Biochemical and Molecular Modeling Analyses Explain the Functional Loss of 17β-HSD3 Mutant G133R in Three Tunisian Patients

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Introduction

17β-Hydroxysteroid dehydrogenase type 3 (17β-HSD3) catalyzes the conversion of Δ4-androstene-3,17-dione to testosterone in testicular Leydig cells and has a key role in male sexual development. Mutations in the HSD17B3 gene can result in reduced enzyme activity and decreased testosterone synthesis, leading to a rare autosomal recessive disease named 46, XY disorder of sex development (46, XY DSD).

![Chemical Structure Diagram](image)

Patients with 46, XY DSD show undervirilization of external genitalia, which often appear female. They are usually raised as females until a virilization occurs at puberty due to extra testicular testosterone synthesis by the enzyme 17β-HSD5, which is not expressed in early development.

We characterized three Tunisian patients from non-consanguineous families with 46, XY DSD and investigated 17β-HSD3 deficiency.

Patients Clinical History

Genomic DNA from patient 1 was directly analyzed for mutations in the HSD17B3 gene by DNA sequencing because of a familial history, recording a paternal cousin with HSD17B3 deficiency. For the patients F2 and F3 a human chorionic gonadotropin stimulation test was performed, due to signs of virilization observed at puberty and the absence of a complete hormonal profile. The results revealed 17β-HSD3 deficiency.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
<th>Testosterone</th>
<th>Estradiol</th>
<th>LH</th>
<th>FSH</th>
<th>SHBG</th>
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<tbody>
<tr>
<td>F1</td>
<td>13</td>
<td>135</td>
<td>45</td>
<td>55 pg/ml</td>
<td>50 pg/ml</td>
<td>5</td>
<td>4</td>
<td>120</td>
</tr>
<tr>
<td>F2</td>
<td>13</td>
<td>133</td>
<td>41</td>
<td>70 pg/ml</td>
<td>45 pg/ml</td>
<td>5</td>
<td>4</td>
<td>120</td>
</tr>
<tr>
<td>F3</td>
<td>13</td>
<td>133</td>
<td>40</td>
<td>60 pg/ml</td>
<td>30 pg/ml</td>
<td>5</td>
<td>4</td>
<td>120</td>
</tr>
</tbody>
</table>

Molecular Modeling Prediction

A homology model of 17β-HSD3 predicted that the loss of activity is due to a disruption of the cofactor binding site. While an alanine at position 133 was still tolerated, more bulky side-chains led to steric hindrance thus preventing cofactor binding. The functional analysis and homology modeling revealed an important role of this residue in the structural arrangement of the cofactor binding pocket. The results provide an improved mechanistic understanding of the 17β-HSD3 structure-function relationship and explained the 17β-HSD3 deficiency observed in the patients.

Conclusion

We characterized three Tunisian patients from non-consanguineous families with 46, XY DSD due to 17β-HSD3 deficiency. Genetic analysis of the HSD17B3 gene revealed two compound heterozygous mutations, i.e. a novel missense mutation (G133R) and a premature stop codon (C206X).

Reference:


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References