Abstract

Purpose
Disorders of sex development (DSD) have been linked to gene defects that lead to gonadal dysgenesis. Herein, we aimed to identify the genetic cause of gonadal dysgenesis in a patient with primary amenorrhoea tracing it to a phenotypic female carrying a 46,XY karyotype of a consanguineous family.

Case presentation
We report the case of a 19-year-old phenotypic female patient of Iraqi background presenting with primary amenorrhoea and absent secondary sex characteristics. There was absence of axillary and pubic hair, and breast development was at Tanner stage I. There was no genital ambiguity. The patient was previously investigated in Iraq at the age of 16 years, where she underwent a diagnostic laparoscopy following the results of her karyotype, which was 46, XY. Initial investigations revealed elevated LH (20.1 IU/L) and FSH levels (48.6 IU/L), with normal TSH (2.29 mIU/L) and PRL (250 mIU/L) levels. The results of the hCG stimulation test (hCG 2000 units for 3 days) are shown in Table 1 and are compatible with absence of testosterone production.

Table 1. Hormonal levels before and after hCG stimulation

<table>
<thead>
<tr>
<th>Testosterone</th>
<th>Adrenocorticotropin</th>
<th>LH</th>
<th>FSH</th>
<th>DHT</th>
<th>T/DHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>0.19</td>
<td>0.7</td>
<td>1.35</td>
<td>1.09</td>
<td>0.012</td>
</tr>
<tr>
<td>After</td>
<td>0.19</td>
<td>0.7</td>
<td>1.45</td>
<td>1.85</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Whole exome sequencing (WES) using the TruSeq Rapid Exome kit on an Illumina NextSeq500 system revealed the rare, only once reported in homozygosity, p.Arg164Pro mutation in heterozygote and homozygote state. Sanger sequencing confirmed p.Arg164Pro in homozygosity in our index patient [2]. Both consanguineous parents, who had no reproductive malformations, were identified as carrying the mutation in the heterozygous state (Figure 1).

Figure 1. Genetic analysis of the patient with 46,XY DSD. A. Pedigree of the family. Squares and circles indicate males and females, respectively. Black shading indicates the presence of the DHH: p.Arg164Pro mutation in both the patient and the parents.

Conclusions
Defects in the DHH gene have been reported as a very rare cause of DSD, and this report increases the number of 46,XY gonadal dysgenesis cases. Additionally, the present study highlights the importance of genetic validation of patients with DSD, since this is likely to alleviate the considerable psychological distress experienced by both the patient and the parents.

References