A NOVEL INACTIVATING COMPOUND HETEROZYGOUS MUTATION IN KISS1R/GPR54: CASES OF THREE SIBLINGS
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Introduction

Idiopathic hypogonadotropic hypogonadism (IHH)

- A rare genetic disorder
- Caused by defect in the secretion of gonadotropin-releasing hormone (GnRH) the action of GnRH on the pituitary gonadotropins
- Incidence: 1–10/ 100 000 live births
- 50 genes have been reported: KISS1R is one of these genes

Kisspeptin

- A neuropeptide encoded by the KISS1 gene
- Acts upstream of gonadotropin-releasing hormone (GnRH) neurons
- Has a critical role for maturation and function of the reproductive axis

We present three siblings with NHH due to a compound heterozygous mutation including c.969C>A (p.Y323X) and novel c.170T>C (p.L57P) in KISS1R in a non-consanguineous family.

Case Report

- In index case, we found a compound heterozygous mutation in the KISS1R, one of these was a nonsense variant (c.969C>A, p.Y323X) which was known as an inactivating mutation caused IHH and the other was a novel missense variant (c.170T>C, p.L57P).
- Molecular analysis of the parents showed that both parents were heterozygous carriers. While the mutation c.969C>A (p.Y323X) was inherited from the father, c.170T>C (p.L57P) was inherited from the mother.
- The molecular analysis of his siblings were performed. Karyotype analysis of all three sisters were 46,XX. Genetic analysis of both sisters who were fourteen and twelve years old revealed the same compound heterozygous mutation in the proband whereas the genetic analysis of the youngest one was normal. Clinical and hormonal characteristics of all cases including the proband are shown in the table 1.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Gender</th>
<th>Puberty</th>
<th>Laboratory</th>
<th>Total Testosterone (ng/ml)</th>
<th>Extradial (μg/ml)</th>
<th>AMH (ng/ml)</th>
<th>Karyotype</th>
<th>Genetic analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>14,08</td>
<td>Male</td>
<td>Tanner stage 1</td>
<td>0.9</td>
<td>15</td>
<td>14</td>
<td>51.2 (2-30.7)</td>
<td>15x15x15</td>
<td>c.969C&gt;A (p.Y323X) ve c.170T&gt;C (p.L57P) compound heterozygous mutation in KISS1R</td>
</tr>
<tr>
<td>14</td>
<td>Female</td>
<td>Tanner stage 3 Amenorrhea</td>
<td>0.13</td>
<td>0.1</td>
<td>4.06</td>
<td>1.21</td>
<td>46XX</td>
<td>c.969C&gt;A (p.Y323X) ve c.170T&gt;C (p.L57P) compound heterozygous mutation in KISS1R</td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>Tanner stage 1</td>
<td>0.13</td>
<td>0.07</td>
<td>&lt;0.07</td>
<td>1.01</td>
<td>46XX</td>
<td>c.969C&gt;A (p.Y323X) ve c.170T&gt;C (p.L57P) compound heterozygous mutation in KISS1R</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>Tanner stage 1</td>
<td>0.13</td>
<td>15</td>
<td>&lt;10</td>
<td>&lt;100</td>
<td>48XX</td>
<td>No mutation.</td>
</tr>
</tbody>
</table>

- Index case applied to our outpatient clinic with delayed puberty when he was 14 years old. On newborn period, he had bilateral cryptorchidism and micropenis and his physical examination:
  - Height was 165.3 cm (0.14 SDS)
  - Weight was 62 kg (0.94 SDS)
  - Pubertal stage was Tanner stage 1
  - Stretched penis size was 4 cm
  - Bilateral testis were in scrotum and testis sizes were 3 ml.
- His parents were nonconsanguineous.
- Laboratory findings (shown in table 1) revealed IHH. The results of GnRH test confirmed IHH.
- Karyotype of peripheral blood lymphocytes was 46 XY.
- Genomic DNA was extracted from peripheral leukocytes and the promoter region, the three exons and exon-intron boundaries of the KISS1R gene (NM_032551) were amplified by polymerase chain reaction (PCR) and sequenced.

Discussion

- In this study, while index case has IHH, two of his sister have uncompleted puberty and amenorrhea (Table 1).
- Thus, the inadequacies of controlling KISS1 protein can manifest itself in different clinical entities.
- In this study, although three of the four siblings have the same inactivating compound heterozygous mutation, because of the phenotypic spectrum of GnRH deficiency resulting from disregulation of kisspeptin, two of them has uncompleted puberty and amenorrhea while one have IHH.
- In conclusion, we found a compound heterozygous mutation of KISS1R gene causes normosmic idiopathic hypogonadotropic hypogonadism and also uncompleted puberty. In previous studies, the loss-of-functional mutations of KISS1R/GPR54 which were inherited as autosomal recessive mutations are more likely reported in consanguineous families.
- We identified these mutation in a non-consanguineous family which illustrates different phenotypic spectrum of KISS1R/GPR54. We recommend genetic counselling for KISS1R gene mutation in IHH patients, although the members are from a non-consanguineous family.