Nephropathy

The genetic basis of diabetic nephropathy

Rudy Bilous, Professor of Clinical Medicine, Newcastle University, Newcastle and Consultant Physician ,James Cook University Hospital, Middlesbrough

The study by Williams et al (2012; summarised below) is by far the largest ever to explore the genetic basis of diabetic nephropathy (DN) in T1D. Ever since the original description of concordance of nephropathy in siblings with T1D (Seaquist et al, 1989), there have been numerous studies in cohorts of varying sizes attempting to identify the culprit candidate gene or genes.

Initial studies explored associations of diabetic nephropathy with the renin–angiotensin system, notably the insertion/deletion polymorphism in the angiotensin-converting enzyme (ACE) gene (Mooyaart et al, 2011). These studies demonstrated associations of variable strength, and the outcomes were not uniformly positive. Part of the problem lay in the definition of the phenotype, which was usually based upon microalbuminuria (which we now know to be more variable than was initially thought; Perkins et al, 2003). The latest meta-analysis of these studies seemed to confirm a significant, if weak, association between the ACE gene polymorphism and nephropathy. Subsequently, two further candidate gene polymorphisms have been found to link to nephropathy – the erythropoietin (EPO) and the engulfment and cell motility 1 (ELMO1) genes (Mooyaart et al, 2011).

The present study by Williams et al combined three large cohorts from the UK and Ireland (903 cases of nephropathy and 1001 controls), Finland (1289 cases, 1577 controls) and the US (774 cases, 821 controls). The subjects were all of European ancestry, and nephropathy was defined as end-stage renal disease (ESRD – dialysis or kidney transplantation). For the EPO gene analysis, subjects were further stratified by the presence or absence of proliferative diabetic retinopathy (PDR). The association of the EPO gene with the extreme phenotype of ESRD and PDR remained significant (but much less than previously thought), but with a marginally meaningful odds ratio of 1.313 (95% confidence interval, 1.20–1.44, $P=2\times10^{-9}$). No association of DN with the ELMO1 gene was found. All other previously reported associations, including association of DN with the ACE gene, were markedly attenuated.

What should we make of these data? The genetic basis of nephropathy remains elusive and the major gene effect that was hoped for has failed to materialise. The original observations of familial concordance of nephropathy are likely to have a largely shared environmental or metabolic basis. Many millions of pounds have been spent searching for a genetic basis for microvascular complications of diabetes and the reason why only a minority of people develop them in their most extreme phenotype.

This study shows us that only suitably powered large cohorts with a carefully defined phenotype can adequately address the questions around the genetic basis of DN. The objective of a precise predictive test for the susceptibility to nephropathy remains as elusive as ever. Meanwhile, striving for the best possible glycaemic control is the main priority for people with T1D.

Mooyaart AL, Valk EJ, van Es LA et al (2011) Genetic associations in diabetic nephropathy: a meta-analysis. *Diabetologia* **54**: 544–53
Perkins BA, Ficociello LH, Silva KH (2003) Regression of microalbuminuria in type 1 diabetes. *N Engl J Med* **348**: 2285–93
Seaquist ER, Goetz FC, Rich S et al (1989) Familial clustering of diabetic kidney disease. Evidence for genetic susceptibility to diabetic nephropathy. *N Engl J Med* **320**: 1161–5

DIABETES

Genetic links with diabetic nephropathy in people with T1D

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 T1D has increased consistently on a global scale and diabetic nephropathy (DN) develops in around 25–40% of people with T1D and T2D.

2 The authors examined genetic links with DN in T1D that had been previously brought to light, including the erythropoietin and engulfment and cell motility 1 genes.

3 The authors were unable to replicate the majority of these previously reported genetic associations in a large, homogeneous group of people of European ancestry with T1D. They concluded that it is highly possible that many of the positive genetic links to DN are false-positive findings.

Williams WW, Salem RM, McKnight AJ et al (2012) Association testing of previously reported variants in a large case-control meta-analysis of diabetic nephropathy. *Diabetes* **61**: 2187–94

DIABETES CARE

High risk of kidney disease and death in young people with T2D

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓✓

1 The authors assessed long-term renal outcomes and survival in young people (aged 1–18 years) with T2D ($n=342$) against that of youth with T1D ($n=1011$), and age- and sex-matched control subjects without diabetes ($n=1710$).

2 Young people born with T2D had a four-fold greater risk of developing renal failure than youths with T1D (hazard ratio, 4.03 [95% confidence interval, 1.64–9.95, $P=0.003$]). The risk factors linked to renal failure were found to be renin angiotensin aldosterone system (RAAS)-inhibitor use and albuminuria during adolescence.

3 Micro- and macroalbuminuria were significantly more persistent in people with T2D versus those with T1D ($P<0.0001$ and $P=0.001$, respectively). Those with persistent albuminuria were significantly more likely to develop renal failure ($P<0.001$).

4 Youth with T2D were 23 times more likely to develop renal failure and 39 times more likely to need dialysis than the control subjects.

5 The study findings showed that there is a marked difference between the risk of developing renal failure in young people with T2D versus those with T1D. The results of the study cast doubt on the effectiveness of RAAS blockade in treating renal disease in youth-onset diabetes.

6 The authors concluded that young people with T2D are at significant risk of detrimental renal outcomes and death. In addition, RAAS-inhibitor use was linked to negative outcomes in early adult life.

Dart AB, Sellers EA, Martens PJ et al (2012) High burden of kidney disease in youth-onset type 2 diabetes. *Diabetes Care* **35**: 1265–71

AM J MED

Awareness of kidney disease and the link to ERSD and mortality

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The number of adults in the US with chronic kidney disease (CKD) is rising, increasing the risk of end-stage renal disease (ESRD) and early death.

2 It is common for people who have CKD to be unaware of the fact. The authors investigated the relationship between disease awareness and ESRD and mortality.

3 The authors evaluated data from the National Kidney Foundation's Early Evaluation Programme from 2000–2009. They established mortality by cross-referencing this data with data from the United States Renal Data System.

4 Twenty-six per cent of participants had CKD; of these people, only 9% reported being aware of the disease. Participants who were aware of having kidney disease had a lower estimated glomerular filtration rate (eGFR) and a higher recurrence of albuminuria, diabetes, cardiovascular disease and cancer.

5 Of the people who were diagnosed with CKD at a health screening, only a small number had previously been informed of their condition by clinicians.

6 The authors concluded that CKD awareness in the US continues to be extremely low in spite of efforts to increase awareness within the community. They also noted that awareness of the disease does not, as a matter of course, reflect improved treatment outcomes.

Whaley-Connell A, Shlipak MG, Inker LA et al (2012) Awareness of kidney disease and relationship to end-stage renal disease and mortality. *Am J Med* **125**: 661–9

DIABETES OBES METAB

Dialysis and kidney transplantation: Timing in T1D

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 People with T1D have a high risk of developing end-stage renal disease and, following its onset, have a high mortality risk. In the last years, dialysis has been started earlier. The authors of this study reassessed this treatment approach.

2 People with T1D who pre-emptively underwent pre-dialysis transplantation had a reduced rate of CKD compared with those treated with dialysis. It was found that living donor kidney transplants can be carried out prior to dialysis and are linked to improved kidney outcomes versus transplantation during dialysis.

3 The authors concluded that there are several obstacles that stand in the way of being offered pre-dialysis transplantation. These include lack of knowledge by clinicians, late transplant referrals and misunderstandings by the patient and family concerning the timing of transplantation and who can be a donor.

Pavlakis M (2012) The timing of dialysis and kidney transplantation in type 1 diabetes. *Diabetes Obes Metab* **14**: 689–93

DIABETES CARE

Serum cystatin-C concentration and risk of ESRD in diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 This authors assessed whether the risk of developing end-stage renal disease (ESRD) in diabetes can be more accurately predicted using one of two chronic kidney disease (CKD) staging techniques.

2 CKD was staged using either creatinine-based estimates of the glomerular filtration rate (eGFRcreat), or by serum cystatin C-based estimates (eGFRcyst).

3 The study results illustrated that, despite CKD staging by eGFRcyst being consistent with that by eGFRcreat for the majority of people, those who received a higher stage by eGFRcyst than with eGFRcreat had a notably higher risk of ESRD than those with consistent staging.

4 The authors concluded that for people with diabetes, ESRD risk stratification based on eGFR is greatly improved by basing CKD staging on eGFRcyst rather than on eGFRcreat.

Krolewski AS, Warram JH, Forsblom C et al (2012) Serum concentration of cystatin C and risk of end-stage renal disease in diabetes. *Diabetes Care* 30 Jul [Epub ahead of print]

DIABETES CARE

Fast GFR decline in people with T2D

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓

1 The authors outlined the widespread nature of hyperfiltration (glomerular filtration rate [GFR] ≥120 mL/min/1.73 m^2) and its causes in people with T2D and hypertension and albuminuria <200µg/min (n=600); 15% had hyperfiltration.

2 Over a median of 4 years' follow-up, GFR declined at a rate of 3.37 (5.71–1.31) mL/min/1.73 m^2 per year. A total of 23.4% of those with persistent hyperfiltration advanced to micro- or macro-albuminuria compared with 10.6% who had their hyperfiltration ameliorated at 6 months (hazard ratio, 2.6 [95% confidence interval, 1.13–4.14])

3 The authors concluded that people with T2D show progressive GFR decline, before developing renal disease, and in spite of having intensified therapy.

Ruggenenti P, Porrini EL, Gaspari F et al (2012) Glomerular hyperfiltration and renal disease progression in type 2 diabetes. *Diabetes Care* **35**: 2061–8

"Youth with T2D were 23 times more likely to develop renal failure and 39 times more likely to need dialysis than the control subjects."