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Uromodulin and Translational Medicine: Will the SNPs Bring Zip to Clinical Practice?

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Tamm-Horsfall protein (THP) was originally described in 1895 as “urinary mucoprotein” and biochemically characterized approximately 50 years ago. Kidney epithelial cells of all placental mammals synthesize THP, and it is the most abundant protein in normal urine.1–3 Pirica, a novel THP-like gene that is induced in response to predation, was recently identified in tadpoles, suggesting that THP family proteins are also present in invertebrate species.4 Uromodulin was originally reported as a unique immunosuppressive glycoprotein from the urine of pregnant women,5 and its amino acid composition is identical to THP.6 Standard nomenclature for THP is now uromodulin.

Uromodulin provides a protein infrastructure for urinary casts used to diagnose various kidney diseases in the clinic. Experimentalists have used both in vitro and in vivo models to define the biology of uromodulin in the urinary tract, and protein chemists have extensively characterized its biochemical properties and domains.6–10 Despite these efforts, the function of uromodulin remains an enigma. Published data suggest uromodulin is glycosyl phosphatidylinositol-anchored along the apical domain of some kidney epithelia and secreted into urine and blood. It inhibits both bacterial colonization of the urinary tract and stone formation, binds and activates leukocytes, and generates the water impermeability of the thick ascending limb of Henle by assembly into filaments through its zona pelucida domain. Tissue distribution of pirica, the amphibian uromodulin-like protein, also supports the hypothesis that uromodulin regulates the water permeability of tissue.11

Mutations in UMOD, the gene that encodes uromodulin, cause rare, autosomal dominant, primary tubulointerstitial...
kidney diseases, particularly familial juvenile hyperuricemic nephropathy (FJHN; OMIM 191845) and a form of medullary cystic kidney disease (MCKD2; OMIM 603860).10,11,12 The Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE) consortium reported a genome-wide association study (GWAS) of common chronic kidney disease (CKD) with single-nucleotide polymorphisms (SNPs) upstream or within noncoding regions of UMOD.13 The sentinel UMOD SNP associates with a 20% reduced risk for CKD. Reports of causal mutations for complex common traits, such as CKD, are plagued with irreproducible results, but these CHARGE consortium findings are robust. The sample size included four white, population-based cohorts (approximately 20,000 subjects) with almost 2000 cases of CKD. Importantly, the association was also replicated in a second, independent data set.

As a clinical nephrologist and an investigator in a consortium to identify genetic variants that regulate diabetic nephropathy,14 I know such findings raise many questions concerning pathogenesis, particularly whether the UMOD association with common CKD will change practice by better defining CKD pathogenesis, identifying drug-modulated pathways, or improving diagnosis or risk stratification. Mechanisms by which genetic variants, discovered by GWAS, regulate common disease phenotypes are often not readily apparent from the initial identification of the associated SNPs, a problem that applies to the UMOD variants associated with common CKD in CHARGE. These UMOD SNPs are located in noncoding regions, and their effects on uromodulin are speculative. The common wisdom suggests these nonfunctional variants are proxies for unidentified, functional variants in UMOD. The UMOD variants, identified by CHARGE, implicate a gene known to cause FJHN/MCKD2. Hypotheses about effects of the GWAS variants on uromodulin function can be inferred from published data on uromodulin in FJHN/MCKD2 pathogenesis.

UMOD mutations in FJHN/MCKD2 delay uromodulin maturation during translation. Mutant uromodulins, expressed in patients with FJHN/MCKD2, are also retained in the endoplasmic reticulum, reducing their expression at the apical plasma membrane.9,15 Consistent with intracellular retention of mutant uromodulin, patients with FJHN/MCKD2 have reduced amounts of uromodulin in urine.16,17 These uromodulin-trafficking defects cause renal tubular epithelial cell dysfunction and apoptosis, resulting in tubulointerstitial fibrosis with progressive CKD. In contrast to diminished apical secretion into urine, mutant FJHN/MCKD2 uromodulins are secreted as efficiently as the wild-type protein from the basolateral compartment.

Some investigators hypothesize that epithelial cell injury and ensuing tubulointerstitial nephritis in FJHN/MCKD2 results from immune mechanisms activated by mutant uromodulin after secretion from the basolateral regions of tubular epithelial cells. Rats or mice immunized with uromodulin develop immune-mediated tubulointerstitial nephritis with basolateral deposits, but tubulitis and immune complex deposits have never been reported in human FJHN/MCKD2. Whereas aberrant uromodulin trafficking in FJHN/MCKD2 is clear, the link between this process and clinical kidney disease requires further study. The abnormalities in FJHN/MCKD2 might predict potential mechanisms for common CKD involving UMOD variants inherited with the SNPs identified by CHARGE; therefore, I predict that patients who have CKD and do not have protective UMOD alleles might have reduced urinary uromodulin, consistent with abnormal uromodulin trafficking.

In this issue of JASN, Köttgen et al.,18 however, report increased urinary uromodulin levels precede CKD. These results reject my hypothesis, suggesting that variant uromodulin in common CKD increases risk for kidney disease by mechanisms distinct from those implicated in FJHN/MCKD2. The CHARGE investigators use a nested, case-control analysis of incident CKD in participants from the Framingham Heart Study (FHS) and the Atherosclerosis Risk in Communities (ARIC) Study. Elevated urinary uromodulin concentrations precede the development of CKD in both cohorts, and for each copy of the protective SNP, log uromodulin concentrations (urinary uromodulin was skewed and therefore transformed to achieve normality) are significantly lower.

A particular strength of this study is the prospective design; uromodulin was measured in urine samples collected before onset of CKD. The authors fairly discuss study limitations, most prominently the small numbers of CKD cases in the discovery and replication cohorts. The difference in urinary uromodulin levels between patients with FJHN/MCKD2 and patients with CKD in FHS and ARIC is not easily explained and will require further confirmation in both population- and disease-based cohorts. Unfortunately, more mechanistic studies will be limited until the common CKD-causing UMOD variants are identified.

This brings me to my final topic: Can UMOD mutations help us treat patients? The data suggest that genetic testing for FJHN/MCKD2 is a reasonable approach in patients with the appropriate clinical phenotypes and family history and is preferable to renal biopsy.9,19 Screening families of candidate transplant donors underscores the clinical utility of genotyping for this disease. In addition, Bleyer19 persuasively argued that carefully phenotyping and research genetic testing of families with autosomal dominant tubulointerstitial disease will improve diagnosis, provide more complete clinical data, and identify novel genes (for more information: ableyer@wfubmc.edu).

In contrast, the clinical utility of UMOD genotyping or measuring levels of urinary uromodulin in patients with common causes of CKD has not been shown, and this defi-
ciency underscores issues plaguing translation of variants identified by GWAS into improved understanding of disease mechanisms. In particular, the contributions of most GWAS disease-associated variants to phenotype variance are small. The UMOD variants reported by CHARGE account for <1% of estimated variability in GFR, suggesting additional, undiscovered loci regulate renal function. In addition, for most genetic variants associated with common diseases, the functional mutations inherited with the sentinel SNPs are not known. Finally, even GWAS with extremely large sample sizes is powered only to identify common genetic variation with allele frequencies >10% in the population. Although frequencies of disease-associated variants differ statistically between patients and control subjects, many unaffected individuals carry the risk/protective variants, and these SNPs are not informative for diagnosis or prognosis.

What next? The last 18 months has been an exciting time in the area of common trait kidney disease genetics. In addition to UMOD SNPs, variants in a myosin motor protein, encoded by MYH9, may explain the excess risk for ESRD in black individuals20; however, the genetic architecture of common disease is just being elucidated. More information is needed before we can use these findings in the clinic. Discoveries that variants in UMOD and MYH9 associate with common CKD should promote creative human and basic experimentation for understanding mechanisms for kidney disease and defining applications in the clinic. To accomplish these goals, physicians and basic and social scientists will need to engage. The intriguing relationship between urinary uromodulin and incident CKD reported by the CHARGE consortium will certainly stimulate such efforts.

DISCLOSURES
None.

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See related article, “Uromodulin Levels Associate with a Common UMOD Variant and Risk for Incident CKD,” on pages 337–344.