Mutation analysis of KDM3A (lysine-specific demethylase 3A) in patients with hypospadias

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Abstract

**Background:** Hypospadias is a relatively common form of 46,XY disorders of sex development. Although several genes have been implicated in the development of hypospadias, molecular basis of the majority of cases remain unknown. Recently, targeted disruption of lysine-specific demethylase 3A (KDM3A) were shown to cause defective sex development in male mice. **Objective and hypotheses:** The aim of this study was to clarify whether KDM3A mutations underlie hypospadias in human. **Method:** We performed mutation screening of KDM3A in 66 patients with hypospadias. The functional consequences of nucleotide changes were assessed by in silico assays. **Results:** We identified a heterozygous nucleotide change in KDM3A (p.D201H, c.601G>C) in a patient. The nucleotide change was assessed as ‘probably damaging’ by PolyPhen2 and ‘damaging’ by SIFT. The p.D201H variant was hitherto unreported. The patient manifested penoscrotal hypospadias and right vesicourethral reflux without microprosphus or undescended testis. Endocrine evaluation at one year of age showed normal levels of testosterone, LH, and FSH. **Conclusion:** The results indicate that sequence alterations in KDM3A may constitute a rare etiology of hypospadias in human.

**Introduction.**

Lysine-specific demethylase 3A (KDM3A or JMJD1A) is known as a gene that control methylation of histone H3K9. Recent study show that KDM3A knockout leads sex reversal in mice.


**Patients characteristics**

A total of 66 patients with hypospadias participated in the study.

<table>
<thead>
<tr>
<th>Position of Urethral Opening</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior</td>
<td>23</td>
</tr>
<tr>
<td>Middle</td>
<td>17</td>
</tr>
<tr>
<td>Anterior</td>
<td>14</td>
</tr>
<tr>
<td>Unknown</td>
<td>12</td>
</tr>
</tbody>
</table>

**Study design**

Mutations in KDM3A were screened using a next-generation sequencer. The results were confirmed by Sanger direct sequencing.

**Results**

We identified a heterozygous nucleotide change in KDM3A (p.D201H, c.601G>C) in a patient

**KDM3A**

<table>
<thead>
<tr>
<th>p.D201H</th>
</tr>
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<tbody>
<tr>
<td>G</td>
</tr>
<tr>
<td>T</td>
</tr>
</tbody>
</table>

**In silico analysis**

PolyPhen-2

- **Prediction:** DAMAGING

SIFT

- **Prediction:** DAMAGING

**Clinical findings of the patient**

- Position of urethral opening – Posterior
- Undescended testis – None
- Micropenis – None
- Familial History – None

**Hormone data**

<table>
<thead>
<tr>
<th>Age at exam.</th>
<th>LH (mIU/mL)</th>
<th>FSH (mIU/mL)</th>
<th>T (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 months</td>
<td>&lt; 0.5</td>
<td>1.0</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

**Conclusion**

The results indicate that sequence alterations in KDM3A may constitute a rare etiology of hypospadias in human.