Study of Turner Syndrome and Presentation of Unique Cases in the Jordanian Population

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Abstract

In the current study, we review 136 positive cases for Turner syndrome that have been referred to the National Center for Diabetes, Endocrinology and Genetics, Amman, Jordan between 1989-2011. As expected, majority of those reported cases (46% of total positive cases) presented with standard monosomy (45, XO) whereas other chromosomal abnormalities such as the presence of isochromosome Xq, deletion of Xp, presence of ring structures were identified in the reminder of samples. We summarize the data obtained, with a special focus on 3 cases with unique karyotypes, including a structural abnormality of the Y chromosome. Experimental approaches utilized include standard karyotyping, probe-specific FISH and *SRY* gene sequencing. Our work confirms the importance of comprehensive cytogenetic and molecular analysis of such cases of Turner syndrome, resulting in better diagnosis and management.

Introduction

Chromosomal number and structure determine the normal gender phenotype in humans. Carrying a copy of the X and Y chromosome determines the male phenotype and carrying two copies of the X chromosome determines the female phenotype. However, in some cases abnormalities in number and/or structure of the chromosomes are associated with a wide range of syndromes, including Turner syndrome. Turner syndrome (TS) affects approximately 1 in 2,500 live-born females, with the most common karyotype in the affected individuals being 45, XO. The reminder of the patients, however, carry mosaic cell lines containing a second sex chromosome (either structurally normal or abnormal X or Y chromosome). In about 6% of the female Turner syndrome patients, the second cell line contains a structurally abnormal Y chromosome (REF). Although symptoms vary, most patients present with amenorrohea, short stature, lymphedema, normal IQ. In general, patients with mosaicism for 46, XX result in milder phenotype whereas patients with mosaicism for 46, XY show more severe phenotype. In ~ 0.05% TS cases, patients carry small supernumerary marker chromosome (sSMC).

Methods

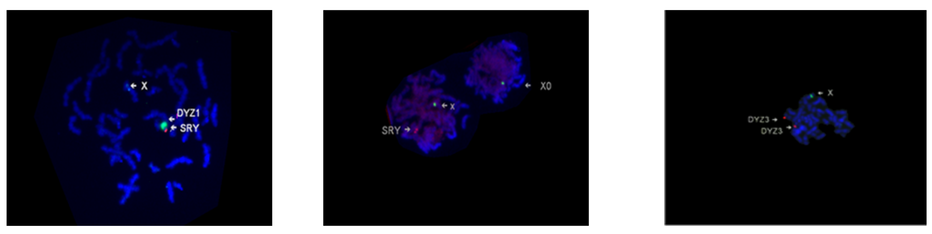
Chromosomal analysis: chromosomal metaphase from blood lymphoycytes were prepared according to the standard procedures two separate culture was prepared for each patient . chromosomal analysis were done using GTG banding at 550 band level according to the ISCN 2009 and 50 metaphases were scored for each patients . Fluorescence in situ hypridization (FISH) :Fish was performed on cell and metaphases optained from blood lymphocytes and the procedure was done according to the probe manufacture manual , using CPEX(DXZ)/Y(DYZ3)(Vysis).SRY probe(YP11.2) /Yqh(DYZ1)/Xcen(DXZ) (CytoCell).

Results

During 1989-2011, 136 cases positive for Turner syndrome were identified through karyotyping. 63 patients showed standard X monosomy whereas 37 had isochromosome Xq present in their cells and 14 presented with X mosaicism. In 3 patients, the karyotyping identified X chromosome ring structures. Interestingly, 11% of TS cases were positive for structurally abnormal Y chromosome and showed more severe phenotype. More detailed analysis of 3 cases with structurally abnormal Y chromosome follows below.

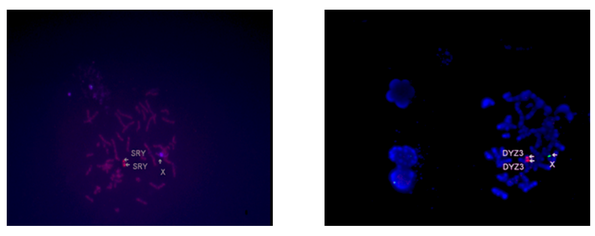
Case 1

A 17 year old female clinically diagnosed with TS presented with short stature, hypertension, primary amenorrhea and sexual infantilism, small ovaries and primary hypogonadism. Chromosomal analysis showed mosaic composition of the cells. Figure 1 shows 3 different cell lines identified in patient's lymphocytes. FISH analysis was also performed and the results are summarized in Figure 2. Furthermore, we sequenced the *SRY* (sex determining region on the Y chromosome) gene in this patient, finding no mutation in the exonic region of the gene.



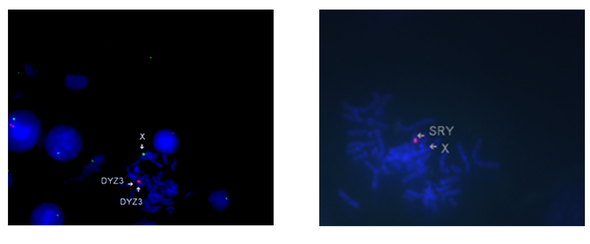
Case 2

A 47 year old female clinically diagnosed with TS presented with short stature, hypertension, primary amenorrhea and sexual infantilism, osteoperosis and congenital abnormality in the ovaries. The patient has undergone a surgery for a removal of uterine-like structure. 2 different cell lines were identified in this patient's lymphocytes (Figure 3). Results of FISH analysis are presented in Figure 4. Also, *SRY* sequence analysis took place and no mutations were identified.



Case 3

A 5 year old male clinically diagnosed with TS presented with ambiguous genitalia and undescended testes. No other clinical information was available. Karyotyping was performed and the patient was found to carry 2 different cell lines (Figure 5). FISH analysis showed the presence of 1 copy of the SRY gene (Figure 6).



Discussion

The aim of the current study was to summarize the data available on patients with Turner syndrome and perform more detailed analysis on cases identified as unique. 3 cases presented above were chosen for further analysis due to; their karyotypes, showing the presence of 2 or 3 different cell lines and presenting with small supernumerary marker chromosome (case 1); their genetic make-up where all 3 patients carried 1 or 2 copies of the *SRY* gene on their isodicentric Y chromosome; phenotypical features and inconsistency between the genotype/phenotype correlation. Presence of 2 copies of *SRY* gene would warrant a predominantly male phenotype unless a functional mutation is identified in the gene. This, however, was not the case in our 2 patients (case 1, 2). Both were phenotypically females, with typical TS presentation. In case 3, only 1 copy of the *SRY* gene was detected and since the patient had an abnormal Y chromosome, he presented as a phenotypical male, with ambiguous genitalia. Unfortunately, no DNA was available for *SRY* sequencing in order to understand if an *SRY* mutation was the underlying cause of this. The inconsistencies observed in the presented cases can possibly be explained by the presence of complex mosaicism within different tissues in these patients. The ratio of cells carrying the X chromosome when compared to cells carrying the Y chromosome might differ from tissue to tissue and karytoyping of lymphocytes could give different results to karytyping of gonadal tissue. Same can be said about the presence of the functional *SRY* gene. In order to better understand the underlying genetic mechanisms in those cases, analysis of gonadal biopsy would need to be performed.

Overall, chromosomal abnormalities causing TS mostly occur on a sporadic bases and therefore the recurrence risk is minimal. Nevertheless, due to the negative effects on fertility, TS patients are offered genetic counseling ,explaining the available options to them. Comprehensive cytogenetic and molecular analysis of patients with TS are crucial for early intervention (eg growth hormone therapy, ovarian hormone therapy) and better management.

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