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REVIEW

Familial states of primary hyperparathyroidism: an update

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Abstract

Background Familial primary hyperparathyroidism (PHPT) includes syndromic and non-syndromic disorders. The former are characterized by the occurrence of PHPT in association with extra-parathyroid manifestations and includes multiple endocrine neoplasia (MEN) types 1, 2, and 4 syndromes, and hyperparathyroidism–jaw tumor (HPT–JT). The latter consists of familial hypocalciuric hypercalcemia (FHH) types 1, 2 and 3, neonatal severe primary hyperparathyroidism (NSHPT), and familial isolated primary hyperparathyroidism (FIHP). The familial forms of PHPT show different levels of PHPT penetrance, developing earlier and with multiglandular involvement compared to sporadic counterpart.
All these diseases exhibit Mendelian inheritance patterns, and for most of them, the genes responsible have been identified. DNA testing for predisposing mutations is helpful in index cases or in individuals with a high suspicion of the disease. Early recognition of hereditary disorders of PHPT is of great importance for the best clinical and surgical approach. Genetic testing is useful in routine clinical practice because it will also involve appropriate screening for extra-parathyroidal manifestations related to the syndrome as well as the identification of asymptomatic carriers of the mutation.
Purpose The aim of the review is to discuss the current knowledge on the clinical and genetic profile of these disorders along with the importance of genetic testing in clinical practice.

Keywords MEN1 · MEN2 · MEN4 · HPT-JT · FIHP · FHH · NSHPT

Introduction

Familial primary hyperparathyroidism (PHPT) represents approximately 10–15% of all cases of PHPT [1]. The most common heritable syndromic form is the multiple endocrine neoplasia (MEN) type 1 (MEN1) syndrome, which affects 2% to 4% of patients with PHPT. Other syndromic disorders include MEN type 4 (MEN4), type 2 (formerly known as MEN2A), and hyperparathyroidism–jaw tumor (HPT–JT). Non-syndromic hereditable PHPT consists of familial (benign) hypocalciuric hypercalcemia (FHH) types 1, 2 and 3, neonatal severe primary hyperparathyroidism (NSHPT), and familial isolated primary hyperparathyroidism (FIHP). All these diseases exhibit Mendelian inheritance patterns, and for most of them, the genes responsible have been identified (Table 1).

Over the past decade, accumulating evidence has shed light on the clinical and genetic underpinnings of familial PHPT. Particularly noteworthy is the advancement in analysis techniques, which has facilitated the identification of novel candidate genes implicated in the so-called phenocopies of MEN1, accounting for approximately 10% of cases. There is now a greater understanding of MEN4, a rare phenocopy of MEN1 associated with germline mutations in the Cyclin Dependent Kinase inNhibitor 1B (*CDKN1B)* gene, confirming its later tumor onset, milder phenotype, and lower prevalence compared to MEN1 [2, 3].

Recent findings describe families carrying mutations in the MYC-associated factor X (*MAX*) gene, predisposing them to pheochromocytoma and paraganglioma development, suggesting the existence of a new syndrome termed MEN5 [4].

Furthermore, the understanding of FIHP has evolved over the past 80 years, culminating in the recognition of incomplete expressions of MEN1, FHH, or HPT-JT. Among FIHP probands who test negative for mutations in *MEN1,* Calcium Sensing Receptor *(CASR),* or Cell Division Cycle 73 (*CDC73*) genes, there is emerging evidence implicating

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germline mutations of the Glial Cells Missing Homolog 2 (*GCM2*) gene, necessitating further investigation [5].

Finally, genes responsible for FHH in patients *CASR* mutation-negative remained elusive for a significant period until the identification of two novel genes (*GNA11* and *AP2S1*) not previously associated with calcium metabolic disorders [6, 7].

The diagnosis of hereditary PHPT should be confirmed by genetic testing for germline mutations involved in familial PHPT preceded by genetic counseling. Early recognition of hereditary disorders of PHPT is of great importance for the best clinical and surgical approach. Genetic testing is also useful in routine clinical practice because it will also involve appropriate screening for other extra-parathyroidal manifestations related to the syndrome as well as the identification of relatives who may be asymptomatic carriers of the mutation. Finally, it helps remove anxiety and costs of monitoring in order to rule out carrier status. The specific clinical impact of genetic testing varies according to the different PHPT disorders.

This review highlights recent advances on the clinical aspects and genetics of familial PHPT along with the importance of genetic testing in clinical practice.

Syndromic forms of primary hyperparathyroidism

These disorders are characterized by the occurrence of PHPT in association with extra-parathyroid manifestations such as MENs and HPT-JT (Fig. 1). MENs are

Table 1 Clinical and genetic features in heritable forms of primary hyperparathyroidism

Disease	Main gene(s)/Chr location	Inheritance	Variant types	Encoded protein	Functional effect	Parathyroid expression	Main associated tumors/manifestations
Syndromic							
MEN1	*MEN1*/11q13	AD	Het	Menin	Inactivating	Multiple adenomas	Pituitary, GEP-NETs
MEN4	*CDKN1B*/12p13.1	AD	Het	p27	Inactivating	Multiple adenomas	Pituitary, GEP-NETs
MEN2	*RET*/10q11.21	AD	Het	RET	Activating	Asymmetric adenomas	Medullary thyroid cancer, Pheochromocytoma
HPT-JT	*CDC73*/1q31.2	AD	Het	Parafibromin	Inactivating	Asymmetric adenomas, atypical tumor, carcinoma	Jaw, kidney and uterine lesions
Non-syndromic							
FHH1	*CASR*/3q13.3-q21.1	AD	Het	CaSR	Inactivating	High set point to inhibit PTH secretion	Lifelong mild hypercalcemia, PTH inappropriate normal or mild elevated, hypocalciuria
FHH2	*GNA11*/19p13.3	AD	Het	Gα11	Inactivating	High set point to inhibit PTH secretion	Same profile of FHH1
FHH3	*AP2S1*/19q13.32	AD	Het	Adaptor protein 2σ-subunit	Inactivating	High set point to inhibit PTH secretion	Most severe form of FHH; may be associated with target-organ involvements (kidney stones or fractures)
NSHPT	*CASR*/3q13.3-q21.1	AR	Homo	CaSR	Inactivating	Marked hyperplasia	Seen in first week of life; severe PHPT, life-threatening
FIHP	*MEN1, CASR, CDC73, GMC2*/6p24.2 Other gene(s) not identified	AD	Het	Menin, CaSR, Parafibromin, GCMb	Inactivating	Multiple adenomas	None

MEN multiple endocrine neoplasia (type 1, 4, or 2), *HPT–JT* hyperparathyroidism-jaw tumor syndrome, *FHH* familial hypocalciuric hypercalcemia (type 1, 2, and 3), *NSHPT* neonatal severe primary hyperparathyroidism, *FIHP* familial isolated primary hyperparathyroidism, *AD* autosomal dominant, *AR* autosomal recessive, *het* heterozygous, *homo* homozygous, *GEP-NET* gastroenteropancreatic neuroendocrine tumor, *PTH* parathyroid hormone

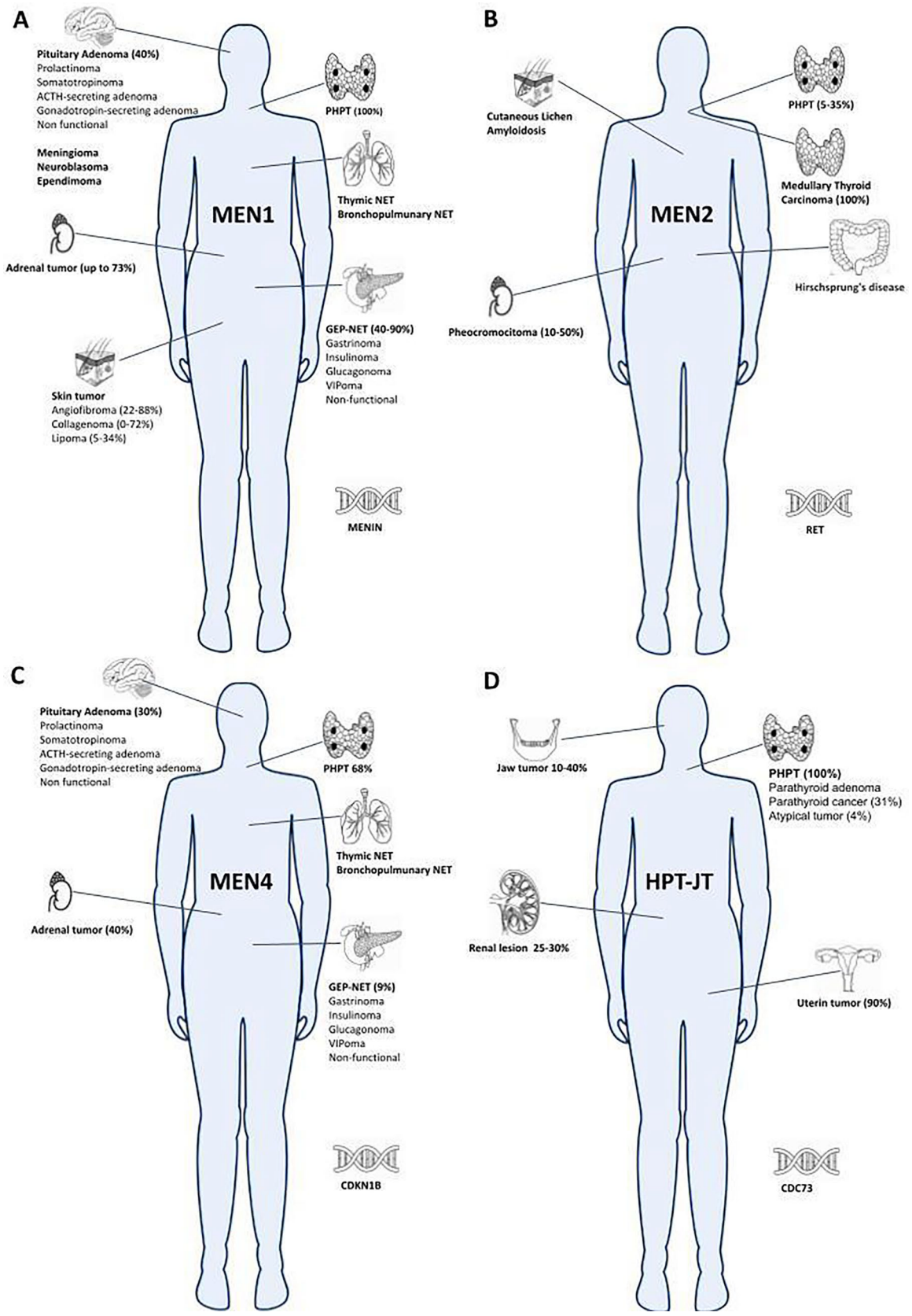

Fig. 1 Clinical features in syndromic forms of primary hyperparathyroidism

characterized by tumors in at least two of the three main endocrine tissues.

Multiple endocrine neoplasia type 1 (MEN1)

MEN1 (MIM#131100) is a rare autosomal dominant syndrome first described by Wermer in 1954 [8], which has an estimated prevalence of approximately 1–20/100,000 inhabitants and 1–18% among patients with PHPT [1, 9].

The most common endocrine manifestations are the "classical triad" namely PHPT, gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs), and anterior pituitary tumors [9]. Other endocrine tumors include thymic and bronchial/lung NETs and adrenocortical tumors [9]. Clinical diagnosis of MEN1 currently requires the combined occurrence of at least two of the three typical manifestations [9].

PHPT is often the first manifestation of the disease, which occurs in ~100% of the patients by the age of 50 years, with no apparent gender predilection [10–12]. Compared to sporadic cases, PHPT in MEN1 often develops earlier in life, with the youngest reported case at the age of four years, and the subjects generally show lower PTH levels [13–15]. It is typically characterized by a multiglandular involvement, asynchronous or metachronous, of the parathyroid glands (Fig. 2). However ectopic localization, particularly in the thymus and anterior mediastinum, along with the presence of supernumerary glands, are also much more frequent in the context of the syndrome than the sporadic form [16–18]. These disease features justify the high rate of persistence and recurrence after surgery reported in these patients compared to sporadic cases [13]. Surgery represents the definitive treatment of PHPT. Preoperative localization is of limited value in this setting as bilateral neck exploration is recommended irrespective of the findings in localization studies [19].

There is no unanimous agreement regarding the timing of initial surgery in index cases and reoperation in those who develop recurrences [9, 20–22]. In cases where symptoms arising from gastrinoma, specifically Zollinger-Ellison syndrome (ZES), are inadequately controlled by medical treatments, parathyroidectomy (PTX) might become necessary, given that hypercalcemia tends to exacerbate hypergastrinemia [23]. The surgery of choice is subtotal PTX (removal of ~3.5 glands) with bilateral transcervical thymectomy [9]. According to the latest guidelines, total PTX with subsequent autotransplantation of the parathyroid tissue (fresh or cryopreserved) may also be considered when no pathologic parathyroid tissue has been identified at neck exploration [9]. Although these more invasive operations reduce the risk of recurrence, they increase the risk of post-surgical hypoparathyroidism [24]. The rate of persistence and recurrence of PHPT depends on the type of surgery. The persistence rate is relatively low for subtotal (0%–22%) and total PTX (0%–19%), whereas it varies between 0%–53% for less than subtotal PTX. The recurrence rate is high following less than subtotal PTX (ranging from 0 to 100%), compared to subtotal (0%–65%) or total PTX (0%–56%) [24–26]. Despite these data, some authors propose a less invasive PTX (i.e., less than subtotal PTX or unilateral clearance) in selected patients with localized disease that was carefully documented on preoperative imaging studies [20, 21, 27, 28].

Cinacalcet, an allosteric modulator of the CaSR that binds to a different site from calcium binding, may be used to control hypercalcemia in patients who are not undergoing surgery as initial treatment or as an alternative to repeated surgery in patients with persistent/recurrent disease. Most patients experienced mild hypercalcemia, which normalized with relatively low daily doses of cinacalcet [29, 31–34]. While some studies suggest that cinacalcet may be more effective in MEN1 compared to sporadic PHPT, the limited sample sizes in these studies prevent definitive conclusions [29, 32–34]. Notably, in a randomized, crossover, double-blind study, the efficacy of cinacalcet in familial and sporadic PHPT with similar severity showed comparable responses [34].

GEP-NETs, mainly duodeno-pancreatic NETs, develop in 40–90% of MEN1 patients, and their prevalence varies depending on the age, the population under study and the diagnostic methods utilized [27]. Magnetic Resonance Imaging (MRI) appears to exhibit greater sensitivity compared to computed tomography (CT) while also avoiding ionizing radiation exposure. Despite its invasiveness and operator-dependency, systematic endoscopic ultrasonography (EUS) remains the most sensitive method. Functioning imaging, particularly 68Ga-DOTATATE PET/CT, seems to have good sensitivity to detect GEP-NETs in MEN1. Moreover, the likelihood of underestimating duodeno-pancreatic NETs is significant, given that pancreatic involvement typically presents as diffuse microadenomatosis (lesions <0.5 mm) in almost all patients [35–40].

GEP-NETs typically manifest after 40 years of age as non-functioning or functioning tumors, i.e., tumors secreting gastrin, insulin, glucagon, or vasoactive intestinal peptide (Fig. 3) [9, 22]. They can occur by the age of 5 years and in 20% of cases, may represent the first manifestation of MEN1. Due to their potential malignancy, they are the most frequent cause of mortality in patients with MEN1 [39, 41]. Compared to sporadic cases, GEP-NETs have a higher propensity for multifocality, exhibit a slower progression rate, and a greater likelihood of recurrence [39, 42]. Consequently, the criteria for surgical intervention

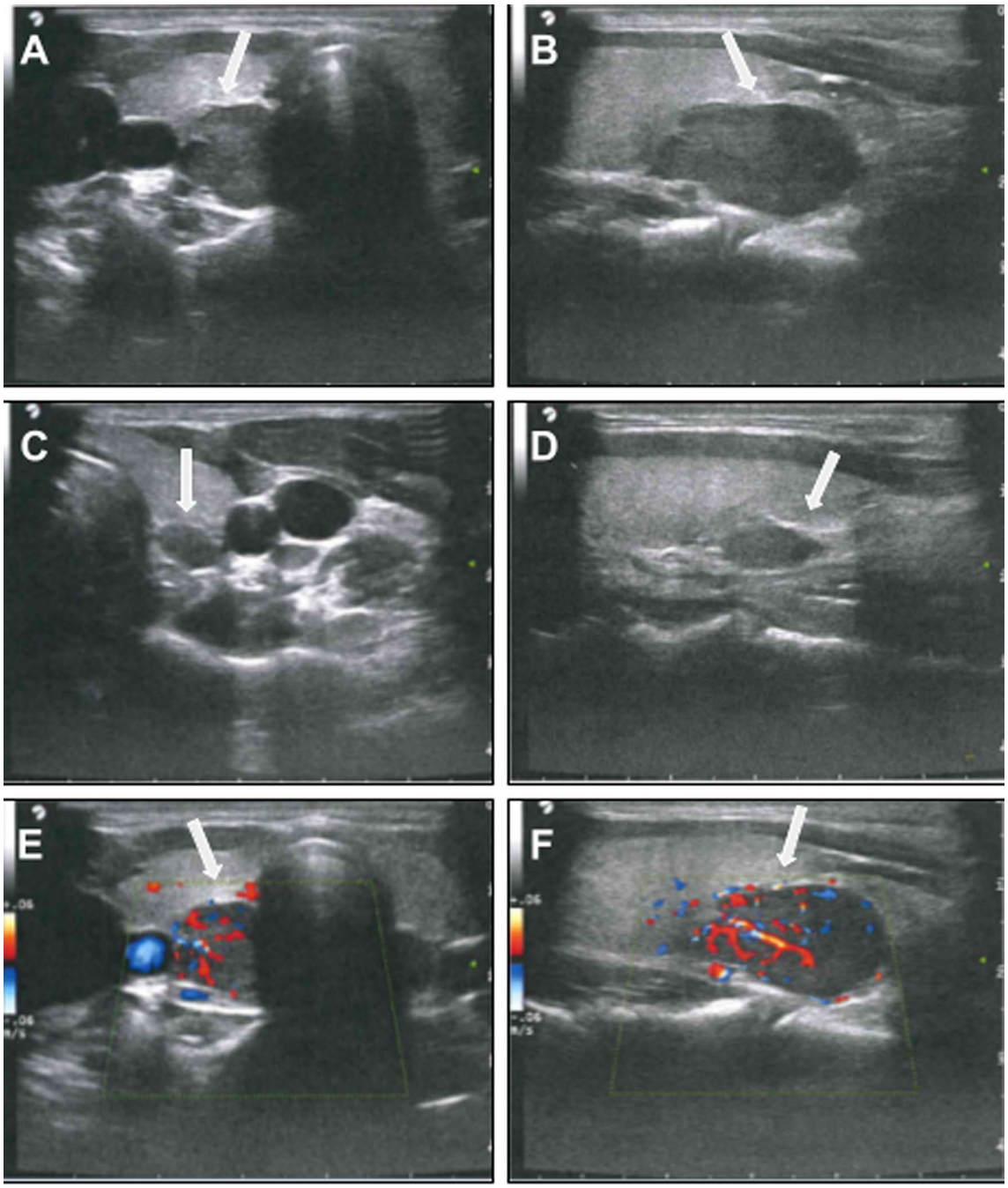

Fig. 2 Ultrasound image of two enlarged parathyroid glands in a 26-year-old woman with MEN1. The tumors (arrows) are located at the lower right pole of the thyroid (**A**, transverse view; **B**, longitudinal view), and at the lower left pole of the thyroid (**C**, transverse view; **D**, longitudinal view), and show a homogeneous pattern, regular shape, and halo sign. Both lesions show the typical color Doppler signals i.e., vascular pole (**E** and **F**, transverse view)

differ from those applied to sporadic cases and that have evolved over time. Key determinants for deciding when and how to proceed with treatment include the tumor grading based on mitotic rate and Ki-67 proliferative index, lesion size, presence or absence of metastasis, and whether the lesion secretes specific hormones [39].

As recently reported by the International Consensus based on the previous guidelines, surgical intervention is recommended for patients with insulinoma, VIPoma, or glucagonoma, regardless of the lesion size [9, 39, 43]. Most gastrinomas are multiple and occur within the duodenum, and most clinical centers undertake non-surgical

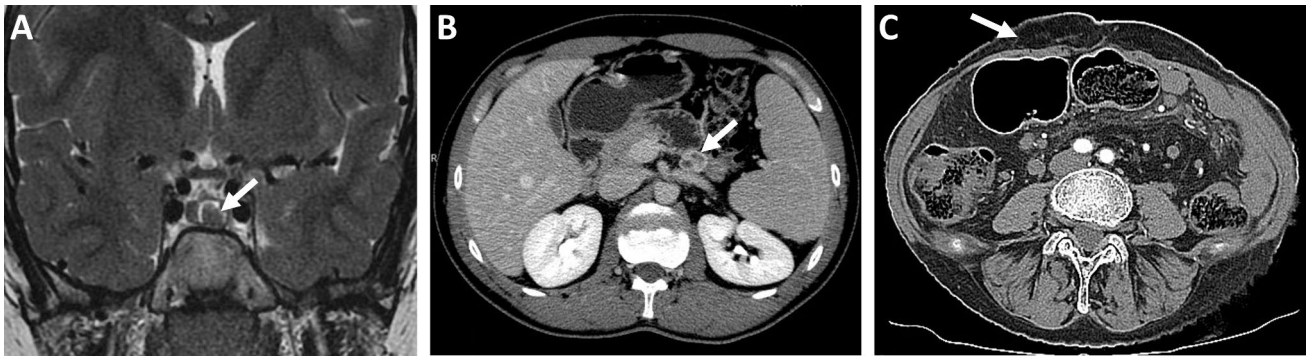

Fig. 3 (**A**) Magnetic resonance imaging of the pituitary (coronal T2 weighted section) shows a hypointense left lesion cleaved from surrounding structure compatible with a 6-mm prolactinoma in a 9-year-old boy with MEN1 syndrome (arrow). (**B**) Contrast-enhanced computed tomography of the abdomen (transverse section) shows a 2-cm lesion of the posterior inferior margin of the pancreatic tail compatible with neuroendocrine tumor in a 28-year-old man with MEN1 syndrome (arrow). (**C**) Contrast-enhanced computed tomography of the abdomen (transverse section) shows a subcutaneous 6×2.5 cm lesion of the right lower abdominal wall compatible with lipoma in a 60-year-old woman with MEN1 syndrome (arrow)

management, unless the tumors are localized within the pancreas and/or > 20 mm. Non-functioning duodenopancreatic NETs < 20 mm can be monitored conservatively in the absence of an aggressive family history, signs of malignancy, or rapid progression on imaging studies under surveillance, whereas tumors > 20 mm should be treated by surgery [9, 39, 43]. For patients for whom surgery is contraindicated or proves unsuccessful, alternative medical therapies become crucial. Medical treatment of the hormone excess states in MEN1 patients with functional duodenopancreatic NETs is similar to that recommended for patients with the sporadic counterpart. Anti-secretory drug requirements can change over time, and patients with ZES are recommended to have their acid-secretory control checked every 6–12 months. Insulinoma management often involves diazoxide [39]. Some studies have highlighted the potential therapeutic effectiveness of somatostatin analogues (SSAs) in MEN1-related NETs smaller than 2 cm, for both secretion control and tumor growth [44, 45]. Specifically, lanreotide appears to be preferable to octreotide in this context, as it allows for dose escalation by shortening the administration interval in case of progression on standard doses [46]. The efficacy of these therapies seems to be more pronounced in MEN1-related NETs compared to sporadic ones, likely due to various factors such as earlier stage presentation, higher prevalence of well-differentiated low-grade tumors with significant SSTR2 positive expression, and a greater frequency of functioning NETs in MEN1 cases vs. sporadic ones [46].

Other treatments based on a case-to-case basis include chemotherapy with agents such as alkylating agents, topoisomerase inhibitors, and antimetabolites, or receptor-targeted therapies involving radiolabeled SSAs, such as 90 Yttrium or 177 Lutetium [47].

Pituitary involvement is present in approximately 40% of patients with a mean age of 38 years, and is more common in women [1]. The most frequent pituitary tumors are prolactinomas (up to 65%) (Fig. 3), followed by somatotropinomas (6–8%), ACTH-secreting adenomas (< 5%), and gonadotropin-secreting adenomas (< 2%). Some cases exhibit co-secreting adenomas with unusual hormonal secretions [5]. Microadenomas, which are generally non-functioning or PRL-secreting tumors, are more common than macroadenomas [29–31].

The management of pituitary adenomas is similar to that of non-MEN1 patients. It typically involves medical therapies to control hypersecretion (such as octreotide and dopamine agonists) or surgical removal. Surgery is recommended in patients with hormone hypersecretion, which is poorly controlled with medical treatment, when there is a compression of the optic nerves or chiasm, or when the diagnosis is uncertain and a biopsy is needed [4, 5]. Radiotherapy should be considered for unresectable residual tumor tissue [5]. Asymptomatic non-functioning adenomas may be followed safely with serial magnetic resonance imaging [48].

MEN1 patients also develop adrenal tumors in up to 73% of cases, as the majority are asymptomatic and carcinoids (thymic, bronchopulmonary, and gastric) [1, 49]. Thymic carcinoids present in 2.8%–8% of cases, are the most aggressive tumors with a poor prognosis [49].

Several non-endocrine manifestations have been observed in individuals with MEN1 syndrome. These include skin lesions such as angiofibromas, lipomas (Fig. 3), collagenomas, tumors of the central nervous system (i.e., meningioma, neuroblastoma, and ependymoma), hibernomas and leiomyomas [9]. The prevalence of these manifestations ranges in different series, with multiple facial angiofibromas

occurring in 22% to 88% of cases, collagenomas in 0% to 72%, and lipomas in 5% to 34% [50–54]. The presence of these lesions, particularly angiofibromas or collagenomas, alongside one of the endocrine tumors from the triad, may suggest the diagnosis of MEN1 syndrome [52]. Non-endocrine malignancies, including breast cancer, melanoma, neuroblastoma, renal cell carcinoma, prostate cancer, lung cancer, and colorectal cancer, have been reported in patients with MEN1 [54–56]. A recent retrospective Chinese study found a significantly higher incidence of non-MEN1 malignant tumors compared to the general population, particularly breast cancer, papillary thyroid cancer, and urologic neoplasms [57]. Intriguingly, these patients also exhibit a more severe clinical presentation of MEN1.

Loss-of-function germline mutations of the *MEN1* gene are responsible for the syndrome and are identified in up to 90% of index cases with familial disease, and in up to 30% of sporadic cases [58–60]. The *MEN1* is an onco-suppressor gene located on chromosome 11q13. Its product, menin, interacts with multiple protein partners and plays a crucial role in cell cycle regulation, DNA repair, and transcriptional regulation of target genes [61–63]. In accordance with Knudson's two-hit model, which is the mechanism of action of tumor suppressor genes, two different hits on the *MEN1* gene are necessary to initiate disease development leading to the complete functional loss of the encoded menin protein [64].

Despite several studies aimed at establishing a potential relation between mutations and clinical manifestations, there is currently no confirmed evidence of a correlation between genotype and phenotype in MEN1 [65, 66]. Genetic testing for *MEN1* mutations is essential for the early identification and management of asymptomatic carriers [9].

A subset of patients (5–25%) with clinically suspected MEN1 syndrome do not have a pathogenic variant within the *MEN1* coding region, potentially due to the technical limitations of the molecular screening or missed alterations in untranslated or uncovered regions of the genome. Five to 10% of such cases may represent MEN1 phenocopies [17, 67]. In fact, germline mutations in *CDKN1A* and *CDKN2B* have rarely been identified in MEN1 kindreds [68].

Surveillance

The patients necessitate lifelong follow-up and surveillance, which can affect their psychologic well-being [46–48]. The current guidelines recommend that patients with MEN1 and their families be monitored by multidisciplinary teams including endocrinologists, gastroenterologists, radiologists, oncologists, cardiothoracic, and pituitary surgeons, pathologists, and clinical geneticists.

Patients and asymptomatic first-degree relatives at risk (i.e., mutant-gene carriers) should have lifelong follow-up at regular intervals (3- to 6-months and annually, respectively) [9]. Biochemical screening should possibly start by the age of five years for screening insulinoma and anterior pituitary tumor, and by the age of 8 years for screening PHPT [9].

Multiple endocrine neoplasia, type 4

MEN4 (MIM#610755) is a heritable autosomal dominant syndrome with a phenotype mimicking MEN1 [69, 70]. Pellegata et al. were the first to report a 3-generation family whose affected members presented MEN1-related tumors, including PHPT, acromegaly and pituitary adenoma, in addition to renal angiomyolipoma and testicular cancer, but tested negative to *MEN1* mutations [69]. The authors identified a pathogenic nonsense mutation (p.W76*) in the *CDKN1B* gene located on chromosome 12p13.1 and encoding the cell cycle inhibitor p27. This was based on the previous discovery of a causative mutation in the homolog gene in a colony of rats that spontaneously developed the combination of multiple endocrine tumors with overlapping features of MEN1 and MEN2 syndromes. Murine *Cdkn1b* was initially described as an atypical tumor suppressor gene characterized by haploinsufficiency, a mechanism that could explain the later onset of tumors in hemizygous compared with homozygous deficient mice in the animal model [71, 72]. Due to the rarity of biallelic inactivation of *CDKN1B*, it has been suggested that haploinsufficiency in MEN4 may also explain the tumorigenic progression [73].

The incidence of *CDKN1B* mutations in patients with MEN1-related neoplasia is difficult to estimate, due to the relatively few cases of MEN4 kindreds being reported or undiagnosed, but it was initially estimated at around 3% [17]. Forty-one MEN1-like index cases harboring germline *CDKN1B* variants and which can be regarded as MEN4, have been described to date [2, 74–76]. Only 53% of the cases with available data have a proven or suspected positive family history for MEN1-like endocrine disorders despite the presence of a germline *CDKN1B* mutation. Consequently, even apparently sporadic PHPT cases carrying a germline *CDKN1B*, especially if developed at an early age, might have suspected MEN4 form [77–79].

The type and distribution of *CDKN1B* mutations vary between MEN4 and sporadic cancers harboring somatic *CDKN1B* mutations [80]. To date, approximately half of the identified *CDKN1B* mutations in MEN4 are missense, and for several of these, the pathogenic role has been established by in vivo or in vitro functional studies [2, 68, 73, 81, 82]. In addition, frameshift and nonsense mutations resulting in p27 protein truncation, which tend to be more common in sporadic cancers, as well as variants in regulatory elements within the promoter or the 5′UTR region of the gene, have been described in 29% (12/41) and 17% (7/41) cases of MEN4, respectively [2, 74–76, 80].

The age of onset of disease in MEN4 patients appears to be later than in those with MEN1 [2]. Given the recent identification of the disease, the penetrance of MEN4-related endocrine tumors is still not well characterized. Similarly to MEN1, despite an autosomal dominant transmission, MEN4 is more common in women (57% vs. 70%, respectively) [2, 56, 74, 75, 83].

The most common endocrine disorder in MEN4 is PHPT, which is present in 68% of index cases (57% if considering all the described *CDKN1B*-mutated cases), and less than in the MEN1 syndrome (nearly 100%, see above) [2, 74, 75, 83]. The average age of onset of PHPT in MEN4, is significantly older than that of MEN1 (mean age 50-years vs. 25-years, respectively) [9]. Of note, the lowest age at diagnosis of PHPT was in a 15-year old subject [78]. Unlike with MEN1, PHPT is mostly caused by a single benign parathyroid adenoma (70%); only one case of carcinoma and atypical tumor have been reported [2, 74, 75, 83]. Interestingly, the risk of developing PHPT within the syndrome seems to be significantly higher in individuals harboring frameshift mutations compared with those with missense variants (66.7% vs. 39.3%, $P=0.029$) [2].

There are currently no specific guidelines on the management of PHPT in MEN4. The surgical approach in MEN4-related PHPT should be personalized, however the indications for surgery should be the same as that of MEN1. A close follow-up for disease recurrence is recommended. Unlike with MEN1, screening for PHPT in asymptomatic carriers with MEN4 should be started at the age of 15 years and not earlier [84].

The second most common manifestation in MEN4 is pituitary adenoma, affecting approximately 30% of cases [2]. The type of pituitary adenomas is predominantly functioning (76%), particularly corticotropinoma (38%), followed by somatotropinoma and prolactinoma (both 19%) [2, 74, 75, 83]. The age of diagnosis for these tumors also varies widely, from 5 to 79 years [2, 85, 86]. Pituitary adenomas generally appear to be less aggressive in MEN4 than in MEN1 patients, however their clinical course is heterogeneous due to the functioning status, size, potential invasive behavior [87]. The management of pituitary tumors in MEN4 does not differ from those of sporadic or other familial cases. Routine surveillance for the development of pituitary tumors in asymptomatic carriers should be performed on a case-by-case basis and following existing guidelines for other MENs [87].

GEP-NET tumors are much rarer than those of MEN1 (9% vs. 30–70%, respectively), half of them are gastrinomas and half are non-functioning NET [2, 9, 74, 75, 83]. No cases of insulin secreting tumors, glucagon or vasoactive intestinal polypeptide have been reported to date. The diagnosis and management of GEP-NETs in MEN4 are similar to that in MEN1 [9]. Other endocrine manifestations of MEN4 include single cases of bronchial, thymic and gastric carcinoid, three cases of breast cancer, five of thyroid, and two of prostate cancer. There have only been three cases of adrenal adenoma (two non-functioning and one cortisol-secreting), which instead is present in up to 40% of MEN1 cases [54, 68, 83, 88–90]. A single case of meningioma has also been described (1.6% of all *CDKN1B*-mutated cases), compared to 8% found in 74 MEN1 cases in an American prospective study, and 2.7% found in 106 MEN1 index cases in an Italian retrospective study [52, 54, 90, 91]. Other clinical manifestations, however, seem specific to MEN4, as they are absent in other MEN syndromes. These are reproductive organ cancers, namely testicular carcinoma and small cell carcinoma of the cervix, described in the son of the first described MEN4 family and in a patient with apparently sporadic MEN4 respectively [69, 92]. Renal carcinoma, although reported in only one case, was also considered a clinical manifestation specific to MEN4, however its association with the syndrome needs confirming in a wider case study [93].

The prognosis for patients with MEN4 is generally better than for MEN1 patients with a similar spectrum of endocrine tumors. Recurrence/persistence of PHPT after surgery is quite rare (25%), compared with the high rate recorded in MEN1 cases and pancreatic, bronchial and thymic malignant tumors, which are the leading cause of death in MEN1 subjects [2, 74, 75, 83].

The suspicion of a MEN4 diagnosis could arise in a proband or relatives within kindred exhibiting a MEN1-like clinical phenotype but testing negative for germline *MEN1* mutations. In such cases, referral for *CDKN1B* genotyping is advisable [2]. Genetic testing for CDKN1B could be considered in specific clinical settings, such as patients with parathyroid adenomas developing before the age of 30 years, multigland parathyroid involvement, multiple GEP-NETs, or pituitary adenoma presenting at a young age. Given the relatively low penetrance of neoplasms diagnosed in MEN4 compared with MEN1 [9], Halperin et al. has suggested that the diagnosis of MEN4 could also rely on at least one clinical hallmark (PHPT, pituitary adenomas, or GEP-NET), coupled with the identification of germline *CDKN1B* variants in the affected individual or one first-degree relative [2].

Multiple endocrine neoplasia type 2 (MEN2)

MEN2 (MIM#162300), formerly known as MEN2A, is an autosomal dominant hereditary syndrome [94]. MEN2 is classically associated with medullary thyroid carcinoma (MTC), pheochromocytoma (PHEO), and PHPT. Three other variants have been described namely MEN2 with cutaneous lichen amyloidosis, MEN2 with Hirschprung's disease, and familial medullary thyroid cancer [1]. The estimated prevalence is 1.3–2.4/100,000 [95].

Almost 100% of patients with MEN2 develop MTC, approximately 50% PHEO (Fig. 4) and 5%–35% PHPT [1, 96, 97]. A recent Danish nationwide study reported a 8% frequency of PHPT [97]. PHPT in patients with MEN2 is usually mild and associated with few or no symptoms [97, 98]. The diagnosis often occurs during the surgical procedure or follow-up for MTC [96, 99]. An international retrospective multicenter study of 1085 MEN2 index cases reported a very low prevalence (0.9%) of PHPT presenting as first manifestation with a median age at diagnosis of 34.5 years [100]. Median age at diagnosis of PHPT was lower (39 years) than the sporadic counterpart (63 years), but higher than in MEN1 (33 years) [13]. However, a recent single-center retrospective study found no difference in mean age at diagnosis of PHPT between MEN1 and MEN2 patients [101].

A higher incidence of parathyroid multiglandular involvement in MEN2 has been reported, although lower than in MEN1. However some studies have reported a significant incidence of solitary gland disease (27%–48%) [96, 97, 102].

MEN2 is due to germline gain-of-function mutations in the REarranged during Transfection (*RET*) proto-oncogene (Table 1). In particular, mutations at codon 634 are associated with the highest penetrance of PHPT, and mutations at codons 609, 611, 618 and 620 with a penetrance of between 1 and 12% [100, 102, 103].

At surgery, bilateral neck exploration to identify all abnormal parathyroid glands is advisable, and the current choice is the resection of only the enlarged gland(s) with intraoperative PTH monitoring [19, 98]. Prophylactic PTX at the time of thyroidectomy for MTC is not advisable given the low penetrance of PHPT [98]. Persistence and recurrence (23%) of PHPT have been reported in 5%–11% and in 9%–23% of cases, respectively [96, 97, 99, 104].

Multiple endocrine neoplasia, type 5

MEN5 is a recently proposed syndrome with an autosomal dominant pattern of inheritance that has extended the well-established inherited MENs. It is a familial pheochromocytomas/paraganglioma syndrome caused by germline variants in the *MAX* tumor suppressor gene [105–107]. A few subjects also develop functioning pituitary adenomas (prolactinomas or somatotropinomas) often occurring after pheochromocytomas and non-endocrine tumors, i.e., ganglioneuromas, ganglioneuroblastoma, and neuroblastomas [108] and renal oncocytoma and pancreatic NET [109, 110]. PHPT/hypercalcemia was reported in four patients, but there was a documented multiglandular parathyroid disease only in one [4, 106, 108]. The potential inclusion of parathyroid disease in the phenotype of this syndrome still remains to be established (Fig. 5).

Hyperparathyroidism-jaw tumor syndrome (HPT-JT)

HPT-JT (MIM#145001) is a rare disorder with an autosomal dominant inheritance. It has an estimated prevalence of 12% among patients suspected of having heritable forms of PHPT. Its full-blown expression is characterized by the combination of PHPT, tumor of the jaw bone, cysts and/or tumors of the kidney, and uterine tumors. The penetrance of the disease is variable and incomplete so that a few patients carrying Cell Division Cycle 73 (*CDC73)* mutations do not show the typical clinical manifestations of the disease throughout their life.

PHPT is the main manifestation of HPT-JT and is highly penetrant with all parathyroid glands at risk for tumor development in an asynchronous manner. PHPT is the initial

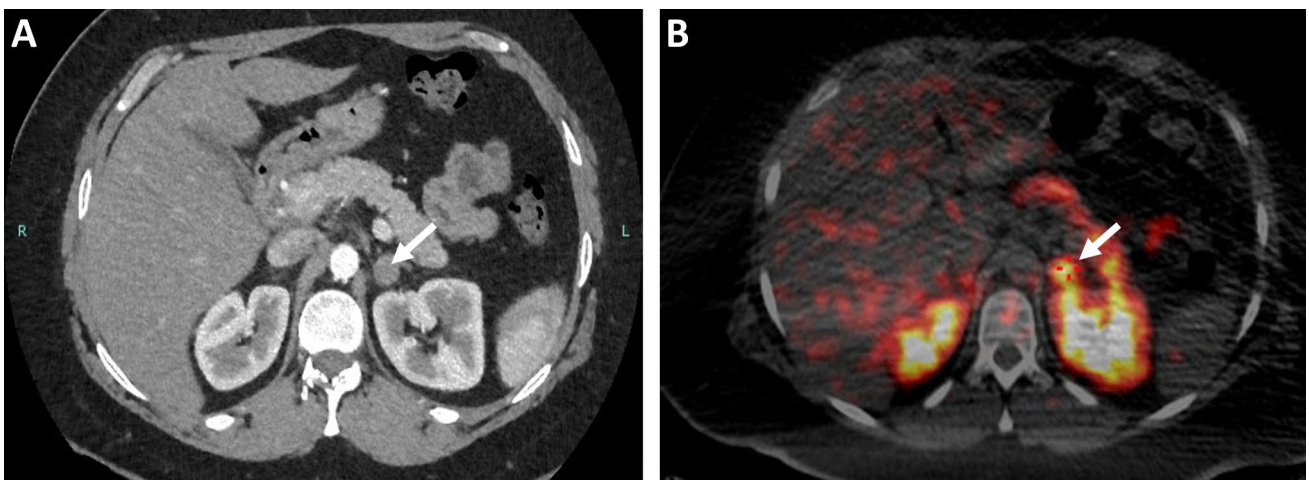

Fig. 4 (**A**) Contrast-enhanced computed tomography of the abdomen (transverse section) shows a 1.9-cm left adrenal lesion in a patient with MEN2 syndrome (arrow). (**B**) 18F-Dopa PET/CT scan of the abdomen shows intense uptake of the radiotracer in the left adrenal gland consistent with the diagnosis of pheochromocytoma (arrow)

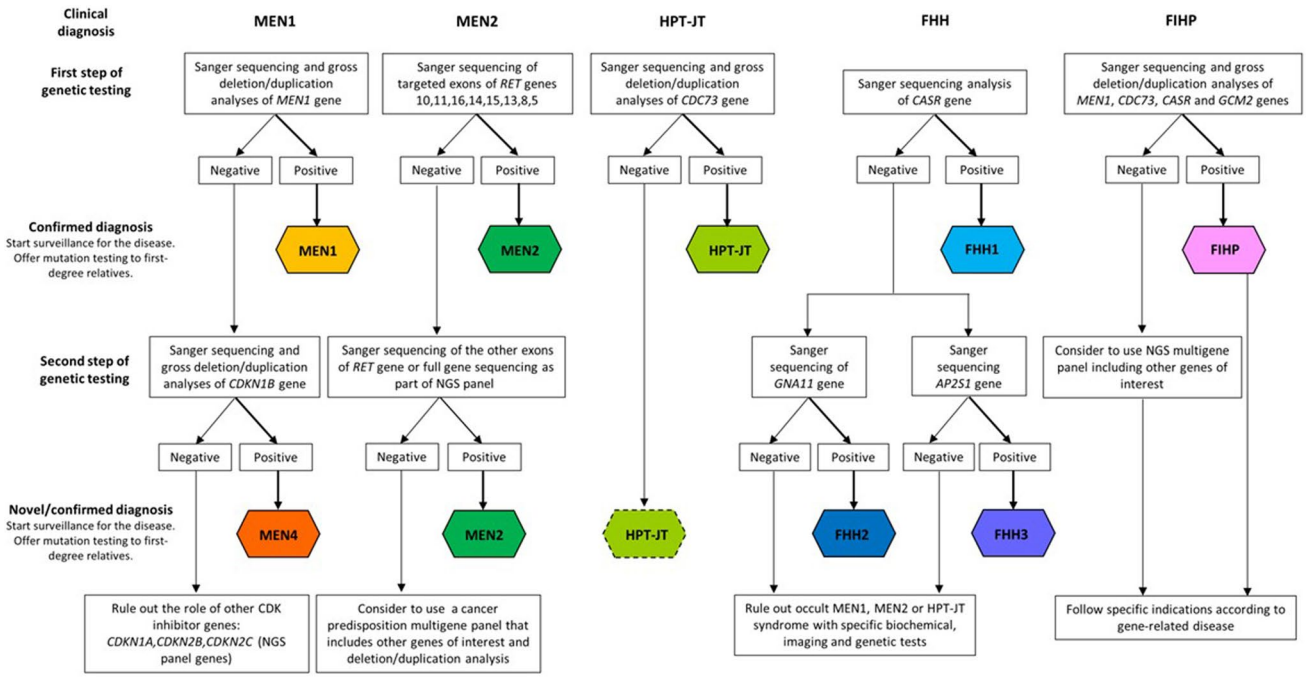

Fig. 5 Suggested decisional algorithm for genetic testing in patients with familial PHPT. The green dashed box indicates a provisional diagnosis of HPT-JT. *MEN1* multiple endocrine neoplasia type 1, *MEN2* multiple endocrine neoplasia type 2, *MEN4* multiple endocrine neoplasia type 4, *HPT-JT* hyperparathyroidism-jaw tumor syndrome, *FHH* familial hypocalciuric hypercalcemia, *FHH1* familial hypocalciuric hypercalcemia type 1, *FHH2* familial hypocalciuric hypercalcemia type 2, *FHH3* familial hypocalciuric hypercalcemia type 3, *FIHP* familial isolated hyperparathyroidism

manifestation of the disease in up to 85% of affected patients [1, 101, 111–113]. It rarely develops as early as the first decade of life, but typically presents in the second or third decade, or even beyond [111]. One of the recently published largest cohort of patients with HPT-JT syndrome, showed that in approximately one-third of patients, PHPT was diagnosed because of symptoms and surveillance of calcium levels due to family history, and in one-fifth on incidental finding of hypercalcemia by routine blood tests [111].

Single-gland parathyroid involvement (up to 86%) is more common than multiglandular disease (up to 54%) in HPT-JT patients compared to other forms of familial PHPT such as MEN1 [1, 114–116]. Parathyroid tumors can be macro- or microcystic, and, whereas most tumors are classified as adenomas, carcinomas (up to 31%) and atypical tumors (up to 4%) are overrepresented in HPT–JT [1, 111, 112].

PHPT is usually mild and/or asymptomatic, although it may be moderate/severe and symptomatic in cases of carcinoma or atypical tumor [117, 118]. Non-functioning parathyroid malignancy very rarely occurs in this setting [119].

The optimal surgical approach to PHPT has not yet been established, varying between bilateral or targeted neck exploration and extensive or limited PTX [26]. Early bilateral exploration is indicated because of the increased risk of parathyroid carcinoma [19]. Given the improvement in imaging techniques, some surgeons offer a focused approach with selective PTX in patients with preoperative concordant imaging studies, a single-gland involvement and without suspicion of parathyroid malignancy [1, 26, 111]. On the other hand, a subtotal PTX should be considered for patients with absent or discordant preoperative localization, because of the increased risk of multiglandular involvement and recurrent PHPT [26]. However, this latter approach may be not favored in view of the adverse consequences of lifelong hypoparathyroidism, the incomplete penetrance of parathyroid cancer in the syndrome, and the likelihood that close biochemical monitoring for recurrent PHPT will promote successful early resection or prevention of cancer. In fact, in a multicenter series Mehta et al. found that routine subtotal or total PTX conferred no benefit and likely leads to an increased risk of permanent hypoparathyroidism [115]. Irrespectively of the surgical approach, according to the literature, the risk of recurrence is as high as 36%, thus requiring lifelong regular PHPT biochemical and instrumental monitoring [1].

Jaw tumors are fibro-osseous lesions that typically involve the mandible or maxilla. and may develop in approximately 10–40% of patients with HPT-JT, and often prior to the third decade of life [1, 26, 111, 114]. Jaw tumors may be the first manifestation of HPT-JT in about 30% of cases and are

multiple in approximately 30% of patients [1]. The majority are ossifying fibromas, benign and slow growing tumors arising from the periodontal ligament in molar or premolar areas and most often appear to be radiographically radiolucent compared to the mixed radiolucent/radiopaque lesions in the sporadic variants [120]. These lesions are distinct from "brown tumors" typically occurring in severe PHPT (reviewed in Jha et al.) [1].

The management of cemento-ossifying fibromas requires complete surgical resection of the jaw based on the symptoms, size, and site of the lesion, along with bone reconstruction and grafting [1]. Patients with a history of jaw tumors should be monitored closely because of the possibility of recurrence.

HPT-JT is also associated with renal lesions in about 25%–30% of patients, with cystic disease being the most common [1, 111, 114]. Patients may also develop benign and malignant renal tumors such as adenomas, hamartomas, mixed epithelial stromal tumor (MEST), Wilms tumors, and carcinomas [1, 111, 112, 121].

Uterine tumors are the most common clinical feature and affect up to 90% of women [1, 111, 114, 122]. The majority are benign, namely endometrial hyperplasia, polyps, benign leiomyomas and adenofibromas, and, very rarely, adenosarcoma or tumors arising from the Mullerian duct system [1, 111, 114]. It was recently suggested that patients with HPT-JT harboring variants at the Met1 residue of parafibromin may have a predisposition to solid kidney tumors [111].

No treatment guidelines for uterine manifestations associated with HPT-JT syndrome are currently available. From a clinical perspective, patients with a uterine tumor should be managed by a gynecologist on a case-by-case basis.

Other manifestations potentially related to HPT-JT are thyroid, and colon carcinoma [123]. The question as to whether there is an association between these less common tumors and HPT-JT syndrome remains unclear.

Heterozygous germline mutation of the *CDC73* tumor suppressor gene, encoding parafibromin, is the major genetic alteration and is detectable in about 75% of classically affected families [124, 125]. Most patients harbor *CDC73* germline mutations in the coding regions [126]. Large deletions/ duplications of the entire gene or whole exon(s) are not uncommon, and account for as many as one-third of all mutations [127]. The remaining families may have other *CDC73* anomalies, such as mutations in the promoter, untranslated regions, or small noncoding mutations. The concomitant presence of a somatic mutation in tumor tissue from a patient with germline *CDC73* mutation is consistent with a biallelic inactivation and a putative tumor suppressor function in accordance with a classical two-hit tumor suppressor mechanism [1]. Loss of parafibromin expression at immunohistochemistry can be a marker of biallelic *CDC73* inactivation in parathyroid tumors [128]. About 20%-30% of cases with apparently sporadic parathyroid carcinoma [126, 129, 130] and 5%–10% of probands presenting with FIHP harbor a germline mutation of *CDC73* [131].

Surveillance

In view of the lack of published guidelines from a consensus of experts, according to the literature subjects who harbor a *CDC73* mutation should undergo to: (1) evaluation of fasting albumin-corrected and/or ionized calcium and plasma PTH for PHPT screening, possibly starting at the age of five, and neck ultrasound yearly; (2) panoramic jaw X-ray every five years; (3) imaging of the kidney by periodic renal ultrasound examination every 5 years, starting at the age of diagnosis; (4) regular gynecologic care, including transvaginal or abdominal ultrasound examination with possible further imaging studies if clinically indicated every 5 years [1, 112].

Familial non-syndromic primary hyperparathyroidism

Familial isolated hyperparathyroidism (FIHP)

FIHP (MIM#145000) is a rare hereditary form of PHPT. It is diagnosed if the patient and at least one first-degree relative have PHPT, in the absence of clinical or radiologic evidence of other endocrine tumors or disorders related to other PHPT syndromic diseases (Table 1) [1]. The diagnosis of FIHP at the time of patient referral might only be provisional. Clinicians thus need to re-evaluate the patient during the long follow-up periods, and be ready to change the diagnosis if one or more extraparathyroidal features occur.

FIHP is estimated to account for approximately 1% of all PHPT cases [131]. PHPT has a later onset and a slightly reduced penetrance compared to MEN1 (98% and 100% at 40 and 69 years of age, respectively [132]. However, the number of true FIHP cases might be overestimated due to a possible contamination of sporadic PHPT occurring in familial siblings by chance, or other familial PHPT disorders whose syndromic manifestations have not yet become evident [126, 131, 133]. Most of the studies involving the largest series of FIHP have reported a median of only two cases of PHPT in each kindred [131, 134–136].

No single driver gene is exclusively responsible for FIHP, since it is characterized by genetic heterogeneity, i.e., about 30% of kindreds carried germline mutations of genes, namely *MEN1* (25%), *CDC73* (7%–26%), or *CASR* (up to 18%) classically associated with other familial PHPT disorders, such as MEN1, HPT-JT syndromes, or FHH, respectively [60, 132, 137]. This would seem to

suggest that FIHP could represent an incomplete phenotype expression of such familial forms of PHPT (Table 1). Nevertheless, most FIHP kindreds lack germline mutations in known PHPT-susceptibility genes.

Using next-generation technologies, activating mutations of the *GCM2* gene, were identified in a subset (18%) of FIHP (Table 1) [138]. *GCM2* is a gene that is primarily expressed in the parathyroid glands and encodes a transcription factor required for their development [139]. *GCM2* mutations are mainly missense variants located in the C-terminal conserved inhibitory domain (CCID) of the encoded protein within the amino acid 379–395 [140].

The most recurrent *GCM2* variant (p.Tyr394Ser) was found to be prevalent in a large group of Ashkenazi Jewish (AJ) ancestry with FIHP or sporadic PHPT (41% and 27%, respectively) [141]. The presence of *GCM2* germline mutations in FIHP has been confirmed in later studies with a prevalence ranging from 4 to 20% [140, 142–146]. Although p.Tyr394Ser and other missense variants located in CCID were found to enhance, at various degree, the transcriptional activity of *GCM2* in functional assays, proposing for *GCM2* the role of proto-oncogene, some concerns about its involvement in the etiology of parathyroid tumors have been raised [140, 147]. Specifically, Vincze et al. suggested that *GCM2* might represent a modifier rather than a driver gene for PHPT considering the reduced penetrance of *GCM2* alterations in familial settings due to the high frequencies of altered alleles in the general population [145]. Furthermore, an in vivo study observed that the knock-in mouse model of the *Gcm2* variant p.Y392S (analogous to human p.Y394S) did not develop PHPT [148].

Minor rare variants in PHPT-related genes were *CDKN1B* and *CDKN2C* [68]. On the other hand, private or low-prevalence germline mutations in *CNGB3, FAT3 PARK2, HDAC4, ITPR2,* and *TBCE* genes identified in a whole exome sequencing study may indicate a predisposition to FIHP development [133, 144].

Management can vary according to the genetic status of the patients. FIHP linked to *MEN1* or *CDC73* mutation should be treated in the same way as MEN1 or HPT-JT, respectively [133]. A more severe clinical phenotype, i.e., a high rate of multigland disease and a low success rate of biochemical treatment, seems to be associated with *CDC73* and *GCM2* variant-positive FIHP cases [149]. Preoperative genetic screening could thus guide the surgeon to using a subtotal PTX to minimize the need for reoperation.

Familial hypocalciuric hypercalcemia (FHH)

FHH (MIM#145980) is an autosomal dominant disorder with a reported prevalence of 1.3/100,000 [150]. It is characterized by lifelong non-progressive mild to moderate hypercalcemia, mild hypermagnesemia, normal or mildly elevated PTH concentrations, and typically low urinary calcium excretion. Hypercalcemia is due to an increase in the parathyroid "set-point" for PTH release and possibly also to low renal calcium excretion [151]. FHH is genetically heterogeneous. It includes three distinct variants, termed FHH types 1–3, which are caused by loss-of-function mutations of genes involved in calcium signaling (i.e., *CASR)*, guanine nucleotide-binding protein subunit alpha- 11(*GNA11*), and adaptor protein complex-2 subunit sigma (*AP2S1*) genes, respectively [1, 152, 153].

From a clinical perspective, FHH has a similar biochemical phenotype to PHPT, but FHH does not require surgical treatment. Thus, some clinical and laboratory findings should alert the physician to the possibility of FHH at the time the patient presents for treatment. This suspicion has clinical benefits because an unnecessary PTX can be avoided. The degree of hypercalcemia does not differentiate between the two disorders due to the marked variation in calcium values in FHH, overlapping with that of PHPT [152, 154]. Patient medical charts should be checked to ascertain the presence of lifelong persistent hypercalcemia, which is a key trait of FHH. Serum magnesium may be mildly elevated or in the normal range, and does not help differentiate FHH from PHPT [155, 156]. PTH levels overlap between FHH and PHPT [156, 157]. However, PTH concentrations greater than 2-swsfold above the upper limit of reference range are suggestive of PHPT [157]. Vitamin D insufficiency should be treated with vitamin D supplements before interpreting PTH concentrations.

Urine calcium excretion should be evaluated using the calcium to creatinine clearance ratio (CCCR), which requires a concomitant blood sample and 24-h urinary collection [152]. A CCCR < 0.01 is seen in 80% to 95% of patients with FHH [158]. However, a CCCR < 0.01 can be present in up to 10% of patients with sporadic PHPT, highlighting the important role of genetic testing. In addition, some patients diagnosed as FHH based on the CCCR do not harbor an identifiable mutation in any of the known genes causing the disease.

An important feature that physicians need to consider is that CCCR has not been validated for diagnosing FHH in patients with renal impairment, vitamin D insufficiency, or pregnancy [152]. The use of thiazide diuretics can cause low CCCR values, as these drugs

stimulate proximal tubular sodium reabsorption resulting in enhanced proximal passive calcium transport. Thus, for a correct interpretation of CCCR values these drugs must have been discontinued for at least a week beforehand [152]. During pregnancy the CCCR may be of less help in diagnosing FHH given the absorptive hypercalciuria caused by placental and breast production of lactogen and PTH-related peptide (PTHrP), stimulating 1-alphahydroxylase activity and increasing levels of $1,25(OH)_2D_3$ [159].

FHH type 1 (FHH1)

FHH1 (MIM#145980) is the first and main type (approximately 65%) with an estimated genetic prevalence of 74.1/100,000 [160] and is generally asymptomatic, although some patients have been reported to have features such as chondrocalcinosis, osteoporosis, and nephrolithiasis [155].

FHH1 is caused by germline heterozygous loss-of-function mutations of *CASR,* which is located on chromosome 3-q21.1 (Table 1). Most (> 85%) mutations are missense, and the remaining nonsense, deletion, insertion and splice site mutations result in truncated CaSR protein [161]. Inactivating mutations affect all regions of the CaSR protein, although they are most common within the first 350 amino acid residues of the extracellular domain [161]. The offspring of FHH1 parents may carry homozygous or compound heterozygous *CASR* mutations that lead to NSHPT (see below). Some patients who have the clinical features of FHH1, but do not carry *CASR* mutations, may have autoimmune hypocalciuric hypercalcemia (AHH), which is associated with the presence of autoantibodies against the CaSR and also lymphocytic infiltration [162–165]. The hypercalcemia caused by AHH may be responsive to glucocorticoids or cinacalcet, a positive allosteric modulator of CaSR which targets its transmembrane domain [162–165],

FHH type 2 (FHH2)

FHH2 (MIM#145981) is the rarest type caused by germline heterozygous loss-of-function mutations of the *GNA11* gene on chromosome 19p13.3, which encodes the Gα11 protein (Table 1) [6]. To date, FHH2 has been reported in four probands [6, 166, 167]. Affected individuals display mild hypercalcemia (serum adjusted-calcium concentrations < 11.2 mg/dL), normal serum PTH levels, and normal or low urinary calcium excretion [6, 166, 167].

Mutations of the *GNA11* gene identified in FHH2 patients include three missense substitutions (p.Thr54Met, p.Leu135Gln and p.Phe220Ser), and an in-frame isoleucine deletion at residue 200 (p.Ile200del) located in various regions of the protein. Interestingly, the p.Phe220Ser mutation is located in the $G\alpha_{11}$ switch region and disrupts PLC-mediated signaling. In fact, in vitro and in vivo studies have shown that cinacalcet can rectify these signaling disturbances, and be used successfully to treat the patient's hypercalcemia [167].

FHH type 3 (FHH3)

FHH3 (MIM#600740) has an estimated prevalence of 7.8/100,000 and represents a more severe form of FHH [168]. It is characterized by significantly higher concentrations of both serum calcium and magnesium than FHH1, and by a lower calcium urine excretion [156, 168]. A relatively high proportion of patients have hypercalcemic symptoms, a lower bone mineral density, osteomalacia, recurrent pancreatitis or cognitive dysfunction [156, 168, 169].

FHH3 is caused by germline heterozygous loss-of-function mutations of the *AP2S1* gene on chromosome 19q13.3, which encodes the AP2σ, a subunit of a multimeric complex involved in clathrin-related endocytosis of G-protein coupled receptors (Table 1). It is notable that > 99% of affected individuals carry a *AP2S1* missense mutation affecting the Arg15 residue of the protein (e.g., p.Arg15Cys, p.Arg15His or p.Arg15Leu), except in one case affecting Met117 residue [6, 156, 170–174]. Patients carrying the p.Arg15Leu mutation have higher serum calcium, with an earlier age of presentation compared to probands with p.Arg15Cys or p.Arg15His mutations [168]. Crystal structure analyses have predicted that these Arg15 mutations disrupt an interaction between the AP2 complex and the intracellular region of the CaSR, thereby reducing the endocytosis of CaSR [168, 175].

Symptomatic hypercalcemic FHH3 patients may benefit from treatment with cinacalcet [167].

Neonatal severe primary hyperparathyroidism (NSHPT)

NSHPT (MIM*#239200*) is a rare autosomal recessive disorder with approximately 100 reported cases [176]. It is a potentially life-threatening disorder presenting as severe hypercalcemia (often > 20 mg/dL), a marked increase in PTH levels early in life with respiratory distress, rib cage deformities, hypotonia and bone demineralization causing fractures**,** marked parathyroid hyperplasia, and generally requires urgent total PTX [177, 178]. NSHP is most often caused by biallelic (homozygous or compound heterozygous) loss-of-function *CASR* mutations. Infrequently, NSHPT may be caused by sporadic heterozygous *CASR* mutations that have a dominant negative effect on CaSR function despite the presence of a wild-type allele [179].

Patients may be responsive to bisphosphonate and cinacalcet in order to manage the marked hypercalcemia and skeletal demineralization prior to PTX [1, 180–182]. In

NSHPT pairings (homozygosity vs. heterozygosity for pathogenic germline-inactivating *CASR* mutation(s)), the homozygotes show higher serum calcium and PTH levels than heterozygotes. Serum calcium levels > 20 mg/dL among NSHPT are frequent and detected only in homozygotes. This cutoff supports early and robust diagnosis of *CASR* dosage promoting an early and definitive total PTX in most homozygotes [176].

Genetic analysis of familial PHPT

DNA testing for predisposing mutations is helpful in clinical practice. In index cases or in individuals with a high suspicion of clinical MEN1, MEN2 or HPT-JT, the screening for *MEN1*, *RET* or *CDC73* gene mutations, respectively, is recommended [3, 162]. The search for germline *RET* mutations is of great importance for the clinical and surgical management of MEN2, especially for the treatment of MTC [79]. In addition, *RET* testing during childhood can provide preventive or curative thyroidectomy. The search for germline *CDC73* may be useful for managing HPT-JT, particularly for the early diagnosis of parathyroid carcinoma [183].

In individuals with suspicion of clinical MEN1 but mutation-negative for *MEN1* gene, screening for *CDKN1B* should be carried out for the diagnosis of MEN4 [69]. Notably, due to the relative late onset of MEN4 clinical manifestations, the genetic testing could be considered in patients even if the disease presents in the sixth decade of life. Genetic testing for *CDKN1B* could be considered in specific clinical settings as reported above.

Since FHH1 is the most frequent type of FHH, *CASR* mutation analysis is recommended for confirming the clinical diagnosis, particularly in sporadic cases or in those with inconclusive clinical evaluation of the kindred. In *CASR* mutation-negative cases, possible mutations in *GNA11* and *AP2S1* genes should be searched for in order to diagnose FHH2 and FHH3, respectively [152].

In cases with mutation-negative genetic testing for the disease-related genes and in index cases with FIHP, it is recommended to use a combination of targeted next-generation sequencing (NGS) analysis of a multi-gene panel (namely *MEN1, CDC73, CDKN1B, RET, CASR, CDKN2B, CDKN2C, CDKN1A, GNA11, AP2S1, GCM2*), with a multiple ligation-dependent probe amplification (MLPA) assay for the detection of large deletion/duplications, which are mostly identified in MEN1, HPT-JT and *CDC73*-associated FIHP [115].

Conclusions

The familial forms of PHPT show different levels of PHPT penetrance. However, PHPT generally represents the initial clinical manifestation of the disease, usually developing earlier and with multiglandular involvement compared to sporadic PHPT. Following the biochemical and clinical diagnosis of PHPT, early age of onset and/or a positive family history should alert the clinician to search for other tumors and manifestations associated with each specific syndrome.

Genetic testing for germline mutations in known genes involved in familial PHPT may help to: (1) diagnose or confirm the clinical diagnosis of the disease; (2) identify family members who may be asymptomatic carriers of the mutation; (3) relieve family members at risk from the burden of long-life surveillance in cases of a negative test; (4) access to preimplantation/prenatal diagnosis; (5) lead to screening for other extra-parathyroid syndrome-related tumors; and (6) offer the most appropriate surgical planning and surveillance.

Few driver genes are involved in hereditary forms of PHPT, some of them, i.e., *MEN1*, *CDC73*, *CASR,* are not exclusive to one syndrome, in fact may be altered in more than one disease. The clinical presentation of PHPT may differ in correlation with the altered gene. In particular, MEN2 shows the mildest and HPT-JT the most aggressive form of familial PHPT due to a more severe hypercalcemia and a higher prevalence of parathyroid carcinoma.

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Ethical approval No approval needed for this study.

Informed consent The authors received the permission from five patients followed-up in the outpatient clinic for anonymous use of their CT, MRI and PET scans for research purposes.

Research involving human participants and/or animals The present Review study did not involve research on human participants and/or animals.

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