The hyperparathyroidism-jaw tumour (HPT-JT) syndrome

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Summary

The hyperparathyroidsim-jaw tumour (HPT-JT) syndrome is an autosomal dominant disorder characterised by the occurence of parathyroid tumours, which may be carcinomas in approximately 15% of patients, and ossifying fibromas, that usually affect the maxilla and/or mandible. More than 15% of HPT-JT patients may also develop renal and uterine abnormalities. The gene causing HPT-JT, referred to as *HRPT2*, is located on chromosome 1q31.2 and consists of 17 exons that encode a 531 amino-acid protein, designated PARAFIBROMIN. PARAFIBROMIN has been shown to be associated with the human homologue of the yeast Paf1 protein complex which interacts with RNA polymerase II, and as part of this protein complex, PARAFIBROMIN may regulate post-transcriptional events and histone modification. To date 63 *HRPT2* mutations have been reported and over 80% of these are nonsense or frameshift mutations that are predicted to result in a functional loss of the PARAFIBROMIN protein because of premature truncation. Moreover, loss of heterozygosity involving chromosome 1q and somatic *HRPT2* mutations have been observed in some HPT-JT associated tumours and this is consistent with a tumour suppressor role for *HRPT2*. *HRPT2* somatic mutations also frequently occur in parathyroid carcinomas but not adenomas. In addition, patients with 'non-familial' parathyroid carcinomas may harbour germline *HRPT2* mutations. The *HRPT2* mutations are scattered throughout the coding region, and there is an absence of a genotype-phenotype correlation. The results of these studies have enabled guidelines for the clinical management and genetic screening for HPT-JT kindreds and patients with parathyroid carcinoma to be proposed.

KEY WORDS: tumour suppressor, PARAFIBROMIN, HRPT2 mutations, parathyroid tumours, parathyroid carcinoma.

Introduction

Primary hyperparathyroidism (HPT) represents the commonest cause of hypercalcaemia in the general population, with an estimated incidence of 1 to 3 per 1000 individuals (1, 2). The parathyroid tumours which cause primary HPT are found at histology to be adenomas in 85% of patients, hyperplastic in <15% of patients, and carcinomas in <1% of patients, and these most commonly arise as a non-familial i.e. sporadic, condition that increases with age and shows a female predominance (1, 2). However, primary HPT may occur as an inherited disorder in approximately 20% of patients (3, 4). These inherited forms (Table I) may either arise as an isolated endocrinopathies, such as familial isolated hyperparathyroidism (FIHP) and neonatal severe primary hyperparathyroidism (NSHPT), or as part of more complex syndromes such as multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2A (MEN2A) or the hyperparathyroidism-jaw tumour syndrome (HPT-JT) (3, 4). These inherited forms of HPT typically present at an earlier age than the non-heritable forms and occur with equal frequencies in both sexes. This review will focus on the HPT-JT syndrome which is associated with the occurrence of parathyroid carcinomas in approximately 15% of patients (5, 6).

Clinical features of the HPT-JT syndrome

The HPT-JT syndrome is an autosomal dominant disorder that is characterised primarily by the occurrence of parathyroid tumours in association with maxillary and/or mandibular ossifying fibromas (7-10). In addition, some patients may develop renal abnormalities and uterine lesions (Fig. 1). Tumours involving other organs have also been reported in a few patients (Table II).

Parathyroid tumours

Parathyroid tumours, detectable by hypercalcaemia, are usually the first manifestation of the disease and occur in >95% of patients (Fig. 1) (6-26). The underlying aetiology of primary HPT in HPT-JT is usually a solitary parathyroid adenoma (4) but multigland disease may also occur and the frequency of parathyroid carcinoma in HPT-JT may be 15% (Fig. 1). These features result in recurrent parathyroid disease, which is common in HPT-JT. The occurrence of recurrent parathyroid disease and the occurrence of parathyroid tumours in isolation and without any evidence of jaw tumours, may cause confusion with other hereditary disorders of parathyroid tumours (Table I) such as MEN1, FIHP and familial benign hypercalcaemia (FBH), which is also referred to as familial hypocalciuric hypercalcaemia (FHH) and is due to inactivating mutations of the calcium sensing receptor (CaSR) (3). HPT-JT can be distinguished from FBH, because in FBH serum calcium levels are elevated during the early neonatal or infantile period, whereas in HPT-JT such elevations are uncommon in the first decade. In addition, HPT-JT patients, in contrast to FBH patients have associated hypercalciuria. The distinction between HPT-JT patients and MEN1 patients, who have developed only the first manifestation of hypercalcaemia (>90% of patients), is more difficult and is likely to be influenced by operative and histologic findings and by the subsequent occurrence of other characteristic lesions in each disorder (4, 27). It is

Table I - Genes involved causing Parathyroid tumours.

Disorder[a]	Protein[b]	Chromosomal location	OMIN[c]	Ref. #[d]
Inherited forms of parathyroid disease				
MEN1	MENIN	11q13	131100	40, 41
MEN2A	RET	10q11.2	171400	4, 42
HPT-JT	PARAFIBROMIN	1q31.2	145001	11, 12
FIHP	MENIN	11q13		43, 44
	PARAFIBROMIN	1q31.2	145000	11, 23, 45
	CaSR	3q21.1		13, 18, 45
NSHPT	CaSR	3q21.1	239200	4, 46
Non-inherited forms of parathyroid disease				
Adenomas	PRAD1/CCND1	11q13	168461	4, 47-49
	RB1	13q14		36, 50, 51
	p53	17p13		52
	Unknown	1p		51, 53-55
Hyperplasia (CRF)	Unknown	Xp11		56
Carcinoma	PARAFIBROMIN	1q31.2		6, 15, 20, 30
	PRAD1/CCND1	11q13		48, 49, 57
	RB1	13q14		36, 48, 58
	p53	17p13		59

[a] MEN1 multiple endocrine neoplasia type 1, MEN2 multiple endocrine neoplasia type 2, NSHPT neonatal severe primary hyperparathyroidism, CRF chronic renal failure.
[b] RET Rearranged during Transfection, CaSR calcium sensing receptor, PRAD1/CCND1 parathyroid adenoma 1/cyclin D1, RB1 retinoblastoma.
[c] Online Mendelian Inheritance in Man (OMIN), http://www.ncbi.nlm.nih.gov.
[d] Ref. #, reference number as stated in References section.

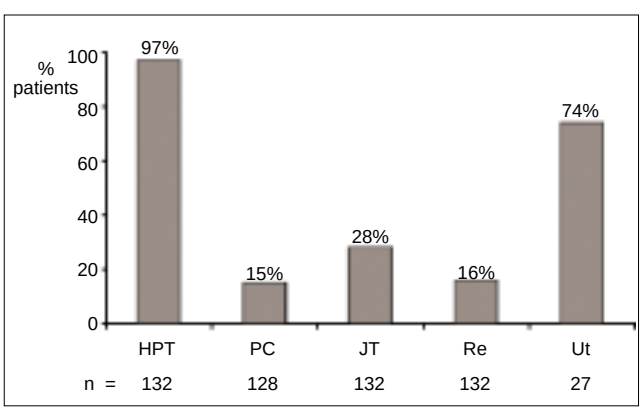

Figure 1 - Occurrence of tumours in patients with the HPT-JT syndrome. A review of the published reports (6, 8-18, 20-24, 33) of 34 kindreds with *HRPT2* mutations was undertaken and the frequency of occurrence of each type of tumour calculated. Tumours showing a frequency of ≥15% are shown. These consist of: parathyroid tumours leading to primary HPT which occurred in 97% of 132 individuals affected with HPT-JT; parathyroid carcinomas (PC) which occurred in 15% of 128 HPT-JT patients with parathyroid tumours; ossifying jaw fibromas (JT) which occurred in 28% of 132 patients with HPT-JT; renal abnormalities (Re) which occurred in 16% of 132 HPT-JT patients; and uterine lesions (Ut) which occurred in 74% of 27 women affected with HPT-JT. Over 75% of the renal abnormalities consisted of multiple renal cysts, and over 85% of the uterine abnormalities consisted of benign lesions such as endometrial hyperplasia, adenomyosis, leiomyomas and adenofibromas. Inclusion of data from from 11 HPT-JT families without reported HRPT2 mutations did not significantly alter these frequencies; thus the frequencies of primary HPT, parathyroid carcinomas, ossifying jaw fibromas, renal abnormalities and uterine lesions were 94% (n=196), 14% (n=185), 31% (n=196), 16% (n=196) and 79% (n=39), respectively. Tumours that have been reported to occur in <2% patients (Table II), such as Hurthle cell thyroid adenomas (25), papillary thyroid carcinomas (11, 12), pancreatic adenocarcinomas (25), testicular mixed germ cell tumours (25), breast cancer (12, 14), prostate cancer (8, 12, 14, 26) and colonic cancer (11-14) are not shown.

important to note that HPT-JT patients usually have single adenomas or a carcinoma, whereas MEN1 patients often have multiglandular parathyroid disease. The distinction between FIHP and HPT-JT in the absence of jaw tumours is difficult but important because HPT-JT patients may be at a higher risk of developing parathyroid carcinomas. These distinctions may be helped by the identification of additional features, and a search for jaw tumours, renal and uterine abnormalities (Fig. 1) may help to identify HPT-JT patients.

Ossifying jaw-tumours

The prevalence of ossifying fibromas of the jaw has been reported to range from >25% to 50% (Fig. 1) (10, 11, 14, 28), and these may appear as early as 13 years of age. The ossifying fibromas are histologically different from the osteoclastic 'brown' tumours of primary HPT and do not regress following curative

Table II - Tumours reported in < 2% of HPT-JT patients.

Tumour	Number of patients	Ref. #[a]
Thyroid		
Goitre	2	12, 24
Hurthle cell adenoma	1	25
Papillary carcinoma	1	11, 12, 22
Pancreatic adenocarcinoma	1	25
Lipoma	2	11, 12, 22
Testicular mixed germ cell tumour	1	25
Colonic carcinoma	3	11-14, 26
Prostate carcinoma	3	8, 11, 12, 14, 26
Breast cancer	2	11-14

[a] Ref. #, reference number as stated in References section.

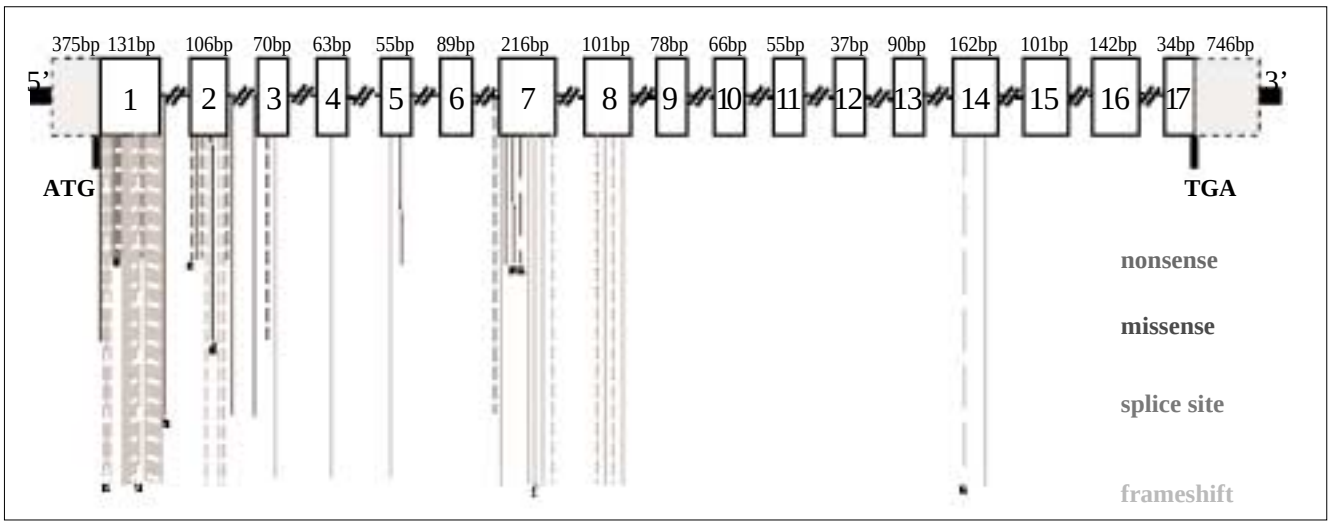

Figure 2 - Schematic representation of the genomic organisation of the *HRPT2* gene and its mutations.
The human *HRPT2* gene spans 1.3Mb of genomic DNA and encodes a 531 amino acid protein, called PARAFIBROMIN (11). The 1593 bp coding region is organised into 17 exons (sizes indicated) and 16 introns. The 5'-part of exon 1 and the 3'-part of exon 17 are untranslated (stippled boxes). The start (ATG) and stop (TGA) sites, in exons 1 and 17 respectively, are indicated. The locations of 63 *HRPT2* mutations that have been reported in the period (6, 11, 12, 15, 17-20, 23, 24, 29, 30) 2002-2005 are shown; these include 12 different nonsense, 4 different missense, 4 different splice site and 32 different frameshift mutations. The 26 different germline mutations are indicated by solid lines, 22 different somatic mutations by short dashed lines and the 4 mutations where the status is unknown (u) by long dashed lines. Germline or somatic mutations which have been reported more than once in unrelated individuals are highlighted: [a] Arg9Stop, reported twice; [b] IVS1+1g→a, reported 3 times; [c] Tyr54Stop, reported twice; [d] Leu64Pro, reported twice; [e] Arg234Stop, reported 3 times and [f] 679insG, reported 5 times. Exons 1, 2 and 7 have significantly more mutations than the other exons, and contain 33%, 18% and 22%, respectively, of the mutations. Indeed, the mutation number per 100 bp of DNA sequence for exons 1, 2 and 7 are 16, 10 and 7, respectively, and these are significantly higher ($p<0.01$ for exons 1 and 2, and $p<0.05$ for exon 7) when compared with other exons. Thus the over-representation of mutations in exons 1, 2 and 7 is not a function of their larger sizes.

parathyroid surgery (7, 10). These ossifying fibromas may occasionally occur in other bones, and a search for these at sites other than the jaw may help to distinguish between those patients with HPT-JT and FIHP. Ossifying fibromas are an important distinguishing feature of HPT-JT from FIHP and the occurrence of these occasionally may precede the development of hypercalcaemia in HPT-JT patients by several decades.

Renal abnormalities

Renal lesions have been reported with varying frequencies in HPT-JT patients and include Wilms' tumour (8), renal hamartomas (9), renal cell carcinomas (25), renal cortical adenomas (25) and multiple renal cysts (9-13, 21, 24). Our analysis (Fig. 1) of the published reports (6-26) indicates that renal abnormalities occur in approximately 16% of HPT-JT patients, with proven germline *HRPT2* mutations, and that >75% of these abnormalities consisted of multiple cysts. Only 2 patients were reported to develop end stage renal failure (9, 11, 21). The occurrence of other renal abnormalities has been reported in only 1 or 2 patients. Thus, Wilms' tumour has been reported in 2 unrelated patients (8, 11, 12), renal hamartomas have been reported in 4 patients from one family (9, 11), and renal cell carcinoma and multiple cortical adenomas in 1 patient (25).

Uterine abnormalities

Uterine abnormalities have been reported to occur in approximately 75% of women affected with HPT-JT (Fig. 1) from 9 families with proven germline *HRPT2* mutations (12). These women suffered from menorrhagia in their second to fourth decades, and often required hysterectomy, which revealed the presence of uterine tumours. Histological analysis revealed the occurrence of benign and malignant uterine tumours. The majority (>85%) of the uterine abnormalities were benign and consisted of adenofibromas, leiomyomas, adenomyosis and endometrial hyperplasia (12). The malignant tumours, which were found in 2 of the 15 women (i.e. <15%) from this study, consisted of adenosarcomas. The affected women from these families often had multiple miscarriages and were found to be significantly impaired in their ability to have offspring when compared with their unaffected female relatives and to their affected male relatives (12).

Other tumours

Other tumours, including Hurthle cell thyroid adenomas, papillary thyroid carcinomas, pancreatic adenocarcinomas, colonic carcinoma, prostate carcinoma, breast cancer, lipomas and testicular mixed germ cell tumours have been reported in 1 to 3 patients with HPT-JT (12, 22, 25) (Table II). An analysis of the frequencies of the occurrence of such tumours in 193 HPT-JT patients from 45 families, of which 34 had proven *HRPT2* mutations, reveals that the frequencies of colorectal, prostate, breast and pancreatic cancers are 1.6%, 1.6%, 1.0% and 0.5%, respectively. These low frequencies are unlikely to be significantly above that of the normal population and it may be possible that these tumours are not associated with the HPT-JT syndrome.

Molecular genetics of the HPT-JT syndrome

Identification of the gene causing HPT-JT and causative mutations

HPT-JT is inherited as an autosomal dominant disorder and linkage studies in families mapped the gene causing HPT-JT, which is referred to as *HRPT2*, to chromosome 1q21-31 (8). Additional

studies refined this location to a 12cM region that contained 67 potential candidate genes. Mutations were identified in one of these genes which consisted of 17 exons and spanned 1.3Mb of genomic DNA (11). This gene, referred to as *HRPT2*, has two transcripts; one of 2.7Kb, which encodes a ubiquitously expressed and evolutionarily conserved 531 amino acid protein named PARAFIBROMIN and the other, of 4.4Kb, which has not yet been characterised (11). To date 63 heterozygous *HRPT2* mutations have been reported (Fig. 2 and Table III). These consist of 26 different heterozygous germline *HRPT2* mutations in patients with HPT-JT, FIHP and parathyroid carcinomas, and 22 different heterozygous somatic *HRPT2* mutations in parathyroid adenomas and carcinomas. The mutations are scattered throughout the coding region (Fig. 2), although currently, no mutations have been reported in exons 6, 9-12 and 15-17. Exons 1, 2 and 7 are more frequently involved and harbour 33%, 18% and 22%, respectively of the mutations. The over-representation of mutations in these exons is not due to their larger sizes as an examination of exons 8, 14, 15 and 16, which are of similar sizes, reveals these to contain between 0% and 7% of all mutations (Fig. 2). Over 80% (6, 11, 12, 15, 17-20, 23, 24, 29, 30) of the *HRPT2* mutations found in germline DNA and in somatic DNA of tumours, are nonsense or frameshift mutations (Table III) that are predicted to result in a functional loss of the PARAFIBROMIN protein because of premature truncation. Four different missense mutations have been reported: one affects the initiation methionine (11) and is thus likely to prevent translation; two affect evolutionary conserved leucines (6, 11, 18, 29) which are replaced by a helix disruptive proline and hence likely to lead to a deleterious structural alteration of the protein; and one affects an evolutionary conserved aspartate (29) within the Paf1 binding domain (see below) and this aspartate is replaced by an asparagine (Table III). The substitution of the normal negatively charged aspartate residue for a polar but uncharged asparagine is predicted to disrupt the interaction between PARAFIBROMIN and the Paf1 complex that interacts with RNA polymerase II.

Loss of heterozygosity (LOH) involving this region of chromosome 1q has been reported in 32% of parathyroid adenomas (n=38) and 70% of parathyroid carcinomas (n=10) (6, 8-10, 15, 19, 21, 22, 25). In addition, LOH of chromosome 1q has been reported in 7 renal hamartomas from 2 HPT-JT patients (9), one renal cell carcinoma (25), and one pancreatic carcinoma (25) from HPT-JT patients. These observations of LOH in tumours from HPT-JT patients and the combined occurrence of inactivating germline and somatic mutations in tumours from these patients, indicate that the *HRPT2* gene acts as a tumour suppressor consistent with the Knudson 'two-hit' model for hereditary cancer (6, 20, 29-31).

Absence of genotype-phenotype correlation

Correlations between *HRPT2* mutations and the clinical manifestations of HPT-JT appear to be absent. An analysis of 5 unrelated patients and their families (11, 12, 23, 30) with the same 2 bp (AG) insertion at codon 679 revealed a wide range of HPT-JT

Table III - Summary of 63 reported *HRPT2* mutations in period 2002-2005.

Mutation type	Clinical data[a,b,c,d]	Exon / Intron	Codon / nt[e,f]	Base change	Predicted effect[g]	Type[h]	Ref. #[i]
Missense							
	HPT-JT	Exon 1	1 / nt3	ATG to ATA	M1L	G	11
	FIHP					G	11, 18, 19
	FIHP	Exon 2	64 / nt191	CTT to CCT	L64P	G	6
	Ad[d]	Exon 3	95 / nt284	CTT to CCT	L95P	S	29
	HPT-JT	Exon 13	379 / nt1135	GAC to AAC	D379N	G	29
Nonsense							
	HPT-JT						
	2 Ca[c]	Exon 1	9 / nt25	CGA to TGA	R9X	G	11
						2S	15
	Ca[c]	Exon 1	24 / nt70	GAA to TAA	E24X	S	30
	FIHP	Exon 1	43 / nt128	TGG to TAG	W43X	S	11
	Ca[c]						
	Ca[c]	Exon 2	54 / nt162	TAC to TAG	Y54X	S	6
						S	30
	HPT-JT						
	Ca[c]	Exon 2	55 / nt165	TAC to TAG	Y55X	G	11
						S	6
	Ca[c]	Exon 2	76 / nt226	CGA to TGA	R76X	S	30
	HPT-JT	Exon 5	136 / nt406	AAG to TAG	K136X	G	11
	Ca[c]	Exon 7	222 / nt664	CGA to TGA	R222X	G	30
	HPT-JT						
	Ca[c]					G	29
	2 Ca[c]	Exon 7	234 / nt700	CGA to TGA	R234X	U	30
						2G	15
Splice Site							
	FIHP					G	15
	Ad[b]	Intron 1	IVS1+1	g to a	10 aa in-frame deletion	S	15
	FIHP					G	17
	FIHP	Intron 2	IVS2+1	g to c	aberrant transcription	G	18
	HPT-JT	Intron 2	IVS2-1	g to a	2 aberrant transcripts	G	20
	Ca[c]	Intron 6	IVS6-1	del g	aberrant transcription	S	6

continued

continued Table III

Mutation type	Clinical data[a,b,c,d]	Exon / Intron	Codon / nt[e,f]	Base change	Predicted effect[g]	Type[h]	Ref. #[i]
Frameshift Insertions							
	HPT-JT	Exon 1	4 / nt12	dup/ins GCTTAGCGTCCTGCGACAGT	fs 16 ms aa Stop	G	12
	Ca[c]	Exon 2	65 / nt195	ins A	fs 16 ms aa Stop	S	15
	Ca[c]	Exon 2	65 / nt195	ins T	fs 15 ms aa Stop	S	15
	Ca[c]	Exon 5	125 / nt373	ins A	fs 4 ms aa Stop	G	30
	FIHP					G	12
	2 HPT-JT					2G	11
	Ca[c]	Exon 7	227 / nt679	ins AG	fs 27 ms aa Stop	G	30
	FIHP					G	23
	FIHP	Exon 8	249 / nt745	dup A	fs 17 ms aa Stop	G	29
Frameshift Deletions							
	Ca[d]	Exon 1	5 / nt13	del CTTAGCGTCCTGCGACAG	6 aa in-frame deletion	S	20
	Ca[c]	Exon 1	6 / nt16	del A	fs 14 ms aa Stop	U	30
	Ca[c]	Exon 1	8 / nt23	TGCG to GTG	fs 12 ms aa Stop	S	30
	HPT-JT	Exon 1	10 / nt30	del G	fs 10 ms aa Stop	G	11
	HPT-JT	Exon 1	12 / nt34	del AACATCC	fs 6 ms aa Stop	G	11
	HPT-JT					G	11
	Ca[c]	Exon 1	13 / nt39	del C	fs 6 ms aa Stop	S	30
	Ad[b]	Exon 1	18 / nt53	del T	fs 2 ms aa Stop	S	11
	Ca[c]	Exon 1	20 / nt60	del GAAGGGAGAC	fs 2 ms aa Stop	U	30
	Ca[c]					S	6
	HPT-JT	Exon 1	26 / nt76	del A	fs 10 ms aa Stop	G	6
	Ca[c]	Exon 1	28 / nt82	del GGGG	fs 7 ms aa Stop	S	30
	Ca[c]	Exon 1	29 / nt 85	del G	fs 7 ms aa Stop	S	20
	Ad[b]	Exon 1	42 / nt126	del TTGGGGGACTGGAAAGGAAGGCCA	fs 46 ms aa Stop	S	11
	Ca[c]	Exon 2	55 / nt165	del C	fs 0 ms aa Stop	S	6
	HPT-JT	Exon 3	102 / nt306	del GTgtgagtacttttt	fs 5 ms aa Stop	G	11
	HPT-JT	Exon 4	119 / nt356	del A	fs 13 ms aa Stop	G	11
	HPT-JT	Exon 7	212 / nt636	del T	fs 5 ms aa Stop	G	11
	HPT-JT	Exon 7	223 / nt669	del AT/insG	fs 33 ms aa Stop	G	12
	HPT-JT	Exon 7	227 / nt679	del AG	fs 36 ms aa Stop	G	6
	Ca[d]	Exon 7	229 / nt686	del GAGT	fs 26 ms aa Stop	S	6
	Ca[c]	Exon 8	244 / nt732	del T	fs 10 ms aa Stop	S	30
	Ca[c]	Exon 8	249 / nt746	del T	fs 6 ms aa Stop	S	30
	HPT-JT	Exon 8	255-6 / nt765-6	del TG	fs 9 ms aa Stop	G	24
	Ca[c]	Exon 14	410 / nt1230	del C	fs 16 ms aa Stop	U	30
	HPT-JT	Exon 14	413 / nt1238	del A	fs 14 ms aa Stop	G	11

[a] HPT-JT, hyperparathyroidism-jaw tumour syndrome; FIHP, familial isolated hyperparathyroidism; PTH, parathyroid.
[b] Ad, sporadic parathyroid adenoma.
[c] Ca, sporadic parathyroid carcinoma.
[d] Familial parathyroid tumour.
[e] Codon and nucleotide (nt) numbering start from initiation codon of *HRPT2* mRNA; upper case letters represent exonic while lower case letters represent intronic sequences.
[f] IVS, intervening sequence i.e. intronic sequence.
[g] fs, frame-shift; ms, mis-sense.
[h] G, germline; S, somatic; U, unknown.
[i] Ref. #, reference number as stated in References section.

associated tumours. Eighteen of the 19 affected members from the 5 families had parathyroid tumours, but parathyroid carcinomas were observed in only 5 patients from 3 of the kindreds; whilst ossifying jaw fibromas were present in only 1 patient from 1 of the kindreds; and uterine abnormalities were present in only 6 females from 2 of the kindreds. Finally, only 3 members of one family had renal abnormalities, which were not present in any of the other families. Thus, there appears to be a lack of genotype-phenotype correlation.

HPT-JT families without detectable HRPT2 mutations

Approximately 25% of HPT-JT families have not been reported to harbour mutations involving the coding region or the adjacent splice junctions of the *HRPT2* gene (8, 11-15, 32, 33). These families may have mutations involving: the promoter regions; the untranslated regions; the alternate transcript that remains uncharacterised; whole exon or gene deletions that may not be detected by PCR or DNA sequence analysis; methylation that may lead to gene silencing; or mutation in a nearby unidentified linked gene. In addition, a comparision of the phenotypic manifestations in such families without *HRPT2* mutations, with those that do have *HRPT2* mutations, revealed no differences (12). Thus, a prediction for the presence or absence of an *HRPT2* mutation in a family based upon the clinical manifestations of HPT-JT is not possible.

Penetrance of HRPT2 mutations

Studies of penetrance in HPT-JT families are limited, but non-penetrance and “skipping” of a generation in a family has been observed (8, 22, 24). Non-penetrance has been reported to be >30% in mutation carriers in a study of 10 families with known

HRPT2 mutations (12). The age-related penetrance for HPT-JT has not yet been defined, as the clinical data from kindreds with *HRPT2* mutations are too few and limited to establish this. However, manifestations of HPT-JT below the age of 10 years have not been reported to date.

HRPT2 mutations in non-familial parathyroid adenomas and carcinomas

HRPT2 mutations do not seem to be common in sporadic parathyroid adenomas (Table III) and the frequency of such mutations has been reported to range from 0% to 4% (6, 11, 15, 29, 34). However, the frequency of *HRPT2* mutations in sporadic parathyroid carcinomas (Table III) is high and ranges from 67% to 100% (6, 15, 20, 30), thereby indicating an important role for this gene in malignant transformation of the parathyroid. In addition, two studies have unexpectedly identified germline *HRPT2* mutations (Table III) in 5 patients with sporadic parathyroid carcinomas (15, 30). These findings indicate that patients with parathyroid carcinomas and their relatives should be clinically assessed for HPT-JT associated tumours and offered mutational analysis with genetic counselling.

HRPT2 polymorphisms

Eleven DNA sequence polymorphisms (Table IV) with allele frequencies ranging from 1% to 25% have also been reported (6, 29). Only one of these polymorphisms is located within the coding region and this is a third base C to T transition involving nucleotide 33 of codon 11 (TAC→TAT) which does not alter the naturally occurring tyrosine residue. None of the polymorphisms is in the vicinity of donor or acceptor splice sites, and an analysis of the altered sequences does not predict splicing abnormalities. The recognition of these polymorphisms, together with their allele frequencies, is important as this will help prevent ambiguities in establishing a genetic diagnosis for patients with HPT-JT and FIHP.

Screening in HPT-JT and *HRPT2* mutational analysis

The size of the *HRPT2* gene, the absence of a genotype-phenotype correlation together with an absence of a 'mutational hotspot' make the implementation of mutational analysis in a diagnostic and clinical setting arduous, time-consuming and expensive. Nevertheless, diagnostic DNA testing for *HRPT2* mutations should be considered in patients with HPT-JT, FIHP and 'non-familial' parathyroid carcinomas, as it is likely to help

Table IV - *HRPT2* polymorphisms and their frequencies.

Location (nt)[a]	Sequence change[b]	Chromosomes[c]	Allele frequencies	Ref. #[e]
5' of ATG (-11)	g→a	54	0.98 / 0.02	29
Exon 1 (33)	C→T	121	0.99 / 0.01	6
Intron 2 (+28)	c→t	171	0.70 / 0.30	6, 29
Intron 2 (+28 to +31)	del ccta	175	0.95 / 0.05	6, 29
Intron 7 (+33)	[d](ga)$_8$	121	0.96 / 0.04	6
Intron 7 (+50)	del ag	56	0.98 / 0.02	29
Intron 12 (+8)	t→c	56	0.98 / 0.02	29
Intron 12 (-86)	c→t	121	0.95 / 0.05	6
Intron 12 (-109)	t→g	121	0.91 / 0.09	6
Intron 13 (+20)	a→c	121	0.99 / 0.01	6
Intron 15 (-17)	c→g	80	0.93 / 0.07	29

[a] nt, nucleotide position in relation to nearest exonic nucleotide of cDNA sequence (Accession number NM_024529; nucleotide positions start from initiation codon).
[b] del, deletion.
[c] Number of chromosomes studied from unrelated individuals.
[d] The wildtype sequence shows nine ga repeats at +33 bp in intron 7 i.e. (ga)$_9$.
[e] Ref. #, reference number as stated in References section.

Table V - HPT-JT suggested guidelines for screening patients; asymptomatic mutation carriers; and first- and second-degree relatives in families without identified germline *HRPT2* mutations.

Tumour[a]	Test[b]	Frequency[c]
Parathyroid	Serum Ca^{2+}, PTH	6 to 12 monthly
Ossifying jaw fibromas	Panoramic jaw X-rays with neck shielding[d]	5 yearly
Renal	Abdominal MRI[d,e]	5 yearly
Uterine	Ultrasound (transvaginal or transabdominal), and additional imaging ± D&C if indicated[f]	Annually

[a] Screening for the most common HPT-JT tumours is considered, but thyroid, pancreatic and testicular tumours have also been reported, and when indicated assessment for these should also be undertaken.
[b] Ca^{2+} (calcium), PTH (parathyroid hormone), MRI (magnetic resonance imaging), D&C (dilatation and curettage).
[c] Frequency of repeating tests once baseline tests have been done.
[d] X-rays and tests involving ionising radiation should ideally be avoided to minimise the risk for generating subsequent oncogenic mutations.
[e] Ultrasound scan recommended if MRI not available.
[f] Such selective pelvic imaging should be considered after obtaining a detailed menstrual history.
[g] These guidelines (12) are reproduced with permission.

in their clinical management and in the genetic counselling and screening of their relatives (12). The genetic counselling and screening should be extended to include second-degree relatives as non-penetrance can be >30% (12). The parathyroid, uterine and renal pathologies that occur in HPT-JT patients indicate that screening for such tumours is likely to result in an earlier detection and hence intervention that will help to reduce morbidity and mortality (12). Guidelines (Table V) for regular screening for the development of HPT-JT associated tumours have recently been published (12), although these suggested guidelines will need to be modified in the light of new clinical and genetic data. Mutational analysis of the *HRPT2* gene is available, e.g. from the Department of Clinical Genetics, Churchill Hospital, Oxford, OX3 7LJ, UK.

Function of *HRPT2* and PARAFIBROMIN

The role of the *HRPT2* gene and its encoded protein, PARAFIBROMIN, in normal cellular function and the mechanisms by which its abnormalities lead to tumours of the HPT-JT syndrome, remain to be elucidated. PARAFIBROMIN has been shown to be a nuclear protein (35-38). Moreover, the ~200 amino acids of the C-terminal segment of PARAFIBROMIN have 27% sequence identity with the yeast protein Cdc73, which is a component of the yeast Paf1 complex that interacts with RNA polymerase II. Furthermore, recent studies have shown that the human homologues of the yeast Paf1 complex are associated with PARAFIBROMIN (35, 39). Thus, as part of this protein complex, PARAFIBROMIN may regulate post-transcriptional events and histone modification (35) and thereby regulate cell proliferation.

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