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GENETICS IN KIDNEY DISEASE IN 2013:

Susceptibility genes for renal and urological disorders

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Abstract

In 2013, substantial progress was made in uncovering the genetic basis of a variety of kidney and urological disorders, including congenital and developmental diseases. The new findings will lead to an increased understanding of the pathophysiology of these diseases, improved risk prediction and the development of novel therapies.

The field of nephrology has progressed far beyond the era in which the term Bright's disease was applied indiscriminately to disorders that resulted in retention of kidney toxins. However, many urinary tract and renal parenchymal disorders continue to defy characterization and modern molecular genetics approaches hold great promise in this regard. 2013 saw several important developments in the genetics of kidney diseases, from congenital disorders affecting the urinary tract to developmental diseases impacting the renal parenchyma (Figure 1).

Although an inherited basis for congenital abnormalities of the kidney and urinary tract (CAKUT) has long been appreciated, disease and genetic heterogeneity, environmental factors and limited sample sizes have hampered the identification of causative gene variants. In 2013, Sanna-Cherchi and colleagues performed linkage analysis in four generations of a family with autosomal dominant CAKUT and detected five linked genomic regions in the seven affected members.¹ Using whole-exome sequence analysis of DNA from two of the affected individuals, the researchers identified a protein-changing variant in exon 2 of the *DSTYK* gene. This G to A mutation was present in affected individuals, obligate carriers, and two seemingly unaffected family members. The mutation is associated with a heterozygous 27 base-pair deletion that causes an in-frame deletion of nine amino acids in a domain that is highly conserved among mammals. Additional sequence analysis of DNA from 311 unrelated patients with CAKUT identified five previously unreported *DSTYK* mutations in seven patients. The spectrum of phenotypes associated with *DSTYK* mutations included renal hypodysplasia, ureteropelvic junction obstruction, and vesicoureteral reflux.

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Competing interests

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DSTYK was expressed in the tubule epithelia, medulla and papilla of developing murine kidneys, and on principal and intercalated cells in the apical and baso-lateral membranes of the collecting duct in a human paediatric kidney. These findings suggest potential roles for altered development or function of these cell types in a subset of patients with CAKUT.

Autosomal dominant forms of tubulo-interstitial nephritis are poorly understood and frequently misdiagnosed. These disorders have overlapping characteristics and are often collectively described as medullary cystic kidney disease (MCKD), although cysts might not be present. In 2002, the *UMOD* gene locus on chromosome 16, which encodes uromodulin, was identified as the cause of MCKD type 2.² The gene that causes MCKD type 1 (MCKD1) on chromosome 1 was identified in 2013. Using cloning, capillary sequencing, and *de novo* assembly in six families with MCKD1, Kirby and colleagues determined that variations in *MUC1* were causative for the disease.³ The families harboured independently arising mutations in *MUC1* consisting of the insertion of cytosine in one copy (different in each family) of the repeat unit forming the guanine and cytosine-rich coding variable-number tandem repeat sequence. *MUC1* encodes the transmembrane glyco-protein mucin 1, which is expressed on distal convoluted tubule epithelial cells and has diverse functions, including roles in cell adhesion and viability. The identified mutations cause a frame shift resulting in the production of altered proteins that lack critical domains and presumably have abnormal functions.

Common (and complex) nondiabetic nephropathies with glomerular, interstitial, and vascular changes result in nearly 50% of cases of end-stage renal disease (ESRD) in the USA.⁴ In African Americans, G1 and G2 coding variants of the *APOL1* gene are strongly associated with nondiabetic ESRD and contribute to nearly 70% of cases.^{5,6} *APOL1* is associated with progression of nephropathy in individuals of African ancestry with idiopathic focal segmental glomerulosclerosis (FSGS), collapsing FSGS, HIV-associated nephropathy, severe lupus nephritis, sickle cell nephropathy, and kidney disease attributed to essential hypertension.

Despite these important findings, the perception that mild-to-moderate systemic hypertension is a common cause of nephropathy in African Americans stubbornly persists, and nephrologists often apply the empiric diagnosis of hypertensive nephropathy to nondiabetic patients with progressive nephropathy who lack heavy proteinuria, particularly if kidney biopsy samples are not available.⁷ The suggestion that many African Americans diagnosed with hypertensive nephropathy have a primary kidney disease in the FSGS spectrum and secondary hypertension is frequently met with scepticism. However, the African American Study of Kidney Disease and Hypertension (AASK) resolved this controversy in 2013.⁸ Not only did AASK demonstrate that aggressive blood pressure control with angiotensin-converting enzyme (ACE) inhibitor-based therapy has weak effects on progression of nephropathy in African Americans (in contrast to the reported favourable effects in patients with European ancestry), but *APOL1* risk variants were strongly associated with kidney disease in AASK participants. The strongest associations were detected in patients whose kidney disease progressed to serum creatinine concentrations >265.2 $\mu\text{mol/l}$ during the study, and in those with baseline urine protein:creatinine ratios >0.6 g/g. As the AASK recruitment criteria were designed to reflect hypertensive

nephropathy, and blood pressure control with ACE inhibitors failed to correlate with clinical outcomes, it can no longer be argued that hypertension is the cause of progressive nephropathy in many African Americans with nondiabetic nephropathy. In the AASK participants, only *APOL1* genotypes correlated with the presence and progression of kidney disease independent of blood pressure control or medication class, proving that the disorder frequently resides in the FSGS spectrum. Now that the pathogenesis of this disorder has been elucidated, rational therapies might emerge.

The search for susceptibility genes for diabetic nephropathy has proven complex, likely because of the variable histology, differing disease definitions, and the influence of glycaemia on risk of nephropathy. The discovery that variants in loci near to the *FRMD3* gene were associated with diabetic nephropathy in patients with type 1 and type 2 diabetes mellitus in multiple populations held great promise for the identification of a susceptibility gene.⁹ However, the single nucleotide polymorphism (SNP) that was most strongly associated with diabetic nephropathy (rs1888747) was found near, not in *FRMD3*.⁹

In 2013, Martini and colleagues used comparative promoter analysis to identify common regulatory elements of *FRMD3*.¹⁰ They based their strategy on the assumption that promoters of functionally linked transcripts were likely associated with a common upstream regulatory element. Pathway analysis of 581 genes coexpressed with *FRMD3* was conducted in 22 American Indians with type 2 diabetes mellitus and chronic kidney disease. This analysis demonstrated strong enrichment of the bone morphogenetic protein (BMP) signalling pathway (with 8 genes represented). Unsupervised hierarchical clustering of coexpressed genes showed statistically significant differences in *FRMD3* expression and associations with renal outcomes and histology. Patients with diabetic nephropathy and increasing albuminuria or greater mesangial expansion showed downregulation of BMP pathway genes, compared with patients who had less-severe diabetic nephropathy. The researchers identified a transcription factor binding site (TFBS) encompassing SNP rs1888747 that was not present in patients with normal variants. This TFBS increased binding of glomerular nuclear extracts to the genomic region associated with diabetic nephropathy. The researchers concluded that rs1888747 affects protein binding and hypothesized that a coregulatory relationship exists between *FRMD3* and BMP pathway genes. Their novel approach provides a framework for future functional genomics analyses when genome-wide association study results suggest association of diseases with noncoding variants.

In summary, several recent studies have elucidated the role of genetic variation in diabetic and nondiabetic forms of complex kidney disease and in tubulointerstitial and congenital kidney disorders. These developments will improve disease classification and risk prediction, as well as lead to novel treatment approaches.

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Key advances

- Mutations in *DSTYK* are associated with congenital abnormalities of the kidney and urinary tract¹
- Mutations in *MUC1* and *UMOD* are associated with medullary cystic kidney disease (MCKD) type 1³ and MCKD type 2,² respectively
- Progressive nondiabetic kidney disease in patients with African ancestry who have hypertension and low-level proteinuria often belong in the focal segmental glomerulosclerosis spectrum and strongly associate with two coding variants in *APOL1*⁸
- A coregulatory relationship might exist between a variant associated with diabetic nephropathy that is located near to the *FRMD3* gene and bone morphogenetic pathway genes¹⁰

Figure 1.

Renal compartments most impacted by risk variants in the *APOL1*, *DSTYK*, *FRMD3*, *MUC1* and *UMOD* genes.