IMAGES **in PAEDIATRIC CARDIOLOGY**

Taliana N, Grech V, Said E, DeGiovanni JV. Y Chromosome in Turner syndrome; a case report. Images Paediatr Cardiol 2016;18(4):5-8
Department of Paediatrics, Mater Dei Hospital, Malta

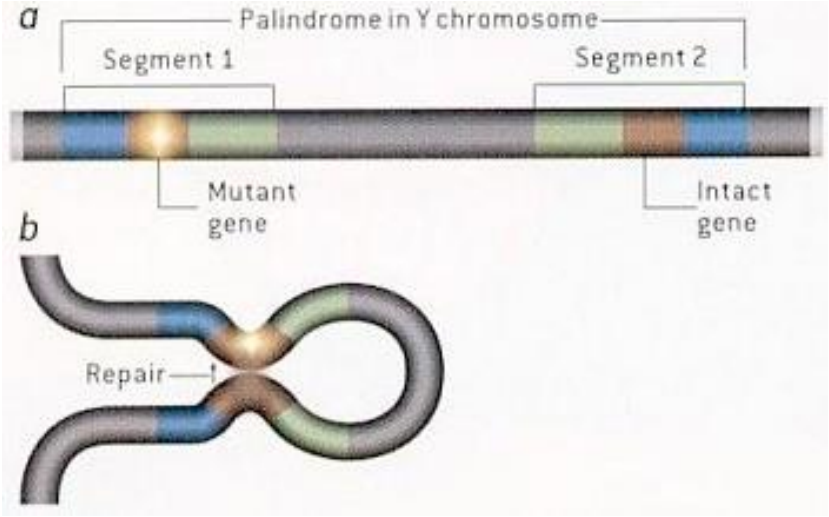
MeSH: Turner syndrome, aortic coarctation,

Introduction

In man, the Y chromosome spans approximately 58 million base pairs and represents just 1% of the total DNA in a male cell.[1] Sex is determined in the SRY locus on the Y chromosome. During the formation of gametes, chromosomal crossover between homologous chromosomes during the meiotic division results in genetic diversity. Genetic recombination can also repair damaged genes. Recombinations between the two X chromosomes for self-repair is possible in females but is not possible for the Y chromosome since this chromosome is present in isolation in the male. This has led to the hypothesis that the Y chromosome may one day become extinct due to cumulative and unrepaired damage.[2] This has occurred, for example, in the Transcaucasian mole vole which does not have an SRY gene or Y chromosome, with both sexes possessing a XO sex chromosome only. Indeed, in this species, sex determining genes are found on a different chromosome.[3]

However, the Y chromosome has recently been shown to have a unique structure, with eight massive areas of mirror-imaged genetic sequences (known as palindromes) which allow the chromosome to undertake a process of self-repair, a process known as intrapalindrome, arm-to-arm recombination. This "recombination" process is also known as gene conversion.[4,5] While this mitigates against the hypothesis of sex chromosome extinction, it has been recently shown that this process can also lead to a range of sex disorders.[4,5]

Figure 1: Palindromes are composed of DNA segments that are mirror images. Facilitates self-repair of the Y chromosome. The Y can correct a mutation in one of the segments (a) by bending and copying the intact version of the other segment (b).



Graphic courtesy of https://universe-review.ca/I11-48-palindromes.jpg

An error in this recombination process can turn the entire Y chromosome into an isodicentric Y chromosome. In this situation, the two centromeres create Y chromosome instability and make chromosome partitioning unpredictable. Outcomes vary, from sperm failure to sex reversal. Furthermore, this instability may be a major cause of Turner's syndrome, which affects over 1 in 2000 females.[1]

In Turner syndrome, the affected individual has one X chromosome, with an absent sex chromosome. It had been assumed that the missing chromosome is an X chromosome, but this may not be the case. It is now proposed that this condition may be caused by a paternal unstable isodicentric Y during the formation of germ cells, such that the Y chromosome is the missing chromosome.[5,6] Evidence for this includes the absence of an increased incidence of Turner's syndrome with increasing maternal age, along with the fact that the X chromosomes present in Turner syndrome are 74% maternally derived.[6]

Approximately 33.3% of females with Turner syndrome, or monosomy X, have congenital heart disease, which most commonly are left-sided cardiac defects. Most common diagnoses include bicuspid aortic valve, aortic stenosis, hypoplastic left heart syndrome, and coarctation of the aorta.[7]

Case report

We present a case of mosaic Turner's syndrome, i.e. a patient with two cell lines, 45X and the other with 46 chromosomes, one of which was an isodicentric Y chromosome. Fluorescence in situ hybridization (FISH) showed that the SRY locus is present on the Y chromosome in this phenotypical female patient.

The child was brought to medical attention when she presented with coarctation of the aorta at nine of age days. She had been born at 39 weeks gestation via emergency section because of foetal distress and meconium stained liquor. She was routinely discharge on day 4 but presented to the accident and emergency department in view of poor feeding. Severe metabolic acidosis with heart failure were present.

On physical examination, the girl had cold peripheries, tachypnoea and a 4 cm liver edge and no fever. A gallop with a systolic murmur 3/6 was audible over the upper and lower left sternal edge. She was admitted to Neonatal Intensive Care where a full septic screen was performed. Venous gases demonstrated pH 7.29, HCO3- 14 mmol/L, base excess 12.7 mmol/L and lactate 8.7 mmol/L. Cardiomegaly was present on chest x-ray. Echocardiography showed a tight coarctation with a hypoplastic arch and the left lung upper lobe draining anomalously to the innominate vein. She was ventilated and a prostin E2 infusion was immediately started at 20 nanograms/kg/min along with a bicarbonate infusion.

Since transfer to London is required for surgical repair for such Maltese patients (in the absence of a local cardiac surgical unit), it was decided to implant a bare metal stent across the coarctation site to improve perfusion to the lower body. A Biotronik, Pro-Kinetic 3.5 x 13mm aortic stent was introduced after ballooning the coarctation site using a Medtronic, Sprinter Legend 4.00 x 15mm balloon, through a femoral artery cut-down. There was instant and rapid metabolic improvement such that prostin and bicarbonate were stopped and extubation was successful at 36 hrs after intervention. The patient was transferred to London self–ventilating. Surgical augmentation of the aortic arch with bovine pericardium and removal of the indwelling stent were performed successfully.[8] At 1 year and 3 months of age severe recoarctation was treated successfully by ballooning of the recoartctation site.

Despite correction of the congenital heart defect, poor growth and failure to thrive persisted. The patient was referred for genetic consultation and chromosomal analysis revealed a mosaic karyotype

with 2 cell lines: one with 45 chromosomes and absence of the Y chromosome and one with 46 chromosomes, one of which is an isodicentric Y. The latter results in a deletion of the spermatogenic loci (AZF region) found on the long arm of chromosome Y which may be associated with disorders of sexual development. She was therefore referred to endocrinology services for further evaluation.

Conclusion

Approximately 99 percent of all fetuses with Turner syndrome are spontaneously terminated during the first trimester of pregnancy.[9] The syndrome thus accounts for approximately 10% of all spontaneous abortions.[10] However, in nonaborted individuals, the syndrome may exhibit subtle phenotypic signs, especially early on in infancy.

For this reason, further evaluation is crucial in patients with unresolved concerns (such as poor growth) which persist after their congenital heart lesion/s are dealt with. It is particularly important to identify such co-morbidities since they may have lifelong effects, such as issues pertaining to initiation of puberty and infertility, as in this case.

Our patient also had partial anomalous pulmonary venous drainage, a recognised association with Turner syndrome and one that should therefore be actively sought in such individuals.[11,12]

Chromosomal analysis should be considered in all cases of cardiac anomalies known to be associated with Turner syndrome: coarctation fo the aorta, anomalous pulmonary venous drainage, bicuspid aortic valve, aortic stenosis and hypoplastic left heart syndrome.

Patient/Parental consent: Obtained
Conflicting interests: None

References

1. Donaldson MD, Gault EJ, Tan KW, Dunger DB. Optimising management in Turner syndrome: from infancy to adult transfer. Arch Dis Child. 2006;91:513-20.
2. Aitken RJ, Marshall Graves JA. The future of sex. Nature. 2002;415:963.
3. Bagheri-Fam, Sreenivasan R, Bernard P, Knower KC, Sekido R, Lovell-Badge R, Just W, Harley VR. Sox9 gene regulation and the loss of the XY/XX sex-determining mechanism in the mole vole Ellobius lutescens. Chromosome Res. 2012,20:191-9
4. Rozen S, Skaletsky H, Marszalek JD, Minx PJ, Cordum HS, Waterston RH, Wilson RK, Page DC. Abundant gene conversion between arms of palindromes in human and ape Y chromosomes. Nature. 2003;423:873-6.
5. Lange J, Skaletsky H, van Daalen SK, Embry SL, Korver CM, Brown LG, Oates RD, Silber S, Repping S, Page DC. Isodicentric Y chromosomes and sex disorders as byproducts of homologous recombination that maintains palindromes. Cell. 2009;138:855-69.
6. Jacobs P, Dalton P, James R, Mosse K, Power M, Robinson D, Skuse D. Turner syndrome: a cytogenetic and molecular study. Ann Hum Genet. 1997;61:471-83.
7. Ashleigh A Richards, Vidu Garg. Genetics of Congenital Heart Disease Curr Cardiol Rev. 2010; 6: 91–97.
8. Bugeja J, Cutajar D, Zahra C, Parascandalo R, Grech V, DeGiovanni JV. Aortic stenting for neonatal coarctation of the aorta - when should this be considered? Images Paediatr Cardiol 2016;1):1-4
9. Urbach A, Benvenisty N. Studying early lethality of 45,XO (Turner's syndrome) embryos using human embryonic stem cells. PLoS One. 2009;4:e4175.
10. Elsheikh M, Dunger DB, Conway GS, Wass JA. Turner's syndrome in adulthood. Endocr Rev. 2002;23:120-40.

11. Mazzanti L, Cacciari E. Congenital heart disease in patients with Turner's syndrome. Italian Study Group for Turner Syndrome (ISGTS). J Pediatr. 1998;133:688-92.
12. Prandstraller D, Mazzanti L, Picchio FM, Magnani C, Bergamaschi R, Perri A, Tsingos E, Cacciari E. Turner's syndrome: cardiologic profile according to the different chromosomal patterns and long-term clinical follow-Up of 136 nonpreselected patients. Pediatr Cardiol. 1999;20:108-12.

Contact Information

Victor Grech
victor.e.grech@gov.mt