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Original Article

Delayed Diagnosis of Sex-Chromosome Aneuploidies in Eastern Libya: Turner and Klinefelter Syndromes in a Five-Year Cytogenetic Series from the First International Laboratory, Benghazi (2021–2025)

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Abstract

Background. Turner and Klinefelter syndromes are the most common sex-chromosome aneuploidies, yet both are frequently recognised late, delaying growth-promoting, hormonal, and fertility-preserving care. We examined the age at which these disorders are diagnosed in eastern Libya, where newborn screening for chromosomal disorders is not performed. **Methods.** We analysed the sex-chromosome aneuploidy cases among all karyotype referrals to the Genome Laboratory, Benghazi, in 2021–2025, a subset of a cytogenetic registry reported separately. Karyotypes were classified per ISCN. Age at diagnosis was compared between syndromes and against the registry's Down syndrome cohort using the Mann–Whitney U test. **Results.** Twenty-seven patients had a sex-chromosome aneuploidy: 19 with Turner syndrome (11 monosomy 45, X, 8 mosaic, of which 2 carried a 46, XY line and presented with ambiguous genitalia) and 8 with Klinefelter spectrum (7 with 47, XXY and 1 with 49, XXXXY). The median age at diagnosis was 14.5 years overall: 9.0 years for Turner syndrome and 29.0 years for Klinefelter syndrome, with 6 of 7 Klinefelter patients diagnosed in adulthood. This was far later than the median of about five weeks for Down syndrome in the same registry ($P < .001$), and Klinefelter syndrome was diagnosed significantly later than Turner syndrome ($P = .006$). Where an indication was recorded, Turner syndrome was identified through short stature, delayed puberty, primary amenorrhea, and premature ovarian insufficiency, and Klinefelter syndrome almost exclusively through adult infertility and azoospermia. **Conclusion.** Sex-chromosome aneuploidies in eastern Libya are diagnosed late, with Klinefelter syndrome typically recognized only during infertility work-up in adulthood. Earlier karyotyping of children with short stature or pubertal delay, and of men with azoospermia, would shorten this diagnostic delay and open a window for timely intervention.

Keywords: Turner syndrome; Klinefelter syndrome; sex-chromosome aneuploidy; age at diagnosis; karyotype; Libya

Introduction

Sex-chromosome aneuploidies are, collectively, at least as common as trisomy 21, affecting roughly one in 400 to 500 live births, yet they are among the most underdiagnosed chromosomal disorders [1,2]. Recent global burden-of-disease analyses reinforce this picture, estimating that a substantial share of both syndromes in children and adolescents worldwide remains undiagnosed, with the shortfall greatest in low- and middle-resource settings where karyotyping access, clinician awareness, and registry infrastructure are limited [13,14]. Turner syndrome (45,X and its variants) occurs in about 50 per 100,000 females and typically presents with short stature, pubertal delay, and ovarian insufficiency; growth-promoting and estrogen therapy are most effective when begun early, so timely diagnosis carries direct clinical benefit [2,3,9,10]. Klinefelter syndrome (47,XXY) is the most common sex-chromosome disorder in males, with a birth prevalence near one in 500 to 660, but only about a quarter of affected men are ever diagnosed, and most who are identified are recognized in adulthood during infertility work-up [4,5,6].

The consequences of delay are substantial. In Turner syndrome, missing the growth window forgoes achievable height and delays the induction of puberty; in Klinefelter syndrome, late recognition means lost opportunities for testosterone replacement and for fertility preservation, which becomes progressively less feasible with age [3,6]. National registry data show that a large share of both conditions is diagnosed late or never, and that diagnostic delay is the rule rather than the exception even in high-income settings with established cytogenetic services [1,7]. In settings without newborn karyotype or hormonal screening, the burden of late diagnosis is expected to be greater still, particularly as neither newborn screening nor routine prenatal karyotyping for sex-chromosome aneuploidy is yet widely implemented even in well-resourced health systems [15].

Sex-chromosome aneuploidies often escape recognition at birth and come to attention later, through the failure of growth, puberty, or fertility. This late presentation contrasts with the autosomal aneuploidies, which are usually identified in infancy. Here we examine the Turner and Klinefelter cases in a five-year cytogenetic registry from the Genome Laboratory in Benghazi,

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describing their cytogenetic composition, the age at which they were diagnosed, and the clinical presentations that prompted testing.

Materials and Methods

Study design, setting, and cohort

This retrospective study analyzed the sex-chromosome aneuploidy cases identified among all patients referred for chromosomal analysis to the Genome Laboratory, Faculty of Biomedical Sciences, University of Benghazi, between 2021 and 2025, drawn from a 319-record cytogenetic registry. The analysis is confined to the sex-chromosome aneuploidies. Records were anonymized before analysis and contained no patient-identifiable information.

Case definition and classification

Sex-chromosome aneuploidy was defined as a constitutional numerical abnormality of the X or Y chromosome. Turner syndrome was defined by the presence of a 45,X cell line (as complete monosomy or mosaic), and Klinefelter syndrome by a 47, XXY karyotype or a higher-grade X polysomy (for example, 49, XXXXY). Cases carrying both a 45, X and a 46, XY line were noted separately as a 45, X/46, XY (mixed gonadal dysgenesis) presentation. Peripheral-blood lymphocytes were cultured and harvested at the Genome Laboratory by standard technique, and metaphase chromosomes were analyzed and described according to the International System for Human Cytogenomic Nomenclature (ISCN) [8]. Metaphase spreads were G-banded by trypsin–Giemsa (GTG). Approximately 20 metaphase cells were examined per case at standard (non–high-resolution) banding resolution, and 3 to 5 metaphases were fully karyotyped; when mosaicism was suspected or detected, the number of cells examined was increased to 50.

Variables and statistical analysis

Recorded variables were sex, age at diagnosis (the age at karyotype referral), karyotype, and the referring clinical indication where documented. Age at diagnosis was summarized as the median with interquartile range (IQR) and compared between Turner and Klinefelter syndromes, and between the sex-chromosome aneuploidy cohort and the registry's Down syndrome cohort, using the Mann–Whitney U test. A two-sided P value below .05 was considered significant. Analyses were performed using IBM SPSS Statistics version 26.0. The study used anonymized records; the institutional ethics determination is stated under Ethics approval.

Results

Cohort composition

Among the 251 patients with an interpretable karyotype in the registry, 27 (10.8%) had a sex-chromosome aneuploidy: 19 with Turner syndrome and 8 with Klinefelter spectrum. Within Turner syndrome, 11 patients had complete monosomy 45, X and 8 were mosaic; 2 of the mosaic cases carried a 46, XY line (45, X/46,XY) and presented in infancy with ambiguous genitalia. Turner patients were female except for these 2 patients with mixed gonadal dysgenesis. The Klinefelter spectrum comprised 7 patients with 47, XXY and 1 with 49, XXXXY (Table 1; Figure 1).

Table 1. Composition of the sex-chromosome aneuploidy cohort (n = 27).

Group	Subtype	n
Turner syndrome (n = 19)	Complete monosomy (45,X)	11
	Mosaic (45,X / 46,XX)	6
	45,X / 46,XY (mixed gonadal dysgenesis)	2
Klinefelter spectrum (n = 8)	47,XXY	7
	49,XXXXY	1

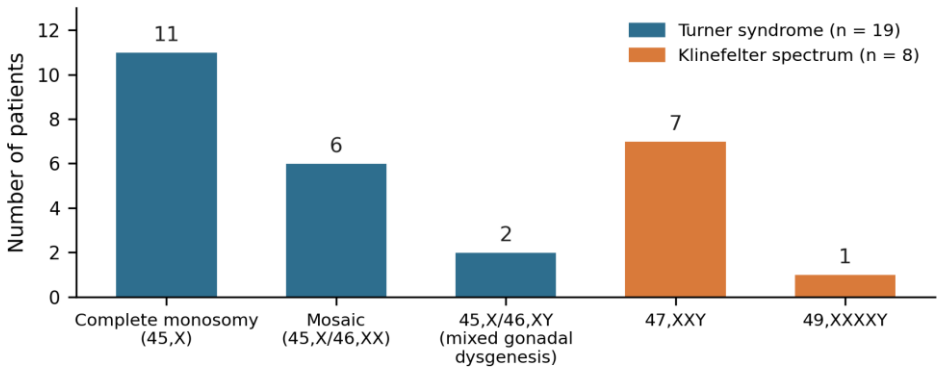

Figure 1. Composition of the sex-chromosome aneuploidy cohort.

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Age at diagnosis

The sex-chromosome aneuploidies were diagnosed late. The median age at diagnosis was 14.5 years for the cohort overall (IQR 4.2–27.2), and 13 of the 24 patients with a recorded age (54.2%) were diagnosed at 12 years of age or older; age at diagnosis was not recorded for the remaining 3 patients, who are excluded from this rate. The two syndromes differed markedly: Turner syndrome was diagnosed at a median of 9.0 years (IQR 1.2–16.0; range, newborn to 38 years), reflecting a mix of early cases identified through dysmorphism or lymphedema in infancy and later cases identified at the age of expected puberty, whereas Klinefelter syndrome was diagnosed at a median of 29.0 years (IQR 26.0–41.0), with 6 of the 7 patients with a recorded age diagnosed in adulthood (Mann–Whitney U test, P = .006). Both were diagnosed far later than Down syndrome in the same registry, which had a median age at diagnosis of about five weeks (P < .001) (Table 2; Figure 2). The single early Klinefelter diagnosis was the 49,XXXXY case, identified at 2 years of age on account of its more severe phenotype.

Table 2. Age at cytogenetic diagnosis, by syndrome, with Down syndrome for comparison.

Group	n with age	Median (y)	IQR (y)	Range (y)
Turner syndrome	17	9.0	1.2–16.0	0.01–38
Klinefelter spectrum	7	29.0	26.0–41.0	2–47
All sex-chromosome aneuploidy	**24**	**14.5**	**4.2–27.2**	**0.01–47**
Down syndrome (for comparison)	56	0.10	0.04–0.33	0–15

Sex-chromosome aneuploidy vs Down syndrome, P < .001; Turner vs Klinefelter, P = .006 (Mann–Whitney U test).

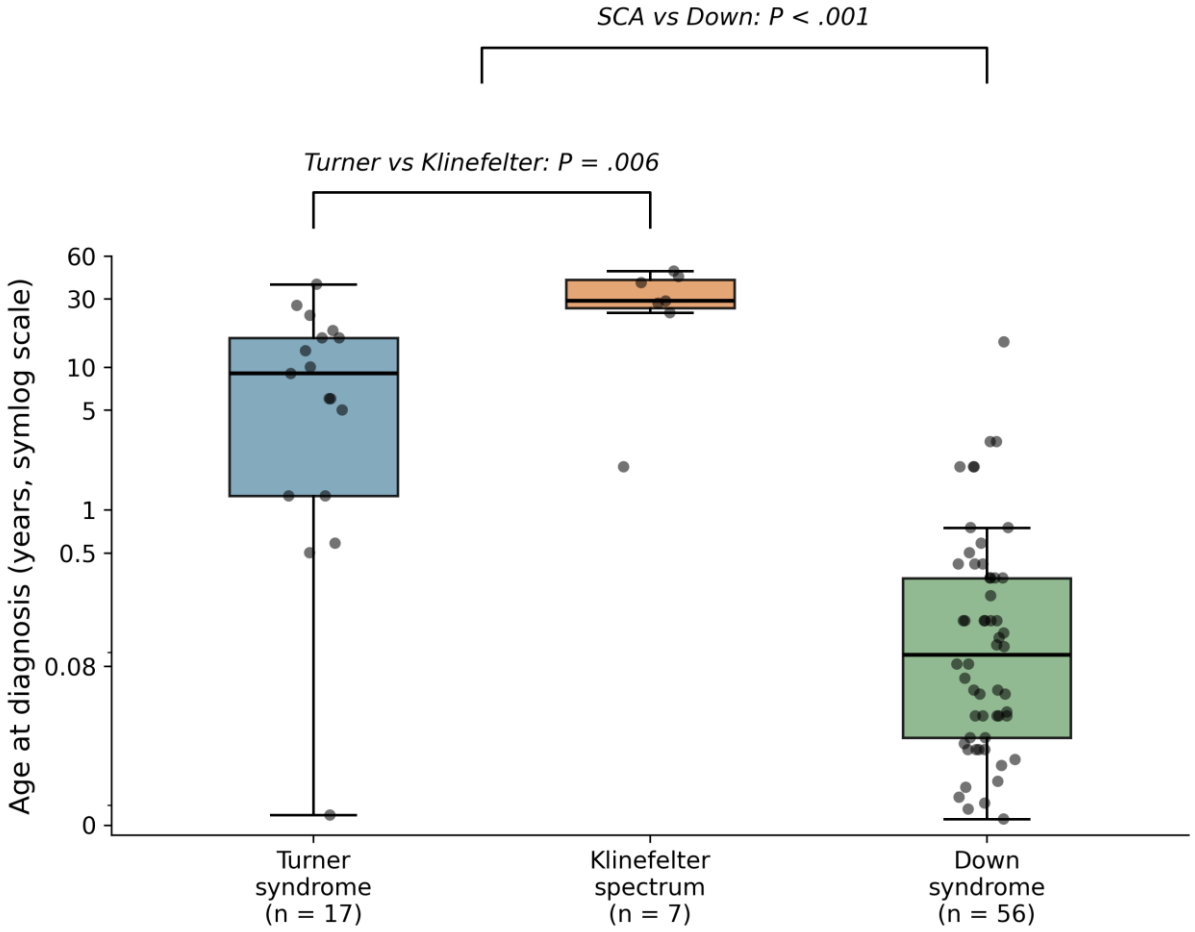

Figure 2. Age at cytogenetic diagnosis by syndrome, with Down syndrome for comparison.

Clinical presentations prompting diagnosis

A referring indication was recorded for 12 of the 27 patients. In Turner syndrome, recorded indications were primary amenorrhea, premature ovarian insufficiency, short stature with delayed puberty, dysmorphic features, and clinical suspicion of Turner syndrome; the 2

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patients with a 45, X/46, XY karyotype were referred for ambiguous genitalia in infancy. In Klinefelter syndrome, every recorded indication related to male infertility: azoospermia, elevated follicle-stimulating and luteinizing hormone with reduced testicular size, and Y-chromosome evaluation (Table 3). No patient in either group was referred because of a routine or newborn screening test.

Table 3. Recorded clinical indications prompting karyotyping, by syndrome.

Syndrome	Recorded indications (n with an indication recorded)
Turner syndrome	Primary amenorrhea; premature ovarian insufficiency; short stature with delayed puberty; dysmorphic features; clinical suspicion of Turner syndrome; ambiguous genitalia (45,X/46,XY)
Klinefelter spectrum	Azoospermia; elevated FSH/LH with reduced testicular size; Y-chromosome evaluation

Discussion

In this five-year cytogenetic series from eastern Libya, sex-chromosome aneuploidies were diagnosed late, at a median age of 14.5 years, and Klinefelter syndrome later still, at a median of 29 years. This contrasts with the autosomal aneuploidies such as trisomy 21, which are typically recognized within weeks of birth through overt dysmorphism. The difference reflects clinical visibility rather than chromosomal severity: trisomy 21 declares itself at birth, whereas Turner and Klinefelter syndromes typically become apparent only through the later failure of growth, puberty, or fertility [1,3,6]. Consistent with this, the two 45, X/46, XY patients whose abnormality produced a visible neonatal sign (ambiguous genitalia) were diagnosed in infancy, while the classic presentations were recognized much later.

The Klinefelter findings are the most striking. Almost every case was identified in adulthood during infertility evaluation, mirroring the international picture in which only about a quarter of affected men are ever diagnosed and most are recognized late [4,5,6]. Because sperm-retrieval success in Klinefelter syndrome declines with age, diagnosis during an adult infertility work-up often comes after the most favourable window for fertility preservation has passed [6]. A similar pattern has recently been reported elsewhere in the Gulf region, where 47, XXY was the predominant sex-chromosome finding among infertile men undergoing assisted-reproduction work-up, suggesting that adult infertility referral is currently the principal route to Klinefelter diagnosis across the Arabian Peninsula and not a peculiarity of this cohort [16]. Turner syndrome was diagnosed earlier and across a wider age range, but a substantial share was still identified only at the age of expected puberty, by which point some of the benefit of growth-promoting therapy has been lost [3,7]. For comparison, a single-centre series from a well-resourced pediatric endocrinology service reported a median age at Turner syndrome diagnosis of only 4.6 years [17], underscoring how much earlier detection is achievable when short stature and pubertal delay reliably trigger karyotyping.

These results localize the diagnostic gap in Libyan cytogenetic services to the sex-chromosome aneuploidies, consistent with recent global burden-of-disease estimates that place low- and middle-resource settings furthest behind in the ascertainment of both syndromes [13,14]; earlier Libyan cytogenetic reports have concentrated on Down syndrome [11,12]. The remedy lies less in more complex technology than in a lower threshold for the karyotype that is already available: chromosomal analysis for girls with unexplained short stature or delayed puberty, for adolescents with primary amenorrhea, and for men with azoospermia or unexplained infertility would move many of these diagnoses years earlier. Where a newborn or a child presents with ambiguous genitalia, prompt karyotyping remains essential, as the 45,X/46,XY cases here illustrate.

Limitations

This analysis is retrospective, single-laboratory, and referral-based: it captures the age at which patients reached testing rather than the age at onset, and cannot estimate undiagnosed community cases, which a laboratory series inevitably misses. The cohort is small, especially the Klinefelter group, so the age-at-diagnosis estimates are imprecise. A clinical indication was recorded for fewer than half of patients, so the presentation data are descriptive, and age at diagnosis reflects the age at referral rather than first clinical suspicion.

Conclusion

Sex-chromosome aneuploidies in eastern Libya are diagnosed late, with Klinefelter syndrome typically recognized only during adult infertility work-up and Turner syndrome often not until the age of expected puberty. Compared with the early diagnosis of Down syndrome in the same population, this marks sex-chromosome aneuploidies as the principal missed opportunity in local cytogenetic practice. A lower threshold for karyotyping in short stature, delayed

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puberty, primary amenorrhea, and male infertility would shorten the diagnostic delay and preserve the window for growth-promoting, hormonal, and fertility-preserving care.

Ethics approval and consent. The study used anonymized laboratory records containing no patient-identifiable data. Institutional permission to use the anonymized dataset was granted by the laboratory (Genome Laboratory, subsequently merged into First International Laboratory, Benghazi, in 2023; approval reference no. 26/91). Informed consent was waived owing to the use of fully anonymized retrospective records containing no patient-identifiable information.

Consent for publication. Not applicable.

Availability of data. The anonymized dataset is available from the corresponding author on reasonable request.

Competing interests. The authors declare no competing interests.

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Author contributions. T. M. Shoeib: resources, supervision, and writing (review and editing). A. Abusneina: conceptualization, data curation, formal analysis, visualization, and writing (original draft). Both authors read and approved the final manuscript.

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References

1. Berglund A, Viuff MH, Skakkebæk A, Chang S, Stochholm K, Gravholt CH. Changes in the cohort composition of Turner syndrome and severe non-diagnosis of Klinefelter, 47,XXX and 47,XYY syndrome: a nationwide cohort study. Orphanet J Rare Dis. 2019;14(1):16. doi:10.1186/s13023-018-0976-2
2. Gravholt CH, Viuff MH, Brun S, Stochholm K, Andersen NH. Turner syndrome: mechanisms and management. Nat Rev Endocrinol. 2019;15(10):601–614. doi:10.1038/s41574-019-0224-4
3. Gravholt CH, Andersen NH, Christin-Maitre S, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2023 Aarhus International Turner Syndrome Meeting. Eur J Endocrinol. 2024;190(6):G53–G151. doi:10.1093/ejendo/lvae050
4. Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. J Clin Endocrinol Metab. 2003;88(2):622–626. doi:10.1210/jc.2002-021491
5. Zitzmann M, Aksglaede L, Corona G, et al. European Academy of Andrology guidelines on Klinefelter syndrome. Andrology. 2021;9(1):145–167. doi:10.1111/andr.12909
6. Samango-Sprouse CA, Counts DR, Tran SL, Lasutschinkow PC, Porter GF, Gropman AL. Update on the clinical perspectives and care of the child with 47,XXY (Klinefelter syndrome). Appl Clin Genet. 2019;12:191–202. doi:10.2147/TACG.S180450
7. Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. J Clin Endocrinol Metab. 2006;91(10):3897–3902. doi:10.1210/jc.2006-0558
8. McGowan-Jordan J, Hastings RJ, Moore S, editors. ISCN 2020: An International System for Human Cytogenomic Nomenclature (2020). Basel: Karger; 2020. ISBN 978-3-318-06706-4.
9. Turner HE, Johannsen EB, Smyth A, Orchard E, Gravholt CH. Approach to the patient with Turner syndrome. J Clin Endocrinol Metab. 2025;111(1):268–279. doi:10.1210/clinem/dgaf517
10. Khan N, Farooqui A, Ishrat R. Turner syndrome: where are we? Orphanet J Rare Dis. 2024;19(1):314. doi:10.1186/s13023-024-03337-0
11. Verma IC, Mathews AR, Faquih A, El-Zouki AA, Malik GR, Mohammed F. Cytogenetic analysis of Down syndrome in Libya. Indian J Pediatr. 1990;57(2):245–248. doi:10.1007/BF02722095
12. Amer AH, Boshahma FH, Shoeib T, Khaled R, Salem K, Mustafa M, Issa F. Types of Down syndrome disorders diagnosed at the First International Laboratory from 2020 to 2025. Libyan J Med Res. 2026;20(1):250–254. doi:10.54361/LJMR.20.1.40
13. Ma G, Li Y, Jia F. The hidden in plain sight: global, regional, and national trends in the pediatric burden of Klinefelter syndrome, 1990–2021. Front Genet. 2025;16:1639699. doi:10.3389/fgene.2025.1639699
14. Ding F, Xu J, Xiong J, Li Q, Cheng Z, Deng L. Epidemiological analysis of Turner syndrome in children aged 0–14 years: global, regional, and national perspectives (1990–2021). Front Endocrinol (Lausanne). 2025;16:1552300. doi:10.3389/fendo.2025.1552300
15. Mehmet B, Dwyer AA, Jayasena CN, Gillard S, Llahana S. Update on physical, psychological, and quality of life management in Klinefelter

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syndrome. J Clin Endocrinol Metab. 2025;110(8):e2435–e2445. doi:10.1210/clinem/dgaf261

16. Upadhyay D, Varghese MM, Anandt S, Albuz F, Almekosh R, Peramo B. Prevalence of chromosomal abnormalities and polymorphisms in 4,672 infertile patients undergoing assisted reproductive techniques in the United Arab Emirates population. Front Reprod Health. 2026;8:1750389. doi:10.3389/frph.2026.1750389
17. Apperley L, Das U, Ramakrishnan R, Dharmaraj P, Blair J, Didi M, Senniappan S. Mode of clinical presentation and delayed diagnosis of Turner syndrome: a single-centre UK study. Int J Pediatr Endocrinol. 2018;2018:4. doi:10.1186/s13633-018-0058-1

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