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 micropenis 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

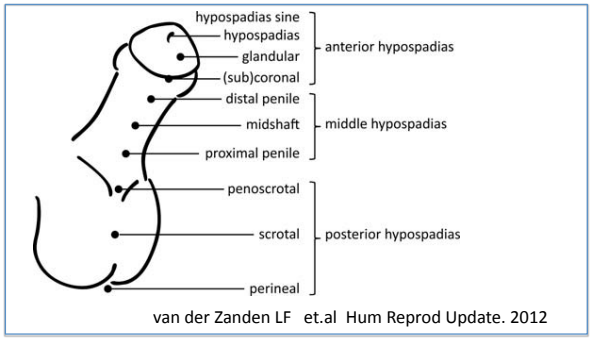
Lysine-specific demethylase 3A (*KDM3A* or *JMJD1A*) is known as a gene that control methylation of histone H3K9.
Recent study show that *KDM3A* knockout leads sex reversal in mice.

Kuroki S, et al. Epigenetic regulation of mouse sex determination by the histone demethylase Jmjd1a. Science. 2013

Patients characteristics

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

Position of Urethral Opening	Number of Patients
Posterior	23
Middle	17
Anterior	14
Unknown	12



van der Zanden LF et.al Hum Reprod Update. 2012

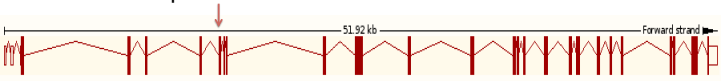
Study design

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

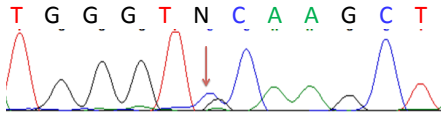
Results

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

KDM3A p.D201H

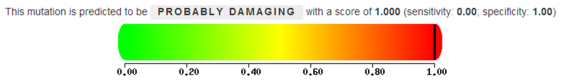


Direct Sequence



In silico analysis

PolyPhen-2



SIFT

ENSP	Pos	Ref	Subst	Prediction
ENSP 00000323659	201	D	H	DAMAGING

Clinical findings of the patient

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

Hormone data

Age at exam.	LH (mIU/mL)	FSH (mIU/mL)	T (ng/ml)
14 months	< 0.5	1.0	< 0.05

Conclusion

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