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MINISYMPOSIUM

Uterine tumours are a phenotypic manifestation of the hyperparathyroidism-jaw tumour syndrome

K. J. BRADLEY[1,*], M. R. HOBBS[2,*], I. D. BULEY[3], J. D. CARPTEN[4], B. M. CAVACO[5], J. E. FARES[6], P. LAIDLER[7], S. MANEK[3], C. M. ROBBINS[4], I. S. SALTI[6], N. W. THOMPSON[8], C. E. JACKSON[9] & R. V. THAKKER[1]

From the [1]Academic Endocrine Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Headington, Oxford, UK, [2]Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA, [3]Department of Cellular Pathology, John Radcliffe Hospital, Oxford, UK, [4]Translational Genomics Research Institute, Tempe, AZ, USA, [5]Centro de Investigação de Patobiologia Molecular, Instituto Português de Oncologia de Francisco Gentil, Rua Professor Lima Basto, Lisboa, Portugal, [6]Division of Endocrinology and Metabolism, Department of Internal Medicine, American University Hospital, Beirut, Lebanon, [7]Department of Pathology, University of Wales College of Medicine, Cardiff, UK, [8]Department of Surgery, University of Michigan, School of Medicine, Ann Arbor, MI, USA, and [9]Department of Medicine, Scott and White Memorial Hospital, Temple, TX, USA

Abstract. Bradley KJ, Hobbs MR, Buley ID, Carpten JD, Cavaco BM, Fares JE, Laidler P, Manek S, Robbins CM, Salti IS, Thompson NW, Jackson CE, Thakker RV (University of Oxford, Oxford, UK; University of Utah School of Medicine, UT, USA; John Radcliffe Hospital, Oxford, UK; Translational Genomics Research Institute, AZ, USA; Instituto Português de Oncologia de Francisco Gentil, Lisboa, Portugal; American University Hospital, Beirut, Lebanon; University of Wales College of Medicine, Cardiff, UK; University of Michigan, MI, USA; and Scott and White Memorial Hospital, Temple, TX, USA). Uterine tumours are a phenotypic manifestation of the hyperparathyroidism-jaw tumour syndrome (Minisymposium). *J Intern Med* 2005; **257:** 18–26.

The hyperparathyroidism-jaw tumour (HPT-JT) syndrome is an autosomal dominant disorder characterized by parathyroid tumours, which are frequently carcinomas, and ossifying jaw fibromas. In addition, some patients may develop renal tumours and cysts. The gene causing HPT-JT, which is referred to as *HRPT2* and is located on chromosome 1q31.2, encodes a 531 amino acid protein called PARAFIBROMIN. To date 42 mutations, of which 22 are germline, have been reported and 97% of these are inactivating and consistent with a tumour suppressor role for *HRPT2*. We have investigated another four HPT-JT families for germline mutations, searched for additional clinical phenotypes, and examined for a genotype–phenotype correlation. Mutations were found in two families. One family had a novel deletional-insertion at codon 669, and the other had a 2 bp insertion at codon 679, which has been reported in four other unrelated patients. These five unrelated patients and their families with the same mutation were not found to develop the same tumours, thereby indicating an absence of a genotype–phenotype correlation. An analysis of 33 HPT-JT kindreds revealed that affected women in 13 HPT-JT families suffered from menorrhagia in their second to fourth decades. This often required hysterectomy, which revealed the presence of uterine tumours. This resulted in a significantly reduced maternal transmission of the disease. Thus, the results of our analysis expand the spectrum of HPT-JT-associated tumours to include uterine tumours, and these may account

*These authors contributed equally to this work.

for the decreased reproductive fitness in females from HPT-JT families.

Keywords: bone tumours, *HRPT2* mutations, kidney cysts, parathyroid cancer.

Introduction

The hyperparathyroidism-jaw tumour syndrome (HPT-JT) is an autosomal dominant disorder characterized primarily by parathyroid tumours in association with maxillary and/or mandibular ossifying fibromas [1–5]. Parathyroid tumours, detected by hypercalcaemia, occur in approximately 90% of HPT-JT patients and are usually the first manifestation of the disease [6]. The underlying aetiology is usually a solitary parathyroid adenoma [6] but multigland disease may also occur and the frequency of parathyroid carcinoma in HPT-JT is approximately 15% [7]. These features result in recurrent parathyroid disease, which is common in HPT-JT. The prevalence of ossifying fibromas of the jaw is approximately 35% in HPT-JT patients and these may appear as early as 13 years of age [5]. The ossifying fibromas are histologically different from the osteoclastic 'brown' tumours of primary hyperparathyroidism and do not regress following curative parathyroid surgery [1, 5]. Some HPT-JT patients may also develop renal abnormalities, which include hamartomas, polycystic disease and Wilms' tumours [2–5, 8, 9]. Other tumours, including Hurtle cell thyroid adenomas, pancreatic adenocarcinomas and testicular mixed germ cell tumours, have also been observed in one or two patients with HPT-JT [9]. It is important to note that in some kindreds, parathyroid tumours may be the sole disease manifestation and this has been referred to as familial isolated hyperparathyroidism (FIHP) [4, 10–12]. However, it is also important to note that germline mutations in other genes are more frequently involved in FIHP [13, 14].

The gene causing HPT-JT, which is referred to as *HRPT2*, is located on chromosome 1q31.2 and consists of 17 exons (Fig. 1) that span 1.3 Mb of genomic DNA [15]. The *HRPT2* gene has two transcripts; one of 2.7 kb which encodes a ubiquitously expressed and evolutionarily conserved 531 amino acid protein named PARAFIBROMIN and the other of 4.4 kb which has not yet been characterized [15]. PARAFIBROMIN has two putative nuclear localization sequences (NLSs) and, given its partial homology to the yeast protein Cdc73p [15], it seems likely that it may act as a transcription factor. However, the role of PARAFIBROMIN in normal cellular function is unknown and the mechanisms by which its abnormalities lead to tumours of the HPT-JT syndrome, remain to be elucidated [15]. To date 18 different heterozygous germline *HRPT2* mutations have been reported in HPT-JT and FIHP (Table 1, Fig. 1) [13, 15–18]. In addition, a total of 14 somatic mutations (Fig. 1) have been identified from analysis of parathyroid tumour DNA [13, 15–17]. The mutations are scattered throughout the coding region (Fig. 1), although currently no mutations have been reported in exons 6, 9–13 and 15–17. Exons 1, 2 and 7 are more frequently involved and contain 38%, 17% and 21%, respectively of the mutations. The over-representation of mutations in these three 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. 1). Over 97% of the mutations found in germline DNA and in somatic DNA of tumours, are nonsense or frameshift mutations that are predicted to result in a functional loss of the PARAFIBROMIN protein because of premature truncation. Two missense germline mutations have been reported, one of which affects the initiation methionine (family K1, Table 1) and the second alters an evolutionarily conserved leucine to a proline (family K9, Table 1). Proline is known to be a helix breaker [19] and is likely, therefore, to affect the function of PARAFIBROMIN by disrupting its tertiary structure. Both the observation of loss of heterozygosity (LOH) involving this region of chromosome 1q in some HPT-JT tumours [3–5, 9] and the inactivating germline and somatic mutations found in patients, suggest that the *HRPT2* gene acts as a tumour suppressor consistent with the Knudson 'two-hit' model for hereditary cancer [20]. This has been supported by the identification of the combined occurrence of a somatic and germline *HRPT2* mutation in a single parathyroid carcinoma from a HPT-JT patient [16]. *HRPT2* mutations do not seem to be common in sporadic parathyroid adenomas

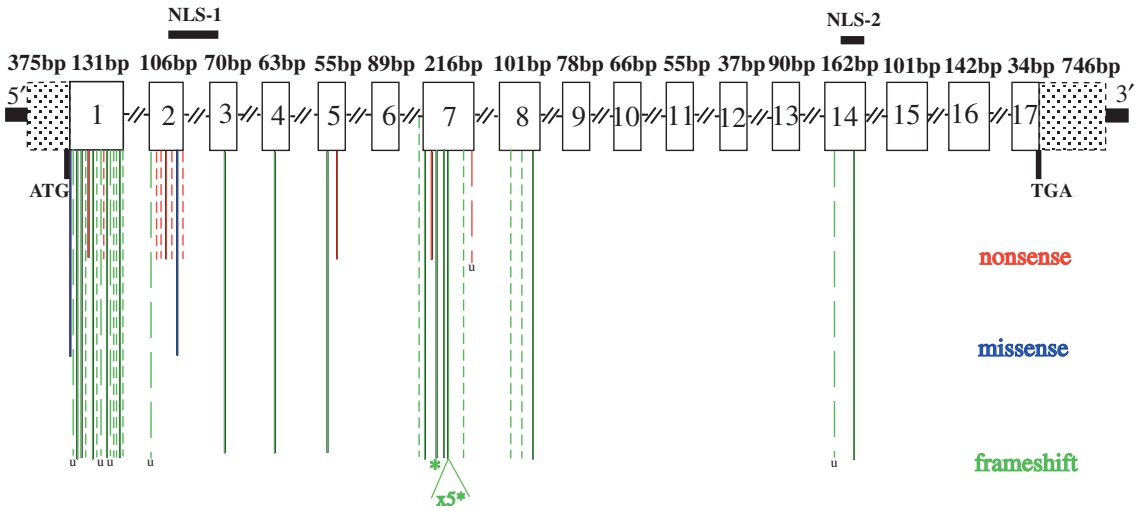

Fig. 1 Schematic representation of the genomic organization of the *HRPT2* gene and its pathological mutations. The human *HRPT2* gene spans 1.3 Mb of genomic DNA and encodes a 531 amino acid protein, called PARAFIBROMIN [15]. The 1593 bp coding region is organized into 17 exons (sizes indicated) and 16 introns. The 5′-part of exon 1 and the 3′-part of exon 17 are untranslated (hatched boxes). The start (ATG) and stop (TGA) sites, in exons 1 and 17 respectively, are indicated. The locations of the two putative nuclear localization signals (NLSs), which lie between codons 76–93 and 393–409 respectively, are represented by thick horizontal lines. The 44 mutations reported [2, 5, 8, 10, 13, 15, 16, 18, 21–23] in the *HRPT2* gene are shown; these include 10 nonsense (red lines), two missense (blue lines) and 32 frameshift (green lines) mutations. The 24 germline mutations are indicated by solid lines, 14 somatic mutations by short dashed lines and the six mutations where the status is unknown (u) by long dashed lines. The two new mutations, detected in kindreds K14 and K18 (Table 1) are identified with an asterisk. Exons 1, 2 and 7 have significantly more mutations than the other exons, and harbour 38%, 17% and 21%, respectively of the mutations. This is further illustrated by an examination of exons 8, 14, 15 and 16, which are of a similar size, and which harbour fewer mutations in the range of 0–7%. Indeed, the mutation number per 100 bp of DNA sequence for exons 1, 2 and 7, are 12, 7 and 5, respectively, and these are significantly higher ($P < 0.01$ for exon 1 and $P < 0.05$ for exons 2 and 7) when compared with the other exons. Thus, the over-representation of mutations in exons 1, 2 and 7 is not a function of their larger sizes.

[15, 16] but two studies [16, 17] have reported a high frequency of *HRPT2* mutations in sporadic parathyroid carcinomas (67–100%), thereby indicating an important role for this gene in malignant transformation of the parathyroid. In addition, one of these studies unexpectedly identified germline *HRPT2* mutations (Fig. 1) in three patients with sporadic parathyroid carcinomas [17]. These findings indicate that patients with parathyroid carcinomas or their relatives should be clinically assessed for HPT-JT-associated tumours and offered mutational analysis with genetic counselling.

In order to further characterize abnormalities associated with this recently identified gene and determine the spectrum of phenotypic manifestations in this disorder, we undertook mutational analysis in four HPT-JT families, and searched for genotype–phenotype correlations and additional phenotypic features. We particularly inquired for gynaecological abnormalities, as we had noticed that five of seven affected women in two previously reported HPT-JT kindreds (families K7 and K31, Tables 1 and 2) [8] did not have offspring, and anecdotal information suggested that women with HPT-JT had developed menstrual irregularities that required hysterectomy at a young age.

Materials and methods

Patients and families

Four HPT-JT kindreds (families K14, K18, K32 and K33, Tables 1 and 2) were ascertained. Family K14 was previously reported as a brother and sister with parathyroid cancers, which were excised with a recurrence in the sister, and other family members were subsequently discovered to have parathyroid tumours [21]. Family K18 was previously reported as having FIHP caused by solitary adenomas and subsequent observations of multiple adenomas in an affected member have been made [22]. Family K32 contained two affected

Table 1 Clinical findings in kindreds with identified germline *HRPT2* mutations

Kindred	Number affected (M/F)[a]	Number of unaffected carriers (M/F)[a]	*HRPT2* mutation	Exon mutated	Cases with tumours[b]					Off-spring M[d]	Off-spring F[d]	Other features[e]	Previous kindred number [reference][f]
					HPT	PTC	JT	RL	UT[c]				
K1	n/a	n/a	M1L	1	4	0	2	4	n/a	n/a	n/a		K05 [15]
K2[g]	5/2	1/0	R9X	1	7	0	4	1	1/2	5/5	1/2		K11690 [2], K15 [15]
K3[g]	4/0	0/0	30delG	1	4	0	3	0	0/0	1/1	0/0		K12 [15]
K4	n/a	n/a	34delAACATCC	1	2	0	1	1	n/a	n/a	n/a		K24 [15]
K5[g]	1/2	0/0	39delC	1	2	1	2	0	1/1	1/1	1/2		K19 [15]
K6	2/0	n/a	76delA	1	0	2	0	0	n/a	n/a	n/a		F3 [16]
K7[g,h]	6/3	0/0	20 bp duplication/ins	1	5	2	6	0	3/3	6/6	0/2	Prostate cancer, pancreatitis	K3304 [8], K16 [15]
K8[g]	4/2	1/0	Y55X	2	5	1	5	4	1/2	4/4	0/0		[5], K10 [15]
K9	1/1	n/a	L64P	2	1	1	0	0	n/a	n/a	n/a		F1 [16]
K10	n/a	n/a	306delGTgtgagtacttttt	3	7	1	2	1	n/a	n/a	n/a		K20 [15]
K11[g]	7/3	1/3	356delA	4	7	3	0	0	n/a	5/5	7/7	Lipomas, polycystic ovarian syndrome, papillary thyroid carcinoma	M/95 [10], K09 [15]
K12	n/a	n/a	K136X	5	3	0	2	1	n/a	n/a	n/a		K22 [15]
K13	n/a	n/a	636delT	7	4	0	2	2	n/a	n/a	n/a		K07 [15]
K14[g]	3/2	0/0	669delAT/insG	7	3	2	0	0	2/2	1/1	2/2	Renal failure	K3765 [21]
K15	n/a	n/a	679insAG	7	5	3	0	3	n/a	n/a	n/a		K01 [15]
K16[g]	1/2	2/1	679insAG	7	3	0	1	0	2/3	3/3	2/3		K3759 [23], K33 [15]
K17	3/1	0/0	679insAG	7	3	1	0	0	n/a	n/a	n/a	Lipomas	K35,900 [13]
K18[g]	4/2	3/3	679insAG	7	6	0	0	0	4/5	7/7	4/5		K3761 [22]
K19	3/0	n/a	679delAG	7	3	0	0	0	n/a	n/a	n/a		F4 [16]
K20[g,i]	1/1	1/0	255/256delTG	8	2	0	0	0	n/a	1/1	1/1	Metastatic adenocarcinoma with unknown primary, multinodular goitre	F1 [18]
K21[g,i]	1/3	1/3	255/256delTG	8	3	0	1	1	3/6	0/0	4/4		F2 [18]
K22[g,i]	0/1	0/1	255/256delTG	8	1	0	0	0	n/a	0/0	1/1		F3 [18]
K23[g,i]	1/0	0/0	255/256delTG	8	1	0	0	1	0/0	1/1	0/0		F4 [18]
K24[g,i]	0/2	2/3	255/256delTG	8	1	0	1	0	n/a	0/0	3/3	Multinodular goitre	F5 [18]
K25[g,i]	1/0	7/1	255/256delTG	8	1	0	0	0	n/a	2/4	0/0		F6 [18]
K26[g]	1/2	0/1	1238delA	14	3	0	2	1	3/3	1/1	3/3		K11 [15]
Total	49/28	18/16			86	17	34	20	20/27	38/40	29/35		

[a]Males (M)/females (F).

[b]Tumours: primary hyperparathyroidism (HPT), parathyroid carcinoma (PTC), ossifying jaw tumours (JT), renal lesions (RL) and uterine abnormalities (UT). Individuals with PTC were not included in the HPT column. Data not available is indicated (n/a).

[c]Uterine pathology (UT); affected or carrier adult women with menorrhagia (and/or) hysterectomy/total number of affected and carrier adult women.

[d]Affected or *HRPT2* mutation carrier adult males (M) and females (F) with offspring/total number of married affected and carrier adults of relevant sex.

[e]Other features that were observed in only one patient within a family.

[f]Kindreds from different reports have been given various numbers, and these are provided together with the appropriate reference.

[g]Family data updated from previous reports.

[h]K7 was reported as K3304 and re-sequencing of the mutated gene in this kindred indicates that the mutation is a 20 bp duplication/insertion (GCTTAGCGTCCTGCGACAGT) encoding 16 missense amino acids and then a premature Stop, not 41 bp as originally reported [8].

[i]K20–K25 are all Romany families from Portugal identified to have the same mutation, most likely due to a founder effect.

Table 2 Clinical findings in kindreds without identified *HRPT2* germline mutations, but in whom there is likely segregation with chromosome 1q loci

Kindred	Number affected (M/F)[a]	Number of unaffected carriers (M/F)[a]	Cases with tumours[b]					Off-spring M[d]	Off-spring F[d]	Other features[e]	Previous kindred number [reference][f]
			HPT	PTC	JT	RL	UT[c]				
K27[g]	7/5	0/0	11	0	6	1	3/4	5/5	1/4	Pancreatitis	F2 [3]
K28[g]	5/0	0/0	5	0	3	0	0/0	3/3	0/0		[1, 25]
K29[g]	2/1	0/0	2	0	3	0	1/1	1/1	1/1	Prostate carcinoma	K11689 [2]
K30[g]	2/3	2/0	4	0	2	0	2/2	3/3	2/2	Prostate carcinoma, colon carcinoma	[26]
K31[g]	1/5	0/0	3	2	4	n/a	5/5	1/1	2/5	Breast, salivary gland, colon and jaw carcinomas	K3349 [8, 27]
K32	1/1	0/0	2	0	1	0	0/0	1/1	1/1		This report
K33	2/1	0/0	2	1	0	0	n/a	0/0	1/1		This report
Total	20/16	2/0	29	3	19	1	11/12	14/14	8/14		

[a]Males (M)/females (F).
[b]Tumours: primary hyperparathyroidism (HPT), parathyroid carcinoma (PTC), ossifying jaw tumours (JT), renal lesions (RL) and uterine abnormalities (UT). Individuals with PTC were not included in the HPT column. Data not available is indicated (n/a).
[c]Uterine pathology (UT); affected or carrier adult women with menorrhagia (and/or) hysterectomy/total number of affected and carrier adult women.
[d]Affected or carrier adult males (M) and females (F) with offspring/total number of married affected and carrier adults of relevant sex.
[e]Other features that were observed in only one to three patients within a family.
[f]Kindreds from different reports have been given various numbers, and these are provided together with the appropriate reference.
[g]Family data updated from previous reports.

members and family K33 contained three affected members. The clinical and genetic data from these four families were pooled with the published and unpublished data from 29 families (Tables 1 and 2) [1, 2, 5, 8, 10, 13, 15, 16, 18, 21–27] for analysis of genotype–phenotype correlations. Anecdotal information that many young women with HPT-JT had required hysterectomy led to more detailed inquiries for menstrual history and uterine surgery in females from 13 of these families that were available for study.

Mutational analysis

Venous blood samples were obtained from the patients according to guidelines approved by the local ethical board. Leucocyte DNA was extracted and used with 17 pairs of primers (details available upon request) for polymerase chain reaction (PCR) amplification of the 17 coding exons and adjoining splice junctions of the *HRPT2* gene, as previously described [15]. The DNA sequences of gel purified PCR products were determined [15]. Tumours, including uterine specimens, were not available for the extraction of DNA to enable the identification of somatic mutations or LOH involving chromosome 1q loci.

Histological analysis of uterine specimens

Thirty-one women from 13 HPT-JT kindreds (families K2, K5, K7, K8, K14, K16, K18, K21, K26, K27, K29, K30 and K31) had a hysterectomy and the reports of histological analysis of 15 uterine specimens were obtained from 15 affected women from nine of these HPT-JT kindreds (families K2, K5, K7, K14, K21, K27, K29, K30 and K31). The histological slides were not available for independent review by a panel of pathologists, and the necessity of relying on pathology reports from medical records represents a limitation of this study. However, histological slides of the uterus from one patient, who was the proband in family K5 (Table 1), were available, and two sections were stained immunohistochemically with CD10, smooth muscle actin, desmin and MiB1 (Ki67) for an independent pathology review by S.M., who was not aware of the first report. The findings of the original report were confirmed, thereby suggesting that the reliance of

this study on the validity of the original pathology reports was generally appropriate.

Statistical analysis

This was performed using a chi-square test as previously reported [28].

Results

Mutational analysis

An analysis of the 1596 bp of the entire coding region and 32 adjacent splice sites identified two separate mutations in two of the four HPT-JT kindreds. Thus, family K14 (Table 1) was found to have a novel deletional-insertion at codon 669 (669delAT/insG), which leads to a frameshift encoding 33 missense amino acids before encountering a premature Stop at codon 256. Family K18 (Table 1) was found to have a 2 bp insertion at codon 679 (679insAG), which has been previously reported in four other unrelated patients and their families [13, 15, 17, 22, 23] and this is predicted to lead to a frameshift encoding 27 missense amino acids before encountering a premature Stop at codon 257.

Genotype–phenotype correlation analysis

Correlations between *HRPT2* mutations and the clinical manifestations of HPT-JT appear to be absent. For example, the five unrelated patients and their families with the 2 bp (AG) insertion at codon 679 reveal a wide range of HPT-JT-associated tumours (Table 1); all the affected members had parathyroid tumours but parathyroid carcinomas were only observed in two kindreds (families K15 and K17); whilst ossifying jaw fibromas were present only in a member of family K16; and three members of family K15 had renal abnormalities which were not present in any of the other families. Moreover, uterine abnormalities (see below) were detected only in individuals from families K16 and K18. Thus, there appears to be a lack of genotype–phenotype correlation. In addition, a comparison of the phenotypic manifestations in the 26 families with *HRPT2* mutations (Table 1) and the seven families without *HRPT2* mutations (Table 2) revealed no differences. 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. Furthermore, nonpenetrance is observed in >30% of mutation carriers, and is observed in 10 of the families with known *HRPT2* mutations (Table 1) and in one family without an *HRPT2* mutation (Table 2). This high degree of nonpenetrance will need to be considered carefully when providing genetic counselling.

Uterine abnormalities

Clinical evaluation of family K18 revealed that four of the five women with the *HRPT2* mutation had experienced menorrhagia-requiring hysterectomy. A review of the clinical data available from this and 12 other HPT-JT families identified that 20 of 27 women with *HRPT2* mutations from nine families (Table 1), and 11 of 12 women from four HPT-JT families in whom *HRPT2* mutations were not detected (Table 2) had suffered from menorrhagia that required hysterectomy at an early age [mean (±SD) age = 35 years (±8), age range = 23–55 years, in 23 women from whom data on age of hysterectomy were available]. Histological analysis of the 15 uterine specimens available led to the identification of benign uterine pathology as well as benign and malignant uterine tumours (Table 3). These consisted of two adenosarcomas (Fig. 2), five adenofibromas, four leiomyomas, eight cases of extensive adenomyosis and four cases of endometrial hyperplasia. Interestingly, the uterine tumours appear to have a common embryological origin from the mesodermal Mullerian duct system. The affected women in 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 ($P < 0.001$) and also to their affected male relatives ($P < 0.01$) (Table 4). A similar analysis of the affected men in

Table 3 Uterine pathology identified in 15 women affected with hyperparathyroidism-jaw tumour (HPT-JT) syndrome

Uterine pathology diagnosis	Number of affected women[a]
Adenosarcomas	2
Adenofibromas	5
Leiomyomas	4
Adenomyosis	8
Endometrial hyperplasia	4

[a]Some women had more than one uterine pathology.

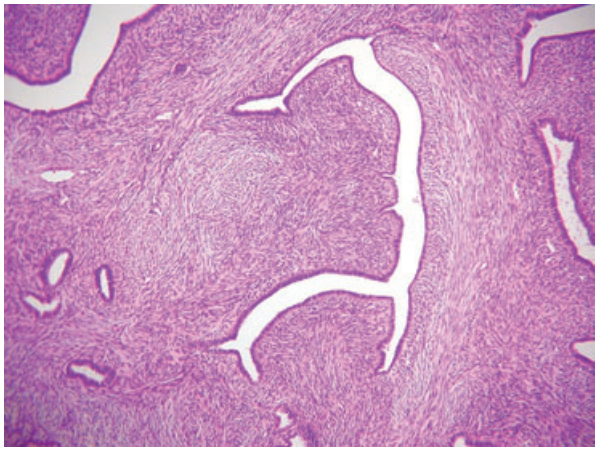

Fig. 2 Uterine histology from proband of family K5 (Table 1). Medium power (×20) view of section from uterus including endometrium. This reveals the typical features of a low-grade Mullerian adenosarcoma, which include a stag-horn neoplastic, benign gland, surrounded by condensed cellular, slightly atypical stroma with very few mitoses. There were also appearances of a likely invasion to the inner half of the myometrium. The immunoprofile (not shown) of the adenosarcoma revealed: stromal positivity with CD10 that was more pronounced in the cambium layer around the glands; a moderate proliferation score with MiB1 staining, which was greater in the stromal compartments; and a marked absence of smooth muscle. The low mitotic count and the lack of marked atypia are the likely results of the progestogen therapy that the patient had received. However, the patient had no prior exposure to tamoxifen therapy.

these families revealed that their ability to reproduce was not significantly different from that of their unaffected male or female relatives (Table 4).

Discussion

Our analysis of HPT-JT families, which has revealed an absence of genotype–phenotype correlation together with a high degree of nonpenetrance, has expanded the spectrum of HPT-JT-associated tumours to include uterine tumours. In addition, our results show that these uterine tumours likely contribute to the decrease in reproductive fitness of women affected with HPT-JT. These uterine tumours are likely to harbour somatic mutations or LOH involving the *HRPT2* gene similar to that reported for parathyroid tumours from HPT-JT patients [16, 17], and a study for these DNA abnormalities is required once suitable uterine tumour specimens become available.

The size of the *HRPT2* gene, the absence of a genotype–phenotype correlation together with an absence of a 'mutational hotspot' will 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

Table 4 Summary of reproductive data from 198 individuals from 19 hyperparathyroidism-jaw tumour (HPT-JT) kindreds

	Affected (or carrier)		Unaffected			
	With offspring	No offspring	With offspring	No offspring	Total	Affected : unaffected
Males	49[b,c]	2[b,c]	43[c]	1[c]	95	1.2 : 1
Females	32[a,b]	12[a,b]	57[a,d]	2[a,d]	103	0.8 : 1
Total	83	14	105	3	198	0.9 : 1
Male : female	1.5 : 1	0.2 : 1	0.8 : 1	0 : 1		

Reproductive data for adult married affected or mutation carrying individuals, and unaffected individuals in 19 HPT-JT kindreds. The affected and carrier females were significantly less likely to have offspring when compared with the unaffected females ([a]$P < 0.001$) and to the affected and carrier males ([b]$P < 0.01$). In contrast, the affected and carrier males did not differ in their ability to have offspring when compared with the unaffected males ([c]$P = 0.7$), or to the unaffected females ([d]$P = 0.9$). *P*-values were calculated using the chi-square test. Updated data, which were available for 11 kindreds (K2, 5, 7, 16, 18, 26–31, Tables 1 and 2) were pooled with the previously published data [5, 10, 15, 18] from nine kindreds (K3, K8, K11, K20–K25, Tables 1 and 2) for this analysis. An analysis utilizing only the updated data from the 11 kindreds yielded the same significant outcomes. For affected individuals, who had offspring, the numbers of offspring per affected (carrier) male and female in 81 individuals (47 males and 34 females) in 19 kindreds (K2, K3, K5, K7, K8, K11, K16, K18, K20–K27 and K29–K31) from whom data were available, were 2.51 and 2.97, respectively. Excluding the six Romany kindreds (K20–K25) who tended to have more children at an earlier age, altered the numbers of offspring per affected male and female to 2.49 and 2.68, respectively.

Table 5 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	6–12 months
Ossifying jaw fibromas	Panoramic jaw X-rays with neck shielding[d]	5 years
Renal	Abdominal MRI[d,e]	5 years
Uterine	Ultrasound (transvaginal or transabdominal), and additional imaging ± D&C if indicated[f]	Annual

[a]Screening for the most common hyperparathyroidism-jaw tumour (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 ionizing radiation should ideally be avoided to minimize 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.

with HPT-JT, FIHP and 'nonfamilial' parathyroid carcinomas, as it is likely to help in their clinical management and in the genetic counselling and screening of their relatives. This genetic counselling and screening should be extended to include second-degree relatives of a patient as nonpenetrance can be >30%. It is important to note that >20% of HPT-JT families will not have mutations involving the coding region and the adjacent splice junctions (Table 2). These families may have mutations involving: the promoter regions; the untranslated regions; the alternate transcript that remains uncharacterized; 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. These HPT-JT families that do not have coding region *HRPT2* mutations cannot be clinically distinguished from those HPT-JT families that have *HRPT2* mutations. The parathyroid, uterine and renal malignancies 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. Guidelines for regular screening for the development of HPT-JT-associated tumours are not available, and we therefore suggest them (Table 5). These suggested guidelines will need to be modified in the light of emerging and future clinical and genetic data, and a notable example of the former is our identification of the association of uterine tumours in 13 HPT-JT families (Table 4), which have been previously emphasized in only one other HPT-JT family in which two sisters had uterine adenomyomatous polyps [29]. These uterine tumours significantly reduced the reproductive fitness of the women affected by HPT-JT (Table 3) and an earlier detection of these uterine abnormalities together with appropriate treatment will not only help to reduce morbidity and mortality, but also enhance the ability for such women to have children. Indeed these uterine abnormalities may partially explain the rarity of large HPT-JT kindreds, and account for the difficulties of finding recombinants for gene localization in past studies [15].

Conflict of interest

None

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Correspondence: Prof. Rajesh Thakker, Academic Endocrine Unit, OCDEM, Churchill Hospital, Headington, Oxford OX3 7LJ, UK. (fax: 44 1865 857502; e-mail: rajesh.thakker@ndm.ox.ac.uk).