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HEREDITARY PAPILLARY RENAL CELL CARCINOMA: CLINICAL STUDIES IN 10 FAMILIES

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ABSTRACT

We recently described a 3-generation family with members affected with papillary renal cell carcinoma, an uncommon histological type of renal cell carcinoma. Possibly family 150 is an isolated occurrence, a reflection of some as yet unknown environmental factor. Alternatively, family 150 may represent a distinct class of inherited cancer. To distinguish between these 2 possibilities we sought additional families with papillary renal cell carcinoma and we identified 9 with members affected with papillary renal cell carcinoma. There were 29 affected male and 12 affected female subjects (ratio 2.41:1), including affected members of family 150. Papillary renal cell carcinomas were often detected incidentally in asymptomatic individuals or during screening of asymptomatic members of renal cell carcinoma families. The penetrance, the proportion of obligate gene carriers that showed clinical evidence of the disease, was reduced. The median survival of affected individuals was 52 years. The results support the concept that the predisposition to develop papillary renal cell carcinomas may be inherited and that hereditary papillary renal cell carcinoma constitutes a distinct class of inherited cancer.

KEY WORDS: carcinoma, renal cell; carcinoma, papillary; hereditary diseases

There are 2 well defined classes of inherited renal cell carcinoma. In von Hippel-Lindau disease the predisposition to develop clear cell renal carcinomas is inherited along with a predisposition to develop tumors in the brain, spine, eye, pancreas and adrenal gland.[1] The von Hippel-Lindau gene has recently been isolated[2] and shown to be mutated in sporadic, clear cell renal carcinomas.[2,3] Individuals with a constitutional, balanced translocation between the short arm of chromosome 3 and chromosome 6 or 8 also have a predisposition for renal cell carcinoma.[4,5] The von Hippel-Lindau gene has been shown to be mutated in a renal tumor from a patient with the 3;8 translocation.[3] Although a gene (HRCA1) that is disrupted by the 3;8 translocation has been identified,[6] it is unknown whether this gene also has a role in the pathogenesis of renal cell carcinoma associated with this translocation. Evidence suggests that there are 2 additional classes of inherited renal cell carcinoma: hereditary papillary renal cell carcinoma[7] and transitional cell carcinoma of the kidney associated with the Lynch syndrome type II.[8,9]

Renal cell carcinomas with a papillary growth pattern comprise about 10% of carcinomas of the kidney.[10-12] Kovacs et al drew attention to genetic differences between papillary and nonpapillary renal cell carcinomas.[13-15] Loss of the short arm of chromosome 3, a genetic change characteristic of sporadic and hereditary clear cell renal carcinomas,[3,16,17] was not present in sporadic papillary renal cell carcinomas. Kovacs et al also found that chromosomes 7, 16, 17 and Y were specifically involved in the karyotypic changes in papillary renal cell carcinoma. Meloni et al found a somatic translocation between chromosome 1 and X [t(X;1) (p11.2; q21)] in papillary renal cell carcinomas from 4 men.[18] de Jong et al found a similar translocation in a 2-year-old child with renal cell carcinoma.[19] A yeast artificial chromosome containing the X;1 translocation breakpoint has recently been isolated.[20,21] Attempts are underway to isolate the gene on chromosome X disrupted by the X;1 translocation.

We recently described a 3-generation family with members affected with papillary renal cell carcinoma.[7] Possibly, family 150 is an isolated occurrence, a reflection of some as yet unknown environmental factor. We describe the affected members of 9 other families with papillary renal cell carcinoma and summarize family 150. This information serves to define the clinical features of hereditary papillary renal cell carcinoma.

MATERIALS AND METHODS

Patients. Families with papillary renal cell carcinoma were identified from the literature[22,23] and by referral to the Surgery Branch, National Cancer Institute. A total of 41 members of families 150, 154, 155, 156 and 157 was examined at the Clinical Center of the National Institutes of Health after informed consent was obtained. This project was approved by the Clinical Research Subpanel of the National Cancer Institute. Members of families 152 and 153 were examined in Sweden. Family 159 was identified and referred by Dr. Kenneth Tartof, Institute for Cancer Research, Philadelphia, Pennsylvania. At the National Institutes of Health the evaluation consisted of a history and physical examination, ophthalmologic examination, magnetic resonance imaging of the brain and spinal cord with gadolinium enhancement, computerized tomography (CT) of the abdomen (with and without contrast material), 24-hour urine to test for catecholamines and for men ultrasound examination of the testes.

An individual with a renal tumor(s) was considered affected if he or she had multiple, bilateral papillary renal cell carcinomas without a family history of renal tumors, or single or multiple papillary renal cell carcinomas with a first or second degree relative with papillary renal cell carcinoma. The diagnosis of papillary renal cell carcinoma of deceased

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family members was made from death certificates, medical records, pathology and autopsy reports. Histological slides on renal tumors were reviewed at the National Institutes of Health by 1 of us (I. L.). In 3 instances (family 153, I-1, family 155, II-1 and family 159, III-2) subjects were reported by family members to have had cancer of the kidney and, although we were unable to obtain medical reports for these 3 subjects, they were classified as affected.

Pathology. Renal neoplasms were characterized in terms of cell type (clear cell, granular cell, mixed or sarcomatoid), growth pattern (papillary, cystic, solid or trabecular) and nuclear grade.[24] The per cent of the renal neoplasm that had a papillary growth pattern was estimated. A renal tumor was classified as papillary when at least 50% of the renal tumor had a tubulo-papillary growth pattern.[10] A papillary growth pattern was defined as the presence of malignant epithelial cells arranged around a central fibrovascular core.

RESULTS

We identified 41 individuals affected with papillary renal cell carcinoma in 10 families (including family 150) (see table and fig. 1). Papillary renal cell carcinomas were identified in members of 1 generation in families 151, 156, 157 and 159, in members of 2 generations in families 152, 154, 155 and 158, and in members of 3 generations of families 150 and 153. The number of affected individuals within a family ranged from 1 (family 156) to 10 (family 152). Eight families were white, 1 family was African American and in 1 the race was not known. There were 29 affected male and 12 affected female subjects for a male-to-female ratio of 2.41:1. The parents in families 150, 151, 152, 154, 155, 157, 158 and 159 transmitted a predisposition to papillary renal cell carcinoma, without showing clinical evidence of the disease. The median age at diagnosis was 45 years. The mean survival in affected individuals and in obligate gene carriers was 52 years (fig. 2).

Renal tumors were detected incidentally in 3 asymptomatic individuals (ages 46, 43 and 63 years) during an abdominal ultrasound examination or during screening of asymptomatic family members (ages 18, 39, 44, 40 and 70 years). The number of renal tumors in affected individuals varied from 1 (family 150, subject III-14) to 26 (family 150, subject III-18). There were 14 children older than 35 years of 26 affected parents (53%) with papillary renal cell carcinomas. On histological slides reviewed from members of families 150, 152, 153, 155, 156, 157 and 158, 90 to 100% of the tumors had a papillary growth pattern. In family 154 the growth pattern was a mixture of papillary and trabecular.

DESCRIPTION OF FAMILIES

Family 150 was described previously.[7]

Family 151. Family 151 was described in 1969 by Pearson.[22] Two brothers (subjects III-2 and III-3) and a first cousin (subject III-6) were affected with papillary renal cell carcinoma. The pathology report on subject III-2 stated, "Since 4

Characteristics of 41 patients with papillary renal cell carcinoma

Family No.*	Individual No.	Sex/Age Diagnosis/ Age Death	Renal Tumors	Growth Pattern†	Nuclear Grade	No. Slide
150	II-3	M/37/46	Unilat.	Papillary		
150	II-7	M/79/80	—	—		
150	II-11	M/72/72	Unilat.	Papillary		
150	III-17	M/54/56	Unilat.	Papillary		
150	III-18	F/70/	Bilat.	—		
150	III-20	M/67/69	Bilat.	Papillary		
150	IV-14	M/46/	Unilat.	Papillary		
150	IV-16	M/39/	Unilat.	—		
150	IV-18	M/43/	Bilat.	Papillary	2	1
151	III-2	M/49/	Bilat.	Papillary		
151	III-3	M/45/47	Bilat.	Papillary		
151	III-6	M/37/	Unilat.	Papillary		
152	II-1	F/51/63	Bilat.	Papillary		
152	II-3	F/49/51	Bilat.	Papillary		
152	II-4	F/53/	Unilat.	Tubular/papillary	2	1
152	II-5	M/37/51	Bilat.	Papillary	2–3	2
152	II-7	M/43/48	Bilat.	Papillary	2	2
152	II-9	F/51/55	Bilat.	Papillary	2	1
152	III-1	M/41/42	Bilat.	Papillary	3	1
152	III-2	M/36/	Bilat.	—		
152	III-4	F/34/	Bilat.	Papillary	2	1
152	III-6	M/29/	Bilat.	—	2	1
153	I-2	M/ /42	—	—		
153	II-2	M/41/43	Bilat.	Papillary	3	2
153	III-2	M/38/42	Bilat.	Papillary	3	2
153	III-3	F/41/	Bilat.	Papillary	3	2
154	II-1	M/40/52	Bilat.	Papillary (0.80) Trabecular (0.20)	3	7
154	II-7	M/43/44	Bilat.	Papillary	4	2
154	II-9	M/53/54	Bilat.	Papillary (0.15) Trabecular (0.85)	4	4
154	III-1	M/39/	Unilat.	Papillary (0.05) Trabecular (0.95)	3	1
155	II-1	M/ /				
155	II-2	F/44/	Unilat.	Papillary		
155	III-4	F/18/19	Unilat.	Papillary	3	1
156	II-3	M/45/45	Bilat.	Papillary	1–2	5
157	II-2	M/60/	Unilat.	Papillary	3	4
157	II-4	M/55/55	Unilat.	Papillary		
157	II-12	F/52/	Unilat.	Papillary (0.90)	3	11
158	II-3	F/66/	Unilat.	Papillary	2	11
158	III-1	M/63/	Bilat.	Papillary		
159	III-2	M/28/				
159	III-3	F/25/	Unilat.	Papillary		

* All families are white except for 155, which is African-American.

† Numbers in parentheses represent per cent of tumor with indicated growth pattern ×100. No parentheses indicate that 100% of the tumor had the indicated growth pattern.

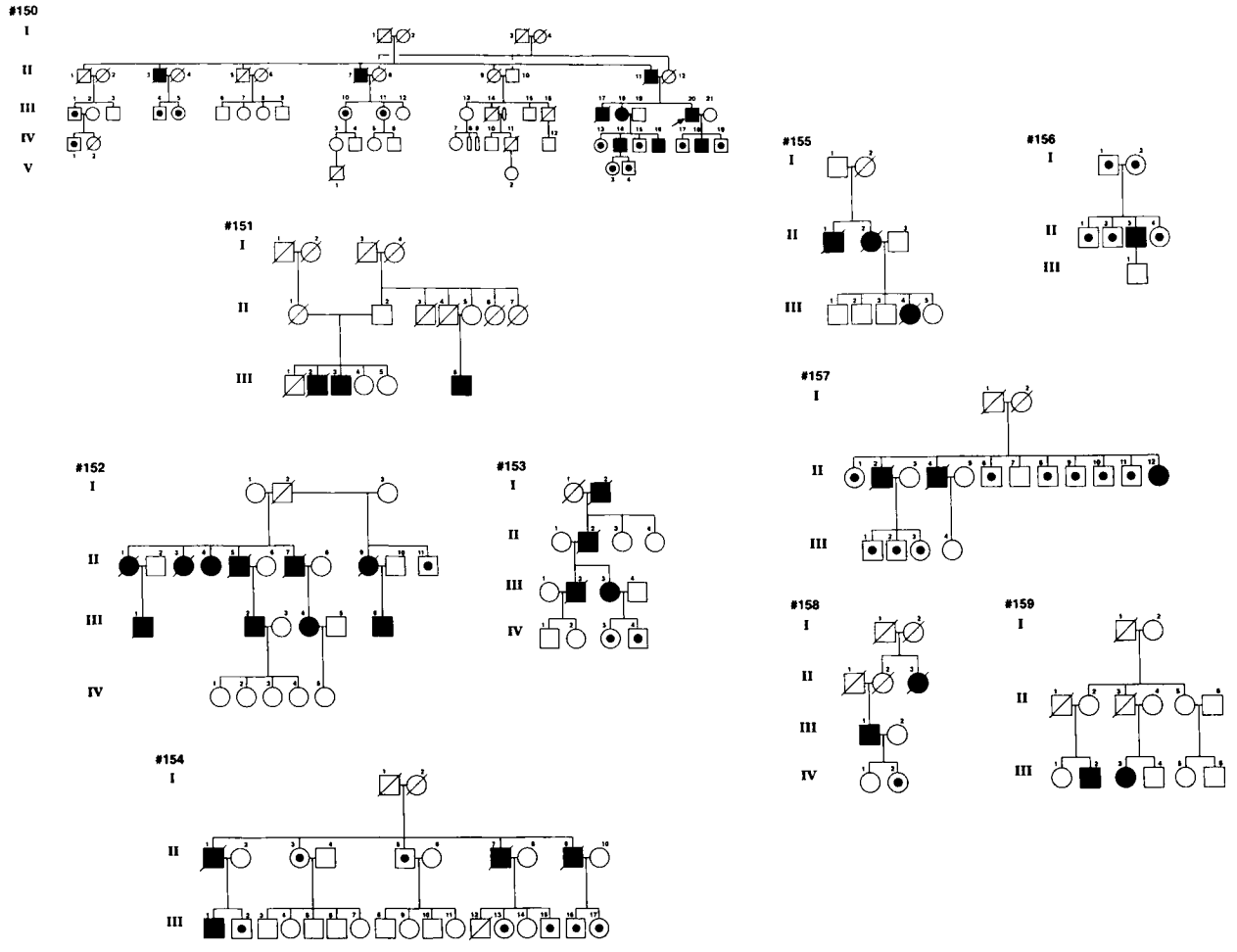

FIG. 1. Pedigrees of 10 families with papillary renal cell carcinoma. Solid symbol represents subject affected with papillary renal cell carcinoma or cancer of kidney by history (family 153, I-2; family 155, II-1 and family 159, III-2). Symbols with central black dot represent subjects examined by CT and/or ultrasound examination of abdomen and no renal tumors were found. Open symbol represents subjects with no history of renal tumors.

of the lesions examined showed similar histological appearance, it is possible that all are extensions of the main growth. However, I think this is unlikely since there are microscopic commencing lesions elsewhere."[22] We have not been able to identify descendents of this Australian family.

Family 152. In 1972, 5 siblings (subjects II-1, II-3, II-4, II-5 and II-7) with multiple, papillary renal cell carcinomas were described.[23] The pathology report stated, "microscopic examination revealed a remarkably consistent pattern in the primary tumors and in the metastases. The tumors consisted of tubular or papillary structures with a poorly developed connective tissue matrix."[23] In the 22 years that have lapsed since that report papillary renal cell carcinoma developed in 3 children (subjects III-1 and III-2, III-4) of affected individuals. Since the time of the original report, we discovered that the father (subject I-2) of the 5 affected siblings had 2 children by a second wife (subject I-3). One of these children (subject II-9) had papillary renal cell carcinoma and a child (subject III-6) with papillary renal cell carcinoma. These results indicate that subject I-2, an obligate gene carrier, transmitted a predisposition to develop papillary renal cell carcinoma to 6 of 7 children, who in turn transmitted this predisposition to their children. There were 10 individuals affected with papillary renal cell carcinoma in this Swedish family. Two affected family members had a second malignancy: subject II-4 had carcinoma of the breast and subject II-5 had fibrosarcoma.

Family 153. This Swedish family has 4 members affected with papillary renal cell carcinoma in 3 generations. A kidney tumor was detected in subject I-1 in 1932. In 1960, 28 years later, papillary renal cell carcinoma was detected in subject II-2. Subjects II-3 and II-4, the sisters of subject II-2, ages 65 and 76 years, respectively, have had no signs of renal tumors. In 1986 papillary renal cell carcinoma was detected in subject III-2 and in 1992 papillary renal cell carcinoma was detected in subject III-3.

Family 154. A 33-year-old man contacted the National Cancer Institute because his father and 2 uncles had died of renal cell carcinoma. The tumors in subjects II-1, II-7 and II-9 were bilateral and multiple. The pathology report on subject II-1 stated, "The tumor is apparently arising in multiple areas throughout the kidney parenchyma each with the same histological pattern, that of a papillary type of growth." The report on subject II-7 stated, "multiple tumor nodules are present in the kidney. Parts of the tumor are poorly differentiated while other areas are tubular or papillary with uniform granular and clear cells." The histology of the renal tumors (reviewed at the National Cancer Institute) showed a mixture of papillary and trabecular growth patterns. In subject II-1, 80% of the renal tumor had a papillary growth pattern and 20% had a trabecular growth pattern, and in subject II-9, 15% of the renal tumor had a papillary growth pattern and 85% had a trabecular growth pattern. There are 8 living descendents of affected individuals ranging in age

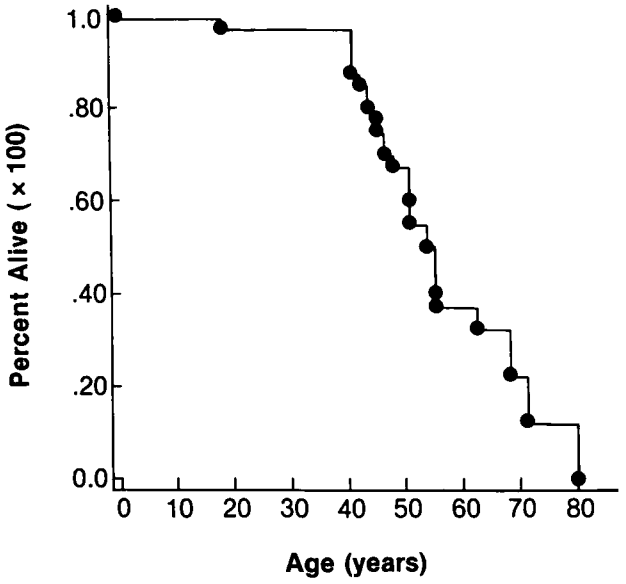

FIG. 2. Survival of individuals affected with papillary renal cell carcinoma. Data were plotted by Kaplan-Meier method.

from 28 to 39 years. In 1 at risk 39-year-old individual (subject III-1) a single renal cell carcinoma developed with a predominantly trabecular growth pattern. The tumor was composed of cells with a granular, eosinophilic cytoplasm.

The difficulty in establishing the hereditary nature of the illness in this family is illustrated by the dates of diagnosis of renal cell carcinoma in generations II and III. The diagnosis of renal cell carcinoma was made in subject II-1 in 1964, in subject II-7 in 1974, in subject II-9 in 1989 and in subject III-1 in 1993. A total of 29 years elapsed from the detection of multiple papillary renal cell carcinomas in subject II-1 until renal cell carcinoma was detected in his asymptomatic son, subject III-1.

Family 155. An 18-year-old African American woman (subject III-4) contacted the National Cancer Institute with interest in experimental immunotherapy. This asymptomatic woman had an ultrasound examination of the kidneys because her mother (subject II-2) and uncle (subject II-1) had a history of renal tumors. A large renal tumor was detected in the young woman. Review of the pathology of the renal tumors of the woman (subject III-4) and her mother (subject II-2) showed renal cell carcinoma with a papillary growth pattern.

Family 156. A 45-year-old asymptomatic man (subject II-3) was found incidentally to have bilateral renal tumors during an ultrasound examination. Surgery revealed multiple, bilateral papillary renal cell carcinomas. The patient's father (subject I-1), mother (subject I-2) and 3 siblings (ages 30, 36 and 40 years, subjects II-1, II-2 and II-4) were examined by CT and/or ultrasound, and no renal tumors were found.

Family 157. A 53-year-old woman (subject II-12) contacted the National Cancer Institute because of a family history of renal cell carcinoma and she had multiple papillary renal cell carcinomas of the left kidney. Subject II-12 and 2 of her brothers (subjects II-2 and II-4) had papillary renal cell carcinoma. No renal tumors were detected by CT in 3 descendents of affected individuals (subjects III-1, III-2 and III-3, ages 28, 32 and 33 years) and in the 6 siblings of subject II-12 (subjects II-1, II-6, II-8, II-9, II-10 and II-11).

Family 158. A 63-year-old man (subject III-1) was found incidentally to have multiple bilateral renal tumors during an abdominal ultrasound examination. The histological appearance of the renal tumors was papillary renal cell carcinoma. The pathology report indicated "multifocal renal cell carcinoma with extensive papillary features." The patient's aunt (subject II-3) had undergone nephrectomy at age 70 years. The pathology report for subject II-3 indicated "well-differentiated renal cortical adenocarcinoma, tubular and papillary type with multiple intrarenal satellite nodules." A daughter of subject III-1 (IV-2, age 34 years) was examined by CT and no renal tumors were detected.

Family 159. Two first cousins were found to have renal cell carcinoma. The diagnosis on subject III-3 was papillary renal cell carcinoma and slides were not available on subject III-2.

Cytogenetic studies were performed on the peripheral blood of 1 affected member of families 150, 152, 153, 154 and 156. No constitutional chromosomal alterations were detected. No consistent cytogenetic alterations were observed in 12 metaphases from the renal tumor from subject III-1 in family 154.

DISCUSSION

We identified 41 patients affected with papillary renal cell carcinoma in 10 families. The identification of multiple family members affected with this uncommon neoplasm, the presence of the neoplasm in 2 or 3 generations and the finding of bilateral, multiple tumors support the concept that the predisposition to develop papillary renal cell carcinoma may be inherited. Additional support for this concept comes from the identification of a pair of identical twins, both of whom have this uncommon renal neoplasm (unpublished data). Because papillary renal cell carcinomas were often asymptomatic, had a late age of onset and required imaging studies for detection, it was difficult to discern the hereditary pattern of this disorder. Families 152, 153 and 154 illustrate the effect of age of onset on recognizing the inherited pattern of papillary renal cell carcinoma. In these 3 families 20 to 30 years elapsed between the detection of renal cancer in 1 generation and the detection of renal cancer in members of the next generation. Presumably, the time required to detect transmission of a predisposition to papillary renal cell carcinoma from 1 generation to the next would have been even greater than 20 to 30 years if family members had not been under strict surveillance. The difficulty of detecting a hereditary pattern was compounded by the fact that individuals who apparently carried the predisposing gene (for example family 152 subject I-2) did not have renal tumors detected within their lifetimes.

Evidence for an inherited predisposition to papillary renal cell carcinoma was particularly striking in family 152. In this Swedish family subject I-2 had 7 children by 2 wives. In 5 of 5 children from 1 marriage and 1 of 2 from the other marriage papillary renal cell carcinoma developed. These 6 affected individuals had 4 children, all of whom had papillary renal cell carcinoma. There are 5 at risk individuals in the current generation.

Although this information indicates that the predisposition to develop papillary renal cell carcinoma may be inherited, we cannot prove an inherited predisposition to papillary renal cell carcinoma in family 156. Although subject II-3 in family 156 had bilateral, multiple papillary renal cell carcinomas, his parents and 3 siblings had no evidence of renal tumors. Previously, the presence of multiple, bilateral renal tumors has provided a clear indication of an inherited predisposition to renal neoplasia. This has been true of the clear cell renal carcinomas associated with von Hippel-Lindau disease[1] and the 3;8 translocation,[4] the angiomyolipomas associated with tuberous sclerosis[25] and the nephroblastomas associated with Wilms tumor.[26] It is unknown whether the bilateral, multiple papillary renal tumors observed in subject II-3 in family 156, but not in his parents, reflect incomplete penetrance of the predisposing gene, a new mutation in the predisposing gene inherited by subject II-3, or a noninherited, neoplastic disorder of the kidneys. Ge-

netic loci may exist that might modify an inherited predisposition to papillary renal cell carcinoma producing a pattern of incomplete penetrance.[27] With continued observation, it will be possible to determine whether papillary renal cell carcinoma will develop in the children of subject II-3. It would be useful to identify other individuals with bilateral, multiple papillary renal cell carcinoma and study their relatives to determine the frequency of renal tumors.

Henn et al recently reported on a patient with bilateral, multiple papillary renal cell carcinomas.[28] By cytogenetic criteria the tumors were independent primaries; trisomy of chromosomes 7, 16 and 17 was found. In normal tissue a wide variety of clonal and nonclonal structural and numeric chromosome aberrations were found. The authors suggested the presence of a tissue-specific karyotypic instability. It is unclear whether this postulated tissue-specific karyotypic instability in this patient with bilateral papillary renal cell carcinoma reflects a germ line or somatic mutation(s).

Kovacs and Kovacs recently examined the entire parenchyma of 15 kidneys with sporadic papillary tumors.[29] There were an average of 42 microscopic, papillary parenchymal lesions per kidney compared to 0.4 per kidney in nonpapillary tumors. As noted previously, a cardinal feature of inherited neoplastic disorders of the kidney is the presence of multiple bilateral renal tumors. In this context the observation of multiple, microscopic tumors in the kidneys of patients with sporadic papillary renal cell carcinoma is puzzling. Among the explanations for this observation are that the predisposition to papillary renal cell carcinoma is inherited in most cases and that sporadic papillary renal cell carcinoma may be a developmental disorder combined with exposure to environmental carcinogens.[15]

Thoenes et al developed a new classification of adenocarcinomas of the kidney, which provides a key to the identification of distinct genes involved in renal neoplasia.[11,12] Germ line or somatic mutations in the von Hippel-Lindau gene are associated with clear cell renal carcinomas with a compact growth pattern.[2,3] Our data suggest that mutations in a different gene, the papillary renal cell carcinoma gene, lead to renal carcinomas with a tubular/papillary growth pattern. The next step will be to identify the chromosomal location of this gene. With many tumors chromosomal rearrangements have suggested the regions that may harbor tumor suppressor genes. Cytogenetic studies of 5 papillary renal cell carcinomas have demonstrated translocations between chromosomes 1 and X [t(X;1) (p11.2;q21)], suggesting that 1 of these chromosomes may harbor a gene that leads to papillary renal cell carcinoma. Since father to son transmission of papillary renal cell carcinoma has been observed in families 150, 153 and 154, it is unlikely that the papillary renal cell carcinoma gene in these families is located on the X chromosome. Chromosome 1 should be studied as a possible location for the papillary renal cell carcinoma gene. The families described in this report will be useful in linkage analysis to identify the chromosomal location of the gene responsible for papillary renal cell carcinoma.

Dr. Roger Ladda, Pennsylvania State College of Medicine, Hershey, Pennsylvania, provided the cytogenetic studies on blood samples from members of family 150.

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