0021-972X/96/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 81, No. 12
Printed in U.S.A.

Autosomal Dominant Primary Hyperparathyroidism and Jaw Tumor Syndrome Associated with Renal Hamartomas and Cystic Kidney Disease: Linkage to 1q21-q32 and Loss of the Wild Type Allele in Renal Hamartomas*

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ABSTRACT

Hereditary hyperparathyroidism-jaw tumor syndrome (HPT-JT) is an autosomal dominant disease (OMIM 145001) that has recently been mapped to chromosomal region 1q21-q32 (HRPT2). Here we report two families with HPT-JT syndrome in which adult renal hamartomas or cystic kidney disease were prominent associated features, possibly representing a new phenotypic variant of the HPT-JT syndrome. In the first family, renal lesions were present in five out of six affected individuals, whereas HPT and JT were seen in four and two cases, respectively. In the second family, JT was found in three of the five affected individuals and two affected members also exhibited polycystic kidney disease. The possibility of the latter cosegregating as a separate autosomal dominant gene can not be ruled out. A sex-dependent penetrance of primary HPT, resulting in predominantly male-affected cases was evident in the two families. Twenty microsatellite markers in the HRPT2 region were typed, in addition to markers in the multiple endocrine neoplasia (MEN) types 1 and 2 regions at 11q13 and 10q11. The disease in these two kindreds was linked to five markers in the 1q21-q32 region (logarithm-of-odds scores: 3.2–4.2), whereas linkage to the MEN1 and MEN2 regions was excluded. Meiotic recombinations detected in affected individuals placed the locus telomeric of D1S215, thus narrowing the HRPT2 region from >60 to ~34 centimorgans. Loss of heterozygosity was studied in seven renal hamartomas from two affected individuals in the first family, as well as in a jaw tumor and a parathyroid tumor from the second family. All renal hamartomas showed loss of heterozygosity at the 1q21-q32 region. The losses invariably involved the wild type allele derived from the unaffected parent, suggesting the inactivation of a tumor suppressor gene in this region. (*J Clin Endocrinol Metab* **81:** 4204–4211, 1996)

PRIMARY hyperparathyroidism (1°HPT) has been associated with a number of distinct hereditary syndromes including multiple endocrine neoplasia types 1 and 2A (MEN1, MEN2A) and familial isolated HPT (1). More recently, the autosomal dominant HPT-jaw tumor syndrome (HPT-JT) was established as a separate entity (2) (McKusick number 145001) and subsequently mapped to chromosomal region 1q21-q32 (3). The gene for the HPT-JT syndrome has been designated HRPT2, whereas HRPT1 is the gene responsible for familial isolated 1°HPT, the chromosomal location of which is yet to be determined (4, 5). In the HPT-JT syndrome, both uniglandular and multiglandular parathyroid disease is seen. The jaw tumors are fibro-osseous lesions found in the mandible and/or maxilla. They are histopathologically distinct from classical 1°HPT-related brown tumors and are not responsive to the correction of HPT. The syndrome has also been associated with a risk of parathyroid carcinoma and Wilms' tumor. In three families with HPT-JT, two affected members had parathyroid carcinoma, further supporting the hereditary nature of the malignancy and its association with HPT-JT (6). Wilms' tumor has been described in three patients from three separate HPT-JT families to date (3, 7). Here we report two new families manifesting the HPT-JT syndrome. In both kindreds there was apparent co-occurrence of renal hamartomas and/or cystic kidney disease, representing a new phenotypic variant of the HPT-JT syndrome. Linkage analyses were carried out,as well as studies of loss of heterozygosity (LOH) in associated tumors.

Received April 17, 1996. Accepted July 30, 1996.

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* This work was supported by the Swedish Medical Research Council, the Swedish Cancer Society, the Fredrik and Ingrid Thuring Foundation, the Magn. Bergwall Foundation, and the Torsten and Ragnar Söderberg Memory Foundation, and by the Princess Alexandra Hospital Research and Development Foundation.

† Recipient of the Paul Bolton Mackay Scholarship (1995/1996).

Patients and Methods

The disease state of the family members was confirmed by biochemical, radiological, or pathological evidence. Both families are of Caucasian origin, one residing in Sweden (family 1) and the other in Australia (family 2).

Family 1

The pedigree of family 1 is shown in Fig. 1. The proband (IV:14) is a 66-yr-old woman who was found in 1986 to have bilateral renal cysts at biliary tract angiography. Following a period of left flank pain, renal ultrasonography and computed tomography (CT) scanning revealed left renal neoplasms, which led to the removal of the kidney in 1993. Two renal neoplasms were identified, 2.5 and 3 cm in diameter, with multiple microcysts (Fig. 2). The kidney also contained multiple larger cysts that had no relationship to the tumors. The histology of the tumors was examined by a number of experts and was considered to be best classified as renal hamartoma (8). They were quite well differentiated and were characterized by three components: a large mesenchymal, a blastemic, and a small epithelial. The tumors were not well circumscribed, showed no necrosis or hemorrhages, and the number of mitoses were low. Immunohistochemical staining using a proliferation marker (MIB-1/Ki-67) showed less than 1% positive cells. Postoperative CT scan and renal angiography showed that two additional tumors were present in the remaining kidney. The patient has normal serum calcium, creatinine, and PTH values.

Her sister's (IV:16) first symptom was a period of flank pain. Her left kidney was removed in 1972 when she was age 39 yr. Three cystic tumors were identified in the specimen, and in 1975 additional tumors were identified in the right remaining kidney. Furthermore, in 1973 three pathological parathyroid glands were identified at neck exploration for 1°HPT. They were reported as the following: one had the characteristic appearance of an adenoma, one had focal hyperplasia, and one had nodular hyperplasia. No microcysts was reported.

The proband's father (III:5) underwent surgery in 1940, at age 56 yr, for 1°HPT, and when he died in 1950, mandibular and maxillary ossifying fibromas were identified at autopsy in addition to bilateral renal hamartoma and renal cysts. The proband's half-brother (IV:2), now age 75 yr, had surgery for a mandibular ossifying fibroma in 1938, and for 1°HPT in 1945, with lasting normocalcemia. His left kidney was removed in 1949 because of renal calculi, but no pathology report was available. Another half-brother (IV:6) of the proband had a prostate

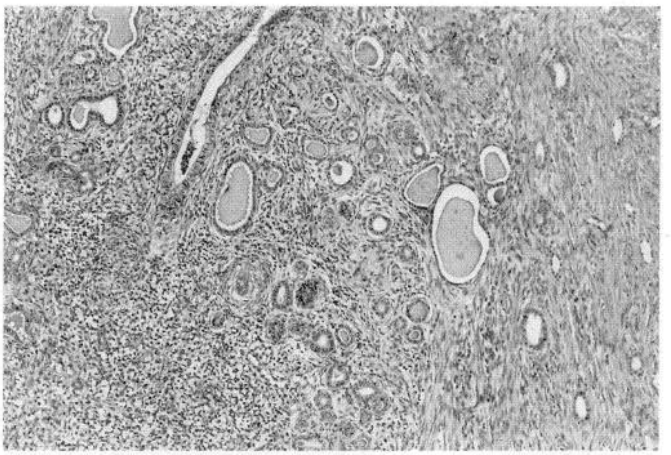

FIG. 2. Light microscopic picture of renal tumor showing small epithelial cysts and abundant mesenchyma. Magnification, ×70.

carcinoma removed at age 64 yr in 1982. 1°HPT was later diagnosed in IV:6, and recently multiple atypical cysts were found in the right kidney. His daughter (V:8) was investigated with renal ultrasonography and CT scanning in 1992 because of microscopic hematuria and flank pain. Neoplasms were then identified in the left kidney, which was subsequently removed. One renal hamartomas (4 cm) was identified in the medulla and five renal hamartomas (1 cm each) were found in the cortex.

Family 2

The pedigree of family 2 is shown in Fig. 1. In 1987, the proband (IV:1) first noticed a fast growing mass in his left maxilla at age 26 yr. The tumor was excised but during that hospitalization he was also found to have 1°HPT. A left inferior parathyroid gland weighing 2.35 g (2.4 × 1.3 × 1.1 cm) was later removed, and he has since remained normocalcemic. The pathology was described as an adenoma consisting almost entirely of oxyphil cells arranged in sheets. In 1991, the patient developed a large recurrent left maxillary mass causing left proptosis, diplopia, and nasal obstruction (Fig. 3). The patient underwent subtotal maxillectomy, followed by reconstruction of maxillary cavity using a left rib graft. Bone

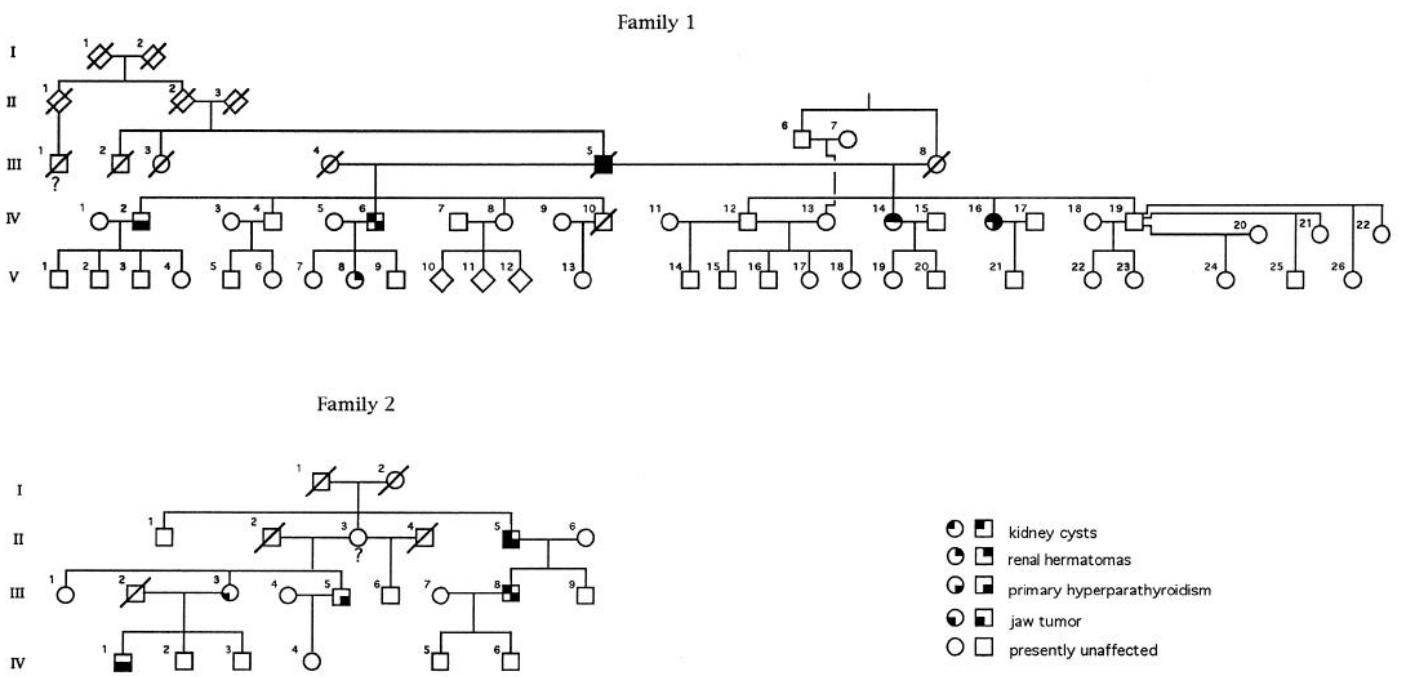

FIG. 1. Pedigrees and phenotypes of the two families in this study.

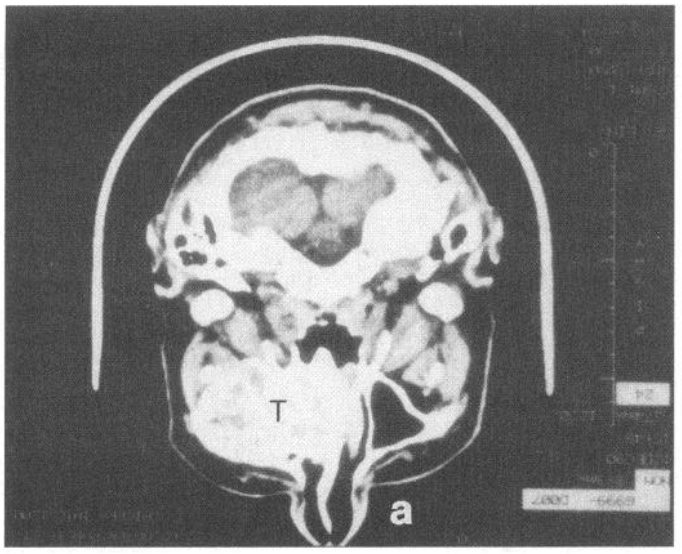

FIG. 3. CT scan showing extensive effacement of left maxillary antrum by jaw tumor (T) in individual IV-1 in family 2. a, Anterior.

scan did not reveal any other skeletal lesions. The jaw tumor consisted of dense fibrocellular connective tissue with plump spindle cells interwoven in bundles and a focally storiform arrangement. There were prominent irregular trabeculae of osteoid and woven and lamellar bone, but no evidence of the abundant multinucleated osteoclasts characteristic of HPT-related brown tumors.

Subsequent investigations revealed that the proband's maternal grand uncle (II:5) had undergone the removal of a large maxillary tumor in 1963, right inferior parathyroid adenomectomy in 1964, and removal of a polycystic kidney in 1989, followed by renal transplantation in 1991. His son (III:8) had 1°HPT and had had removal of two parathyroid adenomas. He remained normocalcemic but ultrasound examination this year revealed polycystic kidneys.

The proband's maternal grandmother (II:3) and mother (III:3) have had no evidence of 1°HPT to date. However, a thumb-sized jaw lesion was found on orthopentography in III:3. Unfortunately, the grandmother (II:3) refused to have orthopentography. One of the proband's maternal uncles (III:5) had a parathyroidectomy for 1°HPT in 1981 and became normocalcemic.

Linkage analysis

Informed consents were obtained from members of both families. Blood samples were obtained and high molecular weight DNA was isolated using standard methods. Two microsatellite markers were used for the MEN1 region at 11q13 (D11S449 and PYGM), and two from the MEN2 region at 10q11 (D10S141 and ZNF22). Twenty microsatellite markers for the 1q21-32 region that were previously ordered (9) were used as shown in Fig. 4. Genotyping was carried out as previously described (10).

Two-point logarithm-of-odds (lod) scores were generated using the LIPED linkage program. To diagnose HPT-JT in a family member, we required any one or combination of the following: 1°HPT diagnosed clinically or surgically, jaw tumor, renal hamartomas, or parathyroid carcinoma. In family 1 unaffected individuals IV:4, 8, 12, and 19 (aged 79, 65, 68, and 61 yr) who had been screened biochemically and by renal ultrasonography were scored as normal. In family 2 unaffected individuals II:1 (aged 75 yr) and III:1 (aged 53 yr) who had been screened repeatedly were scored as normal. The obligate gene carrier (II:3 in family 2) who had no evidence of HPT on biochemical testing but refused any radiological investigations, was scored as unknown. All other members at risk and below the age of 50 yr were scored as unknown. Conventional lod score cut-offs were used, *i.e.* lod >3.0 signifies linkage to a given marker, and lod <-2 excludes linkage.

LOH studies

DNA from paraffin-embedded pathological blocks were obtained as previously described (11) for LOH studies: a parathyroid tumor and a jaw tumor from patient IV:1 in family 2 and seven renal hamartomas from patients IV:14 and V:8 in family 1. Loss of heterozygosity was studied using microsatellite markers as described above. Allele status was identified on autoradiographic films and confirmed by digital images (Bio-imaging analyzer Bas 1000, Fuji, Japan), which allow computerized calculations of relative allele intensities (12).

Results

In the two families with HPT-JT syndrome, renal hamartomas or cystic kidney disease were prominent associated features, possibly representing a new phenotypic variant of the HPT-JT syndrome (Fig. 1). In the first family, renal lesions were present in five out of seven affected individuals, and in the second family, two affected members exhibited polycystic kidney disease. Out of the 11 affected cases and 1 obligate gene carrier (II:3 family 2), 5 were female and 7 were male. All seven men had 1°HPT, whereas this was only found in one of the women (Table 1). This difference is statistically significant ($X^2 = 8.4$; $P < 0.01$) and was not related to age difference, because the four women were still normocalcemic at age 66, 45, 71, and 52 yr, respectively (Table 1). Two of six affected in the first family (33%) and three of five affected in the second family (60%) were found to have jaw tumors.

Linkage to MEN1 and MEN2 was excluded on the basis of haplotype analysis and significantly negative lod scores for markers at both loci ($-\infty$ at recombination fraction = 0). Total two-point lod scores for the chromosome 1q21-q32 markers are summarized in Table 2. All markers except two, D1S242 and D1S215, gave positive lod scores, which varied depending on the informativeness of the markers in the kindreds. Total lod scores were >3 for five markers at recombination fraction = 0, and the highest lod score was obtained with the marker D1S422 (4.15), thus confirming the linkage in this region.

The haplotypes of the 1q21-q32 region markers are shown in Figs. 4 and 5. Meiotic recombinations were detected in affected individuals in each family. In individual IV:16 in family 1, a recombination occurred between D1S242 and D1S191, but because D1S215 and D1S466 were uninformative, the recombination could not be more precisely mapped. In individual II:5 in family 2, cross-over occurred between D1S215 and D1S466, and the recombinant chromosome was transmitted to his affected son (III:8). The HRPT2 locus was previously mapped to a >60 centimorgan (cM) region flanked by D1S104 (centromeric) and D1S245 (telomeric) (3). Taken together, the results place the gene telomeric of D1S215 and centromeric of D1S245, thereby restricting the region to ~34 cM.

Heterozygosity was retained in the parathyroid adenoma and in the jaw tumor, but all seven renal hamartomas showed LOH in seven tested markers in the 1q21-q32 region, as illustrated for D1S412 and D1S413 in (Figs. 4 and 6). Because in all seven renal hamartomas the putative wild type alleles derived from the unaffected parents were lost, this is in agreement with inactivation of a tumor suppressor gene in the region.

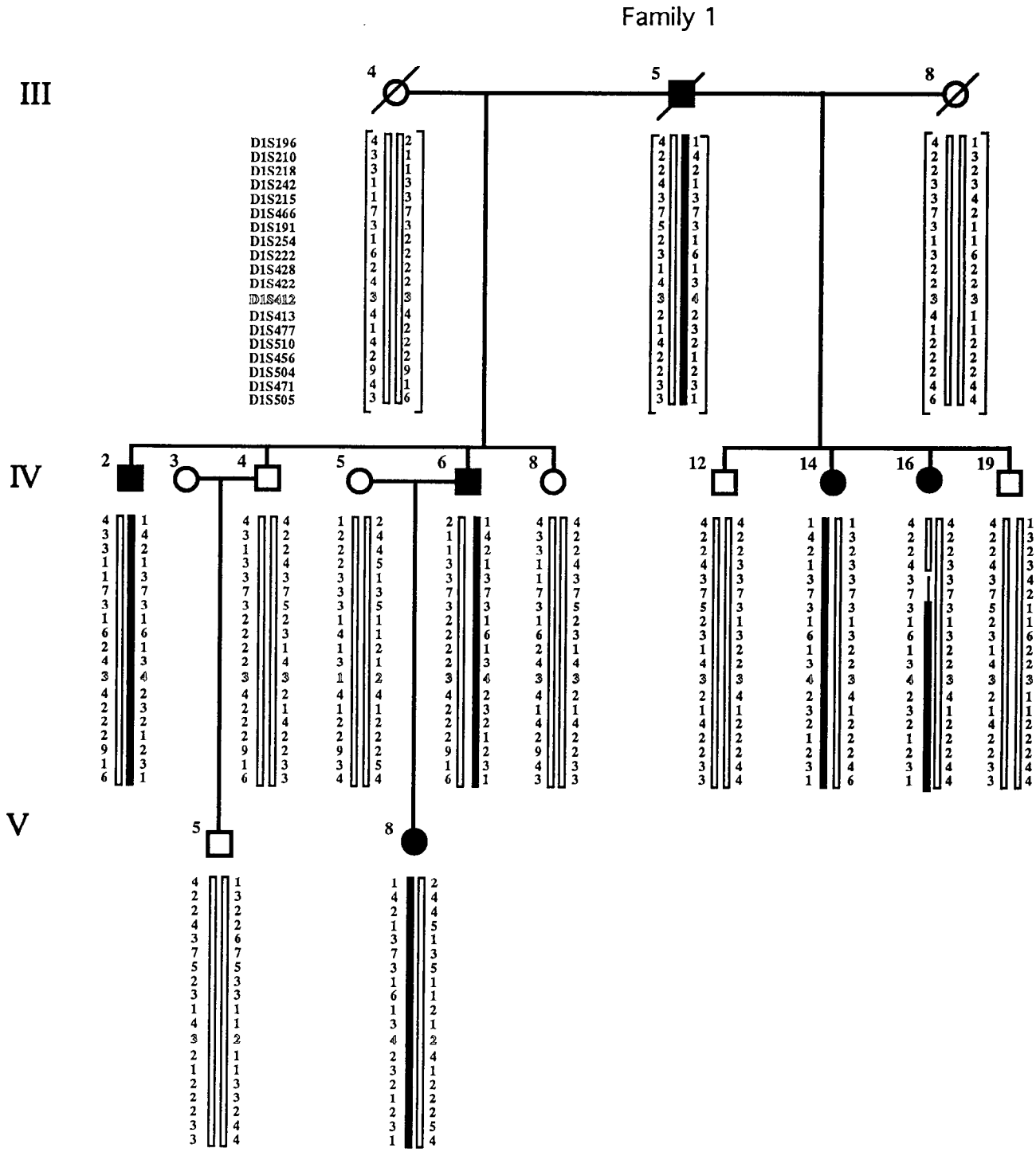

FIG. 4. Haplotypes of chromosome 1q21-q32 in family 1. Markers are listed in order from centromere to telomere at *upper left*. *Filled symbols* indicate affected and *open symbols* unaffected family members. Haplotypes for each individual are depicted along an illustrated chromosome segment. Inferred disease-bearing chromosome is *blackened*. *Bracketed* haplotypes represent those inferred from haplotyping of children. Recombination in individual IV-16 could occur with either marker D1S221 or D1S215 but to be conservative in determining mapping region, the more centromeric one was chosen.

Discussion

The identification of HPT and jaw tumor as a distinct syndrome (2, 13) has given clinicians yet another differential diagnosis to consider when faced with cases of familial 1°HPT. The HPT-JT syndrome encompasses 1°HPT with uniglandular or multiglandular disease and fibro-osseous jaw tumors, and in some cases Wilms' tumor (3 single cases in 3 of the 10 reported families) and parathyroid carcinoma (in 4 of the 10 families).

The parathyroid and jaw lesions found in our two families

closely resemble those reported in other HPT-JT families. The parathyroid neoplasia may represent uniglandular or multiglandular disease, but parathyroid carcinoma has occurred in 3 of the 12 described families (6, 7, 14). Although it has not been observed in the present families, the malignant potential of the parathyroid tumors has to be kept in mind in the follow-up of these patients. In some reports, the malignant nature of the parathyroid lesions was recognized only years after the first operation (14).

TABLE 1. Clinical characteristics of 11 affected members and one obligate gene carrier

Patient	PCK[a]	KC	RH	JT	1° HPT (age)	Sex	Present age
Family 1							
III:5		Yes	Yes	Yes	Yes (56)	M	
IV:2				Yes	Yes (25)	M	
IV:6		Yes			Yes (64)	M	
IV:14		Yes	Yes			F	66
IV:16		Yes	Yes		Yes (40)	F	
V:8			Yes			F	45
Family 2							
II:3						F	71
II:5	Yes			Yes	Yes (38)	M	
III:3				Yes		F	52
III:5					Yes (35)	M	
III:8	Yes				Yes (29)	M	
IV:1				Yes	Yes (26)	M	

[a] PCK, Polycystic kidney disease; KC, kidney cysts; RH, renal hamartomas; JT, jaw tumor.

A sex-dependent penetrance of 1°HPT was evident in the two families studied. The low penetrance of 1°HPT in women suggests the existence of a modifying gene on the X-chromosome. We did not include previously reported families into our calculations because of lack of detailed clinical information about the unaffected members in these families. However, it is noteworthy that in the previous report (3), there were a total of 21 male patients with HPT in contrast with 7 female cases, a ratio of 3:1. Sex-dependent penetrance of 1°HPT in familial cases has not been found in MEN1, which has almost complete penetrance with and equal sex ratio and over 95% of cases having 1°HPT (15). Modifier genes are apparent in all genetically mixed populations and are commonly referred to as the genetic background in which the mutant gene finds itself (16). A recent study demonstrated a possibly novel X-chromosome tumor suppressor gene that is likely to play a role in a subset of parathyroid tumors (17). If this is the case, we can hypothesize that male individuals would be more predisposed to the adverse effects of the mutant gene because only one mutation is required. This would help explain our observation, although the process could be more complex and associated with sex-related differences such as sex hormones and methylation.

The jaw tumors are of the fibro-osseous form, which is not responsive to the correction of HPT. This is exemplified in individual IV:1 in family 2 who had a rapid growth of the

TABLE 2. Total lod scores for linkage to chromosome 1q21-q32 markers in the two kindreds

Locus	Family	Recombination fraction (θ)						
		0.000	0.010	0.050	0.100	0.200	0.300	0.400
D1S242	1	$-\infty$	0.322	0.878	0.991	0.884	0.602	0.241
	2	$-\infty$	−0.701	−0.125	0.023	0.039	−0.003	−0.015
	Total	$-\infty$	−0.379	0.753	1.014	0.923	0.599	0.226
D1S215	1	−0.089	−0.089	−0.088	−0.084	−0.065	−0.035	−0.010
	2	$-\infty$	−0.252	−0.341	0.503	0.504	0.353	0.150
	Total	$-\infty$	−0.341	0.253	0.419	0.439	0.318	0.140
D1S254	1	1.675	1.641	1.503	1.326	0.954	0.563	0.187
	2	1.505	1.470	1.327	1.140	0.747	0.361	0.082
	Total	3.180	3.111	2.830	2.466	1.701	0.924	0.269
D1S428	1	−0.033	−0.033	−0.033	−0.032	−0.026	−0.015	−0.004
	2	1.443	1.412	1.287	1.124	0.777	0.419	0.116
	Total	1.410	1.379	1.254	1.092	0.751	0.404	0.112
D1S422	1	2.342	2.302	2.141	1.930	1.470	0.952	0.382
	2	1.807	1.771	1.628	1.441	1.038	0.609	0.214
	Total	4.149	4.073	3.769	3.371	2.508	1.561	0.596
D1S412	1	2.015	1.977	1.821	1.617	1.179	0.702	0.233
	2	1.505	1.475	1.349	1.186	0.837	0.476	0.166
	Total	3.520	3.452	3.170	2.803	2.016	1.178	0.399
D1S413	1	0.231	0.227	0.209	0.187	0.146	0.105	0.059
	2	1.806	1.771	1.628	1.441	1.039	0.614	0.222
	Total	2.037	1.998	1.837	1.628	1.185	0.719	0.281
D1S477	1	2.241	2.202	2.046	1.841	1.397	0.900	0.360
	2	1.630	1.595	1.452	1.265	0.867	0.460	0.131
	Total	3.871	3.797	3.498	3.106	2.264	1.360	0.491
D1S510	1	1.709	1.679	1.557	1.397	1.051	0.663	0.247
	2	1.630	1.597	1.463	1.288	0.917	0.533	0.193
	Total	3.339	3.276	3.020	2.685	1.968	1.196	0.440
D1S456	1	2.172	2.133	1.975	1.767	1.318	0.820	0.301
	2	0.495	0.492	0.474	0.437	0.327	0.188	0.057
	Total	2.667	2.625	2.449	2.204	1.645	1.008	0.358
D1S504	1	0.281	0.276	0.258	0.235	0.187	0.135	0.750
	2	1.529	1.497	1.365	1.193	0.828	0.452	0.134
	Total	1.810	1.773	1.623	1.428	1.015	0.587	0.884

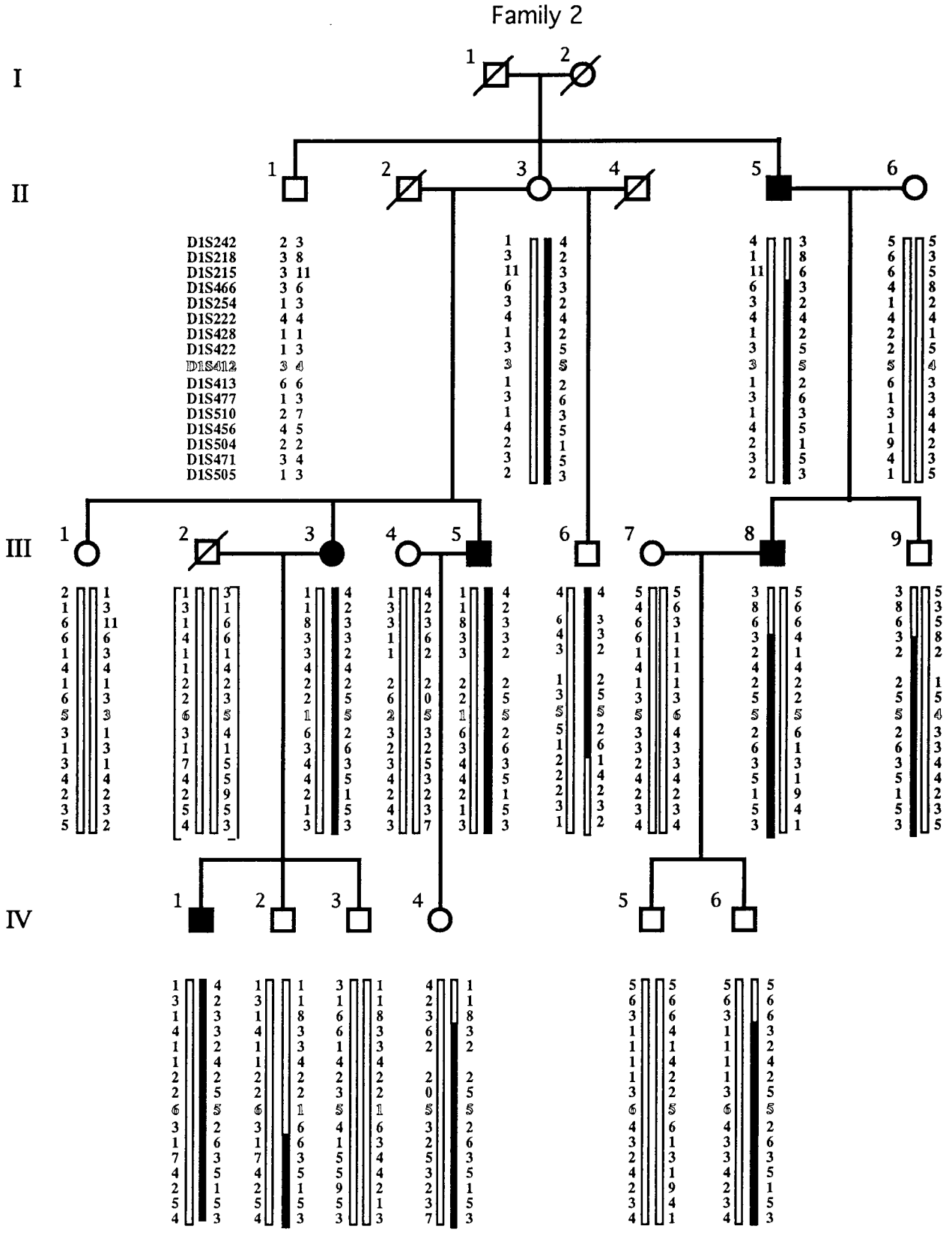

FIG. 5. Haplotypes of chromosomal region 1q21-q32 in family 2, with disease-bearing haplotype *blackened*. Note recombination in II-5 between D1S215 and D1S466, which was transmitted to his son (III-8).

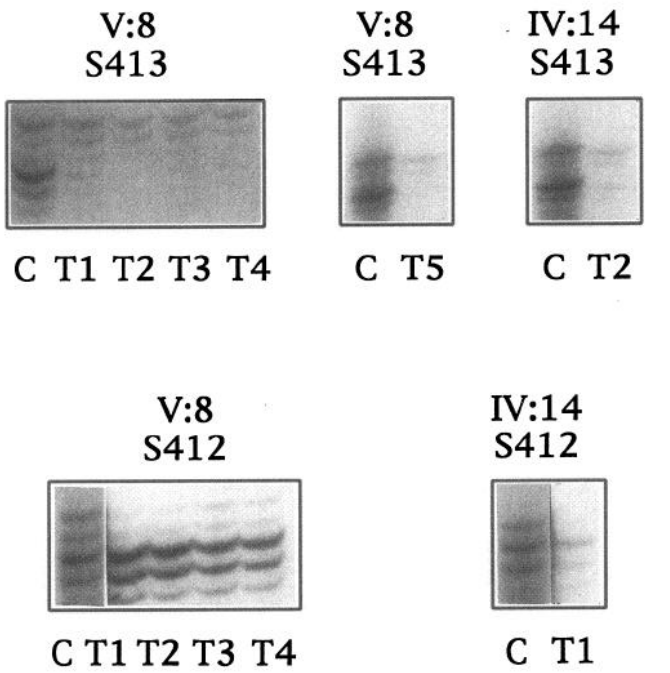

FIG. 6. Autoradiograms showing loss of heterozygosity at D1S413 and D1S412 loci in renal hamartomas from individuals V:8 and IV:14 in family 1. C, Constitutional DNA; T, = tumor DNA. Both individuals had constitutional genotype (alleles 2,4) at D1S413 locus, and renal hamartomas retained the longer allele (allele 2), which was linked to the disease (Fig. 4). Similar results were obtained for D1S412, with retention of the shorter allele (allele 4) derived from affected parents (Fig. 4)

recurrent jaw tumor although he remained normocalcemic postoperatively. Thirty-three to forty percent of our patients have jaw tumors, which is consistent with previously reported families (3).

Wilms' tumor has been reported in single members of three HPT-JT kindreds, suggesting that renal neoplasia may be an integrated part of the HPT-JT syndrome (3, 7). The present report greatly strengthens the proposed association between renal neoplasms and HPT-JT, because renal hamartomas and/or renal parenchymal cysts were found in 7 out of 11 affected patients in the two kindreds examined. The renal hamartomas in family 1 (Fig. 2) are a rarely described tumor type. These tumors were classified as renal hamartomas, but further pathological characterization is warranted. In this family it shows no malignant features and seems to run a relatively benign course. In many cases the renal hamartomas were treated surgically, but none of the deceased affected patients had metastases or died from the disease. This is in contrast to classical Wilms' tumor, which occurs in childhood and is usually a highly malignant tumor requiring surgical treatment and postoperative chemo- or radiotherapy. Furthermore these tumors were bilateral and multiple, not well circumscribed, and of smaller sizes than typical Wilms' tumors. As compared with classical Wilm's tumor, some unusual histological features were also evident, *i.e.* a low number of mitoses, lack of necrosis and hemorrhages, large mesenchymal components, and presence of cysts. In family 2, the polycystic kidney disease in individual II-5 was first assumed to be incidental. The very recent radiological finding of similar lesions in his son who previously also had two parathyroid tumors removed supports its hereditary nature. A separate autosomal dominant polycystic kidney disease gene may cosegregate with HPT-JT in this family, but we think it is more likely that the renal lesions are part of the syndrome. We are persuaded by the existence of cystic and neoplastic renal lesions in both our kindreds, and by the cystic nature of the parathyroid lesions in at least one HPT-JT kindred (13). To date, two loci for polycystic kidney disease have been assigned to chromosomes 4 and 16, whereas the third locus is still unknown (18). Our findings of two individuals with polycystic kidney disease in one of the families makes the HRPT2 region a likely candidate for this third locus. In view of this association of cystic and neoplastic renal lesions with HPT-JT, we suggest that families with HPT-JT be screened by abdominal ultrasound or CT scan. We also propose that the wide spectrum of cystic and neoplastic lesions arising in the kidneys of HPT-JT patients represent phenotypic variants arising from specific mutations of the HRPT2 gene.

The current study further strengthens that the HPT-JT disease gene, HRPT2, maps to chromosomal region 1q21-1q32 (3). Recombinations detected in this area in affected cases narrow the critical region from >60 cM to ~34 cM between the flanking markers D1S215 and D11S245. The phenotypic variation observed in the HPT-JT syndrome most likely represents the effects of different mutations of the HRPT2 gene, for example as demonstrated in MEN2 (19). Familial medullary thyroid carcinoma, medullary thyroid carcinoma with pheochromocytoma, and 1°HPT (MEN 2A), as well as the more severe MEN2B, which also includes neurogangliomatosis and marfanoid habitus, all result from region-specific mutations in the RET-proto-oncogene. Only 12 HPT-JT families are known at present. We speculate as additional families are discovered the phenotypic spectrum of the disorder will be broadened.

The LOH studies suggest that the HRPT2 gene in 1q21-q32 may function as a tumor suppressor gene. All the seven renal hamartomas studied showed LOH in 1q, and the loss involved the wild type allele derived from the unaffected parent, which is consistent with Knudson's two-hit mutation theory suggesting the inactivation of a tumor suppressor gene (20). This LOH in 1q21-q32 might be specific for renal hamartomas because it was not found in HRPT2-related parathyroid tumors (3).

In conclusion, the present study presents the first evidence of hereditary renal hamartomas, widens the spectrum of the 1°HPT-JT syndrome to include renal hamartomas and polycystic kidney disease, and suggests that the HRPT2 gene is a tumor suppressor gene. The parathyroid and renal neoplasms both have malignant potential, and both may have a cystic component. Studies of additional families should help expand the phenotypic profile of hereditary 1°HPT and further the search for the responsible genes.

Acknowledgments

We wish to thank Bruce Beckwith, Steen Olsen, Stig Colleen, Richard Zarbo, Mahul Amin, Bengt Sandstedt, Cesar Baro, Raymond Hackett,

William Pfaff, Robert Bolande, Sven Lindell, Miriam Christ, and Aina Hägermark for expert advice and valuable assistance.

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