TIME COURSE OF CENTRAL PREOCIOUS PUBERTY DEVELOPMENT CAUSED BY AN MKRN3 GENE MUTATION: A PRISMATIC CASE

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Background & Objective

- Loss-of-function mutations in the imprinted gene MKRN3 represent the most common known genetic defects associated with central precocious puberty (CPP).
- The penetrance of these mutations remains to be established.
- To date, all reported individuals with MKRN3 mutations were already in puberty or postpubertal and were identified retrospectively.
- We report the first case of a prepubertal child with an MKRN3 mutation who was followed prospectively and developed CPP.

Patient & Methods

- We describe the complete clinical and laboratory features of a female patient carrying an MKRN3 mutation, detected in childhood, followed until the development of pubertal signs.

Results

- The patient was screened at the age of 4 years because of positive family history – her sister developed CPP at the age of 6 years and was found to harbor the MKRN3 p.Pro161Argf*16 mutation, inherited from their asymptomatic father (FIGURE 1).

• During close follow-up, this young girl initially developed increased growth velocity at age of 6 years (9 cm/year) (FIGURE 2 and TABLE 1).

![FIGURE 2. Girl’s stature-for-age growth chart (CDC) showing the accelerated growth in the patient (II.2) with CPP caused by the MKRN3 p.Pro161Argf*16 mutation.](image)

![FIGURE 3. Rapid breast development (Tanner 3) in a 6.7-year-old girl with CPP caused by the MKRN3 p.Pro161Argf*16 mutation. *The exhibition of this picture was authorized by the patient’s parents.](image)

• FOLLOW-UP: In the context of a loss-of-function MKRN3 mutation and a positive family history, these features established the diagnosis of CPP and supported the initiation of treatment with GnRH analog, with complete regression of thelarche after 6 months of therapy.

Table 1. Time course of the clinical and laboratory features of this prepubertal girl, carrying a loss-of-function MKRN3 mutation, who developed CPP.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Tanner Stage</th>
<th>LH (mIU/mL)</th>
<th>FSH (mIU/mL)</th>
<th>Estradiol (ng/mL)</th>
<th>Δ Bone age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.7</td>
<td>0.4</td>
<td>NA</td>
<td>B1 PH1</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>6.0</td>
<td>0.5</td>
<td>9.0</td>
<td>B1 PH1</td>
<td>0.1</td>
<td>1.3</td>
<td>49.7</td>
</tr>
<tr>
<td>6.3</td>
<td>0.6</td>
<td>7.5</td>
<td>B1 PH1</td>
<td>0.4</td>
<td>5.9</td>
<td>41.3</td>
</tr>
<tr>
<td>6.7</td>
<td>0.8</td>
<td>12</td>
<td>B3 PH1</td>
<td>0.9</td>
<td>3.3</td>
<td>54.1</td>
</tr>
</tbody>
</table>


Normal prepubertal reference values (ICMA): LH <0.3 mIU/mL; Estradiol <20 pg/mL.

Conclusions

- MKRN3 mutations likely present with full penetrance.
- The identification of carriers of MKRN3 mutations may contribute to early diagnosis, facilitating treatment decisions, and guiding genetic counselling and prompt interventions.
- This case illustrates how genetic testing can be useful in the clinical setting.

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