. noA: normal albuminuria.

Supplemental Table 4: Statistical power to detect association with 'combined DKD' with genome-wide significance (p<5×10-8) at the discovery stage.

			Risk Allele frequency				
OR	**RR (Aa)**	**RR (AA)**	**0.01**	**0.05**	**0.10**	**0.20**	**0.50**
1.10	1.07	1.14	0.00	0.00	0.00	0.00	0.00
1.2	1.13	1.28	0.00	0.00	0.00	0.04	0.16
1.3	1.19	1.42	0.00	0.00	0.00	0.04	0.16
1.4	1.25	1.56	0.00	0.05	0.39	0.90	1.00
1.5	1.30	1.70	0.00	0.17	0.76	1.00	1.00
1.55	1.33	1.77	0.00	0.30	0.90	1.00	1.00
1.6	1.36	1.84	0.00	0.46	0.97	1.00	1.00
2.0	1.54	2.37	0.03	0.99	1.00	1.00	1.00

RR: Relative Risk, calculated as RR = OR/((1-prev)+(prev x OR)), where prev is the incidence in non-carrier group, assumed to be 30% for the Combined DKD phenotype. RR (AA) was calculated as RR(Aa)^2

Supplemental Table 5: Association analysis results for the 101 GWAS SNPs selected for *in silico* replication.

Supplemental Table 5 can be found on the Supplemental Excel sheet.

Supplemental Table 6: Statistical power to detect association with 'Combined DKD' with genome-wide significance ($p<5x10^{-8}$) with the two-stage study design.

			Risk allele frequency						
OR	RR (Aa)	RR (AA)	0.01	0.05	0.10	0.20	0.30	0.40	0.50
1.10	1.07	1.14	0	0	0	0	0	0.01	0.01
1.2	1.13	1.28	0	0	0.01	0.09	0.19	0.25	0.25
1.3	1.19	1.42	0	0.02	0.17	0.57	0.78	0.84	0.83
1.4	1.25	1.56	0	0.13	0.57	0.95	0.99	0.99	0.99
1.47	1.29	1.66			**0.80**				
1.5	1.30	1.70	0	0.33	0.87	1	1	1	1
2	1.54	2.37	0.09	1	1	1	1	1	1

RR: Relative Risk, calculated as RR = OR/((1-prev)+(prev x OR)), where prev is the incidence in non-carrier group, assumed to be 30% for the Combined DKD phenotype.

RR (AA) was calculated as $RR(Aa)^2$

Power calculations were performed with Power Calculator for Two Stage Association Studies (CaTS; http://csg.sph.umich.edu//abecasis/cats/)

Parameters used in the calculations:

N= 5,751 cases, 6,500 controls; 42% of samples genotyped in stage 1

11/ 8,578,867 = 0.000128% of markers genotyped at stage 2

Significance level: $p=5\times10^{-8}$

Prevalence: 30%

Additive genetic model

Supplemental Table 7: Association at the *AFF3* locus with 'ESRD vs. non-ESRD' phenotypic comparison, conditional on the previously reported lead SNP rs7583877

					Raw results			Conditional on the other SNP		
Chr	SNP	bp	refA	freq	Beta	se	p	Beta	se	p
2	rs7583877	100460654	T	0.71	-0.26	-0.06	8.71E-05	0.01	0.04	0.78
2	rs7562121	100384354	G	0.77	-0.38	-0.07	8.92E-08	-0.16	0.04	1.97E-04

Supplemental Table 8: Statistical power to detect association with the 'Late DKD' phenotype for varying odds ratio and risk allele frequency.

Power to detect association with p<0.05

			Risk allele Frequency			
OR	**RR (Aa)**	**RR (AA)**	**0.05**	**0.10**	**0.20**	**0.50**
1.10	1.08	1.16	0.17	0.27	0.42	0.56
1.2	1.15	1.33	0.45	0.71	0.91	0.98
1.25	1.19	1.42	0.63	0.88	0.99	1.00
1.3	1.23	1.50	0.79	0.96	1.00	1.00
1.4	1.30	1.68	0.95	1.00	1.00	1.00
1.5	1.36	1.86	0.99	1.00	1.00	1.00
2	1.67	2.78	1.00	1.00	1.00	1.00
2.5	1.92	3.70	1.00	1.00	1.00	1.00

Power to detect association with $p<1.1\times10^{-3}$ (correction for multiple testing)

			Risk allele Frequency			
OR	**RR (Aa)**	**RR (AA)**	**0.05**	**0.10**	**0.20**	**0.50**
1.10	1.08	1.16	0.01	0.03	0.07	0.13
1.2	1.15	1.33	0.08	0.23	0.53	0.79
1.3	1.23	1.50	0.31	0.69	0.95	0.99
1.4	1.30	1.68	0.62	0.94	1.00	1.00
1.5	1.36	1.86	0.84	0.99	1.00	1.00
2	1.67	2.78	1.00	1.00	1.00	1.00
2.5	1.92	3.70	1.00	1.00	1.00	1.00

RR: Relative Risk, calculated as RR = OR/((1-prev)+(prev × OR)), where prev is the incidence in non-carrier group, assumed to be 20% for the Late DKD phenotype. RR(AA) was calculated as $RR(Aa)^2$.

Supplemental Table 9: Evaluation of previously reported candidate genes or GWAS loci on kidney complications in type 1 and type 2 diabetes, or GWAS on CKD in the general population.

						DKD			Early DKD			Late DKD			ESRD vs. no DKD			ESRD vs. non-ESR			CKD			CKD+DKD			
SNP	GENE	Source	Type	EA	NEA	EAF	P	OR	EAF	P	OR	EAF	P	OR	EAF	P	OR	EAF	P	OR	EAF	P	OR	EAF	P	OR	Direction
rs2838302	*SIK1*	Sambo 2014	GWAS, T1D-ESRD	G	A	0.08	0.81	1.04	0.08	0.25	0.9	0.08	0.32	1.09	0.08	0.0017	1.39	0.08	4.10E-05	1.56	0.08	0.0019	1.35	0.09	0.03	1.24	Same
rs7583877	*AFF3*	Sandholm 2012	GWAS, T1D-ESRD	T	C	0.71	0.85	0.99	0.71	0.06	1.13	0.7	0.21	0.94	0.7	0.0044	0.81	0.71	8.70E-05	0.77	0.71	0.02	0.88	0.7	0.01	0.85	same
rs17709344	*RGMA-MCTP2*	Sambo 2014	GWAS, T1D-ESRD	A	G	0.03	0.01	1.39	0.02	0.1	1.4	0.03	0.004	1.56	NA	NA	NA	NA	NA	NA	0.02	0.01	1.56	0.03	8.20E-04	1.73	Same
rs12437854	*RGMA–MCTP2*	Sandholm 2012	GWAS, T1D-ESRD	G	T	0.06	0.03	1.2	0.05	0.31	1.14	0.06	0.03	1.22	NA	NA	NA	NA	NA	NA	0.06	0.01	1.33	0.06	0.0013	1.43	same
rs12137135	*WNT4-ZBTB40*	Sambo 2014	GWAS, T1D-ESRD	G	A	0.16	0.95	1	0.16	0.39	0.94	0.16	0.72	1.02	0.16	0.05	1.21	0.16	0.01	1.28	0.16	0.04	1.18	0.16	0.23	1.08	Same
rs1801282	*PPARG*	Mooyaart 2011	CGM, T1D/T2D	G	C	0.15	0.13	1.08	0.14	0.95	0.98	0.15	0.07	1.12	0.15	0.05	1.16	0.16	0.02	1.18	0.15	0.01	1.18	0.15	0.05	1.16	Opposite, NS
rs12917114	*SEMA6D-SLC24A5*	Sambo 2014	GWAS, T1D-ESRD	T	C	0.13	0.39	0.97	0.12	0.15	0.9	0.13	0.81	1.01	0.13	0.15	1.18	0.13	0.01	1.27	0.13	0.07	1.18	0.13	0.24	1.12	same
rs699	*AGT*	Mooyaart 2011	CGM, T1D/T2D	G	A	0.43	0.14	1.07	0.43	0.01	1.17	0.42	0.67	1.02	0.42	0.49	1.04	0.43	0.74	0.98	0.43	0.59	0.98	0.43	0.98	1.01	Opposite, NS
rs1617640	*EPO*	Tong 2008	CGM, T1D-DN	A	C	0.57	0.03	0.92	0.58	0.45	0.96	0.57	0.02	0.91	0.57	0.49	0.98	0.56	0.71	1	0.56	0.29	0.96	0.57	0.65	0.98	Opposite
rs741301	*ELMO1*	Shimazaki 2005	GWAS, T2D-DN	T	C	0.68	0.54	0.96	0.68	0.69	1.02	0.67	0.34	0.94	0.67	0.04	0.86	0.68	0.02	0.86	0.67	0.3	0.93	0.67	0.31	0.93	Same
rs7588550	*ERBB4*	Sandholm 2012	GWAS, T1D-DN	A	G	0.94	0.05	1.24	0.94	0.66	1.14	0.95	0.02	1.3	NA	NA	NA	NA	NA	NA	0.94	0.05	1.25	0.94	0.03	1.34	same
rs1670754	Chr 4p15.1	Sambo 2014	GWAS, T1D-ESRD	A	G	0.17	0.24	1.07	0.17	0.13	1.13	0.17	0.56	1.04	0.17	0.04	1.21	0.17	0.03	1.2	0.17	0.12	1.11	0.17	0.04	1.16	Same
rs1041466	Chr 13q	Pezzolesi 2009	GWAS, T1D-DN	G	A	0.47	0.54	1.01	0.47	0.86	0.97	0.48	0.38	1.02	0.48	0.09	1.09	0.48	0.03	1.12	0.48	0.14	1.07	0.48	0.64	1.02	same
rs1799987	*CCR5*	Mooyaart 2011	CGM, T1D/T2D	G	A	0.45	0.46	1.04	0.45	0.49	1.05	0.45	0.55	1.04	0.45	0.5	1.07	0.45	0.54	1.06	0.45	0.95	1.01	0.45	0.09	1.11	
rs5186	*AGTR1*	Mooyaart 2011	CGM, T1D/T2D	C	A	0.24	0.11	1.1	0.24	0.57	1.06	0.23	0.21	1.1	0.23	0.93	1.01	0.23	0.82	1	0.23	0.38	0.94	0.24	0.49	1.05	
rs11993333	*PVT1*	Mooyaart 2011	CGM, T1D/T2D	C	T	0.53	0.25	1.05	0.53	0.91	1.02	0.53	0.12	1.07	0.53	0.81	1.02	0.53	0.89	1	0.53	0.83	1.02	0.53	0.37	1.06	
rs833061	*VEGFA*	Mooyaart 2011*	CGM, T1D/T2D	T	C	0.48	0.12	1.07	0.48	0.42	1.05	0.48	0.15	1.07	0.48	0.32	1.07	0.48	0.6	1.04	0.48	0.31	1.05	0.48	0.12	1.1	
rs9298190	*LOC100132891*	Craig 2009	Pooled GWAS on T1D-ESRD	C	T	0.39	0.49	1.03	0.39	0.83	0.99	0.39	0.21	1.06	0.39	0.15	1.09	0.39	0.12	1.09	0.39	0.53	1.04	0.39	0.49	1.04	
rs1564939	*GLRA3*	Sandholm 2014	GWAS, T1D-AER	C	T	0.19	0.26	1.07	0.19	0.61	1.03	0.19	0.27	1.08	0.18	0.37	1.1	0.18	0.47	1.08	0.18	0.24	1.11	0.19	0.13	1.13	
rs2268388	*ACACB*	Mooyaart 2011	CGM, T1D/T2D	A	G	0.15	0.9	1	0.15	0.23	0.92	0.15	0.62	1.04	0.15	0.21	1.11	0.15	0.13	1.12	0.15	0.49	1.05	0.15	0.54	1.05	
rs2070744	*NOS3*	Mooyaart 2011*	CGM, T1D/T2D	T	C	0.62	0.22	1.05	0.61	0.84	1.01	0.62	0.14	1.07	0.62	0.53	1.06	0.63	0.58	1.04	0.62	0.16	1.08	0.61	0.27	1.08	
rs7805747	*PRKGA2*	Köttgen 2010	GWAS CKD	A	G	0.23	0.14	0.94	0.24	0.16	0.91	0.23	0.37	0.97	0.23	0.87	1.02	0.22	0.58	1.04	0.22	0.21	1.07	0.23	0.6	1.03	
rs1749824	*ZMIZ1*	Craig 2009	Pooled GWAS on T1D-ESRD	A	C	0.43	0.31	0.96	0.43	0.29	0.94	0.43	0.44	0.97	0.44	0.47	0.96	0.44	0.83	0.99	0.44	0.14	0.94	0.44	0.42	0.96	
rs10011025	*GLRA3*	Sandholm 2014	GWAS, T1D-AER	G	A	0.18	0.31	1.07	0.18	0.69	1.02	0.18	0.32	1.09	0.18	0.37	1.11	0.18	0.45	1.08	0.18	0.29	1.1	0.18	0.14	1.13	
rs2106294	*LIMK2*	McDonough 2010	GWAS on T2D-DN AA	T	C	0.68	0.46	1.04	0.69	0.27	1.08	0.68	0.61	1.03	0.67	0.84	0.97	0.68	0.14	0.94	0.68	0.34	0.96	0.68	0.83	1.01	
rs6492208	Chr 13q	Pezzolesi 2009	GWAS, T1D-DN	C	T	0.39	0.59	0.99	0.39	0.85	1.01	0.39	0.55	0.99	0.38	0.19	0.94	0.39	0.16	0.94	0.38	0.41	0.97	0.39	0.99	1	
rs1888747	*FRMD3*	Pezzolesi 2009	GWAS, T1D-DN	G	C	0.7	0.78	1	0.7	0.95	1	0.7	0.6	1.02	0.7	0.17	1.11	0.7	0.34	1.07	0.71	0.96	1	0.7	0.49	1.04	
rs1129456	*GREM1*	Mooyaart 2011*	CGM, T1D/T2D	T	A	0.12	0.38	1.06	0.12	0.47	0.95	0.13	0.18	1.1	0.12	0.55	1.04	0.13	0.86	0.99	0.13	0.86	1.01	0.13	0.89	1.01	
rs7989848	Chr 13q	Pezzolesi 2009	GWAS T1D-DN	A	G	0.56	0.62	1.01	0.56	0.97	0.99	0.56	0.51	1.02	0.56	0.22	1.06	0.56	0.19	1.06	0.56	0.36	1.04	0.56	0.58	1.03	
rs10868025	*FRMD3*	Pezzolesi 2009	GWAS T1D-DN	G	A	0.36	0.62	0.98	0.37	0.91	1	0.36	0.38	0.96	0.36	0.2	0.92	0.36	0.34	0.94	0.36	0.75	0.99	0.36	0.29	0.94	
rs16864170	*SOX11*	Köttgen 2010	GWAS CKD	C	T	0.04	0.89	1.03	0.04	0.22	0.82	0.05	0.31	1.12	0.04	0.6	1.07	0.04	0.53	1.09	0.04	0.94	0.99	0.04	0.69	0.95	
rs13293564	*UNC13B*	Mooyaart 2011*	CGM, T1D/T2D	T	G	0.44	0.76	1.01	0.43	0.25	0.94	0.45	0.33	1.04	0.45	0.33	1.05	0.45	0.51	1.03	0.45	0.66	1.02	0.44	0.73	0.96	
rs1411766	*NA*	Pezzolesi 2009	GWAS T1D-DN	A	G	0.36	0.27	0.95	0.37	0.26	0.92	0.37	0.46	0.96	0.37	0.7	1.02	0.36	0.32	1.06	0.37	0.78	1.02	0.37	0.93	1	
rs39075	*CPVL/CHN2*	Pezzolesi 2009	GWAS T1D-DN	A	G	0.39	0.34	0.96	0.39	0.27	0.94	0.39	0.59	0.97	0.4	0.83	0.99	0.39	0.76	1.02	0.39	0.65	1.02	0.4	0.76	1.01	
rs9521445	Chr 13q	Pezzolesi 2009	GWAS T1D-DN	A	C	0.51	0.39	1.03	0.52	0.32	1.06	0.51	0.65	1.02	0.51	0.72	1.01	0.51	0.94	0.99	0.51	0.86	1	0.51	0.96	1	
rs739401	*CARS*	Pezzolesi 2009	GWAS T1D-DN	T	C	0.43	0.34	1.05	0.44	0.43	1.06	0.43	0.54	1.03	0.42	0.76	1.03	0.42	0.94	1.01	0.43	0.66	0.98	0.43	0.64	1.03	
rs451041	*CARS*	Pezzolesi 2009	GWAS T1D-DN	G	A	0.43	0.38	1.05	0.44	0.51	1.05	0.43	0.53	1.03	0.42	0.98	1.01	0.42	0.82	1	0.43	0.57	0.97	0.43	0.72	1.02	
rs17300539	*ADIPOQ*	Mooyaart 2011,	CGM, T1D/T2D	A	G	0.05	0.67	1.06	0.06	0.45	1.09	0.05	0.96	1.02	0.05	0.57	1.11	0.05	0.5	1.11	0.05	0.43	1.08	0.06	0.75	1.05	
rs2410601	*PSD3-SH2D4A*	Sandholm 2014	GWAS T1D-AER	C	G	0.57	0.87	0.98	0.56	0.44	0.93	0.57	0.86	1	0.57	0.9	1	0.57	0.7	1.02	0.57	0.64	1.02	0.57	0.45	0.95	

rs6930576	*SASH1*	McDonough 2010	GWAS T2D-DN AA	A	G	0.34	0.59	1.04	0.34	0.72	1.04	0.34	0.91	1.02	0.33	0.67	1	0.33	0.47	0.97	0.33	0.56	0.98	0.34	0.74	0.98	
rs3767140	*HSPG2*	Mooyaart 2011*	CGM, T1D/T2D	A	C	0.23	0.81	1.02	0.22	0.74	1.03	0.23	0.81	1	0.23	0.79	1.02	0.23	0.88	1	0.22	0.47	1.04	0.22	0.84	0.99	
rs39059	*CPVL/CHN2*	Pezzolesi 2009	GWAS T1D-DN	G	A	0.36	0.48	0.96	0.36	0.66	0.97	0.36	0.52	0.96	0.36	0.67	0.99	0.36	0.92	1	0.36	1	1	0.37	0.96	0.99	
rs12917707	*UMOD*	Köttgen 2010	GWAS CKD	T	G	0.22	0.71	0.99	0.22	0.74	1.02	0.22	0.64	0.98	0.22	0.85	1.01	0.22	0.97	1.02	0.22	0.57	0.97	0.22	0.59	0.96	
rs2358944	*MSRB3-HMGA2*	McDonough 2010	GWAS T2D-DN AA	A	G	0.84	0.66	0.98	0.84	0.82	0.98	0.84	0.66	0.97	0.84	0.8	0.98	0.84	0.92	0.99	0.84	0.8	0.99	0.84	0.75	0.99	
rs7769051	*RPS12*	McDonough 2010	GWAS T2D-DN AA	A	C	0.14	0.89	1	0.14	0.86	0.98	0.14	0.77	0.99	0.14	0.68	0.98	0.14	0.89	1	0.14	0.89	1	0.15	0.94	1.01	
rs841853	*GLUT1*	Mooyaart 2011*	CGM, T1D/T2D	C	A	0.69	0.74	1.01	0.68	0.93	0.99	0.69	0.72	1.01	0.68	0.93	0.99	0.69	0.71	0.97	0.68	0.8	1	0.67	0.75	0.97	
Results excluding the FinnDiane patients for SNPs were the source publication includes FinnDiane patients																										
SNP	**GENE**	**Source**	**Type**	**EA**	**NEA**	**EAF**	**OR**	**P**	**EAF**	**OR**	**P**	**EAF**	**OR**	**P**	**EAF**	**OR**	**P**	**EAF**	**OR**	**P**	**EAF**	**OR**	**P**	**EAF**	**OR**	**P**	**Direction**
rs13293564	*UNC13B*	Mooyaart 2011*	CGM, T1D/T2D	T	G	0.41	0.83	0.03	0.42	0.80	0.02	0.42	0.83	0.11	0.43	0.93	0.87	0.42	1.00	0.78	0.42	0.88	0.31	0.42	0.77	0.02	Opposite
rs2838302	*SIK1*	Sambo 2014	GWAS, T1D-ESRD	G	A	0.09	1.23	0.22	0.08	1.20	0.55	0.09	1.27	0.14	0.08	1.52	0.04	0.09	1.39	0.09	0.09	1.22	0.28	0.09	1.19	0.33	same
rs12137135	*WNT4-ZBTB40*	Sambo 2014	GWAS, T1D-ESRD	G	A	0.15	0.81	0.04	0.16	0.89	0.29	0.16	0.76	0.04	0.17	0.81	0.11	0.16	0.91	0.32	0.15	0.97	0.62	0.15	0.77	0.08	Opposite
rs699	*AGT*	Mooyaart 2011	CGM, T1D/T2D	G	A	0.43	1.09	0.33	0.43	1.24	0.05	0.42	0.98	0.79	0.43	1.08	0.59	0.43	1.08	0.67	0.43	0.98	0.65	0.43	1.00	0.74	
rs7583877	*AFF3*	Sandholm 2012	GWAS, T1D-ESRD	T	C	0.66	1.12	0.19	0.66	1.21	0.07	0.66	1.08	0.72	0.66	1.07	0.49	0.66	1.03	0.89	0.67	1.03	0.98	0.66	1.03	0.83	
rs5186	*AGTR1*	Mooyaart 2011	CGM, T1D/T2D	C	A	0.30	1.17	0.10	0.29	1.08	0.71	0.30	1.21	0.11	0.28	1.10	0.86	0.29	1.07	0.96	0.30	0.94	0.78	0.30	1.17	0.08	
rs1801282	*PPARG*	Mooyaart 2011	CGM, T1D/T2D	G	C	0.11	1.18	0.10	0.11	1.20	0.20	0.11	1.18	0.18	0.11	1.31	0.11	0.12	1.18	0.24	0.12	1.12	0.23	0.12	1.08	0.47	
rs7588550	*ERBB4*	Sandholm 2012	GWAS, T1D-DN	A	G	0.96	0.92	0.57	0.96	0.71	0.10	0.96	1.00	0.95	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
rs1799987	*CCR5*	Mooyaart 2011	CGM, T1D/T2D	G	A	0.45	1.09	0.65	0.46	1.21	0.11	0.45	1.03	0.74	0.44	1.02	0.63	0.45	0.97	0.36	0.44	0.99	0.56	0.45	1.17	0.22	
rs12917114	*SEMA6D-SLC24A5*	Sambo 2014	GWAS, T1D-ESRD	T	C	0.08	0.86	0.13	0.08	0.87	0.27	0.08	0.86	0.24	0.07	0.94	0.68	0.07	1.05	0.94	0.07	1.08	0.98	0.07	0.94	0.74	
rs1564939	*GLRA3*	Sandholm 2014	GWAS, T1D-AER	C	T	0.22	0.92	0.34	0.22	0.94	0.82	0.22	0.90	0.27	0.21	0.82	0.13	0.21	0.84	0.19	0.20	1.02	0.79	0.20	0.92	0.39	
rs10011025	*GLRA3*	sandholm 2014	GWAS, T1D-AER	G	A	0.21	0.92	0.32	0.21	0.92	0.69	0.21	0.91	0.27	0.20	0.83	0.14	0.20	0.85	0.21	0.20	0.98	0.61	0.19	0.91	0.33	
rs12437854	*RGMA–MCTP2*	Sandholm 2012	GWAS, T1D-ESRD	G	T	0.06	1.03	0.73	0.06	1.15	0.47	0.06	0.95	0.99	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.06	1.29	0.19	
rs2410601	*PSD3-SH2D4A*	Sandholm 2014	GWAS T1D-AER	C	G	0.53	1.05	0.41	0.53	0.95	0.92	0.54	1.10	0.31	0.54	1.03	0.83	0.54	1.02	0.86	0.54	0.98	0.96	0.54	0.89	0.25	
rs1670754	*Chr 4p15.1*	Sambo 2014	GWAS, T1D-ESRD	A	G	0.20	0.96	0.82	0.21	1.09	0.46	0.20	0.89	0.32	0.20	1.00	0.90	0.20	0.98	0.76	0.20	0.97	0.93	0.20	1.13	0.25	
N subjects						**Case**	**Ctrl**	**Total**	**Case**	**Ctrl**	**Total**	**Case**	**Ctrl**	**Total**	**Case**	**Ctrl**	**Total**	**Case**	**Ctrl**	**Total**	**Case**	**Ctrl**	**Total**	**Case**	**Ctrl**	**Total**	
SDR + Eurodiab + Cambridge						761	980	1,741	337	980	1,317	418	980	1,398	159	781	940	159	1,234	1,393	276	832	1,108	328	596	924	

Direction: Direction of effect compared between this and the original study; Opposite, NS: Association was non-significant in the previous meta-analysis, trending in the opposite direction. CGM: meta-analysis of candidate gene studies. P-value required for statistical significance after adjustment for multiple testing is 0.0011 (significance level α=0.05, 46 loci), highlighted with green background and bold text. *Variant was significant in the literature-based meta-analysis [56]. Source: Sambo 2014 [57]; Sandholm 2012 [2]; Mooyaart 2011 [56]; Tong 2008 [58]; shimazaki 2005 [59]; Pezzolesi 2009 [60]; Craig 2009 [61]; Sandholm 2014 [62]; Köttgen 2010 [63]; McDonough 2010 [64].

Supplemental Table 10: Association between diabetic kidney complications and genetic risk scores of related phenotypes

DKD phenotype	trait	OR	95% CI	P-value
Late DKD	Body mass index (z transformed)	2,51	1,64 - 3,84	***2,20E-05***
Late DKD	Body mass index (BMI)	2,06	1,37 - 3,07	***4,50E-04***
ESRD vs. no DKD	Body mass index (BMI)	2,52	1,49 - 4,26	***5,40E-04***
Combined DKD	Type 2 diabetes (inclu. lipid SNPs)	1,28	1,11 - 1,47	***6,10E-04***
Combined DKD	Body mass index (z transformed)	1,92	1,32 - 2,78	***6,30E-04***
CKD	Body mass index (BMI)	2,04	1,33 - 3,13	***1,00E-03***
CKD	Body mass index (z transformed)	2,04	1,33 - 3,14	***1,10E-03***
Late DKD	Type 2 diabetes (inclu. lipid SNPs)	1,28	1,1 - 1,5	***1,90E-03***
Combined DKD	Type 2 diabetes	1,19	1,07 - 1,32	***1,90E-03***
ESRD vs. no ESRD	Body mass index (BMI)	2,1	1,3 - 3,39	***2,50E-03***
Late DKD	Type 2 diabetes	1,21	1,07 - 1,36	2,80E-03
Combined DKD	Type 2 diabetes (inclu. glycaemic SNPs)	1,18	1,05 - 1,32	5,60E-03
Late DKD	Fasting proinsulin (BMI+FG adj.)	2,78	1,35 - 5,72	5,70E-03
CKD and DKD	Body mass index (BMI)	1,92	1,2 - 3,09	6,90E-03
ESRD vs. no DKD	Body mass index (z transformed)	2,03	1,2 - 3,44	8,30E-03
ESRD vs. no DKD	Type 2 diabetes (inclu. lipid SNPs)	1,32	1,07 - 1,63	8,30E-03
CKD and DKD	Low-density lipoprotein C	1,79	1,15 - 2,79	9,70E-03
Late DKD	Type 2 diabetes (inclu. glycaemic SNPs)	1,18	1,04 - 1,34	1,30E-02
CKD and DKD	Type 2 diabetes	1,19	1,03 - 1,37	1,70E-02
Late DKD	Waist-Hip Ratio (BMI adj.)	1,76	1,1 - 2,79	1,80E-02
CKD and DKD	Body mass index (z transformed)	1,77	1,09 - 2,86	2,00E-02
Combined DKD	Body mass index (BMI)	1,52	1,06 - 2,17	2,10E-02
Combined DKD	Fasting proinsulin (BMI+FG adj.)	2,13	1,11 - 4,09	2,20E-02
CKD and DKD	Type 2 diabetes (inclu. glycaemic SNPs)	1,19	1,02 - 1,38	2,70E-02
CKD and DKD	Type 2 diabetes (inclu. lipid SNPs)	1,21	1,01 - 1,46	4,00E-02
Late DKD	Insulin resistance	13,96	1,12 - 174,72	4,10E-02
Early DKD	Type 2 diabetes (inclu. glycaemic SNPs)	1,18	1 - 1,39	4,50E-02
Early DKD	Type 2 diabetes (inclu. lipid SNPs)	1,22	1 - 1,49	4,70E-02
CKD	Waist-Hip Ratio (BMI adj.)	1,65	1,01 - 2,71	4,80E-02
Early DKD	Type 2 diabetes	1,16	1 - 1,36	5,30E-02
Combined DKD	Insulin resistance	9,11	0,95 - 87,3	5,50E-02
ESRD vs. no ESRD	Type 2 diabetes (inclu. lipid SNPs)	1,2	0,99 - 1,45	6,30E-02
CKD	Fasting proinsulin (BMI+FG adj.)	2,07	0,95 - 4,5	6,60E-02
ESRD vs. no DKD	Type 2 diabetes	1,16	0,99 - 1,36	7,10E-02
Early DKD	Fasting glucose (BMI adj.)	4,71	0,86 - 25,96	7,50E-02
ESRD vs. no DKD	Low-density lipoprotein C	1,58	0,95 - 2,61	7,70E-02
Late DKD	ln(Fasting insulin) BMI adj.	5,53	0,83 - 37,02	7,80E-02
ESRD vs. no DKD	High-density lipoprotein C	1,95	0,91 - 4,15	8,40E-02
Early DKD	Insulin resistance	15,17	0,61 - 376,25	9,70E-02
ESRD vs. no DKD	Type 2 diabetes (inclu. glycaemic SNPs)	1,15	0,97 - 1,36	1,00E-01
ESRD vs. no ESRD	Low-density lipoprotein C	1,49	0,92 - 2,4	1,00E-01
Combined DKD	ln(Fasting insulin) BMI adj.	4,07	0,74 - 22,36	1,10E-01
Early DKD	Low-density lipoprotein C	1,51	0,91 - 2,5	1,10E-01
ESRD vs. no DKD	Systolic blood pressure	0,45	0,17 - 1,19	1,10E-01

DKD phenotype	trait	OR	95% CI	P-value
CKD and DKD	Waist-Hip Ratio (BMI adj.)	1,56	0,9 - 2,71	1,10E-01
CKD and DKD	Fasting proinsulin (BMI+FG adj.)	1,96	0,85 - 4,5	1,10E-01
CKD	Systolic blood pressure	0,53	0,23 - 1,19	1,20E-01
CKD	Type 2 diabetes (inclu. glycaemic SNPs)	1,11	0,97 - 1,28	1,30E-01
Early DKD	ln(Fasting insulin) BMI adj.	6,39	0,57 - 72,23	1,30E-01
ESRD vs. no ESRD	Body mass index (z transformed)	1,43	0,89 - 2,29	1,40E-01
Combined DKD	Fasting glucose (BMI adj.)	2,45	0,75 - 8	1,40E-01
Combined DKD	Waist-Hip Ratio (BMI adj.)	1,37	0,9 - 2,06	1,40E-01
ESRD vs. no ESRD	High-density lipoprotein C	1,69	0,84 - 3,38	1,40E-01
CKD	Type 2 diabetes (inclu. lipid SNPs)	1,13	0,96 - 1,34	1,40E-01
Late DKD	High-density lipoprotein C	1,52	0,86 - 2,7	1,50E-01
ESRD vs. no DKD	Fasting proinsulin (BMI+FG adj.)	1,94	0,76 - 4,94	1,60E-01
ESRD vs. no ESRD	HbA1c	0,28	0,04 - 1,8	1,80E-01
Late DKD	2hr-Glucose (BMI adj.)	0,75	0,49 - 1,15	1,90E-01
CKD and DKD	ln(Fasting insulin) BMI adj.	4,32	0,46 - 40,29	2,00E-01
CKD and DKD	Insulin resistance	6,99	0,36 - 135,72	2,00E-01
CKD and DKD	Systolic blood pressure	0,56	0,23 - 1,38	2,10E-01
ESRD vs. no DKD	HbA1c	0,29	0,04 - 2,14	2,30E-01
Combined DKD	High-density lipoprotein C	1,36	0,82 - 2,26	2,30E-01
CKD and DKD	Fasting glucose (BMI adj.)	2,65	0,53 - 13,22	2,40E-01
CKD	Type 2 diabetes	1,08	0,95 - 1,23	2,40E-01
ESRD vs. no DKD	Waist-Hip Ratio (BMI adj.)	1,43	0,77 - 2,67	2,60E-01
ESRD vs. no DKD	2hr-Glucose (BMI adj.)	0,74	0,43 - 1,26	2,70E-01
CKD and DKD	Triglycerides	0,67	0,32 - 1,37	2,70E-01
ESRD vs. no DKD	ln(Fasting insulin) BMI adj.	3,84	0,34 - 42,91	2,80E-01
Late DKD	Systolic blood pressure	0,66	0,31 - 1,4	2,80E-01
Early DKD	Body mass index (BMI)	0,76	0,46 - 1,27	3,00E-01
CKD and DKD	High-density lipoprotein C	1,42	0,72 - 2,77	3,10E-01
Combined DKD	Low-density lipoprotein C	1,2	0,84 - 1,71	3,20E-01
Late DKD	HbA1c	0,46	0,1 - 2,21	3,30E-01
ESRD vs. no ESRD	2hr-Glucose (BMI adj.)	0,8	0,48 - 1,31	3,70E-01
ESRD vs. no ESRD	Type 2 diabetes (inclu. glycaemic SNPs)	1,07	0,92 - 1,26	3,80E-01
ESRD vs. no ESRD	Systolic blood pressure	0,67	0,27 - 1,67	3,90E-01
Late DKD	Triglycerides	0,77	0,42 - 1,41	4,00E-01
CKD	Fasting glucose (BMI adj.)	0,54	0,13 - 2,26	4,00E-01
CKD	HOMA-B	0,57	0,15 - 2,17	4,10E-01
CKD	Low-density lipoprotein C	1,19	0,78 - 1,82	4,10E-01
Late DKD	Fasting glucose (BMI adj.)	1,73	0,46 - 6,47	4,10E-01
CKD and DKD	HOMA-IR	3,01	0,2 - 44,97	4,30E-01
Combined DKD	2hr-Glucose (BMI adj.)	0,86	0,58 - 1,26	4,40E-01
Early DKD	Fasting proinsulin (BMI+FG adj.)	1,43	0,56 - 3,65	4,50E-01
ESRD vs. no ESRD	Type 2 diabetes	1,06	0,91 - 1,22	4,60E-01
CKD	High-density lipoprotein C	1,26	0,68 - 2,34	4,60E-01
ESRD vs. no DKD	Insulin resistance	3,4	0,13 - 90,6	4,60E-01
Late DKD	HOMA-IR	2,32	0,24 - 22,65	4,70E-01
CKD	2hr-Glucose (BMI adj.)	1,18	0,74 - 1,86	4,90E-01

DKD phenotype	trait	OR	95% CI	P-value
CKD	HOMA-IR	0,46	0,04 - 4,77	5,10E-01
ESRD vs. no ESRD	Insulin resistance	0,38	0,02 - 8,04	5,30E-01
ESRD vs. no DKD	Triglycerides	0,78	0,35 - 1,74	5,50E-01
ESRD vs. no ESRD	Triglycerides	0,8	0,38 - 1,69	5,60E-01
Early DKD	HOMA-B	0,63	0,13 - 3,03	5,60E-01
Early DKD	HbA1c	1,83	0,22 - 15,06	5,70E-01
CKD and DKD	Type 1 diabetes	0,98	0,93 - 1,04	5,80E-01
ESRD vs. no ESRD	Fasting proinsulin (BMI+FG adj.)	1,28	0,54 - 3,02	5,80E-01
Combined DKD	Systolic blood pressure	0,83	0,42 - 1,63	5,90E-01
ESRD vs. no ESRD	Waist-Hip Ratio (BMI adj.)	1,17	0,65 - 2,09	6,00E-01
ESRD vs. no ESRD	HOMA-IR	0,51	0,04 - 6,97	6,20E-01
Combined DKD	HOMA-IR	1,68	0,22 - 12,67	6,20E-01
Early DKD	Systolic blood pressure	0,79	0,3 - 2,04	6,20E-01
ESRD vs. no ESRD	HOMA-B	1,44	0,33 - 6,25	6,30E-01
CKD	Type 1 diabetes	0,99	0,94 - 1,04	6,80E-01
Early DKD	Body mass index (z transformed)	1,11	0,66 - 1,86	6,90E-01
Combined DKD	HbA1c	0,75	0,18 - 3,14	7,00E-01
Early DKD	High-density lipoprotein C	1,15	0,57 - 2,33	7,00E-01
ESRD vs. no DKD	HOMA-B	1,35	0,28 - 6,59	7,10E-01
ESRD vs. no DKD	Type 1 diabetes	0,99	0,94 - 1,05	7,30E-01
CKD	ln(Fasting insulin) BMI adj.	0,72	0,1 - 5,39	7,50E-01
CKD	HbA1c	1,31	0,23 - 7,44	7,60E-01
CKD	Triglycerides	0,9	0,46 - 1,76	7,60E-01
ESRD vs. no ESRD	Fasting glucose (BMI adj.)	0,78	0,15 - 4,13	7,80E-01
CKD and DKD	HOMA-B	0,81	0,19 - 3,49	7,80E-01
CKD and DKD	2hr-Glucose (BMI adj.)	0,93	0,57 - 1,54	7,90E-01
Early DKD	Waist-Hip Ratio (BMI adj.)	1,08	0,6 - 1,95	7,90E-01
Late DKD	HOMA-B	1,17	0,34 - 3,98	8,00E-01
ESRD vs. no ESRD	ln(Fasting insulin) BMI adj.	1,31	0,14 - 12,29	8,10E-01
ESRD vs. no DKD	Fasting glucose (BMI adj.)	1,24	0,21 - 7,41	8,10E-01
Early DKD	2hr-Glucose (BMI adj.)	1,06	0,61 - 1,86	8,30E-01
ESRD vs. no ESRD	Type 1 diabetes	1	0,94 - 1,05	8,70E-01
Late DKD	Type 1 diabetes	1	0,95 - 1,04	8,70E-01
Combined DKD	Type 1 diabetes	1	0,96 - 1,04	8,70E-01
Early DKD	Type 1 diabetes	1	0,95 - 1,06	8,80E-01
Combined DKD	HOMA-B	0,92	0,31 - 2,76	8,80E-01
Combined DKD	Triglycerides	0,96	0,56 - 1,65	8,80E-01
CKD	Insulin resistance	0,84	0,06 - 12,46	9,00E-01
Early DKD	Triglycerides	1,02	0,47 - 2,19	9,70E-01
ESRD vs. no DKD	HOMA-IR	0,96	0,05 - 17,34	9,80E-01
Late DKD	Low-density lipoprotein C	1	0,67 - 1,5	9,80E-01
Early DKD	HOMA-IR	0,99	0,06 - 17,58	1,00E+00
CKD and DKD	HbA1c	1	0,16 - 6,4	1,00E+00

Significant *p*-values ($p<2.6\times10^{-3}$, α=0.05 Bonferroni corrected for the 19 examined traits) are highlighted with ***bold italics***.

References for the SNPs included in the genetic risk scores (GRS): Waist-Hip-ratio (adjusted for body mass index [BMI], N_{SNPs}=54)[26], BMI (untransformed, N_{SNPs}=96 [27] and z-transformed, N_{SNPs}=24 [28]), systolic blood pressure (SBP, N_{SNPs}=22)[29], low-density lipoprotein cholesterol (LDL-C, N_{SNPs}=24), triglycerides (TRIG, N_{SNPs}=20), high-density lipoprotein cholesterol (HDL-C, N_{SNPs}=26)[30], T1D (N_{SNPs}=51) [31], T2D [32] (including all SNPs (N_{SNPs}=70), and without any other effects other than on T2D or lipids (N_{SNPs}=56)[30] and T2D or glycemic traits (N_{SNPs}=62)[33,34]), 2-hr glucose (adjusted for BMI, N_{SNPs}=15)[35], fasting glucose (FG, adjusted for BMI, N_{SNPs}=21) [34], glycated haemoglobin (HbA1c, N_{SNPs}=15)[36], fasting insulin (natural log transformed and adjusted for BMI, N_{SNPs}=13)[34], fasting pro-insulin (adjusted for BMI and FG, N_{SNPs}=10)[37], HOMA-B (N_{SNPs}=15), HOMA-IR (N_{SNPs}=15)[38] and insulin resistance [39].

Supplemental Table 11: MAGENTA Gene set enrichment results with FDR<0.05

pheno	DB	Gene set	EFF GS SIZE	P	FDR	EXP # GENES	OBS # GENES	# GENES FLAGGED	FLAGGED GENE NAMES
CKDDN	BIOCARTA	Shh pathway	16	1.00E-05	0.0001	1	7	16	*DYRK1A, GLI1, GLI2, GLI3, GSK3B, PRKACB, PRKACG, PRKAR1A, PRKAR1B, PRKAR2A, PRKAR2B, PTCH1, SHH, SMO, DYRK1B, SUFU*
Combined DKD	KEGG	ascorbate and aldarate metabolism	17	9.00E-06	0.0001	1	7	22	*ALDH2, ALDH1B1, ALDH9A1, ALDH3A2, ALDH7A1, UGDH, UGT2B4, UGT2B7, UGT2B11, UGT2A1, UGT2B28, UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A1, UGT1A3, MIOX, UGT2A3*
Combined DKD	KEGG	pentose and glucuronate interconversions	20	3.00E-06	0.0002	1	8	24	*AKR1B1, GUSB, RPE, UGDH, UGP2, UGT2B4, UGT2B7, XYLB, UGT2B11, UGT2A1, DHDH, CRYL1, DCXR, UGT2B28, UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A1, UGT1A3, UGT2A3*
Combined DKD	KEGG	porphyrin and chlorophyll metabolism	31	8.50E-05	0.0020	2	8	38	*ALAD, ALAS1, ALAS2, BLVRA, BLVRB, COX10, COX15, CP, CPOX, EPRS, FECH, FTH1, GUSB, HCCS, HMBS, HMOX1, HMOX2, PPOX, UGT2B4, UGT2B7, UROD, UROS, UGT2B11, UGT2A1, UGT2B28, UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A1, UGT1A3, UGT2A3, FTMT, EARS2, MMAB*
Early DKD	PANTHER BIOLOGICAL PROCESS	Hearing	27	1.00E-04	0.0020	1	8	29	*TIMM8A, DFNA5, COCH, MYO6, MYO7A, MYO7B, P2RX1, P2RX3, P2RX4, P2RX5, P2RX7, TCOF1, WFS1, ZFAND5, P2RX6, KCNQ4, ITM2B, WDR1, P2RX2, DFNB31, TIMM13, TIMM8B, MYO15A, CDHR5, CDH23, ESPN, OTOA, STRC, OC90*
Combined DKD	KEGG	drug metabolism other enzymes	39	3.00E-04	0.0102	2	8	48	*NAT1, NAT2, CDA, CES1, CYP2A6, CYP2A7, CYP3A7, CYP2A13, CYP3A4, CYP3A5, DPYD, DPYS, TYMP, GUSB, HPRT1, IMPDH1, IMPDH2, ITPA, TK1, TK2, TPMT, UGT2B4, UGT2B7, UCK2, UMPS, UPP1, XDH, CES2, GMPS, UGT2B11, UGT2A1, UPB1, UGT2B28, UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A1, UGT1A3, UCKL1, CYP3A43, UGT2A3, UCK1, UPP2, CES5A*
Combined DKD	KEGG	drug metabolism cytochrome p450	49	5.00E-04	0.0107	2	9	68	*ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6, ADH7, ALDH3A1, ALDH1A3, ALDH3B1, ALDH3B2, AOX1, CYP1A2, CYP2A6, CYP2A7, CYP3A7, CYP2A13, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2C18, CYP2D6, CYP2E1, CYP3A4, CYP3A5, FMO1, FMO2, FMO3, FMO4, FMO5, GSTA1, GSTA2, GSTA3, GSTA4, GSTM1, GSTM2, GSTM3, GSTM4, GSTM5, GSTP1, GSTT1, GSTZ1, MAOA, MAOB, MGST1, MGST2, MGST3, UGT2B4, UGT2B7, GSTO1, UGT2B11, UGT2A1, UGT2B28, UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A1, UGT1A3, CYP3A43, UGT2A3, GSTO2, GSTA5, GSTK1*
Combined DKD	KEGG	metabolism of xenobiotics by cytochrome p450	47	5.00E-04	0.0125	2	9	66	*ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6, ADH7, ALDH3A1, ALDH1A3, ALDH3B1, ALDH3B2, AKR1C4, CYP1A1, CYP1A2, CYP1B1, CYP3A7, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2C18, CYP2E1, CYP2F1, CYP3A4, CYP3A5, AKR1C1, AKR1C2, EPHX1, GSTA1, GSTA2, GSTA3, GSTA4, GSTM1, GSTM2, GSTM3, GSTM4, GSTM5, GSTP1, GSTT1, GSTZ1, MGST1, MGST2, MGST3, UGT2B4, UGT2B7, AKR1C3, GSTO1, UGT2B11, UGT2A1, DHDH, CYP2S1, UGT2B28, UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A1, UGT1A3, CYP3A43, UGT2A3, GSTO2, GSTA5, GSTK1*
Combined DKD	KEGG	retinol metabolism	45	1.80E-03	0.0212	2	8	61	*ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6, ADH7, ALDH1A1, CYP1A1, CYP1A2, CYP2A6, CYP2A7, CYP3A7, CYP2A13, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2C18, CYP3A4, CYP3A5, CYP4A11, CYP26A1, RDH5, RPE65, UGT2B4, UGT2B7, PNPLA4, RDH16, DGAT1, ALDH1A2, LRAT, DHRS3, DHRS9, UGT2B11, DHRS4, UGT2A1, RDH8, RDH11, BCMO1, UGT2B28, UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A1, UGT1A3, RETSAT, CYP26B1, CYP3A43, UGT2A3, DGAT2, RDH12, RDH10, AWAT2, CYP4A22, DHRS4L2, CYP26C1*
Combined DKD	REACTOME	Glucuronidation	13	2.84E-04	0.0238	1	5	16	*UGDH, UGP2, UGT2B4, UGT2B7, UGT2B11, UGT2A1, SLC35D1, UGT2B28, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A1, UGT1A3*

pheno	DB	Gene set	EFF GS SIZE	P	FDR	EXP # GENES	OBS # GENES	# GENES FLAGGED	FLAGGED GENE NAMES
CKD	Panther	Cholesterol biosynthesis	10	8.00E-04	0.0252	1	4	11	*FDFT1, FDPS, HMGCR, HMGCS1, HMGCS2, IDI1, MVD, MVK, PMVK, PDSS1, IDI2*
Combined DKD	GOTERM	Glucuronosyltransferase activity	15	1.00E-04	0.0304	1	6	20	*EXT1, EXT2, UGT2B4, UGT2B7, UGT2B11, UGT2A1, UGT2B28, UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A1, UGT1A3, CSGALNACT1, UGT2A3, UGT3A1, UGT3A2*
Combined DKD	KEGG	glutathione metabolism	40	3.20E-03	0.0350	2	7	49	*ANPEP, G6PD, GGT1, GGT7, GGT5, GCLC, GCLM, GPX1, GPX2, GPX3, GPX4, GPX5, GPX7, GSR, GSS, GSTA1, GSTA2, GSTA3, GSTA4, GSTM1, GSTM2, GSTM3, GSTM4, GSTM5, GSTP1, GSTT1, GSTZ1, IDH1, IDH2, MGST1, MGST2, MGST3, ODC1, PGD, RRM1, RRM2, SMS, SRM, GSTO1, OPLAH, RRM2B, LAP3, TXNDC12, GGCT, GSTO2, GGT6, GSTA5, GPX6, GSTK1*
CKD+DKD	BIOCARTA	Cystic Fibrosis Transmembrane Conductance Regulator And Beta 2 Adrenergic Receptor Pathway	12	2.50E-03	0.0366	1	4	12	*ADCY1, ADRB2, CFTR, GNAS, PRKACB, PRKACG, PRKAR1A, PRKAR1B, PRKAR2A, PRKAR2B, EZR, SLC9A3R1*
CKD+DKD	BIOCARTA	Attenuation of GPCR Signaling Pathway	13	3.50E-03	0.0384	1	4	13	*ARRB1, GNAS, GNB1, GNGT1, GRK4, PRKACB, PRKACG, PRKAR1A, PRKAR1B, PRKAR2A, PRKAR2B, PRKCA, PRKCB*
Combined DKD	KEGG	starch and sucrose metabolism	40	4.00E-03	0.0391	2	7	46	*AGL, AMY2A, AMY2B, G6PC, GAA, GANC, GBE1, GCK, GPI, GUSB, GYS1, GYS2, HK1, HK2, HK3, ENPP1, ENPP3, PGM1, PYGB, PYGL, PYGM, SI, UGDH, UGP2, UGT2B4, UGT2B7, MGAM, UGT2B11, UGT2A1, TREH, UGT2B28, UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A1, UGT1A3, PGM2, GBA3, G6PC2, UGT2A3, UXS1, PGM2L1*
CKD+DKD	BIOCARTA	Repression of Pain Sensation by the Transcriptional Regulator DREAM	14	3.60E-03	0.0394	1	4	14	*CREB1, CREM, FOS, JUN, OPRK1, POLR2A, PRKACB, PRKACG, PRKAR1A, PRKAR1B, PRKAR2A, PRKAR2B, MAPK3, KCNIP3*
CKD+DKD	BIOCARTA	Cytokines and Inflammatory Response	26	1.50E-03	0.0404	1	6	29	*CD4, CSF1, CSF2, CSF3, HLA-DRA, HLA-DRB1, IFNA1, IFNB1, IFNG, IL1A, IL2, IL3, IL4, IL5, IL6, IL7, IL8, IL10, IL11, IL12A, IL12B, IL13, IL15, LTA, PDGFA, TGFB1, TGFB2, TGFB3, TNF*
CKD+DKD	REACTOME	Cell extracellular matrix interactions	14	5.00E-04	0.0417	1	5	16	*ACTN1, FLNA, FLNC, ILK, ITGB1, LIMS1, PXN, RSU1, TESK1, VASP, ARHGEF6, FERMT2, PARVB, FBLIM1, LIMS2, PARVA*
Combined DKD	Panther	FAS signaling pathway	22	1.10E-03	0.0424	1	6	22	*PARP1, PARP4, CAPG, CASP6, CASP7, CASP8, CASP10, CYC1, DFFB, GSN, LMNA, LMNB1, CFLAR, PARP2, PARP3, NOD1, FAF1, NLRP1, LMNB2, SCIN, IFLTD1, NLRP10*
CKD+DKD	BIOCARTA	Phospholipase C-epsilon pathway	12	2.10E-03	0.0426	1	4	12	*ADCY1, ADRB2, GNAS, PRKACB, PRKACG, PRKAR1A, PRKAR1B, PRKAR2A, PRKAR2B, PTGER1, RAP2B, PLCE1*
Combined DKD	KEGG	steroid hormone biosynthesis	41	4.70E-03	0.0480	2	7	52	*STS, AKR1C4, COMT, CYP1A1, CYP1B1, CYP3A7, CYP3A4, CYP3A5, CYP7A1, CYP11A1, CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP21A2, AKR1C1, AKR1C2, HSD3B1, HSD3B2, HSD11B1, HSD11B2, HSD17B1, HSD17B3, HSD17B2, SRD5A1, SRD5A2, AKR1D1, SULT1E1, SULT2B1, UGT2B4, UGT2B7, HSD17B8, HSD17B6, AKR1C3, CYP7B1, UGT2B11, UGT2A1, HSD17B12, HSD17B7, UGT2B28, UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A1, UGT1A3, CYP3A43, SRD5A3, UGT2A3*

Supplemental Table 12: Characteristics of the patients selected for the whole exome sequencing

	FinnDiane				Steno				SDR	
Group	**Controls (no DKD)**		**Cases (Late DKD)**		**Controls (no DKD)**		**Cases (Late DKD)**		**Controls (no DKD)**	**Cases (Late DKD)**
Subgroup	**no RT**	**RT**	**maA**	**ESRD**	**no RT**	**RT**	**maA**	**ESRD**	*	**maA**
N (Male%)	125 (26)	125 (50)	125 (51)	125 (56)	46 (54)	74 (42)	139 (57)	49 (78)	130 (49)	62 (61)
Age ± sd (yr)	57±9	56±9	46±10	45±9	53±12 (30-80)	55±10 (31-78)	39±9 (22-70)	38±8 (20-59)	55±13 (33-84)	52±12 (29-84)
Age at Onset ± sd (yr)	13±7	13±7	13±7	15±7	15±10 (0-32)	16±9 (1-35)	13±8 (1-33)	15±8 (0-31)	15±9 (0-35)	14±8 (1-35)
Duration ± sd (yr)	43 ± 7	43 ± 6	34 ± 7	30 ± 7	38±8	39±6	-	-	40±10	38±11
	(32-66)	(33-56)	-	-	(30-63)	(30-53)	-	-	(27-74)	(13-66)
Time to maA ± sd (yr)	-	-	16 ± 3	-	-	-	18±3	-	-	29±11
(range)	-	-	(8-20)	-	-		(12-25)	-	-	(11-64)
Time to ESRD ± sd (yr)	-	-	-	20 ± 3	-	-	-	26±5	-	-
(range)	-	-	-	(15-27)	-		-	(18-24)	-	-
Time to RT/ laser ± sd (yr)	-	26 ± 8	17 ± 5	16 ± 5	-	28±7	19±5	16±4	-	-
(range)	-	(12-47)	(8-33)	(2-33)	-	(12-41)	(8-35)	(6-27)	-	-
HbA1c ± sd (%)	8.4 ± 1.0	8.4 ± 0.9	8.5 ± 1.5	8.9 ± 1.5	8.4±1.0	8.7±1.2	9.5±1.4	9.8±1.5	7.0±0.9	8.1±1.2
Further definitions							all cases had proliferative RT		no record of proliferative retinopathy was available for patients who did not have DN	61/62 cases had proliferative RT

RT: diabetic retinopathy, based on either a clinical diagnosis or laser treatment

Supplemental Table 13. Top 20 results of single variant analysis for WES 'ESRD vs. no DKD' using the score test

Chr:pos	Id	Maf	Pval	Ref/alt	Ctrlcnt	Casecnt	Gene	type
1:224492543	rs188427269	0.0023184	3.3046e-07	G/T	482/0/0	166/3/0	*NVL*	INTRON
2:212243703	rs13003941	0.3524	3.5931e-06	G/T	182/229/71	92/67/10	*ERBB4*	UTR_3_PRIME
9:37729786	rs1359590	0.20015	4.8522e-06	C/T	277/189/16	132/35/2	*FRMPD1*	NON_SYNONYMOUS_CODING
21:34697316	rs112371220	0.0054687	5.4552e-06	C/T	474/1/0	164/4/1	*IFNAR1*	UTR_5_PRIME
19:1782842	rs146522765	0.003864	7.4797e-06	G/T	482/0/0	164/5/0	*ATP8B3*	EXON
7:27168590	rs1801085	0.10974	1.2659e-05	A/G	402/77/3	113/52/4	*HOXA4*	UPSTREAM
7:27159136	rs6969780	0.11283	1.4914e-05	G/C	399/80/3	113/51/5	*HOXA3*	INTRON
2:43518932	2:43518932	0.0092736	1.7014e-05	AC/A	479/3/0	160/9/0	*THADA*	INTRON
2:43804334	rs149038509	0.0092736	1.7014e-05	C/T	479/3/0	160/9/0	*THADA*	EXON
19:4502778	19:4502778	0.0030912	1.7702e-05	G/A	482/0/0	165/4/0	*PLIN4*	DOWNSTREAM
2:212251864	rs3748962	0.3408	2.0785e-05	T/C	192/222/68	94/65/10	*ERBB4*	SYNONYMOUS_CODING
5:157078632	rs13181859	0.0015528	2.9199e-05	G/A	479/0/0	167/2/0	*SOX30*	NON_SYNONYMOUS_CODING
1:64015722	rs41285382	0.0092736	2.9641e-05	T/C	480/2/0	159/10/0	*DLEU2L*	EXON
12:62996508	12:62996508	0.0015576	3.1046e-05	G/A	477/0/0	167/2/0	*C12orf61*	UPSTREAM
5:132086671	rs111822821	0.0015456	3.2297e-05	G/A	482/0/0	167/2/0	*SEPT8*	SYNONYMOUS_CODING
12:53468971	rs142430651	0.0015456	3.2926e-05	G/C	482/0/0	167/2/0	*SPRYD3*	SYNONYMOUS_CODING
8:107531123	8:107531123	0.0015456	3.5069e-05	G/T	482/0/0	167/2/0	*OXR1*	INTRON
X:12908121	rs192357402	0.0015456	3.5163e-05	C/T	482/0/0	167/2/0	.	.
3:188595287	rs182465976	0.0015456	3.7313e-05	A/G	482/0/0	167/2/0	*LPP*	UTR_3_PRIME
7:27146202	rs61384251	0.12133	3.8108e-05	A/G	390/88/4	111/54/4	*HOXA3*	UPSTREAM

Supplemental Table 14. Top 20 associations for WES 'Late DKD' using the single variant score test

Chr:pos	Id	Maf	Pval	Ref/alt	Casecnt	Ctrlcnt	Gene	type
15:75762082	rs117245151	0.011992	4.0048e-05	G/A	458/21/0	478/2/0	*PTPN9*	INTRON
7:27168590	rs1801085	0.1147	5.3839e-05	A/G	400/76/3	352/118/10	*HOXA4*	UPSTREAM
1:35562965	rs2971408	0.10323	6.0045e-05	G/A	2/70/407	5/114/361	*ZMYM1*	NON_SYNONYMOUS_CODING
7:27159136	rs6969780	0.11731	7.3659e-05	G/C	397/79/3	351/118/11	*HOXA3*	INTRON
1:1222958	rs111819661	0.015328	7.7877e-05	C/T	450/25/0	467/4/0	*SCNN1D*	DOWNSTREAM
6:126334041	rs2206941	0.29406	8.2189e-05	G/A	28/187/264	57/207/216	*TRMT11*	INTRON
7:137561465	rs77218976	0.03806	9.2539e-05	G/A	427/52/0	459/21/0	*CREB3L2*	UTR_3_PRIME
1:1195690	rs11260568	0.013034	0.0001173	G/C	457/22/0	477/3/0	*LOC100128842*	INTRON
1:1196374	rs72894077	0.013034	0.0001173	C/T	457/22/0	477/3/0	*LOC100128842*	INTRON
6:126299264	rs9388464	0.29249	0.00013887	A/T	28/187/264	57/204/219	*HINT3*	UTR_3_PRIME
6:126288023	rs3757212	0.29041	0.00013905	T/C	26/189/264	57/202/221	*HINT3*	INTRON
11:10650350	rs190761149	0.0067779	0.00014425	G/A	466/13/0	480/0/0	*MRVI1*	SYNONYMOUS_CODING
6:126300270	rs6909664	0.29145	0.0001443	G/A	27/188/264	57/203/220	*HINT3*	UTR_3_PRIME
19:4945974	rs2250978	0.039749	0.00015331	T/C	2/50/426	0/22/456	*UHRF1*	SYNONYMOUS_CODING
12:70914045	rs5798988	0.028676	0.00015412	A/AAAGT	438/41/0	466/14/0	*PTPRB*	UTR_3_PRIME
15:37109504	rs17417429	0.10949	0.00015916	G/C	358/110/11	409/64/7	*CSNK1A1P*	INTRON
6:126299984	rs10659948	0.29197	0.00016327	A/ACT	27/189/263	56/205/219	*HINT3*	UTR_3_PRIME
2:223783841	rs13000358	0.051616	0.00016344	G/A	414/60/5	453/25/2	*ACSL3*	SYNONYMOUS_CODING
2:212243703	rs13003941	0.34619	0.00017464	G/T	180/228/71	229/208/43	*ERBB4*	UTR_3_PRIME
2:71413771	rs357781	0.20177	0.0001777	G/C	330/136/13	278/179/23	*PAIP2B*	UTR_3_PRIME

Supplemental Table 15: Top 10 associations to WES 'Late DKD' with VT with 4 masks

Position	n.pass.v	P-value	Gene
PTV+missense			
11:68673615-68707139	17	4.9e-05	*IGHMBP2*
13:53035097-53049198	8	0.00012	*CKAP2*
20:57415627-57430300	13	0.00012	*GNAS*
3:123213786-123286612	3	0.00014	*PTPLB*
14:24837601-24846073	12	0.00025	*NFATC4*
10:45798933-45803264	5	0.00036	*OR13A1*
20:1099459-1146882	9	0.00049	*PSMF1*
19:36509815-36518135	5	0.0005	*CLIP3*
11:35454383-35515695	14	0.00056	*PAMR1*
15:59750819-59813476	8	0.00063	*FAM81A*
PTV+broad			
22:38013000-38028693	5	3.1e-05	*GGA1*
11:68673615-68707139	9	0.00012	*IGHMBP2*
19:12954416-12984677	7	0.00028	*MAST1*
11:102094424-102101456	2	0.00029	*YAP1*
20:1099459-1146882	8	0.00049	*PSMF1*
13:28794420-28866586	6	0.00059	*PAN3*
17:38933291-38938348	5	0.00062	*KRT27*
14:24837601-24846073	9	0.00063	*NFATC4*
5:110835655-110835762	2	0.00066	*STARD4*
18:77891038-77896253	6	0.00067	*ADNP2*
PTV+strict			
19:6743822-6744853	2	0.00021	*TRIP10*
10:49931476-50018711	2	0.0006	*WDFY4*
19:19166642-19168396	2	0.00062	*ARMC6*
5:133686100-133702055	3	0.00072	*CDKL3*
11:128781680-128781799	2	0.00087	*KCNJ5*
19:33370070-33450911	4	0.00089	*CCDC123*
2:163124596-163144807	7	0.00103	*IFIH1*
11:76157998-76170978	2	0.00113	*C11orf30*
1:151734628-151734961	2	0.0012	*MRPL9*
3:54952509-54952627	2	0.0012	*LRTM1*
PTV+only			
11:67815031-67818400	2	0.00088	*TCIRG1*
3:54952509-54952627	2	0.00113	*LRTM1*
10:49931476-50018711	2	0.0012	*WDFY4*
2:163124596-163144807	7	0.0015	*IFIH1*
17:8701157-8701167	2	0.0016	*MFSD6L*
2:43458439-43804337	3	0.0022	*THADA*
19:15233517-15235879	2	0.0025	*ILVBL*
6:101079090-101248282	2	0.0027	*ASCC3*
5:149676827-149677481	2	0.0028	*ARSI*
14:50117073-50141063	2	0.003	*POLE2*

N.pass.v = number of variants passing the mask definitions

Supplemental Table 16: Top 10 associations to WES 'Late DKD' using SKAT-O with 4 different masks.

Position	n.pass.v	n.sing.v	P-value	Gene
PTV+missense				
13:53035097-53049198	8	4	0.00012156	*CKAP2*
10:45798933-45803264	5	4	0.00048573	*OR13A1*
3:54952509-54959089	5	2	0.00063959	*LRTM1*
1:151139478-151140817	6	3	0.0006738	*SCNM1*
20:57415627-57430300	13	9	0.00086146	*GNAS*
7:18066456-18067243	5	3	0.0012014	*PRPS1L1*
19:6730150-6736607	19	8	0.0012488	*GPR108*
17:38933291-38938348	6	2	0.0012682	*KRT27*
19:42392130-42410847	17	8	0.0013578	*ARHGEF1*
3:122103120-122128670	3	1	0.0015433	*FAM162A*
PTV+broad				
11:68673615-68707139	9	6	0.00024156	*IGHMBP2*
13:53035097-53049198	7	4	0.0004632	*CKAP2*
7:18066456-18067059	4	3	0.00054833	*PRPS1L1*
3:54952509-54952627	2	0	0.00064301	*LRTM1*
10:45799065-45799733	2	1	0.00076937	*OR13A1*
18:77891038-77896253	6	3	0.0011557	*ADNP2*
13:28794420-28866586	6	3	0.0011976	*PAN3*
17:38933291-38938348	5	2	0.0013916	*KRT27*
5:37815803-37816112	3	1	0.0014264	*GDNF*
3:122103120-122128670	3	1	0.0015433	*FAM162A*
PTV+strict				
3:54952509-54952627	2	0	0.00064301	*LRTM1*
3:150384657-150421396	4	2	0.00066435	*FAM194A*
3:39228815-39229781	3	2	0.0035418	*XIRP1*
6:45909349-45916999	2	0	0.0035639	*CLIC5*
9:75774283-75777764	2	1	0.0072129	*ANXA1*
1:151773808-151774922	4	2	0.0076929	*LINGO4*
17:8701157-8701167	2	1	0.0088381	*MFSD6L*
17:40933276-40948304	4	3	0.0089785	*WNK4*
1:46016829-46034879	3	1	0.0094446	*AKR1A1*
3:38307398-38318485	2	1	0.0094456	*SLC22A13*
PTV+only				
3:54952509-54952627	2	0	0.00064301	*LRTM1*
19:15233517-15235879	2	1	0.0016954	*ILVBL*
17:8701157-8701167	2	1	0.0088381	*MFSD6L*
3:38307398-38318485	2	1	0.0094456	*SLC22A13*
2:43458439-43804337	3	2	0.010444	*THADA*
16:334920-336888	5	1	0.010482	*PDIA2*
17:5486023-5487821	2	1	0.01087	*NLRP1*
22:41257273-41257834	3	2	0.01437	*DNAJB7*
22:19189003-19220052	2	1	0.017846	*CLTCL1*
5:111500816-111519735	2	1	0.018258	*EPB41L4A*

N.pass.v = number of variants passing the mask definitions; N.sing.v = number of singleton variants

Supplemental Table 17: Top 10 associations to WES 'Late DKD' using SKAT with 4 masks

Position	n.pass.v	n.sing.v	P-value	Gene
PTV+missense				
13:53035097-53049198	8	4	0.00041305	*CKAP2*
3:54952509-54959089	5	2	0.00060623	*LRTM1*
10:45798933-45803264	5	4	0.00072656	*OR13A1*
7:18066456-18067243	5	3	0.00091793	*PRPS1L1*
1:151139478-151140817	6	3	0.0011152	*SCNM1*
5:37815803-37816112	5	3	0.0013631	*GDNF*
8:70585265-70744856	14	6	0.0018813	*SLCO5A1*
14:75321989-75330435	10	4	0.0022685	*PROX2*
7:1855776-2269648	13	9	0.0026609	*MAD1L1*
18:42260994-42643270	16	12	0.0028434	*SETBP1*
PTV+broad				
13:53035097-53049198	7	4	0.00056746	*CKAP2*
3:54952509-54952627	2	0	0.00059024	*LRTM1*
10:45799065-45799733	2	1	0.00072803	*OR13A1*
7:18066456-18067059	4	3	0.0010284	*PRPS1L1*
5:37815803-37816112	3	1	0.0013592	*GDNF*
18:42281357-42618578	13	10	0.0023793	*SETBP1*
7:1937887-2269648	11	8	0.0024099	*MAD1L1*
6:45882076-45922972	7	2	0.0029219	*CLIC5*
1:186862169-186946869	3	2	0.0030571	*PLA2G4A*
3:150377770-150421666	10	6	0.0031755	*FAM194A*
PTV+strict				
3:150384657-150421396	4	2	0.00057312	*FAM194A*
3:54952509-54952627	2	0	0.00059024	*LRTM1*
6:45909349-45916999	2	0	0.0025361	*CLIC5*
1:46016829-46034879	3	1	0.0062285	*AKR1A1*
9:75774283-75777764	2	1	0.0062769	*ANXA1*
17:40933276-40948304	4	3	0.0069954	*WNK4*
17:34861135-34881073	3	2	0.0076076	*MYO19*
3:121491422-121544920	5	3	0.0081831	*IQCB1*
3:39228815-39229781	3	2	0.0098747	*XIRP1*
19:15233517-15235879	4	1	0.010502	*ILVBL*
PTV+only				
3:54952509-54952627	2	0	0.00059024	*LRTM1*
19:15233517-15235879	2	1	0.0024413	*ILVBL*
16:334920-336888	5	1	0.0067681	*PDIA2*
3:38307398-38318485	2	1	0.013673	*SLC22A13*
17:8701157-8701167	2	1	0.015528	*MFSD6L*
17:5486023-5487821	2	1	0.018495	*NLRP1*
17:72363857-72366663	2	1	0.021549	*GPR142*
14:24566139-24569423	5	4	0.024283	*PCK2*
22:19189003-19220052	2	1	0.024653	*CLTCL1*
3:149238595-149245675	1	0	0.024785	*WWTR1*

N.pass.v = number of variants passing the mask definitions; N.sing.v = number of singleton variants

Supplemental table 18: Top 10 associations to WES 'ESRD vs. no DKD' with VT and 4 masks

Position	n.pass.v	P-value	Gene
PTV+missense			
12:518580-550003	7	2.1e-05	*CCDC77*
16:28877711-28884952	7	3.1e-05	*SH2B1*
12:102108407-102120196	4	8.6e-05	*CHPT1*
14:23846482-23848306	3	0.00012	*CMTM5*
11:5775980-5776749	5	0.00019	*OR52N4*
12:100685365-100732822	8	0.00032	*SCYL2*
15:44065537-44068996	7	0.00035	*ELL3*
9:130494915-130496639	6	0.00037	*TOR2A*
20:61907925-61919795	12	0.00053	*ARFGAP1*
1:156182876-156209351	6	0.0006	*PMF1*
PTV+broad			
12:102113935-102120196	3	3.4e-05	*CHPT1*
6:31525437-31526261	3	0.000124	*NFKBIL1*
14:23846482-23848306	3	0.00015	*CMTM5*
13:28794420-28866586	6	0.00018	*PAN3*
16:28877939-28884858	5	0.00029	*SH2B1*
6:160543080-160577058	9	0.00054	*SLC22A1*
1:229730547-229738417	4	0.00073	*TAF5L*
1:228612639-228612822	3	0.00077	*HIST3H3*
14:52472205-52534758	18	0.0008	*NID2*
11:5775984-5776749	4	0.00104	*OR52N4*
PTV+strict			
8:22884744-22885843	2	0.00019	*TNFRSF10B*
17:77100210-77102746	2	0.0006	*HRNBP3*
8:133083602-133090167	2	0.00083	*HHLA1*
6:136560616-136560647	2	0.00114	*FAM54A*
4:38798235-38800282	5	0.0012	*TLR1*
19:8138170-8203184	3	0.0016	*FBN3*
17:72954475-72960618	2	0.0017	*C17orf28*
18:21752415-21957382	3	0.0018	*OSBPL1A*
6:34003851-34100981	4	0.0018	*GRM4*
8:38834236-38845519	3	0.0025	*HTRA4*
PTV-only			
8:22884744-22885843	2	0.00017	*TNFRSF10B*
8:133083602-133090167	2	0.00072	*HHLA1*
19:8138170-8203184	3	0.0012	*FBN3*
3:4355014-4355131	2	0.0025	*SETMAR*
11:121008192-121058691	3	0.0035	*TECTA*
4:47538723-47574170	2	0.0035	*ATP10D*
10:75184515-75187483	2	0.0041	*ZMYND17*
3:9960192-9974543	3	0.0049	*IL17RC*
2:169727989-169728004	2	0.0056	*SPC25*
22:42473722-42473986	3	0.0061	*FAM109B*

N.pass.v = number of variants passing the mask definitions

Supplemental Table 19: Top 10 associations to WES 'ESRD vs. no DKD' with SKAT-O with 4 masks

Position	n.pass.v	n.sing.v	P-value	Gene
PTV+missense				
11:5775980-5776749	4	3	2.8913e-05	*OR52N4*
12:102108407-102120196	3	1	4.3482e-05	*CHPT1*
14:23846482-23848306	2	2	8.5563e-05	*CMTM5*
12:100685365-100732822	6	2	8.6197e-05	*SCYL2*
12:518580-550003	7	4	9.0216e-05	*CCDC77*
2:43458176-43819161	21	12	0.00015065	*THADA*
11:62575105-62598496	5	3	0.00016229	*STX5*
15:44065537-44068996	3	2	0.00016763	*ELL3*
20:61907925-61919795	9	4	0.00027894	*ARFGAP1*
13:28794420-28866586	7	5	0.00030024	*PAN3*
PTV+broad				
12:102113935-102120196	2	0	1.8982e-05	*CHPT1*
13:28794420-28866586	5	3	2.0813e-05	*PAN3*
6:31525437-31526261	2	2	8.4194e-05	*NFKBIL1*
14:23846482-23848306	2	2	8.5563e-05	*CMTM5*
11:5775984-5776749	3	2	0.00017668	*OR52N4*
11:62592777-62598496	3	1	0.00021827	*STX5*
20:44047493-44054249	8	7	0.0002694	*PIGT*
5:39376125-39394413	3	1	0.00029884	*DAB2*
17:7094043-7107367	5	4	0.00049654	*DLG4*
19:49407625-49424482	8	6	0.00054261	*NUCB1*
PTV+strict				
8:22884744-22885843	2	2	9.8064e-05	*TNFRSF10B*
4:38798235-38800282	4	3	0.00046089	*TLR1*
17:77100210-77102746	1	0	0.00062522	*HRNBP3*
19:10738409-10748401	3	2	0.0010388	*SLC44A2*
16:61687916-61689548	1	0	0.0012592	*CDH8*
4:186111299-186111306	2	1	0.0013119	*KIAA1430*
8:133083602-133090167	2	2	0.0013399	*HHLA1*
8:38834236-38845519	2	1	0.0013474	*HTRA4*
16:89985750-89986215	2	1	0.0014125	*MC1R*
17:41004777-41006634	2	1	0.0014339	*AOC3*
PTV+only				
8:22884744-22885843	2	2	9.8064e-05	*TNFRSF10B*
8:133083602-133090167	2	2	0.0013399	*HHLA1*
16:89985750-89986215	2	1	0.0014125	*MC1R*
11:67786064-67789293	2	0	0.0020716	*ALDH3B1*
3:4355014-4355131	2	2	0.0020738	*SETMAR*
19:8138170-8203184	1	1	0.0028026	*FBN3*
4:47538723-47574170	1	1	0.0032767	*ATP10D*
22:41257273-41257834	3	2	0.0033414	*DNAJB7*
11:121008192-121058691	2	2	0.0033577	*TECTA*
1:151493123-151508777	1	1	0.0037668	*CGN*

N.pass.v = number of variants passing the mask definitions; N.sing.v = number of singleton variants

Supplemental Table 20: Top 10 associations to WES 'ESRD vs. no DKD' with SKAT with 4 masks

Position	n.pass.v	n.sing.v	P-value	Gene
PTV+missense				
2:43458176-43819161	21	12	8.3459e-05	*THADA*
5:39376125-39394413	8	2	0.00018914	*DAB2*
17:34071959-34079805	9	5	0.00020671	*GAS2L2*
12:102108407-102120196	3	1	0.00021871	*CHPT1*
14:23846482-23848306	2	2	0.00026538	*CMTM5*
11:62575105-62598496	5	3	0.00038847	*STX5*
12:57345928-57351029	3	2	0.00055704	*RDH16*
5:63986481-64013795	5	3	0.00066429	*FAM159B*
5:157053392-157078632	7	5	0.00088391	*SOX30*
4:186111299-186112220	4	3	0.0010538	*KIAA1430*
PTV+broad				
12:102113935-102120196	2	0	0.00021073	*CHPT1*
5:39376125-39394413	3	1	0.00022996	*DAB2*
6:31525437-31526261	2	2	0.00025304	*NFKBIL1*
14:23846482-23848306	2	2	0.00026538	*CMTM5*
11:62592777-62598496	3	1	0.00049172	*STX5*
5:63986481-63991426	4	2	0.00061686	*FAM159B*
17:7094043-7107367	5	4	0.00086232	*DLG4*
5:157053392-157078632	7	5	0.00088391	*SOX30*
17:77100210-77111580	2	1	0.0010418	*HRNBP3*
22:21235389-21242054	1	0	0.0010726	*SNAP29*
PTV+strict				
8:22884744-22885843	2	2	0.0002888	*TNFRSF10B*
17:77100210-77102746	1	0	0.00062522	*HRNBP3*
19:10738409-10748401	3	2	0.00089608	*SLC44A2*
16:89985750-89986215	2	1	0.001117	*MC1R*
17:41004777-41006634	2	1	0.0011256	*AOC3*
4:186111299-186111306	2	1	0.0012193	*KIAA1430*
11:67786064-67789293	2	0	0.001238	*ALDH3B1*
16:61687916-61689548	1	0	0.0012592	*CDH8*
1:104116940-104117921	2	0	0.0022375	*AMY2B*
19:8138170-8203184	1	1	0.0028026	*FBN3*
PTV+only				
8:22884744-22885843	2	2	0.0002888	*TNFRSF10B*
16:89985750-89986215	2	1	0.001117	*MC1R*
11:67786064-67789293	2	0	0.001238	*ALDH3B1*
19:8138170-8203184	1	1	0.0028026	*FBN3*
4:47538723-47574170	1	1	0.0032767	*ATP10D*
12:55863064-55863661	3	1	0.0034269	*OR6C70*
1:151493123-151508777	1	1	0.0037668	*CGN*
2:169727989-169728004	1	1	0.0037668	*SPC25*
13:40235019-40261900	1	1	0.0042598	*COG6*
16:10837724-10846536	1	1	0.0042598	*NUBP1*

N.pass.v = number of variants passing the mask definitions; N.sing.v = number of singleton variants

Supplemental Table 21: Gene-sets which showed enrichment in WES association data on the 'Late DKD' phenotype, with permutation (N=100) results

				Real data				Random data (# of times a better finding is observed in the random data)/100				
Gene set	**Genes**	**SNPs**	**SKATO mask**	***NES***	***Pval***	***FDR***	***FWER***	***NES***	***Pval***	***FDR***	***FWER***	***NES & FDR***
FUNC_meta_T1D-ESRDvsNonESRD_emmax_FD-SDR-ED1	16	120	Ptv.miss.0.01	2,12	0.0022	0.0396	0.044	0.04	0.1	0.08	0.09	0.03
TOP_meta_T1D-macro-ESRD_emmax_FD-SDR-Cam-ED1	43	147	Ptv.strict.broad.0.01	2,3	0.000*	0.012	0.013	0	0	0.02	0.02	0

Non-significant, tested gene sets

Gene set	Genes
Orpha.kidney	466
GWAS.kidney	65
GO.BP.kidney	357
MGI.kidney	836
expression.kidney	1597
LitMS.kidney	1349
overexpressed.in.isolated.mouse.podocytes	756
mouse.K.O.has.abnormal.podocyte	39
causes.rare.human.glomerular.disease	45
TOP_meta_T1D-CKD_emmax_FD-SDR-ED1	67
TOP_meta_T1D-CKDDN_emmax_FD-SDR-ED1	69
TOP_meta_T1D-ESRD_emmax_FD-SDR-ED1	243
TOP_meta_T1D-ESRDvsNonESRD_emmax_FD-SDR-ED1	56
TOP_meta_T1D-micro_emmax_FD-SDR-Cam-ED1	22
TOP_Meta_T1D-T2D_CKDDN_min_emmax_131202	93
TOP_Meta_T1D-T2D_ESRDvsALL_min_emmax	289
TOP_Meta_T1D-T2D_ESRDvsCONTROL_min_emmax_131101	449
TOP_Meta_T1D-T2D_MACROESRD_min_emmax_131101	181
TOP_Meta_T1D-T2D_MICRO_min_emmax_131101	35
TOP_Meta_T2D_CKD_min_emmax_131202	4

TOP_Meta_T2D_DN_min_emmax_131101	6
TOP_Meta_T2D_eGFR_min_emmax_131128	26
TOP_Meta_T2D_ESRDvsALL_min_emmax_131128	186
FUNC_meta_T1D-CKD_emmax_FD-SDR-ED1	13
FUNC_meta_T1D-CKDDN_emmax_FD-SDR-ED1	6
FUNC_meta_T1D-DN_emmax_FD-SDR-Cam-ED1	1
FUNC_meta_T1D-ESRD_emmax_FD-SDR-ED1	30
FUNC_meta_T1D-macro-ESRD_emmax_FD-SDR-Cam-ED1	4
FUNC_Meta_T1D-T2D_CKD_min_emmax_131202	3
FUNC_Meta_T1D-T2D_CKDDN_min_emmax_131202	12
FUNC_Meta_T1D-T2D_MACROESRD_min_emmax_131101	23
FUNC_Meta_T2D_eGFR_min_emmax_131128	14
FUNC_Meta_T2D_MACROESRD_min_emmax_131101	6
FUNC_Meta_T2D_MICRO_min_emmax_131101	2
Podo_Axonal Guidance Signaling	159
Podo_Signaling by Rho Family GTPases	97
Podo_Epithelial Adherens Junction Signaling	66
Podo_ILK Signaling	79
Podo_RhoA Signaling	57
Podo_Integrin Signaling	79
Podo_Germ Cell-Sertoli Cell Junction Signaling	65

*NES= Normalised Enrichment Score

**In the GSEA report, a p value of zero (0.0) indicates an actual p value of less than 1/number-of-permutations. For example, if the analysis performed 100 permutations, a reported p value of 0.0 indicates an actual p value of less than 0.001. For a more accurate p-value, increase the number of permutations performed by the analysis.

Supplemental Table 22: ABACUS association analysis results for the top SNPs from the GWAS discovery

Pheno	Cohort	SNP	CHR	P value	Gene
CKD	FINNDIANE	rs1622208	1	4.80E-06	*MAST2*
CKD	FINNDIANE	rs6682683	1	4.51E-06	*MAST2*
ESRD vs. NO DKD	FINNDIANE	rs17024167	1	7.97E-07	*PHGDH*
CKD	EURODIAB	rs13384229	2	3.16E-06	*ALS2*
CKD+ DKD	EURODIAB	rs11898503	2	4.31E-06	*KLHL29*
DKD & Late DKD	EURODIAB	rs906651	2	4.51E-06	*LRP1B*
CKD+DKD	FINNDIANE	rs7577925	2	7.97E-07	*NCKAP5*
Late DKD	FINNDIANE	rs3773786	3	3.77E-07	*IQCJ-SCHIP1*
Late DKD & CKD+DKD	FINNDIANE	rs6785153	3	3.77E-07	*IQCJ-SCHIP1*
Combined DKD	FINNDIANE	rs1061860	3	7.97E-07	*MB21D2*
Combined DKD	FINNDIANE	rs2986	3	7.97E-07	*MB21D2*
Late DKD	FINNDIANE	rs1434546	4	4.03E-06	*BMPR1B*
Late DKD	FINNDIANE	rs1545326	4	4.27E-06	*BMPR1B*
Late DKD	FINNDIANE	rs17022885	4	4.31E-06	*BMPR1B*
CKD	FINNDIANE	rs4352548	4	6.35E-07	*BTC*
CKD	FINNDIANE	rs3796588	4	6.34E-07	*GUCY1A3*
Late DKD	FINNDIANE	rs10037055	5	1.73E-06	*NSD1*
Late DKD	FINNDIANE	rs2244012	5	4.00E-06	*RAD50*
Early DKD	SDR	rs1970549	6	4.77E-06	*KCNQ5*
Early DKD	EURODIAB	rs1019046	7	1.64E-06	*GLI3*
CKD	SDR	rs7778308	7	3.65E-06	*GRM8*
ESRD vs. NO DKD	FINNDIANE	rs6983307	8	1.09E-06	*ST18*
Late DKD & CKD+DKD & ESRD vs. NO DKD	FINNDIANE	rs10121901	9	1.89E-06	*ABCA1*
Late DKD & CKD+DKD & ESRD vs. NO DKD	FINNDIANE	rs2066720	9	1.96E-06	*ABCA1*
CKD	FINNDIANE	rs2855171	9	4.37E-06	*ABL1*
Late DKD	SDR	rs10794197	10	4.66E-06	*CTBP2*
Early DKD	NFS-ORPS	rs2236418	10	1.73E-06	*GAD2*
Early DKD	NFS-ORPS	rs10508715	10	1.73E-06	*MYO3A*
Early DKD	NFS-ORPS	rs994502	10	1.73E-06	*MYO3A*
CKD	FINNDIANE	rs1784175	11	4.39E-06	*OPCML*
Late DKD & Combined DKD	FINNDIANE	rs3059	11	1.73E-06	*POLR2L*

Pheno	Cohort	SNP	CHR	P value	Gene
Late DKD	FINNDIANE	rs3741935	12	1.80E-06	*PRMT8*
Combined DKD	EURODIAB	rs9540711	13	4.03E-06	*PCDH9*
Late DKD	FINNDIANE	rs2278709	15	2.15E-06	*ARNT2*
Early DKD	SDR	rs678892	15	3.53E-06	*PIGB*
Late DKD	FINNDIANE	rs173839	16	3.65E-06	*CDH13*
ESRD vs. NO DKD	EURODIAB	rs4782574	16	2.89E-06	*OSGIN1*
Late DKD	FINNDIANE	rs8075035	17	2.15E-06	*AIPL1*
CKD+DKD	SDR	rs1972933	17	1.28E-06	*MAP2K6*
Early DKD	NFS-ORPS	rs7234763	18	7.18E-07	*PTPRM*
Late DKD	FINNDIANE	rs2544795	19	3.20E-06	*SULT2B1*
Late DKD	FINNDIANE	rs2665579	19	2.74E-06	*SULT2B1*
ESRD vs. NO DKD	EURODIAB	rs17420378	20	6.34E-07	*STK4*
ESRD vs. NO DKD	EURODIAB	rs6073622	20	6.34E-07	*STK4*
ESRD vs. NO DKD	EURODIAB	rs7266289	20	6.34E-07	*STK4*
ESRD vs. NO DKD	EURODIAB	rs7271519	20	6.34E-07	*STK4*

Supplemental Table 23: ABACUS association analysis results for the top SNPs from the WES discovery

Pheno	Cohort	SNP	CHR	P value	Gene
ESRD vs. no DKD	FINNDIANE	rs2297955_G_A	1	1.66E-06	*ACTN2*
ESRD vs. no DKD	FINNDIANE	rs41293273_C_T	1	1.14E-07	*NSUN4*
ESRD vs. no DKD	FINNDIANE	rs41293275_T_A	1	3.41E-07	*NSUN4*
Late DKD	STENO	rs2289239_A_G	2	4.09E-06	*POLR1A*
Late DKD	SDR	rs6775309_T_C	3	2.15E-06	*GPD1L*
Late DKD	SDR	rs6788436_C_T	3	2.15E-06	*GPD1L*
Late DKD	SDR	rs6799559_G_A	3	2.15E-06	*GPD1L*
Late DKD	SDR	rs6799728_T_A	3	2.15E-06	*GPD1L*
Late DKD	SDR	rs2813_C_T	3	3.08E-06	*GPD1L*
ESRD vs. no DKD	STENO	rs55642964_C_T	4	1.82E-06	*SH3TC1*
ESRD vs. no DKD	STENO	rs2136662_G_T	16	9.10E-07	*OSGIN1*
ESRD vs. no DKD	STENO	rs3087852_A_G	17	8.89E-07	*PSMD3*
ESRD vs. no DKD	STENO	rs12102_A_G	18	2.05E-06	*SERPINB2*
ESRD vs. no DKD	STENO	rs3217292_G_GTGAGA	18	2.05E-06	*SERPINB2*
ESRD vs. no DKD	STENO	rs6093_T_C	18	2.05E-06	*SERPINB2*
ESRD vs. no DKD	STENO	rs6095_G_C	18	2.05E-06	*SERPINB2*
ESRD vs. no DKD	STENO	rs6098_G_A	18	2.05E-06	*SERPINB2*
ESRD vs. no DKD	STENO	var_chr18_61569819_T_TTTAAGTTTCTGGGGC	18	2.05E-06	*SERPINB2*
ESRD vs. no DKD	FINNDIANE	rs2295490_G_A	20	4.64E-06	*TRIB3*
Late DKD	FINNDIANE	rs2073278_A_G	22	2.65E-06	*SBF1*

Supplemental Table 24: DAVID functional clustering of the genes mapped by the SNPs selected by the ABACUS software on GWAS data

Key Terms	Genes	Score
macromolecular complex subunit organization, protein oligomerization	*AGTR1,APC,CCDC88C,COLEC12,GTF3C4,H3F3B,HELLS,KCNQ5,NCK2,NDUFS4 ,PFKP,PPARGC1A,PRKAA2,SYT1,TRIM27,YWHAB*	3.16
kidney & urogenital system development, positive regulation of developmental process	*AGTR1,APC,GLI3,GNAS,HELLS,IL7R,NTN1,ROBO1,SART1,SLIT2,TGFBR2*	2.76
adenyl nucleotide binding, ATP binding, Serine/threonine protein kinase	*ABL1,AOX1,CARM1,CDC7,CELF2,CHST11,CTBP2,GNAS,GTF3C4,HELLS,KARS, KIF13B,KRAS,MAP2K6,MGAT5,MYH6,MYH9,MYO3A,NDUFS4,NUAK2,OPA1, PAK7,PAPOLA,PDE10A,PFKP,PGM1,PIGB,PPARGC1A,PRKAA2,PRKAG2,PTPR M,PTPRN2,STK4,SULT2B1,TEC,TGFBR2,TRIM27,WEE1*	2.15
hemopoietic or lymphoid organ development, leukocyte/lymphocyte activation & differentiation	*APC,BLNK,BRCA2,CD40LG,HELLS,IL7R,KIF13B,MYH9,NCK2,TGFBR2,TLR1,TLR 3*	2.09
positive regulation of kinase activity, positive regulation of transferase activity	*ABL1,AGTR1,ALS2,APC,CASP9,CCDC88C,FSHR,GAP43,GNAS,KRAS,MAP2K6, NCK2,NDUFS4,PRKAG2,RPS3,TGFBR2,TLR3,YWHAB*	2.06
cellular response to stress, regulation of apoptosis	*ABL1,APC,BIRC5,BRCA2,CASP9,CD40LG,CHST11,FOXN3,GLI3,HELLS,KRAS,M AP2K6,NUAK2,PAK7,RPA3,RPS3,SART1,SCAP,STK4,TNFRSF8,YWHAB*	1.91
actin cytoskeleton organization	*ABL1,APC,ATG4A,BIRC5,BRCA2,CNTROB,DIAPH2,KRAS,LIMA1,MYH6,MYH9, MYO3A,NCK2,NUAK2*	1.77
lipid moiety-binding region:S-palmitoyl cysteine, lipoprotein, palmitate	*ABL1,AGTR1,GAD2,GAP43,GNAS,KRAS,LRP1B,RGS7,SYT1*	1.70
glycoprotein, glycosylation site:N-linked (GlcNAc...)	*ABL1,AGTR1,APBB1IP,APC,ARSF,BLNK,CACNA2D1,CBL,CD40LG,CHST11,COL EC12,CTBP2,FSHR,GABRA2,GAD2,GAP43,GNAS,GRB10,GRIK4,GRM8, HLA-E, IGSF21,IL7R,KAL1,KCNK2,KCNQ5,KRAS,LIMA1,LPHN3,LRMP, LRP1B,MGAT5,MYH6,MYH9,NTN1,PCDH9,PIGB,PPARGC1A,PRELP,PTPRM,P TPRN2,RGS7,ROBO1,RPS3,SCAP,SLC34A3,SLC8A1,SLIT2,STAB2,SYT1,TF,TGF BR2,TLR1,TLR3,TLR8,TNFRSF8,TRIM27*	1.62
inflammatory response, Toll-Interleukin receptor, positive regulation of cytokine biosynthetic process	*ALS2,AOX1,BLNK,CD40LG,COLEC12,FSHR,PRELP,SLIT2,STAB2,TF,TLR1,TLR3, TLR8,TNFRSF8*	1.60
leukocyte proliferation/activation, lymphocyte proliferation, mononuclear cell proliferation	*APC,BLNK,CD40LG,HELLS,IL7R,KIF13B,MYH9,NCK2*	1.54
SH2 domain	*ABL1,BLNK,CBL,GRB10,NCK2,TEC*	1.54
axon guidance, axonogenesis, cell morphogenesis involved in differentiation, cell motion	*ABL1,ALS2,APC,CBL,GAD2,GAP43,GLI3,GRIK4,IL7R,KAL1,KRAS,LIMA1,MYH6 ,MYH9,NCK2,NTN1,OPA1,PAK7,PPARGC1A,PTPRM,ROBO1,SLIT2,STK4*	1.52
regulation of myeloid leukocyte differentiation, regulation of osteoclast differentiation	*APC,GNAS,TLR3*	1.43
insulin signalling pathway, regulation of cellular ketone metabolic process,regulation of fatty acid metabolic	*AGTR1,CBL,KRAS,PPARGC1A,PRKAA2,PRKAG2,RAPGEF1,SCAP*	1.38

Key Terms	Genes	Score
process		
apoptosis	*BIRC5,CASP9,EGLN3,KRAS,NTN1,NUAK2,OPA1,RPS3,STK4,YWHAB*	1.37
positive regulation of cellular component organization	*APC,CBL,NCK2,NTN1,PPARGC1A,ROBO1,SLIT2*	1.35
actin-dependent ATPase activity, calmodulin-binding, microfilament motor activity, myosin	*GAP43,KIF13B,MYH6,MYH9,MYO3A,SLC8A1,SYT1*	1.32
angiogenesis, blood vessel endothelial cell migration	*MYH9,ROBO1,SLIT2,STAB2,TGFBR2*	1.32
protein kinase binding	*ALS2,APC,BIRC5,DIAPH2,KIF13B,PRKAG2,RPS3,SUPT5H,TGFBR2,YWHAB*	1.28
positive regulation of leukocyte/lymphocyte activation & differentiation	*IL7R,NCK2,SART1,TGFBR2,TLR3,TLR8*	1.25
low-density lipoprotein binding	*COLEC12,LRP1B,STAB2*	1.24
nuclear lumen, nucleoplasm	*ABL1,BIRC5,BRCA2,CDC7,CTBP2,GLI3,GRHL1,GTF3C4,MYH6,PAPOLA,PPARGC1A,PRKAA2,PRKAG2,PRPF8,RPA3,SUPT5H,TRIM27,WEE1,YWHAB*	1.23
cytokinesis, interphase, tubulin binding	*ABL1,APC,ATG4A,BIRC5,BRCA2,CDC7,CNTROB,DIAPH2,FOXN3,GFI1B,HELLS,MAP2K6,MYH9,SART1,SUPT5H,WEE1*	1.23
cell morphogenesis involved in differentiation, cell motion	*ALS2,APC,GAP43,KAL1,MYH9,NCK2,NTN1,PTPRM,ROBO1,SLIT2*	1.22
cell junction, presynaptic membrane, synaptic vesicle membrane	*ALS2,APBB1IP,APC,CTBP2,GABRA2,GAD2,GAP43,GRIK4,GRM8,KCNQ5,LIMA1,MYH6,MYH9,OPA1,PTPRM,ROBO1,SYT1*	1.21
embryonic development, striated muscle differentiation	*ALS2,BRCA2,GLI3,KRAS,MYH6,MYH9*	1.14
adherens junction, anchoring junction	*APBB1IP,APC,LIMA1,MYH6,MYH9,PTPRM*	1.14
chordate embryonic development	*ALS2,BRCA2,CHST11,GLI3,GNAS,MYH6,MYH9,TGFBR2*	1.10
hypertrophic cardiomyopathy (HCM)	*CACNA2D1,MYH6,PRKAA2,PRKAG2,SLC8A1*	0.97
regulation of lipid metabolic process	*AGTR1,PPARGC1A,PRKAA2,PRKAG2,SCAP*	0.88
Toll-Interleukin receptor, positive regulation of cytokine biosynthetic process	*TLR1,TLR3,TLR8,TNFRSF8*	0.87
domain:EGF-like	*LRP1B,SLIT2,STAB2*	0.86
fatty acid biosynthesis	*ELOVL5,PRKAA2,PRKAG2*	0.84
regulation of system process	*AGTR1,CELF2,GRM8,KRAS,MYH6,SLC8A1,TF*	0.82
negative regulation of cell proliferation	*APC,BRCA2,CTBP2,GLI3,NCK2,PTPRM,TGFBR2,TNFRSF8*	0.80
negative regulation of nucleobase, nucleoside, nucleotide, transcriptional repressor complex	*BRCA2,CTBP2,FOXN3,GFI1B,GLI3,GRM8,HELLS,RPS3,SCAP,SUPT5H,TRIM27,YWHAB*	0.72
metal-binding	*ABL1,ADH1A,AOX1,ARSF,BIRC5,CACNA2D1,CBL,CDC7,COLEC12,CYP4F2,EGLN3,GFI1B,GLI3,KARS,LIMA1,NUAK2,PDE10A,PFKP,PGM1,PRKAA2,STK4,SYT1,TAB3,TEC,TF,TGFBR2,TRIM27,WEE1*	0.70

Supplemental Table 25: DAVID functional clustering of the genes mapped by the SNPs selected by the ABACUS software on WES data

Key Terms	Genes	Score
protein dimerization activity, homodimerization activity	*ACTN2,AMBP,ATF6,AXIN1,BCAT1,CD4,DVL2,FAAH,GCC2,GPD1L,HEXB,IL12B,KYNU,MYO9B,NEUROD1,PCSK9,TAS1R3,TGFB2*	3.90
serpin, serine-type endopeptidase inhibitor activity	*AMBP,CASP3,SERPINA11,SERPINB10,SERPINB2,SERPINF1,TRIAP1,TRIB3*	2.46
lipoprotein, phospholipid metabolic process, phosphotransferase activity	*ACSL3,EPT1,FASN,GGT5,GPD1L,HEXB,LRP1,PCSK9,PIGN,PIGX,PLA2G4D,PRKAB2,SGMS2*	2.26
carboxylic acid, fatty acid metabolic process, pyridoxal phosphate	*ACSL3,ACSL5,BCAT1,EPT1,FAAH,FASN,GGT5,HEXB,KYNU,PIGN,PIGX,PRKAB2,SGMS2,SLC27A6*	2.25
fatty-acid ligase activity, fatty acid metabolic process, long-chain-fatty-acid-CoA ligase activity	*ACSL3,ACSL5,FAAH,FASN,GGT5,PCSK9,PRKAB2,SGMS2,SLC27A6*	1.84
nucleoside and nucleotide biosynthetic process	*AMPD1,ATIC,ATP5A1,BCAT1,KYNU,MYO9B,PPAT,TGFB2*	1.61
transmembrane region	*ABCA4,ABCB11,ACSL3,ACSL5,ALG5,ATF6,ATP5A1,CACNA1D,CD4,CDON,DGKG,EPT1,ERBB4,FAAH,GCC2,GDPD5,GGT5,GLIPR1,GNG4,HLA-DQB1,IL31RA,IMMT,ITPR3,KCNMB2,LRP1,PIGN,PIGX,PLA2G4D,PTGFR,PTPRD,RSAD2,SCN10A,SGMS2,SLC10A6,SLC17A4,SLC27A6,SSR1,ST3GAL1,STOML1,STX2,SYVN1,TAS1R3,TBXA2R,TRPC6*	1.45
glycoprotein, glycosylation site:N-linked (GlcNAc...)	*ABCA4,ABCB11,ALG5,AMBP,ATF6,CACNA1D,CD4,CDON,CGA,DNAH14,ELSPBP1,ERBB4,GDPD5,GGT5,GIP,GLIPR1,HEXB,HLA-DQB1,IL12B,IL31RA,KCNMB2,KLK8,LRP1,PCSK9,PIGN,PIGX,PTGFR,PTPRD,SCN10A,SERPINA11,SERPINB2,SERPINF1,SLC10A6,SLC17A4,SLIT3,SSR1,ST3GAL1,SYVN1,TAS1R3,TBXA2R,TGFB2,TPPP,TRPC6*	1.41
regulation of protein kinase activity	*AXIN1,CASP3,CD4,DGKG,IL31RA,KAT2B,KIF13B,LRP1,MAP2K1,MYO9B,PRKAB2,TGFB2,TRIB3*	1.39
endoplasmic reticulum	*ACSL3,ACSL5,ALG5,ATF6,ATP5A1,CD4,FAAH,IMMT,ITPR3,PCSK9,PIGN,PIGX,RSAD2,SGMS2,SSR1,ST3GAL1,SYVN1*	1.26
carboxylic acid catabolic process	*AMDHD1,BCAT1,FAAH,KYNU*	1.24
cell fraction, insoluble fraction, membrane fraction	*ABCA4,ABCB11,ACSL3,ACSL5,AMBP,CGA,GIP,HEXB,ITPR3,KYNU,LRP1,MAP2K1,MYO9B,PRKCQ,SLC17A4,SLIT3,STX2,TPPP*	1.21
cofactor metabolic process	*AMBP,GGT5,KYNU,NARFL,PPCDC*	1.15
regulation of leukocyte activation, regulation of T cell activation	*CASP3,CD4,IL12B,IL31RA,PRKCQ*	1.11
response to endogenous stimulus, response to hormone stimulus	*ATF6,CASP3,CD4,CGA,ERBB4,GNG4,KAT2B,KYNU,MAP2K1,NEUROD1,PCSK9,PRKCQ,TGFB2*	1.07
adipocytokine signalling pathway	*ACSL3,ACSL5,PRKAB2,PRKCQ*	1.07
regulation of cellular response to stress	*AMBP,AXIN1,KLK8,TGFB2*	1.00
neuron differentiation, positive regulation of cell	*CASP3,CDON,DGKG,ERBB4,KLK8,MAP2K1,NEUROD1,ONECUT2,PCSK9,PRKCQ*	0.99

Key Terms	Genes	Score
migration, positive regulation of cell motion	*,SALL1,SLIT3,TGFB2*	
regulation of protein kinase activity, regulation of transferase activity	*AXIN1,CASP3,CD4,DGKG,DVL2,LRP1,MAP2K1,TGFB2,TRIB3*	0.98
plasma membrane part	*ABCA4,ABCB11,ACTN2,AXIN1,CACNA1D,CD4,ERBB4,GNG4,HLA-DQB1,ITPR3,KCNMB2,LRP1,PCSK9,PLA2G4D,PRKCQ,PTGFR,PTPRD,RSAD2,SCN10A,SGMS2,SLC17A4,STX2,TBXA2R*	0.95
positive regulation of cytokine biosynthetic process, regulation of leukocyte activation, regulation of T cell activation	*ATF6,CASP3,CD4,IL12B,IL31RA,NEUROD1,NPAS2,NR5A2,ONECUT2,PRKCQ,TGFB2*	0.92
ion transport	*ATP5A1,CACNA1D,ITPR3,KCNMB2,SCN10A,SLC10A6,SLC17A4,TRPC6*	0.85
positive regulation of protein modification process	*AXIN1,CD4,IL31RA,PLK1,PSMD3*	0.85
protein kinase C, phorbol ester/diacylglycerol binding	*DGKG,MYO9B,PRKCQ*	0.83
ATP-binding	*ABCA4,ABCB11,ACSL3,ACSL5,ATP5A1,DGKG,DNAH14,ERBB4,KIF13B,MAP2K1,MYLK4,MYO9B,PLK1,PRKCQ*	0.81
calcium channel, Vascular smooth muscle contraction	*ATP5A1,CACNA1D,ITPR3,KCNMB2,MAP2K1,PRKCQ,SCN10A,SLC10A6,SLC17A4,TRPC6*	0.79
negative regulation of growth	*CGA,GNG4,OSGIN1,TGFB2*	0.77
duplication	*ACTN2,AMBP,CD4,DGKG,GIP,PRKCQ*	0.76
cell proliferation	*BCAT1,ERBB4,KLK8,LRP1,MAP2K1,PLK1,SERPINF1,TGFB2*	0.69
negative regulation of response to stimulus, zymogen	*AMBP,CASP3,GGT5,HEXB,KLK8,PCSK9,SERPINF1,TGFB2*	0.54
chemical homeostasis, homeostatic process	*CASP3,ERBB4,HEXB,IL31RA,ITPR3,KCNMB2,NARFL,NEUROD1,NR5A2,PCSK9,TRPC6*	0.52
positive regulation of macromolecule metabolic process	*ATF6,AXIN1,CD4,IL12B,IL31RA,MAP2K1,NEUROD1,NPAS2,NR5A2,ONECUT2,PCSK9,PLK1,PRKCQ,PSMD3,TGFB2*	0.52

Supplemental Table 26: Phenotype definitions. Table A: albuminuria- and eGFR based definitions. Table B: Case – control phenotypes.

Table A:

Class	Definitions
Normoalbuminuria	AER <20 µg/min OR AER <30 mg/24 h OR ACR <2.5 mg/mmol for men ACR <3.5 for women
Microalbuminuria	At least 2 out of 3 consecutive measurements with: AER ≥20 AND <100 µg/min OR AER ≥30 AND <150 mg/24 hr OR ACR ≥2.5 AND <12.5 for men ACR ≥3.5 AND <17.5 for women.
High microalbuminuria	At least one measurement with: AER ≥100 AND <200 µg/min OR AER ≥150 AND <300 mg/24 hr OR ACR ≥12.5 AND <25 for men ACR ≥17.5 AND <35 for women
Macroalbuminuria	At least one measurement* with: AER ≥200 µg/min OR AER ≥300 mg/24 h OR ACR ≥25 mg/mmol for men ACR ≥35 for women *Due to study designs, in some studies at least two out of three consecutive measurements with the given thresholds were required.
ESRD	eGFR ≤15 ml/min/1.73m^2 OR dialysis OR kidney transplantation.
eGFR	eGFR was estimated wither with the MDRD4 [7] or CKD-EPI formula[8], depending of the study. When IDMS-calibrated serum creatinine was used, the MDRD4 formula was multiplied by 175/186 [65].
CKD	eGFR < 60 ml/min/1.73m^2

Table B:

Phenotype name	Cases	Controls
DKD	microalbuminuria OR high microalbuminuria OR macroalbuminuria OR ESRD	normoalbuminuria AND diabetes duration >15 years
Early DKD	microalbuminuria OR high microalbuminuria	normoalbuminuria AND diabetes duration >15 years
Late DKD	macroalbuminuria OR ESRD	normoalbuminuria AND diabetes duration >15 years
ESRD vs. no DKD	ESRD	normoalbuminuria AND diabetes duration >15 years
ESRD vs. non-ESRD	ESRD	patients with no ESRD AND diabetes duration >15 years
CKD	CKD (eGFR<60 ml/min/1.73m^2)	eGFR≥60 ml/min/1.73m^2 AND diabetes duration >15 years
CKD+DKD	(eGFR < 45 ml/min OR ESRD/1.73m^2) AND (High micro OR Macro OR ESRD)	eGFR ≥ 60 ml/min/1.73m^2 AND normo-albuminuria AND diabetes duration >15 years

Supplemental Table 27: Membership of the GENIE Consortium

FinnDiane, Finland:	Niina Sandholm[1,2,3], Carol Forsblom[1,2], Valma Harjutsalo[1,2,4], Ville-Petteri Mäkinen[1,2, 4,6], Aila J Ahola[1,2], Emma Dahlström[1,2], Daniel Gordin[1,2], Outi Heikkilä[1,2], Kustaa Hietala[1,7], Janne Kytö[1,7], Markku Lehto[1,2], Raija Lithovius[1,2], Nicolae Mircea Panduru[1,8], Maija Parkkonen[1,2], Milla Rosengård-Bärlund[1,2], Markku Saraheimo[1,2], Jenny Söderlund[1,2], Aino Soro-Paavonen[1,2], Anna Syreeni[1,2], Lena M Thorn[1,2], Nina Tolonen[1,2], Johan Wadén[1,2], Per-Henrik Groop[1,2,9]
Belfast, UK:	Amy Jayne McKnight[10], Gareth J. McKay[10], Alexander P. Maxwell[10,11]
Boston, MA, USA:	Rany M. Salem[12,13,14], Tamara Isakova[15,16], Cameron Palmer[12,13], Candace Guiducci[12], Andrew Taylor[12,17], Daniel B. Mirel[12], Winfred W. Williams[14,17], Joel N. Hirschhorn[12,13,14], Jose C. Florez[12,14,17]
Dublin, Ireland:	Eoin P. Brennan[18,19], Denise M. Sadlier[18,19], Finian Martin[18,19], Catherine Godson[18,19]
Affiliations:	1. Folkhälsan Institute of Genetics, Folkhälsan Research Center, Helsinki, Finland 2. Department of Medicine, Division of Nephrology, Helsinki University Central Hospital, Helsinki, Finland 3. Department of Biomedical Engineering and Computational Science, Aalto University, Espoo, Finland 4. Diabetes Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland. 5. Department of Integrative Biology and Physiology, University of California Los Angeles, United States 6. South Australian Health and Medical Research Institute, Adelaide, Australia 7. Department of Ophthalmology, Helsinki University Central Hospital, Helsinki, Finland. 8. Chair of pathophysiology, 2nd clinical Department, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania. 9. Baker IDI Heart and Diabetes Institute, Melbourne, Australia. 10. Nephrology Research, Centre for Public Health, Queen's University of Belfast, Belfast, UK. 11. Regional Nephrology Unit, Level 11, Tower Block, Belfast City Hospital, Belfast, UK. 12. Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA. 13. Endocrine Research Unit, Department of Endocrinology, Children's Hospital, Boston, MA, USA. 14. Department of Medicine, Harvard Medical School, Boston, MA, USA. 15. Division of Nephrology and Hypertension, University of Miami, Miami, Florida, USA 16. Center for Translational Metabolism and Health - Institute for Public Health and Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA 17. Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA. 18. Diabetes Research Centre, Conway Institute, School of Medicine and Medical Sciences, University College Dublin, Dublin, Ireland. 19. Mater Misericordiae Hospital, Dublin, Ireland.

Supplemental Table 28: List of the FinnDiane centers and participating physicians and nurses.

FinnDiane Study Centers	Physicians and nurses
Anjalankoski Health Center	S. Koivula, T. Uggeldahl
Central Finland Central Hospital, Jyväskylä	T. Forslund, A. Halonen, A. Koistinen, P. Koskiaho, M. Laukkanen, J. Saltevo, M. Tiihonen
Central Hospital of Åland Islands, Mariehamn	M. Forsen, H. Granlund, A-C. Jonsson, B. Nyroos
Central Hospital of Kanta-Häme, Hämeenlinna	P. Kinnunen, A. Orvola, T. Salonen, A. Vähänen
Central Hospital of Länsi-Pohja, Kemi	H. Laukkanen, P. Nyländen, A. Sademies
Central Ostrabothnian Hospital District, Kokkola	S. Anderson, B. Asplund, U. Byskata, M. Kuusela, P. Liedes, T. Virkkala
City of Espoo Health Centre:	
-Espoonlahti	A. Nikkola, E. Ritola
-Samaria	E. Oukko-Ruponen, T. Virtanen
-Tapiola	M. Niska, H. Saarinen
-Viherlaakso	A. Lyytinen
City of Helsinki Health Centre:	
-Puistola	H. Kari, T. Simonen
-Suutarila	A. Kaprio, J. Kärkkäinen, B. Rantaeskola
-Töölö	J. Haaga, P. Kääriäinen, A-L. Pietiläinen
City of Hyvinkää Health Centre	S. Klemetti, T. Nyandoto, E. Rontu, S. Satuli-Autere
City of Vantaa Health Centre:	
-Korso	R. Toivonen, H. Virtanen
-Länsimäki	R. Ahonen, M. Ivaska-Suomela, A. Jauhiainen
-Martinlaakso	M. Laine, T. Pellonpää, R. Puranen
-Myyrmäki	A. Airas, J. Laakso, K. Rautavaara
-Rekola	M. Erola, E. Jatkola
-Tikkurila	R. Lönnblad, A. Malm, J. Mäkelä, E. Rautamo
Heinola Health Centre	P. Hentunen, J. Lagerstam
Abdominal Center Nephrology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland	M. Feodoroff, C. Forsblom, D. Gordin, PH Groop, V. Harjutsalo, S. Hägg-Holmberg, K. Hietala, M. Kallio, R. Lithovious, M. Parkkonen, M. Rahkonen, M. Rosengård-Bärlund, A.-R. Salonen, L. Salovaara, A. Sandelin, M. Saraheimo, T. Soppela, A. Soro-Paavonen, L. Thorn, N. Tolonen, J. Tuomikangas, J. Wadén,
Ophthalmology, University of Helsinki and Helsinki	P.Summanen

FinnDiane Study Centers	Physicians and nurses
University Hospital, Helsinki, Finland	
Herttoniemi Hospital, Helsinki	V. Sipilä
Hospital of Lounais-Häme, Forssa	T. Kalliomäki, J. Koskelainen, R. Nikkanen, N. Savolainen, H. Sulonen, E. Valtonen
Hyvinkää Hospital	A. Hämäläinen, L. Norvio
Iisalmi Hospital	E. Toivanen
Jokilaakso Hospital, Jämsä	A. Parta, I. Pirttiniemi
Jorvi Hospital, Helsinki University Central Hospital	S. Aranko, S. Ervasti, R. Kauppinen-Mäkelin, A. Kuusisto, T. Leppälä, K. Nikkilä, L. Pekkonen
Jyväskylä Health Centre, Kyllö	K. Nuorva, M. Tiihonen
Kainuu Central Hospital, Kajaani	S. Jokelainen, P. Kemppainen, A-M. Mankinen, M. Sankari
Kerava Health Centre	H. Stuckey, P. Suominen
Kirkkonummi Health Centre	A. Lappalainen, M. Liimatainen, J. Santaholma
Kivelä Hospital, Helsinki	A. Aimolahti, E. Huovinen
Koskela Hospital, Helsinki	V. Ilkka, M. Lehtimäki
Kotka Heath Centre	E. Pälikkö-Kontinen, A. Vanhanen
Kouvola Health Centre	E. Koskinen, T. Siitonen
Kuopio University Hospital	E. Huttunen, R. Ikäheimo, P. Karhapää, P. Kekäläinen, T. Lakka, M. Laakso, E. Lampainen, L. Moilanen, L. Niskanen, U. Tuovinen, I. Vauhkonen, E. Voutilainen
Kuusamo Health Centre	E. Isopoussu, T. Kääriäinen
Kuusankoski Hospital	E. Kilkki, I. Koskinen, L. Riihelä
Laakso Hospital, Helsinki	T. Meriläinen, P. Poukka, R. Savolainen, N. Uhlenius
Lahti City Hospital	A. Mäkelä, M. Tanner
Lapland Central Hospital, Rovaniemi	L. Hyvärinen, S. Severinkangas, T. Tulokas
Lappeenranta Health Centre	P. Linkola, I. Pulli
Lohja Hospital	T. Granlund, M. Saari, T. Salonen
Loimaa Health Centre	P. Eloranta, A. Mäkelä
Länsi-Uusimaa Hospital, Tammisaari	I-M. Jousmaa, J. Rinne
Malmi Hospital, Helsinki	H. Lanki, S. Moilanen, M. Tilly-Kiesi
Mikkeli Central Hospital	A. Gynther, R. Manninen, P. Nironen, M. Salminen, T. Vänttinen
Mänttä Regional Hospital	A-M. Hänninen, I. Pirttiniemi
North Karelian Hospital, Joensuu	U-M. Henttula, P. Kekäläinen, M. Pietarinen, A. Rissanen, M. Voutilainen

FinnDiane Study Centers	Physicians and nurses
Nurmijärvi Health Centre	A. Burgos, K. Urtamo
Oulankangas Hospital, Oulainen	E. Jokelainen, P-L. Jylkkä, E. Kaarlela, J. Vuolaspuro
Oulu Health Centre	L. Hiltunen, R. Häkkinen, S. Keinänen-Kiukaanniemi
Oulu University Hospital	R. Ikäheimo
Päijät-Häme Central Hospital	H. Haapamäki, A. Helanterä, S. Hämäläinen, V. Ilvesmäki, H. Miettinen
Palokka Health Centre	P. Sopanen, L. Welling
Pieksämäki Hospital	V. Javtsenko, M. Tamminen
Pietarsaari Hospital	M-L. Holmbäck, B. Isomaa, L. Sarelin
Pori City Hospital	P. Ahonen, P. Merensalo, K. Sävelä
Porvoo Hospital	M. Kallio, B. Rask, S. Rämö
Raahe Hospital	A. Holma, M. Honkala, A. Tuomivaara, R. Vainionpää
Rauma Hospital	K. Laine, K. Saarinen, T. Salminen
Riihimäki Hospital	P. Aalto, E. Immonen, L. Juurinen
Salo Hospital	A. Alanko, J. Lapinleimu, P. Rautio, M. Virtanen
Satakunta Central Hospital, Pori	M. Asola, M. Juhola, P. Kunelius, M-L. Lahdenmäki, P. Pääkkönen, M. Rautavirta
Savonlinna Central Hospital	E. Korpi-Hyövälti, T. Latvala, E. Leijala
South Karelia Central Hospital, Lappeenranta	T. Ensala, E. Hussi, R. Härkönen, U. Nyholm, J. Toivanen
Tampere Health Centre	P. Alarotu, L. Calonius, S. Gummerus, M. Helin, T. Kaitala, H. Kirkkopelto-Jokinen, E. Kujansuu, T. Niskanen, A. Vaden, T. Vatanen
Tampere University Hospital	I. Ala-Houhala, T. Kuningas, P. Lampinen, M. Määttä, H. Oksala, T. Oksanen, K. Salonen, H. Tauriainen, S. Tulokas
Tiirismaa Health Centre, Hollola	T. Kivelä, L, Petlin, L. Savolainen
Turku Health Centre	I. Hämäläinen, H. Virtamo, M. Vähätalo
Turku University Central Hospital	K. Breitholz, R. Eskola, K. Metsärinne, U. Pietilä, P. Saarinen, R. Tuominen, S. Äyräpää
Vaajakoski Health Centre	K. Mäkinen, P. Sopanen
Vaasa Central Hospital	S. Bergkulla, U. Hautamäki, V-A. Myllyniemi, I. Rusk
Valkeakoski Regional Hospital	T. Immonen, S. Ojanen, M. Rautiainen, E. Valtonen, H. Ylönen
Vammala Regional Hospital	I. Isomäki, R. Kroneld, M. Tapiolinna-Mäkelä

Supplemental Table 29: Membership of the SUMMIT Consortium

Partner	Name	Position
1	**Michael Mark**	**Coordinator, WP6 leader**
Boehringer-Ingelheim	Markus Albertini	Project manager
Ingelheim, Germany	Carine Boustany	Chronic Kidney Disease, Head of Lab
	Alexander Ehlgen	Transmed
	Martin Gerl	Biomarker & Bioanlysis, Groupleader
	Jochen Huber	In vivo Scientist CMDR, Head of Lab
	Corinna Schölch	Biomarker & Bioanlysis, Head of Lab
	Heike Zimdahl-Gelling	Pharmacogenomics, Head of Lab
2	**Leif Groop**	Prof. Endocrinology; Coordinator Managing entity IMI-JU; PI; **WP1 and WP6 leader**
Lund University	Elisabet Agardh	Prof. Ophthalmology
Clinical Research Centre	Emma Ahlqvist	Postdoc
Malmö, Sweden	Tord Ajanki	Communication strategist
	Nibal Al Maghrabi	Research nurse
	Peter Almgren	Biostatistician
	Jan Apelqvist	Diabetologist
	Eva Bengtsson	Assis. Prof. Cardiovascular research
	Lisa Berglund	Postdoc
	Harry Björckbacka	Assis. Prof. Cardiovascular research
	Ulrika Blom-Nilsson	LUDC administrator
	Mattias Borell	Website, server management
	Agneta Burström	Research nurse
	Corrado Cilio	Assoc. Prof. Cellular autoimmunity
	Magnus Cinthio	Assist. Prof. Electrical Measurements, Lund Technical University
	Karl Dreja	Nephrologist
	Pontus Dunér	Postdoc Exp. Cardiovasc. Research
	Daniel Engelbertsen	PhD student Exp. Cardiovasc. Research
	Joao Fadista	Postdoc
	Maria Gomez	Assoc. Prof. Cardiovascular disease, **WP4 co-leader**
	Isabel Goncalves	Assis. Prof. Cardiovascular research
	Bo Hedblad	Prof. Cardiovascular epidemiology
	Anna Hultgårdh	Prof. Vessel Wall Biology
	Martin E. Johansson	Pathologist
	Cecilia Kennbäck	Laboratory Engineer
	Jasmina Kravic	Database manager
	Claes Ladenvall	Genetic statistician
	Åke Lernmark	Prof. Type 1 diabetes and celiac disease
	Eero Lindholm	Physician, Researcher Diabetic Complications
	Charlotte Ling	Assist. Prof. Epigenetics
	Holger Luthman	Prof. Medical genetics

Partner	Name	Position
	Olle Melander	Assoc. Prof. Hypertension and cardiovascular disease
	Malin Neptin	Biomedical analyst
	Jan Nilsson	Prof. Experimental Cardiovascular research, **WP3 leader**
	Peter Nilsson	Prof. Internal medicine
	Tobias Nilsson	PhD student Electrical Measurements, Lund Technical University
	Gunilla Nordin Fredriksson	Prof. Cardiovascular research
	Marju Orho-Melander	Prof. Genetic epidemiology
	Emilia Ottoson-Laakso	PhD student
	Annie Persson	Research nurse
	Margaretha Persson	Laboratory Engineer
	Mats-Åke Persson	Database manager
	Jacqueline Postma	Project manager
	Elisabeth Pranter	Research nurse
	Sara Rattik	PhD student Exp. Cardiovasc. Research
	Gunnar Sterner	Chief physician Internal Medicine Research Unit
	Lilian Tindberg	Research nurse
	Maria Wigren	Postdoc Exp. Cardiovasc. Research
	Anna Zetterqvist	PhD student
	Mikael Åkerlund	Postdoc
	Gerd Östling	Laboratory Engineer
3	**Timo Kanninen**	Technical director; PI
Biocomputing Platforms	Anni Ahonen-Bishopp	Software development manager
(BC Platforms)	Anita Eliasson	Financial and administrative director
Espoo, Finland	Timo Herrala	System (server) specialist
	Päivi Tikka-Kleemola	Service manager
4	**Anders Hamsten**	Prof. Cardiovascular disease; Atherosclerosis Research Unit; PI
Karolinska Institute	Christer Betsholtz	Prof. Vascular biology
Stockholm, Sweden	Ami Björkholm	Administrator
	Ulf de Faire	Professor emeritus Cardiovascular epidemiology
	Fariba Foroogh	Research engineer
	Guillem Genové	Scientist
	Karl Gertow	Research Assist. Prof. Cardiovascular genetics
	Bruna Gigante	Assoc. Professor Cardiovascular epidemiology
	Bing He	Postdoc
	Karin Leander	Assoc. Professor Cardiovascular epidemiology
	Olga McLeod	Postdoc
	Maria Nastase-Mannila	Postdoc
	Jaako Patrakka	Postdoc

Partner	Name	Position
	Angela Silveira	Assoc. Prof. Cardiovascular genetics
	Rona Strawbridge	Postdoc
	Karl Tryggvason	Prof. Medical Chemistry
	Max Vikström	Statistician
	John Öhrvik	Professor
	Anne-May Österholm	Postdoc
5	**Barbara Thorand**	Nutritional scientist, epidemiologist
Helmholtz Centre	Christian Gieger	Statistician
Munich, Germany	Harald Grallert	Biologist
	Tonia Ludwig	Statistician
	Barbara Nitz	Scientist
	Andrea Schneider	Data manager
	Rui Wang-Sattler	Scientist
	Astrid Zierer	Statistician
6	**Giuseppe Remuzzi**	Institute director; PI
Mario Negri Institute for	Ariela Benigni	Head of department Molecular Medicine
Pharmacological Research	Roberta Donadelli	Scientist
	Maria Domenica Lesti	Researcher
Bergamo, Italy	Marina Noris	Head Laboratory Immunology and genetics of transplantation and rare diseases
	Norberto Perico	Senior scientist
	Annalisa Perna	Biostatistician
	Rossella Piras	Postdoc
	Piero Ruggenenti	Head of department Renal medicine, Assist. Prof. Nephrology and dialysis
	Erica Rurali	Postdoc
7	**David Dunger (att: Jane Horsford)**	Prof. Paediatrics; PI
University of Cambridge	Ludo Chassin	Senior Data Manager
UK	Neil Dalton, London	Clinical biochemistry
	John Deanfield, London	Paediatric cardiology
	Jane Horsford	PA to Prof. Dunger
	Clare Rice	Operations manager/financial contact
	James Rudd	Cardiovascular imaging
	Neil Walker	Head Data services
	Karen Whitehead	Technician
	Max Wong	Postdoc
8	**Helen Colhoun**	Prof. Public health and epidemiology; PI; Vice coordinator Managing entity; **WP2 leader**

Partner	Name	Position
	Fiona Adams	
University of Dundee	Tahira Akbar	PA to Helen Colhoun
Scotland	Jill Belch	Prof. Vasucular disease
	Harshal Deshmukh	PhD student
	Fiona Dove	
	Angela Ellingford	NHS Tayside Diabetic Retinopathy Screening Programme manager
	Bassam Farran	Statistician
	Mike Ferguson	Dean of research Biological chemistry and drug discovery
	Gary Henderson	
	Graeme Houston	Consultant radiologist/senior lecturer
	Faisel Khan	Reader, Vascular & Inflammatory Diseases Research Unit
	Graham Leese	Consultant diabetologist/reader
	Yiyuan Liu	PhD student
	Shona Livingstone	Senior statistician
	Helen Looker	Epidemiologist
	Margaret McCann	Project assistant
	Stuart McGurnaghan	Lead data programmer
	Andrew Morris	Prof. Diabetic medicine
	David Newton	
	Colin Palmer	Prof. Pharmacogenomics
	Ewan Pearson	Consultant diabetologist/senior lecturer
	Gillian Reekie	Research Nurse
	Natalie Smith	Research Nurse
9	**Angela Shore**	Prof. Cardiovascular Science, PI
Peninsula Medical School	Kuni Aizawa	Postdoc
Exeter, UK	Claire Ball	Research nurse
	Nick Bellenger	Cardiologist
	Francesco Casanova	Associate Research Fellow Vascular medicine
	Tim Frayling	Prof. Genetics
	Phil Gates	Senior lecturer Cardiovascular science
	Kim Gooding	Postdoc Vascular medicine
	Andrew Hatttersley	Prof. Molecular medicine
	Roland Ling	Consultant opthalmologist
	David Mawson	Research technician
	Robin Shandas	Prof. Bioengineering (Colorado)
	David Strain	Stroke physician, clinical lecturer
	Clare Thorn	Postdoc Vascular medicine
10	**Ulf Smith**	Prof. ; PI
University of	Ann Hammarstedt	Researcher Molecular and clinical medicine

Partner	Name	Position
Gothenburg		
Sweden	Hans Häring	Prof. University of Tübingen
	Oluf Pedersen	Prof. Steno Centre, Copenhagen
	Georgio Sesti	Prof. Universtiy of Catanzaro
11	**Per-Henrik Groop**	Prof. Diabetes genetics; PI
	Emma Fagerholm	PhD student, genetics
Folkhälsan	Carol Forsblom	Clinical coordinator
Helsinki, Finland	Valma Harjutsalo	
	Maikki Parkkonen	Laboratory manager
	Niina Sandholm	DSc(PhD); GWAS and bioinformatics
	Nina Tolonen	MD PhD
	Iiro Toppila	BSc, bioinformatician
	Erkka Valo	MSc, bioinformatician
12	**Veikko Salomaa**	Prof. Epidemiology; PI; **deputy leader WP2**
The National Institute for Health and Welfare	Aki Havulinna	DSc. (tech), statistician
Helsinki, Finland	Kati Kristiansson	Postdoc
	Pia Okamo	THL press officer
	Tomi Peltola	
	Markus Perola	Professor
	Arto Pietilä	Statistician
	Samuli Ripatti	Professor, Statistics
	Marketta Taimi	Research assistant
13	**Seppo Ylä-Herttuala**	Prof.; PI; **WP4 leader**
University of Eastern Finland	Mohan Babu	PhD student
Kuopio, Finland	Marike Dijkstra	PhD student
	Erika Gurzeler	PhD student
	Jenni Huusko	PhD student
	Ivana Kholová	Postdoc
	Markku Laakso	Prof.
	Mari Merentie	PhD student
	Marja Poikolainen	PA Prof Ylä-Herttuala
14	**Mark McCarthy**	Prof. Human type 2 diabetes; Oxford Centre for Diabetes, Endocrinology and Metabolism; Wellcome Trust Centre for Human Genetics; PI; **deputy leader WP1**
University of Oxford	Chris Groves	Technical staff
UK	Thorhildur Juliusdottir	PhD student
	Fredrik Karpe	PI OCDEM

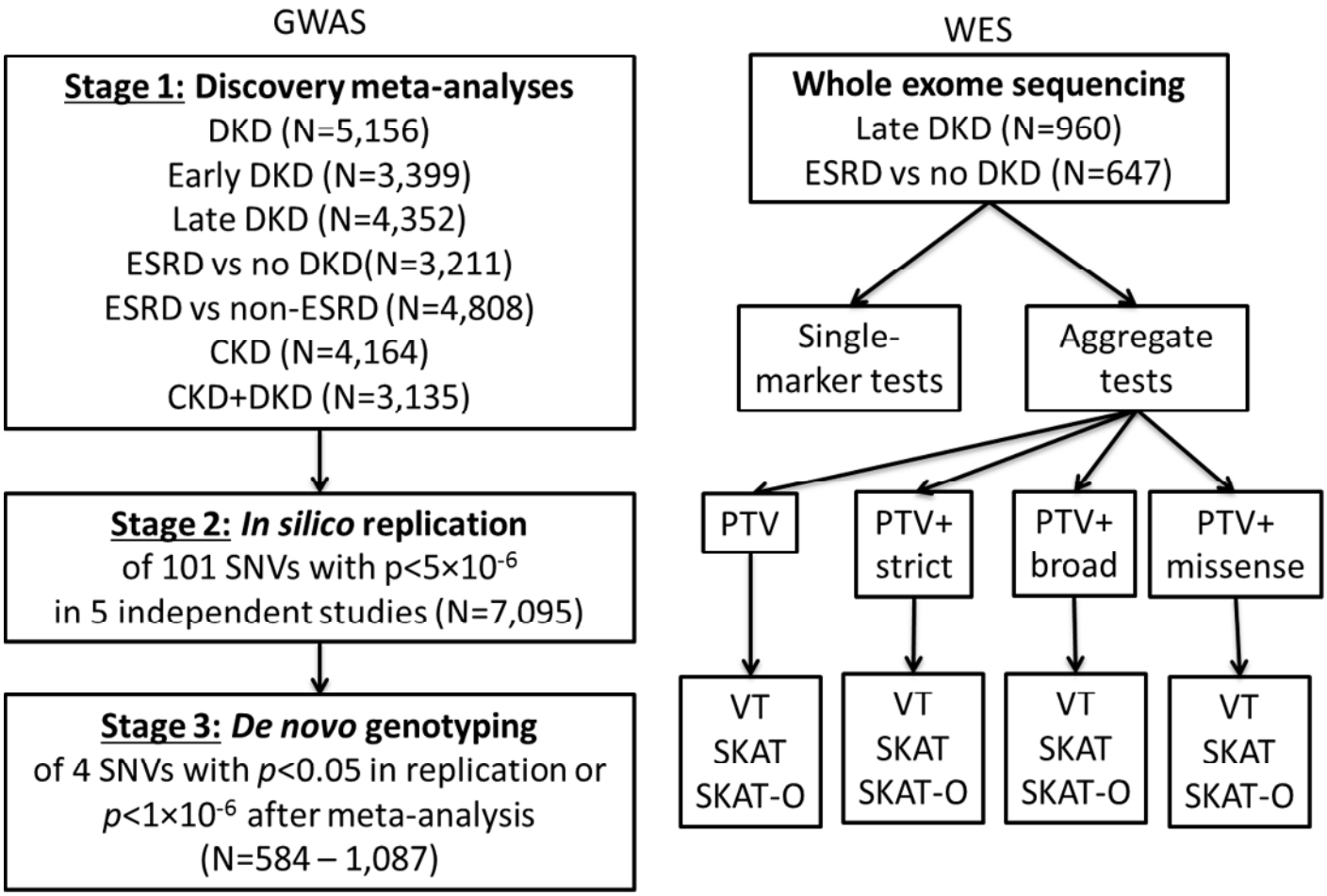
Partner	Name	Position
	Vasiliki Lagou	Postdoc
	Andrew Morris	Wellcome Trust Senior Fellow; Bioinformatics and statistical genetics
	Will Rayner	Database manager
	Neil Robertson	Informatics
	Natalie van Zuydam	Postdoc
15	**Claudio Cobelli**	Prof. ; PI; **WP5 leader**
University of Padova	Barbara Di Camillo	Assist. Prof.
Italy	Francesca Finotello	PhD student
-	Francesco Sambo	Postdoctoral fellow
-	Gianna Toffolo	Prof.
-	Emanuele Trifoglio	PhD student
-	-	-
16	**Riccardo Bellazzi**	Prof. Bioengineering; PI; **deputy leader WP5**
	Nicola Barbarini	Postdoctoral fellow
University of Pavia	Mauro Bucalo	Software engineer
Italy	Christiana Larizza	Assist. Prof.
	Paolo Magni	Assoc. Prof.
	Alberto Malovini	Postdoctoral fellow
	Simone Marini	Postdoctoral fellow
	Francesca Mulas	Postdoctoral fellow
	Silvana Quaglini	Prof.
	Lucia Sacchi	Assist. Prof.
	Francesca Vitali	
17	**Ele Ferrannini**	Prof. Medicine; PI
	Beatrice Boldrini	Postdoctoral fellow
University of Pisa	Michaela Kozakova	Senior investigator Medical Pathophysiology
Italy	Andrea Mari	Senior researcher Biomedical engineering (ISIB-CNR, Padova)
	Carmela Morizzo	Biologist, Sonographer Cardiovascular ultrasound
	Lucrecia Mota	EGIR administrative office
	Andrea Natali	Assoc. Prof. Medicine
	Carlo Palombo	Assoc. Prof. Medicine; **deputy leader WP3**
	Elena Venturi	Researcher
	Mark Walker	Prof. Molecular diabetic medicine (Univ Newcastle-upon-Tyne)
18	**Carlo Patrono**	Prof.Pharmacology; PI
Catholic University of Rome	Francesca Pagliaccia	PhD student
Italy	Bianca Rocca	Assist. Prof. Pharmacology
19	**Pirjo Nuutila**	Prof. ; PI

Partner	Name	Position
University of Turku	Johanna Haukkala	PhD student
Finland	Juhani Knuuti	Prof. ; Director Turku PET Centre
	Anne Roivainen	Prof.
	Antti Saraste	Adj. Prof.
20	**Paul McKeague**	Prof. Genetic Epidemiology; PI
University of Edinburgh	Norma Brown	Research administrator, Public Health Services
Scotland	Marco Colombo	Bioinformaticist
21	**Birgit Steckel-Hamann**	Deputy coordinator; PI, Manager IMI, LRL
Eli Lilly	Krister Bokvist	Biostatistician
	Sudha Shankar	Diabetologist
	Melissa Thomas	Translational Science
22	**Li-ming Gan**	Prof.; Translational Science Director Cardiovascular Disease; PI, **WP3 leader**
AstraZeneca	Suvi Heinonen	PhD, Internal AZ postdoc, Bioscience
	Ann-Cathrine Jönsson-Rylander	PhD, Assoc. Prof., Team Leader Bioscience, **WP4 leader**
	Remi Momo	Postdoctoral fellow
	Volker Schnecke	Informatician Translational Science, **WP5 leader**
	Robert Unwin	Translational Science Director Diabetic Nephropathy
	Anna Walentinsson	Geneticist Translational Science
	Carl Whatling	Bioscientist
23	**Everson Nogoceke**	Pre-clinical and clinical aspects of metabolic and vascular disease; PI; **WP2 leader**
Roche	Gonzalo Durán Pacheco	Senior Research Statistician
	Ivan Formentini	Biomarker & Experimental Medicine Leader
	Thomas Schindler	Pre-clinical and clinical and clinical biomarkers
24	**Piero Tortoli**	Professor of Electronics
University of Florence	Luca Bassi	Postdoctoral fellow
	Enrico Boni	Postdoctoral fellow
	Alessandro Dallai	Postdoctoral fellow
	Francesco Guidi	Technician
	Matteo Lenge	PhD student
	Riccardo Matera	PhD student
	Alessandro Ramalli	PhD student
	Stefano Ricci	Assist. Prof.
	Jacopo Viti	PhD student
25	**Bernd Jablonka**	SAD internal IMI coordinator

Partner	Name	Position
Sanofi-aventis	Dan Crowther	Biomarker researcher
	Johan Gassenhuber	Biostatistician
	Sibylle Hess	Biomarker researcher
	Thomas Hübschle	Pharmacologist Diabetes
	Hans-Paul Juretschke	Imaging
	Hartmut Rütten	Head Translational Medicine
	Thorsten Sadowski	Pharmacologist Diabetes
	Paulus Wohlfart	Pharmacologist Diabetes
26	**Julia Brosnan**	Biochemist, (pre)clinical research CVD, Pfizer US; **WP2 leader**
Pfizer	Valerie Clerin	Cardio-renal biologist, WP2
	Eric Fauman	Computational biologist
	Craig Hyde	Statistician
	Anders Malarstig	Human genetics, Pfizer Europé; **WP1 leader**
	Nick Pullen	Renal Disease Research Director
	Mera Tilley	
	Theresa Tuthill	Imaging specialist
	Ciara Vangjeli	Cardiovascular genetic epidemiologist, Pfizer Europe
	Daniel Ziemek	Computational biologist

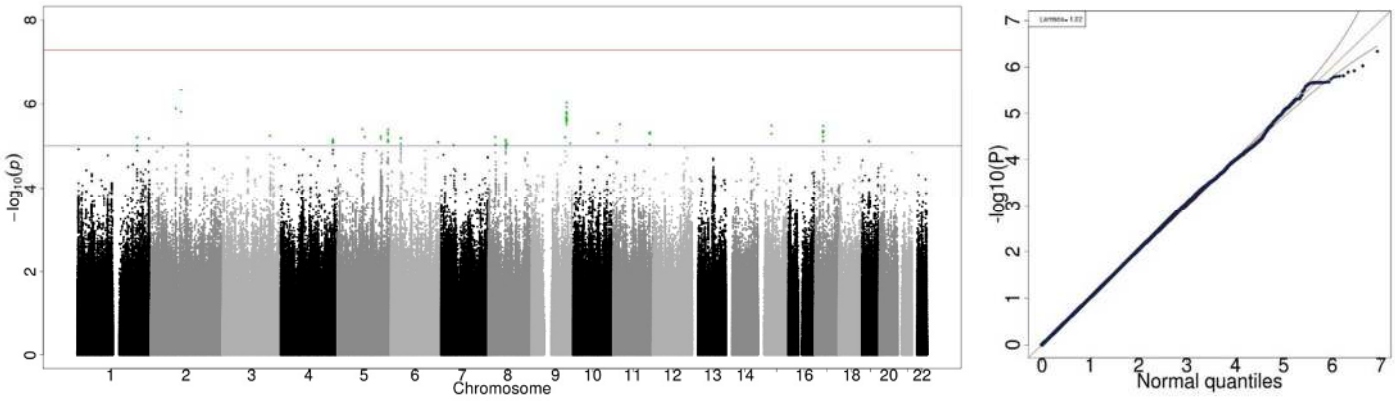
SUPPLEMENTAL FIGURES

Supplemental Figure 1: Schematic picture of the study plan. In the GWAS setting, the stage 1 included T1D patients from the FinnDiane, EURODIAB, SDR, and Cambridge studies. Stage 1 GWAS meta-analysis results were used for evaluation of the previously reported loci, analysis of genetic risk scores, LD score regression, and for the pathway analyses. Stage 2 included patients from the UK-ROI, GoKinD US, French-Danish effort, DCCT/EDIC, and Joslin studies. Stage 3 replication consisted of additional T1D FinnDiane patients not part of the FinnDiane GWAS. Whole exome sequencing (WES) included patients from the FinnDiane, SDR, and Steno studies. Finally, the bivariate association analyses were performed in all GWAS stage 1 studies and in WES studies.

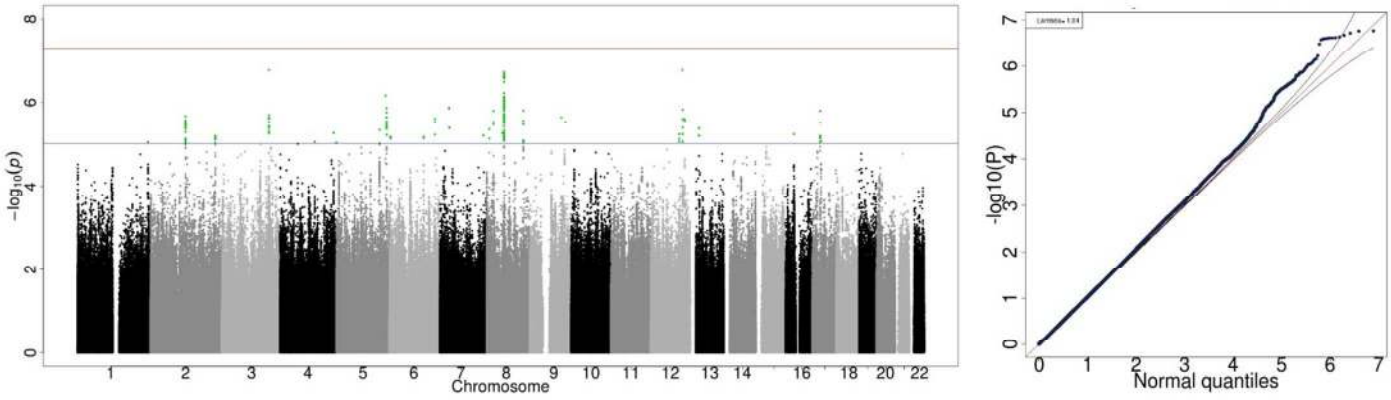


Supplemental Figure 2: Manhattan and QQ-plots for the seven studied phenotype definitions. Manhattan and QQ-plots of the seven studied case-control phenotype definitions: A) Combined DKD (cases with micro- or macroalbuminuria or ESRD vs. controls with normal AER); B) Late DKD (cases with macroalbuminuria or ESRD vs. normal AER); C) ESRD vs. no DKD (cases with ESRD vs. controls with normal AER); D) ESRD vs. non-ESRD (cases with ESRD vs. everyone else); E) Early DKD (cases with microalbuminuria vs. controls with normal AER); F) CKD (cases with CKD (eGFR ≤ 60 ml/min) vs. controls without CKD (eGFR > 60 ml/min); G) CKD+DKD (cases with severe CKD (eGFR ≤ 45 ml/min) and microalbuminuria or worse vs. controls with normal AER and no CKD (eGFR > 60 ml/min).

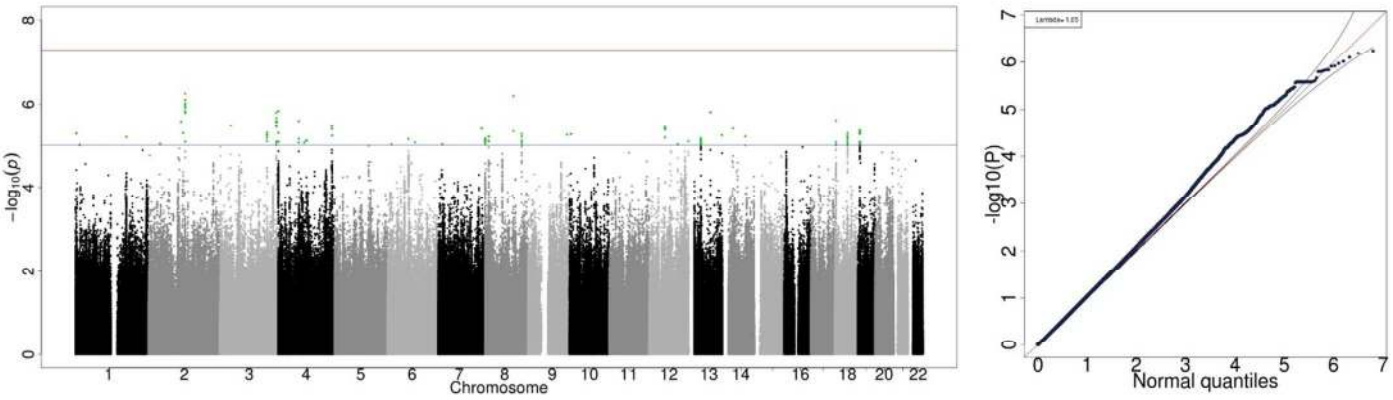
A) Combined DKD



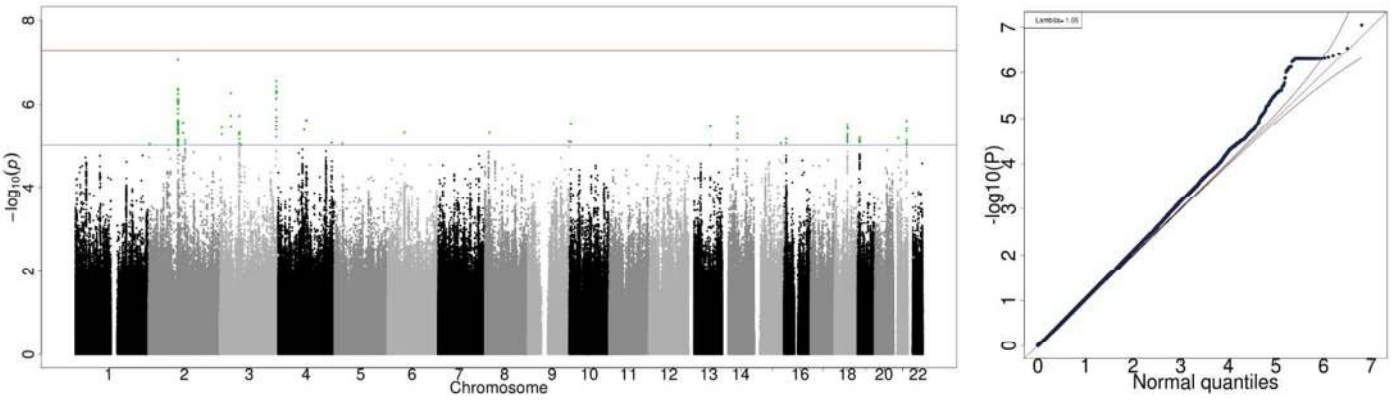
B) Late DKD



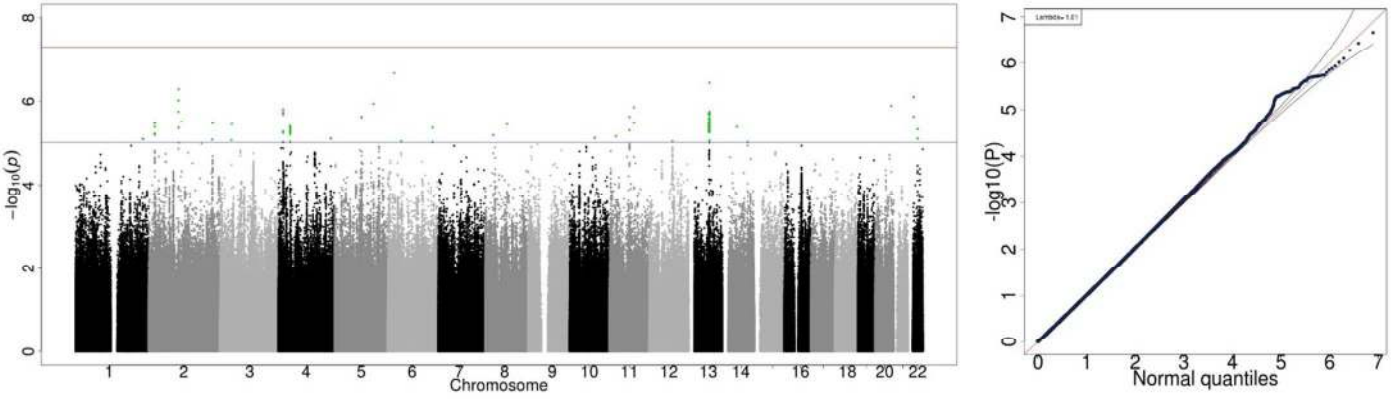
C) ESRD vs. no DKD



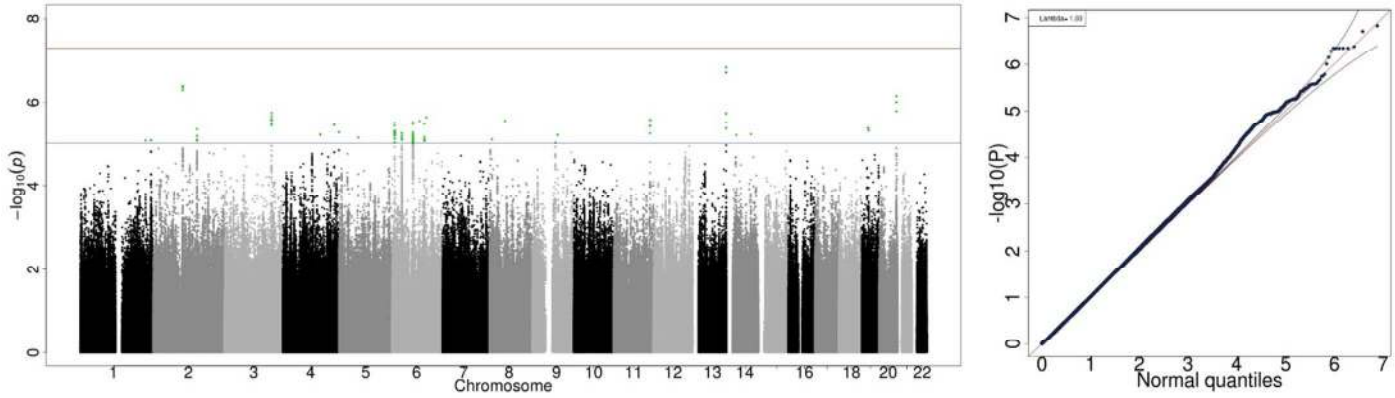
D) ESRD vs. non-ESRD



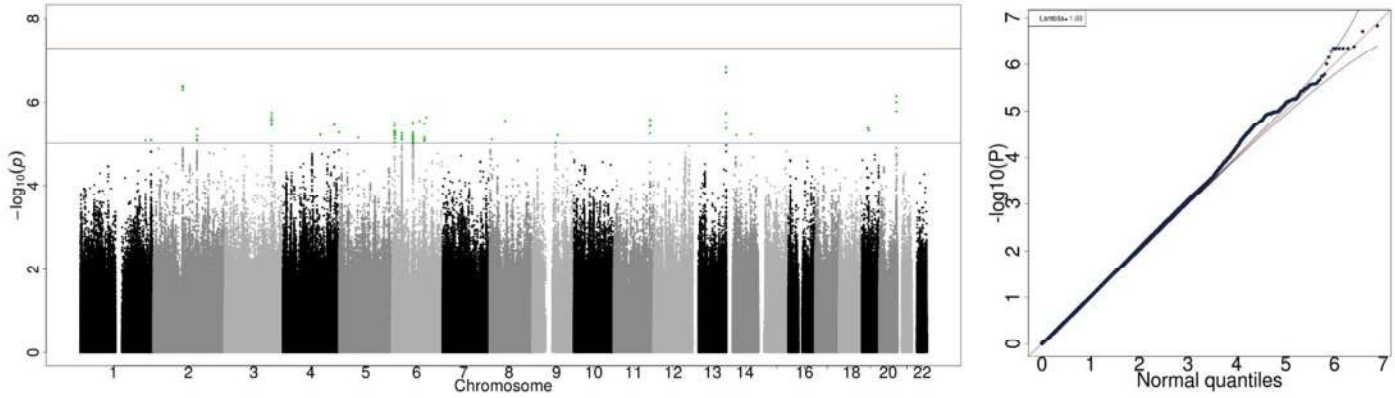
E) Early DKD



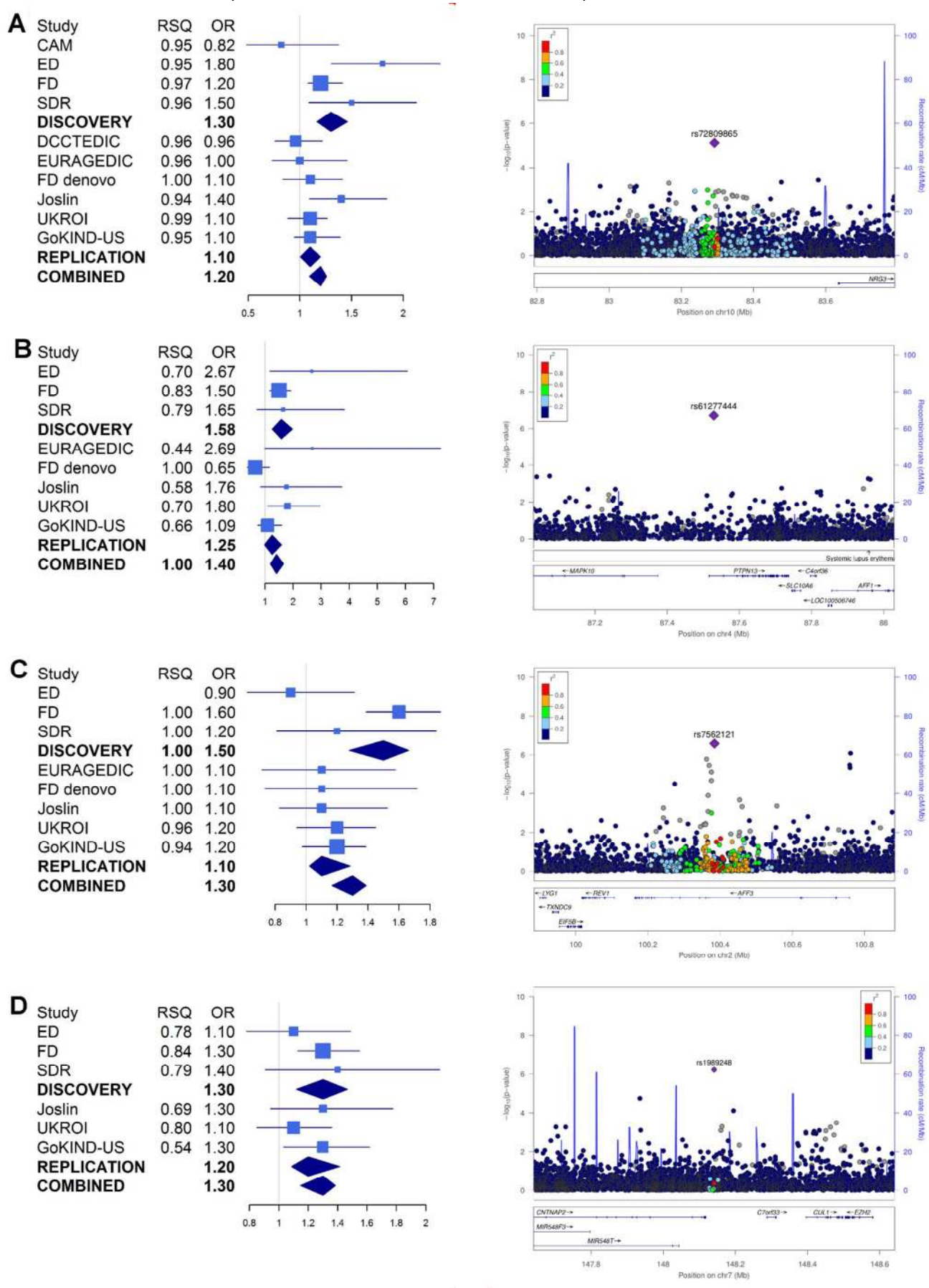
F) CKD



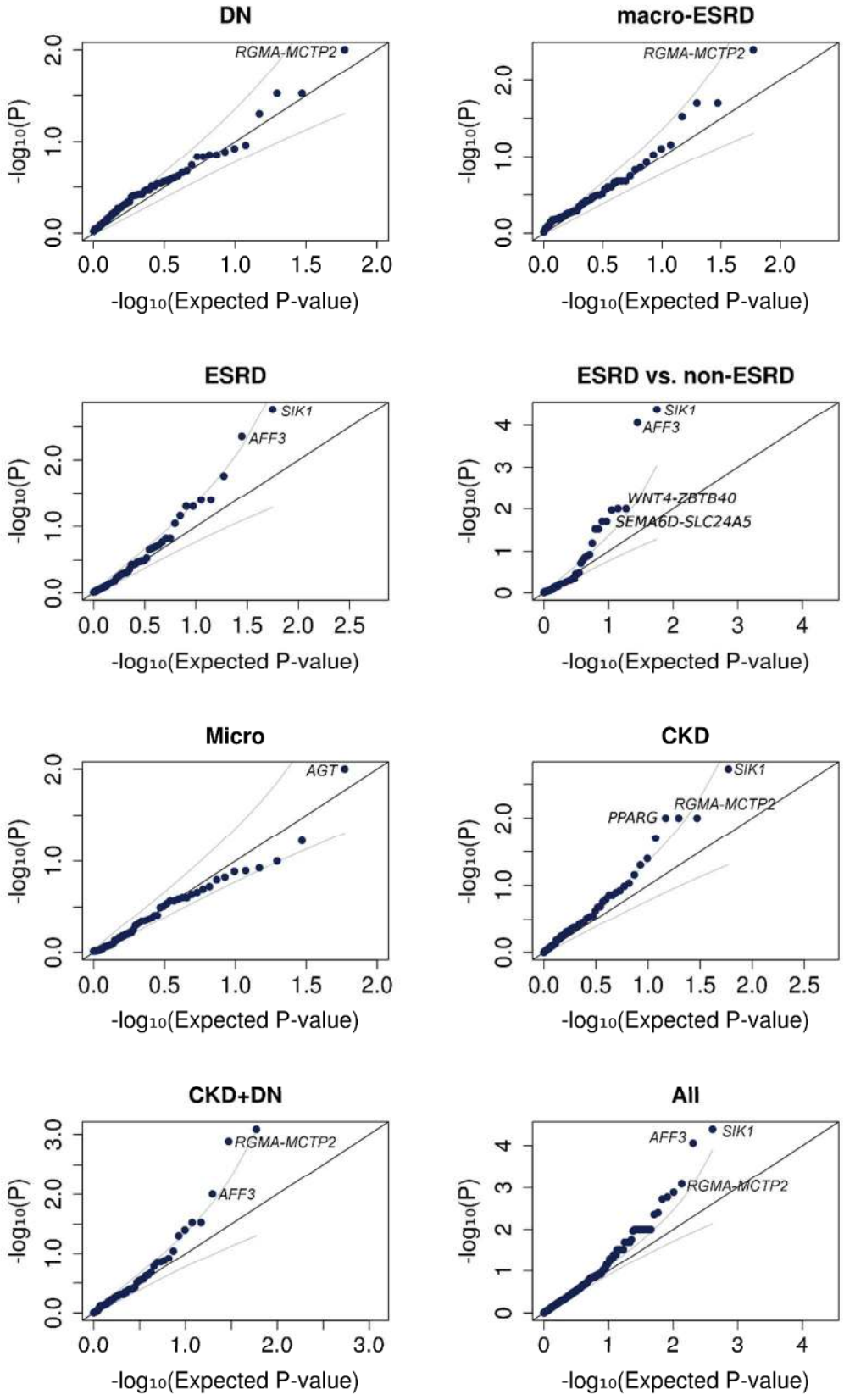
G) CKD + DKD



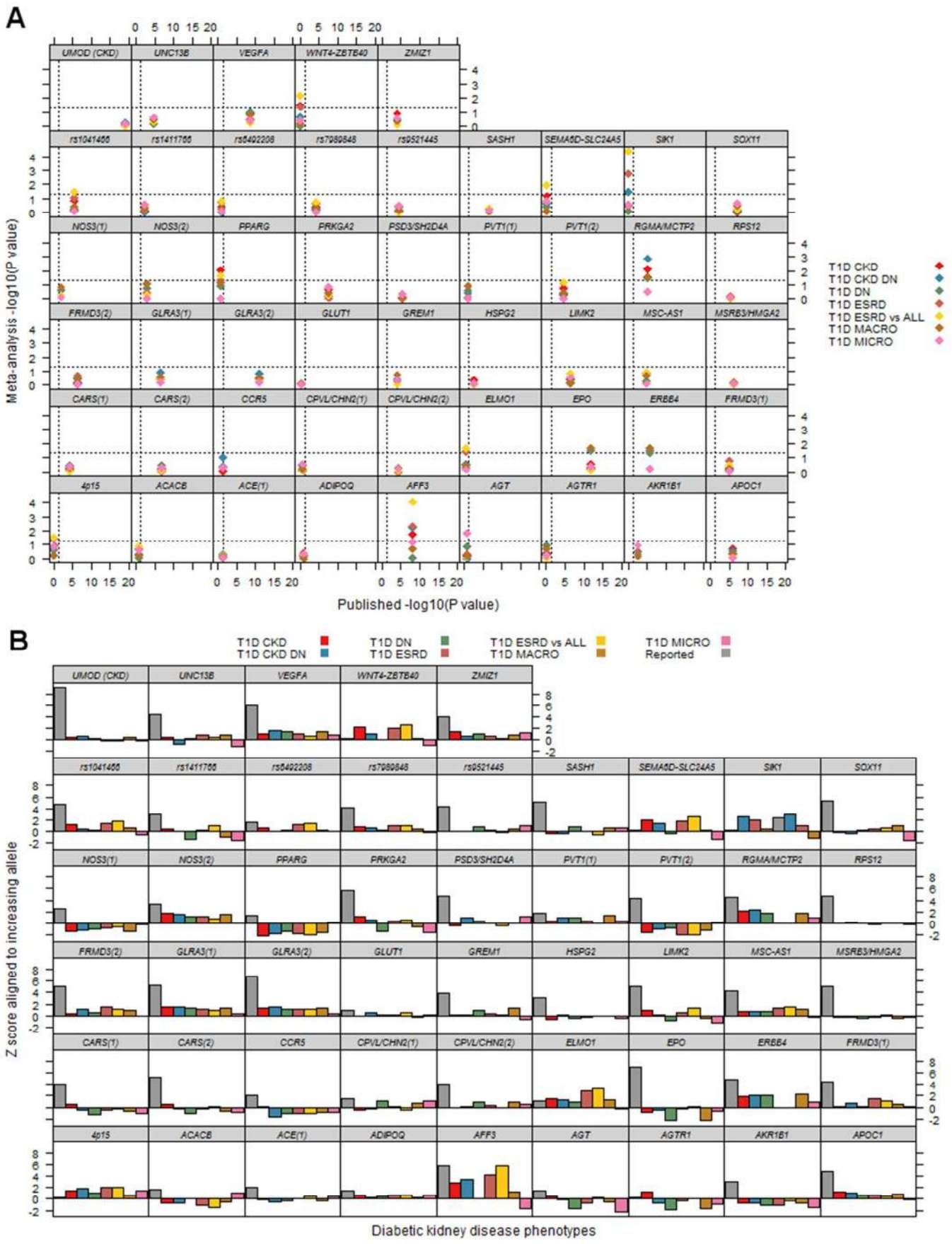
Supplemental Figure 3: LocusZoom and Forest plots of the top loci. A) rs72809865 for DKD. B) rs61277444 for ESRD versus normal AER. C) rs7562121 for ESRD versus non-ESRD. D) rs1989248 for CKD+DKD.



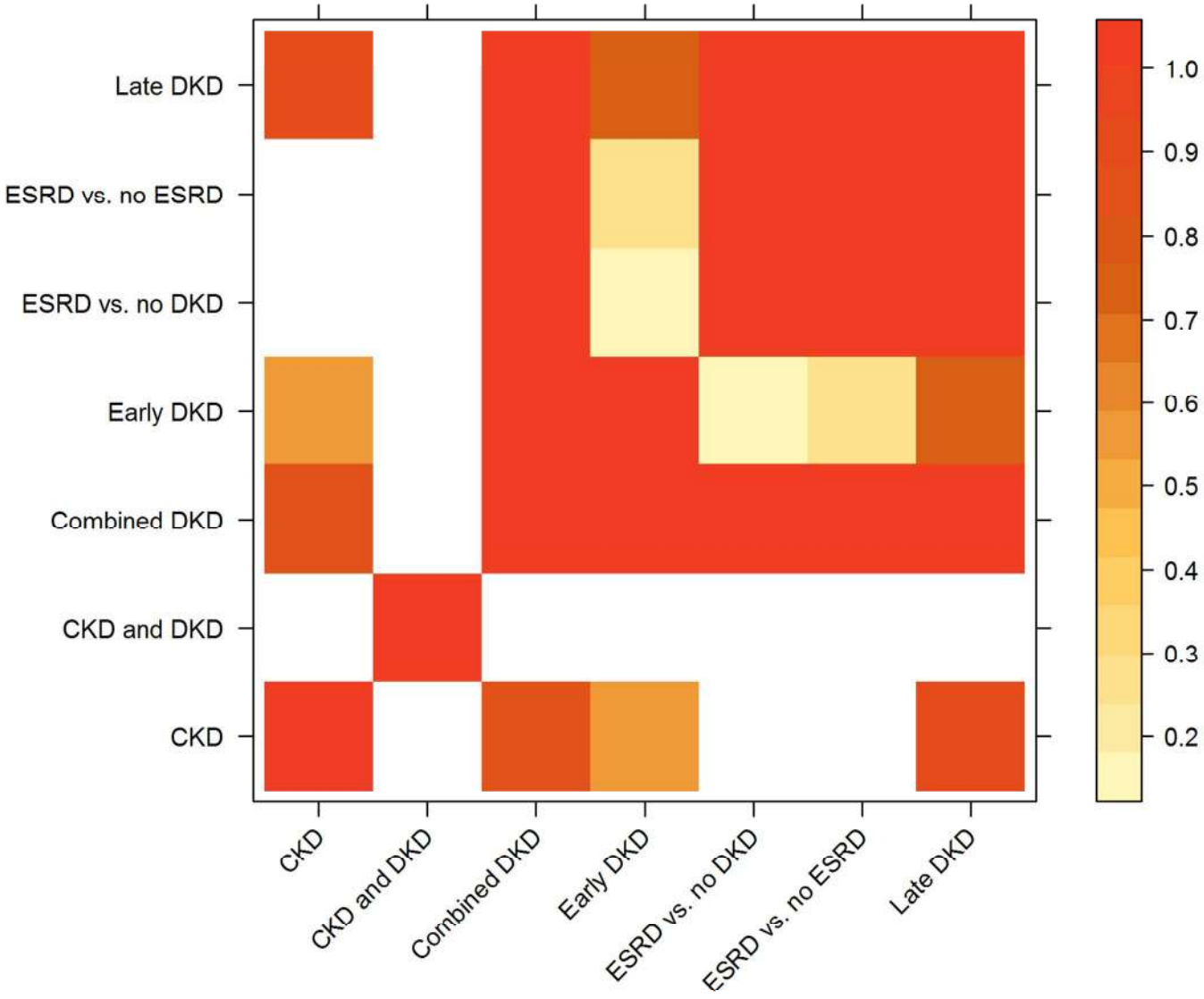
Supplemental Figure 4: P-value distribution of association at the previously reported loci for DKD or CKD in the general population.



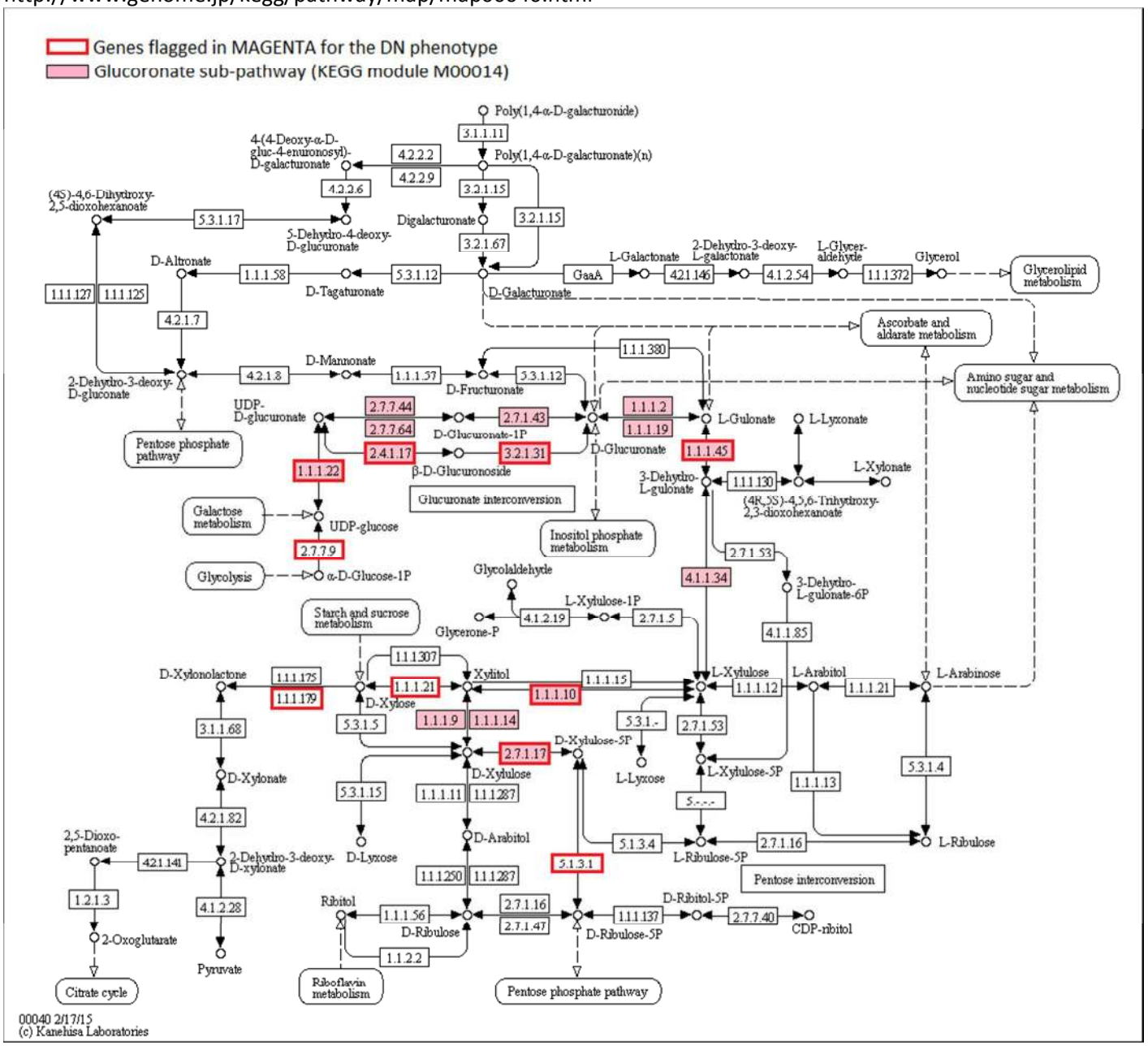
Supplemental Figure 5: Association at previously reported loci plotted by the previously reported A) p-values and by B) Z-scores.



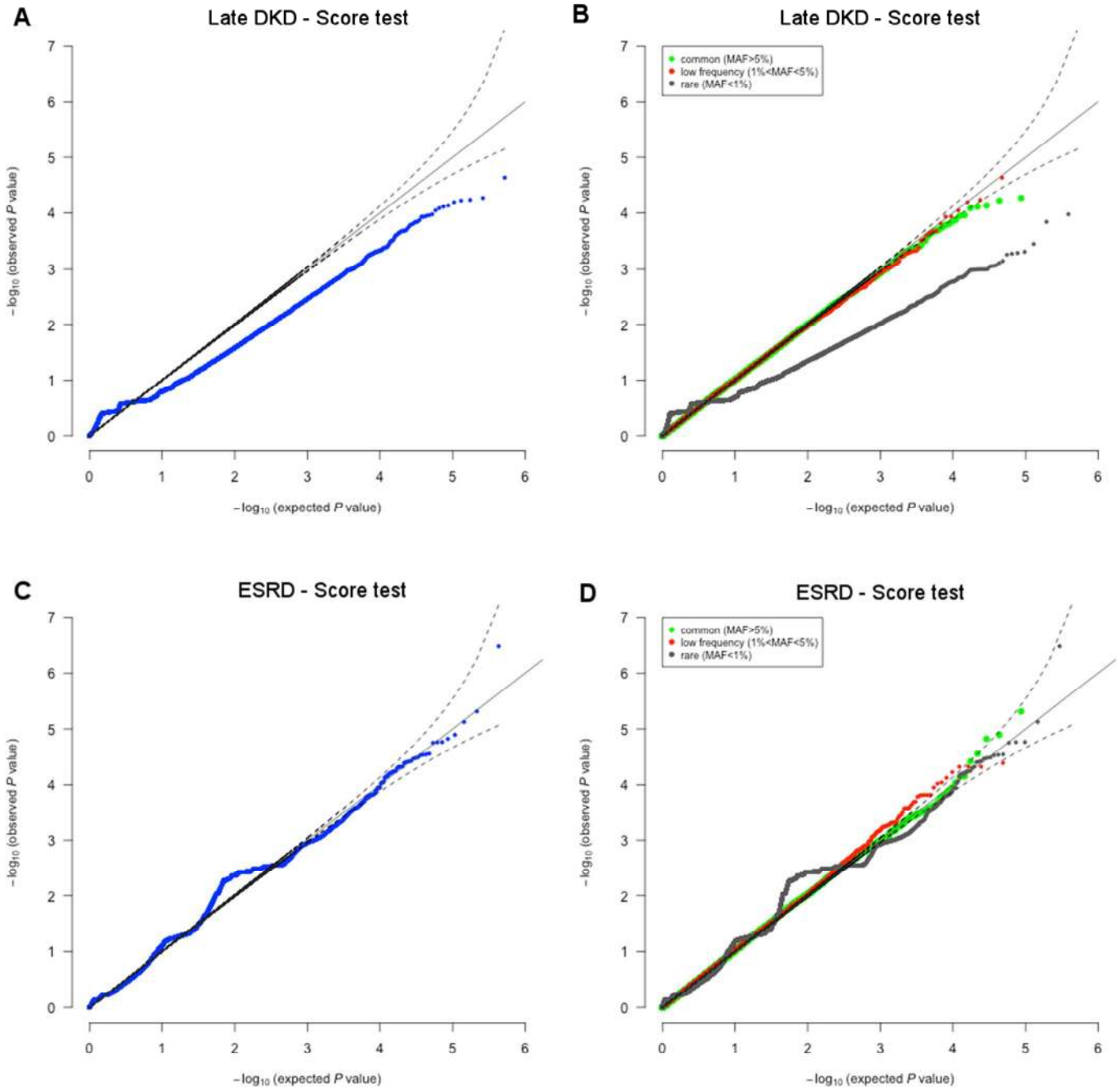
Supplemental Figure 6: Genome-wide comparison of the association results for the seven DKD traits, evaluated with LD score regression, shows high correlation between the DKD traits. Even though the overlapping samples between the DKD traits do not bias the estimates, the overlapping phenotype definitions may do so.



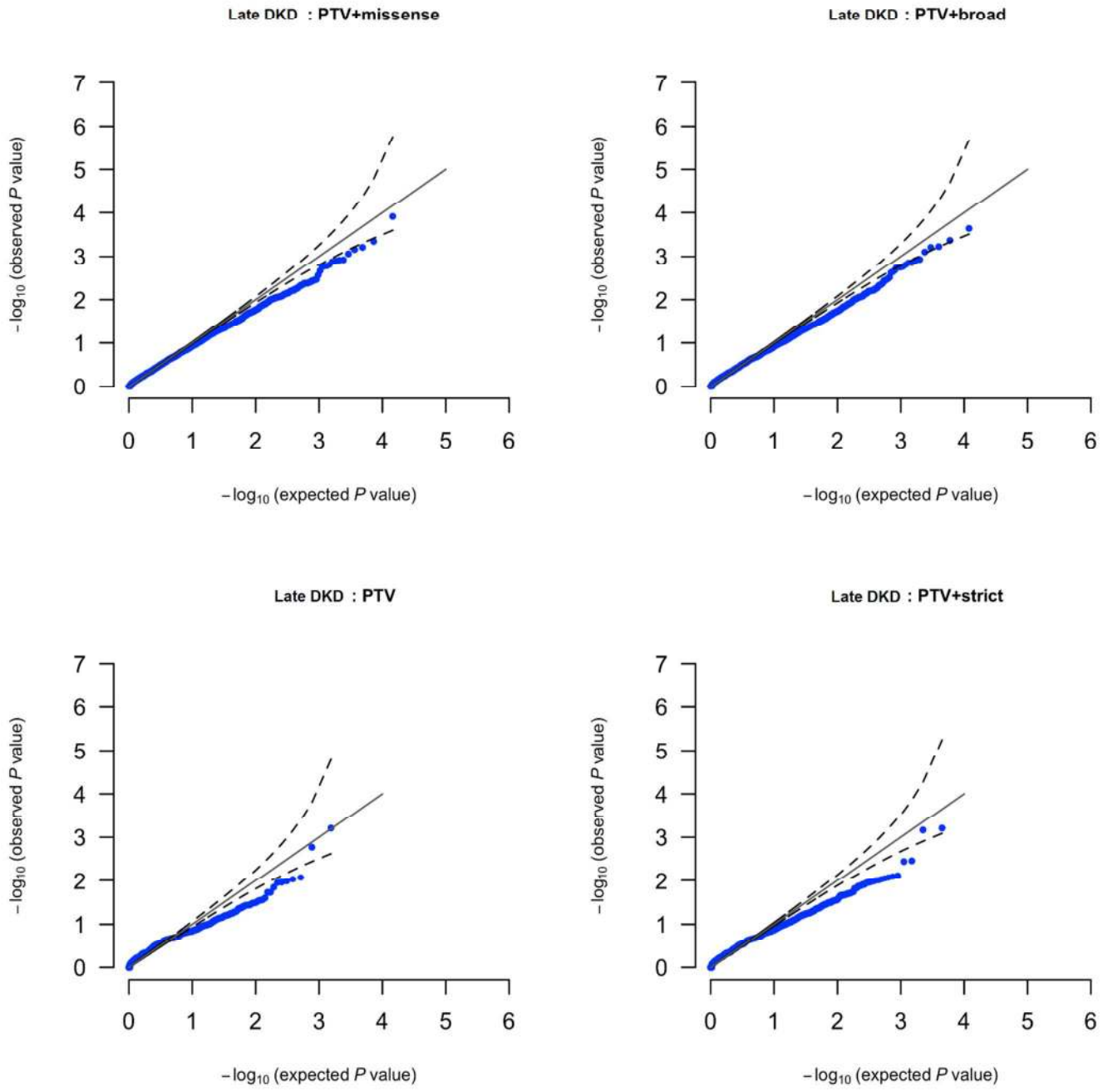
Supplemental Figure 7: KEGG pentose and glucoronate interconversions pathway with the red boxes indicating the genes flagged with MAGENTA enrichment analysis on the DKD phenotype. The Glucuronate sub-pathway (KEGG module M00014) is highlighted with pink background. P-value for enrichment of the glucoronate sub-pathway was tested *post hoc,* $p=1.9\times10^{-5}$, false discovery rate (FDR)$<1\times10^{-6}$. Figure modified from http://www.genome.jp/kegg/pathway/map/map00040.html



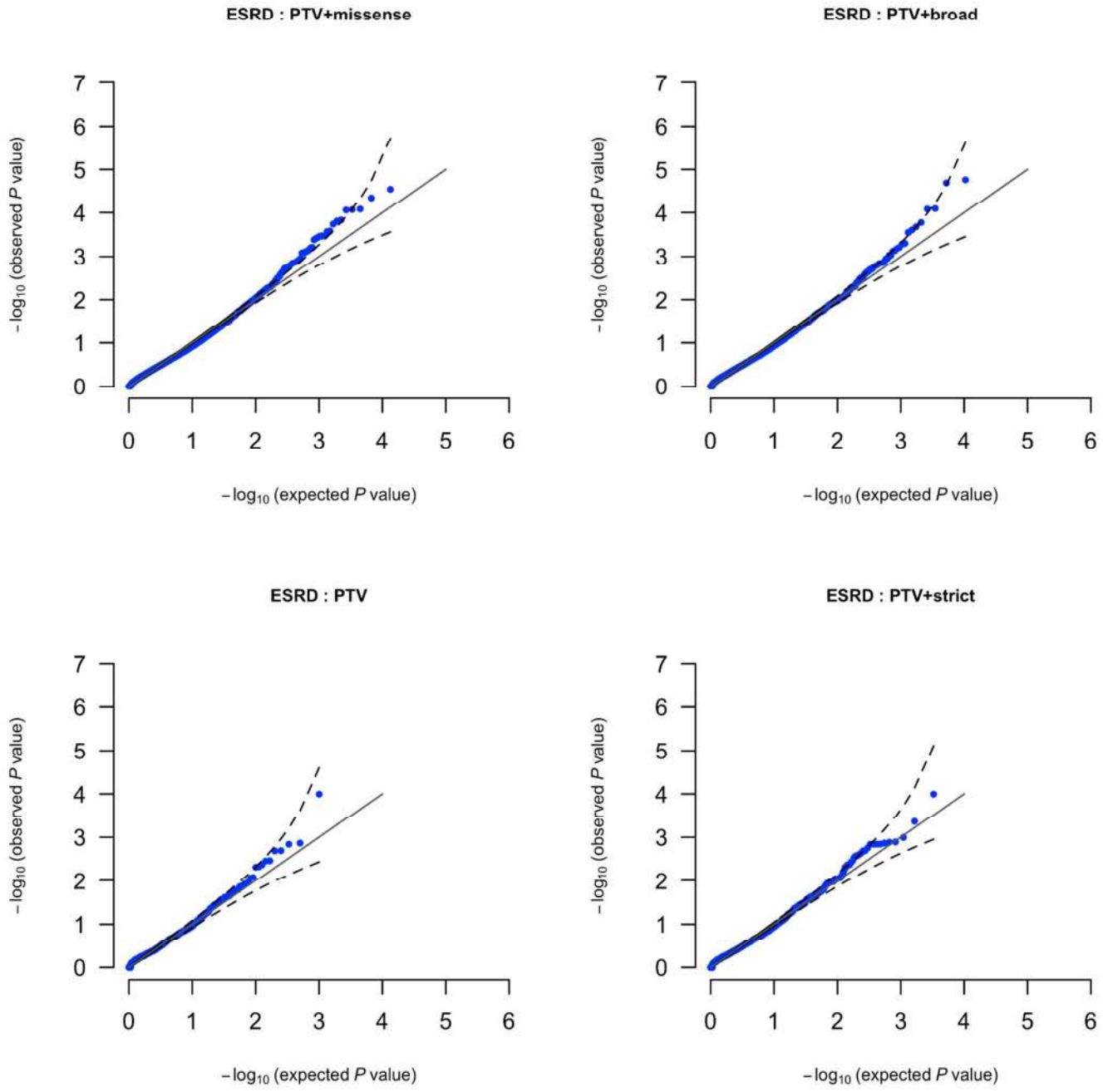
Supplemental Figure 8: WES QQ-plots of the p-value distribution of associations with 'Late DKD' and 'ESRD vs. no DKD' using the score test. A and B: DKD. C and D: ESRD. A and C: all SNPs. B and D: SNPs by MAF.



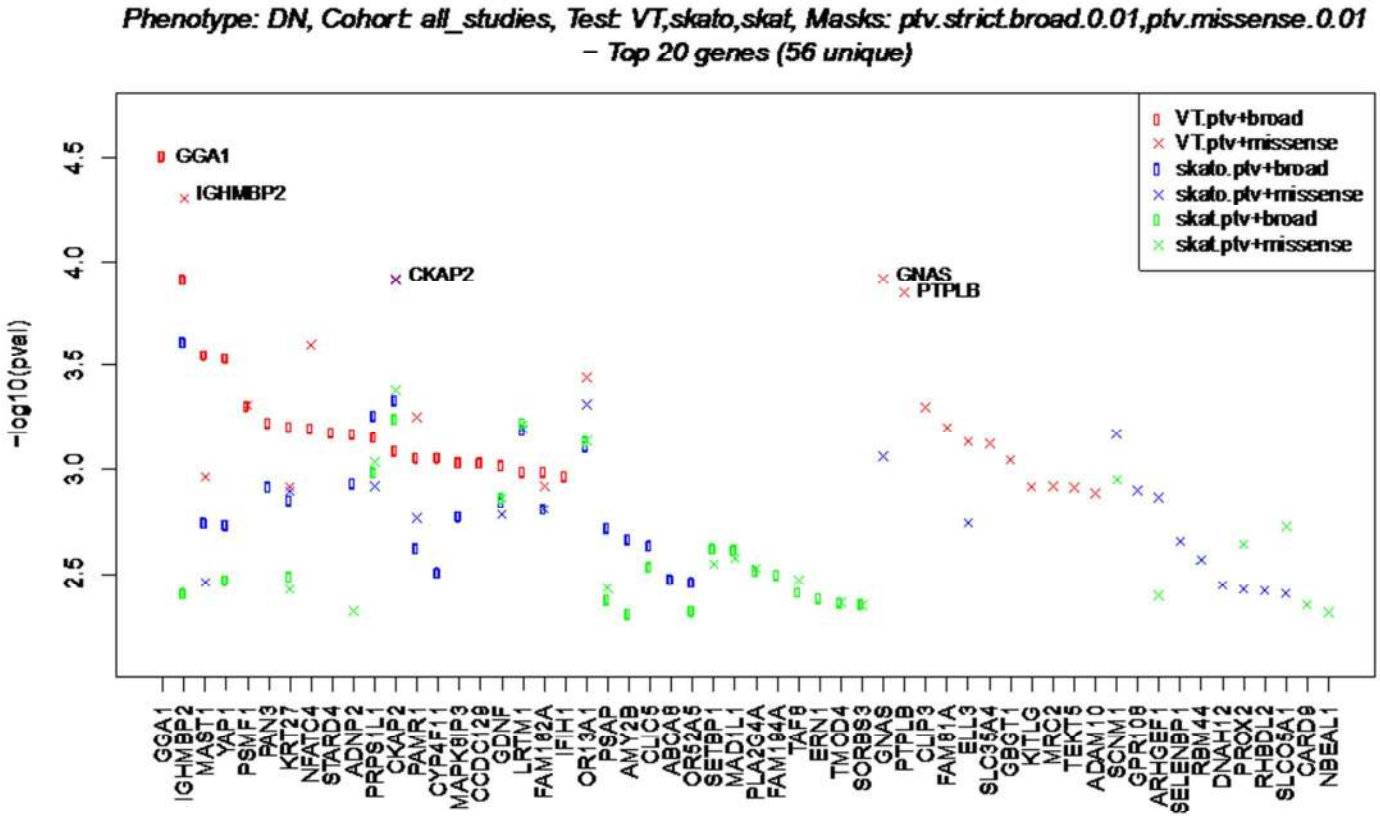
Supplemental Figure 9: WES QQ-plots for 'Late DKD' for different masks using SKAT-O.



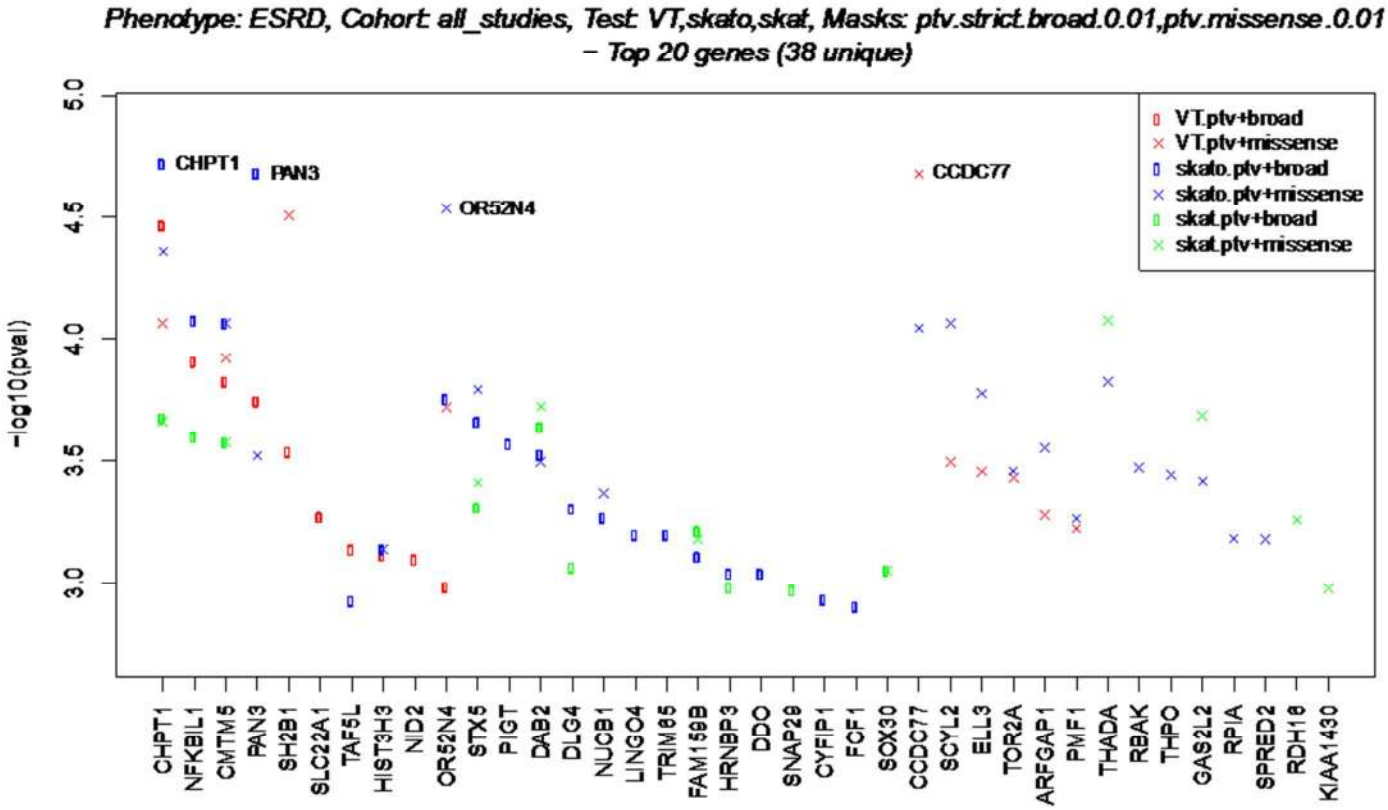
Supplemental Figure 10: WES QQ-plots for 'ESRD vs. no DKD' for different masks using SKAT-O.



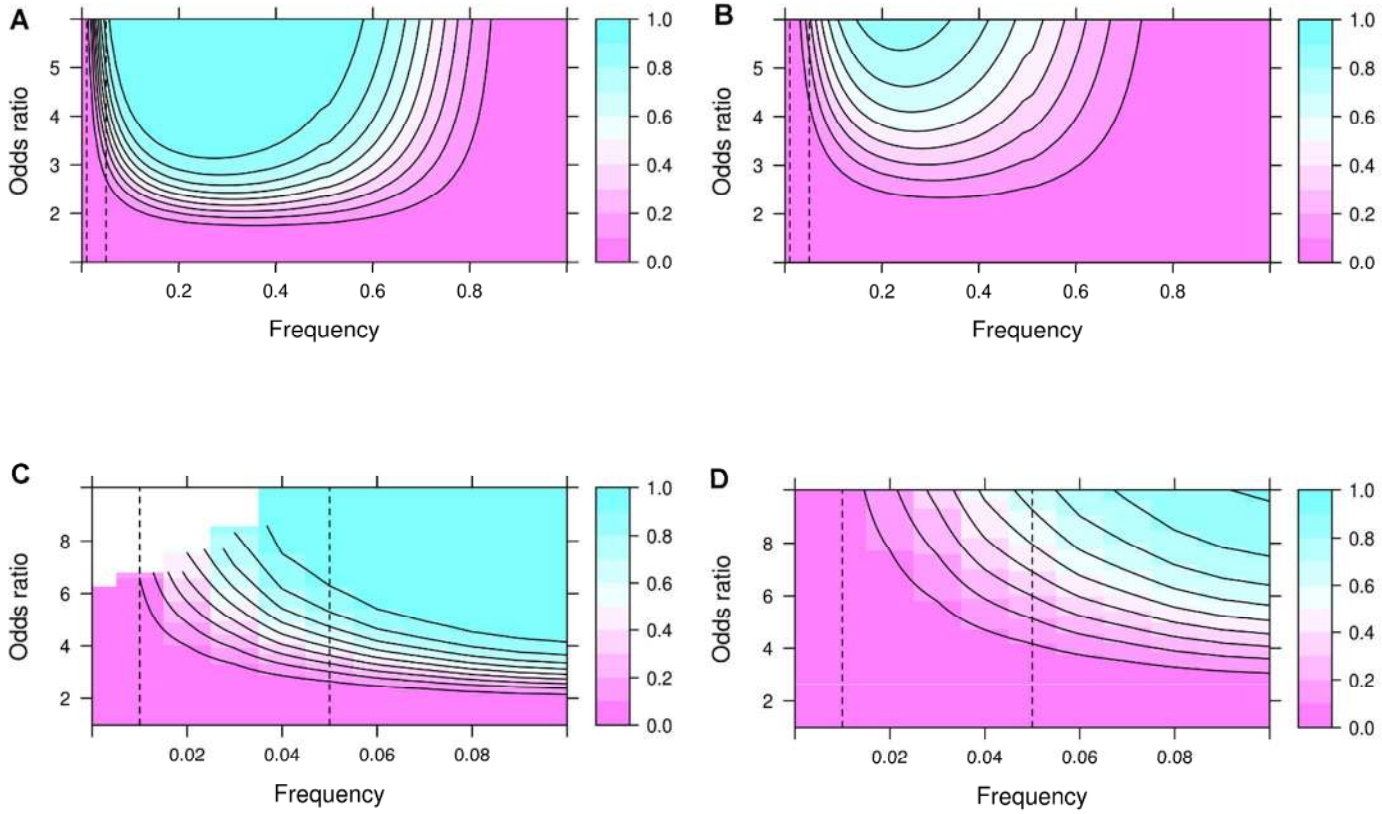
Supplemental Figure 11: Top 20 associations for 'Late DKD' for the three gene based tests; VT, SKAT-O and SKAT with the PTV+broad and PTV+missense masks.



Supplemental Figure 12: Top 20 associations for 'ESRD vs. no DKD' for the three gene based tests; VT, SKAT-O and SKAT with the PTV+broad and PTV+missense masks.



Supplemental Figure 13: Statistical power to detect association at the WES with exome-wide statistical significance (p<9×10-8) for 'Late DKD' setting (panels A and C) and for the 'ESRD vs. no DKD' comparison (panels B and D). The top panels show the statistical power for the effect allele frequency range from 0 to 1. The bottom panels show the statistical power for the effect allele frequency range from 0 to 10%.



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