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Familial Isolated Primary Hyperparathyroidism associated with germline *GCM2* mutations is more aggressive and has lesser rate of biochemical cure

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Abstract

Background—Hereditary primary hyperparathyroidism (PHPT) may be syndromic or nonsyndromic (familial isolated hyperparathyroidism (FIHP)). Recently, germline activating mutations in the *GCM2* gene were identified in a subset of FIHP. This study examined the clinical and biochemical characteristics and the treatment outcomes of *GCM2* mutation–positive FIHP as compared to sporadic PHPT.

Methods—We performed a retrospective analysis of clinical features, parathyroid pathology, and operative outcomes in 18 patients with *GCM2* germline mutations and 457 patients with sporadic PHPT.

Results—Age at diagnosis, sex distribution, race/ethnicity, and preoperative serum calcium concentrations were similar between the two groups. The preoperative serum levels of intact PTH was greater in patients with *GCM2*-associated PHPT (239 ± 394 vs. 136 ± 113, p=0.005) as we3erem rates of multigland disease and parathyroid carcinoma were in the GCM2 group (78% vs. 14.3%, p<0.001 and 5% vs. 0%, p=0.04, respectively), but the biochemical cure rate was less in the GCM2 group (86% vs. 99%, p<0.001).

Conclusions—*GCM2*-associated PHPT patients have greater preoperative PTH levels, a greater rate of multigland disease, a lesser rate of biochemical cure, and a substantial risk of parathyroid carcinoma. Knowledge of these clinical characteristics could optimize the surgical management of *GCM2*-associated FIHP.

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Keywords

familial isolated hyperparathyroidism; *GCM2*; parathyroid; parathyroid cancer; parathyroidectomy; sporadic

Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia and is a relatively common endocrine disorder with an estimated prevalence of one to seven cases per 1,000 persons (1–3). The incidence peaks in the seventh decade of life, and it is more common in postmenopausal women, with a prevalence of up to 3.2% (4). PHPT is due to a parathyroid neoplasm(s), which hypersecretes PTH. PHPT may be sporadic or inherited. Inherited PHPT may be syndromic, such as in multiple endocrine neoplasia types 1, 2, and 4 (MEN1, 2, 4) and the hyperparathyroidism jaw-tumor syndrome (HPT-JT), or PHPT is nonsyndromic, which is also referred to as familial, isolated primary hyperparathyroidism (FIHP) (5). Approximately 10% of PHPT is hereditary. Patients with syndromic PHPT usually present at a younger age, are more likely to have multigland disease and have lesser rates of cure of the hyperparathyroidism, greater rates of recurrent PHPT, and greater risk of parathyroid carcinoma, such as in HPT-JT as compared to sporadic PHPT (5–10).

Genetic studies have identified several susceptibility genes responsible for syndromic PHPT. MEN1 is the most common familial form of PHPT, with 2% to 4% of PHPT patients carrying a germline mutation in the tumor suppressor gene, *MEN1*, located on chromosome 11q13. Almost all MEN1 patients will develop PHPT by the age of 50 and are more likely to have multigland disease. MEN2 is due to a germline mutation in the *RET* proto-oncogene. Nearly all patients with MEN2 develop medullary thyroid carcinoma by the third decade of life, with patients with MEN2 being at risk of pheochromocytomas (50% penetrance) and PHPT (20% penetrance). There is a genotype-phenotype association in MEN2, with a mutation in codon 634 being associated most commonly with PHPT (3). HPT-JT is a rare, autosomal-dominant disorder due to a germline mutation in *CDC73* and has an incomplete penetrance and variable expression (6). PHPT occurs in approximately 90% of carriers, and ossifying fibromas of the mandible and/or maxilla occur in 35% of patients (5). HPT-JT is more aggressive with frequent multigland involvement, increased risk of persistent/recurrent disease, and a gtreater frequency of parathyroid carcinoma in up to 38% of patients (6).

FIHP is an autosomal-dominant disorder characterized by the absence of a non-parathyroid clinical manifestation of known syndromic PHPT. Some patients with FIHP may represent variants of other syndromic PHPT with incomplete penetrance, because germline mutations in *MEN1*, *CDC73*, and *CASR* genes had been reported in some patients with FIHP (11, 12). Recently, Guan and colleagues identified *GCM2* germline activation mutations in seven of 40 (18%) kindreds with FIHP (13). Thus, activating germline mutations in *GCM2* could be one of the more common causes of FIHP and nonsyndromic PHPT.

The aim of our study was to evaluate the clinical, biochemical, and pathologic characteristics as well as outcomes after parathyroidectomy in *GCM2*-associated PHPT as compared to patients with sporadic PHPT.

Methods and Subjects

Patients were enrolled into clinical protocols after providing written informed consent. These protocols were approved by the Institutional Review Boards of the National Institute of Diabetes and Digestive and Kidney Diseases and the National Cancer Institute.

Patients with no family history of PHPT based on a family history questionnaire were considered to have sporadic PHPT (n= 457). Patients with PHPT were diagnosed with FIHP (n= 18) when they had first degree relative(s) with PHPT in the absence of sufficient clinical, radiologic, or biochemical evidence for diagnoses of MEN1, MEN2, HPT-JT, or familial hypocalciuric hypercalcemia (FHH). Index cases from FIHP kindreds had negative genetic testing results for germline mutations in *MEN1*, *CDC73*, or *CASR* and for duplication and deletions in *MEN1* and *CDC73*; these genomic evaluations were performed in a clinical laboratory improvement amendments (CLIA)–certified laboratory. The *GCM2* mutations were identified previously by whole-exome sequencing and Sanger sequencing (13).

Baseline demographic and biochemical characteristics, including age, sex, serum calcium and intact PTH levels, and type and extent of operative intervention and postoperative data were evaluated and compared between patients with *GCM2*-associated FIHP and sporadic PHPT. Biochemical cure was defined as the presence of documented normal serum calcium levels for at least two years of postoperative follow-up.

Statistical Analysis

Dichotomous data were analyzed using the chi-square test, and continuous variables were analyzed using a two-sample t test. Data are presented as mean (± standard deviation) or median (range). For nonparametric, continuous variables, the Kruskal-Wallis test was used to determine statistical significance between variables. If found to be statistically significant, a Mann-Whitney U test was then used for two-group comparison. All p values reported are two-tailed, and a p value < 0.05 was considered statistically significant.

Results

Eighteen patients (12 females and 6 males) had a germline *GCM2*-activating mutation and were diagnosed with PHPT at 17 to 79 years of age. Summarized in Table 1 are the baseline demographics of *GCM2* mutation carriers and patients with sporadic PHPT. There was a similar sex distribution (female: 67% vs. 78.4%; p= 0.31), age at diagnosis (54 ± 16 vs. 59.2 ± 13.5 years; p= 0.105), and race/ethnicity (p= 0.363) between *GCM2* mutation carriers and patients with sporadic PHPT (Table 1). The serum calcium levels were similar between *GCM2* mutation carriers and patients with sporadic PHPT, respectively (Ca: 2.85 ± 0.29 vs. 2.76 ± 0.32; p= 0.183); while the preoperative serum intact PTH level was greater in *GCM2* mutation carriers as compared to patients with sporadic (239 ± 394 vs. 136 ± 113, respectively, p= 0.005).

All *GCM2* mutation carrier patients underwent initial, bilateral neck exploration; this rate of bilateral exploration was significantly greater compared to patients with sporadic PHPT. The multigland disease rate was much greater in *GCM2* mutation carriers compared to patients

with sporadic PHPT (78% vs. 14.3%,, p< 0.001) (Table 2). One patient in the *GCM2* mutation carrier group had a parathyroid carcinoma (5% vs. 0%, p= 0.04) (Table 2). The *GCM2* variant mutation had a lesser biochemical cure rate after parathyroidectomy compared to the sporadic group (87%; vs. 99.1%, p< 0.001). When we evaluated the operative outcomes of patients with *GCM2*-associated PHPT based on whether they were the index case or not, we found non-index cases (i.e., those family members screened for PHPT) had a greater rate of biochemical cure and required less reoperative interventions (Figure 1).

Discussion

FIHP typically has an autosomal-dominant pattern of inheritance. Recently, two different germline, *GCM2*-activating mutations were discovered in a subset of kindreds with FIHP and may account for a substantial fraction of FIHP (13). The diagnosis of FIHP is based on a diagnosis of exclusion and requires the presence of at least two, first-degree relatives with PHPT and no evidence of other non-parathyroid clinical features of syndromic PHPT (MEN1, MEN2, and HPT-JT). These criteria, however, may not exclude the chance occurrence of two, first-degree relatives having non-hereditary PHPT, given that PHPT is common in the general population. Thus, the presence of activating germline mutations in the *GCM2* could have important clinical ramifications in kindreds with FIHP in regard to screening, surveillance, and treatment. Thus, to determine the clinical characteristics of *GCM2*-associated FIHP that may influence the management of PHPT, we compared *GCM2*-activation mutation carriers to patients with sporadic PHPT. We found a significantly greater rate of multigland disease and a case of parathyroid carcinoma on pathology as well as a lesser rate of biochemical cure in the *GCM2* mutation.

The onset of hypercalcemia in syndromic PHPT patients occurs most commonly in the second and third decades of life. PHPT in patients with MEN1 is the earliest and most common manifestation, occurring in 90% of patients between 20 and 25 years of age (11). In MEN2, PHPT usually presents at an average age of 38 years (14–16). HPT-JT is diagnosed at a median age of 27 to 31 years of age (6). Compared to the sporadic PHPT in our study cohort, *GCM2*-associated FIHP patients had a similar age at diagnosis (54 years), with the earliest age at onset being 17 years. The early age of diagnosis in syndromic PHPT could also be due to prospective screening for hypercalcemia once a family member has been identified. In kindreds with *GCM2*-associated FIHP, screening should be considered starting at 17 years of age in *GCM2* variant carriers.

Contrary to our expectation of having an even sex distribution in patients with *GCM2*-associated PHPT, we found a predominance of females affected (12 of 18), which is similar to the sex distribution of sporadic PHPT. The small number of patients with *GCM2*-associated PHPT, along with the fact that some family members may not have been investigated yet or may have died before PHPT symptoms developed or PHPT was diagnosed, may explain the sex distribution in our study cohort. Future screening and surveillance studies of all at-risk family members is needed to ascertain whether there is a sex difference in *GCM2*-associated PHPT manifestation.

One of the cardinal features of inherited syndromic and nonsyndromic endocrine neoplasm is the presence of multiplicity of tumors. Indeed, we observed a rate of multigland disease in *GCM2*-associated PHPT that was significantly greater than sporadic cases of PHPT. Furthermore, one patient had parathyroid carcinoma, which is rare in sporadic PHPT but common in HPT-JT (6, 17). These findings have important implications for management of patients, suggesting that patients with *GCM2*-associated PHPT may require routine, bilateral neck exploration and identification of all parathyroid glands to prevent failure of parathyroidectomy by overlooking the presence of multigland disease. Knowledge that these patients are at risk of parathyroid carcinoma could allow a more cognizant considertion of the possibility of a parathyroid carcinoma intraoperatively and closer long-term follow up (6, 9).

Patients with *GCM2*-associated PHPT had a significantly lesser rate of biochemical cure and required multiple reoperations. This lesser cure rate is similar to that observed in other inherited PHPT, such as MEN1 and HPT-JT, during long-term follow up (6, 9, 18). The high recurrence rate might be explained by the observation that GCM2 is a transcription factor expressed specifically in the parathyroid glands and is critical in the development of parathyroid glands (19). The seven cases of recurrent/persistent PHPT in in carriers of germline *GCM2*-activation mutations highlights the lesser rate of biochemical cure in this disorder—indeed, 16 operative interventions were required, with many of these patients having multiple reoperations. This observation is important, because reoperations are associated with an increased risk of complications. Thus, preoperative knowledge of the carrier status in patients with FIHP who have a germline, *GCM2*-activating mutation should be performed before the initial operation to not only provide the best chance for definitive treatment but also to minimize the need for reoperation and its associated morbidity.

The current study has several limitations. Although patients with sporadic PHPT had no family history of PHPT and not all had genetic testing, some cases may be *de novo* cases of inherited PHPT. We, however, believe this would represent a very low number of cases. The greater rate of parathyroid carcinoma in *GCM2* mutation–positive kindreds we report is also based on only one of 18 patients (Table 2) and in a patient who lacked documented distant metastases (17). Thus, more study and surveillance of *GCM2* mutation–positive kindreds will be necessary to confirm this association. The retrospective study design does not allow us to completely ascertain disease characteristic as well as some data elements, such as metabolic complications associated with PHPT, the rationale for the initial surgical decision-making, and the accuracy of preoperative localizing studies in *GCM2*-associated PHPT to help distinguish between single and multigland disease.

In summary, patients with FIHP due to germline *GCM2*-activating mutation have greater preoperative serum PTH levels, a greater rate of multigland disease, a lesser rate of biochemical cure, and an apparent increased risk of parathyroid carcinoma. Knowledge of these clinical characteristics along with preoperative knowledge of the *GCM2*-activating mutation status could lead to more optimal surgical management of *GCM2* mutation–associated FIHP.

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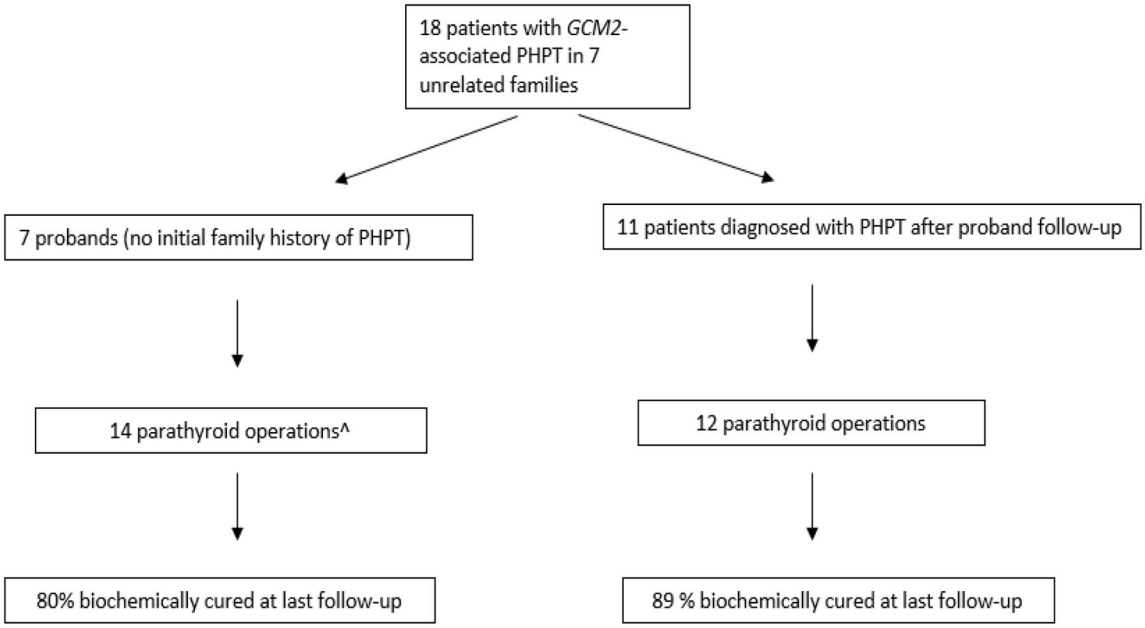

Figure 1.

Number of parathyroidectomy and surgical outcomes based on method of diagnosis in *GCM2*-associated primary hyperparathyroidism (PHPT). ^Proband had a significantly greater rate of requiring a reoperative operative intervention (p= 0.0357 on Fisher's Exact test).

Table 1

Baseline demographic, clinical, and biochemical characteristic of study cohort.

Variables	GCM2	Sporadic^	p-Value
Number	18	457	NA
Families with two affected members	6		
Families with six affected members	1		
Family History (%)	61	-	
Sex			
Female (%)	66.7	78.3	0.30
Age			
Mean age at diagnosis (years) ± SD	54±16	59.2 ±13.5	0.10
Race/Ethnicity			
Caucasian (%)	100	81.3	0.36
African American (%)	-	9.5	
Asian (%)	-	5.2	
Hispanic (%)	-	3.4	
Multiracial (%)	-	0.7	
Laboratory values			
Serum calcium at diagnosis (mmol/l) ± SD	2.85 ± 0.29	2.76 ± 0.32	0.18
Serum intact PTH at diagnosis (pg/ml) ± SD	238 ± 394	136 ± 113	0.005

^Based on no family history of primary hyperparathyroidism as ascertained on a family history questionnaire administered preoperatively.

NA=not applicable, SD=standard deviation.

Table 2

Pathology and parathyroidectomy outcome in study cohort.

Variables	GCM2	Sporadic	p-Value
Patient number	18	457	
Number of parathyroid operations	26	461	
Operative Approach			
Focused PTX (%)	-	38.7	
Unilateral exploration (%)	-	28.3	<0.001
Bilateral exploration (%)	100	32.9	
Mean size of largest parathyroid gland removed (cm)			
Mean number of excised glands ± SD	2.5 ± 0.9	1.25 ± 0.5	0.003
Median Number of parathyroid tumor			
Single (%)	22	85.7	<0.001
MGD (%) [^]	78	14.3	<0.001
Parathyroid Carcinoma (%)	One patient	-	0.04
Parathyroidectomy outcome			
Biochemically cured (%)	86	99.1	<0.001

[^] MGD=multigland disease

SD=standard deviation.

PTX=Parathyroidectomy