Identification of a Missense *MAP3K1* Mutation in a Patient with Hypospadias

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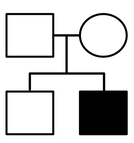
Background

Mitogen activated protein kinase kinase kinase 1 (MAP3K1) encods a serin/threonine kinase involved in mitogen-activated protein kinase (MAPK) signaling pathway.

Recently, eight *MAP3K1* mutations have been identified in patients with 46,XY disorder of sex development (DSD), although detailed clinical findings of the mutation-positive patients remain to be investigated.

We performed mutation screening of *MAP3K1* in 37 patients with 46,XY DSD, and identified a heterozygous nucleotide change (c.745C>T, p.R249C) in a patient with hypospadias.

Clinical information of the mutation-positive patient



A male patient was born to non-consanguineous Japanese parents at 38 weeks gestation. His parents and elder brother were clinically normal.

At birth, the patient manifested bifid scrotum and hypospadias. He had normal penile length (2.5 cm) and testicular volume (1 ml). Abdominal ultrasound analysis detected no abnormalities. He has normal karyotype (46,XY) and SRY.

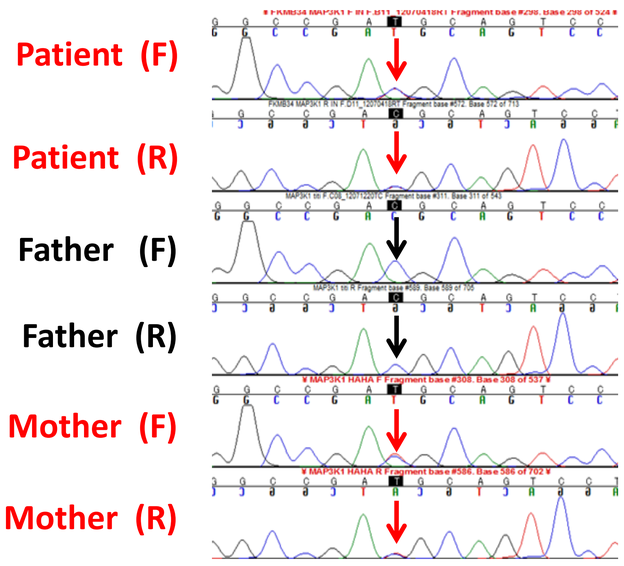
<u>Endocrinological data at 5 days after birth</u>

- GnRH stimulation test — Slightly elevated gonadotropin levels
  - LH : 1.4 to 14.2 mIU/ml
  - FSH : 0.7 to 3.17 mIU/ml
- hCG stimulation test — Normal function of testis
  - T: 3.49 to 8.05 nmol/L
  - Androstenedine : 10.76 to 7.98 nmol/L
  - DHT : 0.62 to 2.64 nmol/L
- ACTH : 58.7 pg/ml — Normal function of pituitary gland
- 17OHP : 1.2 ng/ml — Normal function of adrenal gland

He had normal function of testis, pituitary gland and adrenal gland. Gonadotropin levels was slightly elevated.

Mutational analysis of *MAP3K1*

c.745C>T, p.R249C

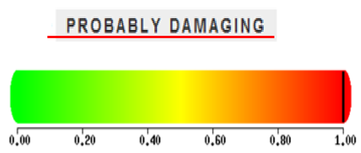


*He had no mutations in *AR, DMRT1, NR5A1, SOX9, SRD5A2* or *SRY*.

***MAP3K1* p.R249C variation derived from maternal origin was identified the patient with hypospadias.**

In silico and database analysis

PolyPhen-2



UCSC database

c.745C>T, p.R249C

	GGC	CGA	CGC	AGT
Human	G	R	R	S
Rhesus	G	R	R	S
Mouse	G	R	R	S
Dog	G	R	R	S
Elephant	G	R	R	S
Chicken	G	R	R	S
Zebrafish	G	R	R	S

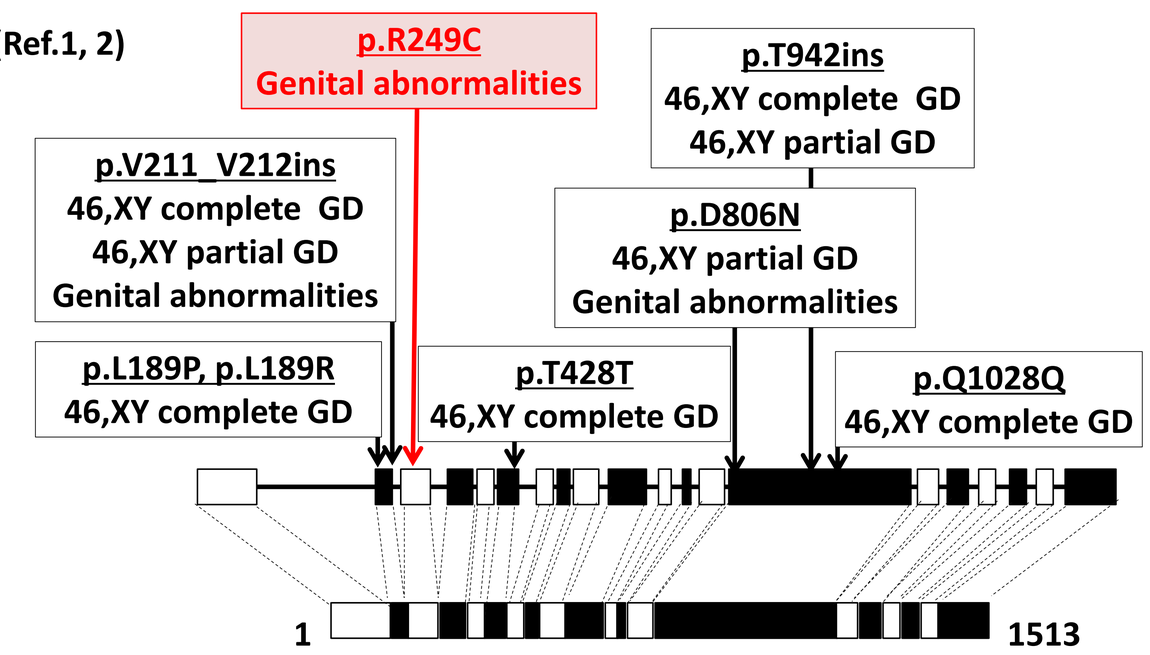
1000 genome database

rs200234617
allele frequency: 0.001
detected only in a female

p.R249C variation is predicted to be a causative mutation of hypospadias.

Previous and present mutations of *MAP3K1* in patients with 46,XY DSD

(Ref.1, 2)



Phenotypic diversity was observed in the *MAP3K1* mutation-positive patients.

Discussion

- Previous studies revealed that Map3k4 was essential for testis development in mice (Ref. 3)
- In human, MAP3K1 is important for male sex determination (Ref. 1).

It is anticipated that MAP3K1 in human has a similar function of Map3k4 in mice.

- This study showed that testicular function was normal in the *MAP3K1* mutation-positive patient.
- Our findings, together with previous data, indicate that testicular abnormalities occur in the *MAP3K1* mutation-positive patients at embryonic stage.

Conclusion

- **The results indicate a possible association between the p.R249C variant and hypospadias.**
- **Endocrine data of the patient suggest that *MAP3K1* mutations permit apparently normal testicular function after birth.**

Refernce

(1) Pearlman A. et al., The American Journal of Human Genetics, 2010.
(2) Das DK., et al., Indian Journal Human Genetics, 2013.
(3) Warr N., et al., Cell, 2012