Genetics of Kidney Disease

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July 31st, 2003
Overview

• Background: From epidemiology to suspicion
• Diabetic nephropathy: a major threat
• Hypertensive kidney disease: close runner-up
• Outlook
Incidences and prevalence of end-stage renal disease are alarming:
- Singapore is in third position of countries publishing renal registers
- Incidence has been rising constantly over the past decades
- The cost of renal failure, both in loss of quality of life to the diseased, and in economic terms to patient and society, call for fast and efficient action.

### Background: Epidemiology

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</table>

Table 1: adapted from the 1997 annual report of USRDS. Counts are registered diseased persons, rates are per million inhabitants.
In developed countries, the majority of ESRD cases is due to:

- Diabetic nephropathy
- Hypertensive nephropathy
Familial clustering of diabetes associated kidney disease:

- Frequency of renal disease in relatives of diabetic individuals with or without renal disease.

  - Graph ref.: D. Bowden, Kidney International 2003
Several metabolic pathways damage the glomerulus in diabetic kidney disease:

- Production of “advanced glycation end products” (AGE) increases basal membrane thickness, activates macrophages, increases cytokines
- Intracellular accumulation of sorbitol
- Decrease of glucoseaminoglycans, especially heparinsulfate, with consecutive disturbance of endothelial function.

Diabetic Nephropathy: Histopathology

Adapted from: Koch: Klinische Nephrologie. Urban & Fischer 2000

Diffuse glomerular sclerosis. PAS stain.

1: hyaline deposits in arterioles
2: diffuse increase in mesangial matrix
Diabetic Nephropathy: Clinical Course

The clinical course of diabetic nephropathy is the same in both types of diabetes:

• Normal glomerular filtration within the first 10 years, then slow reduction over the next years, with ESRD attained from 15 years onwards after diagnosis.

• In type 1 diabetes, only 30% of patients will develop diabetic kidney disease

• For type 2 diabetes, due to large number of unknown cases, no exact figures are available.

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Time course of proteinuria following diagnosis of diabetes (above) and time course of diabetic nephropathy following diagnosis of proteinuria (below).

Adapted from: Koch: Klinische Nephrologie. Urban & Fischer 2000
Diabetic Nephropathy: Familial aggregation studies

Familial aggregation of diabetic nephropathy has been demonstrated:

• Seaquist (NEJM, 1989) compared two diabetic families. The one with prevalent DN showed DN in 83% of diabetic siblings, as opposed to only 17% DN in diabetic siblings of probands from the other family. Logistic regression showed DN to be the only significant risk predictor.

• Pettitt (Diabetologia, 1990) showed parental proteinuria to be prognostic for filial proteinuria in diabetic Pima Indians

• Since then, several supportive studies were published with families from Malta, Italy, Brazil and India.

• Familial aggregation must be treated with caution, as siblings might share the same environmental stressors!
Diabetic Nephropathy:

Co- aggregation with other manifestations of insulin-resistance syndrome (IRS)

Co- aggregation with other manifestations of IRS has been demonstrated:

• Parental hypertension increases the risk of proteinuria in both type 1 & 2 DM. This could be mediated by genetic predisposition to hypertension.

• Diabetic nephropathy is associated with increased risk for cardiovascular disease in both type 1 & 2 DM.

• Offspring of parents with diabetic nephropathy have increased risk for diabetes, but also for microalbuminuria if non-diabetic.
Diabetic Nephropathy: 
Anthropometric parameters

Several large recent studies have shown that low birth weight and ponderal index are linked with manifestations of IRS and cardiovascular disease in later life, and lower life expectancy:

• Intra-uterine malnutrition programmes the fetus to become insulin-resistant, which is detrimental in adequate nutrition ("thrifty phenotype").
• Rossing (Diabetes, 1995) demonstrated same association for DN.
• IUGR may predispose to DN due to decreased nephron number.
• Association does not hold true for twins!
• Possibly, genetic factors (parental habitus) predispose to both low birth weight and features of IRS, including diabetic nephropathy.
• Alternative, inverse explanation: genetic predisposition to insulin resistance causes growth deficit.
Diabetic Nephropathy: Regulation of early renal development

• The Renin- Angiotensin- System (RAS) as well as several other genes that influence growth regulation seem to partake in regulation of renal development.

• Several studies imply that ACE polymorphism plays a crucial role.

• Current data are still inconclusive.

• No single gene action convincingly exerts a unique major effect on development of renal disease.

From: Moritz et al., BioEssays 2003
Diabetic Nephropathy:
Separate inheritance from diabetes?

- Genes that predispose to diabetic nephropathy may also predispose to diabetes:
- McCance (Diabetologica, 1995) found that subjects had a greater risk for diabetes if their diabetic parents had diabetic nephropathy, compared to diabetic parents without diabetic nephropathy.
- Contrarily, non-diabetic offspring of diabetics with diabetic nephropathy have higher albumin excretion compared to non-diabetic offspring of diabetics without diabetic nephropathy (Mc Allister, Diabetes Med 1999).
- The findings may be reconciled by the assumption that a number of genes predispose to diabetes and to diabetic nephropathy. Some, but not all of those, may predispose to both diabetes and renal disease.
Summary: Diabetic Nephropathy

• There is ample evidence for familial aggregation of diabetic nephropathy, but this is not sufficient proof as families share also environmental factors.

• The consistency of findings, along with co-aggregation with other features of the Insulin Resistance Syndrome makes a genetic component likely.

• Proof can be found either from positional cloning based on linkage analysis, or by the candidate gene approach.

• As of now, no single genes have been identified that have a definitive role in diabetic nephropathy.

• It is likely that the contribution of individual genes will be small, but a combination of “bad” genes and environmental factors will cause DN.

• In order to detect the effect of individual genes with sufficient specificity, studies with very large numbers of probands are needed.
Hypertension and renal disease

• In the US, the majority of individuals with long-standing essential hypertension and diabetes do not develop kidney involvement, but African-American individuals develop hypertension-associated ESRD seven times more often than caucasians (US Renal Data System report 1999).

• More than 23% of African-American ESRD patients (14% caucasians) have additional first or second degree relatives on dialysis (Freedman et al., JASN 1997).

• Hypertensive patients were more likely to have relatives with ESRD than others (40% had relatives with advanced renal failure).

• The familial aggregation of ESRD led to the concept that genes producing susceptibility to the initiation or progression of renal failure may explain the familial clustering of cases.
Hypertension: brief introduction

- About 20% of the adult population worldwide suffers from hypertension, the prevalence increases with age and is ~40% in Europeans over age 50.
- Clinical relevance is due to vascular complications that manifest in organs as varied as brain, heart and kidney, increasing morbidity and mortality.
- Essential or primary hypertension (i.e. hypertension of unknown cause) accounts for >90% of cases.
- Secondary forms of hypertension are those of known cause. Renoparenchymal hypertension is the most common cause of secondary hypertension, causing up to 5% of all hypertension.
- The inheritance pattern of hypertension is complex and most likely polygenetic.
Hypertension: brief introduction

Adapted from: Schrier RW. Renal and electrolyte disorders, Philadelphia 1997).
Hypertension: brief introduction

• Importance of the Renin- Angiotensin- System (RAS):
  • an increased activity of the RAS causes angiotensin II–mediated vasoconstriction and aldosterone release with subsequent plasma volume expansion, resulting in hypertension
  • angiotensin II effects on hemodynamics, and on tissue growth, are both thought to be responsible for progressive loss of renal function
  • Inhibition of the RAS decreases speed of progression to ESRD

THE RENIN-ANGIOTENSIN SYSTEM

- AT II causes:
  - Vasoconstriction
  - Increased aldosterone secretion
  - Increased antiuretic hormone secretion
  - Increased thirst
  - Result: increased blood pressure

Hypertensive Nephropathy and the ACE gene polymorphism

• D- allele frequency in the nephropathy significantly higher than in the control group (0.45 vs. 0.32, $\chi^2 = 10.8$, $p < 0.001$)

From: Kario et al., Atherosclerosis, Thrombosis, and Vascular Biology 1997, 17: 252-256
Hypertension: gene polymorphisms in the RAS

- Lovati et al. (Kidney International 2001) demonstrated an association of various single nucleotide polymorphisms within the RAS with the speed of progression of renal disease in a “caucasian population of ethnic homogeneity”.

![Graph showing progression to ESRD for different genotypes](image)
Hypertension: gene polymorphisms in the RAS

- Kunz et al. (Hypertension 1997) conducted a metaanalysis of relevant studies between 1992 and 1996.
- The AGT 235- T allele was significantly associated with hypertension (OR 1.2; 95% CI: 1.11-1.29; p< 0.001), but the methodological weaknesses of the individual studies mean this has to be considered with caution.
Hypertension: gene polymorphisms in the RAS

- Nagel et al. (ASN 2003, submitted) found a variant distribution of AGT polymorphisms in a distinct, but equally homogenous caucasian population.
- In this population, TT isoform was significantly more frequent in controls ($\chi^2$- Test; p = 0.034).
Summary: Hypertensive Nephropathy

• The data addressing the role of ACE insertion/deletion polymorphism in kidney disease pathogenesis remain controversial.

• Results vary according to the definition of subgroups studied—underlying disease, gender, ethnicity…

• For the AGT M235T polymorphism, convincing data exist for a link to the progression of renal disease.

• Yet again, the results are limited to specific subgroups.

• Mayor flaws in the published studies are their either retrospective character, use of subsets of studies with primarily different focus, short follow up time, and often small numbers of cases.
Outlook: the promise of technological advance (1/2).

• Imperatore et al. (Diabetes 2001) found evidence for a linkage between DM-2 and nephropathy on the long arm of chromosome 7 (LOD: 2.7).

• Vardali et al. (JASN 2001, 12 abstract 160A) demonstrated a linkage peak (LOD score 6.6) on chromosome 18 (markers D18S43 and D18S50), providing evidence for the existence of a novel renal disease gene.

• Freedman et al. (Kidney International 2002) mapped several loci on chromosome 10 with linkage to ESRD in 199 Afro- American sib pairs with hypertension.
Outlook: the promise of technological advance (2/2).

• Genome screen analysis: is more difficult, time consuming, and expensive than candidate gene analysis, but has the advantage of being able to locate new, as yet undiscovered genes: it is not limited to the current knowledge of renal disease.

• Analysis of biochemical pathways known to be involved in renal disease, and integration of data discovered by genome screen analysis in a systems biology approach may enhance future understanding of initiation and progression of renal disease.

• As of now, predictions by means of bioinformatics based analysis need clinical proof.