



Mosaic Xq Partial Duplication Leading to Virilisation of an Adolescent Female

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BACKGROUND

Proximal Xq duplications are very rarely reported and usually associated with severe congenital and developmental abnormalities.

XIST (X-Inactive Specific Transcript) is an RNA gene located on the long (q) arm of the X chromosome that plays a major role in the **X inactivation** process.

Failure of X chromosome dosage compensation could result from an unfavourable pattern of inactivation, a **breakpoint separating an X segment from the X-inactivation centre** in cis, or a **small ring chromosome**. [1]

2003 Rotterdam **Diagnostic Criteria for PCOS**[2], requires 2 out of 3 of oligo/anovulation, clinical/biochemical hyperandrogenism, polycystic ovaries.

CONCLUSION

We present a patient with **severe clinical hyperandrogenism**.

In depth investigation revealed a **previously unreported genetic mutation**.

Novel proximal Xq duplication NOT associated with congenital defects.

Hypothesise pathogenesis is due to a **failure of X chromosome dosage compensation**.

- leading to **over expression of the androgen receptor**
- resulting in **increased sensitivity** to circulating androgens.

Highlights importance of further investigation if patients do not fully meet PCOS Diagnostic Criteria.

IMAGES

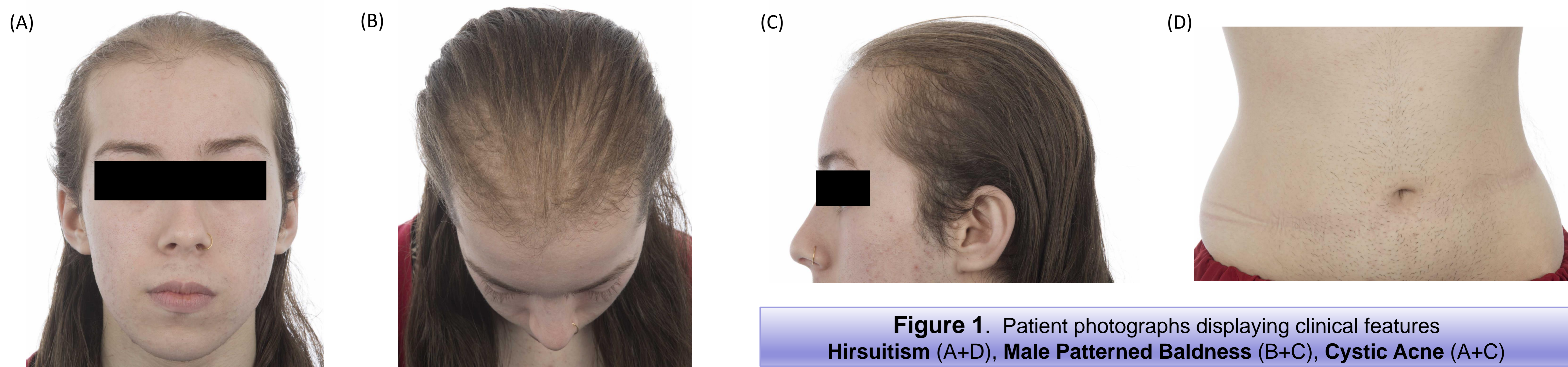


Figure 1. Patient photographs displaying clinical features **Hirsutism (A+D), Male Patterned Baldness (B+C), Cystic Acne (A+C)**

CASE HISTORY

17 year old, **developmentally appropriate** female. **1 year history** of hirsutism, male pattern baldness and marked cystic acne..

Menarche at the age of 15 years and has a **regular menstrual cycle**.

Pubertal on examination (B3, P5, A5) with **mild cliteromegaly**. She had dextrocardia with complete situs inversus.

Past history of a dislocatable hip as a neonate. Born to **Consanguinous (1st cousin)** parents. No family history of note.

Clinical hyperandrogenism but tests reveal **normal biochemical androgens** and **normal appearing ovaries on USS**

She was commenced on Yasmin[®] which she did not respond to after 6 months and has subsequently been commenced on Dianette[®] and Vaniqa[®].

ENDOCRINE RESULTS

Blood Test	Result	Normal Range
Renin	22.4 ng/L	5.1 - 38.7 ng/L
DHAS	10.4 μmol/L	1.7 - 13.4 μmol/L
FT4	13 pmol/L	9 - 20 pmol/L
TSH	1.32 mU/L	0.35 - 4.94 mU/L
LH	11 iU/L	9 - 89 iU/L
FSH	5 iU/L	3 - 17 iU/L
Prolactin	275 miU/L	109 - 557 miU/L
Sex hormone binding globulin	37 nmol/L	0.2 - 2.9 nmol/L
Testosterone	1.7 nmol/L	0.2 - 2.9 nmol/L
17OHP	1.5 nmol/L	0.6 - 6.0 nmol/L

Urinary Steroid Profile: Normal

USS Pelvis: Normal

SYNACTHEN TESTING

Time	0 mins	30 mins	60 mins
Cortisol	328 nmol/L	646 nmol/L	764 nmol/L
17OHP	1.5 nmol/L	3.8 nmol/L	4 nmol/L

GENETIC RESULTS

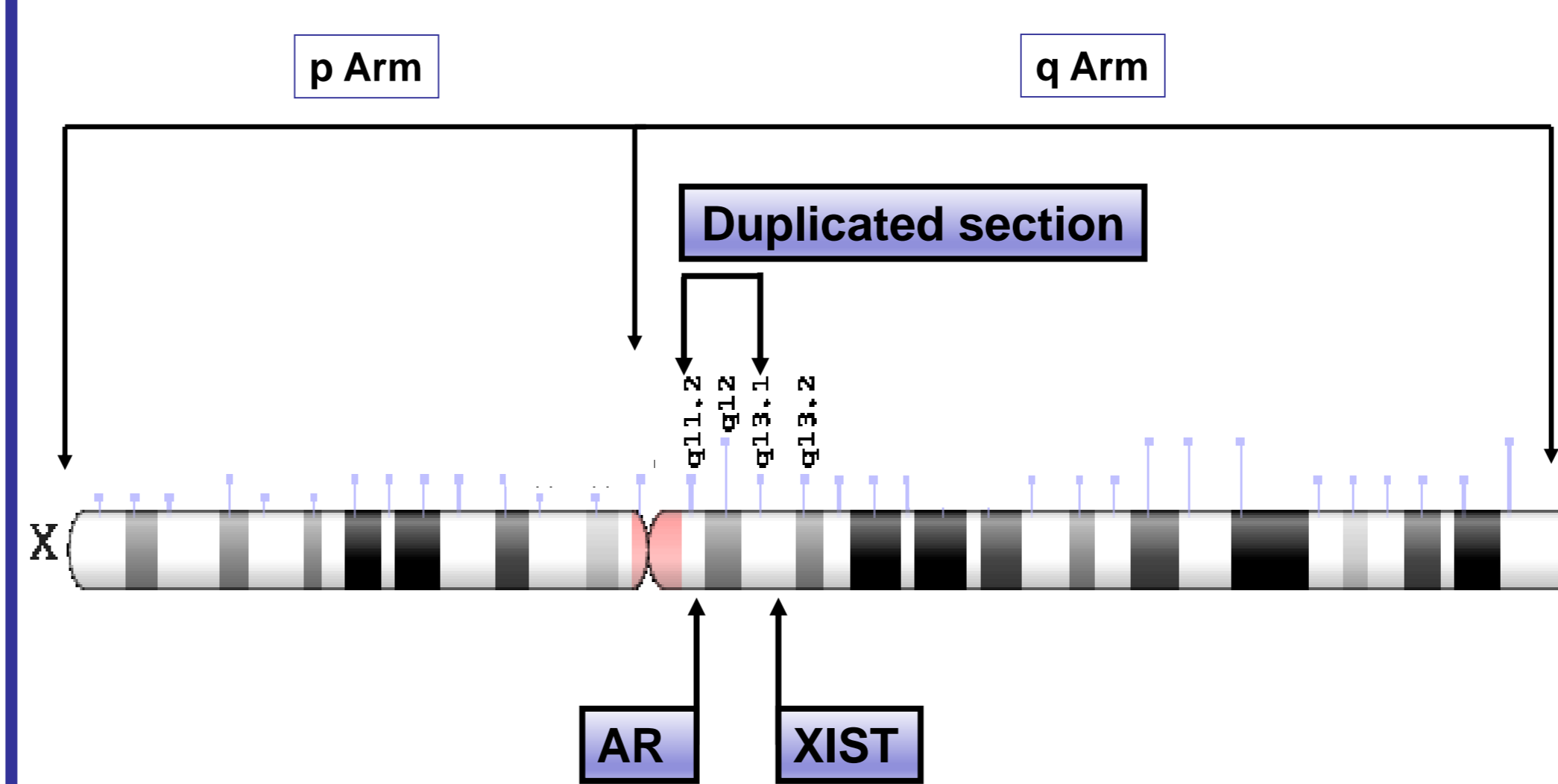


Figure 2: [3] Schematic of X Chromosome with duplicated section highlighted. Androgen receptor and XIST gene locations marked.

47,XX,+mar[14]/46,XX[16].arr Xq11.1q13.1

- **Mosaic** female karyotype with **small additional marker chromosome** present in one cell line.
- Supernumerary marker **derived from the X chromosome**.
- Contains the **androgen receptor gene** but does not contain the XIST gene and thus will **not be subject to X-inactivation**.
- De novo mutation, parents have normal karyotype.

Genetic Methods

Array CGH was carried out using the BlueGenome 8x60k v2.0 ISCA platform. Test DNA was referenced against same sex control DNA and data was analysed in BlueFuse Multi v4.1. This platform should detect the majority of copy number imbalances >15Kb in 500 disease gene/telomeric regions (including all well characterised microdeletion and microduplication syndromes) and >180Kb in the genomic backbone and may detect smaller imbalances in some instances. The DLR quality score given for this hybridisation is 0.15. Probes are mapped to GRCh37.

References

- [1] Sanlaville D, Schluth-Bolard C, Turleau C. Distal Xq duplication and functional Xq disomy. Orphanet Journal of Rare Diseases 2009 4:4
 [2] Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004 Jan;81(1):19-25.
 [3] The National Center for Biotechnology Information, Genome Decoration Page. Accessed and image processed 02/09/2016.

Declaration and Acknowledgments

The authors declare no conflict of interest.
 With thanks to West Midlands Regional Genetics Laboratory.

