

# Karyotypic Variables in Turner Syndrome: A Case Series

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## Abstract

Turner Syndrome (TS) is a medical disorder that affects about 1 in every 2500-3000 female live births worldwide. It is a genetic condition in which a female does not have the usual pair of two X chromosomes. Females who have this condition are usually shorter than average and infertile due to early loss of ovarian function. In order to study, about the different types of karyotypic variations that can result in TS, case studies of 10 different probands were analyzed. Analysis of each proband was done with respect to the clinical presentation, as well as a karyotype. It was observed that Mosaic TS had a much higher percentage of occurrence compared to monosomy X. Mosaics varied with respect to genotype combinations, as well as the presence of structural abnormalities on the X chromosome. The variable phenotype reflected the different possible clinical presentations seen in TS.

**Key words:** Karyotype, Karyotypic variations, Mosaicism, Turner Syndrome

## INTRODUCTION

Turner Syndrome (TS) or Ullrich-TS is a genetic disorder encompassing several conditions, of which monosomy X is most common (45,X). It is caused due to chromosomal abnormality, where in complete or a part of one of the X chromosomes is absent.<sup>1</sup> Cases have also been reported with mosaicism, where 45,X cell line is accompanied by one or more other cell lines having a complete or structurally abnormal sex chromosomes (X or Y).<sup>1,2</sup> Structural abnormalities of the sex chromosome (X) can be due to deletions of the short arm q or long arm p (Xp-, Xq- respectively), duplication of the long arm to form isochromosome (isoXq) or formation of ring (rX). Some mosaic females have also shown to carry additional cell lines, with the Y chromosome (45,X/46,XX; 45,X/46,XY).<sup>3</sup> Mortality rates in TS are about 4- to 5-fold higher than in

the general population, reducing the life expectancy up to 13 years.<sup>4,5</sup>

Typical abnormalities in TS include short stature, gonadal dysgenesis (usually, streak gonads reflecting a failure of ovarian maintenance), characteristic facial features, webbed neck, low posterior hairline, a broad chest with widely spaced nipples, nevi all over the body, shortened metacarpal IV, small fingernails, shield-shaped thorax, poor breast development, and elevated frequency of renal and cardiovascular anomalies. Many patients have coarctation of the aorta, cardiovascular abnormalities, lymphedema in fetal life, causing cystic hygroma, and primary amenorrhea (PA) or secondary amenorrhea.<sup>4,7</sup> TS patients with epilepsy have also been reported with frequently associated malformations of cortical development.<sup>2,8</sup>

Some clinical symptoms of TS are inconsistent, even in individuals with non-mosaic 45,X, which might be due to the fact that the physical manifestations of TS patients mainly depends on the karyotype.<sup>1</sup> Phenotypes may be contributed by the parental origin of the X chromosome.<sup>9</sup> Patients mosaic for 46, XX or iXq have been shown to have milder phenotypes.<sup>1,9</sup> While patients with mosaicism for 46, XY cell line or structural rearrangement of the

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Y chromosome mostly have masculinized external genitalia and are at increased risk for having gonadoblastoma and other gonadal tumors.<sup>1,10</sup> The main objective of our study was to analyze the various karyotypes in patients diagnosed with TS and to record the rare phenotypic variations.

## CASE REPORTS

This study was conducted in the Division of Human Genetics, St. John's Medical College, Bangalore, a referral center for human genetic disorders. About 10 cases with different phenotypic and genotypic profiles were included into the study. For each case, demographic details, pedigree data, clinical history were collected. Clinical and rare phenotypic features associated with the variable Karyotypes were compiled, recorded and the data were analyzed.

The chromosomal analysis was performed by peripheral blood lymphocyte culture on the basis of G-banding technique at high resolution. Number of chromosome present in a specific number of cells referred to as metaphase spreads are counted followed by careful analysis of the banding pattern of each of the individual chromosomes and the total chromosomal count was determined in 10-15 cells. The banding pattern is compared with an idiogram and then formally presented as "karyotype," which will show each chromosome pair arranged in descending order of size.

### Case 1

The patient was a female of 20 years. She had a history of PA. Observations/Examinations (O/E) showed that secondary sexual characteristics were absent with scanty of axillary and pubic hair, breast development was normal, low posterior hairline was absent. She had no webbing of the neck and had normal intelligence. Further, investigations showed that her ECHO results was normal, ultrasound scanning results showed that she had a normal uterus, normal bilateral kidneys, and ovaries were not visualized. Her karyotype was 45,X and hence she was a Turner female with complete monosomy. A pedigree chart is shown in Figure 1.

### Case 2

The patient was a female of 25 years. She had a history of PA. She attained spontaneous menarche at the age of 13. O/E showed that she had decreased secondary sexual characteristics, short stature, complete scalp alopecia, but her external genitalia were normal. Further, investigations included the ultrasound scanning results, which showed that she had a normal uterus, normal bilateral ovaries. Her karyotype was 45,XX (52%)/45,X (48%), and hence she had a mosaic TS. A pedigree chart is shown in Figure 1.

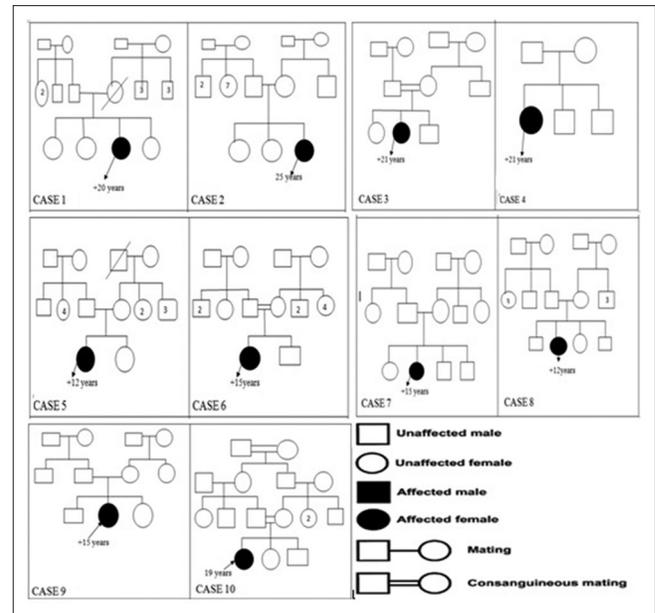


Figure 1: Pedigree charts of the Turner syndrome cases described

### Case 3

The patient was a female of 21 years. She had a history of PA. O/E showed that she had decreased secondary sexual characteristics with normal external genitalia. Further, investigations included the ultrasound scanning results, which showed that she had a rudimentary uterus, bilateral streak ovaries (gonadal dysgenesis). Her karyotype was 45,XX (92%)/45,X (8%), and hence she had a mosaic TS. A pedigree chart is shown in Figure 1.

### Case 4

The patient was a female of 21 years. She had a history of PA. She attained spontaneous Menarche at the age of 17 years. O/E showed that she had decreased secondary sexual characteristics, short stature with normal external genitalia. Further, investigations included the ultrasound scanning results, which showed that she had a hypoplastic uterus ovaries were not visualized (ovarian dysgenesis). Her karyotype was 45,X, del (Xq-), and hence she had a TS with a structural abnormality. A pedigree chart is shown in Figure 1.

### Case 5

The patient was a female of 12 years. She had a history of short stature. O/E showed that she had short stature with delayed pubertal changes. Further, investigations included the X-ray of the wrist, which showed 8 years bone growth, indicating a delayed bone age. Her karyotype was 45,X (80%)/46,X r (X) (ring X chromosome) (20%), and hence she was a Turner mosaic with a structural abnormality. A pedigree chart is shown in Figure 1.

**Case 6**

The patient was a female of 15 years. She had a history of short stature with PA. O/E showed that she had decreased secondary sexual characteristics, cubitus valgus was present. Investigations involved the hormonal assay, which showed high follicle-stimulating hormone (FSH), thyroid profile showed increased thyroid-stimulating hormone (TSH), which indicated hypothyroidism, decreased bone age was noticed, Barr body was not present in cells (Barr body negative). Her karyotype was 45,X del (Xp-) (52%)/45,X (48%), and hence she was mosaic Turner with a structural abnormality. A pedigree chart is shown in Figure 1.

**Case 7**

The patient was a female of 15 years. She had a history of PA. O/E showed that she had decreased secondary sexual characteristics, breasts were not developed, cubitus valgus was present on her right side and her external genitalia were normal. Investigations involved the hormonal assay, which showed high FSH, Luteinizing hormone (LH). The uterus and ovaries were not visualized on the ultrasound. Karyotype was 45,X (64%)/46,XY (36%), and hence she was mosaic Turner with mixed gonadal dysgenesis. A pedigree chart is shown in Figure 1.

**Case 8**

The patient was a female of 12 years. She had a history of short stature. O/E showed that she had short stature and had decreased secondary sexual characteristics. She had normal intelligence. Her external genitalia were normal. Investigations showed decreased bone age. Her ultrasound results showed infantile uterus, streak ovaries. Her karyotype was 45,X (17%)/46,X iso (Xq) (83%), and hence she had a mosaic TS with a structural abnormality. A pedigree chart is shown in Figure 1.

**Case 9**

The patient was a female of 15 years. She had a history of PA. O/E showed that she had decreased secondary sexual characteristics, hypoplastic breast development. Her external genitalia were normal. Ultrasound results showed hypoplastic uterus and bilateral ovaries were not visualized. Her karyotype was 45,X (4%)/46,X iso (Xq) (88%)/47,X, iso (Xq), iso (Xq) (8%), and hence she had a mosaic TS with a structural abnormality. A pedigree chart is shown in Figure 1.

**Case 10**

The patient was a female of 19 years. She had a history of PA. O/E showed that she had short stature and had decreased secondary sexual characteristics. She had normal intelligence. Her external genitalia were normal. Ultrasound results showed that she had a hypoplastic uterus and gonadal dysgenesis. Her karyotype was 45,X, complete monosomy. A pedigree chart is shown in Figure 1.

**RESULTS**

In this study, 10 probands with TS were studied and the corresponding karyotypic variables were recorded as shown in Table 1. Among the 10 karyotypes examined, 7 cases showed Mosaic TS (Case 2, 3, 5, 6, 7, 8, 9).

It was noted that 10% of the cases had complete monosomy (45,X), 10% had complete structural abnormality (46,X, del [Xq]). 70% of the females had Mosaic Turner including 20% complete mosaics (46,XX [52%]/45,X [48%] and 46,X, del [Xq]), 10% mosaics with mixed gonadal dysgenesis (45,X [42%]/46,XY [36%]), 40% mosaics with structural abnormalities (45,X [80%]/46,X, r [X] [20%], 46,X, Xp- [52%]/45,X [48%], 45,X [17%]/46,X iso [Xq] [83%], 45,X [4%]/46,X, iso [Xq] [88%]/47,X, iso [Xq] [8%]), as shown in Table 2.

We observed that both the patients with complete monosomy of 45,X entirely differed in their phenotypic characters with only PA in common. The Patients with mosaicism differed in their clinical presentation which seems to be not affected by the percentage of abnormal cell lines. Rudimentary uterus and bilateral streak ovaries were observed in a patient with only 8% of cell lines with 45,X, while the other patient with 48% of 45,X cell lines had completely normal uterus and ovaries, however, both of them were short stature. Turner females with

**Table 1: Karyotypic variables**

Case no.	Karyotype
1	45, X
2	46, XX (52%)/45, X (48%)
3	46, XX (92%)/45, X (8%)
4	46, X, del (Xq)*
5	45, X (80%)/46, X, r (X) (20%)†
6	46, X, Xp- (52%)/45, X (48%)
7	45, X (42%)/46, XY (36%)
8	45, X (17%)/46, X iso (Xq) (83%)
9	45, X (4%)/46, X, iso (Xq) (88%)/47, X, iso (Xq) (8%)
10	45, X

\*long arm of the X chromosome (Xq) deletion, †ring X chromosome, ‡short arm of the X chromosome (Xp) deletion, long-arm isochromosome X derivative

**Table 2: Observed percentage of occurrence of the different karyotypic variables**

Karyotypic variation	Observed % of occurrence
TS with complete monosomy	20
Structural abnormality	50
TS with complete structural abnormality	10
Mosaic with structural abnormality	40
Mosaic with mixed gonadal dysgenesis	10
Mosaic TS	70
TS: Turner syndrome	

structural abnormalities had a severe phenotype, attained early menarche, had hypoplastic uterus and dysgenesis of ovaries. Female with mixed gonadal dysgenesis had no uterus and ovaries however, had normal external genitalia with no breast development. About 75% of the Turner patients who were mosaics with structural abnormalities presented with delayed or decreased bone age and 50% of them had ovarian dysgenesis. PA, short stature and decreased secondary sexual characteristics were the most common abnormalities found.

## DISCUSSION

TS can vary in its clinical presentation. The various modes of clinical presentations depend on the age of onset as seen in our case studies. We reported 10 different cases of TS with varying severity of the disease. However, the severity of the clinical presentation did not correlate well with the percentage of defected cell lines. The patient belonging to Case 1 despite of having complete monosomy had normal intelligence, normally developed ovaries and no webbing of the neck whereas in Case 2 and Case 3 with only 48% and 8% lines being 45,X respectively TS females presented with slightly more severe clinical symptoms including ovarian dysgenesis. However, Case 10 with complete monosomy had typical TS features. The lack of a second X chromosome leads to the development of streak gonads, because a second X chromosome is essential for full development and functioning of the ovaries.<sup>11</sup>

We observed a higher frequency of Turner Mosaic females with highest number of cell lines having sex chromosome with structural abnormalities i.e. deletions of the short arm q (Xq-) or long arm p (Xp-), duplication of the long arm forming isochromosome (isoXq) or presence of ring (rX). It has been reported that loss of interstitial or terminal long arm material of the X chromosome (Xq) can result in short stature and primary or secondary ovarian failure.<sup>12</sup> This finding correlated well with our Case 4, a 21-year-old TS female with 45,X, del (Xq-) karyotype who was short statured with hypoplastic uterus and ovarian dysgenesis. Deletion of the whole short arm of the X chromosome (Xp) is often associated with short stature with classic stigmata of TS, but the gonadal function is generally preserved.<sup>13</sup> This was seen in our Case 6, a 15-year-old TS female. Case 5, 15 years female with short stature and delayed pubertal changes and delayed bone age was found to have cell line with ring chromosome, resulting in the phenotype due to the functional disomy of genes. The phenotype variability of the patients with ring (marker) X chromosome is mostly dependent on the size of the ring and the presence of a functioning XIST gene, which is expressed exclusively from the inactive X chromosome.

Marker or ring X chromosomes (r(X)) lacking a functional XIST have been associated with several clinical features such as mental retardation and a distinct phenotype of short stature, and facial dysmorphism.<sup>14,15</sup> Case 7, a 15 years female had mixed gonadal dysgenesis with 45,X/46,XY mosaicism, which is a rare and probably underdiagnosed condition and its incidence is 1.5 per 10,000 newborns.<sup>16</sup> The different distributions of the 45,X (X monosomy) and 46,XY (male constitution) chromosomal cell lines among the tissues in individuals with this mosaicism presumably reflect the wide variety of phenotype observed as in Case 7. Mixed gonadal dysgenesis is caused by the loss of the Y chromosome due to non-disjunction subsequent to normal disomic fertilization.<sup>17</sup> Most of the TS patients with isochromosome Xq have mild phenotypes<sup>18</sup> and generally show similar characteristics to those with classical 45,X<sup>19</sup> as found in Cases 8 and 9. An isochromosome is a structurally abnormal chromosome consisting of 2 short or 2 long arms; the abnormal transverse misdivision of the centromere yields unbalanced chromosomal constitution, monosomy for the missing arms, and trisomy for the duplicated arms.<sup>19</sup>

Detection of TS is possible in the prenatal period, in children and even in adult females. The specific nature of the chromosomal abnormality, specific genes affected, or the resulting imbalance of the parts of the genome involved results in the phenotypic characteristics associated with the disease.<sup>20,21</sup> The influence of the maternal age may not be related to the birth of TS children.<sup>22</sup> Moreover, it is now known that in 80% of the TS, the paternal X chromosome may have been lost from a 46,XX, or 46,XY zygote.<sup>23</sup> Hence, TS cannot be correlated to maternal age.<sup>24</sup>

In this study, etiological factors may be difficult to pinpoint in view of the increased variability of presentation indicating a range between chromosomal abnormalities to the possibility of an imprinted X-linked gene that influences the phenotype of these individuals. A variable phenotype reflects the different possible clinical presentations seen in TS. Hence, it becomes imperative that once there is a clinical suspicion of TS, irrespective of the age, it must be confirmed by karyotyping to establish the variable karyotypes associated with the syndrome.<sup>25</sup> Thus karyotype will establish the type and also the prognosis in the cases.

This study also confirms explicitly that almost all patients with TS have short stature and loss of ovarian function, but the severity of these problems varies considerably amongst individuals. The genetic counseling in each of these cases will depend on the clinical presentation, karyotypic variables, early detection, management, and even prevention through prenatal diagnostic facilities.

## CONCLUSION

We reported 10 different cases of TS females from 15 to 25 years of age with varying phenotypic and genotypic profiles. We observed a higher percentage of mosaic TS females including complete mosaics, mosaics with mixed gonadal dysgenesis and mosaics with structural abnormalities. We suggest that chromosome analysis for TS should be considered even in patients presenting with normal intelligence and who attained normal puberty however, when the height is short and autoimmune thyroid disease is accompanied. Chromosome analysis for TS is essential in order to plan an appropriate management of the disease early in life.

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