Genetic renal abnormalities

A Peter Maxwell

Abstract

Inherited disorders of renal structure and function are relatively common causes of end-stage renal disease requiring renal replacement therapy. A family history of haematuria, urinary tract infection or renal failure can alert the clinician to the possible diagnosis of underlying renal genetic abnormalities. In practice, the commonest inherited renal disorder is autosomal dominant polycystic kidney disease (ADPKD), characterized by multiple kidney cysts associated with hypertension and renal failure. Insights into the cell biology of ADPKD are informing new therapeutic approaches to limit cyst growth and prevent progressive renal failure. Non-visible haematuria is a clinical finding that presents a diagnostic challenge because it has so many possible causes. Mutations in the genes encoding collagen proteins within the glomerular basement membrane (GBM) can disrupt its normal barrier function. Thin basement membrane nephropathy, caused by GBM collagen gene mutations, is a relatively common cause of familial haematuria that normally has a good long-term prognosis. Alport syndrome is a rare and genetically heterogeneous condition leading to renal failure in men inheriting the X-linked gene defect. Single-gene defects may cause diverse renal tubular disorders, such as predisposition to renal calculi, diabetes insipidus, renal tubular acidosis or hypertension with associated electrolyte imbalance. Gene mutations responsible for familial renal cancer syndromes, such as tuberous sclerosis complex and von Hippel–Lindau disease, have also been identified.

Keywords Alport syndrome; non-visible haematuria; polycystic kidneys; renal genetics; thin basement membrane nephropathy

At least 10% of the new patients commencing renal replacement therapy annually in the UK have genetic renal abnormalities.[1] These represent the fifth commonest cause of end-stage renal disease (ESRD) after diabetes, hypertension, glomerulonephritis and pyelonephritis, respectively.[2] Some individual renal genetic conditions, such as polycystic kidney disease, are relatively common, with as many as two or three affected patients on an average UK GP list. An inherited defect in glomerular basement membrane protein function should be considered in the assessment of any patient with persistent non-visible haematuria. Single-gene disorders known to cause renal tubular disorders include diabetes insipidus, nephrolithiasis and renal electrolyte wasting (Table 1).

Background

An underlying genetic basis for kidney disease is easiest to appreciate in monogenic or single-gene disorders that obey Mendel's laws for inheritance, such as autosomal dominant polycystic kidney disease (ADPKD). Hypertension is an important clinical risk factor for progression of chronic kidney disease and several genetic variants, acting together, may make a polygenic contribution to raised blood pressure. Common causes of renal failure, such as diabetic nephropathy and glomerulonephritis, are multifactorial with environmental triggers acting against a background of genetic susceptibility to renal injury. Genetic mutations are part of the pathogenesis of sporadic and familial renal cancers.[3] Rarely, renal genetic abnormalities are the result of maternally inherited mitochondrial defects.

Finding a gene mutation associated with a particular renal disorder is the first step in understanding how a DNA sequence variation is related to changes in the level or function of a translated protein. A monogenic disorder, such as ADPKD, which has easily recognized clinical features (phenotype), may arise from different mutations (genotypes) — unique for individual families (private mutations) — in either of two distinct genes (*PKD1* or *PKD2*) linked to the disease. This has practical consequences for genetic counselling within an affected family since it may be technically difficult and expensive to identify the causative mutation.

Some renal genetic abnormalities, either dominant or recessive, may interfere with normal kidney development and differentiation. This can result in abnormal cellular organization of the renal parenchyma (renal dysplasia), morphological abnormalities at birth (congenital renal abnormalities), or a combination of both. Other genetic diseases with a dominant inheritance pattern (i.e. germline mutation) will not present until later in life when a 'second hit' somatic mutation of the normal allele occurs (e.g. von Hippel–Lindau disease).[3,4]

Identifying renal genetic abnormalities

A detailed family history will help identify the presence of an inherited renal disease, and constructing an extended family pedigree can provide evidence of a Mendelian inheritance pattern. Monogenic disorders may be inherited in an autosomal dominant, autosomal recessive, X-linked dominant or X-linked recessive fashion. Recessive disorders are more likely to present in childhood whereas dominant disorders are more often identified in adulthood. For X-linked diseases (e.g. Alport syndrome), males are more severely affected than females. Females can have varying severity of X-linked renal disease, reflecting the degree of lyonization (the random inactivation of maternal versus paternal X chromosomes in cells). In addition, various genetic and environmental influences may alter the age at presentation of a monogenic disorder such as ADPKD: the age at which ESRD occurs in ADPKD can vary widely within an individual family despite the affected members inheriting an identical *PKD1* mutation.

Common renal genetic abnormalities (affecting >1:200 pregnancies) include the congenital abnormalities of kidney and urinary tracts (CAKUT), resulting in renal dysplasia and hypoplasia, and often associated with vesico-ureteric reflux (VUR). Approximately 50% of children with chronic renal failure or ESRD have CAKUT; almost half of these are associated with lower urinary tract obstruction due to posterior urethral valves in boys.[1,5] Familial clustering of renal abnormalities has led to the identification of autosomal dominant inheritance patterns in a number of CAKUT syndromes. The mutated genes code for

A Peter Maxwell *MD PhD FRCP is Professor of Renal Medicine, Queen's University Belfast, Belfast City Hospital, Belfast, UK. Competing interests: none declared.*

Renal tubular disorders

Disease	Phenotype	Inheritance	Locus	Gene	Protein
Liddle's syndrome	Hypertension, hypokalaemia, hypoaldosteronism	AD	16p	*SCNEB*	Beta unit of epithelial sodium channel
Bartter's syndrome	Hypokalaemia, hypercalciuria	AR	15q	*NKCC2*	Na^+—K^+—Cl^- co-transporter
		AR	11q	*ROMK1*	ROMK channel (K^+ channel)
		AR	1p	*CLCNKB*	Clc-Kb channel (Cl^- channel)
Gitelman's syndrome	Hypokalaemia, hypomagnesaemia, hypocalciuria	AR	16q	*NCCT*	Na^+—Cl^- co-transporter
Nephrogenic diabetes insipidus	Polyuria	XR	Xq	*AVPR2*	Arginine vasopressin receptor 2
		AR	12q	*AQP2*	Aquaporin 2
		AD	12q	*AQP2*	Aquaporin 2
Dent's disease (X-linked hypercalciuric nephrolithiasis)	Renal calculi, hypercalciuria, nephrocalcinosis, proteinuria	XR	Xp	*CLCN5*	Clc-5

AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive.

Table 1

transcription factors, or co-factors, which are involved in early kidney development.

Almost 30% of children who present with urinary tract infection (UTI) have VUR. It is worthwhile establishing the family history of children with both UTI and VUR since VUR is reported to be present in 20—40% of siblings and offspring of affected children.[6] It has been suggested that VUR is inherited, but no consistent pattern of inheritance has been established. The evidence for specific VUR gene loci in several recent genetic linkage studies has been inconsistent. This suggests that genetic heterogeneity exists for VUR (i.e. in individual families different genes are responsible for the VUR phenotype). Close working relationships between GPs, paediatricians, nephrologists and geneticists are necessary for efficient clinical assessment of affected children with CAKUT and VUR, and to ensure accurate genetic counselling for families.

Polycystic kidney disease

Genetics

ADPKD is the commonest Mendelian renal genetic disorder with a reported incidence of 1:500 to 1:1000 (Table 2). Approximately 85—90% of persons with ADPKD have a mutation in the *PKD1* gene on chromosome 16p; most of the remaining individuals have mutations in the *PKD2* gene on chromosome 4q. The *PKD1* protein (polycystin-1) has multiple functions including regulation of cellular adhesion, proliferation and apoptosis. The *PKD2* protein (polycystin-2) interacts with polycystin-1 and operates as a non-selective calcium channel. Recent evidence has shown that polycystins are integral components, together with the von Hippel—Lindau protein, of primary renal cilia (structures on the luminal surface of renal tubular epithelial cells that act as mechanosensors and chemosensors of urine flow).[7]

Pathophysiology

Less than 5% of the tubules develop an out-pouch, with focal proliferation of cells. Although initially in contact with the tubular lumen (and glomerular filtrate), they later become separate fluid-filled cystic structures lined by epithelial cells (Figure 1). Abnormal cellular differentiation, maturation and apoptosis is dependent on the germline *PKD* mutation and other factors, including possibly a second somatic 'hit' on the normal *PKD* allele coupled with additional genetic modifiers. Altered renal ciliary function in ADPKD is presumed to blunt sensing of luminal flow rates, altering renal epithelial cell signalling, intracellular calcium concentrations and cyclic adenosine monophosphate (cAMP) levels. The cilia are connected to centrosomal structures involved in cell-cycle control. Bardet—Biedl syndrome, which includes progressive renal cystic and dysplastic change, is associated with defects in centrosomal proteins. In ADPKD, cyst enlargement is accompanied by gradual destruction and atrophy of surrounding renal tissue.

Clinical course

Although ADPKD can lead to ESRD in childhood, it more commonly occurs in middle age or later. A family history of ADPKD may be present, but the diagnosis is often made coincidentally following radiological imaging of the abdomen. Ultrasound is the usual modality used to establish a diagnosis but cannot reliably exclude ADPKD in younger patients with a milder phenotype (Figure 2).[8] Computed tomography (CT) or magnetic resonance imaging (MRI) scans have higher resolution and can be used to screen younger family members being considered for living related kidney donation (Figure 3). MRI is also being used for accurate assessment of kidney volume and kidney growth rates in clinical trials of therapy for ADPKD.[9]

ADPKD is the primary renal diagnosis in 7% of UK and 3% of US incident ESRD patients.[1,2] Risk factors for progressive renal