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.11

2003 Rotterdam Diagnostic Criteria for PCOS®, 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

(A)

(B)

(C)

(D)

Figure 1. Patient photographs displaying clinical features

Hirsuitism (A+D), Male Patterned Baldness (B+C), Cystic Acne (A+C)

CASE HISTORY

17 year old, developmentally appropriate female. 1 year history of hirsuitism, 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 moraote. 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 Diane® and Vaniqa®.

ENDOCRINE RESULTS

<table>
<thead>
<tr>
<th>Blood Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin</td>
<td>22.4 ng/L</td>
<td>5.1 - 38.7 ng/L</td>
</tr>
<tr>
<td>DHA</td>
<td>10.4 µmol/L</td>
<td>1.7 - 13.4 µmol/L</td>
</tr>
<tr>
<td>FT4</td>
<td>13 pmol/L</td>
<td>9 - 20 pmol/L</td>
</tr>
<tr>
<td>TSH</td>
<td>1.32 mIU/L</td>
<td>0.35 - 4.94 mIU/L</td>
</tr>
<tr>
<td>LH</td>
<td>11 IU/L</td>
<td>9 - 89 IU/L</td>
</tr>
<tr>
<td>FSH</td>
<td>5 IU/L</td>
<td>3 - 17 IU/L</td>
</tr>
<tr>
<td>Proctin</td>
<td>275 mIU/L</td>
<td>100 - 557 mIU/L</td>
</tr>
<tr>
<td>Sex hormone binding globulin</td>
<td>37 nmol/L</td>
<td>0.2 - 2.9 nmol/L</td>
</tr>
<tr>
<td>Testosterone</td>
<td>1.7 nmol/L</td>
<td>0.2 - 2.9 nmol/L</td>
</tr>
<tr>
<td>17OHP</td>
<td>1.5 nmol/L</td>
<td>0.6 - 6.0 nmol/L</td>
</tr>
</tbody>
</table>

Urinary Steroid Profile: Normal

GENETIC RESULTS

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.

Figure 2: (X) Schematic of X Chromosome with duplicated section highlighted. Androgen receptor and XIST gene locations marked.

SYNACTHEN TESTING

<table>
<thead>
<tr>
<th>Time</th>
<th>DHA</th>
<th>FT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>328 nmol/L</td>
<td>646 nmol/L</td>
</tr>
<tr>
<td>30 min</td>
<td>764 nmol/L</td>
<td>1087 nmol/L</td>
</tr>
<tr>
<td>60 min</td>
<td>1216 nmol/L</td>
<td>1926 nmol/L</td>
</tr>
<tr>
<td>17OHP</td>
<td>3.8 nmol/L</td>
<td>4 nmol/L</td>
</tr>
</tbody>
</table>

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 >150kb 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


Declaration and Acknowledgments

The authors declare no conflict of interest.

With thanks to West Midlands Regional Genetics Laboratory.