We present three intrafamilial cases of normosmic IHH (nIHH) related to a new association of two heterozygotic TARC3 mutations. Idiopathic hypogonadotropic hypogonadism (IHH) is due to the failure of gonadotropin releasing hormone (GnRH) secretion which impairs the physiological initiation of puberty. About 30 to 50% of IHH is associated with hereditary causes and about 50 mutated genes have been identified. We present three intrafamilial cases of normosomic IHH (nIHH) related to a new association of two heterozygotic TARC3 mutations.

**Background and Methods**

- **16-year-old male (III-1)**
  - Referred due to no pubertal development:
    - Small intrascrotal testes (2-3 ml)
    - Spair pubic hair (P1-P2)
    - Small phallus (4 cm)
    - Height: 161.5 cm (Z-score -1.57) and weight: 61.9 kg (Z-score 0.08)
    - Bone age 12.5 years
    - Normal body proportions
    - Normal sense of smell, no renal or craniofacial abnormalities.

- **Two of his three sisters** also presented complete hypogonadism at 14 and 13 years old (III-3 and III-4), both had a normal sense of smell.
- **Onset of their mother’s** (II-1) menarche was at 15 years-old. Their father (II-2) had a normal pubertal development in adolescence.

**Case Report**

**Investigation**

<table>
<thead>
<tr>
<th>Subject</th>
<th>III-1</th>
<th>III-3</th>
<th>III-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH (mIU/ml)</td>
<td>0.2</td>
<td>&lt;0.1</td>
<td>&lt;0.09</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>0.6</td>
<td>0.7</td>
<td>0.29</td>
</tr>
<tr>
<td>Ratio FSH/LH</td>
<td>3</td>
<td>7</td>
<td>3.2</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>ND</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>0.14</td>
<td>0.15</td>
<td>ND</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>3.42</td>
<td>4.3</td>
<td>ND</td>
</tr>
<tr>
<td>IGF-1 (ng/mL)</td>
<td>272</td>
<td>144</td>
<td>144</td>
</tr>
<tr>
<td>Bone age (years)</td>
<td>12.6</td>
<td>12.5</td>
<td>10</td>
</tr>
<tr>
<td>LH pulsatility Apulsatile</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

The father’s mutation was previously described as pathogenic, but the mother’s mutation was classified as of uncertain significance at date.

**Follow-up**

- **Hormonal replacement** was started in III-1 and III-3 with success (III-4 is awaiting)
- All of them maintain their follow-up at paediatric endocrinology outpatient clinic.

**Conclusion**

Congenital IHH is a very rare genetic disorder that if undiagnosed or untreated may lead to infertility associated to complete or partial absence of GnRH. TAC3/TACR3 mutations have a critical importance on sexual maturation and are an important genetic cause of nIHH that should be particularly searched in patients with high serum FSH/LH ratio. The treatment of nIHH is based on sex steroids replacement, therefore promoting the pubertal development.

**References**