Familial isolated primary hyperparathyroidism due to HRPT2 mutation

with chief cells was confirmed by the histopathological report and the second lesion proved to be a thyroid nodule. After surgery, calcemia and PTH level normalized. Thyroid replacement therapy with 50μg LT4/day was prescribed.

**Genetic tests**

The HRPT2 and menin genes were studied by amplification of exon and intron regions by PCR and direct sequencing of amplicons. The results were expressed according to the nomenclature of the Human Genome Variation Society.

17 exons were studied for HRPT2 gene and the same mutation was found in all three cases. Nucleotide variation was:

- **Exon (s)**: 6
- **Nucleotide nomenclature**: c.505C>T
- **Proteic nomenclature**: p. Gln169X

The pathological presence of a stop-codon leads to the synthesis of a truncated protein.

Using Multiplex Ligation-dependent Probe Amplification, the presence of HRPT2 gene deletion or duplication was disproven.

9 exons were studied for MEN1. No nucleotide variations, gene deletion or duplication were found.

**DISCUSSION**

Compared to sporadic primary hyperparathyroidism, familial hypercalcemia has a lower prevalence, a younger age at diagnosis and an equal ratio between affected men and women. The most frequent histopathological lesion is solitary parathyroid adenoma in sporadic primary hyperparathyroidism and hyperplasia or multiple parathyroid adenomas in familial hypercalcemia (Table 2).

Causes of familial hypercalcemia include hereditary forms of primary hyperparathyroidism and impaired cellular response to extracellular calcium fluctuations.

There are three syndromes associated with primary hyperparathyroidism:
- MEN 1 and 2A;
- hyperparathyroidism-jaw tumor syndrome (HPT-JT);
- familial isolated hyperparathyroidism (FIHP);
- Impaired cellular response to extracellular calcium fluctuations is responsible for:
  - familial benign hypocalciuric hypercalcemia;
  - severe neonatal hypercalcemia.

**MEN1 syndrome** has an autosomal dominant inheritance with 100% genetic penetrance by age of 50. In most cases, primary HPT is the first clinical manifestation. Associated tumors are located in the endocrine pancreas, pituitary, adrenal cortex or carcinoid tumors.

The etiology of MEN1 syndrome is menin inactivation. The **MEN1** tumor suppressor gene was cloned from 11q13 by positional cloning. Its product, menin, has been found to bind specifically to JunD, whereas disruption of this binding activity by **MEN1** mutations leads to inhibition of JunD-activated transcription.

Over 100 germline mutations of this tumor suppressor gene have been reported (exons and introns: missense, nonsense, frameshift, ARNm splicing defects). The type of mutation is not associated with a specific phenotype but is present in all affected family members. Genetic testing is required to confirm the clinical diagnosis.

**MEN2A syndrome** has an autosomal dominant inheritance with 95% genetic penetrance. Only 25% of these patients have primary hyperparathyroidism. Associated tumors are: medullary thyroid carcinoma and feocromocitoma. Etiology of this syndrome is activating mutations of the RET proto-oncogene (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Sporadic primary hyperparathyroidism</th>
<th>Familial hypercalcemia</th>
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</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>7 cases/100,000 inhabitants³</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>&lt;50 years</td>
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<tr>
<td>Women/Men</td>
<td>1/1</td>
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<tr>
<td>Most frequent histopathological lesion</td>
<td>Solitary parathyroid adenoma</td>
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<tr>
<td></td>
<td>Hyperplasia or multiple parathyroid adenomas</td>
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</table>

References:
1. ≤50 years
2. >50 years
3. 3/1
4. 1/1