46,XY DSD due to isolated AMH deficiency resulting in Persistent Müllerian Duct Syndrome (PMDS) as a consequence of a single-base deletion in a SF1-response element of the AMH promoter

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Introduction

PMDS
- Isolated persistence of Müllerian ducts
- Otherwise normally virilised 46,XY newborn
- DSD → defect in AMH secretion or action

Case report

- Full-term (39 wk), normal weight (3.54 kg) and length (51 cm)
- Non dysmorphic
- Normal penis – Empty, underdeveloped scrotum

Bilateral cryptorchidism

Genetic testing

Karyotype: 46,XY

Hormonal Lab work

Day 4 of life
- 17-hydroxy progesterone 61 ng/dL
- FSH 4.2 mIU/mL
- LH 14 mIU/mL

hCG test: 1500UI/m2/day for 3 days

AMH:
1.1 ng/mL (Ref. for age: 15.5 - 48.37 ng/mL) or
7.8 pmol/L (Ref. for age: 110 – 345 pmol/L)

Imaging studies

- Pelvic Sonogram: normal neonatal uterus 5 x 1.4 x 1.9 cm, and without gonads visualized in the scrotum or pelvis
- VCU: normal male urethra without a urogenital sinus
- MRI: did not identify gonads, and again showed normal neonatal uterus with a fluid filled, blind ending vagina

Persistent Mullerian Duct Syndrome PMDS with very low AMH

Conclusion: The single base deletion c.-225delA within the -228 SF1 site of the AMH promoter impairs SF1 binding to and transactivation of the AMH promoter, resulting in extremely decreased AMH production. This is the first description of an AMH promoter mutation leading to PMDS.

Sequencing of AMH promoter gene

- Normal coding sequences (exons, intron boundaries)
- Homozygous mutation in the proximal promoter
- 1-bp deletion at -225, belonging to a presumptive -228 SF1-binding site

Normal: tcaggacag

Patient: tcaggacag

Family pedigree

AMH gene mutation c.-225delA

Mexican origin

EMSA : SF1 binding to -228 site on AMH promoter

Luciferase Assays : Transactivation capacity of AMH promoter SF1 site

SF1 c.-225delA impairs AMH promoter activity in both the 423-bp and 3063-bp promoters.
- Same for artificial mutations at -228 and combinations.
- Artificial mutation at -102 SF1 site impairs the 423-bp but not the 3063-bp promoter activity.