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ORIGINAL PAPER

Outcome of Clinical Genetic Testing in Patients with Features Suggestive for Hereditary Predisposition to PTH-Mediated Hypercalcemia

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Abstract

Primary hyperparathyroidism (pHPT) is associated with familial syndromes such as multiple endocrine neoplasia type 1 (MEN1), 2A (MEN2A), MEN-like syndromes (*CDKN1B*), and *CDC73*-related disorder (hyperparathyroidism – jaw tumor syndrome (HPJT)). Familial hypocalciuric hypercalcemia (FHH) caused by *CASR* variants is an important differential diagnosis for pHPT. In order to evaluate the contribution of hereditary causes to pHPT in patients encountered in a specialized clinic, we conducted a retrospective study on patients with pHPT that underwent germline genetic testing. We evaluated 46 patients referred to a Cancer Genetics Clinic. Reasons for referral were young age (age < 40) for 29 patients (63%), multi-gland disease for 23 patients (50%), and a positive family history of pHPT for 11 patients (24%). All 46 patients underwent genetic evaluation. A total of 11 rare variants were found (*CASR* (4), *CDC73* (2), *MEN1* (2) *CDKN1B* (1), and *RET* (2)). One *MEN1* variant was classified as pathogenic, and all others were variants of uncertain significance (VUS). All patients with *CASR* variants had clinical features of FHH and were counselled against parathyroidectomy. Both patients with *CDC73* variants were counselled about recurrence of pHPT and parathyroid cancer. Neither of the *RET* variants were MEN2-associated. The *CDKN1B* variant was regarded as a true VUS and no action was taken. In this study, genetic testing impacted clinical care in 7 (15%) patients. We suggest that all patients < 40 years of age, with multi-gland disease, single gland disease refractory to treatment, and a positive family history for pHPT or associated tumors should be considered for genetic evaluation.

Keywords Primary hyperparathyroidism · Genetic predisposition syndromes · Familial hypocalciuric hypercalcemia · Germline variants

Introduction

Primary hyperparathyroidism (pHPT) is a common endocrine disorder characterized by elevated or inappropriately normal parathyroid hormone levels and hypercalcemia. Symptomatic pHPT is clinically characterized by the presence of low bone mineral density and kidney stones as well as neuropsychiatric (fatigue, impaired memory), gastrointestinal, and musculoskeletal complaints. Mild asymptomatic pHPT can be monitored and treated conservatively. Symptomatic pHPT is generally treated by parathyroidectomy. However, the surgical approach can differ significantly, depending on whether pHPT is sporadic or whether there is an underlying genetic disorder. Criteria for surgery are serum calcium > 1.0 mg/dl above upper limit of normal, bone mineral density T-score < 2.5 at any, or history of fragility fracture, or vertebral fracture, creatinine clearance < 60 ml/min or 24 urine calcium > 400 mg/day or increased stone risk by stone analysis or presence of nephrolithiasis, age ≤ 50, presence of symptoms, or potential for lack of reliable follow up or if patients desire treatment [1].

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In most instances, pHPT occurs sporadically (90–95%) and is most commonly caused by a benign single parathyroid adenoma (~ 80%), less commonly by multiple adenomas or multi-gland parathyroid hyperplasia (~ 15–20%), and rarely by parathyroid cancer [2]. However, 5–10% of all cases of pHPT arise in patients with genetic inherited syndromes, such as multiple endocrine neoplasia type 1(MEN1), multiple endocrine neoplasia type 2A (MEN2A), and *CDC73*-related disorder (hyperparathyroidism and jaw tumor syndrome (HPJT)) [2, 3]. A small proportion of patients have familial isolated pHPT (FIPH) with no identifiable germline predisposition [4]. The main parathyroid pathologies associated with hereditary syndromes are parathyroid hyperplasia (MEN1) and parathyroid adenomas (MEN2A, HPJTS). Parathyroid carcinoma is a very rare disease but can be observed in patients with germline pathogenic variants in *CDC73* [5, 6].

Identifying a genetic disorder provides the opportunity for concurrent transcervical thymectomy in MEN1 patients to identify ectopic parathyroid glands and possibly reducing the risk for thymic neuroendocrine tumors [7, 8]. It also allows for screening of other associated syndrome manifestations, such as pheochromocytoma and medullary thyroid cancer in (MEN2) and pituitary adenomas or neuroendocrine tumors of the foregut in (MEN1), and increases the suspicion for malignant disease in patients with germline variants in *CDC73* [9].

It is important to consider familial hypocalciuric hypercalcemia (FHH) in the differential diagnosis for pHPT. FHH is usually asymptomatic and caused by loss of function variants in the calcium sensing receptor (*CASR*) leading to elevated serum calcium levels, but low urine calcium excretion [10]. The diagnosis primarily relies on identifying a low urine calcium excretion, a positive family history of hypercalcemia, or failed parathyroidectomy. Therefore, it is imperative to exclude the diagnosis of FHH by performing genetic testing to prevent unnecessary and risk-bearing therapy.

In this study, we conducted a retrospective study of patients with pHPT that were referred for genetic evaluation to a tertiary center Cancer Genetics Clinic. We determined the frequency of variants detected by genetic testing, reviewed patient characteristics, and the impact of genetic testing on clinical management.

Materials and Methods

Patients with pHPT who had been referred to a Cancer Genetics Clinic at a large academic referral center between 2005 and 2017 were included in this retrospective study. Most patients had been referred by endocrine surgeons or endocrinologists. All patients had been seen by an endocrinologist and a genetic counselor. The patient's three generation pedigree (family history), laboratory testing, and treatment were reviewed. To prevent over identification of patients with a hereditary cause of pHPT, we excluded patients with a known hereditary cause of pHPT in their family (e.g., patients with a known MEN1 pathogenic variant in their family). We also excluded patients with a clinical diagnosis of MEN1 together with a supportive family history (e.g., patients with two of the three core manifestations plus family history of hyperparathyroidism). However, due to the low specificity of the clinical diagnosis of MEN1, we included patients that carried an additional diagnosis of neuroendocrine tumor or pituitary adenoma in addition to pHPT in our study. The study was approved by the Institutional Review Board of the University of Michigan (HUM00091004). All patients were evaluated and received genetic counselling and testing as part of clinical care.

Results

A total of 46 patients with pHPT without a family history of a pathogenic variant in any of the pHPT-predisposition genes were identified and evaluated (Table 1). Thirty-six patients were female and the mean age at time of diagnosis was 38.7 years. The mean serum calcium was 11.1 ± 1.02 mg/dl. The mean PTH was 148 ± 149 pg/ml. Reasons for referral were young age (age < 40) for 29 patients (63%), multigland disease in 23 patients (50%), a positive family history of pHPT or hypercalcemia for 11 patients (24%), and parathyroid cancer in 1 patient (2%) (Table 2). A total of 13 patients (28%) were referred for more than 1 reason. Although not the primary reason for referral, several patients had other manifestations suggestive of a hereditary condition. Five patients had pituitary tumors, including 3 prolactinomas, 1 growth hormone-secreting adenoma, and 1 non-functional adenoma. One patient had a pancreatic neuroendocrine tumor. Two patients had bone lesions, including a giant cell tumor of the jaw and an osteochondroma of the right pelvis. One patient had history of a pheochromocytoma and another patient had a history of a melanoma and an acute myeloid leukemia. Another patient had a diagnosis of primary aldosteronism with bilateral disease.

Interestingly, two patients carried other defined genetic conditions, including a female patient with a chromosome 15 microdeletion and a patient with a history of a medulloblastoma, macrocephaly, and multiple basal cell cancers with a pathogenic variant in *SUFU* (causing Gorlin syndrome), which was newly diagnosed during evaluation in our clinic. There is no known association between these genetic findings and pHPT.

All 46 patients underwent genetic testing. Nine patients had single or sequential gene testing (Supplementary Table 1), and thirty-seven patients were evaluated by Next Generation Sequencing (NGS) panels, containing the *CASR*, *MEN1*, *CDC73*, *RET*, and *CDKN1B* genes.

Table 1 Demographics, laboratory values, and surgical history of patients referred for genetic evaluation of pHPT

Female/male (*N*(%))	36 (78%)/10 (22%)
Age at diagnosis (mean ± SD)	38.7 + 15.1 years
Ca/Crea Cl ratio 0.01 mg/dl/< 0.01 mg/dl/UNK (*N*)	14/11/21
Urine calcium (mean ± SD)	250.60 (±144) mg/24HR
Urine calcium ≥ 70 mg/24 h/< 70 mg/24 h/UNK (*N*)	23/6/17
Serum calcium (mean ± SD)	11.14 ± 1.02 mg/dl
PTH (mean ± SD)	148.17 ± 149.90 pg/ml
Patients with parathyroidectomies	39
Patients with multiple parathyroidectomies	3
Total number of patients	46

A total of 11 rare variants were found (*CASR* (4), *CDC73* (2), *MEN1* (2), *CDKN1B* (1), and *RET* (2)). Only one *MEN1* variant was classified as pathogenic. All other variants were classified as variants of uncertain significance (VUS) by the testing laboratories (Table 3).

Seventeen patients were referred prior to surgery. Five of these patients, including three patients in whom variants of uncertain significance in *CASR* were identified, had laboratory constellations suggestive for FHH and were recommended not to undergo surgery. One patient had a non MEN2-associated variant in *RET* and proceeded with a parathyroidectomy. Twenty-nine patients underwent genetic testing after surgery. Two patients were found to have variants of uncertain significance in *CDC73*. One patient with prior parathyroidectomy and clinical features suggestive for FHH was found to have a variant of uncertain significance in *CASR*. Two patients were found to have variants in *MEN1*, one of which was classified as pathogenic. Two other patients were found to have variants of uncertain significance in *CDKN1B* and *RET* respectively. Either prior or post-testing parathyroidectomy was performed in a total of 39 (84.6%) patients, of which 3 (8%) had multiple surgeries. Multi-gland disease was found in 23 (58.9%) patients that underwent surgery (Table 2). Data on parathyroidectomy was unavailable for two patients that received presurgical testing.

All patients were provided with recommendations based on the genetic test results and available other clinical information. The patient with the pathogenic variant of *MEN1* c.1579C>T (p. Arg527X) also had a positive family history for pHPT, but no other MEN1 manifestation. Clinical surveillance for MEN1-associated manifestations was recommended for the patient and cascade genetic testing was recommended for the family. The other *MEN1* variant, c.1618C>T (p.Pro540Ser) was initially reported to be in accordance with a diagnosis of MEN1. The same variant has been reported in at least one other individual with a pituitary adenoma and two individuals without detailed clinical information, but has recently been reclassified as a benign variant in CLINVAR [11–13]. This patient had four gland hyperplasia and a subtotal parathyroidectomy but lacked any other manifestation of MEN1. In addition, review of her family history revealed several family members with kidney stones, but without pHPT. One brother had a diagnosis of ileal carcinoid, which is not a typical manifestation of MEN1-associated neuroendocrine tumors, which usually are found in the foregut. Therefore, we recommended treating this variant clinically as a benign variant and no further surveillance was recommended. Although the variants observed in *CASR* were classified as VUSs, all patients with *CASR* variants had features clinically suggestive of FHH (Table 4) and were counselled against parathyroidectomy. Both patients with *CDC73* VUSs

Table 2 Reason for referral, disease characteristics, and genetic testing in relation to surgery

Young age (< 40)	29/46 (63%)
≥ 2 glands affected	23/46 (50%)
Family history of pHPT or hypercalcemia	11/46 (24%)
Personal history of parathyroid cancer	1/46 (2%)
More than 1 reason for referral	13/46 (28%)
Pathology	
Number of parathyroidectomies	39/46 (84.6%)
Single gland disease	16/39 (41.1%)
Multi-gland disease	23/39 (58.9%)
Genetic testing	
Number of patients who underwent testing before surgery	17/46 (36.9%)
Number of patients who underwent testing and were recommended not to undergo surgery	5/17 (29.4%)

Table 3 Observed variants, variant characteristics, and clinical action

Gene	Variant	Lab interpretation	Allele frequency (gnomAD)	Supporting evidence	FH of pHPT	Clinical action
CASR						
	c.513C>A; p.Ser171Arg	VUS	Not present	FHH phenotype	+	FHH
	c.2332G>C; p.Gly778Arg	VUS	Not present	FHH phenotype	+	FHH
	c.505T>C; p.Ser169Pro	VUS	Not present	FHH phenotype	+	FHH
	c.206G>A; p.Arg69His	VUS	7.07×10^{-6}	FHH phenotype	+	FHH
MEN1						
	c.1579C>T; p.Arg527X	Pathogenic	Not present	Stopgain	+	MEN1
	c.1618C>T; p.Pro540Ser	Benign (historically pathogenic)	Not present	Reported [12, 13]	–	No action
CDKN1B						
	c.280C>T; p.Pro94Ser	VUS	2.84×10^{-5}		+	No action
RET						
	c.1597G>A; p.Gly533Ser	VUS	5.37×10^{-5}	Not MEN2A-related variant	–	Counselled on potential Hirschsprung's disease
	c.718G>C; p.Val240Leu	VUS	1.26×10^{-5}	Not MEN2A-related variant	–	Counselled on potential Hirschsprung's disease
CDC73						
	c.188T>C; p.Leu63Pro	VUS	Not present	Reported once [6, 16]	+	Counselled on risks and surveillance for CDC73-related disorder
	c.238-8G>A, IVS2-8G>A	VUS	not present	Cryptic splice site [14]	–	Counselled on risks and surveillance for CDC73-related disorder

were counselled about recurrence of pHPT and parathyroid cancer and recommended to have a baseline jaw radiograph as well as kidney ultrasound. The patient with the *CDC73* intronic variant, c.238-8G>A (IVS2-8G>A), was reported previously and this variant was clinically deemed to be likely pathogenic [14]. The *CDC73* c.188T>C (p.Leu63Pro) variant was clinically treated as likely pathogenic as the patient had a family history of pHPT in her mother and this variant has been reported in several other HPJT patients [6, 15, 16]. None of the *RET* variants was classical MEN2-associated gain of function mutations, but families were counselled about the possibility of Hirschsprung disease in their offspring [17]. The *CDKN1B* variant was regarded as a true VUS and no action was taken.

Discussion

Most cases of pHPT are sporadic. However, 5–10% of cases are part of familial syndromes [3]. Patients with hereditary pHPT are at higher risk for persistent and recurrent disease, ectopic supernumerary glands, and require further evaluation and monitoring [18]. In this study, we identified a total of 11/46 (24%) patients with rare variants, which impacted clinical care in 7/46 (15%) patients. When considering young patients (< 40), one in four patients had clinical genetic testing that led to altered clinical management. The results of our clinical experience are in accordance with other studies that systematically studied archived clinical samples or patients with a family history of pHPT [19, 20]. Changes in clinical care occurred in four patients with rare variants in *CASR*, two patients with rare variants in *CDC73*, and one patient with a pathogenic

Table 4 Demographics and laboratory characteristics of patients with FHH

Female	4/4 (100%)
Age at time of diagnosis (mean ± SD)	39.8 years
Family history of hypercalcemia	4/4 (100%)
Prior parathyroidectomy	1/4
H/o kidney stones	1/4
Urine calcium (mean ± SD)	24.5(±13.5) mg/dl
Serum calcium (mean ± SD)	10.9(±0.35) mg/dl
PTH (mean ± SD)	46.5(±20.6) pg/ml
Total number of patients	4

variant in *MEN1*. Our study mirrors the clinical experience in a specialized Cancer Genetics Clinic with an endocrine focus. Therefore, a limitation of our study is certainly the referral bias as endocrinologists and endocrine surgeons commonly refer patients with increased likelihood of an underlying genetic disorder. This referral bias is also evident in the fact that several patients had other manifestations suggestive of a hereditary disorder, a clinical diagnosis of MEN1, or other genetic abnormalities.

The majority of FHH is caused by loss of function variants in the calcium sensing receptor (*CASR*) leading to lifelong mildly elevated serum calcium levels and low urine calcium excretion [21]. Most importantly there is no therapy needed and patients need to be counselled against parathyroid surgery. An important additional genetic consideration for carriers of pathogenic *CASR* variants is that inheritance of two pathogenic alleles causes the recessive syndrome of severe neonatal hyperparathyroidism and patients with FHH should be counselled regarding the possibility of partner screening (at least with calcium level). *CASR* variants presented the largest group identified in our study population (8%). However, other genetic causes of FHH, such as germline variants in *AP2S1* or *GNA11*, have not been evaluated in our patients, therefore potentially underestimating the total proportion of FHH in our study population. Although all rare *CASR* variants observed in our study remain classified as VUSs, all patients had a classical clinical phenotype of FHH and we recommended against parathyroid surgeries. The detection of rare variants, not found in other population databases (e.g., EXAC), can be further suggestive for the diagnosis of FHH as *CASR* is fairly intolerant for missense mutations [22]. However, further research and data collection are needed to ultimately classify these *CASR* variants as pathogenic or benign.

CDC73-related disorder is a rare autosomal dominant disorder that manifests with parathyroid tumors, ossifying tumors of the jaw, and uterine tumors. Parathyroid tumors are most commonly the first clinical manifestation. *CDC73*-related disorder bears an increased risk for recurrent pHPT and is associated with parathyroid carcinoma in up to 10–15% of cases [9, 23]. Both patients with rare variants in *CDC73* in this study were clinically recommended to continue follow-up for a potential diagnosis of *CDC73*-related disorder. One variant was clinically treated as pathogenic as there is data available proving the generation of a cryptic splice site and loss of heterozygosity in parathyroid tumors [14]. The other variant had been previously observed in other patients and our patient had a suggestive family history [6, 16]. Furthermore, screening mainly consists of regular calcium and PTH measurements, which is a low-cost and low-morbidity procedure.

The patient with a true pathogenic variant in *MEN1* highlights the importance of identifying the diagnosis of a hereditary syndrome. pHPT is the most penetrant manifestation of MEN1, most commonly caused by 4-gland hyperplasia. MEN1-associated pHPT is treated with a near total parathyroidectomy and often concurrent thymectomy. Thymectomy aims to remove ectopic parathyroid tissue residing in the thymus and potentially reduces the risk for recurrence of pHPT and thymic carcinoids [7, 8, 18, 24]. The definitive diagnosis of MEN1 allows for screening for other associated syndromic manifestations, such as foregut neuroendocrine and pituitary tumors. In addition, family cascade testing can identify at-risk relatives that can benefit from screening for MEN1-related manifestations. The other rare *MEN1* variant had been reclassified to a VUS, significantly impacting clinical recommendations for patient and family, underscoring the importance of variant interpretation in consideration of clinical phenotype, family history, and published evidence. This exemplifies the necessity to review genetic testing results gained in the era predating large databases.

CDKN1B variants have been described in MEN1-like syndromes, characterized by pHPT caused by parathyroid adenomas or hyperplasia, duodenal tumors, and pituitary tumors (GH and ACTH secreting) [25]. Only 9 different rare germline variants have been identified to date and our understanding about this syndrome is very limited [26]. Therefore, clinically there is still a need for caution in basing further screening on observed rare variants.

We did not detect any classical MEN2-associated *RET* variants, which is in accordance with the fact that pHPT is almost never the initial manifestation of MEN2. However, we identified two non-MEN2-related rare *RET* variants incidentally. Some of these variants might increase the risk for Hirschsprung disease and counselling needs to be constructed accordingly [17].

Our study highlights the difficulty in clinical decision-making in the absence of availability of functional data on all variants. In several of the presented cases, the identified variants were deemed to be involved in the underlying pathology, despite the discordant laboratory classification of VUS. Family cascade testing or at least clinical evaluation (in the case of *CASR* variants) was recommended for these patients' relatives.

In conclusion, we confirm that there is a high clinical value in considering genetic testing for young patients (< 40 years), those with multi-gland or recurrent disease, low 24-h urine calcium, a positive family history suggestive for familial pHPT, or other syndrome-related manifestations and particularly for those patients with more than one of the aforementioned characteristics. Genetic testing of selected pHPT patients provides important information, impacting clinical management and surgical planning, provides the unique opportunity for syndrome-specific surveillance and family cascade screening to identify family members at risk.

Authors' Contribution Study design: TE and SK. Study conduct: TE and SK. Data collection: SK. Data analysis: TE and SK. Data interpretation:

TE, SK, JO, MFJ. Drafting manuscript: SK and TE. Revising manuscript content: JO, MFJ, GTC, BSM, DTH, TE. Approving final version of manuscript: JO, MFJ, GTC, BSM, DTH, TE. TE and SK take responsibility for the integrity of the data analysis.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval The study was approved by the Institutional Review Board of the University of Michigan (HUM00091004).

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