

Familial isolated primary hyperparathyroidism caused by mutations of the *MEN1* gene

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SUMMARY

Background Familial isolated primary hyperparathyroidism (FIHP) is an autosomal dominant disorder that can represent an early stage of either the multiple endocrine neoplasia type 1 (MEN1) or hyperparathyroidism-jaw tumor (HPT-JT) syndromes; alternatively, the condition can be caused by an allelic variant of *MEN1* or *HRPT2* (hyperparathyroidism 2 gene), or caused by a distinct entity involving another locus. We have explored these possibilities in a patient with primary hyperparathyroidism, whose mother had a history of renal calculi and primary hyperparathyroidism.

Investigations Serum biochemistry and radiological investigations for primary hyperparathyroidism, MEN1 and HPT-JT, and genetic testing for *MEN1* and *HRPT2* mutations were undertaken.

Diagnosis FIHP with primary hyperparathyroidism as the sole endocrinopathy due to a previously unreported heterozygous missense germline *MEN1* mutation, Tyr351Asn. In addition, another unreported heterozygous missense germline *MEN1* mutation, Trp220Leu, was identified in an unrelated male patient with FIHP, whose mother and sister also had primary hyperparathyroidism. DNA from a parathyroid tumor from the sister revealed a loss of heterozygosity in which the mutant allele was retained. This is consistent with Knudson's 'two-hit' model of hereditary cancer and a tumor suppressor role for *MEN1* in FIHP.

Management The patient underwent parathyroidectomy and has remained normocalcemic over a follow-up period of 6 years. The other four patients have remained normocalcemic for a follow-up period of 4–15 years following parathyroidectomy. None has developed abnormalities of the MEN1 syndrome, providing further support that FIHP is a distinct genetic variant of the MEN1 syndrome.

KEYWORDS endocrine neoplasia, hypercalcemia, parathyroid hormone

CME

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THE CASE

A 43-year-old man (individual II.1 in family 1, Figure 1A) presented with lethargy, polyuria, polydipsia and constipation. Apart from mild asthma, he had no history of previous illnesses and he was not taking any medication. Physical examination of the patient was unremarkable. Investigations revealed elevated serum calcium and parathyroid hormone (PTH) concentrations as well as a urinary calcium:creatinine clearance ratio that was greater than 0.01 (Table 1). He underwent a parathyroidectomy with excision of a single parathyroid adenoma and post-operatively his symptoms and hypercalcemia resolved. Two years later the symptoms as well as the hypercalcemia recurred and at that time localization studies with MRI, sestamibi imaging and parathyroid venous sampling identified a mediastinal parathyroid adenoma. This was excised and the patient remains well and normocalcemic 6 years post-surgery.

His mother (individual I.2 in family 1, Figure 1A) had a history of renal calculi associated with primary hyperparathyroidism that was treated by parathyroidectomy when she was 64 years old (Table 1). At the age of 77 years she developed recurrent hypercalcemia and underwent a neck exploration, which revealed a parathyroid adenoma. This was excised and she remains normocalcemic 6 years post-surgery.

Further investigations were performed in both patients to exclude the presence of other tumors associated with the multiple endocrine neoplasia type 1 (MEN1) syndrome. Serum biochemistry investigations for the development of anterior pituitary tumors (e.g. serum prolactin and insulin-like growth factor I) and pancreatic islet cell tumors (e.g. fasting gastrin, insulin and glucose, vasoactive intestinal peptide, pancreatic polypeptide, glucagon, and chromogranin A) have revealed no abnormalities during the period of follow-up. MRI scans of the pituitary

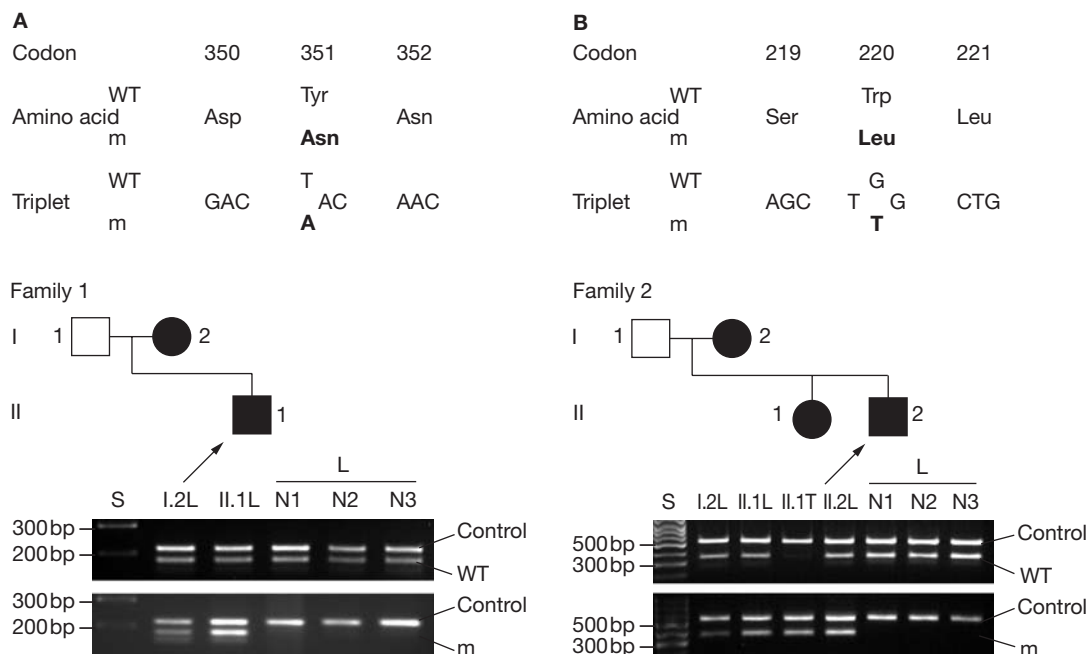


Figure 1 DNA sequence analysis of *MEN1* in two kindreds with FIHP. Each proband is indicated by the arrow. **(A)** In family 1 a heterozygous missense mutation in exon 8 caused by a T>A transversion at codon 351 was detected using leucocyte DNA (I.2L and II.1L). This altered the WT sequence TAC, encoding tyrosine (Tyr) to the m sequence AAC, encoding asparagine (Asn). **(B)** In family 2 a heterozygous missense mutation in exon 4 caused by a G>T transversion at codon 220 was detected using leucocyte DNA. This altered the WT sequence TGG, encoding tryptophan (Trp) to the m sequence TTG, encoding leucine (Leu). ARMS-PCR was used to confirm the presence of the WT and m sequences in leucocyte DNA. All the affected individuals were heterozygous which means that they had WT and m bands, whereas all of 55 unrelated normal individuals (N1–N3 shown) were homozygous for the WT band, and none had the m band. Moreover, ARMS-PCR analysis of parathyroid tumor DNA (II.1T) from individual II.1 in family 2 revealed that the tumor had a loss of the WT allele but had retained the mutant allele, in keeping with Knudson’s two hit hypothesis.⁷ A control primer employed in both reactions confirmed that the ARMS-PCR was amplifying correctly (upper band on both gels). A 1 kb DNA size marker (S) is used to denote the size of the ARMS-PCR bands. The Trp220Leu and Tyr351Asn *MEN1* missense mutations are both located in Jun-D-binding domains of the menin protein and are therefore likely to disrupt protein function by impairing the interaction between menin and Jun-D¹ (See Supplementary Figure 2). Abbreviations: ARMS-PCR, amplification refractory mutation system polymerase chain reaction; FIHP, familial isolated primary hyperparathyroidism; L, leucocyte DNA; m, mutant; *MEN1*, multiple endocrine neoplasia type 1 gene; WT, wild-type.

and abdomen have not revealed any evidence of pituitary tumors, pancreatic tumors or adrenal tumors. In addition, neither patient has developed lipomas, facial angiofibromas or collagenomas, which can occur in association with *MEN1*.¹

Both patients also underwent investigations to exclude other tumors associated with the hyperparathyroidism-jaw tumor (HPT-JT) syndrome or with *MEN2*. An orthopantomogram did not reveal any abnormalities suggestive of ossifying fibromas that normally occur in HPT-JT,² and plasma calcitonin levels were not elevated, which suggests that the patients did not have the medullary thyroid carcinomas that would normally occur in *MEN2*.³

DNA sequence analysis of *MEN1* was undertaken (Supplementary Figure 1) after informed consent had been obtained using nationally approved guidelines. This analysis revealed a T>A transversion at codon 351 in exon 8, which altered the wild-type codon, TAC, encoding a tyrosine (Tyr) residue, to a mutant codon, AAC, encoding an asparagine (Asn) residue (Figure 1). This missense, Tyr351Asn, mutation was confirmed by amplification refractory mutation system polymerase chain reaction (ARMS-PCR; Figure 1). Familial isolated hyperparathyroidism (FIHP) in this kindred is, thus, due to a previously unreported missense mutation of *MEN1*.

Table 1 Biochemical and pathological findings in five members from two families affected with familial isolated hyperparathyroidism (FIHP).

Family (mutation)	Patient	Sex	Age at diagnosis (years)	Follow-up (years)	Corrected serum calcium levels at diagnosis (mmol/l) ^a	Serum parathyroid hormone levels at diagnosis (pmol/l) ^b	24 h urine calcium:creatinine clearance ratio ^c	Number of parathyroid tumors; histology
Family 1 (Tyr351Asn)	I.2	Female	64	19	3.60	49.6	Not known	One; adenoma
	II.1	Male	43	8	2.71	11.9	0.017	One; adenoma
Family 2 (Trp220Leu)	I.2	Female	67	6	2.80	12.7	0.34	Two; hyperplasia
	II.1	Female	49	4	2.97	26.7	11.7 ^d	Two; hyperplasia
	II.2	Male	34	15	2.91	Reported raised ^e	0.056	Three; hyperplasia

^aReference range 2.12–2.62 mmol/l. ^bReference range 1.3–7.6 pmol/l. ^cNormal ratio >0.01. ^dMeasured by 24 h urinary calcium excretion, reference range 2.5–7.5 mmol/24 h. ^eReported raised, but exact value not known.

DISCUSSION OF DIAGNOSIS

Primary hyperparathyroidism may result from parathyroid hyperplasia, or from a parathyroid adenoma or carcinoma. It has a prevalence of 3 per 1,000⁴ and it is most often encountered as a nonfamilial disorder; however, 10% of primary hyperparathyroidism patients have a hereditary disorder. This hereditary disorder may be a complex tumor syndrome such as MEN1, MEN2 or the HPT-JT syndrome (Supplementary Table 1), or it can occur as an isolated endocrinopathy that is referred to as FIHP.^{1–3,5}

The case patient (individual II.1 in family 1) had a Tyr351Asn mutation in *MEN1*. This mutation was also found in the affected mother, but not in 55 unaffected control individuals. FIHP in this kindred is, therefore, due to a novel *MEN1* missense mutation. The MEN syndromes are autosomal dominant disorders characterized by the combined occurrence of tumors in two or more endocrine tissues.^{1,3} In MEN1, inactivating germline mutations of *MEN1* on chromosome 11q13 are associated with the occurrence of tumors of the parathyroids, pancreas and pituitary¹ (Supplementary Figure 2, Supplementary Table 2), whereas in MEN2, activating mutations of the *RET* proto-oncogene located on chromosome 10q11.2 cause medullary thyroid carcinomas, pheochromocytomas and parathyroid tumors.³

In the described male patient (individual II.1 in family 1) FIHP presented with the classical symptoms associated with hypercalcemia, which are polyuria, polydipsia, constipation and lethargy; moreover, the patient's mother had a history of renal calculi, which are a classical complication of chronic primary hyperparathyroidism. It is important to note, however, that FIHP can

also occur in asymptomatic individuals and that it might be detected whilst undergoing investigations for another disease.

This situation is illustrated by another family (family 2, Figure 1B and Table 1) as follows. A previously well 34-year-old man (individual II.2 in family 2, Figure 1B) presented with chest pain and dyspnea. He was diagnosed as having a pulmonary embolism and investigations revealed him to have low circulating protein C levels consistent with heterozygous protein C deficiency.⁶ While he was being investigated, he was also found to have elevated serum calcium and PTH levels (Table 1). He underwent a parathyroidectomy with the excision of three hyperplastic glands and has remained normocalcemic for the past 15 years. During that time he has been treated with warfarin and he has not experienced further thromboemboli.

His family was investigated and his mother (individual I.2 in family 2, Figure 1B) and sister (individual II.1 in family 2, Figure 1B) were also found to have protein C deficiency. Detailed clinical histories revealed that the mother had osteoporosis with T scores of –2.94 at the lumbar spine and –2.11 at the femoral neck and that the sister had a renal calculus. Investigations of the mother and sister revealed them to be hypercalcemic with elevated serum PTH concentrations, and also to be hypercalciuric (Table 1). These results are consistent with a diagnosis of primary hyperparathyroidism and both individuals underwent neck exploration. Two hyperplastic parathyroid glands were removed from each patient and both patients have remained normocalcemic during a follow-up period of 4–6 years (Table 1). Treatment with warfarin has prevented the occurrence of thromboembolic disease.

Family 2 was also investigated for the MEN1, MEN2 and HPT-JT syndromes^{1–3} as detailed above and no abnormalities have been identified during a follow-up period, ranging from 4 to 15 years. An association between protein C deficiency and primary hyperparathyroidism has not been previously reported, and it is likely that this is a coincidental finding in the three patients affected in this family; moreover, the gene for protein C deficiency is located on chromosome 2q13–14,⁶ whereas that for MEN1 is located on chromosome 11q13,¹ and hence it was unlikely that these two disorders had resulted from a contiguous gene deletion.

DNA sequence analysis of *MEN1* was undertaken in family 2 after informed consent had been obtained using nationally approved guidelines. This revealed a G>T transversion at codon 220 in exon 4 that altered the wild-type codon, TGG, encoding a tryptophan (Trp) residue, to a mutant codon, TTG, encoding a leucine (Leu) residue (Figure 1). This Trp220Leu mutation was confirmed by ARMS-PCR (Figure 1B). The analysis of DNA isolated from the parathyroid tumor of individual II.1 in family 2 revealed a loss of the wild-type allele with retention of the mutant allele (Figure 1B). These findings of loss of heterozygosity are consistent with Knudson's two-hit hypothesis for tumorigenesis.⁷ FIHP in this kindred is, therefore, also due to a novel missense mutation of *MEN1*.

DIFFERENTIAL DIAGNOSIS

Primary hyperparathyroidism is the first manifestation of MEN1 in more than 95% of patients, whilst it is less common in MEN2.^{1,3} HPT-JT is an autosomal dominant disorder characterized by adenomatous or carcinomatous parathyroid tumors, fibro-osseous tumors of the jaw bones, renal tumors and cysts, and uterine tumors.² The penetrance of each of these phenotypic features of the HPT-JT syndrome is variable, and FIHP presenting as a mild variant of HPT-JT with incomplete penetrance has been reported in 10 kindreds (Supplementary Table 2).^{8–15} The gene responsible for HPT-JT, a tumor suppressor gene originally termed *HRPT2* (hyperparathyroidism 2) and more recently termed *CDC73* (cell division cycle 73), is located on chromosome 1q25.¹⁶ Hereditary primary hyperparathyroidism occurring without the association of other tumors has also been described as a distinct clinical entity in more than 100 families and this is referred to as FIHP.^{5,17}

All of these hereditary forms of parathyroid neoplasia are associated with hypercalcemia, an elevated serum PTH concentration and usually an increased or normal fractional excretion of urinary calcium. Following parathyroidectomy and removal of the tumors, normocalcemia is restored. These tumors can thus be distinguished from the autosomal disorder of familial benign hypocalciuric hypercalcemia (FBHH), in which the hypercalcemia is not corrected by parathyroidectomy and is associated with a low fractional excretion of urinary calcium, as the underlying defect is due to a mutation of the gene encoding the calcium-sensing receptor (*CASR*). This mutation results in a loss of function that leads to an altered set-point in the calcium-sensing-receptor^{18,19} (Supplementary Table 1). Five kindreds with FIHP, however, have been reported to have *CASR* mutations (Supplementary Table 2),^{20,21} further indicating that FIHP is a heterogeneous disorder.

The distinction between FIHP and the other hereditary hyperparathyroid disorders can, therefore, be difficult at times, particularly as some patients diagnosed as having FIHP have later been reported to develop features of MEN1.^{5,17} In addition, FIHP may represent an allelic variant of *MEN1* in some families, as such FIHP kindreds have associated *MEN1* mutations,^{5,22} and this is demonstrated by families 1 and 2 (Figure 1). It is, therefore, important to emphasize that the diagnosis of FIHP is largely achieved by excluding mutations of *MEN1*, *HRPT2* and *CASR*, as the finding of a mutation in any of these genes in an apparent FIHP kindred would lead to a revised diagnosis of one of the associated syndromes with incomplete penetrance. This emphasizes the value of mutational analysis in resolving the underlying defects and this is well illustrated by our study of the two FIHP kindreds (Figure 1 and Table 1).

Families 1 and 2 have *MEN1* missense mutations (Figure 1), which are consistent with FIHP, as an analysis of the 27 previously published *MEN1* mutations in FIHP reveals that 41% of these are missense mutations and 37% are frameshift or nonsense mutations that are predicted to result in a truncated protein.⁵ This contrasts significantly ($P < 0.001$) with the situation in patients with MEN1, in whom more than 80% of the germline mutations are protein truncating and less than 20% are missense mutations.^{1,5} Other factors consistent with a diagnosis of FIHP are the absence of other MEN1-associated

tumors over a follow-up period for 10.4 ± 6.3 (mean \pm SD) years and the relatively advanced age (51.4 ± 14.0 years) at which primary hyperparathyroidism occurred in the two families when compared with the typical age of onset of 20–25 years in patients with MEN1.²³

TREATMENT AND MANAGEMENT

Parathyroid surgery is the treatment of choice for FIHP, particularly when the disorder is associated with complications such as symptomatic hypercalcemia, bone loss or fractures, and hypercalciuria or nephrolithiasis.^{1,23} Subtotal parathyroidectomy is recommended for multiglandular involvement in FIHP.^{23,24} This is well illustrated by the three patients from family 2 (Table 1), who all had multiglandular disease, and in whom subtotal parathyroidectomy was successful in restoring normocalcemia for a follow-up period ranging from 4 to 15 years.

The management of a solitary parathyroid lesion associated with this disorder is, however, less clear. A study of 14 patients with FIHP, who underwent single gland excision, identified only one recurrence during a 40 month follow-up period.²⁴ The results of that study, which used intra-operative PTH measurements in confirming adequate resection,²⁴ indicated that a limited parathyroidectomy may be appropriate for single gland disease associated with FIHP. This treatment option was, however, not successful in the two patients from family 1 (Table 1) who both had a limited parathyroidectomy for single gland disease and yet developed recurrence of primary hyperparathyroidism, after a period of 2 years in the case patient (individual II.1 in family 1) and after a period of 13 years in his mother (individual I.2 in family 1). It could be that a follow-up period of more than 40 months duration is required before more conclusive recommendations can be made.

The follow-up of patients with FIHP with MEN1 mutations should be similar to that for patients with MEN1^{1,23} as FIHP may represent an early stage of MEN1, because primary hyperparathyroidism is the first manifestation of MEN1 in more than 95% of cases.^{1,5,22,23} Screening should, therefore, include biochemical and radiological investigations for the development of pancreatic islet cell tumors, anterior pituitary tumors, adrenal cortical tumors (Supplementary Table 3) and recurrence of primary hyperparathyroidism.^{1,23} In addition, genetic testing (Supplementary Figure 1) should be offered to

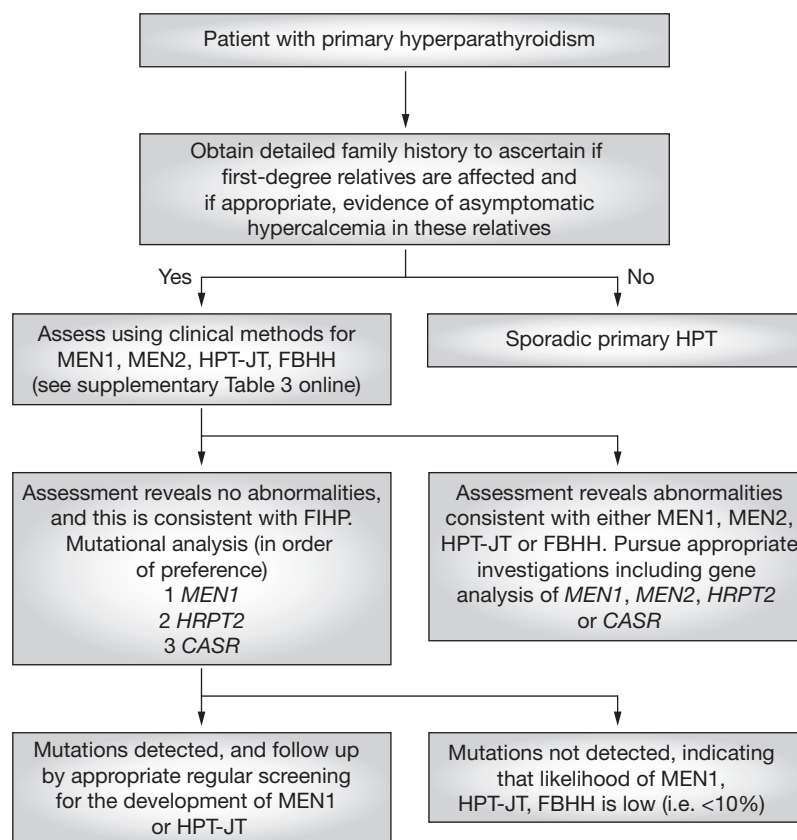


Figure 2 Investigations for familial primary hyperparathyroidism. A detailed family history is obtained to ascertain for the occurrence of primary hyperparathyroidism in a first-degree relative. Familial primary hyperparathyroidism may be associated with MEN1, MEN2 or HPT-JT, or it may be misdiagnosed as FBHH and hence appropriate clinical assessment and investigations should be undertaken (Supplementary Table 3) FIHP may also represent the first manifestation of the MEN1 and HPT-JT syndromes, and may occasionally be due to CASR mutations. Abbreviations: CASR, gene encoding the calcium-sensing-receptor; FBHH, familial benign hypocalciuric hypercalcemia; FIHP, familial isolated primary hyperparathyroidism; HPT-JT, hyperparathyroidism-jaw tumor; MEN, multiple endocrine neoplasia.

the patient's relatives at an early age, as primary hyperparathyroidism has previously been reported in a 13-year-old boy from a kindred with FIHP due to an *MEN1* mutation.²²

CONCLUSIONS

The patients reported by our study highlight that FIHP can present either with symptomatic hypercalcemia and complications of primary hyperparathyroidism such as osteoporosis and renal calculi, or that it can be asymptomatic and diagnosed during investigations for an unrelated disorder. The critical first step in making a diagnosis of FIHP is to obtain a detailed family history to determine if first degree relatives

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Competing interests

The authors declared no competing interests.

are affected (Figure 2). If this is the case, then a comprehensive clinical assessment needs to be undertaken to determine whether the kindred has FIHP, MEN1, MEN2, HPT-JT or FBHH; appropriate genetic testing would also help in establishing the correct diagnosis. It is important to note that FIHP may be an allelic variant of MEN1, as illustrated by the findings of this study which has identified two previously unreported *MEN1* missense mutations causing FIHP.

Supplementary information in the form of three tables and two figures is available on the *Nature Clinical Practice Endocrinology & Metabolism* website.

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