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Autosomal dominant tubulointerstitial kidney disease: of names and genes

Anthony J. Bleyer[1] and Stanislav Kmoch[2]

Autosomal dominant tubulointerstitial kidney disease (ADTKD) refers to a group of conditions characterized by autosomal dominant inheritance, a bland urinary sediment with minimal blood and protein, pathologic changes of tubular and interstitial fibrosis, and slowly progressive chronic kidney disease. This commentary discusses recent advances in our medical knowledge of these conditions, including the recent identification of mutations in the *MUC1* gene as a cause of ADTKD and changes in terminology proposed by Ekici *et al.*

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In this issue of *Kidney International*, Ekici and colleagues[1] provide us with both new information and a new perspective on autosomal dominant tubulointerstitial kidney disease (ADTKD).

ADTKD is an easily understandable term for clinicians. The term 'autosomal dominant' refers to an inherited condition in which one of two gene alleles carries a mutation, and its presence results in clinical disease. An affected parent will have a 50% probability of passing on the mutated gene and its condition to his or her child. A well-recognized autosomal dominant condition in nephrology is autosomal dominant polycystic kidney disease (ADPKD). Because of the mode of inheritance and late onset of the disease, families with ADPKD and ADTKD have many affected family members. The affected individual, one parent, and usually siblings, aunts or uncles, and one grandparent are affected. The term 'tubulointerstitial' refers to the fact that individuals with ADTKD have a bland urinary sediment, with minimal blood or protein. Kidney biopsy reveals tubulointerstitial fibrosis that is nonspecific. The kidney disease is progressive, with a gradual decline in glomerular filtration rate over time, resulting in the need for dialysis in the fourth through seventh decades of life.

How do patients with ADTKD present? A typical patient is found to have an asymptomatic elevation of the serum creatinine on routine laboratory testing. The patient usually volunteers a strong family history of chronic kidney disease. The nephrologist then obtains a urine sample that does not contain blood or protein and recognizes this as a tubulointerstitial kidney disease. A renal ultrasound reveals normal to small kidneys, depending on the stage of chronic kidney disease. For the most common form of this disease (caused by mutations in the *UMOD* gene[2]), there is another important symptom: patients or family members often suffer from gout, frequently beginning in their teenage years. Often, at this point the nephrologist is unclear how to proceed. If he or she decides to perform a kidney biopsy, it reveals tubulointerstitial changes that do not afford a precise diagnosis. Genetic testing is available to diagnose these conditions, but many clinicians are unaware of this possibility.

Why is it so hard for nephrologists to diagnose and recognize this condition? It would not seem that difficult—just autosomal dominant inheritance, bland urinary sediment, chronic kidney disease, and some families with a high preponderance of gout. The reason for the difficulty probably lies in the very confusing, historical terminology that has been used for these conditions. Primarily, these disorders have been described as medullary cystic kidney disease. This is problematic, because

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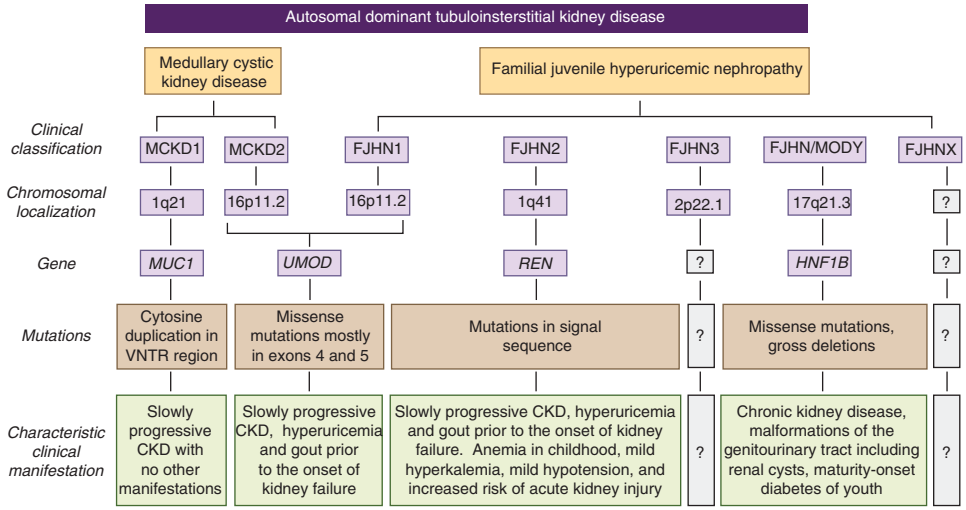

Figure 1 | The diseases classified under the terminology of autosomal dominant tubulointerstitial kidney disease.[2,5,9,10,11] FJHN, familial juvenile hyperuricemic nephropathy; MCKD, medullary cystic kidney disease; MODY, maturity-onset diabetes of youth; VNTR, variable number of tandem repeats. FJHNX refers to the fact that there are other autosomal dominant hyperuricemia syndromes for which a gene has not yet been identified.

most of the patients do not have medullary cysts![3] In addition, before knowledge about the genetic causes of these diseases, it was hard to clinically characterize them with certainty.

To help overcome this confusing terminology, Ekici and colleagues[1] (this issue) point out that tubulointerstitial fibrosis is a common unifying feature of these conditions. They therefore propose the term 'autosomal dominant tubulointerstitial kidney disease' to describe this group of diseases. We believe that this term meets several requirements: it is scientifically accurate, it is insightful to the clinician, and it can be explained easily to the patient. No name is perfect: it is not meant to include a number of other autosomal dominant tubulointerstitial conditions, including autosomal dominant polycystic kidney disease, making the term slightly inaccurate. In addition, hyperuricemia is a very common manifestation of disorders caused by *UMOD* and *REN* mutations and has been previously used in one of the names for *UMOD* mutations (familial juvenile hyperuricemic nephropathy).[4] Loss of 'hyperuricemia' in the terminology for these conditions may make them more difficult especially for a pediatric clinician to identify. However, all in all, there is no perfect term for this group of diseases, and we believe that using ADTKD as an umbrella term for conditions including *UMOD*, *REN*, and *MUC1* mutations is a step in the right direction and may be helpful in diagnosis for both the patient and the clinician.

The first two genetic causes of ADTKD to be identified were mutations in the *UMOD* gene, encoding uromodulin (also known as Tamm–Horsfall protein),[2] and mutations in the *REN* gene, encoding renin[5] (Figure 1). In the form of the disease caused by *UMOD* mutations, many family members suffer from gout at an early age. Mutations in the *REN* gene, encoding renin, were also found to cause ADTKD. In this form, patients also have symptoms of low renin activity: they are mildly hypotensive, hyperkalemic, anemic, and prone to acute kidney injury.[6]

The cause of the third type of ADTKD remained elusive for many years. Initially, a large group of families with this condition were identified by Deltas and colleagues on the island of Cyprus.[7] These and subsequent families were linked to chromosome 1 with refinement of the interval and extensive sequencing efforts by a group of investigators led by Friedhelm Hildebrandt, Edgar Otto, and Matthias Wolf.[8] After laborious and painstaking genetic analysis, investigators at the Broad Institute in Boston were able to identify a particular type of mutation in the *MUC1* gene as a cause of this disease.[9] The *MUC1* gene encodes mucin 1. This is a heavily glycosylated protein that rests on the apical surface of tubular cells, providing a protective covering to lumina in the kidney, lung, skin, and gastrointestinal tract and playing a role in several signal transduction pathways. The mutation identified in *MUC1* is a single cytosine duplication within one of the strings of seven cytosine residues that are present in each of a variable number (20–125) of 60-base-pair tandem repeat (VNTR) units of the gene. This duplication results in a frameshift in translation that causes the formation of a unique mutant protein. This mutant protein is unlike any other protein in the body and nature: The protein has a large number of basic amino acids and cysteine residues and is highly basic (isoelectric point $\sim$12). It cannot fold properly and is prone to aggregation, resulting in deposits of the protein in tubular cells. Although this mutated protein is produced and precipitates in many cells throughout the body, for some unknown reason it causes pathophysiology only in the kidney, with affected individuals developing slowly progressive chronic kidney disease. The rate of progression is very variable—something that also is not yet understood—with individuals requiring

renal replacement therapy between the third and eighth decades of life. The investigation by Ekici and colleagues[1] is the first independent confirmation of this finding and solidifies this particular *MUC1* mutation as a cause of ADTKD.

Identification of the genes for the three types of ADTKD is important for a number of reasons. First, we now have a clear method to diagnose and distinguish these conditions. Precise diagnosis can be made genetically, instead of by a kidney biopsy, which will yield inconclusive results for this group of diseases. Second, family members can be tested for the condition to see whether they are potential kidney donors. Third, these conditions can now be more precisely characterized clinically and pathologically, as has been done in the article by Ekici *et al.*[1] is acceptable. Finally, specific research can now help us explore the pathophysiology, and, most importantly, find cures for these conditions.

In summary, Ekici and colleagues[1] present new and important information about autosomal dominant tubulointerstitial kidney disease. Use of this term should make it easier for clinicians to identify the disease and enhance communication. They also provide confirmation of a specific *MUC1* mutation as one of the primary causes of this condition and propose a diagnostic work-up utilizing the capacities of new methods of DNA sequencing. We believe this will lead to further clinical and research advances in an exciting area of kidney disease.

DISCLOSURE
The authors declared no competing interests.

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Molecular diagnostics in renal allograft biopsy interpretation: potential and pitfalls

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Application of molecular techniques, particularly gene expression microarrays, to the study of T cell-mediated rejection, antibody-mediated rejection (ABMR), and other changes in renal allografts has grown. While studies of gene expression within renal allograft biopsies have elucidated the pathogenesis of rejection and helped lead to recognition of C4d-negative ABMR, the use of molecular studies to achieve greater diagnostic accuracy and precision, guide therapy, and decrease the need for biopsies still remains a hope for the future.

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At the 2007 Banff Conference on Allograft Pathology, Phil Halloran presented ground-breaking findings from his laboratory at the University of Alberta using gene expression microarrays performed on tissue from renal allograft biopsies, identifying changes in expression of pathogenesis-based transcript sets that correlated with histologic lesions of acute rejection.[1] During the lively discussion that followed, I recall making the comment that 'I do not need an Affymetrix chip to diagnose rejection,' a statement affirmed by many other pathologists.

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