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Review of Cytogenetic findings of patients with Turner Syndrome and its variants in Filipinos and the Implications in Genetic Counseling

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Abstract:

BACKGROUND: Turner syndrome (TS) is the most common sex chromosomal abnormality in females resulting from a missing X chromosomal material. This in turn results in a range of clinical manifestations. This study aimed to provide the data on the cases of TS confirmed via chromosomal analysis in a cytogenetics laboratory in the Philippines as well as the role of genetic counseling.

METHODOLOGY: A review of the karyotyping results of the Cytogenetics Laboratory, Institute of Human Genetics, National Institutes of Health, University of the Philippine Manila from 1991 to 2020.

RESULTS: TS accounted for 2.64% of all the samples received from 1991 to 2020. For 30 years, the most common karyotype in TS was the classical TS or the standard monosomy 45, X noted in 195 patients or 37.69% of all patients diagnosed with TS. Mosaicism with a normal female karyotype was noted in 50 patients (9.62%). For the TS variants, the most common is isochromosome Xq seen in 125 patients (24.04%). This is followed by TS with marker chromosome in 55 patients (10.58%) and ring X chromosome in 23 patients (4.42%). Deletion Xp and deletion Xq were noted in 22 patients (4.23%) and 20 patients (3.85%), respectively.

CONCLUSION: From this study, it can be noted that chromosomal analysis or standard karyotyping is a vital and useful diagnostic tool in TS. The information obtained from it may be useful in clinical decision-making of families and healthcare providers. Its importance in providing adequate genetic counseling cannot be overemphasized.

Keywords:

Chromosomes, karyotyping, turner syndrome

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Introduction

Turner syndrome (TS) is a disorder, characterized by partial or complete monosomy of the X chromosome.[1] It is one of the most common sex chromosomal abnormalities, with an estimated prevalence of 1 in 2000.[1,2] However, the true prevalence remains unknown and may be higher since many patients may present with a mild phenotype which may remain unnoticed and undiagnosed.[1] TS is typically associated with hypogonadism, infertility, short stature, various endocrine and metabolic disorders, and an increased risk of autoimmune and cardiovascular disease.[3,4]

In the Philippines, TS is among the key indications for requesting chromosomal analysis or karyotyping. According to the International TS Consensus Group, the diagnosis of TS is established in a phenotypic

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female who has a karyotype showing one X chromosome with a complete or partial absence of the second sex chromosome, accompanied by one or more characteristic clinical features of the syndrome.[3] In addition, it is also recommended not to make a diagnosis of TS in females with one X chromosome and a deletion distal to Xq24 on the other X chromosome, and in women over the age of 50 years with <5% 45, X mosaicism.[3] Phenotypically normal adult women undergoing infertility investigation may be found to have deletion of terminal portions of the long arm of chromosome X without other features of TS. They should not be diagnosed to have TS.[5] Based on studies, most of the genes associated with the physical features observed in TS are located on Xp (Xp11.2-p22)[6,7] while the loci linked to ovarian function reside in Xq (Xq24).[7,8]

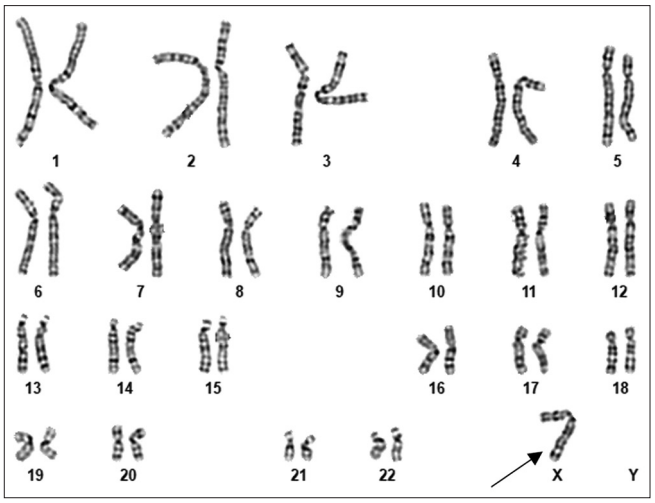

Figure 1: Chromosomal analysis showing a missing X chromosome seen in most cases of turner syndrome

Methodology

Karyotyping results at the Cytogenetics Laboratory, Institute of Human Genetics, National Institutes of Health, University of the Philippines Manila from 1991 to 2020 were reviewed. Results of patients with TS were reviewed and classified. Descriptive statistics using percentages of proportion were applied for the interpretation of data.

Results

A diagnosis of TS was made in 2.64% (520 patients) of all the karyotyping samples sent at the Cytogenetics Laboratory. Of all the abnormal karyotypes, 7.67% turned out to be TS [Table 1]. It comprised 71.23% of all sex chromosome disorders.

Standard monosomy X or classical turner syndrome

Of the 520 patients with TS, 37.69% was standard monosomy X [Figure 1]. For the posttest genetic counseling, it is important to explain that standard 45, X TS typically arises sporadically, due to nondisjunction or loss of a sex chromosome during gametogenesis or early embryonic development. Parental chromosomal abnormalities are rarely involved; hence, the recurrence is extremely low. Included in the counseling is a clear discussion is the potential medical implications like growth and developmental concerns, cardiac and renal surveillance, and hormonal therapy. Psychosocial support is essential, as patients may experience fertility challenges and body image concerns. Families should be reassured that TS is not an inherited condition. It is also helpful to provide them with information on available multidisciplinary management and TS support networks.

Mosaicism with a normal female karyotype

Mosaicism with a normal female karyotype was noted in 50 patients (9.62%). From a genetic counseling perspective, it is important to emphasize that mosaic TS generally results from a postzygotic event, meaning the errors occurs after fertilization rather than being inherited from either parent. As such, the recurrence risk is extremely low. Counseling should address the variable clinical presentation, as individuals with mosaicism may have milder features, retain partial ovarian function, and occasionally achieve spontaneous puberty or fertility. Families should be guided regarding the importance of a long-term follow-up and offered psychosocial support and reproductive counseling given the potential uncertainty on fertility and hormonal function over time.

Isochromosome X

For the TS variants, the most common karyotype is isochromosome Xq in 125 patients (24.04%). During a genetic counseling session, it is important to highlight that patients with this karyotype may have a greater susceptibility to autoimmune disorders particularly autoimmune thyroid disease and should therefore have a targeted endocrine surveillance.

Ring Chromosome [46,X,r(X)]

A ring X chromosome was identified in 23 patients (4.42%). Genetic counseling for individuals with a ring X chromosome focuses on explaining the chromosomal abnormality, its effects, and its associated health implications. Although most cases occur sporadically, parental karyotyping may be recommended to rule out inherited chromosomal rearrangements. Counseling also addresses the potential for variable clinical outcomes, including neurodevelopmental issues, and provides guidance on medical management and supportive care.

Turner syndrome with marker chromosome

TS with marker chromosome was seen in karyotypes of 55 patients (10.58%). Genetic counseling for this

focuses on explaining the presence and significance of the extra, structurally abnormal chromosome. If on additional molecular testing to determine the origin, the Y chromosomal material was detected, patients and families should be counseled on the increased risk of gonadoblastoma and the medical recommendation for prophylactic gonadectomy to prevent malignancy, along with discussion of fertility, hormonal, and psychosocial implications.

Deletion Xp and Deletion Xq

Deletion Xp was noted in 22 patients or 4.23% of TS cases. Deletion Xq, on the other hand, was noted in 20 patients (3.85%). Deletion of the short arm of the X chromosome is associated with short stature while Xq is associated with premature ovarian failure. These should be addressed in the genetic counseling by discussing implications for fertility, hormone therapy, and long-term reproductive health.

Discussion

Karyotyping or chromosomal analysis is a particularly important diagnostic tool for TS. In addition, the information it gives can be utilized to adequately provide genetic counseling. This information obtained in the chromosomal analysis can help in providing adequate education.

Standard Monosomy X is the most common karyotype. Typical range in published studies showed a range of around 30%–50% of TS cases, as in our data, but many modern reviews cite 40%–50%.[9-14] In addition, it is associated with the most abnormal phenotype.[14] Classical TS may have features of short stature, gonadal dysgenesis, deficiencies in sexual development, cardiac and/or renal defects, webbed neck, low-set ears, skeletal deformities including cubitus valgus, hearing deficits and a tendency of having ear infections. Structural cardiac anomalies are also most prevalent in this karyotype.[15,16]

Mosaicism with a normal female karyotype is the most common form of mosaicism in TS. In our data, it accounts for 14.5% of cases. It is comparable to the data in Saudi Arabia at 13%, but lower compared to the 50.8% in a Korean study and higher in a Japanese cohort (6.3%).[11,13,14] TS patients with this karyotype may have a normal phenotype rather than the typical features in TS. Furthermore, spontaneous menstruation occurs in up to 20% of mosaic females, which is higher than those with the classic monosomy X. The mean adult length is also higher and the probability of having somatic anomalies like webbed neck is lower in this group of patients with TS.[17]

One of the most noted karyotypes, both with and without mosaicism, is an isochromosome X. An isochromosome is a mirror-image chromosomal abnormality consisting of two copies of either a short arm or a long arm, often observed for X and acrocentric chromosomes. Based on the literature, isochromosome X with or without mosaicism is the most common structural X chromosome abnormality and accounts for more than 15% of cases of TS, as in our case.[7,14,18] In our data, the isochromosome X karyotype involves mostly the long arm [Figure 2] and accounts for 24% of the cases, both with and without mosaicism. In a large cohort of patients with TS, the risk of developing autoimmune thyroid disease is particularly high with those patients having isochromosome X.[19] This information may help clinicians in the surveillance and monitoring of patients with this karyotype.

The presence of ring chromosomes had also been reported in TS. Our data are comparable to other studies on TS with ring X chromosome at 4%–6%.[13,14] Females having the 46, X, r (X) karyotype [Figure 3] may present with the usual TS findings like short stature, peripheral edema, characteristic facial features, low neck hairline, ovarian dysgenesis, and endocrine disorders. However, it was reported that mental retardation, learning disability, autism spectrum disorders, and structural brain abnormalities are more often seen in TS with ring chromosome than TS with the classic monosomy X. Some patients may even have more severe phenotypes.[17,20]

Marker chromosomes are unidentified structurally abnormal chromosomes which may occur in addition to the normal 46 chromosomes or as a replacement of a normal chromosome. In TS, the latter is frequently found and is called a supernumerary marker chromosome.[21] Our data are a little bit higher to that of a Korean study where TS with marker

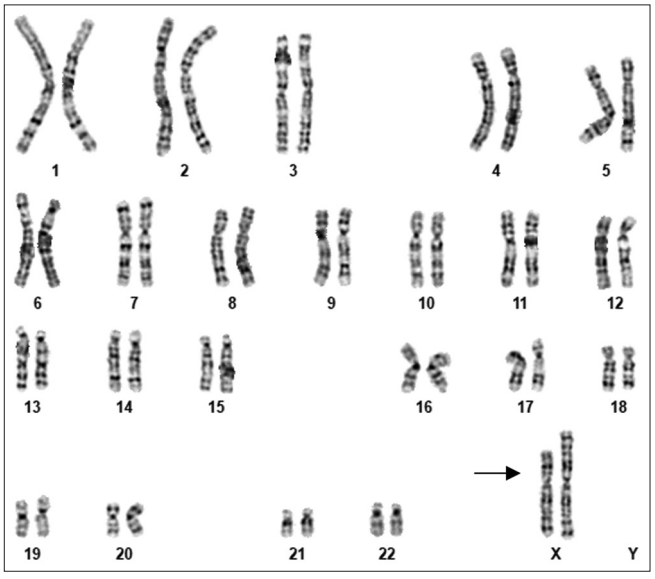

Figure 2: Chromosomal analysis in a patient with Turner syndrome showing 45, X/46,X,i(x)(q10) karyotype

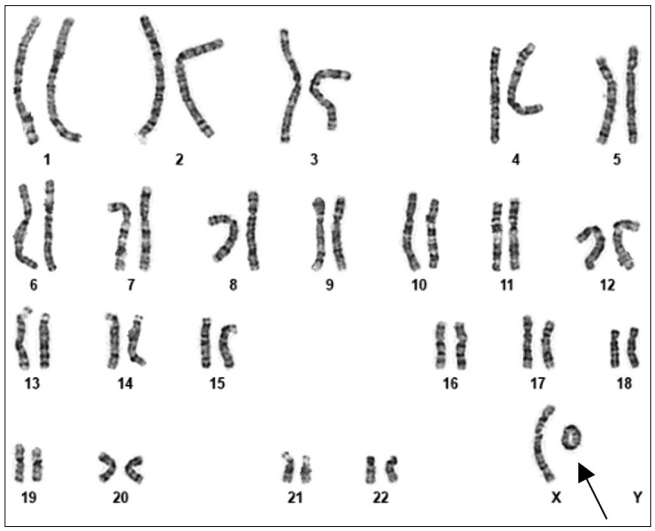

Figure 3: Chromosomal analysis in a Turner syndrome patient showing a ring chromosome

chromosome is at 7.9%.[13] This additional chromosome smaller than one chromosome most often lacks a distinct banding pattern and is rarely identifiable by conventional banding cytogenetic analysis.[22] Hence, TS patients having this karyotype requires further studies to identify the origin and composition of the marker chromosome since those derived from the Y chromosome poses increased risk for malignancies. Patients with TS having a Y chromosome material were noted to have an increased risk of germ cell tumors such as gonadoblastoma and dysgerminoma. Because of a 10% approximate risk of gonadoblastoma in TS with Y chromosome material, prophylactic gonadectomy is recommended.[3,23]

Patients with deletion of the entire short arm of the X chromosome were observed to have short stature and other the TS characteristics as most of the genes responsible for the TS features are located in Xp11.2-p22.[8] The SHOX gene, located in the region Xp22.33-Xp22.12, was known escapes from X inactivation and has a dosage-dependent function. Its haploinsufficiency has been known to be responsible for the short stature in TS. Deletion Xq, on the other hand, is associated with premature ovarian failure. Based on cytogenetic studies, the region Xq13 to Xq28 is important for normal ovarian function.[17] Correlation of these specific karyotypes with the phenotype of TS patients allowed a better understanding to the effect of a specific genotype to the presentation in TS.

As exemplified by the above-mentioned karyotypes in TS, the information obtained provides valuable contribution in the genetic counseling and management plan for patients. TS is generally a sporadic condition that is not linked to advanced maternal age. Based on available literature, the missing X chromosome usually

Table 1: Karyotyping results in patients with Turner syndrome from 1991 to 2020

Karyotype	Count	Subtotal (%)
Standard monosomy		
45,X	195	196 (37.69)
45,X,add(18)(p11)	1	
45,X mosaic (with XX/XXX)		
45,X/46,XX	50	66 (12.69)
45,X/46,XX/47,XX,+21	1	
45,X/47,XXX	15	
X,abn(X) Turner syndrome variants		258 (49.62)
Isochromosome Xp		
46,X,i(X)(p10)	1	3 (0.58)
46,X,i(X)(p10)[40]/45,X[10]	1	
45,X/46,X,idic(X)(q21)	1	
Isochromosome Xq		
46,X,i(X)(q10)	47	125 (24.04)
46,X,i(X)(q10)/46,XX	1	
45,X/46,X,i(X)(q10)	63	
45,X/46,X,i(X)(q10)/47,X,i(X)(q10)x2	1	
45,X/46,X,i(X)(q10)/46,X,+ mar	1	
46,X,idic(X)(q22)	1	
46,X,idic(X)/46,X,idic(X),del(3)(q11.3)	1	
45,X/46,X,idic(X)(p11.1)	1	
45,X/46,X,idic(X)(p11.23)	1	
45,X/46,X,idic(X)(p22;p22)	1	
45,X/46,X,idic(X)(p22.3)	1	
46,X,psu idic(X)(p11.2)	1	
46,X,psu idic(X)(p11.2p11.2)	2	
46,X,psu idic(X)(p12)	1	
45,X/46,X,psu dic(X)(p11)	1	
45,X/46,X,psu idic(X)(p12)	1	
Ring		
45,X/46,X,+ r	16	23 (4.42)
45,X/46,X,r(X)(p22q21)	1	
45,X/46,X,r(X)(p22q22)	1	
45,X/46,X,r(X)(p22.1q21)	1	
45,X/46,X,r(X)(p22.2q12)/46,X,dic r(X;X)(p22.2q12;p22.2q12)	1	
45,X/46,X,r(X)(p22.3q13)/46,X,dic r(X;X)(p22.3q13;p22.3q13)	1	
45,X/46,X,r(X)(p22.3q21)	1	
45,X/46,X,r(X)(q22.1q21.3)	1	
Marker		
46,X,+ mar	17	55 (10.58)
46,X,-9,+ mar1,+ mar2	1	
46,X,+ mar/47,X,+2mar	1	
45,X/46,X,+ mar	35	
45,X/46,X,del(22)(p11.3),+ mar	1	
Deletion Xp		
46,X,del(Xp)	1	22 (4.23)
46,X,del(X)(p11)	2	
46,X,del(X)(p11),inv(9)(p12q21.1)	1	
46,X,del(X)(p11.1)	2	
46,X,del(X)(p11.1)[34]/46,X,i(X)(q10)[16]	1	
46,X,del(X)(p11.1)[41]/46,X,psu idic(X)(p11.23)[9]	1	

Contd....

Table 1: Contd...

Karyotype	Count	Subtotal (%)
46,X,del(X)(p11.2)	3	
46,X,del(X)(p11.23)	1	
46,X,del(X)(p11.3)	2	
46,X,del(X)(p11.4)	2	
46,X,del(X)(p21)	1	
46,X,del(X)(p22.1)	1	
45,X/46,X,del(X)(p10)	2	
45,X/46,X,del(X)(p11.1)	1	
45,X/46,X,del(X)(p11.2)	1	
Deletion Xq		
46,X,del(X)(q12)	1	20 (3.85)
46,X,del(X)(q13)	3	
46,X,del(X)(q21.1)	2	
46,X,del(X)(q21.3)	2	
46,X,del(X)(q22)	1	
46,X,del(X)(q22.2)	1	
46,X,del(X)(q23)	1	
46,X,del(X)(q23)/46,XX	1	
46,X,del(X)(q26)	1	
46,X,del(X)(qter)	1	
45,X/46,X,del(Xq)	1	
45,X/46,X,del(X)(q11.1->qter)	1	
45,X/46,X,del(X)(q21)	2	
45,X/46,X,del(X)(q22.1)	1	
45,X/46,X,del(X)(q23)	1	
Other structural abnormality of X		
46,X,der(X;20)(p10;q10),+20	1	10 (1.92)
45,X/46,X,add(X)(pter)	1	
45,X/46,X,add(X)(qter)	1	
46,X,der(X)del(X)(p21)ins(X;?)(p11.2;?)	1	
45,X/46,X,der(X)del(X)(p21.3)del(X)(q12q21.1)	1	
45,X/46,X,der(X)	1	
45,X/46,X,dup(X)(q11.3→qter)	1	
45,X/46,X,dup(X)(q13q21)	1	
45,X/46,X,inv(Xq)	2	
Grand total		520 (100)

is of paternal origin for those with karyotype of 45, X as repeatedly determined using different methods.[24]

Genetic counseling for TS plays a crucial role not only in clarifying the chromosomal basis of the condition but also in supporting patients and their families throughout diagnosis, treatment, and long-term care.[25] Comprehensive counseling should include education on the genetic and medical aspects of TS – such as potential complications related to growth, fertility, cardiovascular health, and psychosocial development – as well as discussions about the recurrence risk, which is typically low.[26] Beyond medical education, counseling must address gender identity and cultural considerations, provide realistic expectations regarding prognosis, and explore the emotional and social implications for the individual, couple, and family. It also serves as a platform for discussing available interventions, including growth hormone therapy, estrogen replacement, fertility options, and long-term follow-up for associated health risks. Through this multidisciplinary and empathetic approach, genetic counseling empowers patients and their families to make informed decisions, fosters psychological adjustment, and promotes holistic management of TS.

Conclusion

Chromosomal studies of an individual suspected to have TS remain an important element of the diagnostic work-up. Not only does it offer diagnosis, chromosomal analysis or karyotyping also gives additional information critical to the surveillance, monitoring and management of TS patients. It allows having a more informative and adequate genetic counseling, which may help patients and their families with decision-making.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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