

Familial isolated hyperparathyroidism

William F. Simonds

Chief, Endocrine Signaling and Oncogenesis Section
Metabolic Diseases Branch
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, MD 20892

Address for correspondence:
William F. Simonds, M.D.
Bldg. 10 Room 8C-101
10 CENTER DR. MSC 1752
Bethesda, MD 20892-1752
Ph. (301) 496-9299
Fax (301) 402-0374
E-mail: wfs@helix.nih.gov

Summary

The investigation of familial isolated hyperparathyroidism (FIHP) has been greatly facilitated in recent years by the identification of the genes responsible for most cases of syndromic familial hyperparathyroidism (HPT). Kindreds with apparently isolated hyperparathyroidism have been evaluated with clinical, biochemical, imaging and gene mutational tests designed to recognize multiple endocrine neoplasia type 1 (MEN1), the hyperparathyroidism-jaw tumor syndrome (HPT-JT), and familial hypocalciuric hypercalcemia (FHH). Approximately 100 kindreds with the apparent diagnosis of FIHP were studied in clinical series that included screening by germline DNA mutational testing of one or more of the genes for these three syndromes since 1997. Of these provisionally diagnosed FIHP kindreds, some 10 to 20% had occult MEN1 and roughly 10% each had unrecognized HPT-JT or an FHH-related disorder evidenced by mutation of the calcium sensing receptor. Thus nearly 70% of FIHP kindreds are apparently non-syndromic. Even accounting for the likely underestimation in this group of syndromic causes for familial HPT due to shortcomings in current clinical and gene mutational testing methods, this finding suggests the majority of FIHP kindreds have no currently recognized syndromic etiology. Further study of this subset of carefully evaluated and apparently non-syndromic FIHP kindreds should assist in the identification of novel gene(s) important for neoplasia in the parathyroid and whose mutation can result in the FIHP phenotype.

KEY WORDS: hyperparathyroidism, FIHP, endocrine neoplasia, calcium-sensing receptor, parafibromin.

Introduction

Familial isolated hyperparathyroidism (FIHP; HRPT1) is a diagnostic subgroup of familial hyperparathyroidism (HPT) that can be non-syndromic or can result from the incomplete expression of a syndromic form of familial HPT (Fig. 1). Syndromic forms of familial HPT that can present as FIHP include multiple en-

doctrine neoplasia type 1 (MEN1) (1, 2), familial hypocalciuric hypercalcemia (FHH) (also known as familial benign hypercalcemia) (3, 4), and the hyperparathyroidism-jaw tumor syndrome (HPT-JT; HRPT2) (5). Multiple endocrine neoplasia type 2A (MEN2A) (2, 6, 7), unlike MEN1, is not typically a consideration in the differential diagnosis of FIHP, because of the higher penetrance of medullary thyroid carcinoma and pheochromocytoma than of HPT in MEN2A families. It is unknown how

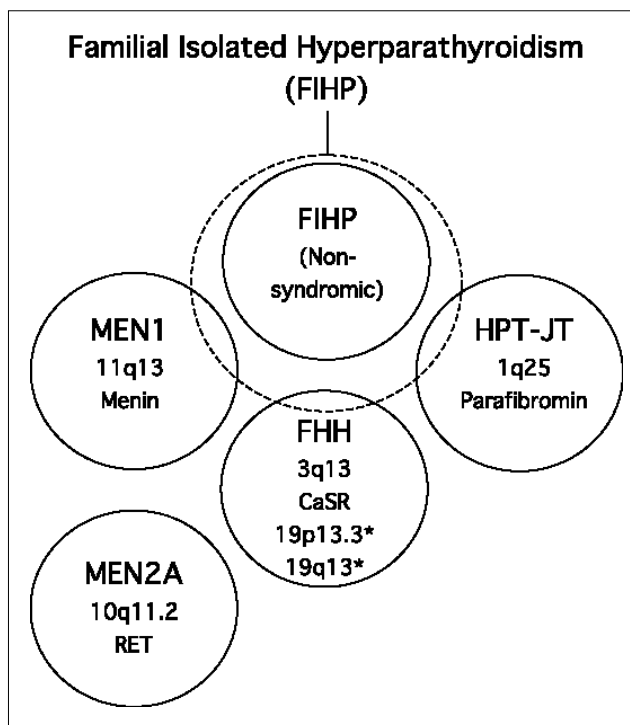


Figure 1 - The relationship as a Venn diagram among familial forms of hyperparathyroidism that may present as familial isolated hyperparathyroidism (FIHP) [modified and updated from reference (11)]. The dashed circle represents the set of patients presenting with the provisional diagnosis of FIHP. Contained entirely within this dashed circle is a subset of families who have subsequently been thoroughly evaluated for, but lack findings diagnostic of, MEN1, FHH and HPT-JT (FIHP (non-syndromic); in a solid circle). Subsets of patients with incomplete expression of MEN1, FHH and HPT-JT (the total set of patients in each syndrome represented by a solid circle) can also present with the FIHP phenotype. The distinction between the FIHP category and the syndromic categories arbitrarily depends on the sensitivity of diagnostic tests used to detect the syndrome. MEN2A is a familial form of hyperparathyroidism seldom if ever presenting as FIHP. Within each circle representing a defined syndrome are included the genetic locus (or loci in the case of FHH) of the syndromic trait and the responsible gene product. An asterisk next to the genetic locus indicates that the gene and gene product are unknown for the form of familial hyperparathyroidism mapping to this site. The relationship among the patient groups is intended to be qualitative, and the area of each circle and the area of overlap between circles are not intended to be proportional to their encountered or predicted values.

many as yet unrecognized genotypes may also present as FIHP (8).

MEN1 is an autosomal dominant disorder characterized by endocrine and non-endocrine tumors, most prominently involving the parathyroids, enteropancreatic endocrine system, and pituitary (1, 9). Because HPT is the earliest and most frequent endocrinopathy in MEN1, some kindreds with apparent FIHP represent early and/or occult expressions of MEN1. The gene responsible for MEN1 has been cloned (10), leading to gene mutational analytical methods applicable to MEN1, FIHP, and other conditions (2, 8, 11).

FHH is an autosomal dominant trait usually causing mild HPT with relative hypocalciuria (3, 4); hypercalcemia in FHH is highly penetrant at all ages, even in the perinatal period (3). FHH cases almost always remain hypercalcemic following partial or subtotal parathyroidectomy (PTX) (3). Mild hypermagnesemia is sometimes seen in FHH but is unusual in other forms of primary HPT (3, 12). Most cases of FHH result from a loss-of-function mutation in the gene for the calcium-sensing receptor (CaSR) on the long arm of chromosome 3 (13-15). However two undiscovered genes have been implicated in rare kindreds with FHH; 1 gene at chromosome 19p (16) and 1 gene at 19q (17).

HPT-JT syndrome is an autosomal dominant disorder with high but incomplete penetrance of HPT. It may present with

parathyroid adenoma, parathyroid carcinoma, and/or fibro-osseous jaw tumors (5, 18). Renal cysts (19, 20) and solid renal tumors (19, 21, 22) have also been associated with HPT-JT. Cystic parathyroid tumors have been associated with HPT-JT (23). *HRPT2*, the gene for HPT-JT, has been identified on the long arm of chromosome 1 (24). FIHP with or without parathyroid carcinoma but lacking evident jaw tumors can result from occult germline *HRPT2* mutation (8, 25-27) as can apparently sporadic parathyroid cancer (26, 28). Uterine tumors have been suggested to be part of the HPT-JT phenotype (29), even though demonstration of somatic *HRPT2* mutation or loss of heterozygosity (LOH) at 1q25-q31 in DNA from such uterine tumors is still lacking. This contrasts with the level of evidence for MEN1-associated uterine leiomyomata, in which most tumors have demonstrable LOH at the MEN1 gene locus (30).

This mini-review will survey the clinical and molecular genetic studies of FIHP kindreds reported since 1997 when the identification of the *MEN1* gene (10) allowed for the first time sensitive evaluation of such families for occult germline mutation of a gene predisposing to a familial form of HPT. Screening for occult germline mutation of the *CASR* gene (13) and the *HRPT2* gene after its identification in 2002 (24) added to the power of such analyses. Particular emphasis will be given to the analysis of 40 kindreds from our own institution with a pro-

Table I - Clinical characteristics and gene mutational screening results in 40 kindreds with a provisional diagnosis of familial isolated hyperparathyroidism, modified from previous reports (8, 11). The kindreds are grouped according to their final diagnostic classification as HPT-JT, *CASR*-mutation-positive, or non-syndromic FIHP (8, 11).

Kindred		Proband		Index case testing results			Notes
I.D.	Number affected (a)	Age at diagnosis of HPT	Sex	Gene mutational screening (b)			
No.	Tot. M F	(Years)	(M/F)	<i>MEN1</i>	<i>CASR</i>	<i>HRPT2</i>	
Hyperparathyroidism-Jaw Tumor Syndrome Group							
417	5 3 2	27	F	N	N	exon 7 679insAG	
2862	7 2 5	48	M	N	N	N	c
27,000	2 1 1	10	F	N	N	exon 1 34delAACATCC	d
35,900	4 3 1	34	M	N	N	exon 7 679insAG	e
Calcium-Sensing Receptor Mutation-Positive Group							
1214	2 2 0	26	M	N	exon 4 V268del-11X273	N	
5780	11 7 4	53	F	N	exon 7 R886P	N	
10,147	3 1 2	30	F	N	exon 4 R220W	N	
23,300	3 2 1	21	M	N	exon 3 L159P	N	
28,300	2 1 1	53	M	N	exon 4 E250K	N	
Familial Isolated Hyperparathyroidism Group							
13	2 0 2	53	F	N	N	N	
225	2 0 2	43	F	N	N	N	
410	2 1 1	53	F	N	N	N	
4318	3 0 3	50	F	N	N	N	
5977	4 1 3	41	F	N	N	N	

continued

continued Table I

Kindred				Proband		Index case testing results			Notes
I.D.	Number affected (a)			Age at diagnosis of HPT	Sex	Gene mutational screening (b)			
No.	Tot.	M	F	(Years)	(M/F)	<i>MEN1</i>	<i>CASR</i>	<i>HRPT2</i>	
6324	2	1	1	61	F	N	N	N	
6325	3	2	1	45	M	N	N	N	
6326	2	0	2	61	F	N	N	N	
6335	2	1	1	39	F	N	N	N	
7751	3	0	3	19	F	N	N	N	
8715	4	0	4	49	F	N	N	N	
9462	2	2	0	37	M	N	N	N	
10,021	2	0	2	74	F	N	N	N	
10,157	2	1	1	40	F	N	N	N	
21,300	3	1	2	34	F	N	N	N	
24,200	2	0	2	44	F	N	N	N	
24,700	3	2	1	43	M	N	N	N	f
25,200	2	1	1	51	M	N	N	N	
26,500	3	1	2	30	F	N	N	N	
27,300	3	0	3	29	F	N	N	N	
28,200	8	5	3	14	F	N	N	N	g
28,400	2	1	1	43	M	N	N	N	
28,500	2	1	1	52	F	N	N	N	
28,600	2	0	2	12	F	N	N	N	
28,700	2	1	1	20	F	N	N	N	
28,800	2	1	1	54	F	N	N	N	
28,900	3	2	1	28	M	N	N	N	
30,300	2	0	2	8	F	N	N	N	
33,100	2	1	1	73	M	N	N	N	
33,800	2	1	1	66	M	N	N	N	
35,100	2	1	1	51	M	N	N	N	

(a) The total (Tot) number of affected refers to the number of individuals in a kindred with biochemically documented HPT, except for kindred 2862 with HPT-JT, in which that number also includes 1 euparathyroid individual with characteristic fibro-osseous jaw tumors. (b) N, or normal results in one of these three columns indicates that no mutations, i.e. sequence alterations affecting transcript splicing or protein coding, in the tested gene were found. (c) Kindred 2862, originally considered as FIHP by Streeten et al. (46), had negative HRPT2 mutational testing but could be clearly diagnosed as HPT-JT after the presence of bilateral renal cysts and cemento-ossifying fibromas in several affected members was determined (8, 11). This kindred also had members with a rare T445A polymorphism in the CASR coding region (11). (d) Kindred 27,000 was previously described (11) and listed as kindred-24 in Table I of Carpten et al. (24). (e) Kindred 35,900 was previously described (8) and is not known to be related to either kindred 417 (11) [listed as kindred-01 in Table I of Carpten et al. (24)] or kindred-33 (24) with the identical mutation in exon 7 of HRPT2. (f) Kindred 24,700 was previously described with a case of parathyroid cancer in the context of FIHP (62). (g) The pedigree for, and further information about, kindred 28,200 is presented in figure 2.

visional diagnosis of FIHP and described in detail in two previous reports (8, 11) (Table I).

Occult MEN1 among kindreds provisionally diagnosed with FIHP

Tests of affected individuals from provisionally diagnosed FIHP kindreds to identify occult MEN1 include blood testing of hormone levels, imaging studies and gene mutational analysis. Clinical studies of FIHP kindreds often utilize biochemical tests and/or pituitary or pancreatic imaging to explore for incomplete expressions of MEN1. Prior diagnosis of gastrinoma or prolactinoma in the proband or any known affected relative in an FIHP family was an exclusion criterion in the studies reviewed here. Molecular genetic analysis of germline DNA for loss-of-function mutation in the *MEN1* gene (10, 31) is the most sensitive test for occult MEN1 in FIHP kindreds.

Taken together, series examining 2 or more FIHP kindreds since the identification of *MEN1* in 1997 have found occult *MEN1* mutation in nearly 20% of families (Table II). Our own studies found no cases of occult MEN1 among 40 FIHP kindreds (Table I) (8, 11), and no family initially characterized as FIHP at study entry was subsequently reclassified as MEN1 and excluded. The typically small size of FIHP kindreds in our studies precluded 11q13 linkage analysis as a test for undiagnosed *MEN1* mutation.

The identification of MEN1 as the etiology for FIHP in none of the kindreds in our series may relate partly to the high average age (39 years) at diagnosis among the FIHP probands (8, 11). The penetrance of all neoplasms in familial tumor syndromes must increase with age, and by age 40 at least 1 non-parathyroid endocrine tumor is expressed in the majority of MEN1 patients (32).

Table II - Syndromic causes of hyperparathyroidism identified among series of kindreds with a provisional diagnosis of FIHP studied by gene mutational and clinical testing since 1997. Only studies that analyzed two or more FIHP kindreds are included. The three genes that account for most cases of syndromic familial HPT are shown (MEN1, CASR, and HRPT2 (HPT-JT), see text) with the number of positive and total kindreds tested in parentheses below each gene. In the MEN1 gene testing column, 20 out of 107 FIHP kindreds tested positive since 1997 (19%), but only 8 of 76 kindreds (10%) tested positive in the more recent studies since 2002 that included testing for all three syndromic HPT genes (8, 11, 27, 34, 35).

FIHP series	Year	MEN1 (+/total)	CASR (+/total)	HPT-JT (+/total)	Ref	Notes
1	1997	0/5			(33)	a
2	1998	0/4			(38)	
3	2000	1/5			(63)	
4	2000	2/2			(67)	
5	2002	2/7			(68)	
6	2002	2/4			(42)	
7	2002	1/2			(69)	
8	2003	4/7			(70)	
9, 10	2002, 2004	0/40	5/40	4/40	(8, 11)	b
11	2004	5/22	4/22	0/22	(34)	
12	2004	0/7	0/7	2/7	(27)	
13	2004			1/3	(26)	
14	2006	3/7	0/7	0/7	(35)	
Totals (%)		20/107 (19%)	9/76 (12%)	7/79 (9%)		

(a) The results from this study (33) were not included in the MEN1 column total since the same five kindreds were subsequently studied in more depth and reported separately (8, 11). (b) The two studies from our center examining a total of 40 provisionally diagnosed FIHP kindreds (see also Table I) were combined into one entry in this table (8, 11).

Some 31 different kindreds with a provisional diagnosis of FIHP have been reported in the literature to have germline mutations of the MEN1 gene (Table III). The types and distributions of MEN1 mutations in these 31 FIHP kindreds are similar to those in typical MEN1 families (33). One mutation was recurrent in 2 apparently unrelated FIHP families, a D418H missense mutation in exon 9 (34, 35). It has been previously observed that a significant excess of germline missense/in-frame mutations was present among FIHP kindreds with MEN1 gene mutation compared to mutation-carrying MEN1 families (36). As more such FIHP families are reported, this significant difference in germline missense/in-frame mutation frequency between FIHP and MEN1 groups has persisted (FIHP, 47%; MEN1, 28%; $p < 0.05$) (Table III) (33, 37). This suggests that MEN1 gene mutations that encode truncated, frame-shifted, or null protein products are more penetrant in non-parathyroid tissues resulting in more frequent pituitary and enteropancreatic tumors and a clinical picture recognizable as MEN1. Interestingly several MEN1 mutations identical to those reported in FIHP kindreds (Table III) have been found in families with full phenotypic expression of MEN1 including 359del4 (33, 38-41), E363del (33), and R527X (33). Long term follow up of some kindreds with germline mutation of MEN1 and initially characterized as FIHP revealed the development of pituitary and/or

enteropancreatic tumors typical of MEN1 that were not evident at the initial evaluation (42). Since HPT is usually the earliest and most penetrant feature of MEN1 (1), evaluation of only younger MEN1 mutation carriers at the time of kindred ascertainment may lead to a provisional diagnosis of FIHP.

Testing directed at recognizing FHH among kindreds provisionally diagnosed with FIHP

Several tests of affected individuals from provisionally diagnosed FIHP kindreds have been utilized to exclude families that might have unrecognized or atypical FHH (Table II) (8, 11, 27, 34, 35). These tests include blood testing of calcium, magnesium and PTH levels and determination of renal calcium and creatinine clearance (3, 4). Review and extension of pedigrees to look for evidence of hypercalcemia in members under the age of 10 improves sensitivity for the detection of FHH, as does CASR gene mutational analysis (11).

Series examining 2 or more FIHP kindreds have found occult CASR gene mutation in some 12% of the total reported families (Table II). Our own studies found 5 cases of occult CASR mutation among 40 FIHP kindreds (Table I) (8, 11), and Warner et al reported 4 cases of CASR mutation in their series of 22 FIHP families (34).

Interestingly, the index cases and other affected members of CASR mutation-positive kindreds initially considered as FIHP often had clinical features atypical of FHH. For example, probands from 3 of the 5 FIHP kindreds diagnosed as CaSR mutation-positive in our studies were hypercalciuric, as were members of 2 of 4 such kindreds in the Warner et al series (11, 34). Nephrolithiasis was reported in affected members in 4 of 9 CaSR mutation-positive kindreds initially considered as FIHP in the 2 studies (11, 34). Two probands presented with intact PTH values >150 pg/ml, more than two times above the value reported to discriminate between FHH and other forms of HPT (43). Eucalcemia in affected members more than 4 years following subtotal parathyroidectomy, an outcome unusual among FHH patients, was also reported in 2 of 4 CaSR mutation-positive kindreds initially considered as FIHP (34).

Several clinical findings among affected members supported the diagnosis of FHH in CaSR mutation-positive kindreds initially considered as FIHP, despite the presence of hypercalciuria and nephrolithiasis in several probands. Hypercalcemic individuals from 3 FIHP kindreds subsequently categorized as CaSR-mutation positive demonstrated mild hypermagnesemia (11), a finding seen in FHH but not in other forms of familial HPT (3, 12). Very significant differences were observed when the mean serum magnesium levels among tested hypercalcemic members of provisionally-diagnosed FIHP kindreds found to be CaSR mutation-positive was compared with that from members of HPT-JT or non-syndromic FIHP kindreds (11). One CASR mutation-positive kindred initially considered as FIHP revealed clear features of FHH including relative hypocalciuria in other affected members ($n = 4$), hypercalcemic members less than 10 years old ($n = 4$), mild hypermagnesemia in hypercalcemic members ($n = 4$), and persistent hypercalcemia following subtotal parathyroidectomy ($n = 2$), even though the proband was hypercalciuric (11).

Some nine different kindreds with a provisional diagnosis of FIHP have been reported in the literature to have germline mutations of the CASR gene (11, 34). As in typical FHH, missense amino-acid substitutions make up the vast majority of germline CASR mutations in kindreds initially considered as FIHP (Table IV). The distribution of missense mutations among the extracellular, 7-transmembrane, and intracellular domains of the CASR in these FIHP kindreds does not differ significantly from those in typical FHH families (44). The R220W CASR mutation in one kindred provisionally diagnosed as FIHP (11) was previously

Table III - Kindreds with familial isolated hyperparathyroidism and germline MEN1 gene mutation from the literature.

Kindred		Affected		MEN1 Germline Mutation		Ref
No.	No.	Sex (M/F)	Exon/ Intron (IVS) (a)	Base (b)	Consequence (c)	
1	4	4/0	2	359	359del4	(64)
2	2	-	2	365	365ins19	(34)
3	3	-	2	369	369ins18	(63)
4	3	0/3	2	444	V112L	(68)
5	2	0/2	3	568	D153V	(70)
6	4	3/1	3	639	639del4	(70)
7	3	2/1	3	661	V184E	(71)
8	-	-	3	700	T197I	(34)
9	8	3/5	3	764	abnl splicing	(72)
10	7	3/4	4	873	E255K	(58)
11	14	6/8	4	889	Q260P	(57)
12	3	2/1	IVS4	894-9	abnl splicing	(35)
13	4	4/0	5	910	L267P	(73)
14	3	1/2	IVS5	934+1	abnl splicing	(35)
15	7	5/2	6	940	P277H	(42)
16	3	1/2	7	1124	G305D	(74)
17	2	2/0	7	1157	1157del4	(70)
18	2	-	8	1167	1167del3	(34)
19	3	1/2	8	1169	Y353X	(75)
20	6	3/3	8	1197	E363del	(36)
21	3	2/1	8	1206	E366X	(67)
22	4	2/2	9	1341	A411P	(70)
23	4	4/0	9	1350	L414del	(65, 76)
24	-	-	9	1362	D418H	(34)
25	2	1/1	9	1362	D418H	(35)
26	11	3/8	IVS9	1460+1	abnl splicing	(77)
27	5	2/3	10	1483	1483del4	(67)
28	-	-	10	1656	1656ins1	(34)
29	8	4/4	10	1658	1658del1	(68)
30	3	2/1	10	1689	R527X	(42)
31	5	1/4	10	1785	1785del1	(69)

(a) Exon or intron (IVS) number refers to numbering of exons in the MEN1 gene (10). (b) Base numbering adjusted to conform to cDNA for human menin (GenBank locus XM 006532) and differs from numbering in several original literature citations (63-65). (c) Consequence of gene mutation shown as: del, deletion; ins, insertion; abnl splicing, disruption of putative exon-intron splice junction; missense or nonsense mutation (in single letter amino acid code, where X = Stop). "-" indicates data not available. MEN1, multiple endocrine neoplasia type 1.

reported in an apparently unrelated typical FHH kindred (15). The R886P mutation maps to the predicted carboxyl-tail of the CASR; a nearby mutation, F881L, was reported in a kindred with FIHP and including some members with features quite different from FHH (45).

Occult HPT-JT among kindreds provisionally diagnosed with FIHP

The principal clinical tests of affected individuals from kindreds provisionally diagnosed as FIHP to identify incomplete forms of HPT-JT are jaw and renal imaging studies. Prior diagnosis in the proband or any known affected relative in a family with isolated HPT of cemento-ossifying fibroma of the maxilla or mandible, the jaw tumor type characteristic of HPT-JT (5), was sufficient to make a presumptive diagnosis of HPT-JT and exclude them the analyses of FIHP kindreds reviewed here (8, 11, 26, 27, 34, 35). The initial evaluation of one kindred (family 2862) included jaw imaging of the proband only, with normal

Table IV - Kindreds with familial isolated hyperparathyroidism and germline CASR gene mutation from the literature.

Kindred		CASR Germline Mutation			Ref
No.	Exon (a)	Base (b)	Consequence (c)	Affected domain (d)	
1	3	299	T100I	ECD	(34)
2	3	476	L159P	ECD	(11)
3	4	658	R220W	ECD	(11)
4	4	748	E250K	ECD	(11)
5	4	801	V268del-11X273	na	(11)
6	4	1008	K336del	ECD	(34)
7	7	1949	L650P	7TM	(34)
8	7	2065	V689M	7TM	(34)
9	7	2657	R886P	ICD	(11)

(a) Exon number refers to numbering of exons in the CASR gene (13) as described in the calcium-sensing receptor locus-specific database (44). (b) Base numbering starts from initiation codon. (c) Consequence of gene mutation shown as: del, deletion; missense mutation (in single letter amino acid code). (d) Location in predicted receptor protein domain according to the "venus flytrap model" (66): ECD, extracellular domain; 7TM, seven transmembrane region; ICD, intracellular, or cytoplasmic, domain; na, not applicable. CASR, calcium-sensing receptor.

findings, leading to a provisional diagnosis of FIHP (46). Subsequent investigation revealed that 3 siblings in this kindred developed jaw lesions, in each case determined to be cemento-ossifying fibrous tumors by histopathologic analysis, leading to its re-categorization as HPT-JT (Table I) (11). One affected member of kindred 27,000 had had multiple mandibular and maxillary surgeries to remove jaw "cysts" decades earlier; medical records documenting the histopathology could not be retrieved (Table I) (11). Subsequent analysis of germline DNA in this FIHP kindred documented *HRPT2* frameshift mutation (Table I) (24).

Renal imaging, usually by ultrasonography, is routinely performed on affected members of kindreds provisionally diagnosed with FIHP since cysts (19, 20) and solid renal tumors (19, 21, 22) have been associated with HPT-JT. In studies from our center, bilateral renal cysts were found in individuals from three kindreds initially considered as FIHP but subsequently categorized as HPT-JT (Table I; kindreds 417, 2862 and 27,000), while no such bilateral cysts were found in *CaSR* mutation-positive or non-syndromic FIHP kindreds (8, 11). No renal hamartoma, nephroblastoma or renal cell carcinoma, lesions also reported in occasional association with HPT-JT (19, 21, 22), has been reported among provisionally diagnosed FIHP kindreds (8, 11, 26, 27, 34, 35). The probands from 2 non-syndromic FIHP kindreds had renal angiomyolipoma diagnosed by ultrasound and/or CT scan (11). Such renal tumors have been rare concomitants of *MEN1* (47, 48).

Review of the surgical findings and histopathology of parathyroid tumors from operated members of provisionally diagnosed FIHP kindreds may add evidence for their re-consideration as occult HPT-JT. Cystic parathyroid tumors have been associated with HPT-JT (5, 23) and parathyroid tumors from some kindreds initially considered as FIHP and later recognized as incomplete expressions of HPT-JT were noted to have cystic features (8, 11, 24, 26, 27, 49). At least one FIHP kindred with cystic parathyroid tumors in several affected members, however, has negative germline *HRPT2* gene mutational testing and

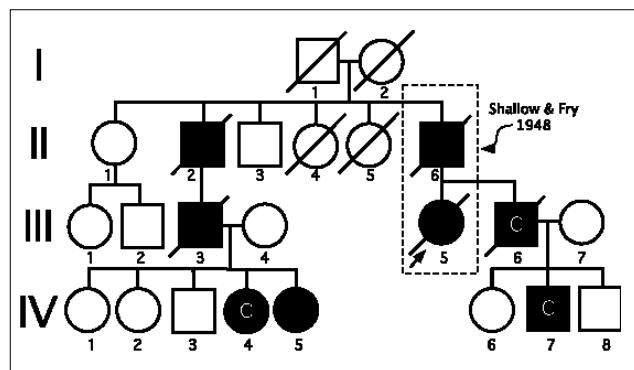


Figure 2 - A kindred with non-syndromic familial isolated hyperparathyroidism, cystic parathyroid tumors, and negative germline *HRPT2* gene mutation testing. This kindred (28,200) with non-syndromic FIHP has been previously reported (8, 11) (Table I). Individuals II-6 and III-5 were separately reported earlier as the father and daughter in Shallow and Fry (50). Filled symbols indicate individuals with primary HPT, and a "C" indicates that cystic parathyroid tumors were noted at surgery. Original surgical records and parathyroid histopathology reports were not available for individuals II-2, II-6 and II-3. Square symbols indicate males, and round symbols indicate females. A diagonal slash mark through the symbol means the individual is deceased. The arrow indicates the proband.

no other features to date suggestive of HPT-JT (Fig. 2) (11, 50). Parathyroid cancer is common in HPT-JT (51-53), but very rare among sporadic cases of HPT (0.8%) (54). In this light, it is interesting to note that the presence of parathyroid carcinoma in some kindreds initially considered as FIHP foreshadowed their subsequent recognition as expressions of HPT-JT (8, 11, 25, 46).

Germline DNA analysis for *HRPT2* gene mutation may also identify occult HPT-JT among provisionally diagnosed FIHP kindreds even though such testing has only some 50% sensitivity in full-featured HPT-JT families (24). Five unique germline *HRPT2* mutations have been identified in eight kindreds initially considered as FIHP (Table V). Three of these mutations are recurrent: a point mutation at a splice junction in *HRPT2* IVS1 that uncovers a cryptic exon 1 donor splice site (49) in two apparently unrelated families with isolated HPT (26, 49); an exon 2 L64P missense mutation in two unrelated FIHP families (24, 25, 27); and a 2-bp insertion in *HRPT2* exon 7 in three apparently unrelated FIHP kindreds (8, 11, 29, 55). The latter exon 7 mutation (679insAG) has also been described in the germline of patients with full-featured HPT-JT (24) and seemingly sporadic parathyroid carcinoma (28). The types of germline *HRPT2* mutation in kindreds initially considered as FIHP resemble those in HPT-JT with the majority resulting in frameshift or splicing abnormalities that cause incomplete parafibromin protein expression (Table V) (24).

Diagnostic approach to FIHP kindreds

Based on the findings from our studies and others reviewed here, it is possible to offer a practical approach for managing patients and families with FIHP, for which an obvious syndromic etiology has been excluded. Sporadic cases of HPT, on the other hand, must be evaluated according to standard recommendations (56). In the context of FIHP, the first step is to review the medical, dental and surgical history of the proband

Table V - Kindreds with familial isolated hyperparathyroidism and germline *HRPT2* gene mutation from the literature.

Kindred No.	<i>HRPT2</i> Germline Mutation			Ref	Note
	Exon/ Intron (IVS) (a)	Base (b)	Consequence (c)		
1	1	34	34 del7	(8, 11)	d
2	IVS1	131+1	abnl splicing	(26, 49)	
3	2	191	L64P	(24, 25, 27)	
4	IVS2	237+1	abnl splicing	(27)	
5	7	679	679ins2	(8, 11, 29, 55)	e

(a) Exon or intron (IVS) number refers to numbering of exons in the *HRPT2* gene (24). (b) Base and amino acid numbering starts from initiation codon. (c) Consequence of gene mutation shown as: del, deletion; ins, insertion; abnl splicing, disruption of putative exon-intron splice junction; missense mutation (in single letter amino acid code). (d) Kindred 27,000 was previously described (11) and listed as kindred-24 in Table I of Carpten et al. (24). (e) This 2-bp insertion in *HRPT2* exon 7 has been reported in three apparently unrelated FIHP kindreds (8, 11, 29, 55) and also in the germline of patients with classic features of HPT-JT (24) and seemingly sporadic parathyroid carcinoma (28).

and all available affected members. This careful review should emphasize features of MEN1 (recurrent HPT, ulcers, and pituitary tumors), features of HPT-JT (parathyroid cancer, fibrous jaw tumors, kidney cysts or tumors), and features of FHH (unsuccessful parathyroid surgery, rare urolithiasis and possible hypermagnesemia in hypercalcemic members, and hypercalcemia in cases below age 10).

If this focused review of systems is negative, the next step is to examine the renal calcium clearance-to-creatinine clearance ratio in all available hypercalcemic members. At the same time obtain blood calcium (preferably ionized) from as many untested first-degree relatives as possible, including young children in this process; any newly identified hypercalcemic members should also be checked for relative hypocalciuria. Imaging studies for gnathic and renal features of HPT-JT should be obtained on all hypercalcemic members at this point.

Gene mutational testing to confirm or further exclude the incomplete expression of a syndromic form of familial HPT can then be pursued. Specific gene tests screening for *CASR*, *MEN1* and *HRPT2* mutation are all commercially available in CLIA-approved laboratories. *CASR* mutation testing can be sought early or late in the workup of the FIHP kindred. *MEN1* mutation testing and periodic blood hormone testing for occult gastrinoma or prolactinoma may be worthwhile, particularly in FIHP patients who continue to appear non-syndromic. Similarly *HRPT2* gene mutation testing and periodic orthopantography of the jaw and renal ultrasound can be considered in affected individuals from FIHP kindreds lacking syndromic features.

If 7 or more affected members are available and the diagnosis is still uncertain, then genetic linkage could be pursued, focusing on loci for the known familial HPT syndromes on chromosomes 3q, 1q25-31, and 11q13. Because the number of affected family members is often small, a definitive syndromic diagnosis is often not possible. Such non-syndromic FIHP families should then be followed with each of the three main syndromic diagnoses in mind.

Distribution of genotypes presenting as FIHP

All reported kindreds so far with the phenotype of FIHP that have undergone successful linkage analysis have had their trait linked to either the *MEN1* locus on 11q13 (57, 58), the HPT-JT locus on 1q25-31 (20, 59), the *CASR* gene locus on 3q (45), or FHH-related but unknown gene loci on 19p (16) and 19q (17). These families each had available for genetic analysis at least 7 affected members or obligate gene carriers, the lower limit of cases necessary to give a significant linkage score. The small number of affected individuals precludes genetic linkage in many non-syndromic FIHP families (11).

Because of the less frequent expression of non-parathyroid features in HPT-JT compared to MEN1, a larger proportion with the former syndrome might be expected to present as FIHP. Yet the combined data from surveys of provisionally diagnosed FIHP kindreds shows occult cases of MEN1 are identified about twice as often as HPT-JT (Table II). This may be due in part to problems of initial kindred ascertainment. As discussed above, consideration of mostly younger affected members at the time of kindred ascertainment may obscure the initial recognition of MEN1 and lead to a provisional diagnosis of FIHP. This is because HPT is usually the earliest and most penetrant feature of MEN1 (1). Another reason for the unexpectedly low number of incomplete expressions of HPT-JT recognized among FIHP kindreds might be the low sensitivity of current PCR-based *HRPT2* gene mutation testing methods (24).

The prevalence of FHH-related disorders may also be underestimated in studies of provisionally diagnosed FIHP kindreds. No mutation in the *CASR* gene has been demonstrated in the probands from as many as 1/3 to 1/2 of kindreds with FHH trait linked to chromosome 3q (60, 61). Furthermore a small number of FHH kindreds have a trait that is not linked to the *CASR* locus at chromosome 3q (16, 17). Thus germline DNA screening of the *CASR* gene is helpful but is not presently a definitive tool to rule out FHH. For these reasons and because relative hypocalciuria is not always present in each affected member of *CASR* mutation-positive kindreds, it is likely that the prevalence of FHH-related syndromes is underestimated in current analyses of FIHP kindreds (8, 11, 27, 34, 35).

Novel genes in the etiology of FIHP

It is unknown how many as yet unrecognized genotypes may also present as FIHP (8). Among 76 families initially considered as FIHP in 5 recent clinical studies that investigated for germline *MEN1*, *CASR* and *HRPT2* gene mutation, 53 families or nearly 70% have no currently recognized syndromic etiology (Table II) (8, 11, 27, 34, 35). Others and we may still be underestimating the number of non-syndromic FIHP kindreds within this 70% that will ultimately be transferred into 1 of the 3 known syndromic categories. Since the strength of an exclusionary diagnosis for a syndrome in any family depends on the size of the family, and the degree of thoroughness in the identification and testing of all affected members, it is necessarily more difficult to exclude syndromic diagnoses in smaller kindreds. In our series the number of affected per kindred was smaller in the non-syndromic than the syndromic FIHP subgroups (11). The number of affecteds was also small in non-syndromic families in other recent FIHP series (27, 34, 35). This supports the possibility that additional syndromic families have not been identified.

Nevertheless a core subset of non-syndromic kindreds likely will remain even after the future optimization of molecular diagnostic tools to detect occult MEN1, HPT-JT and FHH-related syndromes. This strongly suggests that novel gene(s) exist

whose mutation can result in the FIHP phenotype. If so, then the samples and data collected from the subsets of thoroughly evaluated, apparently non-syndromic FIHP kindreds should assist in the identification and characterization of an unknown number of novel genes important for neoplasia in the parathyroid. Genome-wide linkage analysis of the trait predisposing to HPT among well characterized apparently non-syndromic FIHP kindreds would be a logical starting point in this search (78).

Acknowledgements

This research was supported by the Intramural Research Program of the NIH, NIDDK.

The author thanks Dr. Stephen J. Marx and also Drs. Lee S. Weinstein, Monica Skarulis and Allen M. Spiegel of the National Institute of Diabetes and Digestive and Kidney Diseases for their ongoing support and encouragement.

References

- Marx SJ. Multiple Endocrine Neoplasia Type 1. In: Kinzler KW (ed) *The Genetic Basis of Human Cancer*, 2nd ed. McGraw-Hill, New York. 2002;475-500.
- Marx SJ. Molecular genetics of multiple endocrine neoplasia types 1 and 2. *Nat Rev Cancer*. 2005;5:367-75.
- Marx SJ, Attie MF, Levine MA, et al. The hypocalciuric or benign variant of familial hypercalcemia: clinical and biochemical features in fifteen kindreds. *Medicine (Baltimore)*. 1981;60:397-412.
- Fuleihan GH. Familial benign hypocalciuric hypercalcemia. *J Bone Miner Res*. 2002;17 Suppl 2:N51-6.
- Jackson CE, Norum RA, Boyd SB, et al. Hereditary hyperparathyroidism and multiple ossifying jaw fibromas: a clinically and genetically distinct syndrome. *Surgery*. 1990;108:1006-1012.
- Iler MA, King DR, Ginn-Pease ME, et al. Multiple endocrine neoplasia type 2A: a 25-year review. *J Pediatr Surg*. 1999;34:92-6.
- Ponder BA. Multiple Endocrine Neoplasia Type 2. In: Scriver CS, Beaudet AL, Sly WS, Valle D (eds) *The Metabolic & Molecular Bases of Inherited Disease*, 8 ed. McGraw-Hill, New York; 2001; 931-942.
- Simonds WF, Robbins CM, Agarwal SK, et al. Familial isolated hyperparathyroidism is rarely caused by germline mutation in HRPT2, the gene for the hyperparathyroidism-jaw tumor syndrome. *J Clin Endocrinol Metab*. 2004;89:96-102.
- Schussheim DH, Skarulis MC, Agarwal SK, et al. Multiple endocrine neoplasia type 1: new clinical and basic findings. *Trends Endocrinol Metab*. 2001;12:173-178.
- Chandrasekharappa SC, Guru SC, Manickam P, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* 1997;276:404-407.
- Simonds WF, James-Newton LA, Agarwal SK, et al. Familial isolated hyperparathyroidism: clinical and genetic characteristics of 36 kindreds. *Medicine (Baltimore)*. 2002;81:1-26.
- Kristiansen JH, Brochner Mortensen J, Pedersen KO. Familial hypocalciuric hypercalcaemia I: Renal handling of calcium, magnesium and phosphate. *Clin Endocrinol (Oxf)*. 1985;22:103-16.
- Pollak MR, Brown EM, Chou Y-HW, et al. Mutations in the human Ca²⁺-sensing receptor gene cause familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. *Cell*. 1993;75: 1297-1303.
- Brown EM. Familial hypocalciuric hypercalcemia and other disorders with resistance to extracellular calcium. *Endocrinol Metabol Clin North Am*. 2000;29:503-522.
- Hendy GN, D'Souza-Li L, Yang B, et al. Mutations of the calcium-sensing receptor (CASR) in familial hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, and autosomal dominant hypocalcemia. *Hum Mutat*. 2000;16:281-296.
- Heath H, III, Jackson CE, Otterud B, et al. Genetic linkage analysis in familial benign (hypocalciuric) hypercalcemia: evidence for locus heterogeneity. *Am J Hum Genet*. 1993;53:193-200.
- Lloyd SE, Pannett AA, Dixon PH, et al. Localization of familial benign hypercalcemia, Oklahoma variant (FBHOk), to chromosome 19q13. *Am J Hum Genet*. 1999;64:189-195.
- Jackson CE. Hereditary hyperparathyroidism associated with recurrent pancreatitis. *Ann Intern Med*. 1958;49:829-36.
- Teh BT, Farnebo F, Kristoffersson U, et al. 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. *J Clin Endocrinol Metab*. 1996;81:4204-4211.
- Teh BT, Farnebo F, Twigg S, et al. Familial isolated hyperparathyroidism maps to the hyperparathyroidism-jaw tumor locus in 1q21-q32 in a subset of families. *J Clin Endocrinol Metab*. 1998;83: 2114-2120.
- Kakinuma A, Morimoto I, Nakano Y, et al. Familial primary hyperparathyroidism complicated with Wilms' tumor. *Intern Med*. 1994; 33:123-126.
- Tan MH, Teh BT. Renal neoplasia in the hyperparathyroidism-jaw tumor syndrome. *Curr Mol Med*. 2004;4:895-7.
- Mallette LE, Malini S, Rappaport MP, et al. Familial cystic parathyroid adenomatosis. *Ann Intern Med*. 1987;107:54-60.
- Carpten JD, Robbins CM, Villablanca A, et al. HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. *Nat Genet*. 2002;32:676-80.
- Howell VM, Haven CJ, Kahnoski K, et al. HRPT2 mutations are associated with malignancy in sporadic parathyroid tumours. *J Med Genet*. 2003;40:657-63.
- Cetani F, Pardi E, Borsari S, et al. Genetic analyses of the HRPT2 gene in primary hyperparathyroidism: germline and somatic mutations in familial and sporadic parathyroid tumors. *J Clin Endocrinol Metab* 2004;89:5583-91.
- Villablanca A, Calender A, Forsberg L, et al. Germline and de novo mutations in the HRPT2 tumour suppressor gene in familial isolated hyperparathyroidism (FIHP). *J Med Genet*. 2004;41:e32.
- Shattuck TM, Valimaki S, Obara T, et al. Somatic and germ-line mutations of the HRPT2 gene in sporadic parathyroid carcinoma. *N Engl J Med*. 2003;349:1722-9.
- Bradley KJ, Hobbs MR, Buley ID, et al. Uterine tumours are a phenotypic manifestation of the hyperparathyroidism-jaw tumour syndrome. *J Intern Med*. 2005;257:18-26.
- McKeeby JL, Li X, Zhuang Z, et al. Multiple leiomyomas of the esophagus, lung, and uterus in multiple endocrine neoplasia type 1. *Am J Pathol*. 2001;159:1121-7.
- Lemmens I, Van de Ven WJM, Kas K, et al. Identification of the multiple endocrine neoplasia type 1 (MEN1) gene. *Hum Mol Genet*. 1997;6:1177-1183.
- Skarulis MC. Clinical expressions of multiple endocrine neoplasia type 1 at the National Institutes of Health. pp. 486-487. In: Marx S, moderator. *Multiple endocrine neoplasia type 1: clinical and genetic topics*. *Ann Intern Med*. 1998;129:484-94.
- Agarwal SK, Kester MB, Debelenko LV, et al. Germline mutations of the MEN1 gene in familial multiple endocrine neoplasia type 1 and related states. *Hum Mol Genet*. 1997;6:1169-1175.
- Warner J, Epstein M, Sweet A, et al. Genetic testing in familial isolated hyperparathyroidism: unexpected results and their implications. *J Med Genet*. 2004;41:155-60.
- Cetani F, Pardi E, Ambrogini E, et al. Genetic analyses in familial isolated hyperparathyroidism: implication for clinical assessment and surgical management. *Clinical Endocrinology*. 2006;64:146-152.
- Miedlich S, Lohmann T, Schneyer U, et al. Familial isolated primary hyperparathyroidism - a multiple endocrine neoplasia type 1 variant? *Eur J Endocrinol*. 2001;145:155-60.
- Pannett AA, Thakker RV. Multiple endocrine neoplasia type 1. *Endocr Relat Cancer*. 1999;6:449-73.
- Teh BT, Kytola S, Farnebo F, et al. Mutation analysis of the MEN1 gene in multiple endocrine neoplasia type 1, familial acromegaly and familial isolated hyperparathyroidism. *J Clin Endocrinol Metab*. 1998;83:2621-2626.
- Giraud S, Zhang CX, Serova-Sinilnikova O, et al. Germ-line muta-

- tion analysis in patients with multiple endocrine neoplasia type 1 and related disorders. *Am J Hum Genet.* 1998;63:455-67.
40. Bassett JH, Forbes SA, Pannett AA, et al. Characterization of mutations in patients with multiple endocrine neoplasia type 1. *Am J Hum Genet.* 1998;62:232-44.
 41. Sakurai A, Shirahama S, Fujimori M, et al. Novel MEN1 gene mutations in familial multiple endocrine neoplasia type 1. *J Hum Genet* 1998;43:199-201.
 42. Perrier ND, Villablanca A, Larsson C, et al. Genetic screening for MEN1 mutations in families presenting with familial primary hyperparathyroidism. *World J Surg.* 2002;26:907-13.
 43. Stuckey BG, Kent GN, Gutteridge DH, et al. Fasting calcium excretion and parathyroid hormone together distinguish familial hypocalciuric hypercalcaemia from primary hyperparathyroidism. *Clin Endocrinol (Oxf).* 1987;27:525-33.
 44. Pidasheva S, D'Souza-Li L, Canaff L, et al. CASRdb: calcium-sensing receptor locus-specific database for mutations causing familial (benign) hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, and autosomal dominant hypocalcemia. *Hum Mutat.* 2004;24:107-11.
 45. Carling T, Szabo E, Bai M, et al. Familial hypercalcemia and hypercalcuria caused by a novel mutation in the cytoplasmic tail of the calcium receptor. *J Clin Endocrinol Metab.* 2000;85:2042-2047.
 46. Streeten EA, Weinstein LS, Norton JA, et al. Studies in a kindred with parathyroid carcinoma. *J Clin Endocrinol Metab.* 1992;75:362-366.
 47. Dong QH, Debelenko LV, Chandrasekharappa SC, et al. Loss of heterozygosity at 11q13: Analysis of pituitary tumors, lung carcinoids, lipomas, and other uncommon tumors in subjects with familial multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab.* 1997;82:1416-1420.
 48. Marx S, Spiegel AM, Skarulis MC, et al. Multiple endocrine neoplasia type 1: Clinical and genetic topics. *Ann Intern Med.* 1998; 129:484-494.
 49. Bradley KJ, Cavaco BM, Bowl MR, et al. Utilisation of a cryptic non-canonical donor splice site of the gene encoding PARAFIBROMIN is associated with familial isolated primary hyperparathyroidism. *J Med Genet.* 2005;42:e51.
 50. Shallow TA, Fry KE. Parathyroid adenoma-occurrence in father and daughter. *Surgery.* 1948;24:1020-1025.
 51. Haven CJ, Wong FK, Van Dam EWCM, et al. A genotypic and histopathological study of a large Dutch kindred with hyperparathyroidism-jaw tumor syndrome. *J Clin Endocrinol Metab.* 2000;85:1449-1454.
 52. Szabo J, Heath B, Hill VM, et al. Hereditary hyperparathyroidism-jaw tumor syndrome: the endocrine tumor gene HRPT2 maps to chromosome 1q21-q31. *Am J Hum Genet.* 1995;56:944-950.
 53. Williamson C, Cavaco BM, Jauch A, et al. Mapping the gene causing hereditary primary hyperparathyroidism in a Portuguese kindred to chromosome 1q22-q31. *J Bone Miner Res.* 1999;14:230-239.
 54. Wynne AG, van Heerden J, Carney JA, et al. Parathyroid carcinoma: clinical and pathologic features in 43 patients. *Medicine (Baltimore).* 1992;71:197-205.
 55. Allo M, Thompson NW. Familial hyperparathyroidism caused by solitary adenomas. *Surgery* 1982;92:486-90.
 56. Bilezikian JP. Primary hyperparathyroidism. When to observe and when to operate. *Endocrinol Metab Clin North Am.* 2000;29:465-78.
 57. Kassem M, Kruse TA, Wong FK, et al. Familial isolated hyperparathyroidism as a variant of multiple endocrine neoplasia type 1 in a large Danish pedigree. *J Clin Endocrinol Metab.* 2000;85:165-167.
 58. Teh BT, Esapa CT, Houlston R, et al. A family with isolated hyperparathyroidism segregating a missense MEN1 mutation and showing loss of the wild-type alleles in the parathyroid tumors. *Am J Hum Genet.* 1998;63:1544-1549.
 59. Wassif WS, Moniz CF, Friedman E, et al. Familial isolated hyperparathyroidism: a distinct genetic entity with an increased risk of parathyroid cancer. *J Clin Endocrinol Metab.* 1993;77:1485-1489.
 60. Chou YH, Pollak MR, Brandi ML, et al. Mutations in the human Ca(2+)-sensing-receptor gene that cause familial hypocalciuric hypercalcemia. *Am J Hum Genet.* 1995;56:1075-1079.
 61. Heath H, III, Odelberg S, Jackson CE, et al. Clustered inactivating mutations and benign polymorphisms of the calcium receptor gene in familial benign hypocalciuric hypercalcemia suggest receptor functional domains. *J Clin Endocrinol Metab.* 1996;81: 1312-1317.
 62. Mallette LE, Bilezikian JP, Ketcham AS, et al. Parathyroid carcinoma in familial hyperparathyroidism. *Am J Med.* 1974;57:642-648.
 63. Bergman L, Teh B, Cardinal J, et al. Identification of MEN1 gene mutations in families with MEN 1 and related disorders. *Br J Cancer.* 2000;83:1009-14.
 64. Karges W, Jostardt K, Maier S, et al. Multiple endocrine neoplasia type 1 (MEN1) gene mutations in a subset of patients with sporadic and familial primary hyperparathyroidism target the coding sequence but spare the promoter region. *J Endocrinol.* 2000; 166: 1-9.
 65. Sato M, Matsubara S, Miyauchi A, et al. Identification of five novel germline mutations of the MEN1 gene in Japanese multiple endocrine neoplasia type 1 (MEN1) families. *J Med Genet.* 1998;35: 915-9.
 66. Hu J, Spiegel AM. Naturally occurring mutations of the extracellular Ca2+-sensing receptor: implications for its structure and function. *Trends Endocrinol Metab.* 2003;14:282-8.
 67. Takami H, Shirahama S, Ikeda Y, et al. Familial hyperparathyroidism. *Biomed Pharmacother.* 2000;54 (Suppl 1):21s-24s.
 68. Villablanca A, Wassif WS, Smith T, et al. Involvement of the MEN1 gene locus in familial isolated hyperparathyroidism. *Eur J Endocrinol.* 2002;147:313-22.
 69. Cetani F, Pardi E, Giovannetti A, et al. Genetic analysis of the MEN1 gene and HPRT2 locus in two Italian kindreds with familial isolated hyperparathyroidism. *Clin Endocrinol (Oxf).* 2002;56:457-464.
 70. Pannett AA, Kennedy AM, Turner JJ, et al. Multiple endocrine neoplasia type 1 (MEN1) germline mutations in familial isolated primary hyperparathyroidism. *Clin Endocrinol (Oxf).* 2003;58:639-46.
 71. Fujimori M, Shirahama S, Sakurai A, et al. Novel V184E MEN1 germline mutation in a Japanese kindred with familial hyperparathyroidism. *Am J Med Genet.* 1998;80:221-222.
 72. Dwarakanathan AA, Zwart S, Oathus RC. Isolated familial hyperparathyroidism with a novel mutation of the MEN1 gene. *Endocr Pract* 2000;6:268-70.
 73. Poncin J, Abs R, Velkeniers B, et al. Mutation analysis of the MEN1 gene in Belgian patients with multiple endocrine neoplasia type 1 and related diseases. *Hum Mutat.* 1999;13:54-60.
 74. Honda M, Tsukada T, Tanaka H, et al. A novel mutation of the MEN1 gene in a Japanese kindred with familial isolated primary hyperparathyroidism. *Eur J Endocrinol.* 2000;142:138-143.
 75. Shimizu S, Tsukada T, Futami H, et al. Germline mutations of the MEN1 gene in Japanese kindred with multiple endocrine neoplasia type 1. *Jpn J Cancer Res.* 1997;88:1029-32.
 76. Ohye H, Sato M, Matsubara S, et al. Germline mutation of the multiple endocrine neoplasia type 1 (MEN1) gene in a family with primary hyperparathyroidism. *Endocr J.* 1998;45:719-23.
 77. Carrasco CA, Gonzalez AA, Carvajal CA, et al. Novel intronic mutation of MEN1 gene causing familial isolated primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2004;89:4124-9.
 78. Warner J, Nyholt DR, Busfield F, et al. Familial isolated hyperparathyroidism is linked to a 1.7 Mb region on chromosome 2p13.3-14. *J Med Genet.* 2006;43:e12.

Abbreviations

Abbreviations used in this paper: HPT, hyperparathyroidism; FIHP, familial isolated hyperparathyroidism; MEN1, multiple endocrine neoplasia type 1; MEN2A, multiple endocrine neoplasia type 2A; FHH, familial hypocalciuric hypercalcemia; HPT-JT, hyperparathyroidism-jaw tumor syndrome; CASR, calcium-sensing receptor; NIH, National Institutes of Health; MDB, Metabolic Diseases Branch; LOH, loss of heterozygosity; NS, not significant; PTX, parathyroidectomy.