MAP3K1 mutation in a patient with complete XY gonadal dysgenesis

Köhler B[1], Braicu E[2], Gehrmann N[2], Grüters A[1], Bignon-Topalovic J[3], McElreavey K[3], Bashamboo A[3]

[1] Department of Pediatric Endocrinology and Diabetology, Charité Universitätsmedizin, Berlin, Germany

[2] Department of Gynaecology,, Charité, Universitätsmedizin Berlin, Germany, [3]Human Developmental Genetics, Institut Pasteur, Paris, France

Introduction

46,XY gonadal dysgenesis (GD) is a very rare disorder of testes development with an incidence of 1 : 50 -100 000. MAP3K1 is a mitogen-activated protein kinase (MAPK) that mainly regulates the MAPK pathways. High *Map3k1* expression was found in female and male mice gonads at 13.5.dpc. In 2010, *MAP3K1* mutations were identified in 2 families with complete and partial XY GD and in two unrelated sporadic cases with complete XY GD (Pearlman 2010 AJMG). Recently, 4 additional mutations (4 of 40) in XY GD (Baxter 2015 JCEM) were identified.

Methods

Exome sequencing Briefly, exon enrichment was performed using Agilent SureSelect Human All Exon V4. Paired-end sequencing was performed on the Illumina HiSeq2000 platform with an average sequencing coverage of x50. Read files were generated from the sequencing platform via the manufacturer's proprietary software. Reads were mapped using the Burrows–Wheeler Aligner and local realignment of the mapped reads around potential insertion/deletion (indel) sites was carried out with the GATK version 1.6. SNP and indel variants were called using the GATK Unified Genotyper for each sample. SNP novelty was determined against dbSNP138. Datasets were filtered for novel or rare (MAF<0.01) variants. Candidate pathogenic mutations were confirmed by Sanger sequencing.

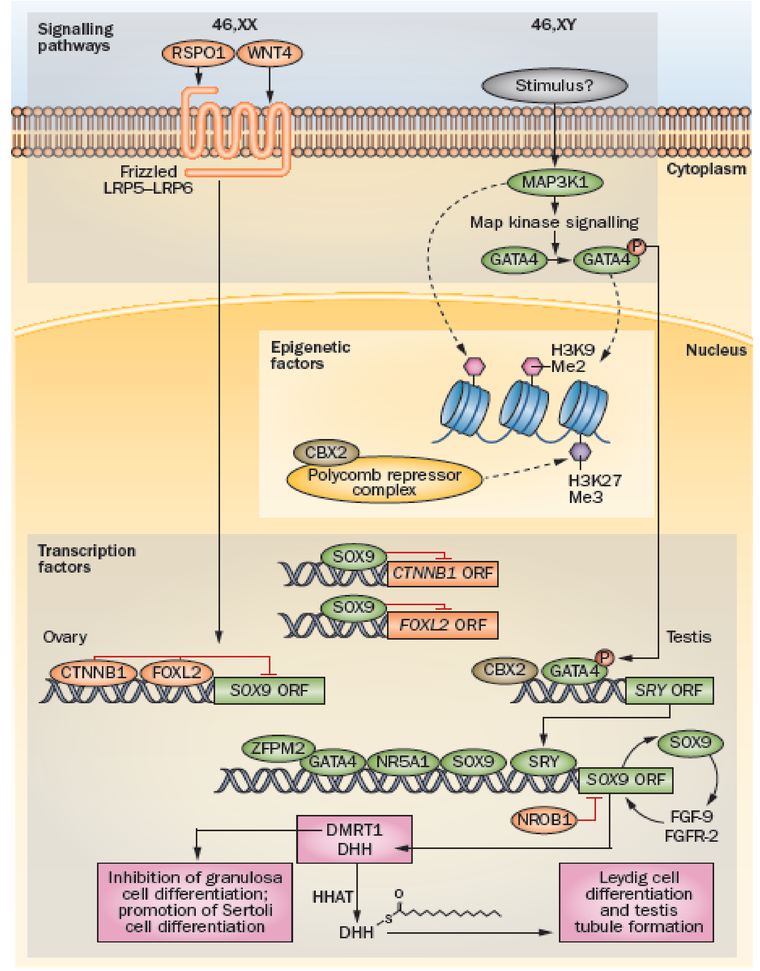

Fig.1 Genetic pathophysiology of human sex determination (Arboleda VA et al Nat Rev Endocrinol 1014)

Results

We detected the a heterozygous mutation (Exon 2, c. 566 T>C, p.Leu189Pro; rs387906788) in the *MAP3K1* gene. The mutation was confirmed by Sanger sequencing. The mutation was not carried by the mother and the fathers DNA was unavailable for study. This mutation was previously reported in a sporadic case with complete XY GD. In cultured primary lymphoblastoid cells, this mutation was previously found to increase phosphorylation of the downstream target p38, ERK1 (MAPK3)/ERK2 (MAPK1) compared to wild-type (Pearlman et al, AJMG).

The mutation is located in the conserved focal adhesion kinase (FAK) binding site.

H. sapiens	IREKLKATC
M. mulatta	IREKLKATC
M. musculus	IREKLKATC
C. familiaris	IREKLKATC
E. caballus	IREKLKATC
D. novemcinctus	IREKLKATC
M. domestica	IREKLKATC
O. anatinus	IREKLKATC
G. gallus	IREKLKATC
X. tropicalis	IREKLKATC

Fig.3 MAP3K1 protein fragment of the mutation site in different mammals

Phenotype

Presentation: primary amenorrhea at 16 years, 6th child of nonconsanguineous parents

Physical exam: B1, P3, normal female external genitalia and vagina

Ultrasound: infantile uterus, absence of gonads, normal kidneys

Hormones: FSH 86 U/l, LH 36 U/l, Testosterone 0.13 ng/ml, Estradiol not measurable.

Karyotype: 46,XY

Mutations in the genes *SRY, NR5A1* and *WT1* were not identified by Sanger sequencing.

Gender identity: The patient reported female gender identity and the wish for further female development

Gonadectomy: Bilateral streak gonads were removed at the age of 17 yrs age due to the increased tumor risk.

Conclusion

MAP3K1 is a novel important regulator of testis development. Mutations in MAP3K1 represent an important and under recognised cause of XY gonadal dysgenesis. In particular the p.Leu189Pro mutation may represent a mutational hotspot in the gene. Exome sequencing is an appropriate tool to reveal the genetic cause in the rare cases of XY GD.

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Sex Differentiation

Birgit Khler

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