Hyperparathyroidism–Jaw Tumor Syndrome

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Andrew C. Calabria and Michael A. Levine

Abstract

Hyperparathyroidism–jaw tumor syndrome (HPT–JT) is an autosomal dominant disorder characterized by the development of parathyroid tumors, ossifying fibromas of the mandible and maxilla, cystic and neoplastic renal abnormalities, and uterine tumors. One of its unique characteristics is its association with a high prevalence of atypical parathyroid adenomas and carcinomas.

HPT–JT is caused by mutations in the HRPT2 gene that reduce expression or function of parafibromin, a nuclear protein that regulates gene expression and inhibits cellular proliferation (Carpten et al., Nat Genet 32(4):676–680, 2002; Yart et al., Mol Cell Biol 25(12):5052–5060, 2005; Zhang et al., Biochem Biophys Res Commun 350(1):17–24, 2006; Woodard et al., Oncogene 24(7):1272–1276, 2005). Prior to recognition of HRPT2, HPT–JT was diagnosed using clinical criteria and was based on the presence of ossifying jaw tumors in a patient with primary hyperparathyroidism (PHPT) who lacked features of other complex syndromes associated with hyperfunctioning parathyroid glands. Patients with HPT–JT also manifest a more aggressive form of PHPT than is typical of sporadic or other genetic forms of PHPT, due in part to the presence of atypical parathyroid tumors and the increased risk of parathyroid carcinoma (Marx, N Engl J Med 343(25):1863–1875, 2000). Moreover, patients

A.C. Calabria, MD
Division of Endocrinology and Diabetes,
The Children' Hospital of Philadelphia,
34th and Civic Center Blvd., 11NW-Ste30, Philadelphia,
PA 19104, USA

M.A. Levine, MD (✉)
Department of Pediatrics, University of Pennsylvania
School of Medicine, Children's Hospital of Philadelphia,
34th and Civic Center Blvd., Philadelphia, PA 19104, USA
e-mail: levinem@chop.edu

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with HPT–JT have asynchronous development of parathyroid tumors, so recurrence of PHPT is common after removal of one or more parathyroid tumors.

Keywords
Hyperparathyroidism • Parafibromin • Atypical parathyroid adenomas • HRPT2 gene

Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia. In most cases, PHPT is a sporadic disorder that occurs in patients in their fifth or sixth decade of life and occurs as a consequence of a single, benign parathyroid adenoma. Inherited forms of PHPT occur in up to 20% of cases, however, and are usually associated with the presence of multiple parathyroid tumors and an earlier onset of hypercalcemia. These disorders exhibit autosomal dominant modes of transmission, and over the past few years, molecular genetic research has led to the identification of many of the responsible genes. In turn, clinical genetic testing has facilitated molecular diagnosis in presymptomatic relatives of affected subjects, enabled the identification of affected patients who lack a family history of PHPT, and enhanced specification and characterization of distinct genetic forms of inherited PHPT. Patients with genetic forms of PHPT may have isolated hyperparathyroidism, in which only the parathyroid glands are involved, or may have more complex syndromes in which parathyroid tumors are associated with cellular defects in other endocrine and nonendocrine tissues (Table 13.1) [1]. The most unique of these complex syndromes is the hyperparathyroidism–jaw tumor syndrome (HPT–JT), an autosomal dominant disorder with incomplete penetrance that is characterized by the development of parathyroid tumors, ossifying fibromas of the mandible and maxilla, cystic and neoplastic renal abnormalities, and uterine tumors. In contrast to other forms of familial PHPT in which parathyroid tumors are generally benign, HPT–JT is associated with a high prevalence of atypical parathyroid adenomas and carcinomas [2–5].

Table 13.1 Familial forms of primary hyperparathyroidism

Familial forms of primary hyperparathyroidism(PHPT)	Genetic mutation	Chromosomal location	Inheritance	PHPT features	Associated endocrinopathies
HPT–JT	*HRPT2*	1q21.q31	AD	Adenomas (cystic) Carcinomas	Jaw tumors Renal tumors Uterine tumors
MEN-1	*MEN1*	11q13	AD	Hyperplasia	Pituitary tumors Pancreatic tumors
MEN-2A	*RET*	10q11.2	AD	Hyperplasia	Medullary thyroid carcinoma Pheochromocytoma
FIHP	*HRPT2* *MEN1* *CASR* *Unnamed*	1q21.31 11q13 3q13.3-q21 2q14-p13.3	AD	Adenomas/carcinomas Hyperplasia/adenoma Normal/hyperplasia Hyperplasia/adenoma	By definition, isolated to PHPT
FHH	*CASR*	3q13.3-q21	AD	Normal/hyperplasia	None

Adapted from Carling, T. and R. Udelsman, *Parathyroid surgery in familial hyperparathyroid disorders.* J Intern Med, 2005. **257**(1): p. 27–37

HPT–JT is caused by mutations in the *HRPT2* gene that reduce expression or function of parafibromin, a nuclear protein that regulates gene expression and inhibits cellular proliferation [6–9]. Prior to recognition of *HRPT2*, HPT–JT was diagnosed using clinical criteria and was based on the presence of ossifying jaw tumors in a patient with PHPT who lacked features of other complex syndromes associated with hyperfunctioning parathyroid glands. Patients with HPT–JT also manifest a more aggressive form of PHPT than is typical of sporadic or other genetic forms of PHPT, due in part to the presence of atypical parathyroid tumors and the increased risk of parathyroid carcinoma [5]. Moreover, patients with HPT–JT have asynchronous development of parathyroid tumors, so recurrence of PHPT is common after removal of one or more parathyroid tumors. Some patients with HPT–JT will not have jaw tumors or other typical features of the syndrome, which in the absence of molecular genetic testing can lead to diagnostic confusion with other hereditary parathyroid disorders (Table 13.1) [1] or sporadic presentations of PHPT.

Pathophysiology

The pathophysiology of the HPT–JT syndrome is similar to other forms of PHPT. The primary abnormality in parathyroid cells leads to excessive and inappropriate secretion of parathyroid hormone (PTH), which results in hypercalcemia and other features of PHPT. PTH binds to specific heptahelical receptors (PTHR1) that are expressed on the plasma membrane of target cells, particularly renal tubular cells and osteoblasts, and activates adenylyl cyclase to produce the second messenger cyclic AMP. In the kidney, PTH increases calcium reabsorption in the renal distal tubule and reduces reabsorption of phosphate and bicarbonate in the proximal tubule. In addition, PTH induces expression of renal CYP27b, the enzyme that converts 25(OH)D to $1,25(OH)_2D$ (calcitriol), with consequent elevation of serum levels of this fully active, hormonal form of vitamin D. Elevated levels of calcitriol increase absorption of calcium, and to a lesser extent phosphorus, from the gastrointestinal tract, and together with PTH induce expression of RANKL (receptor activator of nuclear factor of kB ligand) in osteoblasts. Elevated RANKL induces differentiation and activity of osteoclasts, which lead to increased bone resorption and bone turnover. These direct and indirect actions of PTH lead to the principal features of PHPT: hypercalcemia, hypophosphatemia, and preferential loss of cortical bone. Skeletal abnormalities range from mild osteopenia to the classical lesions of osteitis fibrosa cystica. Overt skeletal disease is now uncommon, occurring in only 1.4–14% patients at presentation, but osteoporosis with associated fractures is now increasing [10]. Symptoms in PHPT are often vague and patients may also complain of anorexia, nausea, abdominal pain, constipation, and rarely acute pancreatitis. Peptic ulcer disease has been described in multiple endocrine neoplasia type 1 (MEN-1) if PHPT is present, but this has not been described with HPT–JT. Psychiatric symptoms such as fatigue, weakness, somnolence, lethargy, dementia, stupor, and depression have long been associated with PHPT and are likely related to effects of hypercalcemia on the neurologic system. Many of these changes may be subtle and may not be truly appreciated until after parathyroidectomy. Acute hypercalcemic crisis with nephrogenic diabetes insipidus may also develop if serum calcium levels are greater than 12 mg/dL (3 mmol/L). The degree of hypercalcemia determines the amount of calcium in the glomerular filtrate, and although the fractional excretion of calcium may be reduced, the absolute amount of excreted calcium in the urine is increased in most patients and increases the risk of nephrocalcinosis and nephrolithiasis. Today, due to the routine measurement of serum concentrations of calcium, at least 70–80% of patients with PHPT fail to show obvious signs or symptoms of disease, and are identified through the incidental finding of mild hypercalcemia [11].

In most patients with PHPT (80–85%), hyperparathyroidism is limited to a single monoclonal adenoma, which in most cases is related to a specific somatic gene defect. The other three glands are normal. The average adenoma ranges from 1

to 3 cm in size and weighs about 0.5 g, which is significantly larger than a normal parathyroid gland (25–35 mg). Cystic elements in an adenomatous gland may call attention to HPT–JT, which was originally characterized as *cystic parathyroid adenomatosis*. Approximately 15–20% of patients with PHPT have diffuse hyperplasia of all four glands, a broad category that includes hyperplasia, multiple adenomas, and polyclonal hyperfunction. Multiglandular disease is more likely to occur in younger individuals, and is usually associated with germ line mutations that cause MEN-1 and MEN-2A (Table 13.1) [1]. PHPT rarely is due to parathyroid carcinoma (~1%), but its identification should raise suspicions for HPT–JT.

Hyperparathyroidism–Jaw Tumor Syndrome

Clinical Presentation

In 1987, Mallette et al. described a father and three sons who at early ages developed severe hypercalcemia; in each case, a single parathyroid adenoma was found at surgery [12]. Three members of this family developed recurrent hypercalcemia due to development of a second parathyroid adenoma 6–13 years after resection of the initial parathyroid adenoma; the fourth affected individual had developed hypoparathyroidism after the first operation. Review of the pathologic specimens showed that each parathyroid tumor was a cystic adenoma, and unexpectedly, similar cystic changes were also present in the normal parathyroid glands in these patients. In the originally described cohort, urinary calcium excretion was elevated in all four patients, and one individual had nephrolithiasis. Interestingly, three other first-degree relatives of the affected subjects were hypercalcemic, but two were hypocalciuric, which initially suggested a possible link between this syndrome and familial hypocalciuric hypercalcemia (FHH) that was later disproved. Three of four patients in this cohort also underwent resection of ossifying fibromas of the mandible or maxilla. However, unlike the classic brown tumors of the jaw (epulis) that occasionally occur in other forms of PHPT, these jaw tumors did not have the distinctive appearance of brown tumors as they were found to lack osteoclasts. Review of the literature disclosed previously reported cases of familial parathyroid adenomas in association with fibro-osseous jaw tumors [13, 14], suggesting that these individuals had the same syndrome. Further review of the parathyroid histology in these other kindreds also identified the adenomas as cystic [15]. To date, approximately 50 families of HPT–JT have been described. Subsequent analysis of these additional cases has extended the phenotype of HPT–JT to include uterine tumors and cystic and neoplastic renal anomalies and extended the spectrum of parathyroid disease to include not only cystic adenomas but also parathyroid carcinomas.

Natural History of PHPT in HPT–JT Syndrome

The most common, and sometimes the only feature of HPT–JT, is primary hyperparathyroidism, which has a penetrance of about 80–90% [5, 16]. HPT–JT, similar to other genetic forms of PHPT, presents earlier in life than sporadic forms of PHPT. On average, about 80% of individuals with HPT–JT will manifest PHPT by the end of the third decade [5]. The average age of diagnosis for HPT–JT probands is 32 years, but in some patients PHPT may occur as early as the first decade [17]. With the exception of its very early onset, the clinical presentation of PHPT in HPT–JT is otherwise indistinguishable from that of sporadic or other inherited forms of PHPT. Patients with PHPT often develop renal complications, such as nephrolithiasis (17–37%), nephrocalcinosis, and hypercalciuria [11]. Patients with HPT–JT develop additional unique renal anomalies, such as renal cysts, hamartomas, and adult onset Wilms tumor.

In contrast to sporadic PHPT or other hereditable forms of PHPT, there is a relatively high prevalence of parathyroid carcinoma in HPT–JT, as well as atypical adenomas that have a high

potential for malignant transformation. Moreover, although all four parathyroid glands are potentially affected in HPT–JT, the development of adenomas is asynchronous, and often only a single parathyroid tumor is present at diagnosis [3]. This asynchronous presentation is unique among the different forms of inherited PHPT, in which development of parathyroid tumors is more likely to be metasynchronous. Removal of the initially affected parathyroid tumor leads to a presumed cure, only to be followed years later by recurrence of PHPT and the need for additional treatment or surgery [3]. As in the original description of HPT–JT, the adenomas may be cystic, either with micro- or macrocysts, which may aid in diagnosis [3]. In addition, there is a significant association of parathyroid carcinoma in HPT–JT syndrome, with 15% of cases presenting with parathyroid carcinoma, compared to an incidence of <1% in other forms of PHPT [17, 18]. Still, while most experts cite a frequency of 15% for parathyroid carcinomas in HPT–JT syndrome, this number is based on a relatively small number of families and may be confounded by ascertainment bias [19]. In general, parathyroid carcinomas are usually larger, firmer, and more easily palpable than benign parathyroid tumors, and are associated with higher serum levels of PTH and serum calcium levels that are often greater than 14 mg/dL (3.5 mmol/L) [20].

Jaw Tumors

In 1958, Jackson et al. reported a unique multigenerational family with hereditary hyperparathyroidism in which four of the five affected members of the first generation had jaw tumors [21]. Three affected members of the third generation developed similar jaw tumors that progressed after surgical correction of hyperparathyroidism. Reinvestigation of this family disclosed that these maxillary and mandibular tumors were histologically distinct from the classical "brown tumors" of hyperparathyroidism. Brown tumors are focal lesions found within the areas of bone resorption. Radiographic evaluation of these tumors reveals well-defined lytic lesions but histologically brown tumors represent a reparative cellular process. Brown tumors consist of foci of hemorrhage, fibrosis, and granulation tissue, and the characteristic brown color is due to hemosiderin deposition. The lesions contain increased numbers of multinucleate giant cells, osteoblasts, and osteoclasts and poorly mineralized woven bone, and often resemble giant cell lesions. Brown tumors are usually slowly growing and locally destructive lesions, and invasion into surrounding structures may cause a variety of symptoms. Patients often develop significant bone pain, and pathologic fractures may occur. When brown tumors occur in the head or neck, they usually involve the mandible, and only rarely affect the maxilla. Most studies have shown that surgical treatment of PHPT and normalization of excessive levels of serum PTH is typically associated with spontaneous regression of the bony lesions, including brown tumors. Nevertheless, local curettage and enucleation of jaw lesions appear necessary in cases where regression of the brown tumor is incomplete or where disfigurement is significant.

By contrast, the jaw tumors in HPT–JT are fibro-osseous lesions that lack giant cells. The jaw tumors are typically fibrous maxillary or mandibular tumors and resemble ossifying fibromas (cemento-ossifying fibromas) (Fig. 13.1) [22]. The ossifying fibromas of HPT–JT are limited to the jaw, whereas the typical brown tumors of hyperparathyroidism occur in the ribs or knees as well as the jaw. Whereas sporadic jaw tumors generally occur in the third and fourth decades of life, jaw tumors in HPT–JT often arise earlier. Jaw tumors occur in 16–50% of patients with HPT–JT [23], and as they are unrelated to parathyroid status it is not surprising that they do not regress after correction of hyperparathyroidism [24]. Similar to the asynchronous development of parathyroid tumors in HPT–JT, jaw tumors may be asynchronous and may even precede the development of hypercalcemia by several decades. Complete surgical removal of jaw tumors is the recommended treatment, but recurrence is possible [25].

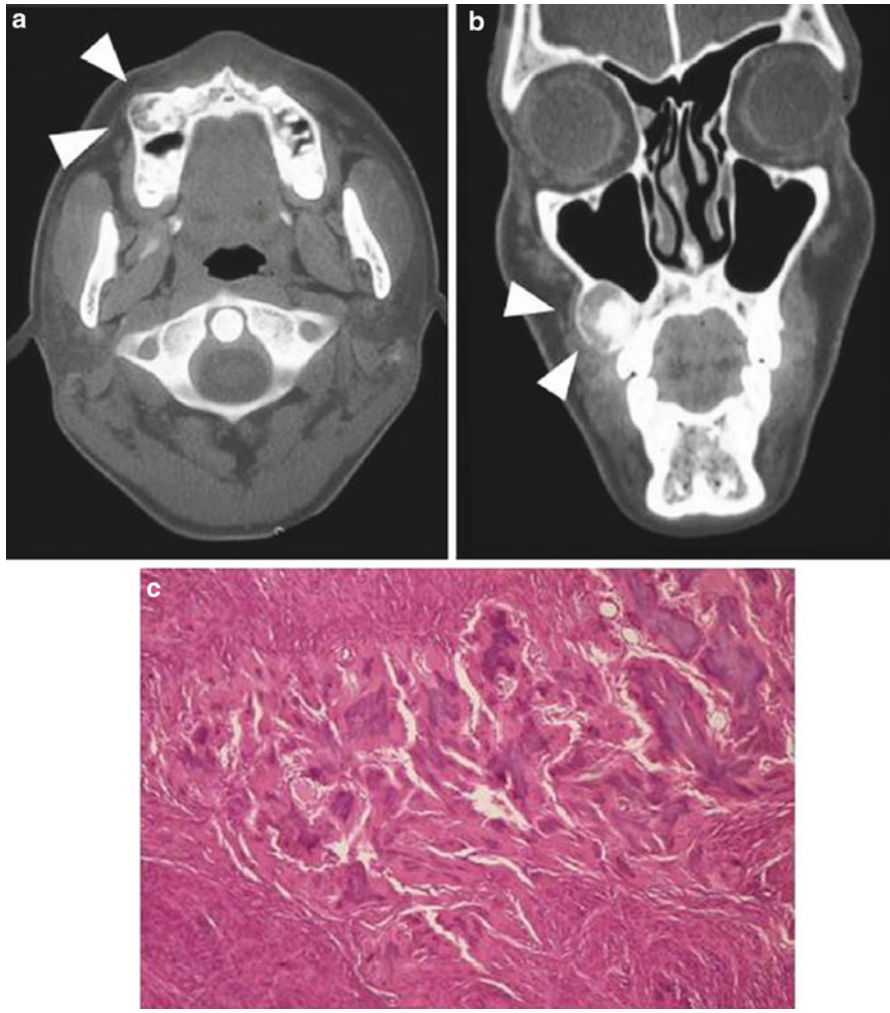

Fig. 13.1 Jaw tumors. Axial (**a**) and coronal (**b**) CT scans showing a well-circumscribed lesion in the right maxilla of an HPT–JT patient, with accompanying histologic evaluation consistent with an ossifying fibroma (**c**) (Reprinted from Int J Oral Maxillofac Surg, 36(4), Yamashita, Y., et al., A case of hyperparathyroidism-jaw tumor syndrome found in the treatment of an ossifying fibroma in the maxillary bone, pp. 365–9, Copyright 2007, with permission from Elsevier)

Kidney Involvement in the HPT–JT Syndrome

The kidney is involved in a limited subset of patients with HPT–JT (~5–15% of cases), raising the possibility that the development of renal cysts and tumors represents a distinct phenotypic variant of HPT–JT [26, 27]. Cystic kidney disease is the most common renal manifestation of this syndrome [26]. The majority of affected HPT–JT patients were discovered to have unsuspected renal involvement by routine ultrasound, but several patients have presented in renal failure [26]. The cysts may range from a few minor cysts to bilateral polycystic lesions that result in renal failure [26]. In addition to renal cysts, some patients often develop rare renal tumors, such as mixed epithelial-stromal tumors and adult Wilms' tumors. The mixed epithelial-stromal tumor, previously reported as a hamartoma, is a very unusual tumor that may be solid or cystic, lacks necrosis, and contains a mesenchymal component with variable

spindle cell proliferation [16]. While these tumors demonstrate loss of the wild-type *HRPT2* allele, surgical resection has been curative and malignant behavior (i.e., metastases) has not been noted. Adult Wilms' tumors have been described in multiple HPT–JT families. Wilms' tumors are typically diagnosed in childhood and are usually highly malignant tumors that require surgical resection, chemotherapy, and radiation. The Wilms' tumors in HPT–JT have been identified in patients as old as 53 years but have neither metastasized nor led to death. They are usually bilateral, poorly circumscribed, and of smaller sizes than classical childhood Wilms' tumor, which is an embryonal tumor (e.g., nephroblastoma) that is associated with loss of both copies of the *WT1* tumor suppressor gene. The Wilms tumor of HPT–JT also has distinctive histological features that distinguish it from the childhood Wilms' tumor, such as a low number of mitoses, lack of necrosis and hemorrhages, large mesenchymal components, and the presence of cysts [4]. Papillary renal cell carcinoma and renal cell adenomas have also been described, albeit infrequently, in HPT–JT [28]. These tumors are also likely part of HPT–JT, as both mixed epithelial-stromal tumors and papillary renal cell carcinomas have all shown allelic deletions in the same region on chromosome 1 [4, 28].

Other Features

Characterization of additional, more recently described subjects with HPT–JT has shed new light on the spectrum of endocrinopathies and tumors that can be associated with syndrome. Uterine tumors have been described in association with HPT–JT and may actually be the most common clinical feature in some patients after PHPT, affecting 75% of HPT–JT female patients in some cohorts [19, 23, 29, 30]. In a Japanese family, two women with HPT–JT had unusual multiple small uterine polyps, which were diagnosed as adenomyomatous polyps [31]. It is unclear if these polyps are a variant of adenomyosis or endometriosis or have more aggressive neoplastic potential. Analysis of 33 HPT–JT kindreds revealed that affected women in 13 families suffered from menorrhagia in their second to fourth decades and often required hysterectomy as definitive treatment [30]. Uterine tumors were only diagnosed after surgery and have been linked to reduced fertility in affected women with HPT–JT [30]. Histological analysis of the uterine specimens revealed both benign and malignant tumors, with adenomyosis, adenofibromas, leiomomas, endometrial hyperplasia, and adenosarcomas identified [30]. Uterine myomas have also been described in several families [31]. A large Dutch kindred has also extended the clinical phenotype of HPT–JT syndrome. Thirteen affected members presented with either parathyroid adenoma or carcinoma, but in addition to associated renal anomalies, testicular mixed germ cell tumor with major seminoma component and Hürthle cell thyroid adenoma were also reported [28]. Other conditions, including thyroid carcinoma, thyrotoxicosis, colonic carcinoma, and pituitary cyst, have also been described, but may represent incidental findings. It is unclear whether a predisposition to these less common tumors truly exists.

The HPT–JT Syndrome and Other Forms of Familial PHPT

HPT–JT is one of the several autosomal dominant forms of familial hyperparathyroidism, that include familial isolated hyperparathyroidism (FIHP), MEN-1, multiple endocrine neoplasia type 2A (MEN-2A), and FHH (Table 13.1). In general, inherited forms of PHPT present at an earlier age than sporadic forms and occur with equal frequencies in both sexes. Genetic analyses of these disorders have helped to elucidate some of the underlying molecular mechanisms that may have significant clinical implications (Fig. 13.2) [32]. Multiple small kindreds with two or three affected members with isolated PHPT have received a diagnosis of FIHP. FIHP is a rare autosomal dominant form of PHPT characterized by hypercalcemia, elevated PTH levels, and uni- or multiglandular parathyroid tumors. FIHP is a diagnosis of exclusion and must be distinguished from other familial hypercalcemic

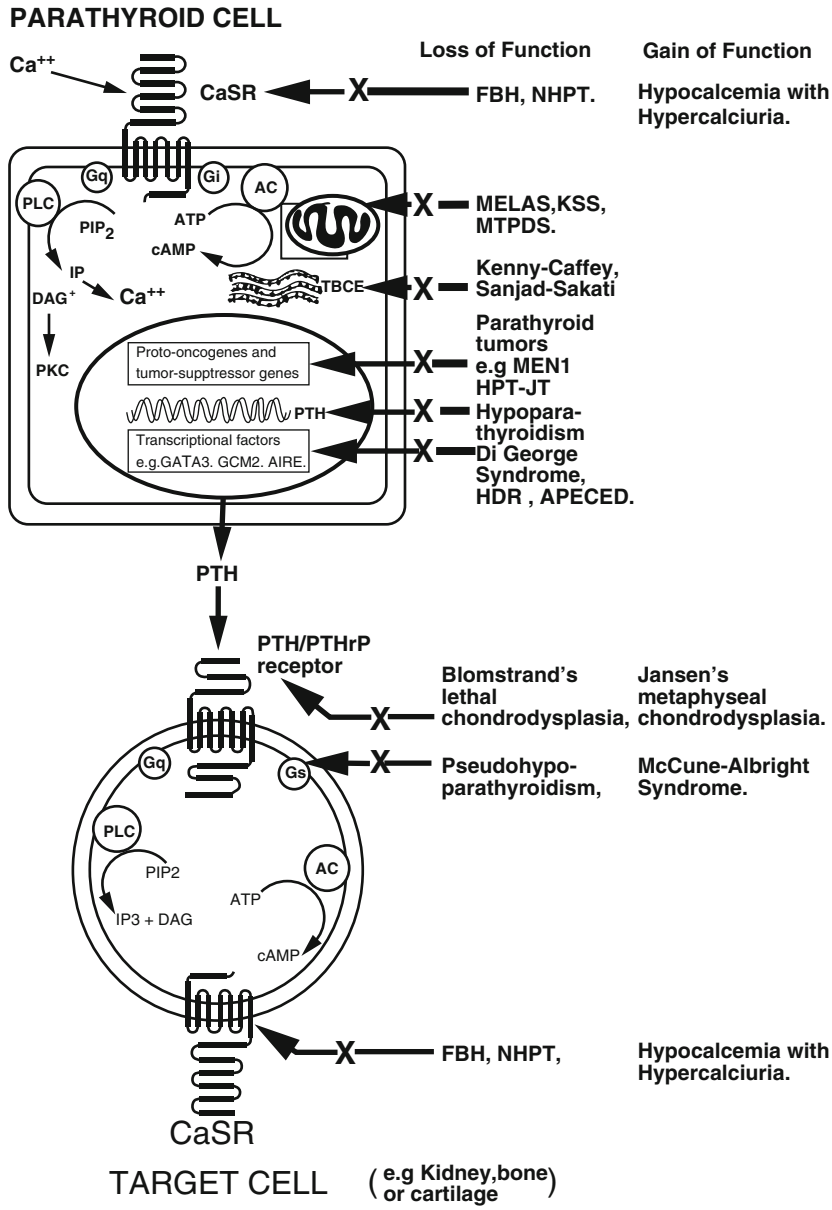

Fig. 13.2 Schematic representation of molecular components of calcium homeostasis. HPT–JT syndrome is caused by a mutation in the *HRPT2* gene and must be differentiated from MEN-1, which is due to inactivating mutations of the tumor suppressor gene *MENIN*; FHH, which is caused by heterozygous loss-of-function mutations of the *CASR* gene encoding the calcium sensing receptor; and FIHP, which has been linked to mutations in *HRPT2*, *MENIN*, and *CASR* in some cases (With kind permission from Springer Science+Business Media: Rev Endocr Metab Disord, Genetics of endocrine and metabolic disorders: Parathyroid, 5(1), 2004, p. 37–51, Thakker, R.V.)

disorders, in particular, FHH, MEN-1, MEN-2A, and HPT–JT (Table 13.1). The genetic locus of FIHP has not yet been disclosed. FHH is a benign autosomal dominant hypercalcemic disorder that is caused by heterozygous loss-of-function mutations of the *CASR* gene encoding the calcium sensing receptor. FHH is characterized by lifelong, nonprogressive hypercalcemia that may be

present from birth, inappropriately elevated PTH levels, and hypocalciuria. FHH is related to neonatal severe PHPT, a life-threatening form of severe hypercalcemia that is most commonly due to homozygous loss-of-function mutations in the *CASR* gene. MEN-1 is due to inactivating mutations of the tumor suppressor gene *MENIN*, and the autosomal dominant MEN-1 syndrome is characterized by tumors of the parathyroid, anterior pituitary (most commonly prolactinomas), and endocrine pancreas (most commonly gastrinomas). MEN-1 has near full penetrance, with hyperparathyroidism present at diagnosis in over 90% of cases and invariably associated with multiglandular disease. The presentation of pituitary and pancreatic tumors is generally much later and more variable than hyperparathyroidism in MEN-1. Like MEN-1, MEN-2A is also an autosomal dominant condition, but instead is due to activating mutations of the *RET* proto-oncogene and associated with medullary thyroid cancer, pheochromocytoma, and hyperparathyroidism. PHPT occurs in only 10–15% of patients with MEN-2A, as opposed to MTC, which has nearly 100% penetrance, and pheochromocytoma, which occurs in 50–60% of affected individuals. In contrast to MEN-1, PHPT in MEN-2A is more often caused by uniglandular disease but occasionally presents with multiglandular disease.

HPT–JT may be difficult to distinguish from other forms of familial PHPT, especially when the parathyroid tumors occur in isolation without any evidence of jaw tumors. HPT–JT syndrome is readily differentiated from FHH, as serum calcium levels are elevated in FHH from the neonatal or early infantile period and fractional excretion of calcium is very low (<1%), whereas hypercalcemia in HPT–JT is uncommon in the first decade. The clinical distinction between HPT–JT and MEN-1 in patients who lack other features can be more challenging. Although HPT–JT patients can have multiple parathyroid adenomas, they more commonly will have a single parathyroid adenoma with unusual histology of a parathyroid carcinoma. By contrast, parathyroid disease in patients with MEN-1 is often multiglandular and parathyroid carcinoma does not occur. Long-term follow-up may be required to disclose the development of other lesions in MEN-1, which may explain why some cases of FIHP have been linked to the MEN-1 locus [33]. The distinction between HPT–JT syndrome and FIHP is equally difficult, especially given the incomplete or asynchronous presentation of the additional features associated with HPT–JT. However, this distinction is very important given the higher risk of developing carcinomas in HPT–JT. A personal or family history of parathyroid carcinoma mandates serious consideration of germ line *HRPT2* mutation status in families with FIHP, regardless of whether features associated with HPT–JT are present [34]. An investigation for additional features of HPT–JT, such as jaw tumors, renal, uterine, pancreatic, thyroid, and testicular anomalies, may provide such a distinction and may help identify HPT–JT patients. Specifically, the finding of ossifying fibromas is an important distinguishing feature of HPT–JT from FIHP, and the occurrence of these jaw tumors may occasionally precede the development of hypercalcemia in HPT–JT patients by decades.

Parafibromin and the *HRPT2* Gene

To gain insight into the mechanisms underlying HPT–JT, family linkage studies were undertaken to determine the chromosomal location of the HPT–JT locus. The HPT–JT locus was mapped to chromosome 1q21-q31 and the putative gene designated hyperparathyroidism type 2, *HRPT2*. Positional cloning studies refined the chromosomal map location of *HRPT2*, and a prioritized DNA sequence analysis of the genes located within the critical interval on chromosome 1q31.2 revealed mutations within a gene that encoded a 531 amino acid protein with 17 exons, designated parafibromin or cell division cycle 73 (CDC73) [6]. The mutations identified in HPT–JT patients were found to be scattered through the coding region, with a higher number of mutations in exons 1–2 and 7–8, but none in exons 9–12 and 14–17, and greater than 80% predicting a functional loss through premature truncation [23, 27, 30]. To date, 111 independent CDC73 mutations

have been recognized and consist of 68 germ line mutations (>60%), 38 somatic mutations (<35%), and 5 others (<5%) whose origin has not been defined [35]. Of the 111 mutations, 50% were frameshift deletions or insertions, 29% nonsense mutations, 13% missense mutations, 6% splice site mutations, and 2% in-frame deletions or insertions [35]. In another study of HPT–JT kindreds, germ line frameshift and nonsense mutations were the most frequent mutations identified, accounting for 88% of mutations, as opposed to the infrequent finding of germ line missense mutations [23]. No genotype–phenotype correlation has been identified to date [30]. In addition, nonpenetrance has been seen in greater than 30% of mutation carriers, which may have important implications for surveillance considerations [30].

In their original work, Carpten et al. were able to detect *HRPT2* mutations in only 14 of 24 HPT–JT families, most of which had full expression of the syndrome and proven linkage to 1q24-q32 [6, 36]. Mutations in the coding region and splice sites have been identified in more than 80% of the 51 reported HPT–JT families [36]. In the remaining cases, mutations may be present in the promoter or untranslated regions or there may be whole exon or gene deletions that are not detected by PCR-based analysis [36]. Gene silencing through methylation is also a potential mechanism, as is involvement of a second genetic locus [36].

Since the identification of *HRPT2*, germ line *HRPT2* mutations have been found in 7% of FIHP (*HRPT1*) kindreds [6, 17, 23, 27, 30, 34, 37, 38]. In several of these apparent FIHP kindreds, parathyroid carcinomas and atypical adenomas have been identified in individuals carrying a germ line *HRPT2* mutation, again pointing to the tendency for malignant proliferation [6, 30, 34]. Other cases of FIHP had previously been linked to mutations in the MEN-1 gene and *CASR* [39]. In addition, hyperparathyroidism type 3 (*HRPT3*) has also been described, with mapping demonstrating linkage to chromosome 2q14-p13.3 in a FIHP kindred [40]. The remaining cases of FIHP are likely due to as of yet unidentified genes or potentially recently described genes, such as *CDKN1B*, which has been associated with the pathogenesis of sporadic parathyroid adenomas and a rare familial MEN-1-like (MEN-4) disorder but whose role in tumorigenesis remains to be fully elucidated [41]. FIHP may represent a phenotypic variant of different genetic syndromes, such as HPT–JT, MEN-1, and FHH, but with reduced or incomplete penetrance. As such, the clinical diagnosis of FIHP should be considered only provisional, and ultimately the term FIHP may be replaced as more causative genes are recognized.

Parafibromin is thought to function as a tumor suppressor, and consistent with Knudson's two-hit model of inherited cancer, mutations in *HRPT2* generally lead to a truncated or inactive protein. Moreover, germline mutations that inactivate *HRPT2* are present in affected members of HPT–JT kindreds and occur as somatic events in sporadic parathyroid adenomas and carcinomas [6, 24]. In some cases, "two hits" affecting *HRPT2*, either an additional mutation or loss of heterozygosity at the *HRPT2* locus, have been identified in a subset of parathyroid tumors [23, 26, 42–44]. Despite this, immunohistochemical analysis has revealed a loss of parafibromin expression in both parathyroid adenomas and carcinomas but not in normal parathyroid glands in the same subjects [23]. This suggests that the loss of parafibromin immunoreactivity in HPT–JT-related adenomas is a pivotal step in parathyroid tumorigenesis [45]. Still, as parafibromin is only involved in approximately 70% of parathyroid carcinomas and loss of parafibromin immunoreactivity may not be observed in all cases of *HRPT2* mutation, the identification of complementary markers would greatly aid diagnosis [46]. One such candidate marker to loss of parafibromin immunoreactivity is protein gene product 9.5 (PGP9.5), encoded by ubiquitin carboxyl-terminal esterase L1 (*UCHL1*) [46]. Diffuse positive staining for PGP9.5 has been exhibited in parafibromin negative carcinomas and adenomas, as well as parafibromin positive tumors, and may have greater sensitivity with similar specificity to parafibromin negativity as a marker of malignancy [46]. Moreover, these findings were supported by RT-PCR analysis that showed high expression of *UCHL1* in the carcinoma group [46].

The association between other affected tissues in HPT–JT and the *HRPT2* gene has also been explored. Masi et al. compared parafibromin expression in HPT–JT-related uterine polyps to sporadic ones. They noted a loss of parafibromin nuclear staining in both stromal and epithelial components of HPT–JT polyps, supporting a pathogenic role for *HRPT2* mutations in the development of uterine polyps in this syndrome [23]. While linkage to 1q markers was not associated with *HRPT2* in six hereditary Wilms' tumor families [26], additional studies have identified somatic *HRPT2* mutations with sporadic renal tumors, including renal cell carcinoma and Wilms' tumor [47]. Somatic and germ line *HRPT2* mutations have also been identified in sporadic ossifying fibromas and support a potential role for *HRPT2* mutations in the pathogenesis of jaw tumors [48]. The presence of such mutations in the fibromas themselves may explain the lack of clinical improvement in these jaw tumors after parathyroidectomy.

Determination of *HRPT2* mutations is particularly important due to the association with parathyroid carcinoma. Overall, somatic *HRPT2* mutations are present in most sporadic parathyroid carcinomas (20 of 26 cases; 77%) [49–51], and are absent in most sporadic parathyroid adenomas (0–4%). This indicates that *HRPT2* mutations confer a high risk for malignant transformation to carcinoma and may have a direct role in the pathogenesis of parathyroid carcinoma. A recent analysis of the full coding sequence and splice sites of the *HRPT2* gene in 21 parathyroid carcinomas from 15 patients without family history of PHPT revealed that 67% of parathyroid tumors had *HRPT2* mutations, and three patients carried germ line *HRPT2* mutations [51]. The unexpected finding of germ line *HRPT2* mutations in 20–30% of patients with sporadic parathyroid carcinomas suggests that these probands and their relatives may have occult HPT–JT with limited expressivity or a phenotypic variant. Thus, *HRPT2* analysis can provide a sensitive and specific molecular marker for parathyroid carcinoma in tumors with ambiguous or atypical histopathology. This has important clinical implications, as up to 50% of parathyroid tumors that behave in a biologically malignant manner (i.e., recurrence and metastasis) will be considered benign using conventional clinicopathological criteria. Moreover, *HRPT2* analysis facilitates DNA-based testing to identify at-risk relatives of patients with parathyroid cancer who carry germ line *HRPT2* mutations.

The *HRPT2* gene is ubiquitously expressed and evolutionarily conserved. Despite its role as a putative tumor suppressor gene, the function of parafibromin was not initially clear. The C-terminal domain shares 27% sequence identity with the yeast Cdc73 protein, which is a component of the yeast polymerase-associated factor 1 (PAF1) complex, a key transcriptional regulatory complex that interacts directly with RNA polymerase II [7]. Studies in yeast as well as mammalian cells have revealed that parafibromin is a nuclear protein and a mediator of key transcriptional events of histone modification, chromatin remodeling, initiation, and elongation [36]. Studies in *Drosophila* support a role for parafibromin in the regulation of translation, through homologs of the mammalian translational regulatory protein, cytoplasmic polyadenylation element binding protein [52]. Parafibromin has also been recognized to have an activating role as a component of the Wnt signaling pathway [53]. Immunohistochemical and functional studies have demonstrated that *HRPT2* mutations lead to loss of parafibromin expression [42, 45], abnormal localization [54], and abolition of antiproliferative activity [8]. In mammalian cells, parafibromin may have a dual role as an oncoprotein and tumor suppressor, depending on cellular environment, and therefore may have opposing effects in different tissues [36]. Interestingly, loss of HRPT2 expression and parafibromin in mice leads to apoptosis, possibly due to decreased expression of the *Igf1*, *Igf2*, *Hmga1,* and *Hmga2* genes, which are important factors for mammalian growth and adult survival [36, 55]. By contrast, similar loss of HRPT2 expression in human adult parathyroid cells results in tumor development due to increased proliferation. Comparison with the *Men1* knockout mouse provides adjunctive evidence for this divergence of expression. Despite ubiquitous expression, *Men1* knockout

mice suggest that loss of a tumor suppressor in susceptible tissues will lead to tumor formation, but will not affect proliferation in nonsusceptible tissues and cells will undergo apoptosis or remain normal [36].

Diagnostic Evaluation

Primary Hyperparathyroidism

The most common clinical presentation of both sporadic and familial forms of PHPT is asymptomatic hypercalcemia. An elevated serum calcium level should be confirmed by repeated measurement of the serum calcium concentration. Measurement of the total serum calcium concentration is generally adequate, but determination of the ionized calcium level may be necessary if serum protein levels and/or acid–base status are abnormal. An ionized calcium level may be more sensitive, as shown in a recent series of patients with PHPT where 12 of 60 subjects had elevated serum ionized calcium levels in the setting of presumed normocalcemia [56]. If possible, previous values for serum calcium levels should be reviewed. The presence of longstanding asymptomatic hypercalcemia raises the possibility of FHH and is also more suggestive of PHPT than nonparathyroid malignancy.

If hypercalcemia is confirmed, PTH levels should be measured using an immunoassay for intact or whole molecule PTH. The diagnosis of PHPT is usually concluded by the combination of an elevated or inappropriately normal serum level of PTH level in a subject with hypercalcemia. Absolute or relative elevations in PTH help to distinguish PHPT from other common causes of hypercalcemia, such as malignancy (Fig. 13.3) [5]. The majority of patients with PHPT have elevated serum levels of PTH, but in some patients the PTH concentration can be within the normal range [57]. These latter cases suggest that not all bioactive PTH can be measured by currently available intact and bioactive assays [57], or that "normal" ranges for serum PTH are not accurate. In suspected cases of PHPT with low-normal PTH levels, it may be helpful to repeat measurement of PTH using assays that detect other epitopes as adenomas may produce a bioactive form of PTH that is not completely measured by the intact or bioactive assays [57]. In addition, the 7–84 PTH peptide makes up roughly 15% of the measured intact assay in normal plasma, whereas the amino-truncated PTH (7–84) may account for at least 30% of the intact assay measurement in PHPT [57]. Conversely, others cases of PHPT may initially present with normocalcemia despite elevated PTH levels, which may represent the earliest manifestation of the disease course of PHPT. In these cases of so-called "incipient" PHPT, elevations of PTH are not associated with frankly elevated levels of serum calcium. In a longitudinal study of 37 patients with normocalcemic PHPT referred to a metabolic bone disease unit, many patients had evidence of classical PHPT, with a history of kidney stones in 14%, fragility fractures in 11%, and osteoporosis in 57% [spine (34%), hip (38%), and/or distal one-third radius (28%)] [58]. Moreover, progressive bone loss was not confined to the distal one-third of the radius, as in classical PHPT, instead occurring at all sites [T scores: spine, -2.00 ± 0.25; hip, -1.84 ± 0.18; distal one-third radius, -1.74 ± 0.22] [58]. Further signs of progressive hyperparathyroidism developed over the duration of the study (median 3 years) in 40% of patients, with 19% developing hypercalcemia [58]. Moreover, the observation that many individuals did not show evidence of hypercalcemia suggests the time course for the development of hypercalcemia in PHPT is highly variable.

Preoperative Imaging

^{99}Tc-labeled sestamibi with single photon emission computerized tomography (SPECT) imaging is the most widely used localization procedure for parathyroid tumors at experienced centers and can help plan the surgical approach in HPT–JT as in other cases of PHPT. However, suspicion for HPT–JT may not arise until the time of surgery, based on operative, histologic, and pathologic findings, or much later, in the event of recurrence

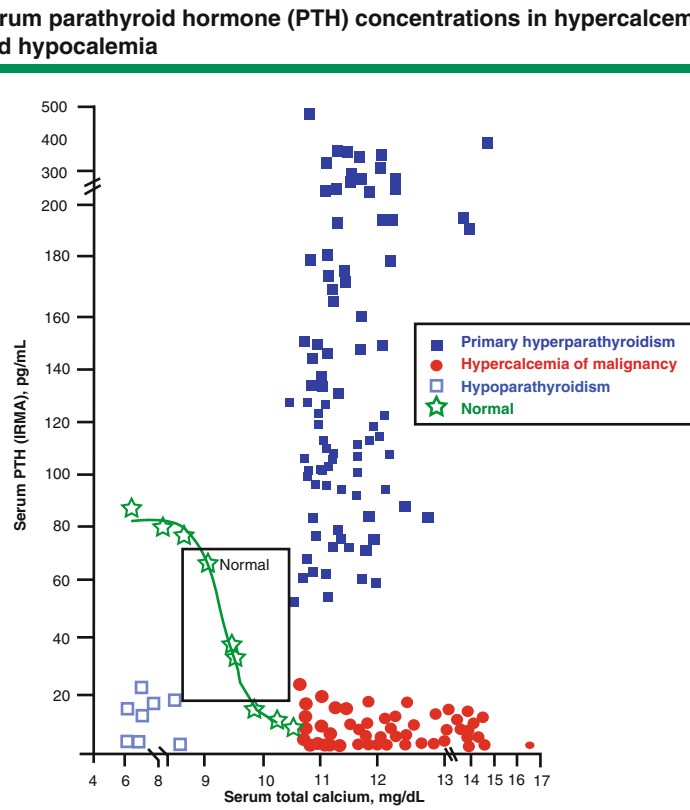

Fig. 13.3 Serum parathyroid hormone (PTH) concentrations (pg/mL) according to serum total calcium concentrations (mg/dL) in various disease states. The normal range is shown in the *white box*. Serum PTH and calcium levels are low in hypoparathyroidism (*open blue squares*) and high in primary hyperparathyroidism (*blue squares*). The serum calcium concentration is high and serum PTH is appropriately low in individuals with hypercalcemia of malignancy (*red circles*). While the diagnosis of a mineral metabolism disorder is usually clear, the PTH levels may overlap with the normal ranges and represent a limitation of the assays available for clinical use today (Reproduced with permission from Fuleihan GE, Silverberg SJ. Diagnosis and differential diagnosis of primary hyperparathyroidism. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA 2011. Copyright © 2011 UpToDate, Inc. For more information visit http://www.uptodate.com)

after initial resection of an isolated adenoma. Overall, the success rate of sestamibi scans is very good, with approximately 85% of parathyroid adenomas identified, but this decreases to about 45% for multiglandular disease [59]. Other modalities such as ultrasound and magnetic resonance imaging (MRI) are less helpful, except in the setting of coexisting thyroid disease and remedial cervical exploration [60]. Invasive localization procedures, such as angiography and venous sampling, are used for patients with recurrent or persistent PHPT [60, 61], and venous sampling in particular has been aided by the introduction of the rapid PTH assay [61].

Additional Diagnostic Testing

Diagnosis of HPT–JT is usually made during the second or third decade of life. Typically, the diagnosis is based on the finding of a single parathyroid adenoma with atypical cystic features and/or parathyroid carcinoma in a patient with jaw tumors. While the finding of carcinoma raises the possibility of HPT–JT, the presentation of a solitary parathyroid adenoma makes it much more difficult to distinguish HPT–JT from other forms of PHPT. Moreover, jaw tumors may be occult, emphasizing the importance of radiological evaluation of the jaw and kidneys in patients with young-onset

Table 13.2 Screening recommendations

Tumor[a]	Test	Frequency[b]
Parathyroid	Serum calcium, parathyroid hormone (PTH)	6 Months
Jaw fibromas	Panoramic jaw X-rays	5 Years
Renal	Renal ultrasound and/or abdominal magnetic resonance imaging (MRI)	5 Years
Uterine	Pelvic ultrasound	Annual

[a]Screening for the most common HPT–JT tumors is listed, but additional tumors, such as thyroid and testicular tumors, have also been reported. When indicated, assessment for these should also be undertaken
[b]Frequency after baseline testing
Adapted from Bradley, K.J., et al., *Uterine tumours are a phenotypic manifestation of the hyperparathyroidism-jaw tumour syndrome.* J Intern Med, 2005. **257**(1): p. 18–26

disease, multiglandular involvement, cystic parathyroid adenomas, and parathyroid carcinoma.

Additional baseline testing in suspected cases of HPT–JT would also be indicated. Pelvic ultrasound may be performed on an annual basis to screen for uterine tumors, which may be more common that originally appreciated [30]. Depending on kindred and any potential known tumors associated with the individual lineage, additional testing, including testicular ultrasound for testicular tumors and thyroid ultrasound for thyroid cancers, can be considered (Table 13.2).

Gene Sequencing and Screening

All patients with young-onset PHPT, multiglandular parathyroid disease, cystic parathyroid adenomas, or positive family history of PHPT should be carefully evaluated for the presence of a germ line gene defect associated with MEN 1, MEN2a, FIHP, FHH, and HPT–JT. The identification of parathyroid carcinoma increases the likelihood of identifying an *HRPT2* mutation. Identification of associated features, such as renal or jaw tumors, which may sometimes precede the identification of PHPT, would also be an indication for gene sequencing for *HRPT2*. Gene sequencing for *HRPT2* as well as other genes that are involved in familial PHPT is available from both several commercial reference laboratories (http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests). The identification of a loss-of-function *HRPT2* mutation in an affected individual has important consequences for ongoing surveillance for additional manifestations of HPT–JT. However, it is equally important to screen at-risk individuals in potential kindreds. Whereas mutation-negative individuals may no longer require close biochemical monitoring, regular surveillance of individuals with a germ line *HRPT2* mutation may allow for earlier detection of hyperparathyroidism, earlier surgical management, and possible prevention or cure of parathyroid carcinoma. DNA testing for *HRPT2* mutations should also be seriously considered for patients presenting with apparent sporadic carcinoma. In addition to sporadic carcinoma, other indications for possible *HRPT2* mutation analysis include young-onset PHPT (less than 35 years of age), sporadic jaw tumors, FIHP (after exclusion of *MEN1* and *CASR*), and parathyroid adenoma, in association with renal cysts or tumors, pancreatic tumors, thyroid tumors, and/or uterine lesions [35].

Screening Recommendations

Semiannual follow-up evaluations have been arbitrarily but appropriately suggested for affected probands with HPT–JT and potentially affected family members. In one such kindred, a 13-year-old boy with parathyroid carcinoma developed a second, albeit more benign, tumor 2 years after the initial malignancy, but his serum calcium and PTH levels were normal 6 months prior to presentation of the second tumor [34]. The rapid progression of PHPT suggests how aggressive this disease can be and reinforces the need for regular and frequent surveillance. Similarly, in the same kindred, an asymptomatic 22-year-old brother developed an aggressive parathyroid tumor that was identified after biochemical monitoring indicated hypercalcemia

and an elevated PTH level [34]. This group recommended screening asymptomatic, previously normocalcemic, mutation-positive siblings of the proband using serum calcium and PTH measurements every 6 months [34].

Guidelines for regular surveillance for the development of HPT–JT associated tumors have been suggested but not formally endorsed and will likely continue to evolve [30]. These apply to asymptomatic mutation carriers and first- and second-degree relatives in families without identified germ line *HRPT2* mutations. Monitoring of serum calcium and PTH levels is warranted in such family members, with the goal of early diagnosis and treatment of early parathyroid cancer. If PHPT develops in an at-risk relative, surgery aimed at identifying and examining all parathyroid glands could be advocated, even if a more limited approach might otherwise have been chosen. However, surveillance limited to biochemical monitoring alone would not capture some at-risk individuals. In a family with a germ line mutation of the *HRPT2* gene, discovery of a recurrent atypical adenoma in the normocalcemic proband 12 years after initial resection and the finding of a parathyroid carcinoma in a normocalcemic carrier suggest that adding neck ultrasound to the surveillance may increase sensitivity and lead to earlier detection of potential neoplasms [19]. Given the high worldwide prevalence of vitamin D deficiency, we recommend determination of serum 25-hydroxyvitamin D levels in patients who have elevated serum PTH levels and normal serum calcium concentrations to exclude mild secondary hyperparathyroidism.

The unexpected finding of germline *HRPT2* mutations in patients with apparent sporadic parathyroid carcinoma has forced a reconsideration of the clinical management approach taken not only for affected patients but also for potentially at-risk relatives. On further investigation, these individuals may ultimately have manifestations of HPT–JT or represent a phenotypic variant. When hyperparathyroidism recurs or worsens in such a patient, a new and distinct primary parathyroid tumor should be carefully sought in addition to recurrence or progression of the original neoplasm due to the asynchronous presentation commonly seen in HPT–JT [51]. Surveillance for jaw and renal tumors would also be indicated. As such, genetic testing for *HRPT2* mutations should be offered to all individuals with presumed sporadic parathyroid carcinoma. Moreover, while the identification of a mutation in the coding sequence would be definitive, this would not rule out the existence of a mutation in the noncoding region, a finding that has been recognized in nearly half of families with classic HPT–JT [6]. Relatives of individuals with germline *HRPT2* mutations may also be at risk for the development of parathyroid carcinoma or other findings consistent with HPT–JT if they likewise possess the mutation. While monitoring serum calcium levels on a semiannual basis may be used as a screening test, definitive genetic testing would allow for focused clinical surveillance for family members who carry the mutation. Monitoring of serum calcium levels in *HRPT2*-positive relatives would allow for earlier diagnosis and treatment of parathyroid carcinoma. Similarly, in at-risk individuals, surgery aimed at identifying and examining all parathyroid glands may be advocated. However, as in probands, current technologies will not capture mutations in the noncoding regions, so continued biochemical monitoring may still be considered in those at-risk relatives negative for *HRPT2* mutations.

Treatment

Although surgical intervention remains the primary treatment for patients with specific signs or symptoms of PHPT, most individuals are asymptomatic. The most recent recommendations for management of patients with asymptomatic PHPT are based on the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism, a consensus conference that was convened in 2008 to reassess previous guidelines from 1990 and 2002 workshops in the context of recent advances in our understanding of the natural history of untreated and treated asymptomatic disease [62–64].

The recommendations for surgery in asymptomatic patients with PHPT include the following criteria:

1. Serum calcium concentration that more than 1 mg/dL (>0.25 mmol/L) above the upper limits of normal.
2. Renal stones but not isolated hypercalciuria.
3. GFR less than 60 mL/min 1.73 m^2.
4. Reduction in bone density. Surgery is recommended for peri- or postmenopausal women and men aged 50 and older who have a *T*-score of −2.5 or less at the lumbar spine, femoral neck, total hip, or 33% (one-third) radius. In premenopausal women and in men younger than 50, the *Z*-score of −2.5 or less is recommended as the cut-point below which surgery is advised.
5. The presence of a fragility fracture, which provides clinical evidence of symptomatic low bone density.
6. Age less than 50 years is a guideline for surgery, as evidence supports a greater risk of complications of PHPT in these individuals over time than in those who are older than 50 years.

The 2008 workshop also acknowledged that patients who appeared to have asymptomatic PHPT frequently have significant neurocognitive symptoms that are only appreciated after parathyroidectomy [65]. Moreover, patients with asymptomatic PHPT often have lower bone mineral density and increased fracture rates that may improve with parathyroidectomy [62].

In HPT–JT, like other forms of PHPT, the standard treatment is surgical, but given the relatively small number of cases that have been studied, surgical recommendations continue to evolve. Prophylactic total parathyroidectomy has been suggested in HPT–JT to reduce the risk of parathyroid carcinoma. This approach seems unduly aggressive, however, given the infrequency of parathyroid carcinoma and the difficulties of managing postsurgical hypoparathyroidism.

In cases of sporadic PHPT where imaging studies provide preoperative confirmation of a single parathyroid tumor, and localization is successful, minimally invasive parathyroidectomy (MIP) is emerging as the surgical procedure of choice. MIP offers the potential for curative treatment of a localized tumor with less damage to surrounding tissue, fewer complications and more rapid postoperative recovery [66]. MIP may be considered as an alternative to standard complete cervical exploration with visualization of all four parathyroid glands in patients with HPT–JT when uniglandular uptake is identified on preoperative imaging (e.g., ultrasound examination, 99mTc-sestamibi scanning with concomitant SPECT/CT, CT, and/or MRI) [66]. Because patients with HPT–JT may have additional parathyroid tumors that escape detection by standard imaging techniques, MIP should incorporate intraoperative PTH measurement, and PTH levels should be obtained prior to and 5 and 10 min after tumor resection [66]. As normal parathyroid glands are suppressed by the hypercalcemia, a decline of PTH of greater than 50% after tumor resection is generally considered indicative of a successful operation where no further exploration is required [66]. However, concerns have arisen regarding the reliability of a drop in PTH levels after resection of an adenoma in patients with multiple parathyroid adenomas or multiglandular disease [67], and some have suggested that an 80% reduction in PTH instead be applied [68, 69].

The surgical approach in HPT–JT is further complicated by the increased risk of parathyroid carcinoma. If parathyroid carcinoma is encountered, a more aggressive *en bloc tumor* resection with ipsilateral thyroid lobectomy and resection of adjacent soft tissues has been recommended as definitive treatment [70]. It is important to avoid damaging the tumor, as this could lead to seeding of tumor cells in the local area. Vascular invasion, fibrous, and large size are hallmarks of parathyroid carcinoma. In most series, the median maximal diameter of parathyroid carcinoma is between 3.0 and 3.5 cm compared with approximately 1.5 cm for benign adenomas.

In one report of 12 patients with germ line *HRPT2* mutations (11 adenomas and 1 carcinoma) who underwent limited parathyroidectomy, all but one achieved initial cure, but three required later reoperation due to recurrent disease at 5, 9, and 27 years, respectively [71]. However,

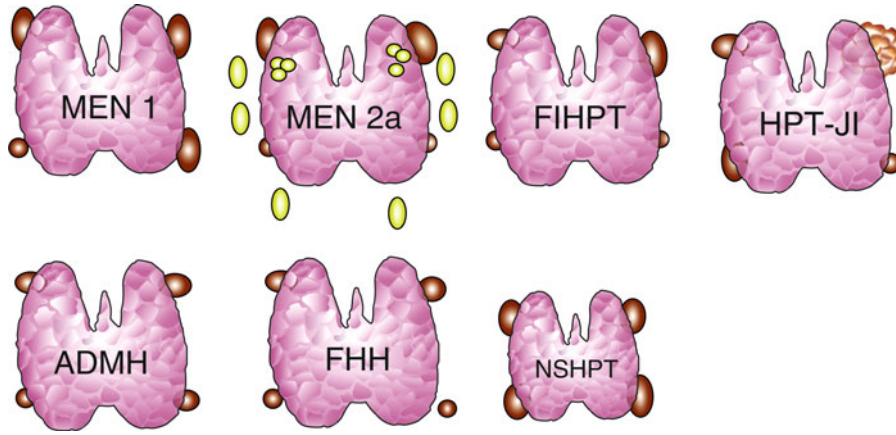

Fig. 13.4 Schematic illustrations of parathyroid abnormalities in familial forms of hyperparathyroidism. Parathyroid tumors in HPT–JT syndrome most commonly present as a single adenoma but may be cystic, and carry a 15% risk of parathyroid carcinoma. By contrast, MEN-1 nearly always has multiglandular involvement, FIHP usually presents with a single adenoma but may also have multiglandular involvement, and FHH exhibits mild hyperplasia. Marked variations exist within each subset (From Carling, T. and R. Udelsman, *Parathyroid surgery in familial hyperparathyroid disorders.* J Intern Med, 2005. **257**(1): p. 27–37)

long-term follow-up of three Brazilian kindreds with germ line *HRPT2* mutations shows that 80% of individuals have either persistence or recurrence of PHPT after focused parathyroidectomy and may support of adoption of a more aggressive initial surgical approach, such as subtotal parathyroidectomy [72]. Still, while no formal consensus exists, neither limited nor subtotal parathyroidectomy is effective for parathyroid carcinoma. By contrast, in other familial forms such as MEN-1, subtotal parathyroidectomy is generally recommended but total parathyroidectomy with heterotopic autotransplantation of resected parathyroid tissue may be considered. A schematic of parathyroid abnormalities in the different familial forms of PHPT is provided in Fig. 13.4 [66].

Conclusion

HPT–JT is a genetic form of PHPT caused by inactivating mutations of the *HRPT2* gene and characterized by parathyroid tumors, jaw tumors, renal and uterine tumors. While the penetrance of PHPT is high, the prevalence of other features is highly variable between kindreds. While only diagnosed in approximately 50 families to date, HPT–JT, unlike other forms of PHPT, is characterized by a high prevalence of atypical adenomas and parathyroid carcinomas. As such, the identification of *HRPT2* mutations in patients has significant clinical implications for screening for related tumors and for screening at-risk asymptomatic relatives for *HRPT2* mutations. As the presentation of the features of HPT–JT may be asynchronous, PHPT may be isolated and it may be difficult to distinguish HPT–JT from other forms of PHPT. Genetic testing for *CASR*, *MEN-1*, and *HRPT2* can help differentiate cases and may even provide a more definitive diagnosis than the provisional diagnosis of FIHP given to some individuals. In HPT–JT, after treatment of an initial parathyroid tumor, additional tumors may occur or the initial tumor may recur, again emphasizing the importance of genetic testing in suspected cases as it may affect surgical management. Identification of *HRPT2* mutations in cases of sporadic parathyroid carcinomas have also provided further justification for genetic testing in these individuals. Screening for jaw tumors, renal tumors, uterine tumors, and other related tumors and endocrinopathies should be pursued on a semiannual basis in affected individuals with HPT–JT and mutation-positive relatives. Treatment for affected cases is surgical.

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