Familial bilateral macronodular adrenal hyperplasia due to a new ARMC 5 germline mutation. Clinical status and possible association with other neoplasms.

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Abstract

Mutations in the ARMC5 gene (armadillo repeat containing 5, OMIM 615549), a putative tumor suppression gene, have recently been identified as a common cause of sporadic and familial bilateral macronodular adrenal hyperplasia (HAMB). HAMB in familial cases is believed to be determined by two mutations, one germinal and the other somatic, as pointed out by the theory of the 2 hits. We present an affected family with 11 members carrying a new mutation of the ARMC5 gene (NM_001288767.1): c.2162T > C p. (Leu721Pro). Two of the carrier patients developed clinical Cushing Syndrome (CS), two possible autonomous cortisol secretion (ACS) and 1 presented with autonomous cortisol secretion (ACS). Four patients suffered from malignant neoplasms. Three of them died from these tumors.

Introduction

There are genes responsible for protecting human genetic material. Tumor suppressor genes act as guardians of the genome, hindering the development of neoplasms. The inactivation of these genes is a fundamental event in the pathogenesis of human cancer\(^1\). In this sense, the armadillo repeat containing 5 (ARMC5) gene acts as a tumor suppressor gene\(^2,3,4\). In vitro studies have shown that ARMC5 induces cellular apoptosis, while the inactivation of ARMC5 nullifies this effect\(^5\). That is why the inactivation of ARMC5 could lead to a situation of resistance to apoptosis.

It has also been proven that germline mutations in the ARMC5 gene determine adrenal hyperplasia of adrenocortical cells with the development of nodules with hyperproduction of cortisol, being a frequent cause of bilateral macronodular adrenal hyperplasia (HAMB). Theoretically, these mutations of the ARMC5 gene could also increase vulnerability to the appearance of other neoplastic processes, and the concurrence of other tumors in patients with HAMB has been described\(^5,6\).

We present a family with 11 carriers of a new mutation of the ARMC5 gene. Several carriers presented with HAMB: 2 developed clinical Cushing syndrome (CS), 2 presented with possible autonomous cortisol secretion (PACS) and 1 presented with autonomous cortisol secretion (ACS). Four carriers presented with malignant neoplasms. one prostate carcinoma and three obligate carriers of the mutation (not tested) due to having offspring carrying it, died of malignant neoplasms - carcinoma of the larynx, gastric carcinoma and carcinoma of the lung.

Methods

A retrospective observational study was carried out in which a family with ARMC5 gene mutation carriers was included.

The variables included were: age, sex, presence of ARMC5 gene mutation, imaging tests performed, results of cortisol suppression test with 1mg dexamethasone, surgeries performed, presence of tumors and exits.
Genetic study was performed in all living relatives by capillary sequencing of exon 7 of the ARMC5 gene (NM_001288767.1). The adrenal function of the patients was classified according to the Criteria of European Society of Endocrinology.

**Case Description**

The index case was a 48-year-old woman, referred to our consultations for bilateral adrenal incidentalomas. She had no relevant personal history. In the initial study, she presented with a dexamethasone suppression test (1mg) with a result in the range of probable autonomous cortisol secretion. 2 years later, she developed symptoms suggesting hypercortisolism (weight gain, asthenia, capillary fragility and hypertension). The diagnosis of CS was confirmed by pathological tests: with a 1mg dexamethasone suppression test, 2 urinary free cortisol and 2 nocturnal salivary cortisol pathological tests. An I-cholesterol scintigraphy and a SPECT-CT showed a predominantly right bilateral nodular adrenocortical hyperplasia. The patient underwent a total right and subtotal left adrenalectomy, remaining in a situation of normocortisolism.

A 77-year-old uncle of the index case was diagnosed at another center of HAMB with SC and underwent a 2-stage adrenalectomy. Given the suspicion of familial HAMB syndrome, a genetic study of the mutation in the ARMC5 gene was performed in both patients, finding a new mutation: (NM_001288767.1): c.2162T > C p. (Leu721Pro).

Figure 1 shows the family tree and Table 1 shows their most relevant clinical data.
Table 1

<table>
<thead>
<tr>
<th>Number</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Adrenal image</th>
<th>Overnight dexamethasone suppression test (dexamethasone 1mg)</th>
<th>Adrenal surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>48</td>
<td>D: Adenoma (32mm) I: Adenoma (31mm)</td>
<td>CS</td>
<td>Right &amp; subtotal left</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>77</td>
<td>D: Adenoma (36mm) I: Augmented and lobed</td>
<td>CS</td>
<td>Bilateral adrenalectomy</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>68</td>
<td>D: normal I: 2 adenomas (12 &amp; 31mm)</td>
<td>PACS</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>46</td>
<td>D: Normal I: Adenoma (19mm)</td>
<td>N</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>49</td>
<td>D: Adenoma (20mm) I: normal</td>
<td>PACS</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>42</td>
<td>D: 2 adenomas (36mm &amp; 18mm) I: adenoma (22mm)</td>
<td>ACS</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>40</td>
<td>Normal</td>
<td>N</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>37</td>
<td>Normal</td>
<td>N</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>17</td>
<td>Normal</td>
<td>N</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>30</td>
<td>Normal</td>
<td>PACS</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>28</td>
<td>D: normal I: atypical adenoma (16mm)</td>
<td>N</td>
<td>No</td>
</tr>
</tbody>
</table>

CS = Cushing syndrome; PACS = possible autonomous cortisol secretion; N = normal; ACS = autonomous cortisol secretion.
Discussion

We consider the description of this mutation relevant due to its novelty and its association with the presence of tumors not previously associated with the ARMC5 gene.

Recent studies published on mutations in the ARMC5 gene show that adrenal nodes in patients with HAMB tend to be more aggressive and have a larger size when compared to patients without genetic alteration\(^5\). At the same time, a correlation between phenotype and genotype has been described\(^6\). The evolution from a subclinical CS stages (PACS and ACS) to a more open form of hypercortisolism as described in the index case is consistent with other published studies, in which initially there are no functional alterations\(^8\), with a later slow progression towards subclinical and even aggressive clinical forms.

The characteristic slow development of the hormonal hypersecretion determines this diseases diagnosis to be usually delayed until between 40 and 70 years of age and also determines a correlation between the size of the nodules, the basal cortisol levels, the ACTH concentration and the age of the patient\(^4,6,8,9\). Thus, the follow-up of patients genetically affected by an ARMC5 mutation must be carried out indefinitely. The underestimation of the penetrance of the disease would be in line with what has been commented\(^10\).

Knudson's "two-hit" theory\(^11\), described for tumor suppressor genes such as ARMC5\(^12\), implies that the heterozygous germline mutation needs to add a somatic mutation to express phenotypically. In the absence of somatic mutation, the phenotypic expression either does not appear, or it does so late, since due to the inefficiency in the synthesis of cortisol of the adrenal nodules, these would need to reach a large size to cause SC\(^10\). This would explain that not all members of the same family suffer from the disease despite carrying the mutation. In the cases reported in this paper, the mutation could be studied in the germ line, but not the somatic one. Other cases have been described in which the somatic mutation was not found either\(^4,6,8,13,14\).

Somatic mutations in genes such as ARMC5 could contribute to the appearance of neoplasms in other locations, although with mechanisms that are not well clarified\(^8\). Meningiomas\(^15,16\), breast cancer\(^8\), thyroid cancer\(^8\) and parathyroid cancer\(^8\) have been described in patients with ARMC5 mutations. Kyo C et al\(^8\) recently described the existence of extra-adrenal tumors in patients with ARMC5 germline mutation without somatic mutation. In the family described in our publication, 4 carriers of the mutation presented with neoplasms, specifically prostate, larynx, lung and stomach cancer. The high prevalence of neoplastic processes among first-generation family members and what has been referenced above, makes us suspect the existence of a possible relationship between this novel ARMC5 mutation and the incidental presence of these tumors. It remains to be determined whether patients with ARMC5 mutations, and specifically the ARMC5 c.2162T > C p mutation (Leu721Pro), should be screened for the early detection of certain neoplasms.
Conclusions
We have described a new mutation of the ARMC5 gene related to HMAB, as well as its phenotypic characteristics. The added peculiarity is the high incidence of other accompanying malignant neoplastic processes in carriers. It would be interesting to introduce a close monitoring of carriers not only aimed at the early diagnosis of the development of HMAB, but also at the appearance of other neoplastic processes.

Declarations

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Conflicts of interest: The authors declare no conflicts of interest.

Authors’ Contributions: APL and MAMC designed the study, IDLR and APG wrote the first draft of the manuscript. All authors corrected and approved the manuscript.

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The authors have no relevant financial or non-financial interests to disclose.

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ana Piñar, Irene de Lara and Diego del Can. The first draft of the manuscript was written by Alfonso Pumar and Miguel Ángel Mangas and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

This is an observational study. The HUVR Research Ethics Committee has confirmed that no ethical approval is required.

Informed consent was obtained from all individual participants included in the study.

The authors affirm that human research participants provided informed consent for publication of any individual details.

References


Figures

![Family tree](image)

**Figure 1**

Family tree.