The hyperparathyroidism-jaw tumour syndrome in a Portuguese kindred

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Summary

The hyperparathyroidism-jaw tumour (HPT-JT) syndrome is an autosomal dominant disease characterized by the occurrence of parathyroid tumours and fibro-osseous tumours of the jaw bones. Some HPT-JT patients may also develop renal abnormalities, which include Wilms’ tumours, hamartomas and polycystic disease. The HPT-JT gene has been mapped to chromosome 1q25-q31, and we report the clinical and genetic findings in a kindred from central Portugal. HPT-JT was observed in six members from three generations; all had primary hyperparathyroidism (five had parathyroid adenomas, one a parathyroid carcinoma). Ossifying jaw fibromas affecting the maxilla and/or mandible were observed in 5/6. Renal cysts (<2.5 cm) were observed in four. Genetic studies using 18 polymorphic loci from chromosome 1q25-q31, together with leukocyte DNA from 11 family members and tumour DNA from three parathyroids (two adenomas and one carcinoma), revealed loss of tumour heterozygosity in the parathyroid carcinoma only, and the retained haplotype was found to cosegregate with the disease in the six affected members. A new Portuguese kindred with the HPT-JT syndrome that maps to chromosome 1q25-q31 has been identified, and these findings will help in the further characterization of this inherited disorder.

Introduction

Primary hyperparathyroidism (HPT), which may result from parathyroid adenomas, hyperplasia, or carcinoma, has an incidence of 1:1000 and is most frequently encountered as a non-familial disorder.2 However, approximately 10% of patients with primary HPT will have a hereditary form which may either be part of the multiple endocrine neoplasia (MEN) type 1 (MEN1) or type 2 (MEN2) syndromes,3 or part of the hereditary HPT-jaw tumour (HPT-JT) syndrome.4,5 In addition, hereditary primary HPT may develop as a solitary endocrinopathy, and this has also been referred to as familial isolated HPT (FIHP).6 Investigations of these hereditary and sporadic forms of primary HPT have
helped to identify some of the genes and chromosomal regions that are involved in the aetiology of parathyroid tumours (Table 1). The HPT-JT syndrome is an autosomal dominant disorder characterized by the occurrence of parathyroid tumours, ossifying fibromas of the jaw bones, Wilms’ tumours, renal cysts, renal hamartomas, renal cortical adenomas, papillary renal cell carcinomas, pancreatic adenocarcinomas, testicular mixed germ cell tumours with a major seminoma component, and Hurthle cell thyroid adenomas. The gene causing HPT-JT has been mapped to chromosome 1q25-q31, and one study reported a localization to a 0.7 cM region. However, a re-evaluation of the data together with the genetic and physical maps of this region has indicated that the region containing the HPT-JT gene is likely to be much bigger, and within a 14.0 cM region flanked centromerically by the locus CHLC.12F10 and telomerically by D1S1632. We have recently identified a Portuguese kindred with the HPT-JT syndrome, and performed clinical and genetic studies to define further the features of this hereditary parathyroid disorder.

Methods

Family and case histories

Eleven members of a kindred originating from the central region of Portugal were clinically and biochemically assessed for manifestations of HPT-JT. Biochemical investigations included estimations of serum calcium, phosphate, magnesium, alkaline phosphatase, 24-h urinary calcium estimation (by colorimetric determination using a Beckman Synchron clinical systems CX7D) and parathyroid hormone (PTH) (measured by immunoradiometric assay with the kit ELSA-PTH, CIS, France).

Six individuals were found to have hypercalcaemia (Table 2) with elevated serum PTH and underwent parathyroidectomy. Six parathyroid tumours (five adenomas and one carcinoma) were removed from the six affected members. Five of the six affected family members were found to have radiological evidence of jaw tumours, and three underwent surgery to remove them. Wilms’ tumours or renal hamartomas were not found, but four patients had renal cysts. The detailed case histories of the affected individuals (Figure 1, Table 2) are as follows.

Patient II.1, who was the proband, developed, in 1975, at the age of 31 years, a swelling at the angle of the left jaw (Figure 2). This enlarged over the next 2 years, and radiology revealed it to be a mandibular cyst associated with bone destruction. He was noted to be hypercalcaemic with an elevated serum PTH and alkaline phosphatase, and he underwent parathyroidectomy with removal of a left parathyroid adenoma. He became normocalcaemic but the mandibular cyst enlarged, and was treated initially with radiotherapy and later, at 43 years of age, by surgery. Histology revealed that this was an ossifying fibroma. Renal ultrasonography revealed a 1.8 cm cyst in the right kidney. He had hypertension and developed chronic renal failure that required haemodialysis, and he died aged 51 years old.

Patient I.1, who was the father of the proband, was known to have undergone excision of a maxillary jaw tumour in 1938, aged 18 years. He remained well, but was found to have primary HPT at the age of 73 years. Parathyroidectomy revealed a parathyroid carcinoma invading the right side of the thyroid. He remained hypercalcaemic and died aged 76 years. Renal ultrasonography revealed no abnormalities.

Patient II.3, who was the brother of the proband, presented with a right mandibular jaw tumour aged 23 years (Figure 3). He was found to have primary
### Table 2. Clinical details of family members affected with HPT-JF

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>1-HPT</th>
<th>Age of diagnosis (years)</th>
<th>Parathyroid tumours (number and histology)</th>
<th>Location of jaw tumours (number and histology)</th>
<th>Serum PTH (ng/ml)</th>
<th>Urine PTH (mg/dl)</th>
<th>Urine Ca (mg/dl)</th>
<th>Serum ALP (IU/L)</th>
<th>Urine ALP (IU/L)</th>
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<tbody>
<tr>
<td>I.1</td>
<td>51</td>
<td>M</td>
<td>73</td>
<td>23</td>
<td>Maxilla</td>
<td>Mandible</td>
<td>81.9</td>
<td>2.2</td>
<td>11.7</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
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<td>76 (deceased)</td>
<td>M</td>
<td>32</td>
<td>23</td>
<td>Maxilla</td>
<td>Mandible</td>
<td>380</td>
<td>4.0</td>
<td>14.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>II.2</td>
<td>51 (deceased)</td>
<td>M</td>
<td>42</td>
<td>23</td>
<td>Maxilla</td>
<td>Mandible</td>
<td>1500</td>
<td>15.0</td>
<td>35.4</td>
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<td>1.0</td>
</tr>
<tr>
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<td>28</td>
<td>M</td>
<td>24</td>
<td>21</td>
<td>Mandible and maxilla</td>
<td>Mandible</td>
<td>181</td>
<td>1.9</td>
<td>12.1</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>III.2</td>
<td>25</td>
<td>M</td>
<td>24</td>
<td>21</td>
<td>Mandible and maxilla</td>
<td>Maxilla</td>
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<td>3.8</td>
<td>14.9</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
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<td>14</td>
<td>F</td>
<td>13</td>
<td>13</td>
<td>Maxilla</td>
<td>Mandible</td>
<td>674</td>
<td>1.7</td>
<td>12.0</td>
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<td>1.0</td>
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<tr>
<td>III.4</td>
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<td>F</td>
<td>13</td>
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<td>Maxilla</td>
<td>Mandible</td>
<td>194</td>
<td>3.0</td>
<td>12.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

HPT at the age of 42 years, and neck exploration revealed a parathyroid adenoma. At age 53 years, he remains well and normocalcaemic, with a normal serum PTH. Renal ultrasonography and computerized tomography scanning have revealed two right renal cysts measuring 1 cm each.

Patient III.1, who is the son of the proband, developed renal stones at the age of 24 years. He was found to have primary HPT, and following removal of a parathyroid adenoma has remained normocalcaemic at age 28 years. Radiology has not revealed jaw tumours but renal ultrasonography and CT scanning have revealed several bilateral renal cysts that are <2.0 cm.

Patient III.3, who is the daughter of the proband, presented with a right mandibular tumour, at the age of 21 years, which was excised and found to be an ossifying fibroma (Figure 4). She was also found to have primary HPT, and following removal of a parathyroid adenoma, has remained normocalcaemic, at age 25 years. Renal ultrasonography has not detected any abnormalities.

Patient III.4, who is the niece of the proband, was asymptomatic and found to be affected with primary HPT and jaw tumours by biochemical and radiological screening at the age of 13 years. Parathyroidectomy, in 1999, which revealed the presence of an adenoma, restored normocalcaemia for 3 months, following which she had recurrent hypercalcaemia with elevated serum PTH concentrations. The right mandibular and left maxillary jaw tumours are being managed conservatively. Renal ultrasonography has revealed ~1.5 cm and 2.0 cm cysts in the left and right kidneys, respectively.

Individual IV.1 (Figure 1) who is 7 years old and has the affected haplotype (Figure 1) is normocalcaemic with normal serum PTH, and does not have jaw tumours.

### Microsatellite polymorphisms and linkage analysis

Venous blood samples were obtained from four living members (II.3, III.1, III.3, III.4) of the six affected individuals, one unaffected family member and four spouses. In addition, normal thyroid and parathyroid tissue embedded in paraffin were obtained from the affected members I.1 and II.1, respectively. Three parathyroid tumours (one carcinoma and two adenomas) from patients I.1, III.1 and III.4 were also obtained, and all of these samples were used for genetic mapping studies. DNA from leukocytes, normal tissue and tumours was prepared as described previously.28,29

The DNA was used to detect microsatellite polymorphisms as described previously.20,28,30
Figure 1. Pedigree of the family segregating for HPT-JT and 18 polymorphic loci from chromosome 1q25-q31. The loci are shown in the correct order. The affected haplotype is shown by the solid bar and the unaffected haplotype is shown by the open bar. Deduced haplotypes are illustrated within the squared brackets. In some individuals, the inheritance of paternal alleles can be ascertained, and in these the paternal haplotype is shown on the left.
Eighteen polymorphic microsatellite loci (locus order: 1cen – D1S215 – D1S466 – D1S2701 – D1S240 – D1S2848 – D1S254 – D1S444 – D1S191 – D1S222 – D1S428 – D1S422 – D1S412 – D1S413 – D1S2853 – D1S2622 – D1S306 – D1S456 – D1S245 – 1qter) from chromosome 1q25-q31 (Figure 1), four polymorphic markers from chromosome 11q13 (D11S1883, D11S4946, D11S449, D11S913) and six polymorphic markers from chromosome 13q (D13S221, D13S260, D13S171, D13S267, D13S153, D13S170) were used as reported.\textsuperscript{18,20,28,30} The microsatellite polymorphisms obtained from the tumours were compared with those from the leukocytes (or normal tissue) of the same patient, and LOH (loss of heterozygosity) in the tumours was scored only if there was an absence or a marked reduction in the visually assessed intensity of one of the bands.\textsuperscript{18,20,28} Two-point Lod scores were calculated, using the LINKAGE computer programs as described,\textsuperscript{30} with a disease penetrance of 90\%.\textsuperscript{18,30}

Results

Clinical studies

Five of the six individuals (Table 2) presented with symptoms or signs at between 18 and 31 years of age. Four of these five presented with swelling of the mandibular or maxillary bones, and in two these were histologically proven to be ossifying fibromas. All of these four patients (II.1, II.1, II.3, III.3) also developed parathyroid tumours (three had adenomas and one had a carcinoma). The other symptomatic patient (III.1) presented with renal stones and primary HPT due to an adenoma; he has not developed jaw tumours. One patient (III.4), who is 14 years old, was asymptomatic and the primary HPT and jaw tumours were detected by biochemical and radiological screening, respectively. Four patients had renal cysts (<2.5 cm) detected by renal ultrasonography and/or CT scanning. Finally, one individual who is 7 years old and has inherited the affected haplotype remains asymptomatic and biochemically normal. These studies indicate that this family from central Portugal suffers from the HPT-JT syndrome, which is likely to have a variable penetrance. The results indicate that this autosomal disorder is unlikely to present before the age of 7 years, but is likely to have a high penetrance by the third decade, and that most patients will develop both primary HPT and ossifying fibromas of the jaw. The young (i.e. $<40$ years age) onset of primary HPT and the higher likelihood of the occurrence of parathyroid
carcinoma\textsuperscript{11,13,17,26,27} distinguishes this disorder from the commoner forms of sporadic primary HPT.

**Genetic studies**

The gene causing HPT-JT has been localized to chromosome 1q25-q31, and studies of two parathyroid adenomas and one carcinoma revealed LOH involving loci from 1q25-q31 in the parathyroid carcinoma (Figure 5). A similar analysis of loci from chromosome 11q13, the location of the MEN1 gene, did not reveal LOH in any of the parathyroid tumours. However, an analysis of loci on chromosome 13q detected LOH in the parathyroid carcinoma from patient I.1 involving D13S153, which is located in the vicinity of the retinoblastoma (RB1) gene. The RB1 gene frequently shows LOH in parathyroid carcinoma\textsuperscript{19,20} LOH was not detected.
at the other chromosome 13q loci in the parathyroid carcinoma. In addition, the analysis of the chromosome 13q loci did not detect LOH in the adenomas from patients III.1 and III.4 (Figure 5). Segregation studies using the chromosome 1q25-q31 loci revealed that the retained haplotype in the parathyroid carcinoma is the same as the affected haplotype in the family (Figure 1). Thus, this finding of LOH involving the chromosome 1q25-q31 loci in the parathyroid carcinoma is consistent with the hypothesis that HPT-JT is due to a tumour suppressor gene.\textsuperscript{10,17} The co-segregation of the chromosome 1q25-q31 haplotype with the disease (Figure 1) (maximum LOD score 1.7, at 0\% recombination with D1S215 and D1S2848) indicates that HPT-JT in this kindred is likely to involve the same locus as that described in other Northern European and American kindreds.\textsuperscript{5,10-13} However, a detailed comparison of the haplotype in this HPT-JT kindred from central Portugal with that from a previously reported kindred with HPT from Southern Portugal,\textsuperscript{18} indicates that the two kindreds are unrelated. Thus, these studies have identified another family with the HPT-JT syndrome that is located on chromosome 1q25-q31.

**Discussion**

Our studies report on the clinical and genetic findings in a Portuguese family with the HPT-JT syndrome, which is a rare autosomal dominant disorder characterized by the development of parathyroid adenomas and fibro-osseous jaw tumours.\textsuperscript{4,5,10,11,13,17,26,27} In addition, some patients may also develop renal, pancreatic, thyroid and testicular tumours.\textsuperscript{5,10,11,13,17,27} It is important to note that the parathyroid tumours may occur in isolation and without any evidence of jaw tumours,\textsuperscript{4,5,10,11,13,17,26,27} and this may cause confusion with other hereditary hypercalcaemic disorders such as MEN1, familial benign hypercalcaemia (FBH), also referred to as familial hypocalciuric hypercalcaemia (FHH), and FIHP. HPT-JT can be distinguished from FBH, as in FBH serum calcium is elevated from the early neonatal or infantile period,\textsuperscript{24,25} whereas in HPT-JT such elevations are uncommon in the first decade, as illustrated by individual IV.1 (Figure 1 and Table 2). In addition, HPT-JT patients, unlike those with FBH, will have associated hypercalciuria (Table 2). The distinction between HPT-JT patients and MEN1 patients who have only developed the usual first manifestation of hypercalcaemia (>90\% of patients\textsuperscript{5}), is more difficult and is likely to be influenced by the operative and histological findings, and the occurrence of other characteristic lesions in each disorder. HPT-JT patients will usually have single adenomas or a carcinoma, while MEN1 patients will often have multiglandular and hyperplastic parathyroid disease.\textsuperscript{4,5,26} The distinction between FIHP and HPT-JT in the absence of jaw tumours is difficult but important, as HPT-JT patients may be at a higher risk of developing parathyroid carcinomas.\textsuperscript{11,13,17,26,27} These distinctions may be helped by the identification of additional features, and a search for jaw tumours, renal, pancreatic, thyroid and testicular abnormalities\textsuperscript{4,5,10,11,13,17,26,27} may help to identify HPT-JT patients. Indeed in our study, >80\% of the HPT-JT patients had jaw
Figure 5. LOH (loss of heterozygosity) studies on chromosome 1q25-q31 and 13q11-q31 in one carcinoma (C) from patient I.1, one adenoma (A) from patient III.1 and one adenoma from patient III.4. At each represented locus, the leukocytes (L) are heterozygous. Some tumours (T) have lost an allele, which is indicated by the arrow. LOH involving chromosome 1q25-q31 was found in the parathyroid carcinoma only; the retained allele segregated with the disease (Figure 1). These results are consistent with HPT-JT being caused by a tumour suppressor gene. LOH on chromosome 13q was found in the carcinoma of patient I.1 involving D13S153, which is at the RB1 locus, and D13S170 which is telomeric of the RB1 locus, but not the BRCA2 locus (data not shown). No LOH was found in the two adenomas from patients III.1 and III.4.
tumours and ~67% of the HPT-JT patients had renal cysts. Furthermore, the jaw tumours in HPT-JT are different to the brown tumours observed in some patients with primary HPT, and do not resolve after parathyroidectomy.4,5,26 as illustrated by the case history of the proband, II.1 (Figure 2). Indeed, ossifying fibromas of the jaw are an important distinguishing feature of HPT-JT from FIHP, and the occurrence of these may occasionally precede the development of hypercalcaemia in HPT-JT patients by several decades, as illustrated by patient I.1.

The use of polymorphic genetic markers from chromosome 1q25-q31 for the detection of LOH in parathyroid and renal tumours, and for segregation studies may also help to clarify the differences between HPT-JT and the other hyperparathyroid disorders (Table 1). However, of the 22 HPT-JT parathyroid tumours studied to date (19 adenomas and three carcinomas) only the three carcinomas showed LOH.5,10,11,13,17 Our results, showing that this LOH involved deletions of the unaffacted chromosomal loci (Figure 1 and Figure 5), are the first to demonstrate that such parathyroid tumour development in HPT-JT is consistent with the Knudson two-hit hypothesis,31 this provides support for the involvement of a tumour suppressor gene in the aetiology of HPT-JT tumours. The absence of LOH in the parathyroid adenomas suggests that inactivation by gross deletion of the HPT-JT gene is unlikely to be frequent, and that microdeletions, point mutations or other mechanisms such as methylation, may also be involved in the inactivation of the wild-type allele. However, an alternative explanation is that the LOH of chromosome 1q may be a late and non-specific event,13 particularly as it is only observed in parathyroid carcinomas and not adenomas. The use of such genetic markers in distinguishing between HPT-JT and FIHP needs to be used with caution, as previously reported studies of kindreds with FIHP17,18 have shown that one form of FIHP also maps to the chromosome 1q22-q31 region. Thus, detailed clinical studies are likely to be of importance in distinguishing families with HPT-JT from the other hereditary hypercalcaemic disorders, and studies similar to ours, which document the manifestations of HPT-JT together with their variable penetrance, are likely to help characterise the features of this rare inherited tumour syndrome.

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References


