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/m^2/day for 3 days

	Testosterone ng/dL	Δ4 androstenedione ng/dL	DHT ng/dL
Day 1	358	21	50
Day 5	783	66	146

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

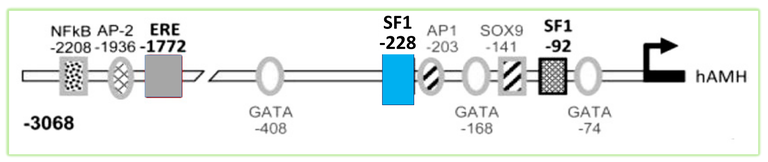
- Pelvic Sonogram: normal neonatal uterus 5 x 1.4 x 1.9 cm, and without gonads visualized in the scrotum or pelvis
- VCUG: normal male urethra without a urogenital sinus
- MRI: did not identify gonads, and again showed normal neonatal uterus with a fluid filled, blind ending vagina

Persistent Mullerian Duct Syndrome PMDS with very low AMH

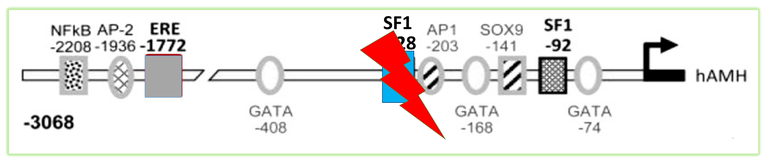
Sequencing of AMH promoter gene

- 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

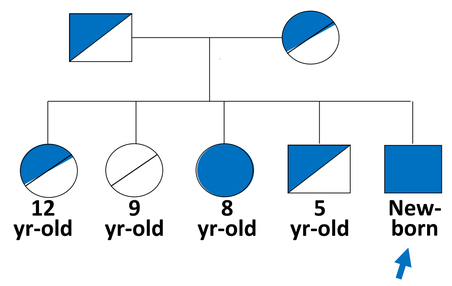
➢ Normal: tca**a**ggacag



➢ Patient: tcaggacag



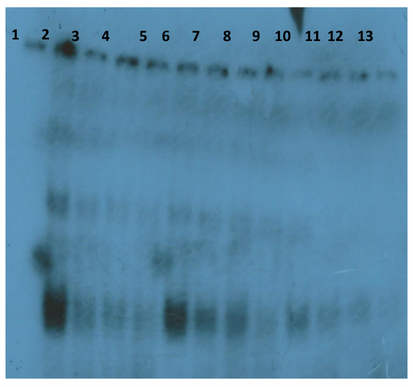
Family pedigree



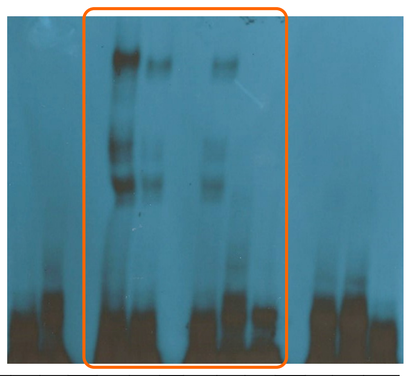
AMH gene mutation c.-225delA

Mexican origin

EMSA : SF1 binding to -228 site on *AMH* promoter

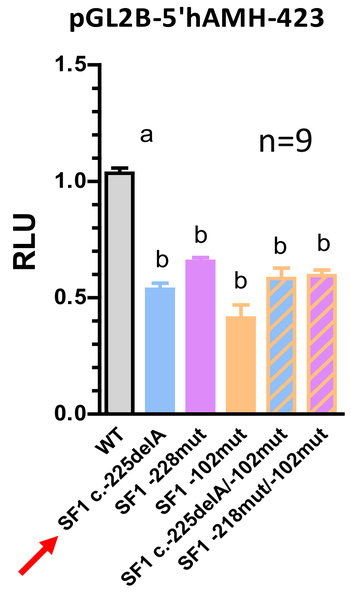


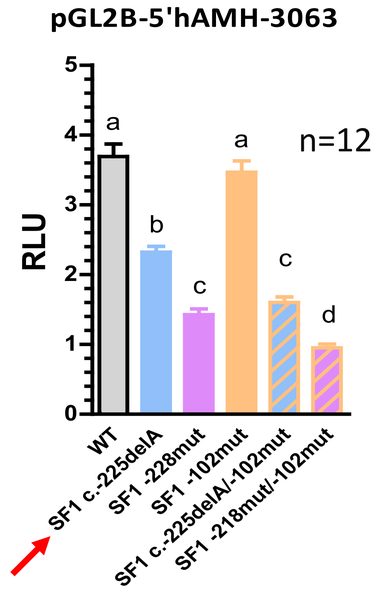
^{32}P SF1 228 WT	+	+	+	+	+	+	+	+	+	+	+	+	+
Nuclear extract 10 µg		+	+	+	+								
Nuclear extract 5 µg						+	+	+	+				
Nuclear extract 1 µg										+	+	+	+
SF1 228 WT 50x			+				+				+		
SF1 228 WT 100x				+				+				+	
SF1 228 WT 250x					+				+				+



Nuclear extract				+	+		+	+	+		+	+	+
^{32}P SF1 228 WT	+			+	+		+				+	+	+
^{32}P SF1 c.-225delA		+						+					
^{32}P SF1 228mut									+				
SF1 228 WT 250x											+		
SF1 228 WT 500x												+	
SF1 c.-225delA 500x													+
Anti-SF1 Ab				+									
Normal IgG					+								

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.

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.

55ESPE 1--LBP
Late Breaking
Rodolfo Rey
DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS