The Genetics of Renal Disease

I have heard about a gene that causes high blood pressure. Did I hear that right? Is testing for this gene available now?

African-Americans have a higher risk for chronic kidney disease (CKD), including end-stage renal disease (ESRD; defined as kidney failure requiring dialysis or transplant), than any other racial or ethnic group in the United States.1 Previously, this has been attributed to poorly controlled hypertension and diabetes, as well as socioeconomic factors such as limited access to health care.

Research now shows that autosomal recessive genetic variations on chromosome 22q, the gene that encodes apolipoprotein-1 (APOL1; an HDL protein), promote hypertension. This subsequently increases the risk for and progression of CKD in black patients (who have up to 29x higher risk than white patients without this genetic variation).2

The APOL1 gene has two alleles. Having at least one of them provides resistance to Trypanosoma brucei, the cause of “sleeping sickness” transmitted by the tsetse fly, but increases risk for hypertension-related CKD.2,3 This is especially true in black patients with CKD who have two altered alleles are at highest risk for focal segmental glomerulosclerosis, HIV nephropathy, and CKD attributable to hypertension.2,3 The African-American Study of Kidney Disease and Hypertension found that black patients with hypertension controlled by ACE inhibitors had slower progression of CKD, regardless of allele variation.2,3 Currently, there is no treatment for this genetic alteration.4

One could posit that black patients undergoing renal transplant would have a higher risk for renal failure in the transplanted kidney due to APOL1-related hypertension, compared to nonblack renal transplant recipients. Additionally, a donor kidney with an altered APOL1 gene may have a higher risk for failure.6

Genotyping for APOL1 (CPT code: 81479) is available in select laboratories at a cost of approximately $400.7 For a family that has a member affected by kidney failure at a young age, knowing whether the APOL1 gene is carried in the family would allow early aggressive hypertension management to help prevent a lifetime of severe CKD.

Foster et al reported that black patients with two altered alleles had a 31% higher risk for CKD and ESRD, compared with individuals with hypertension-induced nephrosclerosis who had zero to one altered alleles.4 Nondiabetic black patients with CKD who have two altered alleles are at highest risk for focal segmental glomerulosclerosis, HIV nephropathy, and CKD attributable to hypertension.2,3 The African-American Study of Kidney Disease and Hypertension found that black patients with hypertension controlled by ACE inhibitors had slower progression of CKD, regardless of allele variation.2,3 Currently, there is no treatment for this genetic alteration.4

In school, they always emphasized the abdominal exam to rule out Wilms tumors. Are Wilms tumors still with us? Has treatment and evaluation changed?

Wilms tumor is a renal cancer found most commonly in children younger than 9 and represents approximately 7% of all malignancies in children.8,9 It can occur in one or both kidneys, with earlier diagnosis noted with bilateral involvement. Risk is highest among non-Hispanic white persons and African-Americans and lowest among Asians.8

Wilms tumor develops due to a genetic mutation in the WT1 gene located on the 11p13 chromosome. Continued on page 33...
mosome. Defects are also noted on the 11p15 chromosome and the p53 tumor suppressor gene.

Urbach et al recently identified a relationship between the LIN28 gene and Wilms tumor. Tumors develop when embryonic renal cells that should cease growing at the time of birth continue to grow in the postnatal period. Wilms tumor can be familial or sporadic. It can also be associated with various congenital anomalies manifested within various syndromes (see Table 2), as well as isolated genitourinary abnormalities, especially in boys.

Most children present with a palpable, smooth, firm, generally painless mass in the abdomen; those who have bilateral renal involvement usually present earlier than those with unilateral involvement. Palpation of the abdomen during examination, if vigorous, can result in rupture of the renal capsule and tumor spillage. Additional symptoms include hematuria, fever, and hypertension.

Referral to pediatric oncology is imperative. Definitive diagnosis is made by histologic evaluation following biopsy or surgical excision. Other possible diagnostic tests include but are not limited to abdominal ultrasound or CT; chest CT (to rule out metastatic lung disease); urinalysis (to evaluate for hematuria and proteinuria); liver function studies (to evaluate for hepatic involvement); and laboratory studies to measure coagulation, serum calcium, blood urea nitrogen, creatinine, and complete blood count.

Histologic examination for staging (I-V) occurs following surgical excision of the tumor. There are two staging systems available: the National Wilms Tumor Study, based on postoperative tumor evaluation, and the International Society of Pediatric Oncology, based on post-chemotherapy evaluation. Treatment options include surgical excision (including complete nephrectomy of the affected kidney), chemotherapy based on tumor staging, and internal and/or external radiation therapy.

**Table 2**

**Congenital Abnormalities Associated With Wilms Tumor**

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<thead>
<tr>
<th>Syndrome</th>
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<tbody>
<tr>
<td>Beckwith-Weidemann syndrome</td>
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<td>Bloom syndrome</td>
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<td>Simpson-Golabi-Bechmel syndrome</td>
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<td>Sotos syndrome</td>
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<td>WAGR syndrome</td>
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Note: This list is not exhaustive.

**REFERENCES**