INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common endocrine disorder. However, a familial hyperparathyroid syndrome is diagnosed in less than five percent of cases. We present two related cases of CDC73-related familial hyperparathyroidism due to a rarely described germline Leu63Pro missense mutation in CDC73 exon 2.

CASE REPORT

The index patient, a 24-year old female, presented acutely unwell with symptoms of hypercalcaemia. Her blood tests showed PTH 186.1 pmol/L, Ca 4.20 mmol/L. Parathyroid imaging demonstrated bilateral parathyroid adenomas. Her life-threatening hypercalcaemia was treated with intravenous saline and bisphosphonates. However despite treatment with cinacalcet, persistent severe symptomatic hypercalcaemia was treated withintravenous saline and bisphosphonates. Her recovery was complicated by severe hangybonesyndrome.

The patient’s parents are unaffected by hyperparathyroidism. However it transpired that her 35-year old brother had a history of resected Wilms’ tumour aged 5. He also had PHPT with a left inferior parathyroid adenoma. Further enquiry into the family history revealed that a paternal cousin also had hypercalcaemia and had more than one parathyroid glands removed. In addition, the paternal grandmother had also suffered from renal stones.

Genetic testing revealed germline Leu63Pro missense mutation in CDC73 exon 2, gene coding for the parafibromin protein.

<table>
<thead>
<tr>
<th>Family Mutation</th>
<th>Leu63Pro missense</th>
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<tbody>
<tr>
<td>Patient</td>
<td>Sister Brother</td>
</tr>
<tr>
<td>Age at diagnosis (yrs)</td>
<td>24 32</td>
</tr>
<tr>
<td>Corrected Ca (mmol/L)</td>
<td>4.20 2.80</td>
</tr>
<tr>
<td>Serum PTH (pmol/L)</td>
<td>186.1 31.2</td>
</tr>
<tr>
<td>No. of parathyroid tumours removed; histology</td>
<td>4 Hyperplasia 3 adenoma</td>
</tr>
<tr>
<td>Other non-parathyroid features</td>
<td>Nil Wilms’ tumour at age 5 years</td>
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Table 1: Biochemical and pathological findings

DISCUSSION

CDC73-related familial hyperparathyroidism encompasses a spectrum of parathyroid disorders including the following phenotypes:

- hyperparathyroidism-jaw tumour syndrome (HPT-JT)
- Parathyroid carcinoma
- Familial isolated hyperparathyroidism (FIHP)

HPT-JT is an autosomal dominant condition with incomplete penetrance, characterised by atypical parathyroid tumours (~15% malignant) with tumours of one or more of the jaw, kidneys or uterus. Approximately 100 affected families have been reported in the medical literature.

CDC-73 (formerly known as HRPT2) is a gene that encodes the tumour suppressor protein parafibromin. More than 44 pathologic sequence variants have been described for CDC-73 and account for the spectrum of disorders. Most reported mutations are small deletions or insertions leading to truncation of the parafibromin protein. CDC-73 mutations have been implicated in the malignant transformation of parathyroid tumours.

CDC-73 mutations are predominantly found in exons 1, 2 and 7. Most mutations appear to be unique to individual families; however some mutations have been found in unrelated families. The CDC73 germline Leu63Pro missense mutation, documented in our case, was previously identified only once, in 2008 in an Italian kindred with FIHP.

Patients with HPT-JT are at high risk of recurrent parathyroid and non-parathyroid tumours and require long-term surveillance. Similarly, genetic testing must be offered to at-risk relatives starting around age 5-10 years if the family-specific CDC73 germline mutation is identified.

REFERENCES