TWO TESTES AND TWO X CHROMOSOMES – WHY ?

FAHED ALJASER AND DIANE WHERRETT
DIVISION OF ENDOCRINOLOGY
THE HOSPITAL FOR SICK CHILDREN, TORONTO, CANADA

INTRODUCTION

- 46, XX Testicular Disorder of Sex Development is characterized by :-
  - 46, XX karyotype.
  - Normal to ambiguous male external genitalia.
  - 2 testicles.
  - Azoospermia.
  - Absence of Mullerian structures.
- 80-90% of patients present after puberty with infertility, gynecomastia, and small testes.
- 10-20% present at birth with genital ambiguity.

CLINICAL PRESENTATION

- 2 month old infant was referred to our Multidisciplinary Urogenital clinic with genital ambiguity.
- Birth history : full term, with no complications, birth weight of 3.4kg.
- Called a boy at birth, genital anomalies noted.
- Antenatal history : non-contributory .
- Family history: non-consanguineous parents, no history of CAH, infertility or genital ambiguity.
- 3 year old brother who is healthy.

PHYSICAL EXAMINATION

- No dysmorphic features or malformations.
- General exam was unremarkable.
- Genital Exam:-
  - Well developed scrotum that was bifid with rugae and pigmentation.
  - Bilateral gonads were palpable in the scrotum, of a normal size and consistency.
  - Phallus size in the normal range, with ventral curvature, penoscrotal transposition and penoscrotal hypospadias.

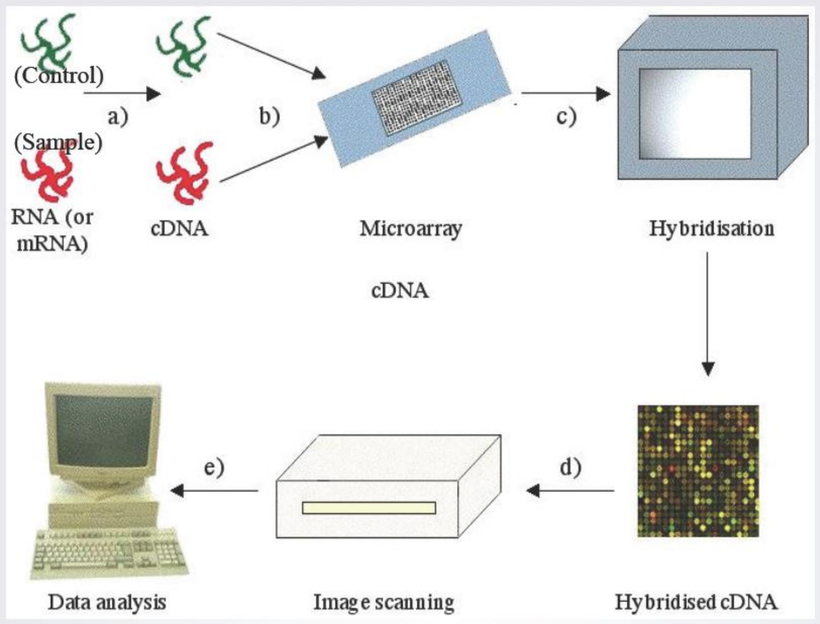
INVESTIGATIONS AT 2 MONTHS

TESTS	RESULTS	REF. RANGE
LH	1.3 IU/L	(0.1-4.8)
FSH	2.0 IU/L	(0-15)
TESTOSTERONE	3.7 nmol/L	< 16.0
ANDROSTENEDIONE	2.5 nmol/L	(0.2-1.6)
17-OHP	2.1 nmol/L	(0-9.9)
DHEA-S	1.8 µmol/L	< 4.0

IMAGING

- US Abdomen: Normal adrenals, normal appearing kidneys with mild left pelviectasis. No Mullerian structures seen.
- US scrotum: Both gonads were 1 x 0.8 x 0.6 cm in size, consistent with testes, no abnormalities seen.

GENETIC TESTING



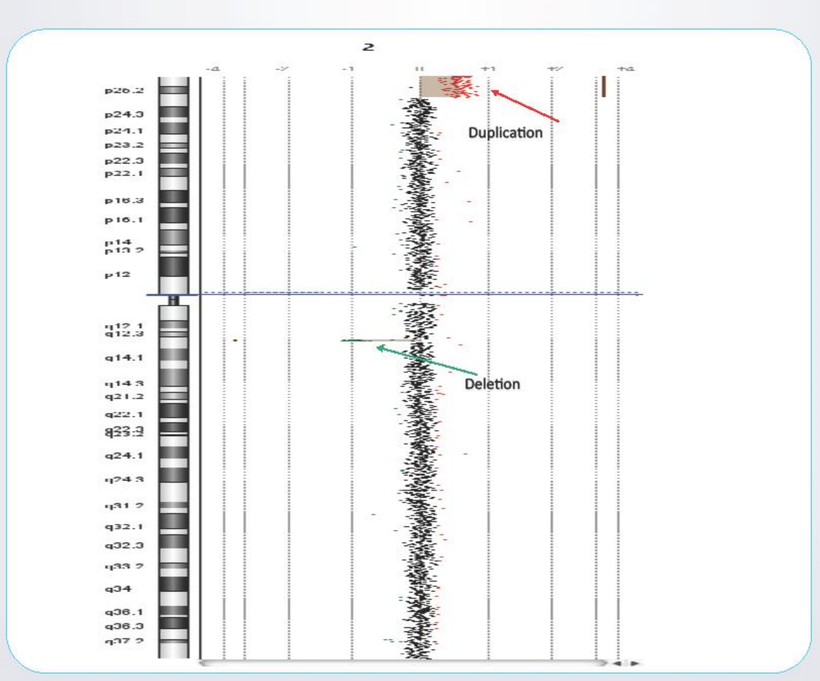


FIGURE 1: MICROARRAY ANALYSIS

- Karyotype: 46, XX (36 cells). FISH and PCR for SRY were negative.
- Microarray Analysis: a copy number gain in chromosome region Xq27.1. This region contains SOX3 gene.

CLINICAL COURSE

- Underwent 1st stage hypospadias repair at 1 year of age. 2nd stage scheduled at 18 months of age.
- Clinically doing well.
- Microarrays for both parents were negative.

DISCUSSION

- **SRY** (sex determining region Y) is a transcription factor that regulates testis development.
- **SOX** (SRY-box) are a family of genes that encode proteins homologous to SRY.
- **SOX** genes are involved in a wide range of developmental processes including neurogenesis and **sexual determination**.
- **SOX3** : located in a highly conserved region on the X chromosomes.
- **SOX9** : activate testis differentiation pathway.
- **SOX3** upregulates **SOX9** and initiates Sertoli cell differentiation.
- Transgenic mice overexpressing SOX3 led to frequent XX Testicular DSD.
- A cohort of 3/16 patients with SRY(-), 46, XX Testicular DSD, rearrangements of SOX3 locus were identified.
- This case strongly emphasize the major role of SOX3 gene in testes determination.

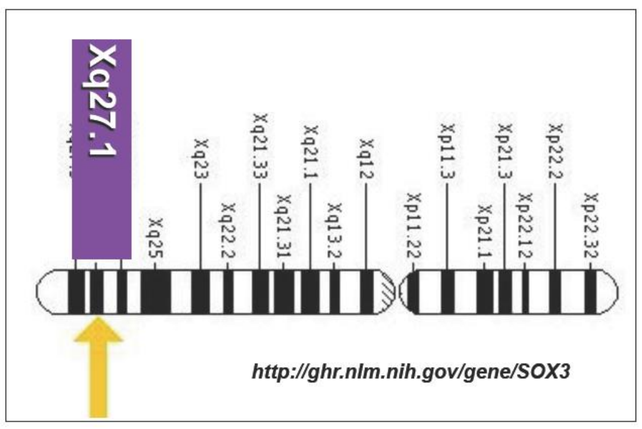


FIGURE 2: SOX3 LOCATION

IN CONCLUSION

- 46, XX Testicular Disorder of Sex Development are rare, and can range from normal male external genitalia to ambiguous.
- Following those patients in a multidisciplinary clinic is crucial, to address each aspect of their care.
- The clinical variation in 46XX males can't be completely explained by the presence and absence of SRY gene.
- Other genetic mutations have been identified in 46XX Testicular DSD (RSPO1, SOX9,10, SF-1, DMRT1, BPESC1, and DAX1).

CONTACT DETAILS

FOR FURTHER QUESTIONS OR COMMNETS, FEEL FREE TO CONTACT ME:
fahed.aljaser@gmail.com

ESPE 2015 306--P2
Sex Differentiation
fahed Aljaser
DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology
PosterSessionOnline.com