0021-972X/98/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 83, No. 6
Printed in U.S.A.

Familial Isolated Hyperparathyroidism Maps to the Hyperparathyroidism-Jaw Tumor Locus in 1q21-q32 in a Subset of Families*

BIN TEAN TEH, FILIP FARNEBO, STEPHEN TWIGG, ANDERS HÖÖG, SOILI KYTÖLÄ, EEVA KORPI-HYÖVÄLTI, FUNG KI WONG, JÖRGEN NORDENSTRÖM, LARS GRIMELIUS, KERSTIN SANDELIN, BRUCE ROBINSON, LARS-OVE FARNEBO AND CATHARINA LARSSON

Department of Molecular Medicine (B.T.T., F.F., F.K.W., C.L.), Department of Pathology (A.H., L.G.), Department of Surgery (K.S., L-O.F.), Karolinska Hospital, Stockholm, S-17176 Sweden; Kolling Institute of Medical Research, Royal North Shore Hospital, Sydney, 2065 Australia; Department of Clinical Genetics (S.K.), Oulu University Hospital, Oulu, 90220 Finland; Department of Internal Medicine (E.K-H.), Seinäjoki Central Hospital, Seinäjoki, 60220 Finland; Department of Surgery (J.N.), Huddinge Hospital, S-14186 Sweden

ABSTRACT

Approximately 70 families with familial isolated hyperparathyroidism (FIHP) have been reported. Whether it is a separate entity or a variant of multiple endocrine neoplasia type 1 (*MEN1* at 11q13) or hyperparathyroidism-jaw tumor (HPT-JT or *HRPT2* at 1q21-32) syndrome is not known. We describe here 3 unreported families with familial primary hyperparathyroidism and evaluate their clinical, pathological, and genetic profiles. Biochemical and radiological screenings for MEN1 were negative for all families. In 2 families with a total of 10 affected cases and 3 female obligate carriers, there is no evidence of jaw or renal lesions despite careful radiological investigations. In both families the disease was linked to the 1q21-q32 region with the maximum logarithm of the odds (lod) scores of 3.10 and 3.43 for markers D1S222 and D1S249 respectively, at recombination fraction of 0. In 1 family 2 types of parathyroid pathology were found: 3 of chief cell type and 1 of oxyphil/oncocytic cell type. Two chief cell tumors and 1 oxyphil tumor were found to have loss of heterozygosity (LOH) involving loss of the wild-type alleles for chromosome 1q markers. In the third family, with 4 affected siblings, a parathyroid carcinoma and 2 cases of polycystic kidney disease were found. The parathyroid carcinoma also showed loss of heterozygosity in the 1q region. In conclusion, we found that the hyperparathyroidism traits in a subset of FIHP families are linked to the 1q21-32 markers in the HRPT2 region. We describe the spectrum of parathyroid disease in 1q-linked families involving 3 different types of pathology and demonstrate for the first time loss of wild-type alleles in these parathyroid tumors. Taken together, the results suggest that some of the FIHP are a variant of HPT-JT and that the gene involved is a tumor suppressor gene. (*J Clin Endocrinol Metab* **83:** 2114–2120, 1998).

FAMILIAL isolated hyperparathyroidism (FIHP or HRPT1; OMIM 145000) without association of other tumors has been described as a separate entity, and to date approximately 70 FIHP families have been reported (1). Clinically these patients more frequently present with profound hypercalcemia or hypercalcemic crisis as compared with multiple endocrine neoplasia type 1 (MEN1) patients who have a milder course of hyperparathyroidism (2). One or more abnormal parathyroid glands may be found, and there is a tendency towards malignant transformation (3–6). Whether FIHP is a variant of multiple endocrine neoplasia type 1 (MEN1; OMIM 131100) or hyperparathyroidism-jaw tumor syndrome (HPT-JT or HRPT2; OMIM 145001) is yet to be established. With the advance in positional cloning, the genetics of these syndromes have recently been elucidated. The gene for MEN1 which is characterized by tumors of parathyroids, enteropancreas, and anterior pituitary, has been mapped to 11q13 and recently cloned (7, 8). Frequent loss of heterozygosity (LOH), which is found in the MEN1-related tumors (7, 9, 10), as well as identification of inactivating mutations in MEN1 patients, indicate that the gene is a tumor suppressor gene (8, 11). The HPT-JT gene or HRPT2, on the other hand, has been mapped to 1q21-q32 but is yet to be cloned (12). Clinically, HPT-JT is characterized by one or more parathyroid adenomas/carcinomas and fibro-osseous jaw tumors (13). Recently, the spectrum of the syndrome has been extended to include renal lesions, namely Wilm's tumors, polycystic kidney disease, and renal hamartomas (14, 15). Unlike in MEN1-related parathyroid tumors, LOH has never been described in the HPT-JT-related parathyroid tumors (12, 15).

The frustration in managing FIHP mainly concerns genetic counselling and screening for other tumors associated with MEN1 and HPT-JT, which obviously entails expensive multimodal investigations on the patients as well as related family members. This problem can be alleviated if the genetics of this condition are elucidated. To date, only two FIHP families that

Received December 31, 1997. Revision received March 4, 1998. Accepted March 11, 1998.

Address correspondence and requests for reprints to: Bin Tean Teh M.D., Ph.D., Department of Molecular Medicine, Endocrine Tumor Unit, CMM L8:01, Karolinska Hospital, S-171 76 Stockholm, Sweden; E-mail: Bin.Teh@cmm.ki.se.

* This work was supported by the Swedish Cancer Foundation, the Torsten and Ragnar Söderberg Foundations, the Gustav V Jubilee Fund, the Sven och Ebba-Christina Hagbergs Foundation, and the Cancer Society of Stockholm (96-113).

are large enough for linkage analysis have been studied genetically. One family with a case of parathyroid carcinoma was previously excluded from MEN1 (16). However, subsequent studies confirmed that it is a classic HPT-JT family showing linkage to 1q21-q32, the HRPT2 region (Wassif W, Farnebo F, Teh BT, et al., submitted). Genetic analysis of the other FIHP family produced positive linkage results in the MEN1 region indicating that it is a variant of MEN1, but yet to be proven by mutation analysis (18). Obviously, more genetic studies of FIHP families are needed to dissect out its genetic basis. Here we describe our clinical, histopathological, and genetic findings of three previously unreported families.

Patients and Methods

Family 1

Family 1 is of Caucasian origin residing in Australia (Fig. 1). The proband (IV-7) is a male who at age 22 was found to have hypercalcemia (corrected total serum calcium 3.24 mmol/L; normal range 2.20–2.60) during hospitalization for treatment of incidental head injury. Further investigations confirmed primary hyperparathyroidism with a 10-fold elevation of PTH when corrected total serum calcium was 2.90 mmol/L and 24-h urinary calcium 16.9 mmol (normal range 1.25–7.5). In hindsight, he had been symptomatic of hypercalcemia for at least 2 yr with symptoms including polyuria and polydipsia. The hyperparathyroidism was treated with parathyroidectomy, where one enlarged gland was found, weighing approximately 4 g. Family history revealed that the proband's paternal grandmother (II-1) had had a parathyroid gland, also weighing about 4 g, removed at age 58, after recognition of primary hyperparathyroidism that presented with multiple renal calculi. Three grand aunts (II-3, II-4, and II-5) were clinically unaffected, but the son (III-8) of II-4 was found to have primary hyperparathyroidism. The father (III-6) had parathyroidectomy at age 25, also for renal calculi due to hyperparathyroidism. A further parathyroidectomy was performed at age 42, after recurrence of hypercalcemia. The gland removed at the second operation weighed 1.5 g. A paternal aunt (III-5) was found to have borderline elevated ionized serum calcium and upper limit of normal parathyroid hormone. The other 2 aunts (III-1) and (III-3), now aged in their 40's, have normal range total serum calcium levels, most

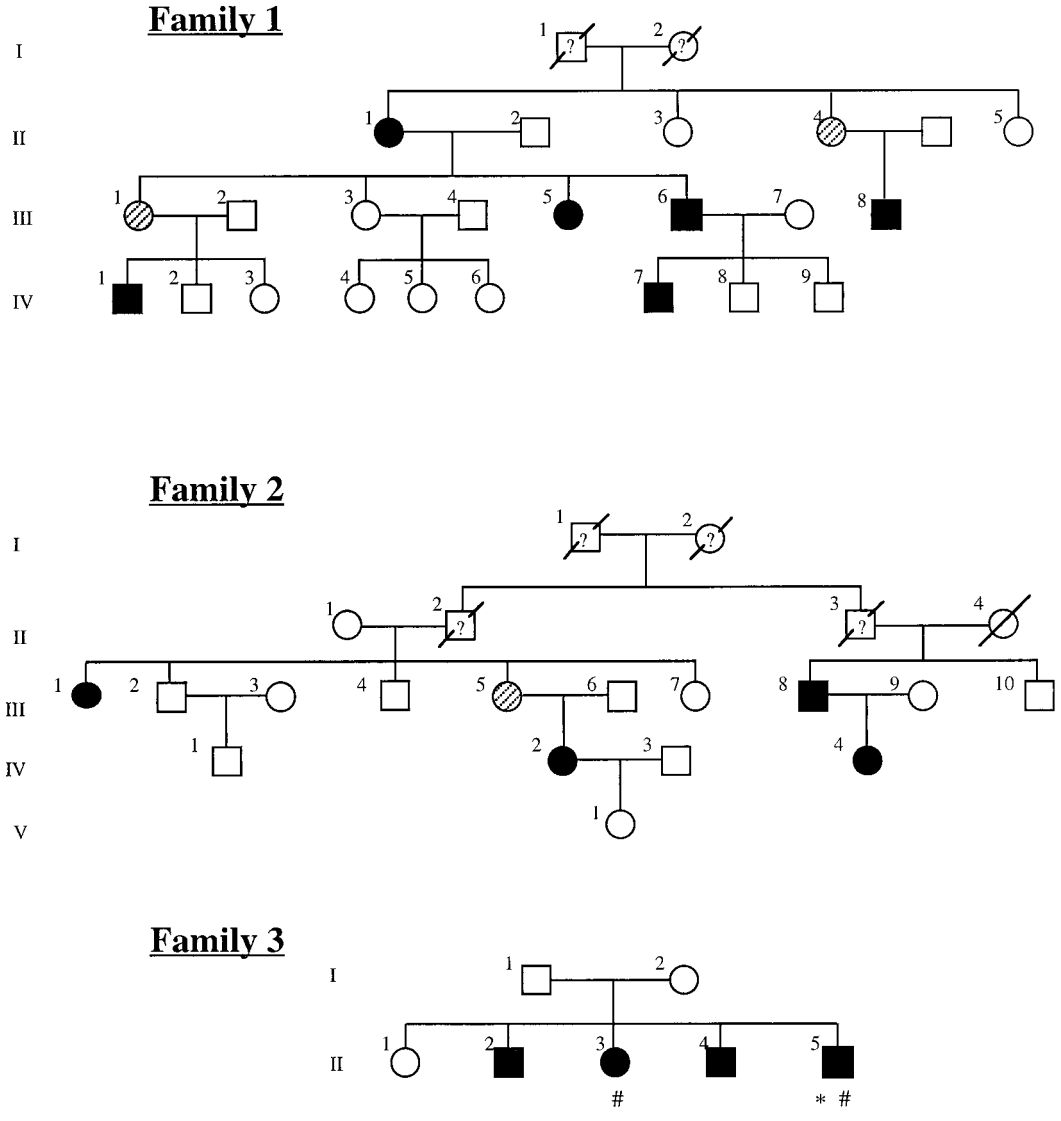

FIG. 1. Pedigree and phenotypes of the members of the three families with hyperparathyroidism. *Filled symbols* (■, ●) indicate members affected with hyperparathyroidism; *open symbols* (□, ○), unaffected; *hatched symbols* (▨), unaffected family members who are obligate gene carriers; family members with an unknown status are marked with a *question mark*. #, polycystic kidney disease; *, parathyroid carcinoma.

recently 2.28 mmol/L and 2.47 mmol/L. A year after the proband's parathyroidectomy, a male cousin (IV-1) was found to have hypercalcemia (3.02 mmol/L) at age 20 during investigation for incidental head injury. Subsequent investigations confirmed primary hyperparathyroidism, and at parathyroidectomy a single enlarged gland weighing 0.41 g was removed. Orthopentography of the jaw, renal ultrasound, and biochemical screening for MEN1 were performed on all members of the family. No case of jaw or renal tumors, and no evidence of MEN1 was found.

Family 2

Family 2 is also of Caucasian origin residing in Sweden (Fig. 1). The proband (III-1) initially presented in 1964 at age 31 with renal calculi, nephrocalcinosis, and primary HPT, with a preoperative serum calcium 3.4 mmol/L (reference range 2.20–2.60 mmol/L). X-ray examinations of the skull and jaws were normal. Two abnormal parathyroid glands with a total weight of 4.4 g were removed, and the patient has remained normocalcemic during 31 yr of follow-up. An orthopentogram of the mandible and maxilla performed in 1996 did not reveal any signs of fibrous osteoma or cysts. Her nephew (IV-2) was found to have asymptomatic primary HPT in 1991 at the age of 27, and two abnormal parathyroids were removed (total weight 1.2 g). Primary HPT was diagnosed in 1994 at age 28 in patient IV-4 following a period of extreme fatigue. Preoperative serum calcium was 3.0 mmol/L, and one pathological gland (1.2 g) was removed. No recurrence has been seen in patients IV-2 and IV-4 after 6 and 3 yr of follow-up, respectively. Individual III-8 is asymptomatic but was recently found to have an elevated serum-PTH, which was repeated on several occasions. Serum creatinine, prolactin, gastrin, and pancreatic polypeptide were normal at follow-up in all these patients, and no case of jaw tumor or renal tumor were found on orthopentography or renal ultrasound. No family member had a history of jaw tumors. In addition individuals III-2, III-4, III-5, III-7, III-10, IV-1, and V-1 were all normocalcemic and had normal PTH levels.

Family 3

Family 3 is an unreported Finnish family with four affected siblings (Fig. 1). All of them had parathyroidectomy between the ages of 31 and 38 yr. One of them (II-5) was operated at the age of 31 with a diagnosis of parathyroid carcinoma. He was reoperated 4 yr later because of recurrence that showed invasive growth to the neck muscle. Multiple cysts were noted in his kidneys. His sister (II-3) had two parathyroid adenomas removed at the age of 37. Multiple renal cysts were detected in both of her kidneys. The other two siblings each had a single parathyroid adenoma removed at the ages of 36 and 37, respectively. In both cases, there is no evidence of recurrence after 5 and 7 yr of follow-up. Both parents and the remaining healthy child (II-1) were screened repeatedly, but no evidence of hyperparathyroidism was found, and radiological investigation also failed to detect any jaw or renal lesions.

Linkage analysis

Informed consent was obtained from all participating members. Peripheral blood samples were obtained from 41 members of 3 families, and high molecular weight DNA was isolated according to standard protocols. In one case (II-2 in Family 2) where a blood sample could not be obtained, DNA was extracted from normal paraffin-embedded tissues as previously described (19). Three microsatellite markers, cen-D11S1883-PYGM-*MEN1*-D11S913-tel, located close to and flanking the *MEN1* gene at 11q13 were used (20). The *HRPT2* locus has been mapped to a region between 26cM region between markers D1S215 and D1S249 in 1q21-q32 region (12, 15, Wassif et al. submitted), and 20 microsatellite markers from this region were used: cen-D1S218, D1S215, D1S222, D1S238, D1S428, D1S461, D1S422, D1S492, D1S412, D1S413, D1S477, D1S306, D1S510, D1S456, D1S249, D1S504, D1S471, D1S245, D1S491 and D1S425-tel (21). Genotyping was performed as previously described (22). Two-point analysis was performed using the FASTLINK (version 2.3P) linkage program and multipoint analysis using the GENEHUNTER program (23, 24). Using a conservative approach, all unaffected cases were considered as unknown except 2 who were over 80 yr old. These 2 individuals (II-3 and II-5) were labelled as unaffected after repeated negative screening. Conventional cut-off levels were used, *i.e.* lod score of more than 3.0 signified linkage to a given marker, and that of less than -2 excluded linkage.

Loss-of-heterozygosity (LOH) studies

Tissue blocks from the following patients were studied: II-1, III-6, IV-1, and IV-7 in Family 1; IV-2 and IV-4 in Family 2; II-4 and II-5 in Family 3. DNA was extracted from microdissected 5 μm sections of fixed, paraffin-imbedded, parathyroid tumors by standard methods. Paired somatic and tumor DNA samples were analyzed for LOH using D1S218, D1S222, D1S422, D1S412, D1S413, D1S477, D1S510, D1S491, and D1S249 at 1q21-q32, and PYGM and D11S913 at 11q13.

Histochemical stainings

For routine histopathological examination, sections were stained with hematoxylin and eosin, and by the van Gieson method, the latter in particular for visualizing collagenous connective tissue. To differentiate between blood vessels and cysts in the sections, antibodies against Factor VIII related protein (Dakopatts, Glostrup, Denmark) and CD34 (Immunotech, Marseille, France) were used (25, 26). Deparaffinized sections were incubated with primary antiserum overnight and stained according to the Avidin-Biotin-peroxidase Complex method, following the manufacturers instructions (Vectastain, Vector Laboratories, Burlingame, Ca). Diaminobenzidine was used as chromogen, and counterstaining was made with Mayer's hematoxylin.

Results

Linkage analysis and haplotyping

The pedigrees of the 3 families analysed are shown in Fig. 1. Genetic linkage analysis was performed in a total of 42 individuals, including 13 affected members, 6 spouses, 22 presently unaffected family members, and 1 deceased individual (II-2 Family 2 in Fig. 1) whose disease state was unknown. Linkage to *MEN1* was excluded on the basis of haplotype analysis and significantly negative lod scores (< -2) in all families (data not shown). We thus focused on the other candidate region, *i.e.* the *HRPT2* locus in chromosome 1q21-q32. Families 1 and 2 were considered as a homogenous group as they shared the same clinical phenotypes without evidence of jaw or renal lesions and thus were analyzed together. Cystic kidney disease and parathyroid carcinoma were found in Family 3, which was therefore considered as affected by the classic HPT-JT syndrome. In this family (Fig. 1), although both parents were clinically normal, the disease haplotypes were thought to be transmitted from the father (I-1) based on two factors: first, all 4 affected cases shared the same haplotypes from the father, and second, in the parathyroid carcinoma, loss of the maternal alleles were found.

In Families 1 and 2, the two-point lod scores for seven of the chromosome 1 markers are detailed in Table 1. All markers except D1S218 and D1S491 gave positive lod scores, which varied depending on the informativeness of the markers in the kindreds. Five markers gave the total lod scores of more than 2 and two of them more than 3. Markers D1S222 and D1S249 gave the maximum lod scores of 3.10 and 3.39 respectively at recombination fraction of $\theta = 0.00$. This was further confirmed by multipoint linkage analysis, which gave the lod scores of over 3 in 13 markers from markers D1S222 to D1S504. These results confirmed that the disease in these two kindreds are linked to the 1q21-q32 region. Haplotypes were constructed (data not shown), and meiotic recombinations were detected in affected individuals in both families. Centromeric recombination was detected between

TABLE 1. Two-point lod scores for linkage of FIHP to microsatellite markers in 1q21-q32.

Locus	Family	Recombination fraction (θ)						
		0.000	0.010	0.050	0.100	0.200	0.300	0.400
D1S218	1	$-\infty$	−2.70	−1.35	−0.83	−0.37	−0.15	−0.04
	2	$-\infty$	−2.95	−1.60	−1.05	−0.54	−0.28	−0.11
	total	$-\infty$	−5.65	−2.95	−1.88	−0.91	−0.43	−0.15
D1S222	1	1.72	1.69	1.55	1.37	0.97	0.56	0.19
	2	1.38	1.35	1.23	1.08	0.76	0.46	0.19
	total	3.10	3.04	2.78	2.45	1.73	1.02	0.38
D1S238+ +D1S428	1	0.84	0.83	0.78	0.43	0.58	0.40	0.19
	2	1.38	1.35	1.24	1.09	0.79	0.49	0.21
	total	2.76	2.70	2.47	2.17	1.55	0.95	0.40
D1S422	1	1.42	1.39	1.27	1.11	0.77	0.41	0.11
	2	0.85	0.83	0.76	0.67	0.49	0.32	0.16
	total	2.27	2.22	2.03	1.78	1.26	0.73	0.27
D1S477	1	2.00	1.96	1.81	1.60	1.16	0.69	0.26
	2	0.84	0.83	0.76	0.67	0.49	0.32	0.16
	total	2.84	2.79	2.57	2.27	1.65	1.01	0.42
D1S249	1	2.02	1.99	1.83	1.62	1.18	0.71	0.27
	2	1.37	1.34	1.22	1.06	0.75	0.45	0.19
	total	3.39	3.33	3.05	2.68	1.93	1.16	0.46
D1S491	1	$-\infty$	0.07	0.63	0.75	0.67	0.45	0.21
	2	1.26	1.23	1.11	0.97	0.68	0.40	0.17
	total	$-\infty$	1.30	1.74	1.72	1.35	0.85	0.38

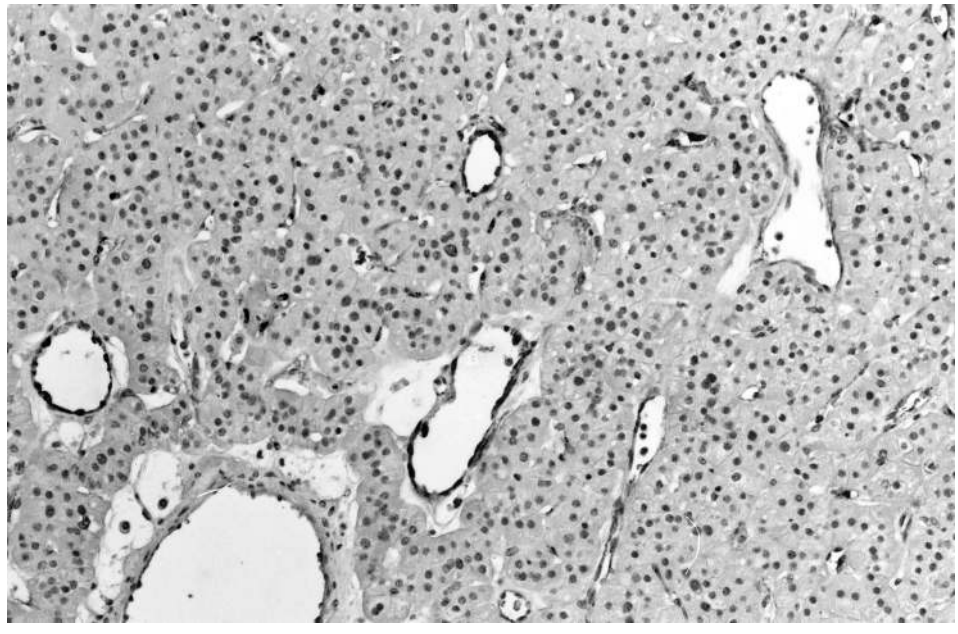

FIG. 2. Microphotograph showing hematoxylin-eosin staining of the oxcyphil/oncocytic adenoma of case II-1 in Family 1. (Enlargement 165×)

D1S218 and D1S222 in affected members III-5 and IV-7 in Family 1, and between D1S215 and D1S222 in the affected members III-1 and IV-2 in Family 2. A telomeric cross-over was identified in affected individual III-5 in Family 1, between D1S491 and D1S425. The disease region, flanked by D1S215 and D1S425, spans approximately 37 cm, which overlaps with the *HRPT2* region between D1S215 and D1S249 (15).

Histopathological studies

Four abnormal glands from Family 1, two from Family 2, and four from Family 3 were reexamined. One or two enlarged glands had been identified and removed from each of the cases, while at least one normal-sized gland had been identified and left *in situ*. The enlarged glands were one carcinoma and nine adenomas that consisted of one oxyphil/oncocytic type (II-1 Fig. 2) and eight chief cell type (Fig. 3). The parathyroid carcinoma from II-5 in Family 3 consists mainly of solidly arranged cells with large nuclei and nucleoli (Fig. 4). Mitoses are frequently seen with foci of coagulation-type necrosis and fibrosis (27). All tumors except one contained cysts of varying size, and some of the cysts were lined by parenchymal cells (Fig. 3). Immunohistochemical staining for factor VIII and CD34 showed numerous vessels

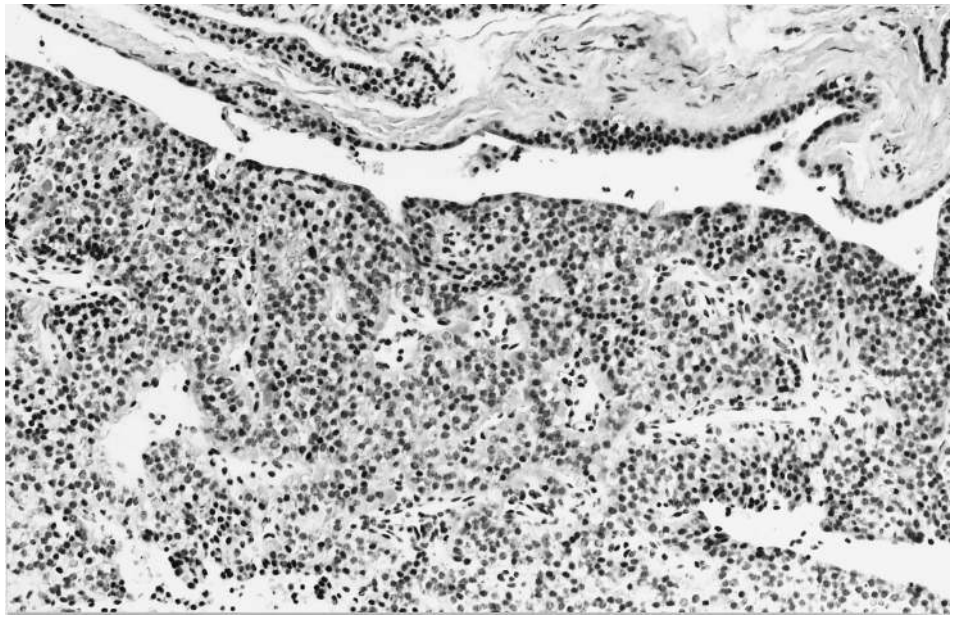

FIG. 3. Microphotograph showing hematoxylin-eosin staining of the chief cell adenoma of case III-6 in Family 1. The tumor has peripherally localized cysts, which are partly lined by chief cells. (Enlargement 165×)

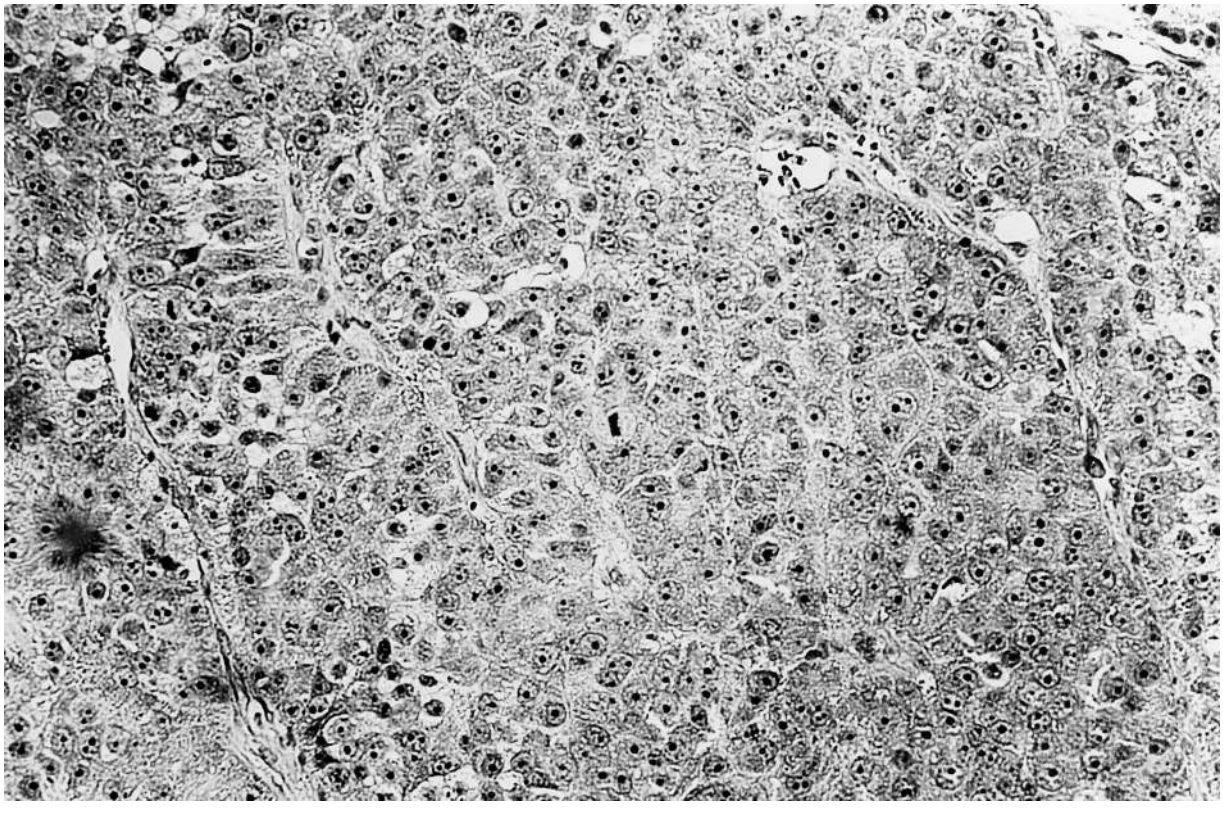

FIG. 4. Microphotograph showing nuclear atypia with mitosis in the parathyroid carcinoma of individual II-5 in Family 3.

and not the cysts. These stainings results thus verified that the small thin-walled cysts did not represent dilated capillaries. Except in the parathyroid carcinoma, no signs of infiltrative growth was seen in any of the tumors.

LOH studies

Loss of heterozygosity was sought in parathyroid tumors from four patients from Family 1, two from Family 2, and two from Family 3. In Family 1, the tumor from III-6 did not amplify with any of the markers, but the other three tumors, one oxyphil tumor and two chief cell tumors, showed LOH in the 1q21-q32 region. In all three cases the losses invariably involved the loss of the wild-type allele derived from the unaffected parent (Fig. 5, Table 2). The two tumors from Family 2 remained heterozygous for markers at 1q21-q32. In Family 3, unfortunately, one chief cell adenoma did not am-

plify despite several attempts by different methods, but the parathyroid carcinoma showed LOH of the maternal alleles (Table 2).

Discussion

Kindreds having first degree HPT as their only endocrinopathy have frequently been reported, and some of them were considered as a separate entity. Evidence for this was obtained when one large family was excluded from the *MEN1* locus (16) and was therefore designated as a separate entity (HRPT1; OMIM 145000). Following the establishment of another familial first degree HPT-related entity, *i.e.* HPT-JT syndrome, and its mapping to chromosome 1q (HRPT2; OMIM 145001), it was assumed that FIHP (OMIM 145000) has a different locus yet to be determined. However, because the original FIHP family has subsequently been found to be an HPT-JT family, whether OMIM 145000 still exists is questionable as there are no reported FIHP families that are not linked to either the *MEN1* or *HRPT2* loci. We describe here two previously unreported families with familial first degree HPT, and we found that they are linked to 1q21-q32 where *HRPT2* is located. After careful screening, there was no evidence of jaw tumors or renal lesions in either family, suggesting that they represent a variant of HPT-JT. These results further indicate that the existence of OMIM 145000 or HRPT1 needs to be reconsidered. The phenotypic variation of the present two FIHP families, without evidence of jaw or renal tumors, might represent the effects of different mutations of the putative *HRPT2* gene, as demonstrated in MEN2 (28). MEN2A, MEN2B, and familial medullary carcinoma of thyroid (FMTC), which all share overlapping clinical features but are distinguished by distinct features, have different mutations in the *RET* proto-oncogene (28).

The finding of cystic kidney disease in two siblings in the third family further confirms our previous findings (15) that it is part of HPT-JT, and it should be investigated in all 1q-linked FIHP families. Its association with HPT-JT, together with that of Wilm's tumor and renal nephroblastoma (12, 15) suggests that *HRPT2* might play an important role in the organogenesis of kidney (29). It will be worthwhile to test the 1q markers in those polycystic kidney disease families that are not linked to *PKD1* (chromosome 16p) or *PKD2* (chromosome 4p).

Clinically, there is a reduced penentrance of HPT, especially in the females, which is consistent with our previous findings in HPT-JT families linked to the same locus (15). In the two FIHP families, there are three female obligate gene carriers who have not shown any biochemical signs of primary HPT despite careful screening (Families 1 and 2, Figure 1). The father in Family 3 cannot be confirmed as an obligate carrier as no affected individuals besides his children are known. He can be a mosaic or new mutant. This reduced penetrance is in contrast with MEN1, in which primary HPT occurs in over 95% of cases. This observation has clinical implications: in dealing with small families with familial HPT whereby both parents of a proband appear to be normal, the extended family of the parents, especially the maternal side, should be investigated carefully.

Histopathologically, we demonstrate a spectrum of parathyroid pathology in 1q-linked primary HPT. The parathyroid neoplasia seen in FIHP may represent one or more adenomas. Unlike MEN1, in which patients invariably develop multiglandular or hyperplastic disease and subsequent recurrence if less than total or three and a half parathyroidectomies are performed (30), the majority of patients with 1q-linked primary HPT are cured after the removal of single adenoma. Another distinction of 1q-linked primary HPT is its associated risk of carcinoma in these patients (3–6), which has not been reported in MEN1. This is exemplified in the third family, in which a case of parathyroid carcinoma was found.

Besides the parathyroid carcinoma, the rest of the tumors classified as adenomas showed no sign of malignancy, although our previous studies have indicated that parathyroid tumors from 1q-linked families have increased expression of Ki-67, a marker for cell proliferation (31). These results suggest that the 1q-linked tumors might have transforming potential. The occurrence of cysts may be over-represented in these families as all tumors studied except one have either cystic formations or microcysts. The significance of these cystic structures is not known and needs to be further explored. In addition, we found two types of benign parathyroid tumors in the same family: chief cell and oxyphil/oncocytic cell types. The latter has not been reported in 1q-linked families. Case II-1 in Family 1 fulfills all the criteria of an oxyphil cell tumor (32): the gland weighing 4 g con-

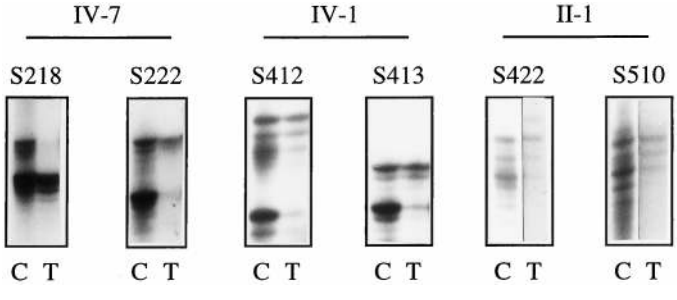

FIG. 5. Autoradiograms showing loss of heterozygosity in three parathyroid tumors from II-1, IV-1, and IV-7 from Family 1. (C), Constitutional DNA; (T), Tumor DNA.

TABLE 2. Parathyroid tumors showing LOH in chromosome 1q21-q32

Case no.	Family	Sex	Pathology	Chromosome 1 locus								
				S218	S222	S422	S428	S412	S413	S477	S510	S491
II-1	1	F	oxyphil/oncocytic	nd	LOH	LOH	nd	–	–	nd	LOH	LOH
IV-1	1	M	chief cell	–	–	nd	nd	LOH	LOH	–	nd	LOH
IV-7	1	M	chief cell	LOH	LOH	–	nd	–	–	LOH	–	LOH
II-5	3	M	carcinoma	LOH	–	nd	LOH	–	LOH	–	nd	nd

LOH, loss of heterozygosity; −, noninformative (*i.e.* constitutional homozygosity); nd, not done.

sisting entirely of oxyphil cells, with normal biopsy of other glands, and the patient remaining normocalcemic for the last 17 yr. The other three affected family members all have chief cell tumors. Oxyphil/oncocytic parathyroid cells have been considered to be aged, degenerate, nonfunctioning forms of the parathyroid chief cell (2). Interestingly, this particular oxyphil tumor was detected in the oldest affected member when she was 58 yr of age, compared with the other three chief cell tumors, which occur at the ages of 20, 22, and 25 yr, respectively. What might be relevant is the fact that oxyphil parathyroid adenomas are usually nonfunctional. This might explain our clinical observation of reduced penetrance of HPT in the 1q-linked families because in these cases, oxyphil tumors might have occurred but were not detected due to their nonfunctional nature.

One important finding of the present studies is our demonstration of loss of the wild-type allele in four tumors involving the whole spectrum of the parathyroid pathology: chief cell tumor, oxyphil/oncocytic tumor, and carcinoma. These findings suggest that *HRPT2* is involved in the tumorigenesis of all three pathological entities and this phenomenon, which implicates the *HRPT2* gene as a tumor suppressor gene, has not been reported previously in 1q-related parathyroid tumors. The absence of LOH in previous studies, eight tumors from reference 12, and one tumor from reference 15 did not exclude the possibility that microdeletions could still exist in these tumors but were beyond the detection of the markers used. In the studies of the eight tumors (12) for example, the only three heterozygous markers the authors reported (D1S191, D1S196, D1S212) are located outside the refined HRPT2 region. Furthermore, inactivating mechanisms other than LOH (such as methylation) might play a role in these tumors (33).

In conclusion, FIHP is a genetically heterogenous disease, and a subset is genetically linked to HRPT2, most likely representing a variant of HPT-JT. In encountering families with FIHP, it is thus important to first establish whether they are genetically linked to *HRPT2* or *MEN1*. Once this is confirmed, appropriate clinical screening should be carried out for other associated tumors, although some of these families might only have FIHP without ever expressing any other tumors. Finally, studies of additional families will enhance our understanding of the clinical expression and natural history of the disease besides contributing to the positional cloning of the gene involved.

References

1. **Huang S-M, Duh Q-Y, Shaver J, Siperstein AE, Kraimps J-L, Clark OH.** 1997 Familial hyperparathyroidism without multiple endocrine neoplasia. World J Surg. 21:22–29.
2. **Mallette LE.** 1994 The functional and pathologic spectrum of parathyroid abnormalities in hyperparathyroidism. In: Bilezikian JP, Marcus R, Levine MA, eds. The parathyroids: basic and clinical concepts. New York: Raven; pp 423–455.
3. **Frayha RA, Nassar VH, Dagher F, Salti IS.** 1972 Familial parathyroid carcinoma. Leban Med J. 25:299–309.
4. **Leborgne J, Le Neel J-C, Buzelin F, Malvy P.** 1975 Cancer familial des parathyroides: interet de l'angiographie dans le diagnostic des recidives locoregionales-considerations a propos de deux cas. J Chir Paris. 109:315–326.
5. **Dinnen JS, Greenwood RH, Jones JH, Walker DA, Williams DE.** 1977 Parathyroid carcinoma in familial hyperparathyroidism. J Clin Pathol. 30:966–975.
6. **Streeten EA, Weinstein LS, Norton JA, et al.** 1992 Studies in a kindred with parathyroid carcinoma. J Clin Endocrinol Metab. 75:362–366.
7. **Larsson C, Skogseid B, Öberg K, Nakamura Y, Nordenskjöld M.** 1988 Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. Nature 332:85–87.
8. **Chandrasekharappa SC, Guru SC, Manickam P, et al.** 1997 Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science. 276:404–407.
9. **Thakker R, Bouloux P, Wooding C, et al.** 1989 Association of parathyroid tumors in multiple endocrine neoplasia type 1 with loss of alleles on chromosome 11. N Engl J Med. 321:218–224.
10. **Friedman E, Sakaguchi K, Bale AE, et al.** 1989 Clonality of parathyroid tumors in familial multiple endocrine neoplasia type 1. N Engl J Med. 321:213–218.
11. **European Consortium on MEN1.** 1997 Identification of the Multiple endocrine neoplasia type 1 (MEN1) gene. Hum Mol Genet. 6:1169–1175.
12. **Szabo J, Heath B, Hill VM, et al.** 1995 Hereditary hyperparathyroidism-jaw-tumor syndrome: the endocrine-tumor gene HRPT2 maps to chromosome 1q21–q31. Am J Hum Genet. 56:944–950.
13. **Jackson CE, Norum RA, Boyd SB, et al.** 1990 Hereditary hyperparathyroidism and multiple ossifying jaw fibromas: a clinically and genetically distinct syndrome. Surgery. 108:1006–1013.
14. **Kakinuma A, Morimoto I, Nakano Y, et al.** 1994 Familial hyperparathyroidism complicated with Wilm's tumour. Intern Med. 33:123–126.
15. **Teh BT, Farnebo F, Kristoffersson U, et al.** 1996 Autosomal dominant primary hyperparathyroidism-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. J Clin Endocrinol Metab. 81:4204–4211.
16. **Wassif W, Moniz CF, Friedman E, et al.** 1993 Familial isolated hyperparathyroidism: a distinct genetic entity with an increased risk of parathyroid cancer. J Clin Endocrinol Metab. 77:1485–1489.
17. Deleted in proof.
18. **Kassem M, Zhang X, Brask S, Eriksen EF, Mosekilde L, Kruse TA.** 1994 Familial isolated primary hyperparathyroidism. Clin Endocrinol. 41:415–420.
19. **Shibata D.** 1994 Extraction of DNA from paraffin-embedded tissue for analysis by polymerase chain reaction: new tricks from an old friend. Human Pathol. 25:561–563.
20. **European Consortium on MEN1.** 1996 Definition of the minimal *MEN1* area based on a 5-Mb integrated map of proximal 11q13. Genomics. 37:354–365.
21. **Gyapay G, Morissette J, Vignal A, et al.** 1994 The 1993–1994 Généthon human genetic linkage map. Nature Genet. 7:246–339.
22. **Teh BT, Silburn P, Linblad K, et al.** 1995 Familial periodic cerebellar ataxia without myokimia maps to a 19-cM region on 19p13. Am J Hum Genet. 56:1443–1449.
23. **Cottingham RW, Idury RM, Schaffer AA.** 1993 Faster sequential genetic linkage computations. Am J Hum Genet. 53:252–263.
24. **Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES.** 1996 Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet. 58:1347–1363.
25. **Sehested M, Hou-Jenson K.** 1981 Factor VIII related antigen as an endothelial cell marker in benign and malignant diseases. Virchows Arch. 391:217–225.
26. **Fina L, Molgaard HV, Robertson D, et al.** 1990 Expression of the CD34 gene in vascular endothelial cells. Blood. 75:2417–2426.
27. **Bondeson L, Sandelin K, Grimelius L.** 1993 Histopathological variables and DNA cytometry in parathyroid carcinoma. Am J Surg Pathol. 17:820–829.
28. **Mulligan LM, Ponder BAJ.** 1995 Genetic basis of endocrine disease: multiple endocrine neoplasia type 2. J Clin End Metab. 80:1989–2068.
29. **Vainio S, Muller U.** 1997 Inductive tissue interactions, cell signaling, and the control of kidney organogenesis. Cell. 90:975–978.
30. **Teh BT, McArdle J, Parameswaran V et al.** 1996 Sporadic primary hyperparathyroidism in the setting of multiple endocrine neoplasia type 1. Arch Surg. 131:1230–1232.
31. **Farnebo F, Auer G, Farnebo L-O, et al.** Evaluation of RB and Ki-67 immunostaining as diagnostic markers in benign and malignant parathyroid disease. World J Surg. In press
32. **Wolpert HR, Vickery AL, Wang CA.** 1989 Functioning oxyphil cell adenomas of the parathyroid gland. A study of 15 cases. Am J Surg Pathol. 13:500–504.
33. **Gnarra JR, Zhou SB, Merrill MJ et al.** 1996 Mutations of the VHL-tumor suppressor gene in renal carcinoma. Nature Genet. 7:85–90.