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Genetic basis of diabetic kidney disease and other diabetic complications

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Diabetic kidney disease and other long-term complications are common in diabetes, and comprise the main cause of co-morbidity and premature mortality in individuals with diabetes. While familial clustering and heritability have been reported for all diabetic complications, the genetic background and the molecular mechanisms remain poorly understood. In recent years, genome-wide association studies have identified a few susceptibility loci for the renal complications as well as for diabetic retinopathy, diabetic cardiovascular disease and mortality. As for many complex diseases, the genetic factors increase the risk of complications in concert with the environment, and certain associations seem specific for particular conditions, for example, *SP3-CDCA7* associated with end-stage renal disease only in women, or *MGMT* and variants on chromosome 5q13 associated with cardiovascular mortality only under tight glycaemic control. The characterization of the phenotypes is one of the main challenges for genetic research on diabetic complications, in addition to an urgent need to increase the number of individuals with diabetes with high quality phenotypic data to be included in future genetic studies.

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Diabetes is a true epidemic with 415 million adults with diabetes worldwide [1]. One third of these patients develop severe microvascular complications such as diabetic kidney disease (DKD), sight threatening diabetic retinopathy (DR), and diabetic neuropathy. Furthermore, individuals with diabetes carry an increased risk of cardiovascular disease (CVD), a risk that is particularly high in those with DKD. Consequently, those that develop end stage renal disease (ESRD) requiring dialysis or kidney transplant for survival have 18 times higher premature mortality compared with the general population [2].

Although there is strong evidence for a genetic influence on the development of diabetic complications, environmental factors such as exposure to high blood glucose also contribute, and the disease outcomes are likely a complex interplay between genetics, epigenetic gene regulation, and environment. In this review, we will highlight recent large-scale genetic studies on various diabetic complications. Apart from improving our understanding of the molecular mechanisms behind the diabetic complications, the genetic findings also hold promise of identifying novel biomarkers for earlier identification of patients at risk, and novel therapeutic target molecules.

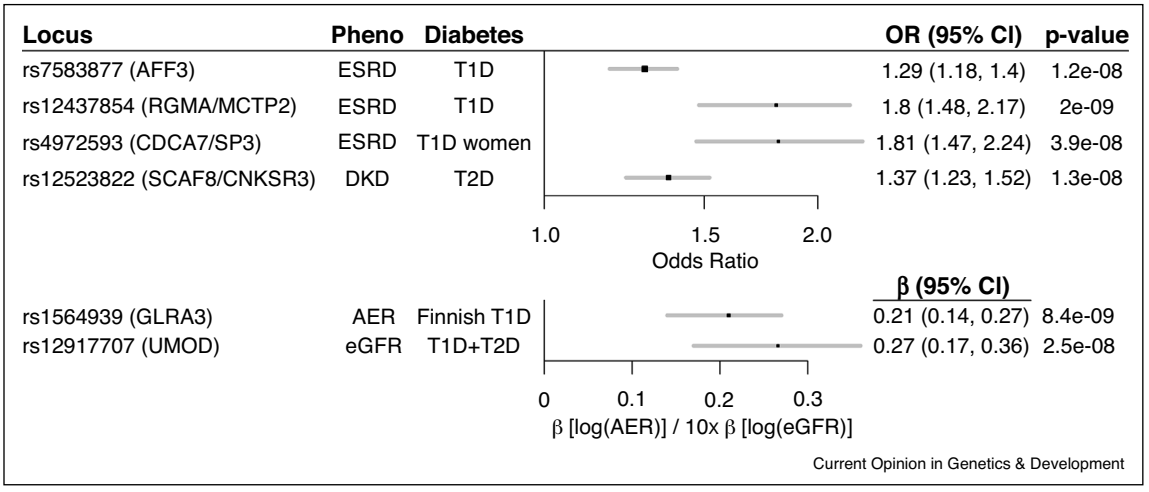
Diabetic kidney disease

Diabetic kidney disease (DKD) clusters in families [3,4]. While the 25-year cumulative incidence of DKD was 25% in diabetic siblings of probands without DKD, the risk was 43% and 58% in siblings of probands with DKD or ESRD, respectively, resulting in a more than twofold sibling risk ratio for DKD [5]. Recently, by using genome-wide genotyping data of unrelated individuals, the narrow sense heritability of DKD was estimated to be 35% [6••] .

Genome-wide association studies on DKD

Multiple candidate genes have been studied for DKD, but robust replication has been challenging [7,8]. One of the first genome-wide association studies (GWAS) on DKD suggested association at rs10868025 in the *FRMD3* gene ($P = 5.0 \times 10^{-7}$) [9], and the finding was supported by many [9–11], although not all subsequent studies [6••,8]. The first genome-wide significant findings for ESRD were reported from a GWAS meta-analysis from the GEnetics of Nephropathy — an International Effort (GENIE) consortium including 6691 individuals with T1D from three discovery cohorts, and up to 11 847 individuals in the joint meta-analysis including the replication cohorts. Variants in the *AFF3* (rs7583877, $P = 1.2 \times 10^{-8}$) and on the *RGMA — MCTP2* gene region (rs12437854, $P = 2.0 \times 10^{-9}$) were associated with ESRD (Figure 1), while suggestive evidence of association with

Figure 1



Loci reaching genome-wide significant association ($P < 5 \times 10^{-8}$) with renal complications in diabetes. Effect size estimates are given as odds ratios for diabetic kidney disease (DKD) and end stage renal disease (ESRD), but as β for continuous traits (β [log(AER)], 10 × β [log(eGFR)]). References for the loci: rs7583877 (*AFF3*) and rs12437854 (*RGMA/MCTP2*) [12]; rs4972593 (CDCA7/SP3) [13]; rs12523833 (*SCAF8/CNKSR3*) [15••]; rs1564939 (*GLRA3*) [14]; rs12917707 *(UMOD)* [16•].

DKD was found for variants in the *ERBB4* gene (rs7588550 $P = 2.1 \times 10^{-7}$) [12].

A gender-stratified GWAS identified variants between the *SP3* and *CDCA7* genes to be associated with ESRD in women with T1D, and the finding replicated in other GENIE cohorts (rs4972593 $P = 3.9 \times 10^{-8}$) [13]. Intriguingly, the nearby *SP3* shows higher expression in female glomeruli (top 0.3%), and Sp3 transcription factor directly binds to estrogen receptor α, providing a plausible explanation for the gender-specific association.

Urinary albumin excretion rate (AER) is one of the early signs of renal complications in diabetes, and commonly used to diagnose and classify DKD. A GWAS on AER in 1925 individuals with T1D from the Finnish Diabetic Nephropathy Study (FinnDiane) found variants in the *GLRA3* gene associated with AER (rs1564939 $P = 8.4 \times 10^{-9}$), however, replication in non-Finnish Europeans showed a trend in the opposite direction ($P = 0.03$), suggesting a population specific effect [14]. Replication in further Finnish individuals is ongoing to confirm the finding

A trans-ethnic GWAS meta-analysis with 6197 individuals with T2D identified rs12523822 on the *SCAF8/CNKSR3* locus associated with DKD with a particularly strong effect seen in American Indians ($P = 5.7 \times 10^{-9}$, odds ratio (OR) = 0.57). Furthermore, variants in the *MYH9* locus were near genome-wide significant in the African American group, likely due to a large proportion of the individuals with T2D with co-occurring non-diabetic renal disease, as *MYH9* is one of the main susceptibility loci for ESRD in the general population with African ancestry [15••].

GWAS on estimated glomerular filtration rate (eGFR) in 133 413 individuals from the general population identified 53 loci for eGFR. The rs12917707 in the *UMOD* gene was significantly associated with eGFR also in the subset of 16 477 individuals with diabetes (mainly T2D). Nominal association ($P < 0.05$) was found in the subset of individuals with diabetes for 19 of the lead loci [16•]. Whereas nearly all individuals with T1D and DKD show histological findings characteristic of diabetic nephropathy, in T2D only 30–50% of individuals with albuminuria have true DKD, while the rest may have kidney disease related to hypertension, overweight or ageing [17]. Thus, the genetic factors affecting eGFR in the general population may also contribute to the renal complications in individuals with T2D, while little overlap is found in T1D.

A recent GWAS in 5156 individuals with T1D from the SUrrogate markers for Micro- and Macro-vascular hard endpoints for Innovative diabetes Tools (SUMMIT) consortium utilised multiple phenotypic definitions based on various thresholds of either AER, eGFR, or both [6••]. No locus reached genome-wide significance after joint analysis including 12 540 individuals, but variants in the previously reported *AFF3* were among the lead SNPs; of note, there was a substantial overlap between this and the previous studies. Variants associated with T2D and body mass index (BMI) were associated with DKD, suggesting that metabolic changes leading to T2D, and BMI, are causal risk factors for DKD.