Genetic determinants of albuminuria and renal disease in diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) is increasing in epidemic proportions. The worldwide prevalence of diabetes was estimated to be 171 million cases in 2000 and is projected to rise to 366 million cases by 2030 [1]. Given current trends, the lifetime risk for developing T2DM is 30% in European Americans born in 2000, contrasted with 40% in African American males and 49% in African American females [2]. This global epidemic will clearly increase the development of diabetic nephropathy (DN) and cardiovascular disease (CVD) for decades to come. The dramatic change in prevalence of T2DM is clearly rooted in environmental shifts, with westernization leading to obesity, metabolic syndrome and hypertension. However, diabetes and its associated nephropathy and CVD strongly aggregate in families [3–5]. Here, we review our current understanding of the impact of genetic factors on the development of DN.

Dissection of the trait ‘diabetic nephropathy’

Reports evaluating the linkage and/or association of genes or genomic regions with DN have often yielded conflicting results. Discordant findings probably relate to true genetic heterogeneity, coupled with study design flaws such as population stratification between cases and controls, small sample sizes lacking in statistical power, and evaluation of inadequate numbers of polymorphisms in genes to determine their true involvement. However, the definitions of DN in each report typically differ, contributing to the confusion.
The genetic bases of albuminuria and progressive DN or end-stage renal failure (ESRF) appear to differ [6]. Albuminuria and glomerular filtration rate (GFR) are both heritable, but GFR to a greater degree [7]. Albuminuria, especially of mild degree, is more strongly predictive of risk for CVD death than for development of progressive nephropathy [8]. The phenotype ‘albuminuria’, whether using timed urine collection or the albumin:creatinine ratio (ACR), is highly variable [9,10]. While it is likely that overt albuminuria (>300 mg/dl) is a useful surrogate for ESRF, the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that more overt albuminuric patients will die of CVD events than survive to initiate renal replacement therapy [8]. Therefore, we will attempt to dissect the existing genetic analyses in diabetic subjects into those evaluating predominantly albuminuria (i.e. in cohorts with presumed endothelial dysfunction and at relatively low risk for progressive DN) and those with overt DN/diabetic ESRF. We focus on genes and genomic regions that have demonstrated reproducible results.

Genetic factors involved in overt diabetic nephropathy and ESRF

Imperatore et al. conducted a genome scan on 98 Pima Indian sibling pairs with type 2 diabetic ESRF or macroalbuminuria and found the strongest evidence for linkage on chromosome 7q35 [11]. Other regions of potential interest included chromosomes 3q26, 9q22 and 20p12. Although originally investigated as a functional candidate, the gene for endothelial nitric oxide synthase (NOS3) falls within the 7q region of linkage detected in the Pima Indian families [11]. Studies in a number of different populations have found evidence for association with either NOS3 T-786C or an intron 4 insertion/deletion polymorphism and persistent proteinuria and ESRD in type 1 diabetes [12]; overt nephropathy (ESRF excluded) in type 2 diabetes [13], non-DN and DN [14]; and increased ACR in families enriched for type 2 diabetes [15]. There have also been negative reports with these and other variants of this gene with chronic renal failure [16] and DN [17]. The gene for aldose reductase (AKR1B1), also located in the vicinity of the 7q linkage peak, has been investigated extensively as a functional candidate for DN (reviewed in [18] and, more recently, see [19–22]).

In a genome scan of 18 extended Turkish families, Vardarli et al. localized a type 2 DN gene to 18q22.3–q23 [23] and confirmed this result in a study of 101 Pima Indian sib pairs [23], although the modest evidence for linkage to this locus had not been noted in the original Pima Indian scan [11]. Bowden et al. [24] found evidence to support early-onset ESRF loci at 3q13 (~45 cM proximal to the Pima Indian peak [11]) and 18q22 in a genome scan of 206 African American sib pairs with ESRF, chronic renal failure or macroalbuminuria, while the strongest overall evidence for linkage was at chromosome 7p21. After excluding the Kruppel-like zinc-finger gene ZNF236 gene [25] on 18q, Janssen et al. [26] investigated carnosinase genes CNDP1 and CNDP2 as positional candidates. They found that the shortest allele of a trinucleotide repeat coding for leucine in the leader peptide of carnosinase-1 precursor (five leucines) was more common in diabetic patients without overt nephropathy, and individuals homozygous for this allele also possessed the lowest serum carnosinase activity. Carnosine functions as a scavenger of reactive oxygen species and an inhibitor of the formation of advanced glycation end-products. Therefore, lower levels of carnosinase would be expected to increase renal levels of carnosine and protect from the development of nephropathy. Replication of the CNDP1 association in African American and European American patients with T2DM-associated ESRF was unsuccessful [27]. However, the role of the carnosinase gene in DN remains under intense study.

A genome scan of GFR measured by serum cystatin C in 63 extended Caucasian pedigrees (426 individuals with type 2 diabetes, 431 without diabetes) detected linkage peaks on chromosomes 7p and 6q [6], with the latter overlapping with the 7p linkage peak of Bowden et al. [24]. By genotyping >80,000 single nucleotide polymorphisms (SNPs) in a gene-centric genome-wide association approach, Shimazaki et al. [28] identified an association between the engulfment and cell motility 1 gene (ELMO1) and overt nephropathy in patients with type 2 diabetes. They also demonstrated that ELMO1 expression was increased in the kidneys of diabetic mice, compared with controls. This gene is located on chromosome 7p14, ~29 cM distal to the peak marker of the 7p locus identified by Bowden et al. [24].

Genetic factors involved in diabetic albuminuria

Moczulski et al. [29] investigated three candidate regions in a study of type 1 diabetes patients with ESRF, persistent macroalbuminuria and persistent microalbuminuria, and found evidence for linkage around 3q24. This locus was confirmed in a case–control comparison of type 1 diabetes patients from Russia with (≥300 mg/24 h) or without (≤200 mg/24 h) persistent proteinuria [30]. Both studies concluded that the angiotensin II type 1 receptor (AT1B) gene was unlikely to be responsible for this signal [29,30].

A scan of the ACR as a quantitative trait in 63 extended Caucasian families with type 2 diabetes [6] detected linkage peaks on chromosomes 7q and 22q, with the 7q linkage peak in the same region as that reported by Imperatore et al. [11]. The Diabetes Heart Study, a family study assessing for genes underlying type 2 diabetic atherosclerosis, found strong association between the P-selectin gene [31] and albuminuria in 565 European American siblings from 227 families (84% had diabetes). P-selectin is involved in leukocyte adhesion to the endothelium during inflammation and has been
postulated to play a role in atherosclerosis. Each copy of the 290Asn (S290N) allele was associated with a significant 45% absolute increase in ACR, and a higher risk for the presence of albuminuria (odds ratio 1.71 for each 290Asn allele). The N-N-T haplotype, containing asparagine codons at sites S290N and N562D, was associated with a significantly increased risk of albuminuria (odds ratio 1.77 for each additional copy of the N-N-T haplotype).

‘Nephropathy genes’ underlying diabetic and non-diabetic nephropathy

Apart from evidence for linkage to creatinine clearance/serum creatinine concentration on chromosomes 3q [32] and 18q [33], there are few overlapping peaks for DN and non-DN or albuminuria [33–37]. This suggests that susceptibility to chronic renal failure may differ in diabetic and non-diabetic settings, despite the fact that both often cluster in the same families [5]. Although GFR and urinary albumin excretion are known to be heritable [7,38], the only known scans to date for these quantitative traits in diabetic populations are in press [6]. Lastly, given the clear association between microalbuminuria and CVD [39], the identification of genes contributing to albuminuria and calcified vascular plaque are urgently required.

Conclusions

The genes underlying susceptibility to DN/ESRF and albuminuria have, thus far, been elusive. It appears likely that multiple genes, each having an intermediate effect and in an appropriate hyperglycaemic environment, are required for full disease expression. Large studies searching for DN susceptibility are underway. For example, the Genetics of Kidneys in Diabetes (GoKinD) Study has recruited large numbers of cases with type 1 DN and their parents (DN-affected trios), as well as large numbers of controls with longstanding type 1 diabetes and no evidence for nephropathy and their parents (control trios). This study will have DNA available for the performance of association analyses and transmission disequilibrium testing (TDT) (http://www.gokind.org/access). Similarly, the Family Investigation of Nephropathy and Diabetes (FIND) Study has collected renal phenotype data, DNA and cell lines from large numbers of European American, African American, Native American and Hispanic American families [40]. All families consist of at least one diabetic sibling pair that is either concordant or discordant for DN. Mapping by admixture disequilibrium (MALD) studies will also be performed in Mexican American and African American DN cases and diabetic, non-nephropathy controls. It is hoped that the combination of existing genome-wide scans and candidate gene analyses in DN, coupled with the larger FIND and GoKinD studies, will identify the genes underlying susceptibility to DN and provide novel pathways for the prevention and treatment of diabetic kidney disease.

Conflict of interest statement. None declared.

References

Angiotensin II: a key factor in the inflammatory and fibrotic response in kidney diseases

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Abstract

Angiotensin II (AngII) participates in the pathogenesis of renal diseases, through the regulation of two key processes inflammation and fibrosis. AT₁ and AT₂ are the main receptors of AngII. AT₁ mediates most of the actions of AngII. This receptor regulates...