A new mutation of MAMLD1 (CXorf6) associated with NR5A1 (SF1) variant in a patient with 46,XY DSD

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Background

The investigation of patients with 46,XY DSD is often difficult, with no definitive diagnosis in more than 50% of cases investigated. We describe a new mutation of MAMLD1 in a patient with 46,XY DSD who also showed an alteration in the NR5A1 gene.

Case report

A 5-year-old boy was referred to our clinic for DSD. He was born to non-consanguineous parents and was diagnosed with ambiguous genitalia at birth but had not been previously investigated.

Examination (fig.1a, fig.1b) showed undescended testes, peno-scrotal hypospadias and microphallus (3 cm).

Investigations showed 46,XY karyotype; basal testosterone 0.11 nmol/l with an impaired response to hCG stimulation (peak: 0.5 nmol/l after 1500 UI×6 (every 2 days); basal FSH and LH 1.76 and <0.001 mUI/ml respectively; AMH low at 85.8 pmol/l.
No testes could be seen on pelvic ultrasound but genitogram (Fig.2) showed the presence of a Mullerian duct remnant connected to the urethra.
At laparoscopic surgery two small testes were found. After three i.m. injections of Testosterone Enanthate 50 mg penile length increased from 3 to 5 cm.
Orchidopexy and surgical correction of the hypospadias have been performed.

Molecular studies

With written informed consent from parents, DNA was extracted from peripheral blood lymphocytes of the patients.
Mutation analysis of the **MAMLD1 (CXorf6) gene** showed a heterozygous mutation of MAMLD1 (c.1868G>A//p.Arg623His).
Mutation analysis of the **NR5A1 (SF1) gene** revealed the presence OF the variant p.Gly146A1a. (Dr P.Philibert and Pr C.Sultan, Montpelier).

Discussion

Mutations of MAMLD1 have been recently described in patients with complex 46,XY DSD including micropenis, cryptorchidism and peno-scrotal hypospadias. We describe a new heterozygous MAMLD1 (CXorf6) mutation causing 46, XY DSD with partial gonadal dysgenesis. Moreover, our patient presented a variant in the SF1 gene which has been reported more frequently in patients with cryptorchidism and microphallus. It is possible that the two gene alterations have had a digenic effect, with the MAMLD1 having a predominant effect on Leydig cell function while the SF1 variant has contributed to impaired Sertoli cell function.

Illustrations

Fig.1a

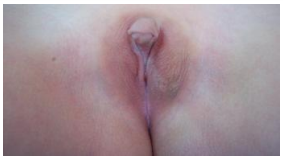

Fig.1b

Fig.1. hypoplastic scrotum, no palpable gonads, microphallus and peno-scrotal hypospadias.

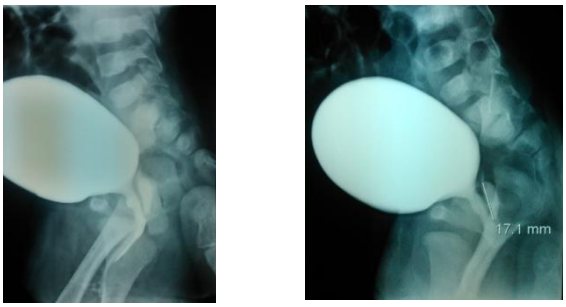

Fig.2: Genitogram: Mullerian structure (17 mm) connected to the bulbar urethra

Table. 1 Investigations	
Karyotype	46 XY
•Pelvic ultransonography •Genitography	No testes Mullerian structure
Endocrine evaluation (Age: 5 years)	
•FSH	1.76 mUI/ml
•LH	0.01 mUI/ ml
•17 OHP	0.45 nmol:l
•SDHEA	6.6 µg/ dl
•Delta 4-Androstenedione	0.07 ng/ml
•Dihydrotestosterone	< 0.15 nmol/l
•Testosterone ✓ basal ✓ After Human Chorionic Gonadotrophin	0.11 nmol/l **0.5 nmol/l**
•AMH	**85.8 pmol/l** (316-650)
Androgen sensitivity Test Penile Length	
• initial	3 cm
•After 3x 50 mg of testosterone heptylate	5 cm

References

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The authors have no conflict of interest