Renal Cell Carcinoma of End-Stage Renal Disease: A Histopathologic and Molecular Genetic Study\textsuperscript{1,2}

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ABSTRACT

Renal cell carcinomas (RCC) are responsible for the deaths of 3% to 4% of patients with ESRD. The clear cell carcinoma of the kidney, which comprises 80% of sporadic RCC within the general population, shows a deletion of gene sequences in the short arm of chromosome 3 (3p) in as many as 100% of cases. The von Hippel-Lindau tumor suppressor gene at 3p25-26 is found to be mutated in the nondeleted allele in 57% of these sporadic clear cell carcinomas. This study was undertaken to determine the histopathologic types of RCC occurring in ESRD patients in the United States and to investigate the frequency with which 3p genetic changes can be found in these ESRD tumors. Seventeen end-stage kidneys containing RCC were collected from 15 ESRD patients at ten US medical centers. The tumors were classified by Thoenes' histopathologic typing. DNA extracted from paraffin blocks of tumor and nontumorous tissue was analyzed by single-stranded conformational polymorphism analysis for von Hippel-Lindau mutations and by microsatellite amplification for deletion of 3p gene sequences. Twenty-one RCC were identified in the 18 kidneys. The 21 RCC were classified histopathologically as follows: clear cell, compact, three cases; chromophilic, tubulopapillary, 15 cases; chromophilic, compact, three cases. Among the three clear cell carcinomas, one showed 3p genetic loss. None of the chromophilic RCC showed a 3p deletion and none of 19 tumors studied by single-stranded conformational polymorphism analysis disclosed von Hippel-Lindau mutations. In contrast to the general population, clear cell RCC with 3p abnormalities represent only a small proportion of the renal carcinomas in this collection of ESRD tumors. The findings indicate that the genetic changes underlying the development of most ESRD tumors are different from those occurring in sporadic clear cell RCC and do not characteristically involve the inactivation of a 3p tumor suppressor gene.

Key Words: Renal cell carcinoma, cancer genetics, ESRD

Malignancy is now the sixth most frequent specific cause of death among ESRD patients (1,2). This appears to be the result of a four- to fivefold increase in the annual incidence of renal cell carcinoma (RCC) above the rate seen in the general (non-dialysis) population (3). RCC is also reported as the cause of death in 2% of kidney transplant patients (4).

The RCC of ESRD are found with high frequency in diseased kidneys that also are involved by acquired renal cystic disease (ARCD) (5–7). Histopathologic studies of ARCD have shown cellular changes that suggest many of the carcinomas of ESRD develop from papillary cystic hyperplasia (8). The carcinomas of the end-stage kidney have been classified as papillary or clear cell RCC. Papillary RCC seem to occur in disproportionately high numbers and clear cell carcinomas in disproportionately low numbers among ESRD patients (9,10).

The classic clear cell carcinoma represents 80% and the papillary carcinoma represents 10% of sporadically occurring RCC (11,12). The remaining carcinomas are classified as chromophobe (4%), collecting duct (1%), spindle-shaped/pleomorphic "sarcomatoid" (1%), and mixed (3%) histologic types. Clear cell carcinomas are shown to have a deletion of gene sequences in the short arm of chromosome 3 (3p) in 50% to 100% of cases (13,14). The frequency of this genetic abnormality has suggested that tumor development is caused by the loss of a tumor suppressor gene in the involved chromosomal segment. Latif \textit{et al.}
Tumor Classification

Ann Arbor, MI; Little Rock, AR; Los Angeles, CA; Rochester, were performed in 1984, 1988, and 1990. Blocks of formalin-

VHL mutations and cytogenetically defined 3p dele-
tions have not been found in histopathologic types of RCC other than clear cell carcinomas (13,18). This study was undertaken to investigate the frequency of 3p deletions and VHL mutations in carcinomas of end-stage kidneys. The findings are correlated with tumor histopathology to determine whether genetic events associated with the development of specific types of tumors in ESRD are similar to those observed in sporadic kidney cancer.

MATERIALS AND METHODS

Materials

Cases of RCC occurring in ESRD were solicited from colleagues at ten United States medical centers (Oklahoma City, OK; Chapel Hill, NC; Charleston, SC; Milwaukee, WI; Ann Arbor, MI; Little Rock, AR; Los Angeles, CA; Rochester, NY; Dallas, TX; Hershey, PA). Seventeen specimens were submitted from 14 nephrectomies and three autopsies. The 17 specimens contained 21 tumors. Four of the specimens were from two patients who had both kidneys removed at nephrectomies performed 3 and 5 months apart. Each kid-
necy from both patients had separate surgical pathology accession numbers and, for the purpose of this study, the kidneys and tumors from each operation are given separate case numbers (Table 1). All specimens were from patients with ESRD who had been treated by maintenance dialysis except for Case 14 in which the nontumorous kidney from a patient with ESRD who had been treated by maintenance dialysis. The nephrectomies had been accessioned as surgi-

cases Human Map-Pairs® Weissbach set. Polymerase chain reaction (PCR) was performed in 12.5-μL reaction mixtures consisting of 10 mM Tris HCl, 50 mM KCl, 1.5 mM MgCl2, 0.1% gelatin, 1% Triton X-100, 12.5 pmol of each primer, 50 to 100 ng template DNA, 200 μM dGTP, 200 μM dCTP, 200 μM dATP, 1.5 μCi α-35S-dATP, and 0.625 U of Taq polymerase (Promega, Madison, WI). PCR was performed at 94°C for 1 min, at 55°C for 1 min, at 72°C for 1 min for 30 cycles, followed by 5 min final extension at 72°C. After cycling, an equal volume of stop solution was added to the reaction mixtures, and 3.5 μL of the final solutions were run on 0.5X MDE gels (Hydrolink, AT Biochemi-

DNA Extraction

After examination of histologic sections and identification of tumor and normal tissue boundaries, tumor and normal tissue was dissected from paraffin blocks, minced into small fragments, and placed in separate 1.5-ml microcentrifuge tubes. The specimens were then deparaffinized in three 60-min changes of xylene, held in xylene overnight, and then hydrated through a graded series of ethanol (100%, 95%, and 70%; three changes 60 min each) into 1.0 mL of proteinase K buffer (50 mM Tris HCl, 1 mM EDTA, 0.5% Tween 20, pH 7.4). Specimens were then deproteinized with 0.5 μg protein-

RCC were classified according to the new cytomorphic typing of Thoenes et al. (11). This classification attempts to resolve histopathologic difficulties presented by some clear cell carcinomas that have papillary growth patterns and by tumors composed of the eosinophil staining cells usually seen in papillary carcinomas that have compact or actinar growth patterns. Thoenes' classification separates the two most common RCC into clear cell carcinoma and chromo-

The cloned cDNA of the VHL gene consists of three exons (19). Four PCR primer sets that span regions in the three exons known to be mutated in primary human RCC were used in this study (Table 2). PCR was performed in 10.0-μL reaction mixtures consisting of 50 to 100 ng of template DNA, 1× PCR buffer (Perkin Elmer Cetus, Norwalk, CT), 15 pmol of each primer, 200 μM dGTP, 200 μM dCTP, 200 μM dATP, 30 μM dTTP, 1.5 μCi α-35S-dATP, and 0.5 U of Taq polymerase (Perkin Elmer Cetus). PCR reactions for Exon 1 included 8% dimethyl sulfoxide. PCR was performed for 40 cycles at 95°C for 1 min, at 62°C for 1 min, and at 72°C for 2 min. A 1:3 volume (6 μL) of stop solution was added to the reactions and the entire reaction products were run as paired normal-

Microsatellite Analysis

Primers for chromosome 3 microsatellites at D3S2406 (3p13), D3S1285 (3p14), D3S1241 (3p21), D3S1217 (3p21), D3S1745 (3p21), D3S1766 (3p21), D3S1304 (3p24-p24.2), D3S192 (3p25), D3S1768 (3pter), D3S1766 (3pter), D3S1769 (3q13), and D3S1237 (3q22-q24) were purchased from Research Genet-

Tumor Classification

RCC were classified according to the new cytomorpholog-
cytic, and cystic. Clear cell carcinomas have compact growth patterns in 95% of cases. Chromopholic RCC are further divided into eosinophilic, granular (oncocyte-like) and small/cuboidal cell types. Chromopholic RCC have tubulopapillary growth patterns in more than 90% of cases.

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<table>
<thead>
<tr>
<th>Case (Kidney Specimen)</th>
<th>Histologic Classification of Renal Cell carcinomas</th>
<th>Renal Disease and Kidney Size</th>
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<tbody>
<tr>
<td>Age/Sex/Race Histologic Classification Treatment: Time</td>
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</tr>
<tr>
<td>1. 23/M/B First nephrectomy Dialysis: 3 months</td>
<td>T1: Chromophilic, eosinophilic/granular cell, compact T2: Chromophilic, eosinophilic/granular cell, compact</td>
<td>ADPKD, end-stage Left kidney, 6290 g</td>
</tr>
<tr>
<td>2. Same patient as Case 1, second nephrectomy Dialysis: 5 months</td>
<td>T1: Chromophilic, eosinophilic/granular cell, tubulopapillary</td>
<td>ADPKD, end-stage Right kidney, 8440 g</td>
</tr>
<tr>
<td>3. 49/M/B First nephrectomy Dialysis: 4 yr Transplant: 2 yr, 9 months</td>
<td>T2: Chromophilic, eosinophilic/granular cell, compact Clear cell with eosinophilic/granular cell elements</td>
<td>HTN, ARCD 4+ Right kidney, 350 g</td>
</tr>
<tr>
<td>4. Same patient as Case 3, second nephrectomy Dialysis: 4 yr Transplant: 3 yr, 2 months</td>
<td>Chromophilic, eosinophilic/granular cell, tubulopapillary</td>
<td>HTN, ARCD 4 Left kidney, 220 g</td>
</tr>
<tr>
<td>5. 46/M/B Dialysis: 11 yr</td>
<td>T1: Chromophilic, eosinophilic/granular cell, tubulopapillary T2: Chromophilic, eosinophilic/granular cell, tubulopapillary with spindle cell change</td>
<td>MPGN, ARCD 4+ Left kidney, 1600 g</td>
</tr>
<tr>
<td>6. 59/M/B Dialysis: 5 yr</td>
<td>Chromophilic, eosinophilic/granular cell, tubulopapillary</td>
<td>HTN, left renal agenesis ARCD 2+ Right kidney, 120 g</td>
</tr>
<tr>
<td>7. 49/M/B Dialysis: 1 month</td>
<td>Chromophilic, eosinophilic/granular and small/cuboidal cell, tubulopapillary</td>
<td>HTN, no ARCD. Left kidney, 156 g</td>
</tr>
<tr>
<td>8. 66/M/B Dialysis: 20 yr</td>
<td>Chromophilic, eosinophilic/granular cell, tubulopapillary</td>
<td>HTN, ARCD 4+ Right kidney, 592 g</td>
</tr>
<tr>
<td>9. 29/F/B Dialysis: 11 yr</td>
<td>Chromophilic, eosinophilic/granular cell, tubulopapillary</td>
<td>CPN, HTN, ARCD 2+ Left kidney, 592 g</td>
</tr>
<tr>
<td>10. 48/M/B Dialysis: 3 yr</td>
<td>Chromophilic, eosinophilic/granular cell, tubulopapillary</td>
<td>CGN, ARCD 2+ Left kidney, 121 g</td>
</tr>
<tr>
<td>11. 52/M/B Dialysis: 4 yr</td>
<td>T1: Chromophilic, eosinophilic/granular and small/cuboidal cell, tubulopapillary T2: Chromophilic, small/cuboidal cell, tubulopapillary</td>
<td>Right kidney, 700 g</td>
</tr>
<tr>
<td>12. 58/M/W Dialysis: 2 yr Transplant: 9 yr</td>
<td>Clear cell</td>
<td>ESRD-NOS, ARCD 3+ Right kidney, 155 g</td>
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<td>13. 39/M/W Dialysis: 8 yr</td>
<td>Chromophilic, eosinophilic/granular cell, tubulopapillary</td>
<td>Anti-GBM disease, ARCD 4+ Right kidney, 235 g</td>
</tr>
<tr>
<td>14. 46/M/W CRF, no dialysis</td>
<td>Chromophilic, small/cuboidal cell, tubulopapillary</td>
<td>FSGS, ARCD 1+ Partial left nephrectomy</td>
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<td>15. 36/M/W Dialysis: 2 yr Transplant: 2 yr</td>
<td>Chromophilic, eosinophilic/granular cell, tubulopapillary</td>
<td>FSGS, ARCD 2+ Right kidney, 135 g</td>
</tr>
<tr>
<td>16. 64/M/W Dialysis: 3 yr Transplant: 2 months</td>
<td>Clear cell (with 3p deletion)</td>
<td>ADPKD, end-stage Right kidney, 1120 g</td>
</tr>
<tr>
<td>17. 47/M/B Dialysis: 9 yr</td>
<td>Chromophilic, eosinophilic/granular cell, tubulopapillary with spindle cell change</td>
<td>HTN, ARCD 4+ Right kidney, 20 × 11.5 × 9 cm</td>
</tr>
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*ARCD, acquired renal cystic disease with semiquantification of degree of cystic change, mild 1+ to severe 4+; ADPKD, autosomal dominant polycystic kidney disease; MPGN, membranoproliferative glomerulonephritis; CGN, chronic glomerulonephritis; CPN, chronic pyelonephritis; FSGS, idiopathic focal segmental glomerulosclerosis; HTN, primary hypertension; 3p deletion; genetic deletion of short arm of chromosome 3; T, tumor; ESRD-NOS, end-stage renal disease, not otherwise specified; GBM, glomerular basement membrane; CRF, chronic renal failure.*
TABLE 2. Primers used for the single-stranded conformational polymorphism analysis of the von Hippel-Lindau gene

<table>
<thead>
<tr>
<th>Exon</th>
<th>Primers and Sequences</th>
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<tbody>
<tr>
<td>1</td>
<td>MA2A GGC CCG TGC GCT CGG TGA ACT sense</td>
</tr>
<tr>
<td></td>
<td>101 CCC TGC TGG GTC GGG CCT AAG CGC CGG GCC CGT antisense</td>
</tr>
<tr>
<td>1</td>
<td>MA8A TGG TCT GGA TCG CGG AGG GAA T sense</td>
</tr>
<tr>
<td></td>
<td>108 GAC TGC GAT TGC AGA AGA TGA CCT GGG antisense</td>
</tr>
<tr>
<td>2</td>
<td>K55 GTG GCT CIT TAA CAA CCT TIG C sense</td>
</tr>
<tr>
<td></td>
<td>K56 CCT GTA CIT ACC ACA ACA ACC TTA TC antisense</td>
</tr>
<tr>
<td>3</td>
<td>Y1A TIC CIT GTA CTG AGA CCC TAG T sense</td>
</tr>
<tr>
<td></td>
<td>68 TAC CAT CAA AAG CTG AGA TGA AAC AGT GTA AGT antisense</td>
</tr>
</tbody>
</table>

cal, Malvern PA) in a sequencing gel apparatus at 8 watts overnight. Dried gels were autoradiographed for 2 to 4 days and autoradiographs examined for abnormal electrophoresis bands in single-stranded conformational polymorphism (SSCP) and/or heteroduplex analysis. Reaction products that produced abnormal bands were directly sequenced by using a United States Biochemical Corporation sequencing kit (Cleveland, OH) and Dynabeads (Dynal, Inc., Oslo, Norway). One biotinylated and one nonbiotinylated primer were used in the PCR reaction for sequencing with Dynabeads, and the procedure was conducted according to the manufacturer's protocol.

RESULTS

Seventeen end-stage kidneys from 15 patients contained renal cell tumors that could be classified as carcinomas (Table 1). Twenty-one RCC were identified in these 17 kidneys. Three were clear cell carcinomas (Figure 1) that were solitary tumors in each case. The other 18 tumors were classified as chromophilic RCC. Fifteen had a tubulopapillary growth pattern (Figure 2). Eleven of the 15 tubulopapillary tumors were composed of eosinophilic/granular cells, two of small/cuboidal cells, and two of a mixture of eosinophilic/granular and small/cuboidal cells. Two of the eosinophilic/granular cell RCC showed spindle cell change (Figure 3). The spindle cell change might be considered sarcomatoid by some pathologists, but the cytologic changes were not notably pleomorphic. Three chromophilic RCC from one patient with autosomal dominant polycystic kidney disease (ADPKD) had compact or solid growth patterns (Figure 4). These tumors were composed of eosinophilic/granular cells and showed no clear cell features. They occurred together with an ordinary appearing chromophilic tubulopapillary RCC in one of the patient's kidneys.

Kidneys represented by Cases 1, 2, 5, and 11 each contained two tumors. Cases 1 and 2 were from the ADPKD patient mentioned in the previous paragraph. In Cases 5 and 11, each tumor was classified as a chromophilic tubulopapillary RCC. Chromophobe carcinomas, collecting duct carcinomas, and benign oncocytomas were not found in this series.

Two patients (Cases 1, 2, and 16) had end-stage ADPKD. In 13 cases, the kidneys were involved by ARCD. One case (Case 14) showed the early development of ARCD, although the patient had not received dialysis at the time a partial nephrectomy was performed to remove a tumor. One case (Case 7), in which the patient had been on dialysis just 1 month before nephrectomy, showed no cystic disease. The mean duration of renal replacement therapy, which in three patients included transplantation, was 6.2 yr with a range of no dialysis and 1 month dialysis to 20 yr. All but one of the patients were male and ten were black. The mean age of the patients was 47 yr (range, 23 to 66 yr).

DNA was extracted from all normal and tumor tissue except Tumor 1 of Case 5. In this case, the
amount of tumor tissue was limited, and it was elected to save the paraffin block. This was a tubulopapillary RCC composed of eosinophilic/granular cells identical with other tumors classified in this histologic category. Microsatellite studies and SSCP analysis were performed successfully on all specimens except normal and tumor tissue from the 1984 autopsy (Case 9) in which no PCR products could be obtained. Only degraded low molecular weight DNA could be extracted from the paraffin blocks of this case.

The clear cell RCC of Case 16 from an ADPKD showed a deletion of gene sequences at 3p13-pter by microsatellite analysis (Figure 5). None of the other RCC showed evidence of a 3p deletion. By SSCP analysis, a heteroduplex with a different mobility from the homoduplex band was observed in Exon 2 in the clear cell RCC of Case 16, but no SSCP was detected, and direct forward and reverse sequencing of the PCR product showed normal nucleotide sequences. VHL mutations were not found in normal or tumor tissue in any of 16 cases and 19 tumors in which molecular genetic studies could be completed.

DISCUSSION

Small chromophilic renal cell tumors begin to be found in the general population at age 40 and increase in frequency as patients become older (20). The prevalence of these tumors is additionally correlated with the presence and severity of nephrosclerosis which also begins to be seen at about 40 yr of age, and it has been suggested that tumor development is promoted by renal scarring (20). The severe nephrosclerosis of ESRD dissects the nephron into unattached tubular and cystic elements that show both atrophic and hyperplastic changes. Hyperplasia seems to represent attempts at regeneration promoted by renotropic substances that have the attributes of growth factors (21,22). Normal regeneration is impossible in these diseased kidneys, and the outcome of attempted growth seems to be acquired renal cystic disease, papillary cystic hyperplasia, and renal tumors. Papillary cystic hyperplasia may be the precursor of most of the tumors.

The development of ARCD has been estimated to increase the prevalence of RCC to a rate approximately four to six times greater than that found in the general population (3,5,6). Fifteen of the 21 RCC in this study occurred in kidneys that were involved by ARCD, and five RCC were found in two patients with ADPKD. Bilateral RCC occurs 10 times more frequently in ADPKD than in the general population (23). RCC have been reported in several patients with end-stage ADPKD, and it has been suggested but not conclusively demonstrated that the risk of RCC is increased in ADPKD by long-term dialysis (5,23,24). This study provides a report of two additional ADPKD
dialysis patients who have developed RCC, with multiple bilateral tumors being present in one patient. Regarding the cases of ARCD, our findings support studies that indicate the severity of ARCD, that the risk of developing RCC is greater in males, and that the carcinomas develop at an age that is more than 10 yr younger than in control nondialysis populations (3,5,25–28). Also similar to other studies, these cases show that the RCC tend to be found several years after renal replacement therapy is begun, but that ARCD and tumors can be seen in renal failure patients who have not been dialyzed or who have been dialyzed for short periods (5). The tumors described here in a patient who had not been dialyzed and in a patient dialyzed 1 month were chromophilic RCC and were histologically similar to those found in the long-term dialysis patients.

In contrast to the general population, clear cell carcinomas make up only 14% of the RCC in this collection of tumors from ESRD patients. Although an ideal determination of tumor types in a population at risk would require a sequential and inclusively collected series of cases, no single institution in the United States has had enough ESRD kidney cancers to conduct this type of survey. The cases reported in this study were collected from several major U.S. medical centers. Except for literature reviews, this is the first examination of a sizable number of such carcinomas undertaken in this country. No specific histopathologic type of tumor was solicited from contributors, and cases should be selected only for ESRD.

The findings in this series of ESRD patients show a marked predominance of chromophilic RCC (86% of tumors). Ishikawa and Kovacs (9) reviewed the pathologic typing of RCC of ESRD patients in Japan and found that 48.8% of cases were papillary neoplasms. Most sporadically occurring chromophilic RCC have a papillary growth pattern and are classified as papillary RCC by the classic pathologic typing of the World Health Organization (29). Kovacs has observed that papillary RCC differ from clear cell carcinomas by an absence of chromosome 3p deletions and by trisomy or tetrasyndrome of chromosome 7 (+7) in 75% of cases and trisomy of chromosome 17 (+17) in 80% of cases (13). Kovacs (13) and DalCin et al. (30) have suggested that tumors having the chromosomal alterations of trisomy or tetrasyndrome of chromosome 7, trisomy of chromosome 17, and loss of the Y chromosome may be benign (i.e., adenomas). Kovacs et al. (31) also have shown that malignant progression is characterized by additional increases in chromosomal number, most commonly trisomy of chromosomes 12, 16, and 20. Storkel et al. (32) demonstrated that most chromophilic RCC in Thoenes’ pathologic typing are identical with papillary carcinomas in the WHO classification by finding the cytogenetic abnormality +7, +17, and the absence of 3p deletions in chromophilic RCC.

The genetic changes of the chromophilic RCC of ESRD are likely to be the same as those found in sporadically occurring tumors. Two RCC of ESRD have been karyotyped including Case 15 in this series (33–35). Both of these tumors were classified as papillary RCC by classic pathologic typing and would be considered chromophilic tubulopapillary RCC in the classification of Thoenes et al. (11). The karyotype of Case 15 showed a 54,XY,+2,+4,+7,+10,+12,+16,+17,+17,+20 mainline (34,35). The karyotype of the other tumor, reported by Ishikawa et al. (33), disclosed trisomy of chromosomes 5, 16, and 20, and loss of the Y. Neither case had a 3p deletion. The study presented here does not show any molecular genetic evidence of a 3p abnormality in 18 ESRD chromophilic RCC including Case 15.

The findings suggest that factors that promote the development of papillary renal cortical tumors are exaggerated in ESRD and involve mitotic abnormalities that alter chromosome numbers. Increases in chromosomal number are the result of nondisjunction during mitosis which distributes two chromatids of a separating chromosome to one daughter cell of a potentially developing tumor stem line. The presence of extra gene copies, or increased gene dosage, seems to provide a selective growth advantage and to result in a transformed cell type (36).

Nondisjunction does not have a known cause, but nonrandom autosomal trisomies are found as the only chromosomal abnormalities in neoplasms other than papillary RCC. Acute myelogenous leukemia having karyotypes showing trisomy of chromosome 8 and chronic lymphocytic leukemia characterized by trisomy of chromosome 12 are hematologic malignancies in which nondisjunction appears to play a role in disease development (37).

Chronic renal failure seems to promote chromosomal abnormalities. Cengiz et al. (38) studied karyotypes of peripheral blood lymphocytes from chronic hemodialysis patients and found an increased frequency of structural chromosomal abnormalities. They also noted ballooning of centromeres, the point that the mitotic spindle attaches to separating chromosomes at metaphase. Trisomy 7 has been found in kidney tissue adjacent to renal tumors and from kidneys with nonneoplastic renal disease (39,40). In a previous study, we found that some cyst cells of an autosomal dominant polycystic kidney from an ESRD patient showed a pseudotetraploid karyotype indicating that in some dividing cells there was a near absence of chromosomal separation and nuclear division (41). Trisomy 12 was also seen in cells from the noncystic tissue of this kidney.

A major question about the genetics of diseases associated with chromosomal trisomies is whether the synchronous separation of chromosomes at metaphase is genetically controlled. The presence of familial cases of papillary (chromophilic tubulopapillary) RCC suggests that a genetic mutation is involved in the pathogenesis of this disease (42). The increased prevalence of chromophilic tubulopapillary RCC in ESRD further indicates that a genetic factor modulating tubular cell growth is affected by chronic renal
failure. The scarcity of 3p changes and the absence of VHL mutations in this case series implies that the loss of the 3p tumor suppressor gene does not play an important role in tumor development in ESRD. Presently, our laboratories are directing their efforts toward studying the frequency and type of numerical chromosomal abnormalities that occur in end-stage kidney tumors and in the papillary cystic hyperplasias that are found in acquired and hereditary polycystic kidney diseases (5,8,24). Such studies may help establish a link between papillary hyperplasia and the formation of RCC in ESRD.

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