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Genetics of microvascular complications in diabetes

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1 INTRODUCTION

Diabetic microvascular complications are a familiar burden to the diabetic patient. One third of patients will develop diabetic kidney disease (DKD), which is the leading cause of end-stage renal disease (ESRD) in adult patients and linked to increased cardiovascular morbidity and premature death. Diabetic retinopathy is the most common cause of blindness in working age people in the world. Diabetic neuropathy takes many forms, the most common ones being peripheral neuropathy and cardiovascular autonomic neuropathy. Most diabetic patients will develop at least milder forms of neuropathy. The microvascular complications are inter-related and it may sometimes be difficult to study one of the complications in particular, completely independent of the two others.

It is evident that the microvascular complications are complex disorders where many genetic factors are involved. In this chapter, we will mainly focus on the genome-wide hypothesis-free approaches to identify common genetic variation related to the diabetic microvascular complications (nephropathy, retinopathy, and neuropathy). Some interesting recent or larger scale candidate gene efforts are also mentioned. Understanding the genetic basis of the microvascular complications may give us clues to a better understanding of the pathogenesis of diabetic microvascular disease and thus potentially provide us with tools to develop new therapeutic strategies to prevent the complications.

2 Genetics of diabetic kidney disease

2.1 Heritability of DKD

Heritability of DKD was first suggested by studies indicating familial clustering of DKD, with the phenotype definitions ranging from microalbuminuria to persistent proteinuria and ESRD[1-4]. Heritability

estimates of albuminuria in subjects with type 2 diabetes (T2D) range from 30% to 40%[5-7], and up to 75% for estimated glomerular filtration rate (eGFR)[7]. While the sibling risk of DKD was estimated as 2.3-fold in 537 families with at least two siblings with type 1 diabetes (T1D), a higher risk ratio of 2.9 was obtained in a subset of probands with ESRD[4]. Similar increase of heritability along the severity of DKD was obtained from a recent study that utilized genome-wide genotyping data of 2,843 subjects with T1D to estimate the heritability of DKD with varying phenotype definitions: the narrow-sense heritability of broadly-defined DKD (micro- or macroalbuminuria or ESRD) was estimated to be 35%, when it was as high as 47% for ESRD[8].

2.2 Candidate genes for DKD

Over the decades, genetic variants in a myriad of positional and biological candidate genes have been investigated for DKD, but few candidate genes were robustly replicated. Among the most studied polymorphisms is an insertion/deletion variant rs1799752 (also tagged by another variant, rs4344) which affects the cellular concentration of angiotensin converting enzyme (ACE)[9]. ACE inhibitors and other medical agents inhibiting the renin-angiotensin-aldosterone system (RAAS) are currently the main treatment option to slow down the progression of DKD. Despite a striking 26,000 subjects included in a meta-analysis of 63 candidate gene studies for the *ACE* variant, only modest evidence of association with DKD was found, mainly in the subgroup of Asian subjects with T2D[10]. Characteristic to the candidate gene studies, the vast majority of the 63 included studies only had tens or few hundreds of subjects, which may also partially explain the vague results.

One large-scale candidate gene effort tested 344 single nucleotide polymorphisms (SNPs) and other variants from 127 candidate genes for DKD in a meta-analysis of three studies including 2499 European subjects with T1D. A variant in the *UNC13B* gene was deemed significant after correction for multiple

testing, with an odds ratio (OR) of 1.63 and p-value of 2.3×10^{-5} for rs13293564 after fine-mapping and combined meta-analysis with the replication study[11].

In order to systematically evaluate the cumulative evidence of the reproduced candidate genes, Mooyaart *et al.* conducted a literature-based meta-analysis investigating 132 publications on genetic variants for DKD in T1D and/or T2D. The meta-analysis yielded positive results for 24 variants from 17 distinct loci, including the ACE insertion/deletion variant[12]. However, such analysis may suffer from publication bias, and the results may be overly optimistic.

Another effort to assess the role of the previously suggested genetic loci was conducted in the Genetics of Nephropathy – an International Effort (GENIE) consortium by Williams *et al.* where they re-evaluated a selection of previously supported genetic variants for DKD in up to 6,366 subjects with T1D, out of which 2,966 were defined as cases with persistent proteinuria or ESRD[13]. A previously reported association with a combined phenotype of ESRD and proliferative diabetic retinopathy (PDR) at rs1617640 in the *EPO* gene (encoding erythropoietin) was not replicated, but the association remained genome-wide significant after a combined meta-analysis though attenuated (p-value 2×10^{-9}). While nominal evidence (i.e. p-value < 0.05) was obtained for some of the other loci, most of the previously reported associations were not replicated[13].

2.3 Linkage studies for DKD

The family-based linkage studies provided a hypothesis-free way to search for novel chromosomal loci linked with a disease, without prior knowledge of the biological mechanisms behind it. The linkage studies on DKD have resulted only in few chromosomal regions reaching a robust logarithm of odds (LOD) score. Even though first reported in a candidate region linkage analysis of chromosomal regions

containing genes for the renin-angiotensin system[14], many whole-genome linkage studies on DKD found suggestive evidence of linkage on broadly the same chromosomal region in chromosome 3q21-25[15-18], well summarized in[15]. However, this region never reached robust statistical significance. To fine-map the linkage region, a positional case-control candidate gene meta-analysis of multiple cohorts identified variants near the *NCK1* gene with relatively high p-values (7×10^{-6})[19]. A more recent multi-cohort study including 175 families from Finland, Denmark and France identified a linkage with DN at chromosome 22q11 with LOD score 3.6, but no fine-mapping efforts were performed to narrow down the source of the linkage[18].

2.4 Genome-wide association studies on DKD

The vague results from the whole-genome linkage studies, and the lack of robust replication of the candidate genes highlighted the need of genome-wide, hypothesis free search for genetic variants associated with DKD in a larger number of subjects. Early high-throughput association studies in Japanese subjects with T2D initially evaluated with 50,000 polymorphisms[20], and later with 80,000 polymorphisms, suggested association with DKD at *ACACB* gene encoding acetyl coenzyme A [CoA] carboxylase 2[(21)], and with rs741301 in the *ELMO1* gene[22]; Despite multiple subsequent replication attempts, the role of rs741301 and other variants in *ELMO1* remains unclear with some studies supporting and others refuting the finding[8,13,23-27]. A further early implementation of a genome-wide association study (GWAS) utilized pooled DNA of 547 ESRD cases and 549 T1D subjects without DKD, genotyped on a GWAS chip with 555,352 SNPs, but found only suggestive evidence of association with ESRD with $p<0.0001$ for variants in in *ZMIC1* and musculin genes[28].

In a GWAS on DKD including 820 cases and 885 controls of European ancestry from the US Genetics of Kidneys in Diabetes collection, no locus reached statistical significance required for genome-wide

significance, defined as p-value < 5×10^{-8}, but suggestive associations were found near *FRMD3* ($p=5.0\times10^{-7}$) and *CARS* genes ($p=3.1\times10^{-6}$), and on chromosomes 7p and 13q. Supportive evidence of association was found for the *FRMD3* and *CARS* loci in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study[29]. In subsequent studies, variants in the *FRMD3* were associated with ESRD in African American subjects with T2D after accounting for a major genetic risk factor for non-diabetic renal disease at *MYH9* locus[30] and in a family study of European American patients with T2D[31], but not in subjects of European ancestry with T1D[13]. The association at the *MYO16/IRS2* locus on chromosome 13q was supported by Japanese[32] and European American patients with T2D[33]. Subsequent analysis of the US GoKinD GWAS data using SNP imputation revealed four additional loci with a suggestive p-value < 10^{-5}, e.g. rs7071071 in the *SORBS1* gene[34]. Of note, other variants in the *SORBS1* gene were later reported as potentially associated with DKD in a GWAS of European subjects with T1D; after evaluation in GoKinD US, rs1326934 was strongly associated with DKD with $p=3.5\times10^{-9}$, but the signal was attenuated to p=0.009 after replication in two additional European cohorts[35].

The first GWAS meta-analysis with genome-wide significant findings was performed by the Genetics of Nephropathy, an International Effort (GENIE) consortium. With 6231 subjects with T1D at the discovery stage, and a total of 11,847 patients in a meta-analysis including the replication cohorts, the study identified two loci genome-wide significantly associated with ESRD: rs7583877 in *AFF3* ($p=1.2\times10^{-8}$) and rs12437854 intergenic between the *RGMA* and *MCTP2* genes ($p=2.0\times10^{-9}$). Functional studies on renal epithelial cells suggested that *AFF3* is involved in the renal fibrosis[36]. While little is known of the *RGMA* and *MCTP2* genes, and the affected gene may be located much further away from the main association signal, the same locus was one of the main findings also in a GWAS data mining approach performed in a subset of the subjects [37]. For the DKD phenotype the strongest association in the GENIE

GWAS was obtained at the *ERBB4* gene ($p=2.1\times10^{-7}$ for rs7588550); *ERBB4* gene expression analysis indicated co-expression with collagen genes, also associated with renal fibrosis[36]. Conditional mouse overexpression and knock-out models suggest that *ERBB4* has an important role on the development of kidneys[38], and ErbB4 has been previously suggested as a therapeutic target molecule for the treatment of cardiovascular disorders, scitsofrenia and cancer[39]. Recent work showed protection from albuminuria in STZ-induced hyperglycemic wild-type and miR-146a$^{-/-}$ mice when pan-ErbB inhibitor was administered, suggesting ErbB4/EGFR as a druggable target for DKD[40].

A gender stratified GWAS analysis in 3652 Finnish subjects with T1D identified rs4972593 between the *SP3* and *CDCA7* genes on chromosome 2q31.1 associated with twofold risk of ESRD in women with p-value $<5\times10^{-8}$, and the finding was replicated in other cohorts in the GENIE consortium[41]. No effect was seen in diabetic men or in subjects with T2D. While the RegulomeDB suggest potential regulatory activity for a SNP in full linkage with rs4972593, no eQTL association was identified to link the SNP to expression of any flanking genes. Nevertheless, the gene expression of *SP3* is among the most gender specific ones in human glomeruli of diabetic patients[42], and Sp3 transcription factor has been shown to directly bind to the estrogen receptor α[43], providing a potential link with the gender specific association.

A trans-ethnic GWAS including 13,736 subjects with T2D with European American, African American, Mexican American, or American Indian ancestry from the Family Investigation of Nephropathy and Diabetes (FIND) study found variants between the *SCAF8* and *CNKSR3* genes associated with DKD with p-value $< 5\times10^{-8}$, with particularly strong association in the American Indian population (rs12523822 $p=5.7\times10^{-9}$)[44]. *CNKSR3* is a scaffolding platform that stimulates epithelial sodium channel in response to aldosterone[45]. As inhibition of the renin-angiotensin-aldosterone system is the main therapy to DKD and other proteinuric kidney diseases, *CNKSR3* is a plausible target gene behind the association. The *MYH9* locus, which is one of the main genetic risk factors for non-diabetic kidney

disease in African Americans, was near genome-wide significantly associated ($p=7.7\times10^{-8}$) with kidney disease in African American subjects with T2D. However, the authors note that this is likely due to a proportion of study subjects with non-diabetic kidney disease[44].

Even though the current view of the clinical course of DKD is more versatile, albuminuria has been considered as the classical hallmark of diabetic nephropathy[46]. GWAS on albuminuria as a continuous trait in 1925 Finnish patients with T1D identified 5 SNPs with $p<5\times10^{-8}$ in the *GLRA3* gene. The replication attempt in 3771 additional patients of European ancestry resulted in a nominally significant ($p=0.04$) association at rs1564939 in the opposite effect direction[47]. The authors hypothesized a population specific effect and warrant further replication in Finnish patients to confirm or refute the finding.

To account for the various phenotypic manifestations of DKD, a recent work from the SUrrogate markers for Micro- and Macro-vascular hard endpoints for Innovative diabetes Tools (SUMMIT) consortium reported GWAS in 12,540 subjects with T1D using seven phenotypic definitions of renal complications of varying severity, based on either albumin excretion rate (AER), estimated glomerular filtration rate (eGFR), or both. Suggestive associations were identified in or near *PTPN13*, *AFF3*, *CNTNAP2* and *NRG3* loci, even though no locus reached genome-wide significance[8]. Evaluation of previous loci supported association with ESRD at rs2838302 at *SIK1*, originally identified in a GWAS data mining approach of 3464 subjects with T1D[37]. Genetic comparison with related traits showed that alleles known to increase body mass index (BMI), and risk of T2D, were associated with DKD traits, suggesting that BMI and metabolic changes leading to T2D are causal risk factors for DKD in subjects with T1D. Analysis of genome-wide correlation also suggested a shared genetic background with DKD and failure at smoking cessation[8].

The GWAS on CKD and eGFR in the general population have identified multiple loci affecting the kidney function[48,49]. Previous efforts to assess the effect of the loci affecting general population in diabetic subjects suggested that variants in *GCKR*, *SHROOM3* and *UMOD*[50], and in *MYH9/APOL1* locus in African Americans[44,51], play a role also in subjects with T2D, while no association has been found in subjects with T1D[8,36]. The observed associations may to some extend arise due to a substantial proportion of subjects with T2D having coincident T2D and non-diabetic kidney disease[44]. The largest GWAS meta-analysis on chronic kidney disease (CKD) and eGFR in the general population to date included 133,413 individuals at the discovery stage and up to 42,166 individuals in replication, and resulted in 53 robust loci (p-value<5×10^{-8}) for kidney traits[52]. Evaluation of these 53 loci among the 16,477 included subjects with diabetes (mostly T2D) revealed significant association with eGFR at rs12917707 at *UMOD* (p-value=2.5×10^{-8}) and nominal associations (p<0.05) at 19 loci. Another GWAS studying albuminuria as a continuous trait in up to 54,450 subjects from the general population, with a subset of 7787 subjects with diabetes (mainly T2D), found suggestive evidence of association at *HS6ST1* (rs13427836 p=6.3×10^{-7}) and *RAB38/CTSC* loci (rs649529 p=5.8×10^{-7}) in subjects with, but not without diabetes[53]. Even though the *CUBN* locus, previously associated with albuminuria in the general population,[54] did not reach genome-wide significance in diabetic subjects, the effect was larger in subjects with than without diabetes[53].

2.5 Sequencing efforts for DKD

In addition to the chip-based approaches, next-generation sequencing based studies are also emerging in order to address the low frequency and rare variants affecting the disease risk, with a premise of higher effect sizes because of either capturing the true causal variant rather than a proxy, or capturing underlying direct changes in the protein structure rather than changes in the gene regulation. A sub-study of a larger

whole-exome sequencing (WES) of subjects with and without T2D investigated the role of *RREB1* (ras-responsive element binding protein-1) gene for diabetic ESRD in 529 African American cases with T2D and ESRD and in 535 population based controls. The findings were followed up by subsequent genotyping in replication and trait segregation studies, suggesting that variants in *RREB1* modulate the risk of T2D, ESRD, and non-diabetic renal disease, but the results should be taken with caution as the locus has been previously associated with T2D[55].

WES of 997 subjects with T1D from the SUMMIT consortium did not identify any variant that would reach the exome-wide significance ($p<5\times10^{-7}$), but among the strongest associations was a common variant in the 3'UTR of *ERBB4* gene[8]; other variants not in LD were previously suggestively associated with DKD in the GENIE consortium GWAS with partially overlapping subjects[36] (See previous section 2.4 Genome-wide association studies on DKD).

3 GENETICS OF DIABETIC RETINOPATHY

3.1 Heritability of diabetic retinopathy

There is evidence that genetic factors may play an important role in the development of diabetic retinopathy. Familial clustering of various degrees of retinopathy have been reported worldwide[56-59]. In the DCCT, first degree relatives (with type 1 or type 2 diabetes) of type 1 diabetic probands were studied and they reported a strong familial clustering with an OR of 3.1 for severe diabetic retinopathy in relatives of probands with and without diabetic retinopathy[56]. Only weak evidence was shown for the phenotype "any retinopathy"[56]. In a study of sib-pairs with T1D, the risk of a T1D proband was 9.9-fold if a T1D sibling had retinopathy, and the risk of the proband was higher if the proband was female[59]. Heritability estimates for retinopathy are on average around 25%, but the estimates vary and may be as high as 52% depending on ethnicity, severity of retinopathy and type of diabetes[60-62]. As for DKD, it seems that the heritability is higher with a more severe phenotype.

3.2 Candidate genes for diabetic retinopathy

Biologically relevant candidate genes for diabetic retinopathy have been extensively assessed in both T1D and T2D but thus far any positive findings have been difficult to replicate[63,64]. Abhary and co-workers performed a systematic meta-analysis in September 2008 where they identified 702 publications on candidate genes for diabetic retinopathy. Twenty genes and 34 variants had been studied in multiple cohorts. In a meta-analysis, the aldose reductase gene (*AKR1B1*) was highlighted as an important susceptibility gene for retinopathy ($p=1\times10^{-4}$) together with suggestive evidence of association ($p<0.05$) for genetic variants in genes *NOS3, VEGF, ITGA2* and *ICAM1*[65]**.**

In another meta-analysis, SNPs in 2000 cardiovascular candidate genes were genotyped in 2691 subjects with T2D from the CARe (Candidate gene Association Resource) cohort. After Bonferroni correction, they found the strongest associations with diabetic retinopathy for rs6128 (p=0.0001) in *SELP* (P-selectin) and rs6856425 tagging α-L-iduronidase (*IDUA*) ($p=2.1\times10^{-5}$). However, the findings could not be replicated in independent cohorts[64].

Few candidate gene studies reach genome-wide significance ($p < 5.0\times10^{-8}$). A recent paper studied 134 SNPs in two thiamine transporters and two transcription factors and identified two potentially interesting SNPs in the *SLC19A3* gene that were associated with a lower rate of severe retinopathy. When a combined phenotype of severe retinopathy and ESRD was used, the association became even stronger[66]. The association with the combined phenotype at rs12694743 reached genome-wide significance ($p = 2.30\times10^{-8}$ after correction for HbA_{1c} and BMI) in a meta-analysis including the discovery cohort (The FinnDiane Study) and two replication cohorts (WESDR and DCCT/EDIC)[66].

Regarding positional candidate genes see also replication/validation studies of GWAS loci in section 3.4.

3.3 Linkage studies for diabetic retinopathy

Some linkage analyses for diabetic retinopathy have been performed in T2D, but they have so far provided only suggestive linkage to a number of chromosomal regions with the strongest linkage observed at Chr1p36[60,67,68].

3.4 Genome-wide association studies on diabetic retinopathy

A compilation of current GWAS data on interesting genetic loci for diabetic retinopathy is shown in Figure 1. Most of the GWASs so far have been performed in patients with T2D. Only one studied patients with T1D[69]. Half of the studies have been performed in Asian populations (Chinese, Taiwanese and Japanese)[70-72], one in Mexican Americans[73] and two in Caucasians[69,74]. The phenotype has varied from any retinopathy to severe sight-threatening retinopathy.

The first GWAS for diabetic retinopathy was performed by Fu et al in a Mexican Americans cohort of only 103 cases with PDR (more severe moderate non-proliferative diabetic retinopathy [NPDR]) and 183 controls without retinopathy (ad early NPDR). Only nominally significant findings ($p<0.0001$) were observed as two directly genotyped and 32 imputed SNPs were associated with severe retinopathy in 13 different chromosomal regions.[73]

Genome-wide significant findings have so far been shown by only two GWASs, as presented in Figure 1. In a study of 749 Chinese T2D patients, Huang et al. first identified 12 SNPs with $p<1\times10^{-6}$ for DR, which after adjustment for HbA_{1c} and duration of diabetes resulted in four genome-wide significant loci (rs17376456 in *KIAA0825* on Chr5q.15, rs2038823 in *HS6ST3* on Chr13q, rs4838605 in *ARHGAP22* on Chr10q, and rs12219125 in *PLXDC2* on Chr10p)[72]. Out of these loci, supporting evidence ($p<0.05$) has been subsequently reported for *ARHGAP22* and *PLXDC2* [75,76] (Figure 1).

The most recent GWAS was performed in 844 Caucasian T2D patients for sight-threatening diabetic retinopathy. They replicated their top SNPs from the discovery cohort in two T2D and one T1D independent cohort and performed a meta-analysis, which ended up with one genome-wide significant SNP rs9896052 ($p=4.15\times10^{-8}$) located upstream from the *GRB2* gene. They further used a mouse model of proliferative retinopathy and showed increased GRB2 expression in the retina[74].

The fact that several of the early GWASs on diabetic retinopathy never tried to replicate their main findings in independent cohorts, highlights the importance of "positional candidate gene" studies that have tried to replicate or validate the earlier identified loci[75-79]. Figure 1 summarizes the replicated findings ($p<0.05$). Of these studies, the ones by Grassi[77] et al and Hosseini et al.[76] were performed in T1D, the rest in T2D. Of note, only variants in *API5*[(78)]. Figure 1 summarizes the replicated findings ($p<0.05$). Of these studies, the ones by Grassi[79] remained significant after correction for multiple testing.

In a meta-analysis of 1907 well-characterized subjects with T1D from the DCCT/EDIC Study and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), none of the tested 34 SNPs from four previous GWASs was replicated after correction for multiple testing[76]. Nominally significant associations ($p<0.05$) were observed for severe diabetic retinopathy at the *PLXDC2* locus and for mild diabetic retinopathy in the *PPARG* gene in the same direction as the original findings. Cheung and co-workers studied 2566 Chinese T2D patients with and without retinopathy[79] in an attempt to replicate 38 SNPs with suggestive evidence for association ($p<5\times10^{-4}$) from four previous GWASs[69,70,72,73]. The strongest association was found for an intronic SNP rs2115386 of *INSR* for both sight-threatening DR (STDR) and PDR. Four other SNPs were nominally significantly associated with either STDR or PDR[79].

3.5 Sequencing efforts for diabetic retinopathy

So far, no large attempts have been published. A small WES study with 43 subjects with and 63 without DR despite 10 years duration of diabetes observed excess rare variants in three genes (*NME3*, *LOC728699* and *FASTK*, $p<5\times10^{-8}$) in subjects without diabetic retinopathy[80]. Validation of the findings is still needed.

4 GENETICS OF DIABETIC NEUROPATHY

4.1 Heritability of diabetic neuropathy

Diabetic neuropathy is a complex and quite heterogeneous disorder with a plethora of potential phenotypes to study. While there are many established environmental risk factors for neuropathy such as poor glycemic control, overweight and smoking, the genetic component of diabetic neuropathy is largely unknown. In a family study, the risk for neuropathy in a T1D proband was 2-fold if a T1D sibling had neuropathy and the risk was twice as high if the proband was female[59]. Based on GWAS data in the GoDARTS cohort, the authors estimated the narrow-sense heritability of painful neuropathy to be 11.0%[81]. In a later sex-specific analysis, they continued by reporting heritability estimates for painful neuropathy of 30.0% for men and 14.7% for women[82].

Heritability results regarding cardiac autonomic neuropathy are less consistent. In the Framingham Heart Study, the variance in hear rate variability (HRV) attributable to genetic factors was estimated to be 13% - 23%, when first-degree relatives and unrelated subjects were studied[83]. On the other hand, in a Hungarian twin cohort, genetic factors did not seem to substantially influence cardiac autonomic function[84].

4.2 Candidate genes for diabetic neuropathy

Much fewer candidate gene studies have been performed for diabetic neuropathy than for nephropathy and retinopathy partly because of the complex phenotype. In addition, only few findings from the candidate gene studies have been confirmed. A recent meta-analysis of 5 studies on the *ACE* insertion/deletion polymorphism and 4 studies on the 677C>T polymorphism in the methylenetetrahydrofolate reductase (*MTHFR)* gene suggested that there might be a role for these genes

in the development of diabetic neuropathy[85]. Other potentially interesting candidate genes for diabetic neuropathy that has been suggested include among others *GLO1*[(86)], APOE[87], VEGF[88], eNOS[89] and GPX1[(90)] and are well reviewed in Politi 2016[(91)]. An interesting finding comes from the German Diabetes Study (GDS) where in a population of 538 recently onset (<1 year) subjects with T1D (n=163) and T2D (n=373), Ziegler and co-workers investigated the association of 18 different quantitative measures of neuropathy with 9 tagging SNPs in the transketolase gene (*TKT)*. The association of the *TKT* SNPs rs7648309 with total symptom score (p=0.024) and rs62255988 with warm thermal detection threshold in the hand (p=0.049) remained statistically significant after strict adjustment for multiple testing with the number of phenotypes and SNPs[92]**.**

4.3 Genome-wide association studies on diabetic neuropathy

To our knowledge only two GWASs, both from the GoDARTS (Genetics of Diabetes and Audit Research Tayside Study) cohort, have to date been performed for diabetic neuropathy[81,82]. Both papers used a robust phenotype of neuropathic pain in patients with T2D. The case definition was based on the use of at least one of five drugs known to be prescribed specifically for neuropathic pain (duloxetine, gabapentin, pregabalin, capsaicin cream/patch, and lidocaine patch) as well as a sign of sensory neuropathy (in the first study only). Controls did not take any of these five drugs or any other more unspecific pain relieving medication. No minimum duration of diabetes was required for the controls. The main finding of the first study was a cluster of markers with a suggestive association for neuropathic pain next to the *GFRA2* gene[81]. The top SNP rs17428041 in this region had an OR of 0.67 (95%CI 0.57-0.78) and a p-value of 1.77×10^{-7}. In a second study with a slightly larger cohort, they performed sex-specific analyses for painful neuropathy and found suggestive evidence (top SNP rs71647933

p=2.74×10^{-7}) between the genes *ZSCAN20* and *TLR12P* in women and near *HMGB1P46* (top SNP rs6986153 p=8.02×10^{-7}) in men[82]. No replication of the findings in the two studies was performed.

5 Future directions

During the last five years, the genetic research on diabetic complications has moved from candidate gene and linkage studies to GWAS and WES studies, with novel genetic risk factors emerging. However, many of the reported signals still require further confirmation in independent studies, and these can be assumed to explain only a small proportion of the heritability of microvascular complications. Larger studies with careful phenotyping, as well as novel approaches are needed to identify additional genetic risk factors for diabetic complications.

5.1 Larger studies are needed

Increasing the number of samples has markedly increased the number of susceptibility loci for many common traits including T2D[93]. While genetic consortia to perform GWAS meta-analyses already exist for DKD, albeit still moderate in size[8,36,44,53], no GWAS meta-analyses have been performed on DR or diabetic neuropathy, except for the GWAS on DR by Grassi et al. including 2829 subjects from two studies[69]. Furthermore, the number of subjects included in some of the GWAS on DR is very small, in many cases with limited replication. Therefore, continuous recruitment of subjects and international collaboration to increase the total number of subjects is essential for discovery of further genetic susceptibility loci for diabetic complications. Preliminary reports from larger GWAS meta-analyses are emerging, e.g. a GWAS on DKD in up to 8000 subjects with T2D from the Hong Kong Diabetes Registry[94], a GWAS meta-analysis on DKD including both T1D and T2D subjects from the SUMMIT

consortium[95]; and GWAS meta-analysis on DKD with up to 20,000 subjects with T1D from the Diabetic Nephropathy Collaborative Research Initiative (DNCRI)[96].

While much of the genetic research on common traits has concentrated on subjects of European origin, the GWAS on diabetic microvascular complications, particularly diabetic retinopathy, have been performed on various ethnic groups[69-74]. Furthermore, a large-scale candidate gene study of diabetic retinopathy including over 2000 genes was performed as a multi-ethnic meta-analysis[64]. Recently, a trans-ethnic GWAS analysis identified a novel susceptibility locus for DKD near *CNKSR3* gene particularly evident in the American Indian population, but directionally consistent also in subjects of European and Mexican ancestry[44]. Both further GWAS in various ethnicities, as well as trans-ethnic GWAS meta-analyses can provide novel cues to genetic factors behind diabetic complications.

5.2 How to define the phenotype?

The choice of the best potential phenotype is crucial. Even though the numbers increase statistical power, in some cases it may be fruitful to concentrate on more homogenous sub-groups of subjects, as demonstrated by the *SP3-CDCA7* locus associated with ESRD only in women[41]. In search for susceptibility genes for DKD, multiple phenotypic definitions have been employed with the aim to discover genes affecting various stages of the disease with different pathogenic mechanisms[8,36]. A similar approach may be particularly useful for diabetic neuropathy with its spectrum of diverse symptoms.

Studies on early phenotypic alterations have been criticized because of the uncertain final outcome of these early traits, e.g. microalbuminuria is sometimes classified as case and sometimes as control or early signs of cardiac autonomic neuropathy (CAN) may be even reversible[97]. Theoretically, more severe forms of complications, like ESRD, should be more robust and reduce potential misclassification bias. However, there is high mortality in CVD already before the development of ESRD. In a Finnish study

of patients with T1D more than 25% of the patients with proteinuria died before developing ESRD[98]. For genetic variants that increase the risk of both ESRD and cardiovascular mortality, the risk allele would be diluted, or even inversed, due to selective mortality.

5.2.1. Variability in the phenotypic definitions

The large variability in the definitions of the microvascular phenotypes creates difficulties for the comparison of data between studies and for fruitful collaboration attempts. The variability and quality of studied phenotypes may explain lack of replication in for example diabetic retinopathy. While laser treatment of the retina may be considered a robust case phenotype, in contrast absence of laser treatment is not a good control definition. However, there is always a delicate balance between achieving the best phenotype quality and reaching large enough patient numbers. One solution has in this case been to use several different case/control cut-offs for the same phenotype[8]. In large consortia, a good harmonization is important to reduce the heterogeneity in phenotype between participating cohorts. While some cohorts may not be able to provide cases and controls fulfilling the primary harmonized phenotype definition, using several phenotype definitions enables the maximal use of all patients in addition to assessing various disease stages.

5.2.2. Criteria for controls

In general, in case-control settings the duration of the controls often seems to be rather short. Since the beginning of candidate gene studies in diabetic complications, especially DKD, durations such as 15 years for T1D and 10 (or even less) years for T2D have been considered sufficient to classify patients as controls if no signs of complication are present. The treatment of diabetes has evolved and postponed the onset of complications. Therefore, much longer duration of diabetes for controls is probably needed. There is a need for studies addressing the potential risk of misclassification with short diabetes duration in controls, and on the other hand, loss of statistical power with too stringent requirements.

5.2.3. Do genetics of microvascular complications in T1D and T2D differ?

Part of the genetic background in the pathogenesis of diabetic complications is most likely the same in both types of diabetes, however, there may also be genetic markers specific for one or the other type. Some papers analyze pooled diabetes cohorts and do not even report specific characteristics on the diabetic population. Especially for DKD, it should be noted that a significant proportion of subjects with T2D may have kidney disease due to non-diabetic causes, while the majority of kidney disease in subjects with T1D is due to diabetic nephropathy[99]. Therefore, the genetic risk factors for non-diabetic kidney disease may also be relevant in the T2D population[52], but less evident in subjects with T1D.

5.3 Low-frequency and rare variants may affect diabetic complications

5.3.1. Sequencing of rare and low frequency variants

The research focus for the genetics of microvascular complications of diabetes has thus far been mainly on the common variants detectable with GWASs. Preliminary reports of whole genome sequencing for DKD are emerging[100]. While eventually whole genome sequencing should cover all coding and non-coding, common and low-frequency or rare variants, and the WES studies targeting the protein coding parts of the human genome are a suitable starting point for the search of rare variants. However, thus far the WES efforts on DKD have not robustly identified any rare variants, or genes enriched for protein truncating or changing variants[8]. For DR, three genes were reported enriched for rare variants in subjects without DR, but replication in other studies is required to confirm these findings as well[80]. Currently, the genotyping chips targeting the exonic content simultaneously with GWAS genotyping provide an interesting and cost-effective approach to detect low-frequency and rare variants. While very rare and *de novo* mutations cannot be identified with the exome chip approach, it is feasible in large studies of thousands of subjects[96].

5.3.2. Linkage analysis with GWAS data

Most of the current genetic studies, including candidate gene, GWAS and WES, are based on association tests. Nevertheless, the previously much employed family based linkage studies are still a valid approach, as when combined with the exome- and genome-wide genotyping and sequencing platforms, they may be particularly efficient in the search for low frequency and rare variants. Family-based association analysis was used to support the role of *FRMD3* in DKD[31], and preliminary reports for genome-wide linkage studies on DKD based on modern-day, dense SNP genotyping in small pedigrees are emerging[101].

5.4 Genetics may reveal biology and infer causality

Genetic findings of related traits can be utilized in many ways to improve our understanding of diabetic complications. Analysis of genetic risk scores for related traits suggested that high body-mass-index (BMI) and metabolic changes leading to T2D are causal risk factors for DKD[8]; furthermore, inverse genome-wide correlation was found with the LD-score regression method between DKD and smoking cessation, supporting the clinical finding that smoking cessation is beneficial for avoiding DKD[8,102].

In biomarker research, the causality of certain biomarkers for diabetic complications has been evaluated with the Mendelian Randomization method, based on the genetic factors that affect the biomarker levels. For example, urinary kidney injury molecule 1 (KIM1) predicts progression of DKD even though it does not add prognostic benefit on top of AER or eGFR. Nevertheless, Mendelian Randomization suggested that KIM1 is a causal risk factor for reduced eGFR in subjects with T1D[103]. On the contrary, serum uric acid was independently associated with the decline in eGFR, but Mendelian Randomization suggested that it is not a causal risk factor for DKD, but rather a downstream marker of kidney damage[104]. In addition to serum or urine biomarkers, the Mendelian Randomization approach was also applied on BMI suggesting that elevated BMI is a causal risk factor for DKD[105].

6 Conclusions

In the future, better phenotyping, more collaboration and larger consortia, and exploration of the low frequency and rare variation are essential to identify the genetic causes behind diabetic microvascular complications. By guiding us into the complex biology behind the complications, genetics may help us develop new therapeutic tools to improve the prognosis of the diabetic patient.

7 Bibliography

1. Seaquist ER, Goetz FC, Rich S, Barbosa J: Familial clustering of diabetic kidney disease. [Electronic version]. *N Engl J Med* 320: 1161-1165, 1989

2. Borch-Johnsen K, Norgaard K, Hommel E, Mathiesen ER, Jensen JS, Deckert T, Parving HH: Is diabetic nephropathy an inherited complication. [Electronic version]. *Kidney Int* 41: 719-722, 1992

3. Quinn M, Angelico MC, Warram JH, Krolewski AS: Familial factors determine the development of diabetic nephropathy in patients with IDDM. [Electronic version]. *Diabetologia* 39: 940-945, 1996

4. Harjutsalo V, Katoh S, Sarti C, Tajima N, Tuomilehto J: Population-based assessment of familial clustering of diabetic nephropathy in type 1 diabetes. [Electronic version]. *Diabetes* 53: 2449-2454, 2004

5. Fogarty DG, Rich SS, Hanna L, Warram JH, Krolewski AS: Urinary albumin excretion in families with type 2 diabetes is heritable and genetically correlated to blood pressure. [Electronic version]. *Kidney Int* 57: 250-257, 2000

6. Forsblom CM, Kanninen T, Lehtovirta M, Saloranta C, Groop LC: Heritability of albumin excretion rate in families of patients with type II diabetes. [Electronic version]. *Diabetologia* 42: 1359-1366, 1999

7. Langefeld CD, Beck SR, Bowden DW, Rich SS, Wagenknecht LE, Freedman BI: Heritability of GFR and albuminuria in caucasians with type 2 diabetes mellitus. [Electronic version]. *American Journal of Kidney Diseases* 43: 796-800, 2004

8. Sandholm N, Van Zuydam N, Ahlqvist E, Juliusdottir T, Deshmukh HA, Rayner NW, Di Camillo B, Forsblom C, Fadista J, Ziemek D, Salem RM, Hiraki LT, Pezzolesi M, Tregouet D, Dahlstrom E, Valo E, Oskolkov N, Ladenvall C, Marcovecchio ML, Cooper J, Sambo F, Malovini A, Manfrini M, McKnight AJ, Lajer M, Harjutsalo V, Gordin D, Parkkonen M, FinnDiane Study Group, Jaakko Tuomilehto, Lyssenko V, McKeigue PM, Rich SS, Brosnan MJ, Fauman E, Bellazzi R, Rossing P, Hadjadj S, Krolewski A, Paterson AD, DCCT/EDIC Study Group, Jose C. Florez, Hirschhorn JN, Maxwell AP, GENIE Consortium DD, Cobelli C, Colhoun HM, Groop L, McCarthy MI, Groop PH, SUMMIT Consortium: The genetic landscape of renal complications in type 1 diabetes. [Electronic version]. *J Am Soc Nephrol* 28: 557-574, 2017

9. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F: An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. [Electronic version]. *J Clin Invest* 86: 1343-1346, 1990

10. Wang F, Fang Q, Yu N, Zhao D, Zhang Y, Wang J, Wang Q, Zhou X, Cao X, Fan X: Association between genetic polymorphism of the angiotensin-converting enzyme and diabetic nephropathy: A meta-analysis comprising 26,580 subjects. [Electronic version]. *J Renin Angiotensin Aldosterone Syst* 13: 161-174, 2012

11. Tregouet DA, Groop PH, McGinn S, Forsblom C, Hadjadj S, Marre M, Parving HH, Tarnow L, Telgmann R, Godefroy T, Nicaud V, Rousseau R, Parkkonen M, Hoverfalt A, Gut I, Heath S, Matsuda F, Cox R, Kazeem G, Farrall M, Gauguier D, Brand-Herrmann SM, Cambien F, Lathrop M, Vionnet N, EURAGEDIC Consortium: G/T substitution in intron 1 of the UNC13B gene is associated with increased risk of nephropathy in patients with type 1 diabetes. [Electronic version]. *Diabetes* 57: 2843-2850, 2008

12. Mooyaart A, Valk EJJ, van Es L, Bruijn J, de Heer E, Freedman B, Dekkers O, Baelde H: Genetic associations in diabetic nephropathy: A meta-analysis. [Electronic version]. *Diabetologia* 54: 544-553, 2011

13. Williams WW, Salem RM, McKnight AJ, Sandholm N, Forsblom C, Taylor A, Guiducci C, McAteer JB, McKay GJ, Isakova T, Brennan EP, Sadlier DM, Palmer C, Soderlund J, Fagerholm E, Harjutsalo V, Lithovius R, Gordin D, Hietala K, Kyto J, Parkkonen M, Rosengard-Barlund M, Thorn L, Syreeni A, Tolonen N, Saraheimo M, Waden J, Pitkaniemi J, Sarti C, Tuomilehto J, Tryggvason K, Osterholm AM, He B, Bain S, Martin F, Godson C, Hirschhorn JN, Maxwell AP, Groop PH, Florez JC, GENIE Consortium: Association testing of previously reported variants in a large case-control meta-analysis of diabetic nephropathy. [Electronic version]. *Diabetes* 61: 2187-2194, 2012

14. Moczulski DK, Rogus JJ, Antonellis A, Warram JH, Krolewski AS: Major susceptibility locus for nephropathy in type 1 diabetes on chromosome 3q: Results of novel discordant sib-pair analysis. [Electronic version]. *Diabetes* 47: 1164, 1998

15. Rogus JJ, Poznik GD, Pezzolesi MG, Smiles AM, Dunn J, Walker W, Wanic K, Moczulski D, Canani L, Araki S, Makita Y, Warram JH, Krolewski AS: High-density single nucleotide polymorphism genome-wide linkage scan for susceptibility genes for diabetic nephropathy in type 1 diabetes. [Electronic version]. *Diabetes* 57: 2519-2526, 2008

16. Osterholm AM, He B, Pitkaniemi J, Albinsson L, Berg T, Sarti C, Tuomilehto J, Tryggvason K: Genome-wide scan for type 1 diabetic nephropathy in the finnish population reveals suggestive linkage to a single locus on chromosome 3q. [Electronic version]. *Kidney Int* 71: 140-145, 2007

17. Bowden DW, Colicigno CJ, Langefeld CD, Sale MM, Williams A, Anderson PJ, Rich SS, Freedman BI: A genome scan for diabetic nephropathy in african americans. [Electronic version]. *Kidney Int* 66: 1517-1526, 2004

18. Wessman M, Forsblom C, Kaunisto MA, Soderlund J, Ilonen J, Sallinen R, Hiekkalinna T, Parkkonen M, Maxwell AP, Tarnow L, Parving HH, Hadjadj S, Marre M, Peltonen L, Groop

PH, FinnDiane Study Group: Novel susceptibility locus at 22q11 for diabetic nephropathy in type 1 diabetes. [Electronic version]. *PLoS One* 6: e24053, 2011

19. He B, Österholm AM, Hoverfält A, Forsblom C, Hjörleifsdóttir EE, Nilsson AS, Parkkonen M, Pitkäniemi J, Hreidarsson A, Sarti C, McKnight AJ, Maxwell AP, Tuomilehto J, Groop PH, Tryggvason K: Association of genetic variants at 3q22 with nephropathy in patients with type 1 diabetes mellitus. [Electronic version]. *The American Journal of Human Genetics* 84: 5-13, 2009

20. Tanaka N, Babazono T, Saito S, Sekine A, Tsunoda T, Haneda M, Tanaka Y, Fujioka T, Kaku K, Kawamori R, Kikkawa R, Iwamoto Y, Nakamura Y, Maeda S: Association of solute carrier family 12 (sodium/chloride) member 3 with diabetic nephropathy, identified by genome-wide analyses of single nucleotide polymorphisms. [Electronic version]. *Diabetes* 52: 2848-2853, 2003

21. Maeda S, Kobayashi MA, Araki S, Babazono T, Freedman BI, Bostrom MA, Cooke JN, Toyoda M, Umezono T, Tarnow L, Hansen T, Gaede P, Jorsal A, Ng DP, Ikeda M, Yanagimoto T, Tsunoda T, Unoki H, Kawai K, Imanishi M, Suzuki D, Shin HD, Park KS, Kashiwagi A, Iwamoto Y, Kaku K, Kawamori R, Parving HH, Bowden DW, Pedersen O, Nakamura Y: A single nucleotide polymorphism within the acetyl-coenzyme A carboxylase beta gene is associated with proteinuria in patients with type 2 diabetes. [Electronic version]. *PLoS Genet* 6: e1000842, 2010

22. Shimazaki A, Kawamura Y, Kanazawa A, Sekine A, Saito S, Tsunoda T, Koya D, Babazono T, Tanaka Y, Matsuda M, Kawai K, Iiizumi T, Imanishi M, Shinosaki T, Yanagimoto T, Ikeda M, Omachi S, Kashiwagi A, Kaku K, Iwamoto Y, Kawamori R, Kikkawa R, Nakajima M, Nakamura Y, Maeda S: Genetic variations in the gene encoding ELMO1 are associated with susceptibility to diabetic nephropathy. [Electronic version]. *Diabetes* 54: 1171-1178, 2005

23. Pezzolesi MG, Katavetin P, Kure M, Poznik GD, Skupien J, Mychaleckyj JC, Rich SS, Warram JH, Krolewski AS: Confirmation of genetic associations at ELMO1 in the GoKinD collection supports its role as a susceptibility gene in diabetic nephropathy. [Electronic version]. *Diabetes* 58: 2698-2702, 2009

24. Leak TS, Perlegas PS, Smith SG, Keene KL, Hicks PJ, Langefeld CD, Mychaleckyj JC, Rich SS, Kirk JK, Freedman BI, Bowden DW, Sale MM: Variants in intron 13 of the ELMO1 gene are associated with diabetic nephropathy in african americans. [Electronic version]. *Ann Hum Genet* 73: 152-159, 2009

25. Wu HY, Wang Y, Chen M, Zhang X, Wang D, Pan Y, Li L, Liu D, Dai XM: Association of ELMO1 gene polymorphisms with diabetic nephropathy in chinese population. [Electronic version]. *J Endocrinol Invest* 36: 298-302, 2013

26. Bodhini D, Chidambaram M, Liju S, Revathi B, Laasya D, Sathish N, Kanthimathi S, Ghosh S, Anjana RM, Mohan V, Radha V: Association of rs11643718 SLC12A3 and rs741301

ELMO1 variants with diabetic nephropathy in south indian population. [Electronic version]. *Ann Hum Genet* 80: 336-341, 2016

27. Mehrabzadeh M, Pasalar P, Karimi M, Abdollahi M, Daneshpour M, Asadolahpour E, Razi F: Association between ELMO1 gene polymorphisms and diabetic nephropathy in an iranian population. [Electronic version]. *J Diabetes Metab Disord* 15: 43, 2016

28. Craig DW, Millis MP, DiStefano JK: Genome-wide SNP genotyping study using pooled DNA to identify candidate markers mediating susceptibility to end-stage renal disease attributed to type 1 diabetes. [Electronic version]. *Diabet Med* 26: 1090-1098, 2009

29. Pezzolesi MG, Poznik GD, Mychaleckyj JC, Paterson AD, Barati MT, Klein JB, Ng DPK, Placha G, Canani LH, Bochenski J, Waggott D, Merchant ML, Krolewski B, Mirea L, Wanic K, Katavetin P, Kure M, Wolkow P, Dunn JS, Smiles A, Walker WH, Boright AP, Bull SB, 'DCCT/EDIC Research Group', Doria A, Rogus JJ, Rich SS, Warram JH, Krolewski AS: Genome-wide association scan for diabetic nephropathy susceptibility genes in type 1 diabetes. [Electronic version]. *Diabetes* 58: 1403-1410, 2009

30. Freedman BI, Langefeld CD, Lu L, Divers J, Comeau ME, Kopp JB, Winkler CA, Nelson GW, Johnson RC, Palmer ND, Hicks PJ, Bostrom MA, Cooke JN, McDonough CW, Bowden DW: Differential effects of MYH9 and APOL1 risk variants on FRMD3 association with diabetic ESRD in african americans. [Electronic version]. *PLoS Genet* 7: e1002150, 2011

31. Pezzolesi MG, Jeong J, Smiles AM, Skupien J, Mychaleckyj JC, Rich SS, Warram JH, Krolewski AS: Family-based association analysis confirms the role of the chromosome 9q21.32 locus in the susceptibility of diabetic nephropathy. [Electronic version]. *PLoS One* 8: e60301, 2013

32. Maeda S, Araki S, Babazono T, Toyoda M, Umezono T, Kawai K, Imanishi M, Uzu T, Watada H, Suzuki D, Kashiwagi A, Iwamoto Y, Kaku K, Kawamori R, Nakamura Y: Replication study for the association between four loci identified by a genome-wide association study on european american subjects with type 1 diabetes and susceptibility to diabetic nephropathy in japanese subjects with type 2 diabetes. [Electronic version]. *Diabetes* 59: 2075-2079, 2010

33. Pezzolesi MG, Poznik GD, Skupien J, Smiles AM, Mychaleckyj JC, Rich SS, Warram JH, Krolewski AS: An intergenic region on chromosome 13q33.3 is associated with the susceptibility to kidney disease in type 1 and 2 diabetes. [Electronic version]. *Kidney Int* 80: 105-111, 2011

34. Pezzolesi MG, Skupien J, Mychaleckyj JC, Warram JH, Krolewski AS: Insights to the genetics of diabetic nephropathy through a genome-wide association study of the GoKinD collection. [Electronic version]. *Semin Nephrol* 30: 126-140, 2010

35. Germain M, Pezzolesi MG, Sandholm N, McKnight AJ, Susztak K, Lajer M, Forsblom C, Marre M, Parving HH, Rossing P, Toppila I, Skupien J, Roussel R, Ko YA, Ledo N, Folkersen L, Civelek M, Maxwell AP, Tregouet DA, Groop PH, Tarnow L, Hadjadj S: SORBS1 gene,

a new candidate for diabetic nephropathy: Results from a multi-stage genome-wide association study in patients with type 1 diabetes. [Electronic version]. *Diabetologia* 58: 543-548, 2015

36. Sandholm N, Salem RM, McKnight AJ, Brennan EP, Forsblom C, Isakova T, McKay GJ, Williams WW, Sadlier DM, Makinen VP, Swan EJ, Palmer C, Boright AP, Ahlqvist E, Deshmukh HA, Keller BJ, Huang H, Ahola AJ, Fagerholm E, Gordin D, Harjutsalo V, He B, Heikkila O, Hietala K, Kyto J, Lahermo P, Lehto M, Lithovius R, Osterholm AM, Parkkonen M, Pitkaniemi J, Rosengard-Barlund M, Saraheimo M, Sarti C, Soderlund J, Soro-Paavonen A, Syreeni A, Thorn LM, Tikkanen H, Tolonen N, Tryggvason K, Tuomilehto J, Waden J, Gill GV, Prior S, Guiducci C, Mirel DB, Taylor A, Hosseini SM, DCCT/EDIC Research Group, Parving HH, Rossing P, Tarnow L, Ladenvall C, Alhenc-Gelas F, Lefebvre P, Rigalleau V, Roussel R, Tregouet DA, Maestroni A, Maestroni S, Falhammar H, Gu T, Mollsten A, Cimponeriu D, Ioana M, Mota M, Mota E, Serafinceanu C, Stavarachi M, Hanson RL, Nelson RG, Kretzler M, Colhoun HM, Panduru NM, Gu HF, Brismar K, Zerbini G, Hadjadj S, Marre M, Groop L, Lajer M, Bull SB, Waggott D, Paterson AD, Savage DA, Bain SC, Martin F, Hirschhorn JN, Godson C, Florez JC, Groop PH, Maxwell AP: New susceptibility loci associated with kidney disease in type 1 diabetes. [Electronic version]. *PLoS Genet* 8: e1002921, 2012

37. Sambo F, Malovini A, Sandholm N, Stavarachi M, Forsblom C, Makinen VP, Harjutsalo V, Lithovius R, Gordin D, Parkkonen M, Saraheimo M, Thorn LM, Tolonen N, Waden J, He B, Osterholm AM, Tuomilehto J, Lajer M, Salem RM, McKnight AJ, The GENIE Consortium, Tarnow L, Panduru NM, Barbarini N, Di Camillo B, Toffolo GM, Tryggvason K, Bellazzi R, Cobelli C, The FinnDiane Study Group, Groop PH: Novel genetic susceptibility loci for diabetic end-stage renal disease identified through robust naive bayes classification. *Diabetologia* 57: 1611-1622, 2014

38. Veikkolainen V, Naillat F, Railo A, Chi L, Manninen A, Hohenstein P, Hastie N, Vainio S, Elenius K: ErbB4 modulates tubular cell polarity and lumen diameter during kidney development. [Electronic version]. *J Am Soc Nephrol* 23: 112-122, 2012

39. Paatero I, & Elenius K: ErbB4 and its isoforms: Patentable drug targets? [Electronic version]. *Recent Patents on DNA & Gene Sequences* 2: 27-33, 2008

40. Lee HW, Khan SQ, Khaliqdina S, Altintas MM, Grahammer F, Zhao JL, Koh KH, Tardi NJ, Faridi MH, Geraghty T, Cimbaluk DJ, Susztak K, Moita LF, Baltimore D, Tharaux PL, Huber TB, Kretzler M, Bitzer M, Reiser J, Gupta V: Absence of miR-146a in podocytes increases risk of diabetic glomerulopathy via up-regulation of ErbB4 and notch-1. [Electronic version]. *J Biol Chem* 292: 732-747, 2017

41. Sandholm N, McKnight AJ, Salem RM, Brennan EP, Forsblom C, Harjutsalo V, Makinen VP, McKay GJ, Sadlier DM, Williams WW, Martin F, Panduru NM, Tarnow L, Tuomilehto J, Tryggvason K, Zerbini G, Comeau ME, Langefeld CD, FIND Consortium, Godson C, Hirschhorn JN, Maxwell AP, Florez JC, Groop PH, FinnDiane Study Group and the GENIE

Consortium: Chromosome 2q31.1 associates with ESRD in women with type 1 diabetes. [Electronic version]. *J Am Soc Nephrol* 24: 1537-1543, 2013

42. Woroniecka KI, Park AS, Mohtat D, Thomas DB, Pullman JM, Susztak K: Transcriptome analysis of human diabetic kidney disease. [Electronic version]. *Diabetes* 60: 2354-2369, 2011

43. Stoner M, Wang F, Wormke M, Nguyen T, Samudio I, Vyhlidal C, Marme D, Finkenzeller G, Safe S: Inhibition of vascular endothelial growth factor expression in HEC1A endometrial cancer cells through interactions of estrogen receptor alpha and Sp3 proteins. [Electronic version]. *J Biol Chem* 275: 22769-22779, 2000

44. Iyengar SK, Sedor JR, Freedman BI, Kao WH, Kretzler M, Keller BJ, Abboud HE, Adler SG, Best LG, Bowden DW, Burlock A, Chen YD, Cole SA, Comeau ME, Curtis JM, Divers J, Drechsler C, Duggirala R, Elston RC, Guo X, Huang H, Hoffmann MM, Howard BV, Ipp E, Kimmel PL, Klag MJ, Knowler WC, Kohn OF, Leak TS, Leehey DJ, Li M, Malhotra A, Marz W, Nair V, Nelson RG, Nicholas SB, O'Brien SJ, Pahl MV, Parekh RS, Pezzolesi MG, Rasooly RS, Rotimi CN, Rotter JI, Schelling JR, Seldin MF, Shah VO, Smiles AM, Smith MW, Taylor KD, Thameem F, Thornley-Brown DP, Truitt BJ, Wanner C, Weil EJ, Winkler CA, Zager PG, Igo RP,Jr, Hanson RL, Langefeld CD, Family Investigation of Nephropathy and Diabetes (FIND): Genome-wide association and trans-ethnic meta-analysis for advanced diabetic kidney disease: Family investigation of nephropathy and diabetes (FIND). [Electronic version]. *PLoS Genet* 11: e1005352, 2015

45. Soundararajan R, Ziera T, Koo E, Ling K, Wang J, Borden SA, Pearce D: Scaffold protein connector enhancer of kinase suppressor of ras isoform 3 (CNK3) coordinates assembly of a multiprotein epithelial sodium channel (ENaC)-regulatory complex. [Electronic version]. *J Biol Chem* 287: 33014-33025, 2012

46. Mogensen CE, & Christensen CK: Predicting diabetic nephropathy in insulin-dependent patients. [Electronic version]. *N Engl J Med* 311: 89-93, 1984

47. Sandholm N, Forsblom C, Makinen VP, McKnight AJ, Osterholm AM, He B, Harjutsalo V, Lithovius R, Gordin D, Parkkonen M, Saraheimo M, Thorn LM, Tolonen N, Waden J, Tuomilehto J, Lajer M, Ahlqvist E, Mollsten A, Marcovecchio ML, Cooper J, Dunger D, Paterson AD, Zerbini G, Groop L, SUMMIT Consortium, Tarnow L, Maxwell AP, Tryggvason K, Groop PH, FinnDiane Study Group: Genome-wide association study of urinary albumin excretion rate in patients with type 1 diabetes. [Electronic version]. *Diabetologia* 57: 1143-1153, 2014

48. Köttgen A, Glazer NL, Dehghan A, Hwang SJ, Katz R, Li M, Yang Q, Gudnason V, Launer LJ, Harris TB, Smith AV, Arking DE, Astor BC, Boerwinkle E, Ehret GB, Ruczinski I, Scharpf RB, Chen YD, de Boer IH, Haritunians T, Lumley T, Sarnak M, Siscovick D, Benjamin EJ, Levy D, Upadhyay A, Aulchenko YS, Hofman A, Rivadeneira F, Uitterlinden AG, van Duijn CM, Chasman DI, Pare G, Ridker PM, Kao WH, Witteman JC, Coresh J,

Shlipak MG, Fox CS: Multiple loci associated with indices of renal function and chronic kidney disease. [Electronic version]. *Nat Genet* 41: 712-717, 2009

49. Köttgen A, Pattaro C, Boger CA, Fuchsberger C, Olden M, Glazer NL, Parsa A, Gao X, Yang Q, Smith AV, O'Connell JR, Li M, Schmidt H, Tanaka T, Isaacs A, Ketkar S, Hwang SJ, Johnson AD, Dehghan A, Teumer A, Pare G, Atkinson EJ, Zeller T, Lohman K, Cornelis MC, Probst-Hensch NM, Kronenberg F, Tonjes A, Hayward C, Aspelund T, Eiriksdottir G, Launer LJ, Harris TB, Rampersaud E, Mitchell BD, Arking DE, Boerwinkle E, Struchalin M, Cavalieri M, Singleton A, Giallauria F, Metter J, de Boer IH, Haritunians T, Lumley T, Siscovick D, Psaty BM, Zillikens MC, Oostra BA, Feitosa M, Province M, de Andrade M, Turner ST, Schillert A, Ziegler A, Wild PS, Schnabel RB, Wilde S, Munzel TF, Leak TS, Illig T, Klopp N, Meisinger C, Wichmann HE, Koenig W, Zgaga L, Zemunik T, Kolcic I, Minelli C, Hu FB, Johansson A, Igl W, Zaboli G, Wild SH, Wright AF, Campbell H, Ellinghaus D, Schreiber S, Aulchenko YS, Felix JF, Rivadeneira F, Uitterlinden AG, Hofman A, Imboden M, Nitsch D, Brandstatter A, Kollerits B, Kedenko L, Magi R, Stumvoll M, Kovacs P, Boban M, Campbell S, Endlich K, Volzke H, Kroemer HK, Nauck M, Volker U, Polasek O, Vitart V, Badola S, Parker AN, Ridker PM, Kardia SL, Blankenberg S, Liu Y, Curhan GC, Franke A, Rochat T, Paulweber B, Prokopenko I, Wang W, Gudnason V, Shuldiner AR, Coresh J, Schmidt R, Ferrucci L, Shlipak MG, van Duijn CM, Borecki I, Kramer BK, Rudan I, Gyllensten U, Wilson JF, Witteman JC, Pramstaller PP, Rettig R, Hastie N, Chasman DI, Kao WH, Heid IM, Fox CS: New loci associated with kidney function and chronic kidney disease. [Electronic version]. *Nat Genet* 42: 376-384, 2010

50. Deshmukh HA, Palmer CN, Morris AD, Colhoun HM: Investigation of known estimated glomerular filtration rate loci in patients with type 2 diabetes. [Electronic version]. *Diabet Med* 30: 1230-1235, 2013

51. McDonough CW, Palmer ND, Hicks PJ, Roh BH, An SS, Cooke JN, Hester JM, Wing MR, Bostrom MA, Rudock ME, Lewis JP, Talbert ME, Blevins RA, Lu L, Ng MC, Sale MM, Divers J, Langefeld CD, Freedman BI, Bowden DW: A genome-wide association study for diabetic nephropathy genes in african americans. [Electronic version]. *Kidney Int* 79: 563-572, 2011

52. Pattaro C, Teumer A, Gorski M, Chu AY, Li M, Mijatovic V, Garnaas M, Tin A, Sorice R, Li Y, Taliun D, Olden M, Foster M, Yang Q, Chen MH, Pers TH, Johnson AD, Ko YA, Fuchsberger C, Tayo B, Nalls M, Feitosa MF, Isaacs A, Dehghan A, d'Adamo P, Adeyemo A, Dieffenbach AK, Zonderman AB, Nolte IM, van der Most PJ, Wright AF, Shuldiner AR, Morrison AC, Hofman A, Smith AV, Dreisbach AW, Franke A, Uitterlinden AG, Metspalu A, Tonjes A, Lupo A, Robino A, Johansson A, Demirkan A, Kollerits B, Freedman BI, Ponte B, Oostra BA, Paulweber B, Kramer BK, Mitchell BD, Buckley BM, Peralta CA, Hayward C, Helmer C, Rotimi CN, Shaffer CM, Muller C, Sala C, van Duijn CM, Saint-Pierre A, Ackermann D, Shriner D, Ruggiero D, Toniolo D, Lu Y, Cusi D, Czamara D, Ellinghaus D, Siscovick DS, Ruderfer D, Gieger C, Grallert H, Rochtchina E, Atkinson EJ, Holliday EG, Boerwinkle E, Salvi E, Bottinger EP, Murgia F, Rivadeneira F, Ernst F, Kronenberg F, Hu FB, Navis GJ, Curhan GC, Ehret GB, Homuth G, Coassin S, Thun GA, Pistis G, Gambaro G, Malerba G, Montgomery GW, Eiriksdottir G, Jacobs G, Li G, Wichmann HE, Campbell H,

Schmidt H, Wallaschofski H, Volzke H, Brenner H, Kroemer HK, Kramer H, Lin H, Leach IM, Ford I, Guessous I, Rudan I, Prokopenko I, Borecki I, Heid IM, Kolcic I, Persico I, Jukema JW, Wilson JF, Felix JF, Divers J, Lambert JC, Stafford JM, Gaspoz JM, Smith JA, Faul JD, Wang JJ, Ding J, Hirschhorn JN, Attia J, Whitfield JB, Chalmers J, Viikari J, Coresh J, Denny JC, Karjalainen J, Fernandes JK, Endlich K, Butterbach K, Keene KL, Lohman K, Portas L, Launer LJ, Lyytikainen LP, Yengo L, Franke L, Ferrucci L, Rose LM, Kedenko L, Rao M, Struchalin M, Kleber ME, Cavalieri M, Haun M, Cornelis MC, Ciullo M, Pirastu M, de Andrade M, McEvoy MA, Woodward M, Adam M, Cocca M, Nauck M, Imboden M, Waldenberger M, Pruijm M, Metzger M, Stumvoll M, Evans MK, Sale MM, Kahonen M, Boban M, Bochud M, Rheinberger M, Verweij N, Bouatia-Naji N, Martin NG, Hastie N, Probst-Hensch N, Soranzo N, Devuyst O, Raitakari O, Gottesman O, Franco OH, Polasek O, Gasparini P, Munroe PB, Ridker PM, Mitchell P, Muntner P, Meisinger C, Smit JH, ICBP Consortium, AGEN Consortium, CARDIOGRAM, CHARGe-Heart Failure Group, ECHOGen Consortium, Kovacs P, Wild PS, Froguel P, Rettig R, Magi R, Biffar R, Schmidt R, Middelberg RP, Carroll RJ, Penninx BW, Scott RJ, Katz R, Sedaghat S, Wild SH, Kardia SL, Ulivi S, Hwang SJ, Enroth S, Kloiber S, Trompet S, Stengel B, Hancock SJ, Turner ST, Rosas SE, Stracke S, Harris TB, Zeller T, Zemunik T, Lehtimaki T, Illig T, Aspelund T, Nikopensius T, Esko T, Tanaka T, Gyllensten U, Volker U, Emilsson V, Vitart V, Aalto V, Gudnason V, Chouraki V, Chen WM, Igl W, Marz W, Koenig W, Lieb W, Loos RJ, Liu Y, Snieder H, Pramstaller PP, Parsa A, O'Connell JR, Susztak K, Hamet P, Tremblay J, de Boer IH, Boger CA, Goessling W, Chasman DI, Kottgen A, Kao WH, Fox CS: Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function. [Electronic version]. *Nat Commun* 7: 10023, 2016

53. Teumer A, Tin A, Sorice R, Gorski M, Yeo NC, Chu AY, Li M, Li Y, Mijatovic V, Ko YA, Taliun D, Luciani A, Chen MH, Yang Q, Foster MC, Olden M, Hiraki LT, Tayo BO, Fuchsberger C, Dieffenbach AK, Shuldiner AR, Smith AV, Zappa AM, Lupo A, Kollerits B, Ponte B, Stengel B, Kramer BK, Paulweber B, Mitchell BD, Hayward C, Helmer C, Meisinger C, Gieger C, Shaffer CM, Muller C, Langenberg C, Ackermann D, Siscovick D, DCCT/EDIC, Boerwinkle E, Kronenberg F, Ehret GB, Homuth G, Waeber G, Navis G, Gambaro G, Malerba G, Eiriksdottir G, Li G, Wichmann HE, Grallert H, Wallaschofski H, Volzke H, Brenner H, Kramer H, Mateo Leach I, Rudan I, Hillege HL, Beckmann JS, Lambert JC, Luan J, Zhao JH, Chalmers J, Coresh J, Denny JC, Butterbach K, Launer LJ, Ferrucci L, Kedenko L, Haun M, Metzger M, Woodward M, Hoffman MJ, Nauck M, Waldenberger M, Pruijm M, Bochud M, Rheinberger M, Verweij N, Wareham NJ, Endlich N, Soranzo N, Polasek O, van der Harst P, Pramstaller PP, Vollenweider P, Wild PS, Gansevoort RT, Rettig R, Biffar R, Carroll RJ, Katz R, Loos RJ, Hwang SJ, Coassin S, Bergmann S, Rosas SE, Stracke S, Harris TB, Corre T, Zeller T, Illig T, Aspelund T, Tanaka T, Lendeckel U, Volker U, Gudnason V, Chouraki V, Koenig W, Kutalik Z, O'Connell JR, Parsa A, Heid IM, Paterson AD, de Boer IH, Devuyst O, Lazar J, Endlich K, Susztak K, Tremblay J, Hamet P, Jacob HJ, Boger CA, Fox CS, Pattaro C, Kottgen A: Genome-wide association studies identify genetic loci associated with albuminuria in diabetes. [Electronic version]. *Diabetes* 65: 803-817, 2016

54. Böger CA, Chen MH, Tin A, Olden M, Kottgen A, de Boer IH, Fuchsberger C, O'Seaghdha CM, Pattaro C, Teumer A, Liu CT, Glazer NL, Li M, O'Connell JR, Tanaka T, Peralta CA, Kutalik Z, Luan J, Zhao JH, Hwang SJ, Akylbekova E, Kramer H, van der Harst P, Smith

AV, Lohman K, de Andrade M, Hayward C, Kollerits B, Tonjes A, Aspelund T, Ingelsson E, Eiriksdottir G, Launer LJ, Harris TB, Shuldiner AR, Mitchell BD, Arking DE, Franceschini N, Boerwinkle E, Egan J, Hernandez D, Reilly M, Townsend RR, Lumley T, Siscovick DS, Psaty BM, Kestenbaum B, Haritunians T, Bergmann S, Vollenweider P, Waeber G, Mooser V, Waterworth D, Johnson AD, Florez JC, Meigs JB, Lu X, Turner ST, Atkinson EJ, Leak TS, Aasarod K, Skorpen F, Syvanen AC, Illig T, Baumert J, Koenig W, Kramer BK, Devuyst O, Mychaleckyj JC, Minelli C, Bakker SJ, Kedenko L, Paulweber B, Coassin S, Endlich K, Kroemer HK, Biffar R, Stracke S, Volzke H, Stumvoll M, Magi R, Campbell H, Vitart V, Hastie ND, Gudnason V, Kardia SL, Liu Y, Polasek O, Curhan G, Kronenberg F, Prokopenko I, Rudan I, Arnlov J, Hallan S, Navis G, CKDGen Consortium, Parsa A, Ferrucci L, Coresh J, Shlipak MG, Bull SB, Paterson NJ, Wichmann HE, Wareham NJ, Loos RJ, Rotter JI, Pramstaller PP, Cupples LA, Beckmann JS, Yang Q, Heid IM, Rettig R, Dreisbach AW, Bochud M, Fox CS, Kao WH: CUBN is a gene locus for albuminuria. [Electronic version]. *J Am Soc Nephrol* 22: 555-570, 2011

55. Bonomo JA, Guan M, Ng MC, Palmer ND, Hicks PJ, Keaton JM, Lea JP, Langefeld CD, Freedman BI, Bowden DW: The ras responsive transcription factor RREB1 is a novel candidate gene for type 2 diabetes associated end-stage kidney disease. [Electronic version]. *Hum Mol Genet* 23: 6441-6447, 2014

56. The DCCT Research Group: Clustering of long-term complications in families with diabetes in the diabetes control and complications trial. [Electronic version]. *Diabetes* 46: 1829-1839, 1997

57. Rema M, Saravanan G, Deepa R, Mohan V: Familial clustering of diabetic retinopathy in south indian type 2 diabetic patients. [Electronic version]. *Diabet Med* 19: 910-916, 2002

58. Hallman DM, Huber JC,Jr, Gonzalez VH, Klein BE, Klein R, Hanis CL: Familial aggregation of severity of diabetic retinopathy in mexican americans from starr county, texas. [Electronic version]. *Diabetes Care* 28: 1163-1168, 2005

59. Monti MC, Lonsdale JT, Montomoli C, Montross R, Schlag E, Greenberg DA: Familial risk factors for microvascular complications and differential male-female risk in a large cohort of american families with type 1 diabetes. [Electronic version]. *J Clin Endocrinol Metab* 92: 4650-4655, 2007

60. Looker HC, Nelson RG, Chew E, Klein R, Klein BE, Knowler WC, Hanson RL: Genome-wide linkage analyses to identify loci for diabetic retinopathy. [Electronic version]. *Diabetes* 56: 1160-1166, 2007

61. Hietala K, Forsblom C, Summanen P, Groop PH, FinnDiane Study Group: Heritability of proliferative diabetic retinopathy. [Electronic version]. *Diabetes* 57: 2176-2180, 2008

62. Arar NH, Freedman BI, Adler SG, Iyengar SK, Chew EY, Davis MD, Satko SG, Bowden DW, Duggirala R, Elston RC, Guo X, Hanson RL, Igo RP,Jr, Ipp E, Kimmel PL, Knowler WC, Molineros J, Nelson RG, Pahl MV, Quade SR, Rasooly RS, Rotter JI, Saad MF, Scavini M,

Schelling JR, Sedor JR, Shah VO, Zager PG, Abboud HE, Family Investigation of Nephropathy and Diabetes Research Group: Heritability of the severity of diabetic retinopathy: The FIND-eye study. [Electronic version]. *Invest Ophthalmol Vis Sci* 49: 3839-3845, 2008

63. Uhlmann K, Kovacs P, Boettcher Y, Hammes HP, Paschke R: Genetics of diabetic retinopathy. [Electronic version]. *Exp Clin Endocrinol Diabetes* 114: 275-294, 2006

64. Sobrin L, Green T, Sim X, Jensen RA, Tai ES, Tay WT, Wang JJ, Mitchell P, Sandholm N, Liu Y, Hietala K, Iyengar SK, Family Investigation of Nephropathy and Diabetes-Eye Research Group, Brooks M, Buraczynska M, Van Zuydam N, Smith AV, Gudnason V, Doney AS, Morris AD, Leese GP, Palmer CN, Wellcome Trust Case Control Consortium 2, Swaroop A, Taylor HA,Jr, Wilson JG, Penman A, Chen CJ, Groop PH, Saw SM, Aung T, Klein BE, Rotter JI, Siscovick DS, Cotch MF, Klein R, Daly MJ, Wong TY: Candidate gene association study for diabetic retinopathy in persons with type 2 diabetes: The candidate gene association resource (CARe). [Electronic version]. *Invest Ophthalmol Vis Sci* 52: 7593-7602, 2011

65. Abhary S, Hewitt AW, Burdon KP, Craig JE: A systematic meta-analysis of genetic association studies for diabetic retinopathy. [Electronic version]. *Diabetes* 58: 2137-2147, 2009

66. Porta M, Toppila I, Sandholm N, Hosseini SM, Forsblom C, Hietala K, Borio L, Harjutsalo V, Klein BE, Klein R, Paterson AD, DCCT/EDIC Research Group, Groop PH, FinnDiane Study Group: Variation in SLC19A3 and protection from microvascular damage in type 1 diabetes. [Electronic version]. *Diabetes* 65: 1022-1030, 2016

67. Imperatore G, Hanson RL, Pettitt DJ, Kobes S, Bennett PH, Knowler WC: Sib-pair linkage analysis for susceptibility genes for microvascular complications among pima indians with type 2 diabetes. pima diabetes genes group. [Electronic version]. *Diabetes* 47: 821-830, 1998

68. Hallman DM, Boerwinkle E, Gonzalez VH, Klein BE, Klein R, Hanis CL: A genome-wide linkage scan for diabetic retinopathy susceptibility genes in mexican americans with type 2 diabetes from starr county, texas. [Electronic version]. *Diabetes* 56: 1167-1173, 2007

69. Grassi MA, Tikhomirov A, Ramalingam S, Below JE, Cox NJ, Nicolae DL: Genome-wide meta-analysis for severe diabetic retinopathy. [Electronic version]. *Hum Mol Genet* 20: 2472-2481, 2011

70. Sheu WH, Kuo JZ, Lee IT, Hung YJ, Lee WJ, Tsai HY, Wang JS, Goodarzi MO, Klein R, Klein BE, Ipp E, Lin SY, Guo X, Hsieh CH, Taylor KD, Fu CP, Rotter JI, Chen YD: Genome-wide association study in a chinese population with diabetic retinopathy. [Electronic version]. *Hum Mol Genet* 22: 3165-3173, 2013

71. Awata T, Yamashita H, Kurihara S, Morita-Ohkubo T, Miyashita Y, Katayama S, Mori K, Yoneya S, Kohda M, Okazaki Y, Maruyama T, Shimada A, Yasuda K, Nishida N, Tokunaga K, Koike A: A genome-wide association study for diabetic retinopathy in a japanese

population: Potential association with a long intergenic non-coding RNA. [Electronic version]. *PLoS One* 9: e111715, 2014

72. Huang YC, Lin JM, Lin HJ, Chen CC, Chen SY, Tsai CH, Tsai FJ: Genome-wide association study of diabetic retinopathy in a taiwanese population. [Electronic version]. *Ophthalmology* 118: 642-648, 2011

73. Fu YP, Hallman DM, Gonzalez VH, Klein BE, Klein R, Hayes MG, Cox NJ, Bell GI, Hanis CL: Identification of diabetic retinopathy genes through a genome-wide association study among mexican-americans from starr county, texas. [Electronic version]. *J Ophthalmol* 2010: 10.1155/2010/861291. Epub 2010 Sep 2, 2010

74. Burdon KP, Fogarty RD, Shen W, Abhary S, Kaidonis G, Appukuttan B, Hewitt AW, Sharma S, Daniell M, Essex RW, Chang JH, Klebe S, Lake SR, Pal B, Jenkins A, Govindarjan G, Sundaresan P, Lamoureux EL, Ramasamy K, Pefkianaki M, Hykin PG, Petrovsky N, Brown MA, Gillies MC, Craig JE: Genome-wide association study for sight-threatening diabetic retinopathy reveals association with genetic variation near the GRB2 gene. [Electronic version]. *Diabetologia* 58: 2288-2297, 2015

75. McAuley AK, Wang JJ, Dirani M, Connell PP, Lamoureux E, Hewitt AW: Replication of genetic loci implicated in diabetic retinopathy. [Electronic version]. *Invest Ophthalmol Vis Sci* 55: 1666-1671, 2014

76. Hosseini SM, Boright AP, Sun L, Canty AJ, Bull SB, Klein BE, Klein R, DCCT/EDIC Research Group, Paterson AD: The association of previously reported polymorphisms for microvascular complications in a meta-analysis of diabetic retinopathy. [Electronic version]. *Hum Genet* 134: 247-257, 2015

77. Grassi MA, Tikhomirov A, Ramalingam S, Lee KE, Hosseini SM, Klein BE, Klein R, Lussier YA, Cox NJ, Nicolae DL: Replication analysis for severe diabetic retinopathy. [Electronic version]. *Invest Ophthalmol Vis Sci* 53: 2377-2381, 2012

78. Peng D, Wang J, Zhang R, Jiang F, Tang S, Chen M, Yan J, Sun X, Wang S, Wang T, Yan D, Bao Y, Hu C, Jia W: Common variants in or near ZNRF1, COLEC12, SCYL1BP1 and API5 are associated with diabetic retinopathy in chinese patients with type 2 diabetes. [Electronic version]. *Diabetologia* 58: 1231-1238, 2015

79. Cheung CY, Hui EY, Lee CH, Kwok KH, Gangwani RA, Li KK, Chan JC, Woo YC, Chow WS, Yuen MM, Wong RL, Fong CH, Xu A, Wong DS, Sham PC, Lam KS: Impact of genetic loci identified in genome-wide association studies on diabetic retinopathy in chinese patients with type 2 diabetes. [Electronic version]. *Invest Ophthalmol Vis Sci* 57: 5518-5524, 2016

80. Shtir C, Aldahmesh MA, Al-Dahmash S, Abboud E, Alkuraya H, Abouammoh MA, Nowailaty SR, Al-Thubaiti G, Naim EA, ALYounes B, Binhumaid FS, ALOtaibi AB, Altamimi AS, Alamer FH, Hashem M, Abouelhoda M, Monies D, Alkuraya FS: Exome-based case-control

association study using extreme phenotype design reveals novel candidates with protective effect in diabetic retinopathy. [Electronic version]. *Hum Genet* 135: 193-200, 2016

81. Meng W, Deshmukh HA, van Zuydam NR, Liu Y, Donnelly LA, Zhou K, Wellcome Trust Case Control Consortium 2 (WTCCC2), Surrogate Markers for Micro- and Macro-Vascular Hard Endpoints for Innovative Diabetes Tools (SUMMIT) Study Group, Morris AD, Colhoun HM, Palmer CN, Smith BH: A genome-wide association study suggests an association of Chr8p21.3 (GFRA2) with diabetic neuropathic pain. [Electronic version]. *Eur J Pain* 19: 392-399, 2015

82. Meng W, Deshmukh HA, Donnelly LA, Wellcome Trust Case Control Consortium 2 (WTCCC2), Surrogate markers for Micro- and Macro-vascular hard endpoints for Innovative diabetes Tools (SUMMIT) study group, Torrance N, Colhoun HM, Palmer CN, Smith BH: A genome-wide association study provides evidence of sex-specific involvement of Chr1p35.1 (ZSCAN20-TLR12P) and Chr8p23.1 (HMGB1P46) with diabetic neuropathic pain. [Electronic version]. *EBioMedicine* 2: 1386-1393, 2015

83. Singh JP, Larson MG, O'Donnell CJ, Tsuji H, Evans JC, Levy D: Heritability of heart rate variability: The framingham heart study. [Electronic version]. *Circulation* 99: 2251-2254, 1999

84. Osztovits J, Horvath T, Littvay L, Steinbach R, Jermendy A, Tarnoki A, Tarnoki D, Metneki J, Kollai M, Jermendy G: Effects of genetic vs. environmental factors on cardiovascular autonomic function: A twin study. [Electronic version]. *Diabet Med* 28: 1241-1248, 2011

85. Wu S, Han Y, Hu Q, Zhang X, Cui G, Li Z, Guan Y: Effects of common polymorphisms in the MTHFR and ACE genes on diabetic peripheral neuropathy progression: A meta-analysis. [Electronic version]. *Mol Neurobiol* 2016

86. Groener JB, Reismann P, Fleming T, Kalscheuer H, Lehnhoff D, Hamann A, Roser P, Bierhaus A, Nawroth PP, Rudofsky G: C332C genotype of glyoxalase 1 and its association with late diabetic complications. [Electronic version]. *Exp Clin Endocrinol Diabetes* 121: 436-439, 2013

87. Monastiriotis C, Papanas N, Trypsianis G, Karanikola K, Veletza S, Maltezos E: The epsilon4 allele of the APOE gene is associated with more severe peripheral neuropathy in type 2 diabetic patients. [Electronic version]. *Angiology* 64: 451-455, 2013

88. Zhang X, Sun Z, Jiang H, Song X: Relationship between single nucleotide polymorphisms in the 3'-untranslated region of the vascular endothelial growth factor gene and susceptibility to diabetic peripheral neuropathy in china. [Electronic version]. *Arch Med Sci* 10: 1028-1034, 2014

89. Shah VN, Cheema BS, Kohli HS, Sharma R, Khullar M, Bhansali A: Endothelial nitric oxide synthase gene polymorphism and the risk of diabetic neuropathy in asian indian patients with type 2 diabetes. *J Diabetes Metab* 4: 243, 2013

90. Tang TS, Prior SL, Li KW, Ireland HA, Bain SC, Hurel SJ, Cooper JA, Humphries SE, Stephens JW: Association between the rs1050450 glutathione peroxidase-1 (C > T) gene variant and peripheral neuropathy in two independent samples of subjects with diabetes mellitus. [Electronic version]. *Nutr Metab Cardiovasc Dis* 22: 417-425, 2012

91. Politi C, Ciccacci C, D'Amato C, Novelli G, Borgiani P, Spallone V: Recent advances in exploring the genetic susceptibility to diabetic neuropathy. [Electronic version]. *Diabetes Res Clin Pract* 120: 198-208, 2016

92. Ziegler D, Schleicher E, Strom A, Knebel B, Fleming T, Nawroth P, Haring HU, Papanas N, Szendrodi J, Mussig K, Al-Hasani H, Roden M, GDS Group: Association of transketolase polymorphisms with measures of polyneuropathy in patients with recently diagnosed diabetes. [Electronic version]. *Diabetes Metab Res Rev* 33: 10.1002/dmrr.2811. Epub 2016 May 15, 2017

93. DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, Asian Genetic Epidemiology Network Type 2 Diabetes (AGEN-T2D) Consortium, South Asian Type 2 Diabetes (SAT2D) Consortium, Mexican American Type 2 Diabetes (MAT2D) Consortium, Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in muylti-Ethnic Samples (T2D-GENES) Consortium, Mahajan A, Go MJ, Zhang W, Below JE, Gaulton KJ, Ferreira T, Horikoshi M, Johnson AD, Ng MC, Prokopenko I, Saleheen D, Wang X, Zeggini E, Abecasis GR, Adair LS, Almgren P, Atalay M, Aung T, Baldassarre D, Balkau B, Bao Y, Barnett AH, Barroso I, Basit A, Been LF, Beilby J, Bell GI, Benediktsson R, Bergman RN, Boehm BO, Boerwinkle E, Bonnycastle LL, Burtt N, Cai Q, Campbell H, Carey J, Cauchi S, Caulfield M, Chan JC, Chang LC, Chang TJ, Chang YC, Charpentier G, Chen CH, Chen H, Chen YT, Chia KS, Chidambaram M, Chines PS, Cho NH, Cho YM, Chuang LM, Collins FS, Cornelis MC, Couper DJ, Crenshaw AT, van Dam RM, Danesh J, Das D, de Faire U, Dedoussis G, Deloukas P, Dimas AS, Dina C, Doney AS, Donnelly PJ, Dorkhan M, van Duijn C, Dupuis J, Edkins S, Elliott P, Emilsson V, Erbel R, Eriksson JG, Escobedo J, Esko T, Eury E, Florez JC, Fontanillas P, Forouhi NG, Forsen T, Fox C, Fraser RM, Frayling TM, Froguel P, Frossard P, Gao Y, Gertow K, Gieger C, Gigante B, Grallert H, Grant GB, Grrop LC, Groves CJ, Grundberg E, Guiducci C, Hamsten A, Han BG, Hara K, Hassanali N, Hattersley AT, Hayward C, Hedman AK, Herder C, Hofman A, Holmen OL, Hovingh K, Hreidarsson AB, Hu C, Hu FB, Hui J, Humphries SE, Hunt SE, Hunter DJ, Hveem K, Hydrie ZI, Ikegami H, Illig T, Ingelsson E, Islam M, Isomaa B, Jackson AU, Jafar T, James A, Jia W, Jockel KH, Jonsson A, Jowett JB, Kadowaki T, Kang HM, Kanoni S, Kao WH, Kathiresan S, Kato N, Katulanda P, Keinanen-Kiukaanniemi KM, Kelly AM, Khan H, Khaw KT, Khor CC, Kim HL, Kim S, Kim YJ, Kinnunen L, Klopp N, Kong A, Korpi-Hyovalti E, Kowlessur S, Kraft P, Kravic J, Kristensen MM, Krithika S, Kumar A, Kumate J, Kuusisto J, Kwak SH, Laakso M, Lagou V, Lakka TA, Langenberg C, Langford C, Lawrence R, Leander K, Lee JM, Lee NR, Li M, Li X, Li Y, Liang J, Liju S, Lim WY, Lind L, Lindgren CM, Lindholm E, Liu CT, Liu JJ, Lobbens S, Long J, Loos RJ, Lu W, Luan J, Lyssenko V, Ma RC, Maeda S, Magi R, Mannisto S, Matthews DR, Meigs JB, Melander O, Metspalu A, Meyer J, Mirza G, Mihailov E, Moebus S, Mohan V, Mohlke KL, Morris AD, Muhleisen TW, Muller-Nurasyid M, Musk B, Nakamura J, Nakashima E, Navarro P, Ng PK, Nica AC, Nilsson PM, Njolstad I, Nothen MM, Ohnaka K, Ong TH, Owen KR, Palmer CN, Pankow JS, Park KS, Parkin M, Pechlivanis

S, Pedersen NL, Peltonen L, Perry JR, Peters A, Pinidiyapathirage JM, Platou CG, Potter S, Price JF, Qi L, Radha V, Rallidis L, Rasheed A, Rathman W, Rauramaa R, Raychaudhuri S, Rayner NW, Rees SD, Rehnberg E, Ripatti S, Robertson N, Roden M, Rossin EJ, Rudan I, Rybin D, Saaristo TE, Salomaa V, Saltevo J, Samuel M, Sanghera DK, Saramies J, Scott J, Scott LJ, Scott RA, Segre AV, Sehmi J, Sennblad B, Shah N, Shah S, Shera AS, Shu XO, Shuldiner AR, Sigurdsson G, Sijbrands E, Silveira A, Sim X, Sivapalaratnam S, Small KS, So WY, Stancakova A, Stefansson K, Steinbach G, Steinthorsdottir V, Stirrups K, Strawbridge RJ, Stringham HM, Sun Q, Suo C, Syvanen AC, Takayanagi R, Takeuchi F, Tay WT, Teslovich TM, Thorand B, Thorleifsson G, Thorsteinsdottir U, Tikkanen E, Trakalo J, Tremoli E, Trip MD, Tsai FJ, Tuomi T, Tuomilehto J, Uitterlinden AG, Valladares-Salgado A, Vedantam S, Veglia F, Voight BF, Wang C, Wareham NJ, Wennauer R, Wickremasinghe AR, Wilsgaard T, Wilson JF, Wiltshire S, Winckler W, Wong TY, Wood AR, Wu JY, Wu Y, Yamamoto K, Yamauchi T, Yang M, Yengo L, Yokota M, Young R, Zabaneh D, Zhang F, Zhang R, Zheng W, Zimmet PZ, Altshuler D, Bowden DW, Cho YS, Cox NJ, Cruz M, Hanis CL, Kooner J, Lee JY, Seielstad M, Teo YY, Boehnke M, Parra EJ, Chambers JC, Tai ES, McCarthy MI, Morris AP: Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. [Electronic version]. *Nat Genet* 46: 234-244, 2014

94. Ma RCW, Tam CHT, Jiang G, Luk AO, Lee HM, Lim CKP, Tsui SKW, Yu W, Tomlinson B, Huang Y, Lan H-, Szeto CC, So WY, Chan JCN, TRANSCEND Consortium: Genome wide association study identifies novel loci associated with end stage renal disease in chinese patients with type 2 diabetes. *Diabetologia* 59: S21-S21, 2016

95. Rayner NW, Ahlqvist E, Deshmukh H, Van Zuydam N, Sandholm N, Ladenvall C, Lajer M, Marcovecchio L, Rurali E, SUMMIT Collaborators, SUMMIT Consortium: Genome-wide association studies of diabetic kidney disease in patients with type 2 diabetes. [Electronic version]. *Diabetologia* 58: S200-S200, 2015

96. Todd J,N., Salem R, Sandholm N, Valo E,A., Hiraki L,T., Di Liao C, Pezzolesi M,G., Smiles A, Onengut-Gumuscu S, Chen WM, McGurnaghan S, McKeigue P, McKnight A,J., Maxwell A,P., Colhoun H,M., Krolewski A,S., Paterson A,D., Rich S,S., Hirschhorn J,N., Florez J,C.: Novel genetic determinants of diabetic kidney disease. [Electronic version]. *Diabetes* 65: A100, 2016

97. Rosengard-Barlund M, Bernardi L, Fagerudd J, Mantysaari M, Af Bjorkesten CG, Lindholm H, Forsblom C, Waden J, Groop PH, FinnDiane Study Group: Early autonomic dysfunction in type 1 diabetes: A reversible disorder? [Electronic version]. *Diabetologia* 52: 1164-1172, 2009

98. Forsblom C, Harjutsalo V, Thorn LM, Waden J, Tolonen N, Saraheimo M, Gordin D, Moran JL, Thomas MC, Groop PH, FinnDiane Study Group: Competing-risk analysis of ESRD and death among patients with type 1 diabetes and macroalbuminuria. [Electronic version]. *J Am Soc Nephrol* 22: 537-544, 2011

99. Parving HH, Gall MA, Skott P, Jorgensen HE, Lokkegaard H, Jorgensen F, Nielsen B, Larsen S: Prevalence and causes of albuminuria in non-insulin-dependent diabetic patients. [Electronic version]. *Kidney Int* 41: 758-762, 1992

100. Öhman MK, Eng E, Sun Y, Österholm AM, He B, Guo J, Valo EA, Harjutsalo V, Sandholm N, Forsblom C, Groop P, Tryggvason K: Diabetic nephropathy candidate genes revealed by whole-genome sequencing in finnish type 1 diabetic sib pairs discordant for complications. *J Am Soc Nephrol* 27: 429A-Poster presentation at the American Society of Nephrology Kidney Week 2016, Chicago, IL, 2016

101. Haukka J, Sandholm N, Toppila I, Valo EA, Forsblom C, Groop P: Pedigree-based analysis of diabetic nephropathy in T1D patients. [Electronic version]. *Diabetes* 65: A73, 2016

102. Feodoroff M, Harjutsalo V, Forsblom C, Thorn L, Waden J, Tolonen N, Lithovius R, Groop PH: Smoking and progression of diabetic nephropathy in patients with type 1 diabetes. [Electronic version]. *Acta Diabetol* 2015

103. Panduru NM, Sandholm N, Forsblom C, Saraheimo M, Dahlstrom EH, Thorn LM, Gordin D, Tolonen N, Waden J, Harjutsalo V, Bierhaus A, Humpert PM, Groop PH, FinnDiane Study Group: Kidney injury molecule-1 and the loss of kidney function in diabetic nephropathy: A likely causal link in patients with type 1 diabetes. [Electronic version]. *Diabetes Care* 38: 1130-1137, 2015

104. Ahola AJ, Sandholm N, Forsblom C, Harjutsalo V, Dahlstrom E, Groop PH, FinnDiane Study Group: The serum uric acid concentration is not causally linked to diabetic nephropathy in type 1 diabetes. [Electronic version]. *Kidney Int* 91: 1178-1185, 2017

105. Todd JN, Dahlstrom EH, Salem RM, Sandholm N, Forsblom C, FinnDiane Study Group, McKnight AJ, Maxwell AP, Brennan E, Sadlier D, Godson C, Groop PH, Hirschhorn JN, Florez JC: Genetic evidence for a causal role of obesity in diabetic kidney disease. [Electronic version]. *Diabetes* 64: 4238-4246, 2015

Table 1: GWAS on DKD. Findings reaching genome-wide statistical significance (p-value < 5×10^{-8}) are highlighted with bold text.

Study	Trait	Discovery population, N (cases/ controls)	Replication/ meta-analysis, $N_{REP/META}$ (cases/ controls)*	Loci identified for DKD
Tanaka 2003[20] Shimazaki 2005[22]	DKD	Japanese T2D, N=188 (94/94)	N_{REP}=732 (466/266)	rs11643718 (*SLC12A3*) $p=8.7\times10^{-5}$, OR=2.53 rs741301 (*ELMO1*) $p=8\times10^{-6}$, OR=2.67
Maeda 2010[21]	DKD	Japanese T2D, N=188 (94/94)	N_{REP}=1312 (754 /558)	rs2268388 (*ACACB)* $p=5.35\times10^{-8}$, OR=1.61
Pezzolesi 2009[29] Pezzolesi 2010[34]	DKD	European American T1D, N=1705 (820/885)	N_{REP}=1304 (132/1172)	rs10868025 (*FRMD3*) $p=5.0\times10^{-7}$, OR=1.45 rs451041 (*CARS*) $p=3.1\times10^{-6}$, OR=1.36 Imputation suggested 4 additional loci, eg. rs7071071 (*SORBS1*) $p=4.5\times10^{-6}$
McDonough 2011[51]	ESRD	African American T2D, N=1994 (965 T2D-ESRD cases/1029 NDCtrl)	709 T2D-ESRD/ 690 NDCtrl; 1246 T2D controls w/o DKD; 1216 non-diabetic ESRD	19 potential loci for kidney disease in T2D
Sandholm 2012[36]	DKD, ESRD	Caucasian T1D. DKD: N=6231 (2916/3315); ESRD: N=6652 (1399/5253);	N_{META}=11,847	**ESRD: rs7583877 (*AFF3*) $p=1.2\times10^{-8}$, OR=1.29** **ESRD: rs12437854 (*RGMA/MCTP2*) $p=2.0\times10^{-9}$, OR=1.8** DKD: rs7588550 (*ERBB4*) $p=2.1\times10^{-7}$, OR=0.66
Sandholm 2013[41]	ESRD	Finnish T1D; N=3652; $N_{Females}$=1193 (258/935)	N_{META}=2697 (688/2009) women	**rs4972593 (*SP3/CDCA7*) $p=3.9\times10^{-8}$, OR=1.81 in women**
Sandholm 2014[47]	AER/ ACR	Finnish T1D, N=1925	N_{REP}=3750 Caucasian T1D	**rs1564939/rs10011025 (*GLRA3*) $p=1.5\times10^{-9}$ in Finnish discovery.** rs2410601 (*PSD3/SH2D4A*) $p=3.9\times10^{-6}$
Sambo 2014[37]	DKD, ESRD	Finnish T1D, N=3464 (multiple phenotypes)	N_{REP}=4263 European T1D (multiple phenotypes)	Data mining suggested 6 loci: rs12137135 (*WNT4-ZBTB40*), rs17709344 (*RGMA-MCTP2*), rs1670754 (*MAPRE1P2*), rs12917114 (*SEMA6D-SLC24A5*), rs2838302 (*SIK1*)
Germain 2015[35]	DKD	Caucasian T1D, N=1462 (683/779)	N_{META}=7861 (3661/4200)	rs1326934 (*SORBS1*) $p=0.009$, OR=0.83 in random-effect meta-analysis
Iyengar 2015[44]	DKD	multiethnic T2D, N=6197 (3223 DKD cases/ 1686 T2D ctrls/ 1288 NDCtrl)	N_{META}=13,736 (including 6229 NDCtrl)	**rs12523822 (*SCAF8/CNKSR3*) $p=5.7\times10^{-9}$, OR=0.57 in American Indians**
Teumer 2016[53]	ACR	up to 54,450 Caucasians, including 5825 diabetic (mostly T2D)	N_{META}=7787 diabetic	rs649529 (*RAB38*) $p=5.8\times10^{-7}$, rs13427836 (*HS6ST1*) $p=6.3\times10^{-7}$
Pattaro 2016[52]	eGFR, CKD	up to 133,413 Caucasians, out of which 16,477 diabetic	N_{META}=16,477 diabetic	**eGFR: rs12917707 (*UMOD*) $p=2.5\times10^{-8}$;** In diabetic subset $p<0.05$ for 19/53 loci for eGFR in general population.

Sandholm 2017[8]	DKD, CKD, ESRD	European T1D, N=5156 (multiple phenotypes)	N_{META}=12,540 Caucasian T1D (multiple phenotypes)	Suggestive associations at rs61277444 (*PTPN13),* rs7562121 (*AFF3),* rs1989248 *(CNTNAP2)* and rs72809865 *(NRG3)*

*Replication/meta-analysis population description (e.g. "European T1D") is the same as the discovery population unless otherwise stated. N_{REP}: N in replication studies, divided to (cases/controls). N_{META}: N in combined meta-analysis of discovery and replication studies. N_{META} is given, rather than N_{REP}, if joint meta-analysis was performed to obtain the final results. NDCtrl: Non-diabetic control (without kidney disease).

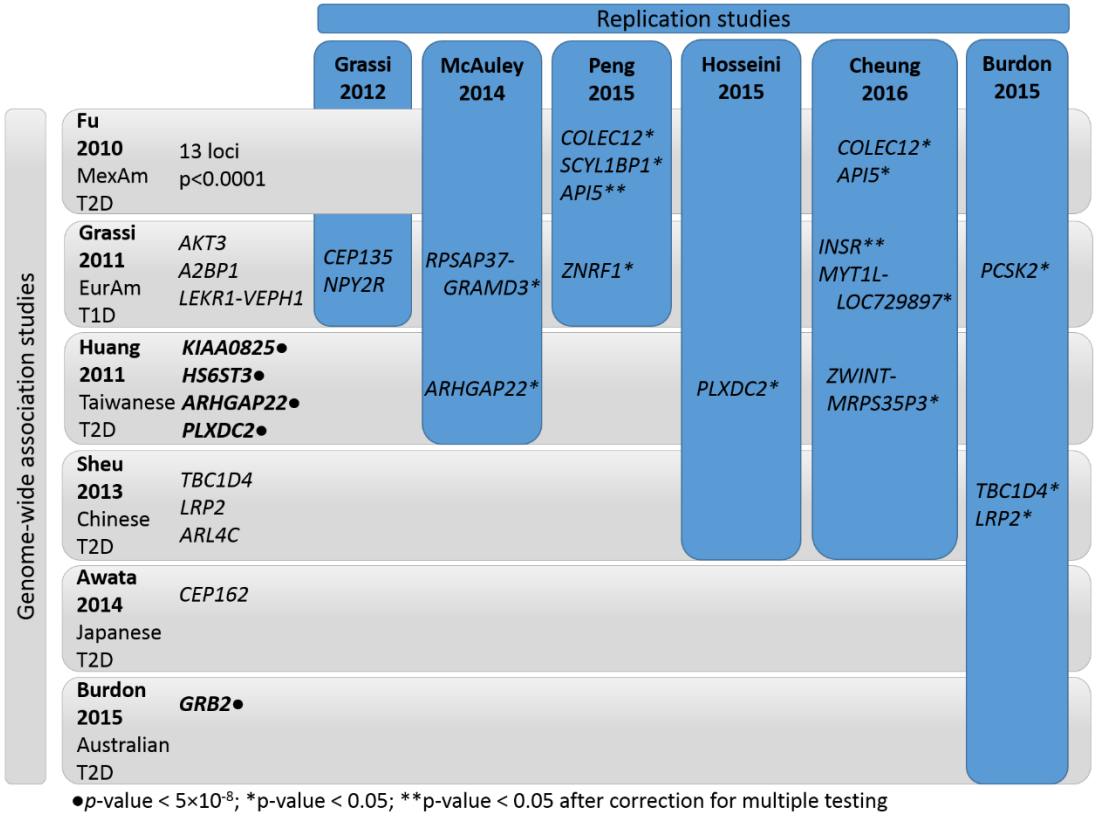

Figure 1: Genome-wide association studies on diabetic retinopathy, and subsequent replication attempts. The horizontal bars indicate GWASs and list their key findings. The vertical bars indicate replication studies; loci with evidence of replication (p<0.05) are indicated on the horizontal level corresponding to the GWAS on left. Of note, the loci are named according to one or more nearest or flanking genes, even though no functional link is established between the gene and the association signal. **p-value <0.05 after correction for multiple testing was calculated based on the number of evaluated SNPs. References for the GWAS and replication studies: Fu 2010[73]; Grassi 2011[69]; Huang 2011[72]; Sheu 2013[70]; Awata 2014[71]; Burdon 2015[74]; Grassi 2012[77]; McAuley 2014[75]; Peng 2015[78];Hosseini 2015[76]; Cheung 2016[79].