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KARYOTYPIC HETEROGENEITY AND TEMPORAL DIAGNOSTIC PATTERNS IN TURNER SYNDROME: INSIGHTS FROM A LARGE REFERRAL COHORT IN INDIA

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ABSTRACT

Background: Turner syndrome (TS) is a common sex chromosome disorder in females resulting from total or partial X-chromosome monosomy. Given its marked phenotypic and cytogenetic heterogeneity, conventional karyotyping remains the diagnostic gold standard for identifying structural and numerical X-chromosome aberrations.

Aim: To characterise the cytogenetic spectrum and demographic trends of X-chromosome abnormalities in suspected Turner syndrome cases.

Methods: This retrospective study analysed peripheral blood lymphocyte cultures from 5,045 individuals referred for cytogenetic evaluation between 2021 and 2025 using standard Giemsa–trypsin G-banding (GTG-banding). Suspected TS cases were categorized by cytogenetic variant, age distribution, and temporal presentation.

Results: Diagnosed TS cases peaked in 2024, predominantly among individuals of reproductive age. Cytogenetic analysis revealed significant karyotypic diversity: classic 45,X monosomy comprised 58.5% of cases, followed by numerical mosaicism/anomalies (14.6%), isochromosomes [i(Xq)] (9.8%), structural deletions (8.5%), complex/rare rearrangements (4.9%), and other chromosomal variants (3.7%).

Conclusion: GTG-banding remains indispensable for detecting the diverse cytogenetic spectrum of Turner syndrome. Highlighting this karyotypic heterogeneity reinforces the need for prompt cytogenetic evaluation to ensure timely clinical management and genetic counselling.

Keywords: Monosomy X; Cytogenetic Variability; Karyotyping; Mosaicism; Structural X Chromosome Abnormalities.

1 INTRODUCTION

Turner syndrome (TS) is a common sex chromosome aneuploidy characterized by the complete or partial structural loss of one X chromosome in females, with an estimated live-birth incidence of approximately 1 in 2,500 female neonates. However, its true conceptional prevalence is markedly higher, as monosomy X accounts for a significant proportion of early spontaneous miscarriages [1]. Turner syndrome exhibits considerable phenotypic heterogeneity, with clinical features ranging from short stature, gonadal dysgenesis, primary amenorrhea, and infertility to congenital cardiovascular malformations, renal anomalies, endocrine co-morbidities, sensorineural hearing impairment, and specific neurocognitive profiles [2]. The expressivity and severity of these clinical features are strongly modulated by the underlying constitutional cytogenetic architecture.

The cytogenetic landscape of Turner syndrome encompasses a diverse spectrum of karyotypic aberrations. While classic monosomy X (45,X) constitutes the most frequent entity, structural anomalies—including isochromosomes [i(Xq)], ring chromosomes [r(X)], interstitial or terminal deletions [del(X)], and balanced or unbalanced translocations—as well as numerical X-chromosome mosaicism (e.g., 45,X/46,XX) and heteromorphic variants are frequently observed. Patients harboring mosaic or subtle structural X-chromosome variants often exhibit atypical or attenuated phenotypes. Consequently, these individuals experience diagnostic delays, frequently presenting only during late adolescence or adulthood during clinical evaluations for short stature, delayed puberty, or primary reproductive failure [3].

Although advanced cell-free fetal DNA screening methodologies, such as non-invasive prenatal testing (NIPT), have expanded early screening for sex chromosome aneuploidies, definitive diagnostic confirmation continues to rely on conventional cytogenetic analysis [4]. Standard metaphase karyotyping via Giemsa-trypsin G-banding (GTG-banding) on cultured peripheral blood lymphocytes remains the diagnostic gold standard. GTG-banding uniquely enables the definitive identification, structural characterization, and classification of both numerical aneuploidies and complex structural rearrangements across metaphases [5]. Precise resolution of the cytogenetic spectrum—particularly the detection of cryptic mosaicism or Y-chromosome-derived material—is clinically imperative for tailoring long-term surveillance, informing gonadectomy decisions to prevent gonadoblastoma, and guiding hormone replacement strategies [6].

Despite well-characterized clinical guidelines, empirical data detailing the precise distribution and temporal patterns of cytogenetic variants within routine referral populations remain limited. Therefore, this retrospective study aimed to characterize the comprehensive spectrum of X-chromosome abnormalities, assess their age-specific distribution, and evaluate multi-year diagnostic trends among individuals referred for conventional karyotypic evaluation with clinical suspicion of Turner syndrome.

2 SUBJECTS AND METHODS

A retrospective cytogenetic evaluation was conducted on a cohort of 5,045 individuals referred to the Department of Genetics and Molecular Medicine at Manipal TRUtest Diagnostics (Hyderabad, Telangana, India) for the diagnostic workup of suspected sex chromosome abnormalities, including Turner syndrome. Approximately 5 mL of peripheral blood was collected from each participant via venipuncture into sodium heparin tubes under strict aseptic conditions. Lymphocyte cultures were subsequently established by inoculating 1.0 mL of whole blood into 10 mL of RPMI-1640 medium supplemented with 10% fetal bovine serum, phytohemagglutinin (100 μ L) for mitogenic stimulation, penicillin (100 U/mL), and streptomycin (100 μ g/mL).

The cultures were incubated at 37 °C in a humidified atmosphere containing 5% CO₂ for 72 hours. Metaphase arrest was induced by adding colchicine, after which cells were harvested, exposed to hypotonic treatment, and fixed using freshly prepared Carnoy's fixative (methanol and glacial acetic acid, 3:1 v/v). Chromosome spreads prepared on clean glass slides were subjected to trypsin digestion followed by Giemsa staining (GTG-banding). A minimum of 20 metaphases per sample were analyzed using brightfield light microscopy, with karyotypic descriptions structured and reported in strict compliance with the International System for Human Cytogenomic Nomenclature (ISCN) guidelines [7].

3 RESULTS

Out of 5,045 individuals referred for cytogenetic evaluation between 2021 and 2025, 82 cases were confirmed with Turner syndrome (TS), yielding an overall diagnostic yield of 1.63%. Annual case detection demonstrated a baseline from 2021 to 2023 (12, 14, and 13 cases, respectively), followed by a marked peak in 2024 ($n = 23$) and a slight decline in 2025 ($n = 20$), reflecting an overall upward diagnostic trajectory across the study period (Figure 1). Diagnoses occurred predominantly during adolescence and early adulthood (Figure 2), with the majority of cases identified in individuals

aged 10–20 years ($n = 56$, 68.3%), followed by those aged 20–30 years ($n = 23$, 28.0%), and only 3 cases (3.7%) in individuals over 30 years.

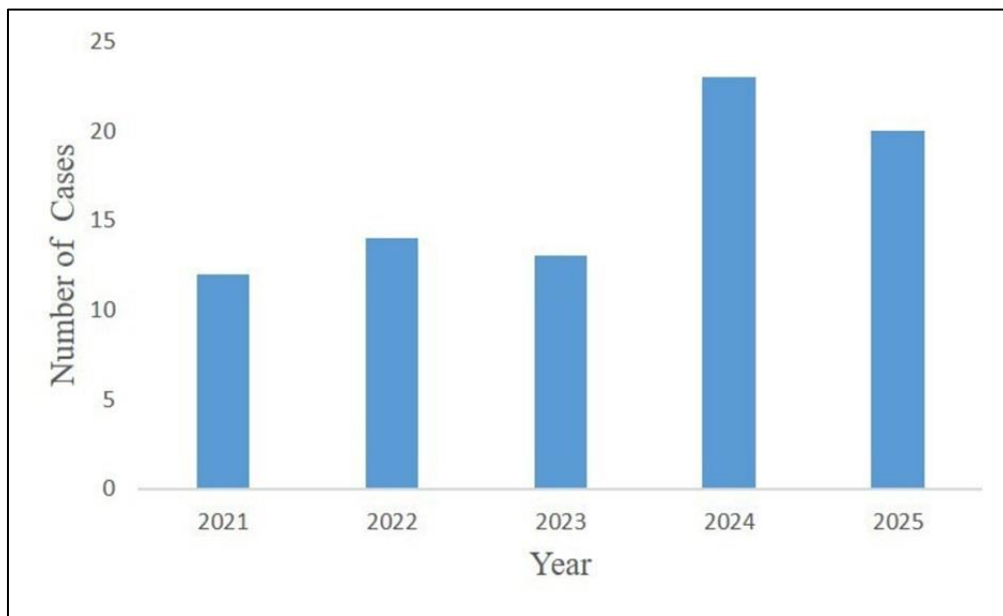


Figure 1: Year-wise distribution of Turner syndrome cases

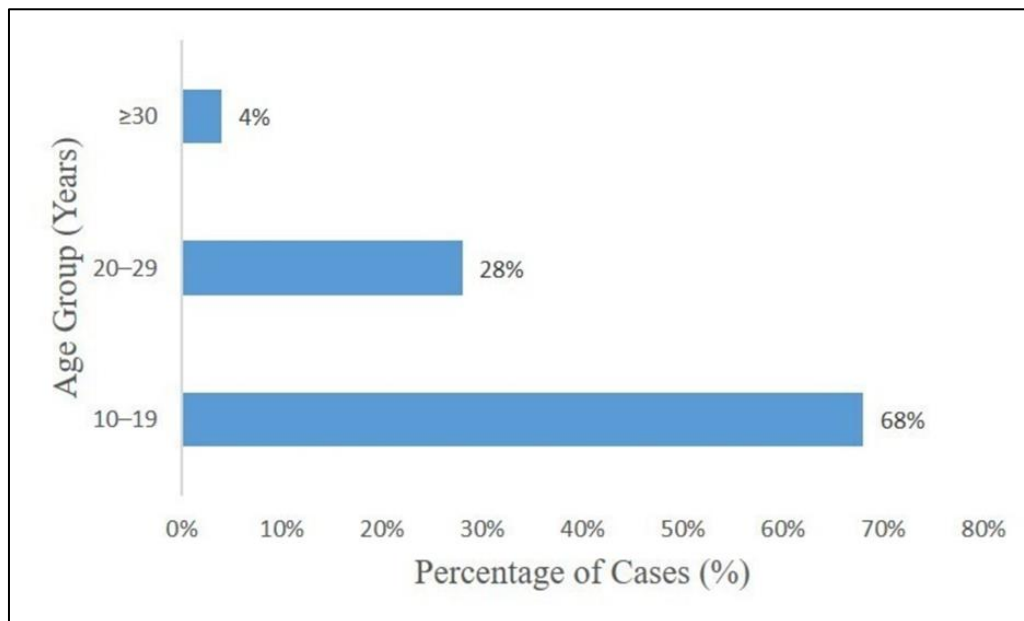


Figure 2: Age-wise distribution of Turner syndrome cases

Cytogenetic analysis revealed significant karyotypic heterogeneity across the cohort (Table 1; Figures 3–8). Classic monosomy X (45, X) was the predominant finding, accounting for 58.5% ($n = 48$) of cases, while the remaining 41.5% ($n = 34$) exhibited mosaicism, structural rearrangements, or heteromorphic variants. Numerical X-chromosome mosaicism was observed in 12 cases (14.6%), including 45,X/46,XX, 45,X/47,XXX, and 45,X/46,XY cell lines. Isochromosomes [i(Xq)]—present as both non-mosaic [46,X,i(X)(q10)] and mosaic [45,X/46,X,i(X)(q10)] karyotypes—were identified in 8 cases (9.8%). Partial short- or long-arm X-chromosome deletions [del(X)] constituted 7 cases (8.5%). Complex structural rearrangements and rare mosaic cell lines—including triple-line mosaicism (45,X/46,XX/47,XXX) and ring X chromosomes [45,X/46,X,r(X)]—were identified in 4 cases (4.9%). Finally, 3 cases (3.7%) presented with concomitant benign chromosomal heteromorphisms (45,X,9qh+ and 45,X,21pstk+).

Table 1: Cytogenetic patterns of Turners Syndrome

Chromosome Status	Karyotype	Number (%)
Monosomy X	45,XO	48 (58.5%)
Numerical X chromosomal anomalies	45,XO/46,XX; 45,XO/47,XXX; 45,XO/46,XY	12 (14.6%)
Isochromosome	46,X,i(X)(q10); 45, XO/46, X, i(X)(q10); 45(XO)/46X, i(X)(q10)/46,XX	8 (9.8%)
Deletions	46, XO, del(X)(q13q28); 46X,del(X)(p21p22.3); 46,X,del(X)(p22.3q12); 45,XO/46,X,del(X)(p11.3p22.3); 45,XO/46,X,del(X)(q23q28); 45(XO),46,X,del(X)(q11q28)	7 (8.5%)
Variants	45, XO,9qh+; 45, XO,21pstk+	3 (3.7%)
Complex/Rare	45, XO/46, XY/47, XYY; 45, XO/46, XX/47, XXX; 45XO/46,X, r(X)(p22.3q28); 45(XO)/45,XO, 9qht+/46,X, i(X)(q10), 9qht+	4 (4.9%)

Abbreviations:del, deletion; i, isochromosome; p, short arm of chromosome; q, long arm of chromosome; q10, centromere; qh+, enlarged heterochromatin region; pstk+, enlarged stalk region; r, ring chromosome; X, X chromosome; Y, Y chromosome; /, denotes cell line mosaicism.

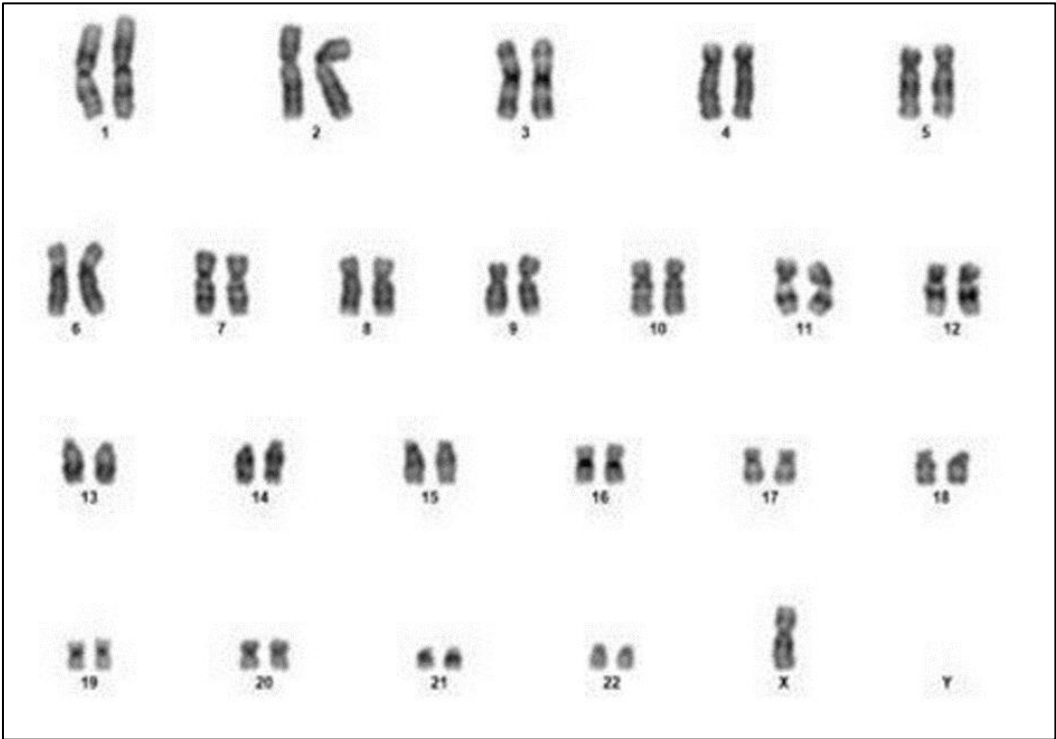


Figure 3: Representative GTG-banded karyotype demonstrating classic monosomy X (45,X).

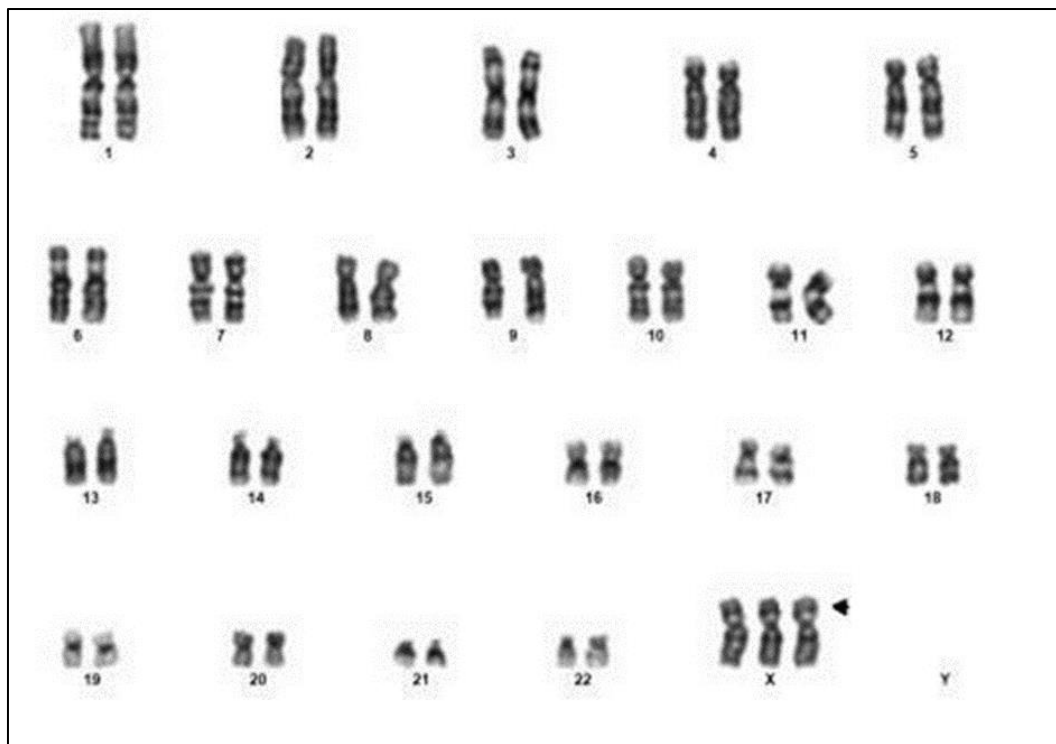


Figure 4: GTG-banded karyotype displaying trisomy X (47,XXX).

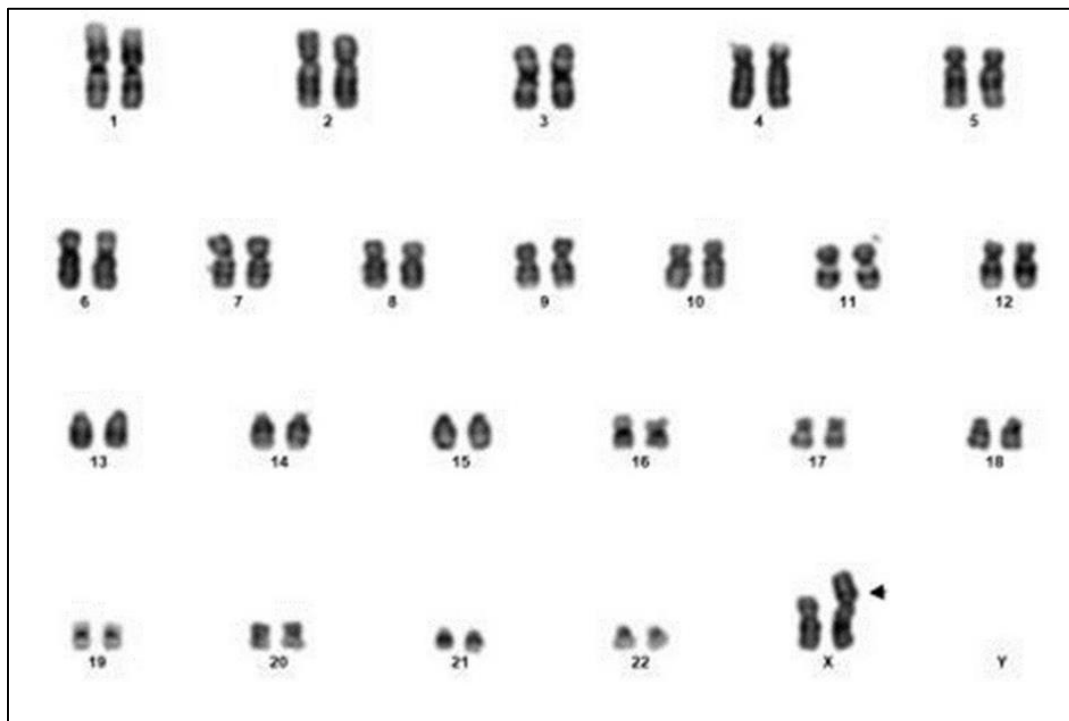


Figure 5: Representative GTG-banded karyotype showing an isochromosome of the long arm of the X chromosome [46,X,i(X)(q10)].

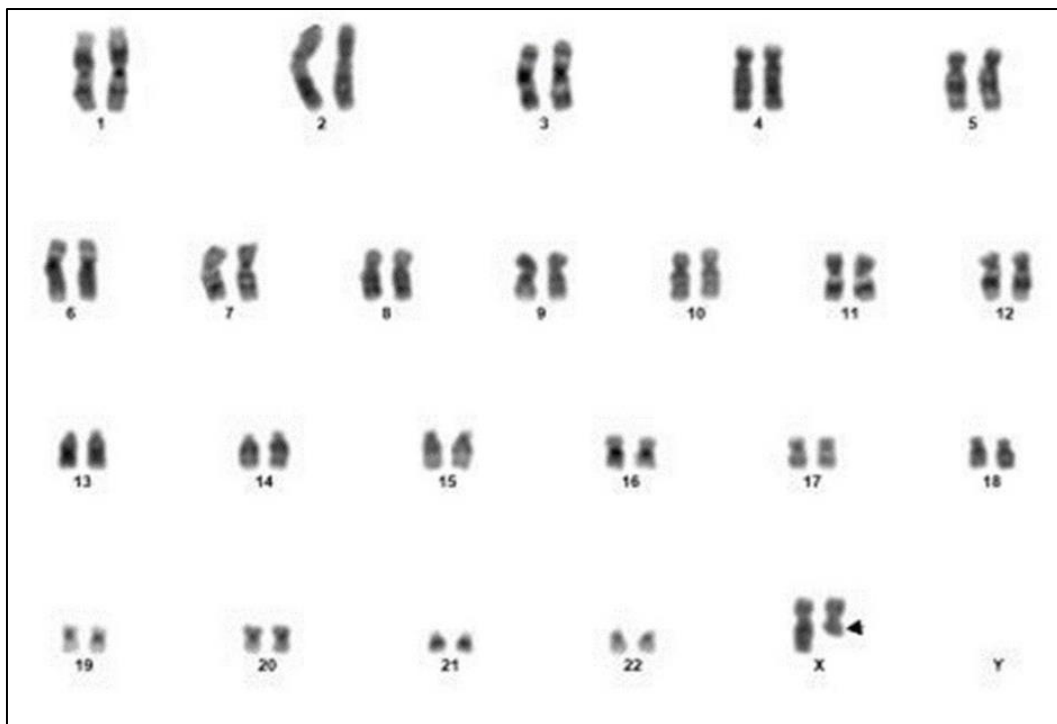


Figure 6: Representative GTG-banded karyotype demonstrating a long-arm X-chromosome deletion [46, X, del(X)(q11q28)].

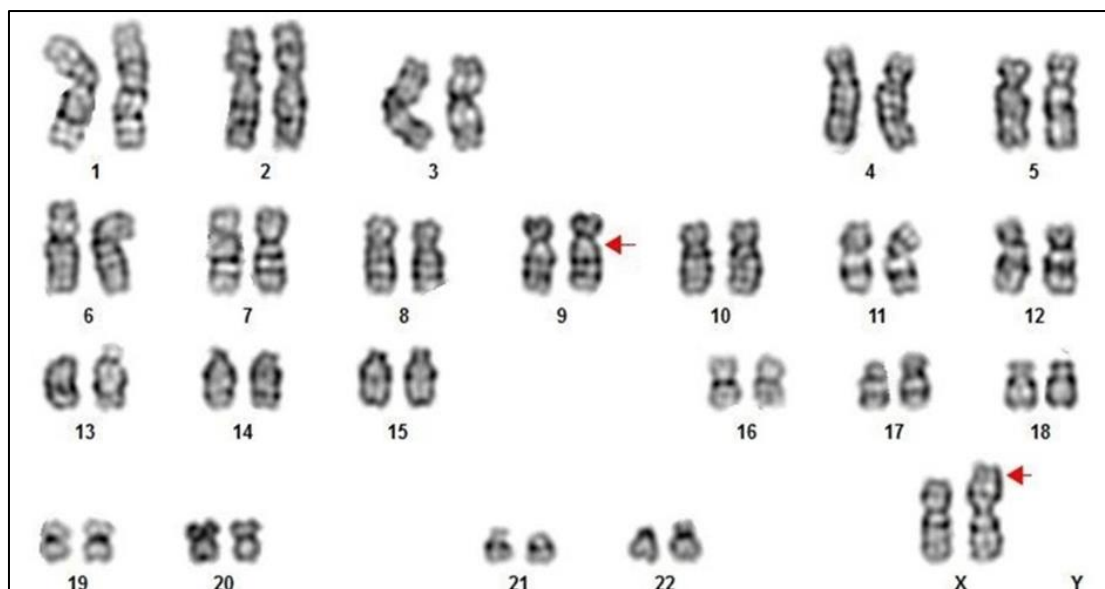


Figure 7: Representative GTG-banded karyotype showing an isochromosome of the long arm of the X chromosome alongside a pericentromeric heteromorphism of chromosome 9 [46, X,i(X)(q10),9qh+].

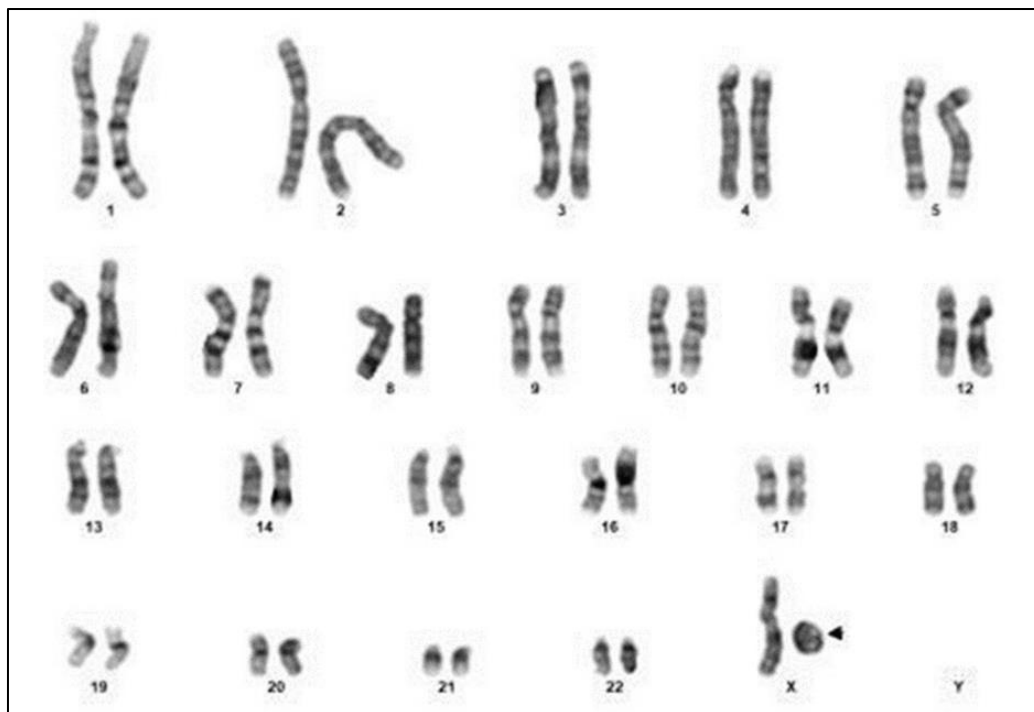


Figure 8: Representative GTG-banded karyotype demonstrating a ring X chromosome formed by terminal breakpoints at Xp22.3 and Xq28 [46,X,r(X)(p22.3q28)]

4 DISCUSSION

This study evaluated the cytogenetic landscape, multi-year diagnostic trends, and age-specific distribution of Turner syndrome (TS) in a large referral cohort, highlighting both classic monosomy X and a broad array of structural and mosaic variants. Classic monosomy X (45,X) constituted 58.5% of diagnosed cases. This predominance aligns with established global literature, where 45,X accounts for 45%–60% of TS cases [8-10, 13-16]. Complete loss of an X chromosome typically produces the classic phenotype—comprising severe short stature, streak gonads, primary amenorrhea, and congenital cardiovascular malformations—thereby prompting earlier clinical suspicion and referral for cytogenetic confirmation [11,12].

Mosaicism and structural X-chromosome rearrangements accounted for the remaining 41.5% of cases, underscoring the marked cytogenetic heterogeneity of the condition. Numerical mosaic constitutions—such as 45,X/46,XX, 45,X/47,XXX, and 45,X/46,XY arise from post-zygotic mitotic non-disjunction or chromosome loss. The clinical severity in mosaic TS is largely dictated by the proportion and tissue-specific distribution of the altered cell lines, frequently attenuating the phenotype and contributing to diagnostic delays [17]. Identifying cell lines containing Y-chromosome material (45,X/46,XY) is particularly crucial due to the elevated risk of gonadoblastoma, necessitating prophylactic gonadectomy.

Structural aberrations—including isochromosomes [i(Xq)], terminal and interstitial deletions [del(X)], ring chromosomes [r(X)], and complex rearrangements—further illustrate this diversity. Isochromosome X [i(Xq)] leads to short-arm pseudoautosomal region (PAR1/PAR2) gene dosage loss alongside long-arm duplication, whereas terminal or interstitial deletions directly disrupt key loci governing linear growth (such as the *SHOX* gene) and ovarian maintenance [18]. Ring X chromosomes, formed by dual telomeric breakages and end-to-end fusion, exhibit dynamic mitotic instability that contributes to variable clinical expressivity [19]. Detailed karyotypic resolution is therefore paramount for establishing precise genotype–phenotype correlations and guiding targeted clinical interventions, including recombinant human growth hormone (rhGH) therapy, estrogen replacement, and cardiovascular surveillance.

In our cohort, the majority of diagnoses occurred during adolescence and early adulthood (aged 10–30 years), indicating persistent diagnostic latency. While advanced prenatal screening technologies—such as cell-free DNA/NIPT—and routine pediatrics have improved early detection [20], subtle mosaicism or structural variants often remain unrecognized until patients present with short stature, delayed puberty, or primary reproductive failure. Early screening protocols targeting girls with unexplained short stature remain vital for preventing delayed care.

Although conventional G-banded karyotyping remains the diagnostic gold standard for detecting numerical and structural chromosomal abnormalities, its sensitivity is limited in identifying low-level tissue mosaicism or

submicroscopic structural rearrangements. Integrating complementary molecular cytogenetic modalities—such as fluorescence *in situ* hybridization (FISH), chromosomal microarray analysis (CMA), and targeted PCR assays—can significantly enhance diagnostic resolution [21]. Future multicenter prospective studies incorporating molecular cytogenetics alongside long-term clinical registries will be essential to further delineate the genetic complexities and phenotypic spectrum of Turner syndrome.

5 CONCLUSION

In conclusion, this study underscores the marked cytogenetic heterogeneity of Turner syndrome within a large clinical referral cohort. While classic monosomy X (45,X) remains the predominant etiology, a substantial proportion of cases exhibit complex numerical mosaicism and structural X-chromosome rearrangements. These findings highlight the enduring clinical utility of conventional G-banded karyotyping as a foundational, cost-effective diagnostic tool. Comprehensive cytogenetic characterization is essential for establishing precise genotype–phenotype correlations, guiding personalized therapeutic interventions—including growth hormone and hormone replacement therapies—and facilitating early risk stratification and genetic counseling.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare that they have no competing financial or non-financial interests.

Statement of ethical approval

This study was conducted in accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki and its later amendments. Ethical approval was granted by the Institutional Ethics Committee of Manipal TRUtest Diagnostics, Hyderabad, India.

Statement of informed consent

Written informed consent for the publication of clinical details, cytogenetic findings, and accompanying imagery was obtained from the patients or their parents/legal guardians (for minor participants).

Availability of Data and Materials

All data generated or analyzed during this study are included within this published article. Additional datasets are available from the corresponding author upon reasonable request.

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