TREATMENT AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

There is no specific therapy for ARPKD. Appropriate neonatal intensive care, blood pressure control, dialysis, and kidney transplantation increase survival into adulthood. Complications of hepatic fibrosis may necessitate liver transplantation. Patients with severe Caroli's disease may need portosystemic shunting. Upcoming therapies may target abnormal cell signaling mechanisms, as described above for ADPKD.

OTHER DISEASES CHARACTERIZED BY LARGE KIDNEY CYSTS

TUBEROUS SCLEROSIS

Tuberous sclerosis (TS) is a rare autosomal dominant syndrome caused by mutations in one of two genes, *TSC1*, encoding hamartin, or, *TSC2*, encoding tuberin. Published estimates of prevalence vary widely, but it certainly occurs in less than 1:5000 births. Kidney cysts are a frequent feature of this condition, as are two other abnormalities of kidney growth, renal cell carcinoma and renal angiomyolipomas. TS is a syndrome affecting multiple organ systems. Other features of TS include benign growths in the nervous system, eyes, heart, lung, liver, and skin. Essentially all TS patients have associated skin lesions, and a large proportion of patients have neurologic and cognitive manifestations. The *TSC2* gene is adjacent to *PKD1* in the human genome. Some patients have deletions in their genomic DNA that inactivate these two genes. Such individuals may have manifestations of both ADPKD and TS.

The most common kidney finding in TS is the presence of angiomyolipomas. These growths tend to be multiple and bilateral. Although they are usually benign, they may bleed. Surgical removal is often recommended as a prophylactic measure in people with angiomyolipomas larger than 4 cm in diameter. The cysts in TS are radiographically similar to those seen in ADPKD. In contrast to ADPKD, there is a clearly increased risk of renal cell carcinoma in TS patients. Regular periodic imaging is recommended in TS patients with kidney involvement to screen for the development of renal cell carcinoma.

Although not common, TS may lead to significant chronic kidney disease (CKD) and progress to end-stage kidney failure. Patients with TS and CKD typically have an unremarkable urine sediment and only minimal to mild amounts of proteinuria.

Mechanistically, the *TSC1* and *TSC2* gene products tuberin and hamartin interact physically. This protein complex is localized to the base of the cilia and inhibits intracellular signaling processes mediated by mTOR, leading to abnormal growth in a number of tissues. Investigation of mTOR inhibitors as therapy for TS is ongoing.

VON HIPPEL-LINDAU DISEASE

Von Hippel-Lindau disease (VHL) is an inherited cancer syndrome with renal manifestations. VHL is an autosomal dominant condition caused by mutations in the VHL tumor-suppressor gene. VHL is localized to the primary cilia and is necessary for the formation of primary cilia. Like many autosomal dominant cancer syndromes, VHL is recessive at the cellular level: a somatic mutation in the second VHL allele leads to loss of VHL in the cell and abnormal growth. Kidney manifestations of VHL include multiple bilateral kidney cysts and renal cell carcinomas. Kidney cysts and carcinoma affect the majority of VHL patients. Nonrenal features of VHL include pheochromocytomas, cerebellar hemangioblastomas, and retinal hemangiomas.

Annual screening of the kidneys by imaging with CT or MRI is recommended for early detection of renal cell carcinomas. Increasingly, nephron-sparing surgical approaches are being used for removal of cancerous lesions in order to preserve kidney function.

OTHER INHERITED DISEASES OF TUBULE GROWTH AND DEVELOPMENT

ADPKD is by far the most common adult-onset, single-gene form of kidney disease. The large cysts that are sometimes seen in VHL and TS are similar in appearance to the cysts seen in ADPKD. A variety of other inherited disorders affecting primarily tubule and renal interstitial function can lead to CKD and eventual end-stage kidney disease in the absence of large tubule-derived cysts.

Inherited diseases affecting the tubulointerstitial compartment of the kidney can lead to secondary glomerular stress and glomerulosclerosis with some degree of concomitant proteinuria. Similarly, disorders of glomerular function will typically lead to secondary interstitial fibrosis and tubule atrophy. From a clinical perspective, therefore, distinguishing between a genetic disease of the renal tubules and a disease of the glomerulus may not be easy, particularly in the absence of a gross phenotype such as large kidney cysts.

MEDULLARY CYSTIC KIDNEY DISEASE (AUTOSOMAL DOMINANT INTERSTITIAL KIDNEY DISEASE)

The medullary cystic kidney diseases (MCKD) are autosomal dominant disorders. Despite the nosology, kidney cysts are not invariably present. Older literature often grouped MCKD together with the childhood-onset disorders known as the nephronophthises, but these are distinct clinical and genetic entities.

Medullary Cystic Kidney Disease Type I Patients with MCKD type I (MCKD I) have mutations in the mucin 1 gene *MUC1*. In contrast to MCKD type II (MCKD II) patients, individuals with MCKD I do not have elevated uric acid levels. The disease-causing *MUC1* mutations that have been reported all alter a repeat region within the *MUC1* gene, leading to a large "neoprotein" fragment that may lead to toxic effects on the kidney tubule.

Clinically, patients with MCKD I exhibit slowly progressive CKD in adulthood, with only minimal amounts of increased urine protein and occasional renal cysts seen on ultrasound examination. Kidney histology shows tubulointerstitial fibrosis and tubular atrophy. The mechanisms by which *MUC1* mutations cause human kidney disease are not known.

Medullary Cystic Kidney Disease Type II MCKD II is caused by mutations in the *UMOD* gene, which encodes the protein uromodulin, also known as Tamm-Horsfall protein. Uromodulin is also found on the centrosome, the mitotic spindle, and the primary cilia; it colocalizes with nephrocystin-1 and KIF3A on the cilia. *UMOD* mutations also cause the conditions that have been referred to as familial juvenile hyperuricemic nephropathy (HNFJ1) and glomerulocystic kidney disease (GCKD), although it is not clear that these different names represent clearly distinct disorders. The term *uromodulin-associated kidney disease* (UAKD) has been suggested as a better name for MCKD II and the various other related *UMOD*-associated diseases. Despite the name, kidney cysts are not a common feature of MCKD II. MCKD II should be suspected clinically in patients with a family history of late-onset kidney disease, benign urine sediments, absence of significant proteinuria, and hyperuricemia. Large genome-wide association studies have suggested that certain common noncoding sequence variants in *UMOD* are associated with a moderately increased risk of CKD in the general population.

Other Forms of Familial Tubulointerstitial Kidney Disease A small number of families have been identified with autosomal dominant tubulointerstitial kidney disease and hyperuricemia who lack *UMOD* mutations. Some of these families carry disease-segregating mutations in the renin gene *REN*. There are other families who lack mutations in *UMOD*, *MUC1*, or *REN*. Thus, mutations in other yet-to-be identified genes are able to produce similar interstitial kidney disease, both with and without hyperuricemia.

Kidney biopsies in patients with any of the various forms of MCKD typically show interstitial fibrosis. These histologic features are not diagnostic of any particular genetic entity, and the specific diagnosis must be made by other means. Genetic tests for alterations in specific genes are increasingly available in the clinical setting.

Patients with autosomal dominant interstitial kidney disease, *UMOD* or *REN* mutations, or hyperuricemia and gout should be treated similarly to others with these findings, with uric acid–lowering agents, such allopurinol or febuxostat.