The Genetics of Renal Tumors in End-Stage Renal Failure Differs from Those Occurring in the General Population

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Abstract. The genetics of renal cell tumors (RCT), which occur at a high frequency in patients with end-stage renal failure (ESRF), is not yet known. Using a fluorescence microsatellite assay and comparative genomic hybridization, 18 renal tumors obtained from nine patients with ESRF were analyzed for genetic alterations, which are known to be characteristic of common nonpapillary and papillary RCT in the general population. Deletion of chromosome 3p was detected in six non-papillary tumors, whereas trisomies of 7 and 17 or 3, 8, and 16 were seen in four of 18 tumors. No alterations were found in four tumors, and another four tumors had unspecific changes.

Renal cell tumors (RCT) occur in kidneys with or without acquired cystic disease at a higher frequency in patients with end-stage renal failure (ESRF) than in the general population (1–3). Metastatic disease develops in approximately 20% of the cases, confirming the malignant potential of tumors (4). Renal cell carcinoma (RCC), therefore, is a life-threatening complication for patients undergoing long-term renal replacement therapy. The tumors are frequently asymptomatic, and even computed tomography may miss large tumors in kidneys with diffuse cystic changes. Given that the number of ESRF patients with RCT is underestimated and that the number of patients with ESRF is increasing worldwide, the development of renal tumors in patients with chronic renal insufficiency is a nephrologic and oncologic problem of increasing magnitude.

The natural history and genetics of RCT and the differentiation between benign and malignant tumors developing in the general population is established (5). The biological behavior and genetics of ESRF tumors, however, remains unknown due to the small series of clinicopathologic studies and rare case reports. Histologic or genetic hallmarks for differentiation between benign and malignant tumors and also between "proliferating" cysts and carcinomas are not yet established. Of interest, nearly 50% of the neoplasms in ESRF show papillary or tubulopapillary growth patterns, whereas in the general population papillary RCC make up only approximately 10% of cases (5,6). The molecular mechanism responsible for these differences is not yet known. Cytogenetic studies of three papillary RCT from ESRF patients revealed karyotype abnormalities similar to those seen in tumors of the general population (7–9). A recent microsatellite study analyzing the chromosome 3p region, which is specifically deleted in nonpapillary RCC, detected loss of heterozygosity (LOH) in one of the 21 tumors from ESRF patients (10). To obtain more information on the genetics, we analyzed 18 renal tumors obtained from nine patients with ESRF for all genetic alterations, which are implicated in the development of renal cysts in ESRF, the alteration of both genes in tumor cells was analyzed. No abnormal expression of the FHIT gene or mutation of the p53 gene were found. This study suggests that the genetics and also the morphology of some of the ESRF RCT differ from those known for RCT in the general population. (J Am Soc Nephrol 9: 1045–1051, 1998)

Materials and Methods
Tumor Samples and Histologic Classification

Fresh specimens from 18 tumors and corresponding parenchymal tissues of nine patients with ESRF were obtained from the United Kingdom, Germany, Slovenia, and Hungary (Table 1) and processed for analysis on the day of nephrectomy. None of the patients under-
concentration of each sample was adjusted to 10 ng/μl.

**DNA Isolation**

Short-term cultures of tumor cells were established after collagenase treatment and mechanical dissociation of cell clusters as described elsewhere (16). The culture flasks were monitored under an inverted microscope for tumor cell growth and possible contamination with normal cells. DNA was isolated from cultures containing tumor cells and also from corresponding normal parenchymal tissues after proteinase K digestion followed by phenol/chloroform extraction and ethanol precipitation. In case HD173, DNA was isolated from frozen tissues. The DNA concentration of each sample was adjusted to 10 ng/μl.

**Microsatellite Allelotyping**

Nonradioactive microsatellite analysis was performed for the following markers: D1S1656 (1q32), D1S162 (1p32), D2S423 (2p), D2S1391 (2q), D3S1786 (3p21), D3S1784 (3q22 to 24), D5S412 (5pter), D7S817 (7p15), D7S1824 (7q11), D8S261 (8p21), D8S264 (8p23 to pter), D8S1469 (8p), D9S171 (9p21), D9S162 (9p), D14S267 (14qter), D14S71 (14q), D16S520 (16q), D16S539 (16q24 to ter), D17S799 (17pcen to p12), D17S807 (17q), and D20S194 (20p). Five microliters (50 ng) from each sample was used as a template in 10 μl of PCR containing 50 mM KCl, 10 mM Tris, pH 8.3, 1.5 mM MgCl2, 200 μM dNTP each, 5 pmol of each primer (forward primer 5' labeled with Cy5 fluorescence marker), and 1 U of Taq polymerase (Promega, Madison, WI). Amplification was performed using PTC 200 thermocycler (M. J. Research, Watertown, MA), with initial denaturation at 94°C for 2 min, 30 cycles of denaturation at 94°C for 40 s, annealing at 55°C for 30 s, and extension at 72°C for 40 s, followed by final extension for 5 min at 72°C. Twenty microliters of stop solution (100% formamide with 5 mg/ml dextran blue 2000) was added to each sample. An automated laser detection system (ALFexpress, Pharmacia Biotech, Freiburg, Germany) was used for evaluation of PCR products separated on 5% denaturing polyacrylamide gels. Primers from X-Y homologous region (AMXY) were used to detect loss of the X or Y chromosome (17). PCR amplification was performed as described (16). Products were separated on 1% agarose gels and visualized by staining with ethidium bromide.

**Table 1. Pertinent clinical data and results of genetic analysis of ESRF tumors**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Age/Gender</th>
<th>Renal Disease</th>
<th>Kidney Size (cm)</th>
<th>Tumor Size (cm)</th>
<th>Histologic Diagnosis</th>
<th>Genetic Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD94A</td>
<td>76/M</td>
<td>NS</td>
<td>9.5 × 6 × 3 (ACKD)</td>
<td>0.8</td>
<td>npRCC</td>
<td>-3p, -3q, +7p, +7q, -Y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.2</td>
<td>pRCT</td>
<td>+7p, +7q, +16q, -Y</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>0.3</td>
<td>pRCT</td>
<td></td>
</tr>
<tr>
<td>HD105</td>
<td>71/F</td>
<td>Unknown</td>
<td>12 × 6.5 × 5 (ACKD)</td>
<td>4.0</td>
<td>RO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.1</td>
<td>pRCT?</td>
<td>+3p, +3q, +16q</td>
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<tr>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>2.6</td>
<td>npRCC</td>
<td>-3p, -14q, -Y</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td>2.2</td>
<td>npRCC</td>
<td></td>
</tr>
<tr>
<td>HD123A</td>
<td>77/M</td>
<td>GN</td>
<td>15 × 8 × 7 (ACKD)</td>
<td>3.0</td>
<td>npRCC</td>
<td>-3p, +5q, -8p, -9p, -14q, -17p, -17q, +20p, -Y</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>0.8</td>
<td>chRCC?</td>
<td>-17p</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td>0.5</td>
<td>chRCC?</td>
<td>-1q, -2, -16q</td>
</tr>
<tr>
<td>HD137</td>
<td>61/M</td>
<td>NS</td>
<td>6.5 × 3 × 3 (ACKD)</td>
<td>1.6</td>
<td>chRCC?</td>
<td>-17p</td>
</tr>
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<td></td>
<td>1.0</td>
<td>chRCC?</td>
<td>-17p, -19</td>
</tr>
<tr>
<td>HD173A</td>
<td>68/M</td>
<td>GN</td>
<td>5.5 × 3 × 1.5 (ACKD)</td>
<td>3.5</td>
<td>npRCC</td>
<td>-3p, +7p, +7q, +16q, -Y</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>0.8</td>
<td>npRCC</td>
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</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td>0.5</td>
<td>npRCC</td>
<td></td>
</tr>
<tr>
<td>HD192A</td>
<td>49/M</td>
<td>NS</td>
<td>10 × 5.5 × 3 (ACKD)</td>
<td>3.0</td>
<td>npRCC</td>
<td>-3p, -14q</td>
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<tr>
<td>HD195</td>
<td>43/M</td>
<td>Unknown</td>
<td>9 × 5 × 4 (ACKD)</td>
<td>4.1</td>
<td>pRCT</td>
<td>+3p, +3q, +5q, +7p, +7q, +16q, +17p, +17q, -Y</td>
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<td>HD203A</td>
<td>48/M</td>
<td>Unknown</td>
<td>6.5 × 3.5 × 2.5</td>
<td>0.3</td>
<td>pRCT</td>
<td>+3p, +3q, +7p, +7q, +8p, -14q, +16q</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD217</td>
<td>71/M</td>
<td>NS</td>
<td>5.8 × 3.5 × 2</td>
<td>2.9</td>
<td>npRCC</td>
<td>-3p</td>
</tr>
</tbody>
</table>

* ESRF, end-stage renal failure; NS, nephrosclerosis; GN, glomerulonephritis; ACKD, acquired cystic kidney disease; npRCC, nonpapillary renal cell carcinoma; pRCT, papillary renal cell tumor; RO, renal oncocytoma; chRCC, chromophobe renal cell carcinoma.

*b Cases analyzed by comparative genomic hybridization as well.
Microsatellite Analysis of Chromosome 3p Region

For detailed deletion mapping of chromosome 3p, we applied 16 polymorphic microsatellite markers (Figure 1). Additional markers (D3S1613, D3S3719, D3S1606, D3S3616, D3S1295, D3S1313) located between D3S1760 and D3S1289 were used for mapping a breakpoint in case HD195. Sequences of all oligonucleotides were obtained from the Genome Database. DNA amplification was carried out in 20-μl reactions with 100 ng of genomic DNA, 50 mM KCl, 10 mM Tris, pH 8.3, 1.5 mM MgCl2, 200 μM each dNTP, and 2 pM of each primer (forward primer 5' labeled with 2 μCi 32P) and 1 U of Taq polymerase. The PCR program was 10 cycles touchdown (−1°C per cycle) starting at 65°C annealing temperature followed by an additional 15 cycles of 30 s at 94°C, 20 s at 55°C, and 20 s at 72°C.

Additional informative loci in tumors HD94A, HD192A, HD123B, HD137, HD217, and HD195, respectively. Deletion breakpoint was defined at chromosomal bands 3p11.2, 3p13 to 14.1, and 3p14.3 in tumors HD137, HD217, and HD195, respectively. Microsatellite markers, their physical locations and locus of the VHL, and FHT genes are indicated on the left. ■, LOH; □, not informative; •, retention of constitutional heterozygosity.

Figure 1. Deletion map of nonpapillary renal cell carcinomas (RCC) at chromosome 3p. Note the loss of heterozygosity (LOH) at all informative loci in tumors HD94A, HD192A, and HD123B. Deletion breakpoint was defined at chromosomal bands 3p11.2, 3p13 to 14.1, and 3p14.3 in tumors HD137, HD217, and HD195, respectively. Microsatellite markers, their physical locations and locus of the VHL, and FHT genes are indicated on the left. ■, LOH; □, not informative; •, retention of constitutional heterozygosity.

After adding 10 μl of sequencing stop solution and heating the samples for 2 min to 80°C, 7 μl of the products was separated on 5% denaturing polyacrylamide gels. The signals were visualized by autoradiography after 1 or 2 d of exposure.

Comparative Genomic Hybridization Analysis

Approximately 50 ng of DNA from tumor and normal tissues (normal DNA was not from the same individual as tumor DNA) was amplified in a 50-μl reaction volume by degenerate oligonucleotide primer-PCR (18), and 25 μl of the amplified DNA was labeled by nick translation, using Texas Red dUTP (Dupont/New England Nuclear, Boston, MA) for normal DNA and FITC dUTP (Dupont/New England Nuclear) for tumor DNA. The in situ hybridization was carried out according to Kallioniemi et al. (19). The probes were hybridized over 3 d at 37°C in a moist chamber. Slides were washed in 2× SSC/50% formamide 3 times for 12 min each at 45°C and then in 2× SSC at 45°C and at room temperature. Finally, the slides were washed twice for 10 min in phosphate buffer, pH 8.0, and 3 times for 5 min in distilled water. The chromosomes were counterstained with 4',6-diamidine-2'-phenylindole (0.1 to 0.2 mg/ml in antifade). Hybridization efficiency was defined directly, using an epifluorescence microscope. Comparative genomic hybridization (CGH) analysis was performed using digitized images of FITC, Texas Red, or 4',6-diamidino-2-phenylindole fluorescence acquired with a multicolor quantitative image processing system based on a regular fluorescence microscope (Zeiss Axiophot, Jena, Germany) equipped with a cooled charge-coupled device camera (Photometrics, Tucson, AZ). Images of five metaphases of the highest quality were collected from each slide. For the acquisition and display of multicolor images, software based on the Scilimage package (Netherlands Central Organization for Applied Scientific Research, Delft, Netherlands) was used.

Reverse Transcription-PCR Analysis of the FHIT Gene

Total RNA was isolated from cell cultures with Trizol™ (Life Technologies, Eggenstein, Germany), according to the supplier's protocol. The RNA concentration was measured, and the RNA quality was checked on a formaldehyde gel, showing always intact rRNA bands. For the reverse transcription, 5 μg of total RNA, 100 pmol of PolyT4 primer, 1 mM of each dNTP, and 400 U of Superscript II (Life Technologies) in a 40-μl reaction volume was used. After incubating the reaction at 42°C for 1 h, the enzyme was heat-inactivated. The RNA was degraded with NaOH, and the cDNA was precipitated with ethanol and dissolved in 20 μl of water.

Amplification of exons 3 to 10 of the FHIT gene was carried out with nested PCR, as described by Ohta et al. (16). The reaction contained 1 μl of cDNA (diluted 1:10) and 10 pmol of each primer. As an internal control, in each reverse transcription (RT)-PCR reaction we also amplified exons 1 and 2 of the β2-microglobulin gene, using primers: 5'-CTC GCG CTA CTC TCT CTT-3' (forward) and 5'-TGT GCG CCT TCT CTT CAA-3' (reverse). The PCR products were separated on 1.5% agarose gels and visualized under ultraviolet light after ethidium bromide staining.

Mutation Analysis of the p53 Tumor Suppressor Gene

The p53 mutation analysis was performed using the MisMatch Detect™ II kit, according to the manufacturer’s specifications (Ambion, Austin, TX). DNA was amplified with three sets of primers supplied in the Ambion p53 Genomic DNA Screening Module. PCR was performed in a 50-μl volume using 50 mM KCl, 10 mM Tris, pH 8.3, 1.5 mM MgCl2, 0.01% bovine serum albumin, 12.5 pmol of each primer, 12.5 μM of each dNTP, and 1 U of Taq polymerase. Ampli-
fication was performed in a thermal cycler PTC 100 (M. J. Research) with initial denaturing for 5 min at 95°C, 30 cycles of 20 s at 94°C, 20 s at 55°C, and 40 s at 72°C followed by 5 min final extension at 72°C. Each PCR product was transcribed separately with T7 and SP6 RNA polymerase. After transcription, an equal-volume hybridization buffer was added. Equal volumes of the T7 product of the sample were hybridized to the SP6 product of the normal control and vice versa. Four microliters of the hybridization products were digested in 16 μl of diluted RNase solution, equal amounts of stop buffer were added, and the products were separated on 2% agarose gels.

Samples that displayed cleavage products were then sequenced directly with the T7 and SP6 primers, using the fmol DNA Sequencing kit (Promega). In cases in which tumor DNA was contaminated with normal DNA, the PCR product was subcloned into pGEM-T vector (Promega), and individual clones were sequenced as described above.

Results

The histologic diagnosis was established according to the Heidelberg classification (15). Tumors HD94A, HD123B, HD123C, HD137, HD192A, HD195, and HD217 showed morphologic patterns of a common, nonpapillary RCC. Tumors HD94B, HD94C, and HD203A were diagnosed as papillary RCT. Tumor HD105 consisting of granular eosinophilic cells, which were arranged in acinar formation, was diagnosed as a renal oncocytoma. Some tumors, however, showed unusual morphology. All tumors in case HD173 showed morphologic characteristics resembling either renal oncocytoma or chromophobe RCC, but an unusual nonpapillary RCC could not be excluded with certainty. HD203E was a small tumor 3 mm in diameter with tubulopapillary growth of hobnail-like cells. Tumor HD123A showed a solid-tubular growth of extremely large eosinophilic cells, most having a large intracytoplasmic vesicle that we had not seen among more than 700 RCT diagnosed in patients without ESRF before. Of interest, different types of tumors developed in the same kidney in cases HD94 and HD123. Some examples are shown in Figure 2.

Results of the microsatellite study at chromosomal regions characteristic for subtypes of RCT and of CGH analysis are shown in Table 1. LOH at chromosome 3p was found in six of the 18 tumors, confirming the diagnosis of nonpapillary RCC. Additional LOH at chromosomes 8p, 9p, and 14q and duplication of one allele at chromosome 5q in cases HD123B, HD137, and HD195 are in line with the histologic diagnosis. Thus, a molecular analysis at tumor type-specific genomic regions suggests a diagnosis of nonpapillary RCC in cases HD94A, 123B, 123C, 137, 192A, 195, and 217. These cases were diagnosed as a nonpapillary RCC by histologic means as well. Results of the microsatellite analysis of tumor HD137 is shown in Figure 3.

A combination of chromosomal duplication at 7q and 17q occurred only in tumor HD203A, which is shown in Figure 3. Of interest, duplication of chromosomes 3q, 8p, and 16q, which are suggested to mark the progression of papillary RCT, were found in cases HD94B, HD203A, and HD203E. These tumors were diagnosed as papillary RCT based on the histology. Although tumor HD123A showed a very unusual histologic pattern (Figure 2), the molecular analysis suggested that this tumor may belong to the papillary subtype.

Three of the four tumors in case HD173 revealed LOH at chromosome 17p. One tumor showed multiple losses of chromosomes 1q, 2, and 16q. Tumor HD173C was without any changes at the chromosomal regions analyzed. This finding was confirmed by CGH analysis as well. Altogether, we were unable to detect any genetic changes in four of 18 tumors, i.e., in cases HD94C, HD105, 123C, and HD173D. Tumor HD105 was diagnosed as a renal oncocytoma, and therefore the lack of chromosomal alterations may be in line with the diagnosis. A small tubulopapillary tumor consisting of “blue” cells (HD94C), and a nonpapillary tumor (HD123C) were expected to show trisomies and LOH at specific chromosomes, respectively. Microsatellite analysis, however, was not able to detect any genetic alterations in these cases. The CGH analysis confirmed the lack of gross genetic alterations in tumors HD94C, HD105, and HD123C. Both CGH and microsatellite analyses revealed identical alterations in tumors HD123A and HD173C.

Detailed deletion mapping of chromosome 3p showed LOH at all informative loci in tumors HD94A, HD123B, and HD192A, corresponding to monosomy of chromosome 3. Three other tumors showed a terminal deletion of chromosome 3p (Figure 1). One of the breakpoints was localized between D3S1271 and D3S1101, the other one between D3S1577 and D3S1480, and the third between D3S3616 and D3S1606. Thus, a smallest overlapping deletion corresponding to an approximately 78-cM terminal region of the chromosome 3p included one allele of the VHL gene in all six cases and one allele of the FHIT gene in five cases. Tumor HD195 showed a large terminal deletion of chromosome 3p but retained both alleles of the FHIT gene. Expression of a normal size of the FHIT gene was observed in all cases by RT-PCR. Analysis of exons 5 through 9 of the p53 tumor suppressor gene did not reveal mutations in any of the ESRF tumors.

Discussion

This study shows that the genetics of tumors in ESRF may be similar or may differ from those established for RCT of non-ESRF patients. Allelic duplication at chromosomes 7 and 17 (85 to 90% of the cases), trisomies of chromosomes 3q, 8, 12, 16, and 20 (22 to 62% of the cases), and loss of the Y chromosome mark papillary RCT in the general population (5). Chromosomal alterations in three papillary RCC from ESRF patients described in the literature (7–9) and also the results in our case HD203A match those genetic changes. Of interest, some of the papillary RCT in ESRF patients do not show the initial genetic changes of trisomy 7 and 17. Trisomy of chromosomes 5, 16, and 20 occurred in four of six histologically verified papillary RCT obtained from Japanese ESRF patients (I. Ishikawa, personal communication). In our series, trisomies of chromosomes 3, 8, and 16, with or without trisomy of chromosome 7, occurred in two cases, and together with trisomy of chromosome 7 and 17 in one case. Tumor HD123A showed trisomy of chromosomes 3 and 16, but not of 7 and 17. The molecular basis for the differences in the genetics of papillary RCT in the general population and in ESRF is not yet known. From the chromosome and microsatellite analyses, we cannot exclude that duplications of small regions of chromo-
some 7 harboring genes important for tumor development might be present in some cases. Amplification and/or increased expression of HGF/SF and its receptor MET oncogene, mapped to chromosome 7q21 and 7q31, respectively, have been shown in different types of tumors. It was suggested that the HGF/SF and MET autocrine loop triggers tumor cell proliferation (20–22). The germ-line mutation of the MET oncogene in patients with hereditary papillary RCT also points to the importance of this gene in papillary RCT in the general population (23).

LOH at chromosomes 3p (98%), 8p (33%), 9p (33%), and 14q (47%) and duplication of chromosome 5q22 (70%) are specific changes in common, nonpapillary RCC in the general population (5). Mutation of the VHL gene occurs in 50% of common nonpapillary RCC (24). We detected deletion of chromosome 3p in six of seven ESRF tumors resembling common nonpapillary RCC by histologic analysis. The only nonpapillary RCC without LOH at chromosome 3p (HD123C) did not show any alterations even after CGH analysis. Thus, the nature of this tumor based on histopathology and genetics could not unequivocally be established. Hughson et al. (10) analyzed the chromosome 3p region in 21 tumors from ESRF patients. None of these tumors had a mutation of the VHL gene, and only one showed LOH at chromosome 3p.

Hughson et al. (10) used Thoenes' classification, whereas we applied the Heidelberg classification for diagnosis. Thoenes' classification system is based on tumor cytology (25). The phenotype of RCT, however, is variable within a given tumor and in different tumors, resulting in observer variation in the diagnosis. The genetic classification is based on highly specific genetic alterations, which characterize each type of tumor and allow an accurate diagnosis even in cases with overlapping phenotype in the general population (16). RCT in ESRF frequently have an unusual morphology. A
Figure 3. Results of allelotyping from tumors HD137, HD203A, and HD203E. The lack of any signal at one allele of locus \( D3S1766 \) in tumor HD137 indicates that the tumor DNA was not contaminated with normal nucleic acid. Thus, the increased signal at allele 1 at locus \( D5S412 \) in tumor cells could be evaluated as a duplication. Similarly, a duplication is clearly seen as an allelic imbalance at chromosomes 3, 5, 7, 16, and 17 in tumor HD203A and at chromosomes 3, 7, 8, and 16 in tumor HD203E.

genetic analysis may be helpful in some cases, but the diagnosis of some tumors remains uncertain even after molecular characterization. For example, all tumors in case HD173 in our series show a cytology resembling chromophobe RCC or renal oncocyteomas or unusual nonpapillary RCC. Microsatellite and CGH analyses, however, detected only in one of the tumors a combination of LOH at chromosomes 1 and 2, which is characteristic for chromophobe RCC in the general population (26).

Many factors have been implicated in the pathogenesis of cystic changes and tumor development in nonfunctioning kidneys. Despite histochemical and molecular genetics studies, the nature of proliferating parenchymal and interstitial cells, as well as the molecular mechanisms leading to formation of multiple cysts and tumors, remains unknown. Chronic renal diseases lead to loss of kidney function and to a profound loss of cellular components of nephrons. Of interest, an increased rate of cell division has been found among cells of atrophic tubuli, as well as among stromal cells in ESRF kidneys (27). Increased expression of "renal cyst growth factor," epidermal growth factor, platelet-derived growth factor, and ERBB-2 was also documented in end-stage kidneys (28–32). It is likely that loss of function and sclerosis in chronic renal failure promotes compensatory proliferation of remnant nephrons and contributes to the development of benign and malignant tumors. Toxic effects and genetic instability due to uremic status have also been implicated in the pathogenesis of cysts and tumors in ESRF patients. Cengiz et al. (11) found an increased number of structurally altered chromosomes and an elevated rate of sister chromatide exchange in peripheral blood lymphocytes from uremic patients. The efficiency of DNA repair was decreased to approximately 60% in uremic patients but remained nearly normal in patients having a maintenance dialysis (12). The tumor suppressor gene p53 is a target of many environmental mutagenic agents. Although we found LOH at chromosome 17p in four of the 18 tumors, we failed to detect mutations in exons 5 through 9 of the p53 gene in normal and tumor tissues. The genomic plasticity and instability around the FRA3B/FHIT region on chromosome 3p14.2 is well documented in normal and tumor tissues as well. Recently, an association between cigarette smoking and alterations of the FHIT gene was shown in lung cancer, suggesting that the FRA3B/FHIT region may be the target of environmental toxic-mutagenic agents (33). We did not find DNA alterations at the FRA3B/FHIT region, or altered expression of the FHIT gene in renal cancers of the general population (14) or in tumors arising in ESRF. It is likely, therefore, that an increased mutagenic effect and/or deficient DNA repair do not alter the integrity of the p53 and FHIT genes in renal parenchymal and tumor tissues of patients with chronic renal failure.

In summary, genetic alterations in some of the ESRF tumors match those found in common nonpapillary and papillary RCT occurring in the general population, but others have distinct genetic changes or do not show any alterations. The histologic characteristic of some tumors also may differ from those known in the general population. The diagnosis and biological behavior of some of the ESRF tumors, even after these genetic studies, remain uncertain. Additional genetic and clinical studies are necessary to establish the biology of RCT developing in ESRF patients.

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References