Novel AMH and AMHR2 Mutations in Two Egyptian Families with Persistent Mullerian Duct Syndrome

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OBJECTIVE

- Studying molecular pattern of 46,XY DSD with persistent mullerian ducts

METHODS

- The entire coding regions of AMH and AMHR-II were amplified by PCR and directly sequenced in both directions
- The sequenced data were compared with the reference genomic and cDNA sequence of the two genes.

Graphs and tables

Patient (1)
Graph (1) Family Pedigree:

Patient (2)
Graph (3) Family Pedigree:

Graph (2): Portion of the sequencing electrophoregram showing The novel missense mutation identified in exon 6 of the AMHR2.


Wild type

Graph (4): Portion of the sequencing electrophoregram showing the novel frameshift mutation identified in exon 1 of the AMH gene

Normal: Patient: c.203_203delC (p.L70Cfs*7)

Wild type

Table (1) Predicted effect of AMH and AMHR2 mutations identified in the in this study.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Protein</th>
<th>Gene</th>
<th>Exon</th>
<th>Mutation Taster</th>
<th>Polyphen2 (Score)</th>
<th>SIFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.203_203delC</td>
<td>p.L70Cfs*7</td>
<td>AMH 1</td>
<td>1</td>
<td>Disease causing</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>c.767A&gt;C</td>
<td>p.H256P</td>
<td>AMHR2</td>
<td>6</td>
<td>Disease causing</td>
<td>Probably damaging(0.95)</td>
<td>Affect protein function</td>
</tr>
</tbody>
</table>

RESULTS

- Two Egyptian 46,XY DSD patients presented with bilateral cryptorchidism, and both had persistent mullerian ducts
- Mutational analysis of the AMH and AMHR2 genes identified pathogenic mutations in the two families confirming the diagnosis of PMDS
- A new missense mutation in exon 6 of the AMHR2 gene was identified in patient 1(Graph 2).
- A novel single nucleotide deletion in exon 1 of the AMH gene was identified in patient 2(Graph 4).
- The two mutations co-segregated perfectly with the phenotype in both families being homozygous in the probands and heterozygous in their respective parents
- The two mutations were not present in the 1000G and ExAC databases and are predicted to be pathogenic by various bioinformatics software (Table 1).

CONCLUSIONS

- We presented two new Egyptian families with PMDS having novel mutations in the AMHR2 and AMH genes.
- Our results, expands the mutational pattern of this rare disorder and emphasize that persistent mullerian ducts should be included in differential diagnosis of cryptorchidism.