The novel founder homozygous V225M mutation in the 17HSDB3 gene causes aberrant splicing and severe XY-DSD

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**Background**

- Mutations in the gene HSD17B3 encoding the 17-β hydroxysteroid dehydrogenase 3 enzyme cause testosterone insufficiency leading to XY-DSD.
- There are fourteen known isoenzymes of HSD17B in mammals with isoenzyme 3 being the major one expressed in the testes.
- Defects in the function of this enzyme may cause ambiguous or female external genitalia in a genotypically male at birth, or become overt only at puberty when an affected XY female presents with primary amenorrhea or progressive virilization.
- XX homozygous females appear to be asymptomatic.

**Patients**

- Patient II-5 is 8 years old female born with ambiguous genitalia, clitoris 0.7 mm and gonads in the inguinal canal.
- Karyotype was XY
- The results of ACTH stimulation test in this patient are shown below:

<table>
<thead>
<tr>
<th>Time</th>
<th>Testosterone Nmol/l</th>
<th>Androstenedione Nmol/l</th>
<th>DHEAS Micromole/l</th>
<th>Cortisol Nmol/l</th>
<th>ACTH Pmol/l</th>
<th>17OHP Nmol/l</th>
<th>PRA Nmgl/hr</th>
<th>Aldosterone Pmol/l</th>
<th>Testosterone/Androstenedione ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.96</td>
<td>4.48</td>
<td>&lt;0.41</td>
<td>86.6</td>
<td>15.5</td>
<td>0.5</td>
<td>2.6</td>
<td>&gt;2500</td>
<td>0.21</td>
</tr>
<tr>
<td>60</td>
<td>1.14</td>
<td>9.97</td>
<td>&lt;0.41</td>
<td>1059</td>
<td>201</td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
</tbody>
</table>

- Her sister II-5 was diagnosed at age 8 years with the same phenotype
- A non related 8 months old patient was diagnosed with the same phenotype and genotype at 8 months

**Molecular Analysis**

HSD17B3 genomic chromatogram sequence. The mutation in the first nucleotide of exon 10 is indicated with circle

Cross-species conservation of the residues adjacent to V225 bordered by vertical dashed lines (adapted from http://genome.ucsc.edu/). The mutation in the first nucleotide of exon 10 is indicated with circle

**Conclusions**

- Here we describe a novel homozygote founder mutation c.673G>A p.V225M in 2 unrelated families
- Functional studies using normal human testes show that this mutation leads to skipping of Exon 10 and changes in the transcription of the gene
- While some of the patients undergo profound virilization during puberty, the issue of gender assignment in these patients may be challenging