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Renal fibrosis is the common feature of autosomal dominant tubulointerstitial kidney diseases caused by mutations in mucin 1 or uromodulin

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For decades, ill-defined autosomal dominant renal diseases have been reported, which originate from tubular cells and lead to tubular atrophy and interstitial fibrosis. These diseases are clinically indistinguishable, but caused by mutations in at least four different genes: *UMOD*, *HNF1B*, *REN*, and, as recently described, *MUC1*. Affected family members show renal fibrosis in the biopsy and gradually declining renal function, with renal failure usually occurring between the third and sixth decade of life. Here we describe 10 families and define eligibility criteria to consider this type of inherited disease, as well as propose a practicable approach for diagnosis. In contrast to what the frequently used term 'Medullary Cystic Kidney Disease' implies, development of (medullary) cysts is neither an early nor a typical feature, as determined by MRI. In addition to Sanger and gene panel sequencing of the four genes, we established SNaPshot minisequencing for the predescribed cytosine duplication within a distinct repeat region of *MUC1* causing a frameshift. A mutation was found in 7 of 9 families (3 in *UMOD* and 4 in *MUC1*), with one indeterminate (*UMOD* p.T62P). On the basis of clinical and pathological characteristics we propose the term 'Autosomal Dominant Tubulointerstitial Kidney Disease' as an improved terminology. This should enhance recognition and correct diagnosis of affected individuals, facilitate genetic counseling, and stimulate research into the underlying pathophysiology.

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Chronic kidney disease (CKD) is defined by a reduction in glomerular filtration rate and/or structural abnormalities of the kidney. It affects >10% of the adult population in Europe and North America. CKD is not only a major burden on health-care costs but also an important and independent predictor of cardiovascular morbidity and mortality.[1] Independent of the initial cause, the progression of renal disease involves increasing interstitial fibrosis and tubular atrophy (IF/TA), which is also the parameter with the highest predictive value for decline in kidney function.[2] Heterogeneous and frequent conditions (such as hypertension, diabetes mellitus, inflammatory diseases, and drug use) can lead to renal IF/TA. Multiple molecular pathways are believed to be involved in the development of IF/TA, with activation of molecules such as transforming growth factor-β1, connective tissue growth factor, and basic fibroblast growth factor-2

being some of the many leading to epithelial dedifferentiation and fibrogenesis.[3] However, the initial signals giving the impulse to fibrosis are largely unknown. In general, the clarification of monogenic hereditary diseases promises identification of priming signals. This may improve the understanding of the pathogenesis of disease far beyond the usually rare hereditary forms and lead to novel and specific ways of therapeutic intervention.

Over the past couple of decades, families with autosomal dominant tubulointerstitial kidney diseases have been repeatedly described, in which affected individuals slowly develop end-stage renal disease (ESRD) between the third and sixth decade of life because of progressive IF/TA, with or without extrarenal symptoms, such as early gout, renal cysts, or diabetes mellitus.[4] Until recently, the genes causing this disease were incompletely described; hence, the disease is not well known and it has been impossible to correctly diagnose, classify, and counsel families. Another profound difficulty, the rather unfortunate name 'medullary cystic kidney disease' (MCKD), has hampered the correct handling of the disease. Indeed, the finding of cysts in the renal medulla does not appear to be typical[4,5] and seems to have confused clinicians in correctly diagnosing the disease. Moreover, the term includes only two subtypes of the disease, when at least four can be differentiated (see below). Furthermore, numerous parallel names and abbreviations have been given to this group of diseases, such as TIN (tubulointerstitial nephritis), FJHN (familial juvenile hyperuricemic nephropathy), UMAK (uromodulin-associated kidney disease), MCD (medullary cystic disease), or ADMCKD (autosomal dominant MCKD), that has further increased the clinical bafflement. Finally, these autosomal dominant renal diseases have been clubbed together into one disease entity with the different forms of 'Familial Juvenile Nephronophthisis' (FJN) under the term 'nephronophthisis complex,'[6] despite significant clinical and genetic differences, with autosomal recessive inheritance observed in pediatric FJN patients.

Mutations in at least four genes can be implicated in the autosomal dominant disease: *MUC1* encoding mucin 1 (chromosomal location and gene at Online Mendelian Inheritance in Man (OMIM) 1q22 and 158340, respectively),[7] *UMOD* encoding uromodulin[8] (OMIM 16p12.3 and 191845), *HNF1B* encoding hepatocyte nuclear factor-1β[9,10] (OMIM 17q12 and 189907), and *REN* encoding renin[11] (OMIM 1q32.1 and 179820). Although some of these disorders may be accompanied by typical extrarenal features, these are not obligatory. The common and often the only feature of all of these variants is autosomal dominant inheritance and renal IF/TA.[4,5] Therefore, these four entities cannot be differentiated clinically but can only be reliably identified by genetic analysis.

To date, the proportion of these phenotypically similar autosomal dominant diseases due to mutations in either of the four genes is not known. However, two forms have been prominent: MCKD1 and MCKD2. MCKD2 is caused by mutations in the *UMOD* gene[8] that codes for the Tamm–Horsfall glycoprotein/uromodulin. The functions of Tamm–Horsfall glycoprotein have still not been fully resolved, but among other tasks it appears to be involved in renal clearance of uric acid, either directly or indirectly. This may explain why some families develop hyperuricemia and early gout that may precede renal insufficiency. However, numerous MCKD2 families have been described without this clinical feature (for review see Bleyer *et al.*[12]). The search for the disease-causing gene of MCKD1 has taken considerably longer. The locus on chromosome 1q21 was first identified in 1998,[13] and has subsequently been confirmed by numerous independent studies.[14–18] However, despite widespread efforts, the link to the responsible gene *MUC1* was only recently identified.[7] *MUC1* contains a coding GC-rich region of 'variable number of tandem repeat' (VNTR) sequences that was originally believed to lie between the second and third exons, consisting of up to 100 or more repeating stretches of 60 base pairs.[19] Because of this complex structure, the VNTR region of the *MUC1* gene has been impossible to analyze by straight Sanger sequencing, whole-genome, or whole-exome massive parallel sequencing. The 60 base-pair repeat includes a sequence of seven cytosine (C) residues. The only disease-causing mutation in the *MUC1* gene described to date is a duplication of one cytosine in the heptanucleotide cytosine tract that leads to a frameshift mutation and reaches an early stop after the VNTR region.[7]

In this study we analyzed 10 novel families with European ancestry with autosomal dominant CKD, and developed a systematic approach for a reliable genetic diagnosis. On the basis of clinical and genetic findings, we suggest a new term, 'Autosomal Dominant Tubulointerstitial Kidney Disease' (ADTKD). We anticipate that this improved terminology would facilitate the recognition and stimulate further research on prevalence and underlying pathophysiology.

RESULTS

Characterization of families

Aiming to improve the clinical and genetic description of the ADTKD family of renal diseases, we searched for families who fulfilled four criteria: (1) autosomal dominant inheritance; (2) development to ESRD usually between the third and sixth decade of life or at least profound CKD; (3) predominant IF/TA on renal biopsy (where available) with absence of immunohistological staining or any signs of primary glomerulopathy; and (4) bland urine sediment and absent or mild proteinuria. Our search criteria did not include the presence or absence of renal cysts.

We analyzed 10 incident, unrelated families who met the inclusion criteria and were of European descent (Table 1). Two of these families were quite large (families 1 and 2); their pedigrees are shown in Figure 1 (see Supplementary Figure S1 online for the pedigrees of families 3 to 10). The inheritance pattern in these 10 families showed full penetrance in terms of each affected individual having an affected parent. Affected family members were equally dispersed in both sexes and in each generation. Two families displayed