

Original article

Cytogenetic Profile of Patients Referred for Chromosomal Analysis in Eastern Libya: A Five-Year Retrospective Study

Abdelmuhsen Abusneina^{1*} , Tarek Shoeib² ¹Department of Molecular Diagnostics, Faculty of Biomedical Sciences, University of Benghazi, Benghazi, Libya²Department of Forensic Sciences, Faculty of Biomedical Sciences, University of Benghazi, Benghazi, LibyaCorresponding Email. abdelmuhsen.abusneina@uob.edu.ly

Abstract

Chromosomal abnormalities are an important cause of congenital malformation, intellectual disability, disordered sexual development, and infertility, yet population-level cytogenetic data from Libya are scarce. We describe the spectrum of chromosomal findings among patients referred for karyotyping in eastern Libya. We retrospectively reviewed all patients referred for peripheral-blood metaphase karyotyping to the Genome Laboratory, a private clinical cytogenetics laboratory in Benghazi, between 2021 and 2025, using anonymized records. Karyotypes were classified by cytogenetic outcome. Frequencies were expressed with 95% confidence intervals (CIs); the chi-square test compared abnormality rates between subgroups. Of 319 referred individuals, 251 had an interpretable karyotype and formed the analytic cohort (130 female, 51.8%; median age 3.0 years, interquartile range 0.2–27.0). A clinically significant chromosomal abnormality was identified in 106 patients (42.2%; 95% CI 36.3–48.4). Numerical abnormalities accounted for 88.7% of abnormal results. Down syndrome was the most frequent diagnosis (58 patients, 23.1% of the cohort), of which 93.1% were free trisomy 21. Turner syndrome (19, 7.6%), Klinefelter spectrum (8, 3.2%), trisomy 18 (7, 2.8%), and trisomy 13 (2, 0.8%) followed, alongside 11 structural rearrangements (4.4%). The abnormality detection rate fell steeply with age at referral, from 80.4% in neonates to 15.1% in adults, and did not differ by sex ($p = 0.60$). Mothers of children with Down syndrome were older than mothers of other referred children (median 37.0 vs 31.0 years). Referral-based cytogenetic testing in eastern Libya yields a chromosomal abnormality in over four in ten patients, dominated by free trisomy 21. The strong inverse relationship between age at referral and diagnostic yield points to delayed recognition of sex-chromosome and structural disorders, supporting earlier clinical suspicion and referral.

Keywords. Karyotype, Chromosomal Abnormalities, Down Syndrome, Turner Syndrome, Libya.

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Introduction

Chromosomal abnormalities are a leading cause of congenital malformation, intellectual disability, disordered sexual development, and infertility, and they are detected in a substantial minority of individuals referred for cytogenetic investigation. Conventional metaphase karyotyping remains the reference method for identifying numerical aneuploidies, balanced and unbalanced structural rearrangements, and mosaicism at the whole-chromosome level, and it continues to anchor diagnosis and genetic counseling in settings where chromosomal microarray and sequencing are not yet routine [1,2]. Results are reported using the International System for Human Cytogenomic Nomenclature, which provides the standardized descriptions that make caseloads comparable across laboratories and over time [3].

Down syndrome (trisomy 21) is the most common autosomal aneuploidy compatible with survival and the leading genetic cause of intellectual disability, with a birth prevalence on the order of one per 700 to 1,000 live births that varies with maternal age structure and access to prenatal screening [1,4]. It arises through three cytogenetic mechanisms: free trisomy 21, which accounts for roughly 95% of cases and rises steeply in frequency with advancing maternal age; Robertsonian translocation, some 3% to 4%, a proportion of which is inherited and carries a recurrence risk that makes parental karyotyping essential; and mosaicism, about 1% to 2% [1,2,5]. Beyond the intellectual phenotype, affected individuals carry an elevated burden of congenital heart disease and a markedly increased risk of leukemia, underscoring the clinical value of early cytogenetic confirmation [1,6].

Sex-chromosome aneuploidies are collectively at least as common as trisomy 21 but are far more often recognized late. Turner syndrome (45, X and its variants) affects roughly 50 per 100,000 females and typically presents with short stature, pubertal delay, and ovarian insufficiency [7,8,9]; a large share of cases is not diagnosed until childhood or adolescence, deferring growth-promoting and estrogen therapy [10,11]. Klinefelter syndrome (47, XXY) is the most frequent sex-chromosome disorder in males, present in up to 3% to 4% of infertile men and 10% to 15% of those with non-obstructive azoospermia, yet an estimated half or more of affected men are never diagnosed, and most who are identified are recognized only in adulthood during infertility work-up [12,13]. Because these disorders are frequently detected only when the failure of puberty or fertility prompts a karyotype, the age at which patients are referred is itself informative about how well they are being recognized [11]. Regional context shapes both the burden and the presentation of these conditions. Across the Middle East and North Africa, high rates of consanguineous marriage and a tendency toward later maternal

childbearing coexist with limited population-based prenatal screening, a combination expected to influence the cytogenetic caseload and the timing of diagnosis [14,15,16].

For Libya, and eastern Libya in particular, published cytogenetic data are sparse and largely historical: an early series established that trisomy 21 in the country was dominated by free trisomy and linked to advanced maternal age [17], and subsequent Libyan reports have addressed associated morbidity such as congenital heart disease and thyroid dysfunction rather than the referral spectrum itself [18,19]. A recent single-laboratory series from Benghazi characterized the subtypes of Down syndrome over the same period examined here, but focused on that one condition [20], leaving the broader profile of chromosomal abnormalities among cytogenetic referrals in the region largely undescribed. We therefore reviewed five years of consecutive karyotype referrals to the Genome Laboratory in Benghazi. We aimed to describe the frequency and type of chromosomal abnormalities detected, to characterize the referred population by age and sex, and to examine how the diagnostic yield of karyotyping varied with the age at which patients were referred.

Methods

Study design and setting

This was a retrospective, laboratory-based cross-sectional study of all patients referred for chromosomal analysis to the Genome Laboratory, a private clinical cytogenetics laboratory in Benghazi, Libya, during the period 2021–2025. The laboratory receives referrals from pediatric, obstetric, endocrine, and fertility services across the Cyrenaica region and neighboring governorates. In 2023, the Genome Laboratory was merged with First International Laboratory, Benghazi, and its operations and records were fully integrated into that organization; referral intake and karyotyping continued without interruption before and after this administrative change. This history is relevant to the interpretation of a separately published, overlapping-period report from First International Laboratory (see Discussion). To the authors' knowledge, this laboratory was, throughout the study period, the principal and effectively the only provider of conventional karyotyping services in eastern Libya, such that referrals from the region were not substantially distributed across competing laboratories.

Cytogenetic analysis

Peripheral-blood lymphocytes were cultured for 72 hours in RPMI-1640 medium supplemented with fetal bovine serum, L-glutamine, penicillin–streptomycin, and phytohemagglutinin-M at 37 °C. Cell division was arrested with colcemid, after which cultures were exposed to hypotonic 0.075 M potassium chloride and fixed in 3:1 methanol–glacial acetic acid. Metaphase spreads were prepared on glass slides and G-banded by trypsin–Giemsa (GTG). Karyotypes were examined by light microscopy and described according to the International System for Human Cytogenomic Nomenclature (ISCN) [3]. 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.

Data management and variable definitions

Demographic and cytogenetic data were extracted from laboratory records into a single dataset. Records were anonymized before analysis and contained no patient-identifiable information. Each karyotype was classified into one of the following mutually exclusive categories: normal (46, XX or 46, XY); normal variant, comprising benign acrocentric short-arm and satellite-stalk heteromorphisms (for example, pstk+ and ps+ variants); autosomal aneuploidy; sex-chromosome aneuploidy; structural abnormality; and other or complex. Cases with two or more cell lines were additionally flagged as mosaic. Down syndrome was subclassified as free trisomy 21, translocation, or mosaic. Age was recorded at referral and grouped as neonate (<1 month), infant (1 month to <2 years), child (2–11 years), adolescent (12–17 years), and adult (≥18 years). Consanguinity was coded conservatively as present, absent, or unknown; ambiguous entries were treated as unknown rather than inferred.

Statistical analysis

Categorical variables are summarized as counts and percentages, and continuous variables as the median with interquartile range (IQR). The analytic denominator for cytogenetic outcomes was the number of patients with an interpretable karyotype. The proportion with a clinically significant abnormality is reported with a 95% Wilson confidence interval. Abnormality detection rates were compared across sex and age groups using the Pearson chi-square test; the exploratory comparison of maternal age between Down syndrome and other referrals used the Mann–Whitney U test. A two-sided p-value below 0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics version 26.0.

Ethical considerations

The study used anonymized laboratory karyotype records that contained no patient-identifiable data. No individually identifiable information was accessed, and no clinical intervention was involved. Institutional permission to use the

anonymized dataset for research purposes was granted by the laboratory (Genome Laboratory, subsequently merged into First International Laboratory, Benghazi, in 2023; approval reference no. 26/91). Because the study used fully anonymized retrospective records containing no patient-identifiable information, informed consent was waived.

Results

Characteristics of the referred cohort

During the study period, 319 individuals were referred for chromosomal analysis. An interpretable karyotype was available for 251 patients (78.7%), who constituted the analytic cohort; for the remaining 68 records, no karyotype result had been recorded in the registry. The cohort comprised 130 females (51.8%) and 118 males (47.0%), with sex not recorded in 3. The median age at referral was 3.0 years (IQR 0.2–27.0; range, newborn to 60 years). Referrals spanned all age bands, with the largest contributions from adults (73, 29.1%) and infants (57, 22.7%). A place of origin was recorded for 109 patients, of whom 103 (94.5%) were from Cyrenaica, most commonly Benghazi. Referral volume rose over the period: among all 319 individuals referred, annual totals increased from 23 in 2021 to a peak of 92 in 2024 before falling to 75 in the partial 2025 collection year (Figure 1). Restricted to the 251 patients with an interpretable karyotype (the analytic cohort), annual totals rose from 23 in 2021 to 84 in 2024 and 33 in 2025 (Table 1); the widening gap between the two series in 2024–2025 (8 and 42 records, respectively) reflects karyotype results that had not yet been finalized in the registry at the time of data extraction, consistent with a processing lag for the most recent referrals.

Table 1. Characteristics of the karyotyped cohort (n = 251)

Characteristic	Category	n (%)
Sex	Female	130 (51.8)
	Male	118 (47.0)
	Not recorded	3 (1.2)
Age group	Neonate (<1 mo)	46 (18.3)
	Infant (1 mo–<2 y)	57 (22.7)
	Child (2–11 y)	41 (16.3)
	Adolescent (12–17 y)	18 (7.2)
	Adult (≥18 y)	73 (29.1)
	Not recorded	16 (6.4)
Year of referral	2021	23 (9.2)
	2022	48 (19.1)
	2023	59 (23.5)
	2024	84 (33.5)
	2025 (partial)	33 (13.1)
	2020 / not recorded	4 (1.6)
Region	Cyrenaica (East)	103 (41.0)
	Fezzan / South	6 (2.4)
	Not recorded	142 (56.6)

Region was not recorded for 56.6% of patients; percentages are of the full karyotyped cohort (n = 251).

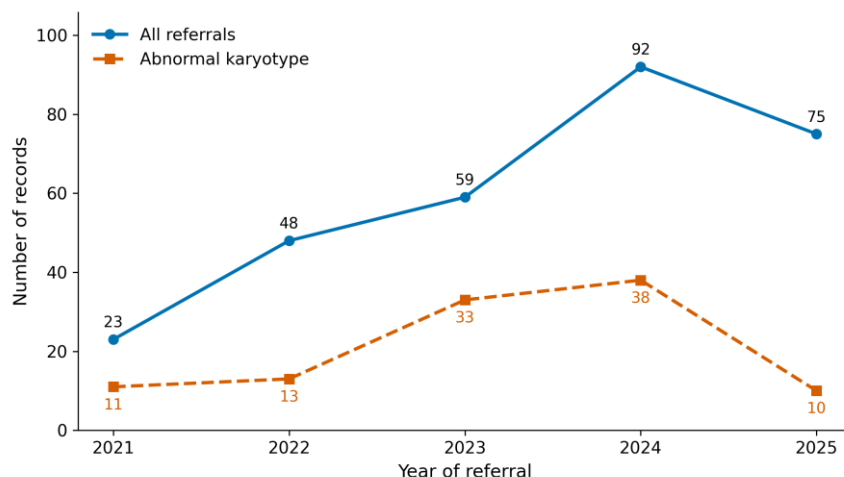


Figure 1. Annual referral volume, 2021–2025. The solid line shows all referrals received in each year regardless of karyotype outcome (23, 48, 59, 92, and 75 in 2021–2025, respectively; sum = 297), which together with 3 referrals from 2020 and 19 referrals with unrecorded year make up the full referred cohort (n = 319). The dashed line shows, among those referrals, the number with a clinically significant abnormal karyotype (11, 13, 33, 38, and 10, respectively; total = 105, plus 1 abnormal case with unrecorded year = 106). Figures here differ from the by-year counts in Table 1, which are restricted to the 251 patients with an interpretable karyotype result.

Median age 3.0 years (IQR 0.2–27.0). Percentages are of the analytic cohort (n = 251); the "Year of referral" row therefore reflects only referrals with an interpretable karyotype and is not directly comparable to the total referral counts in Figure 1 (n = 319, all referrals regardless of karyotype outcome).

Spectrum of cytogenetic findings

A normal karyotype was reported in 130 patients (51.8%) and a benign heteromorphism in a further 15 (6.0%). A clinically significant chromosomal abnormality was identified in 106 patients, giving an overall abnormality detection rate of 42.2% (95% CI 36.3–48.4). Numerical abnormalities predominated, accounting for 94 of the 106 abnormal results (88.7%), while structural rearrangements comprised 11 (10.4%), and a single case had complex or atypical findings. Autosomal aneuploidies (67) outnumbered sex-chromosome aneuploidies (27) by roughly two-and-a-half to one (Table 2; Figure 2). 95% confidence interval for any abnormality, 36.3–48.4%.

Table 2. Cytogenetic classification of the analytic cohort (n = 251)

Cytogenetic category	n (%)
Normal (46, XX / 46, XY)	130 (51.8)
Normal variant (heteromorphism)	15 (6.0)
Autosomal aneuploidy	62 (24.7)
Autosomal aneuploidy, mosaic	5 (2.0)
Sex-chromosome aneuploidy	18 (7.2)
Sex-chromosome aneuploidy, mosaic	9 (3.6)
Structural abnormality	11 (4.4)
Other/complex	1 (0.4)
Any clinically significant abnormality	106 (42.2)

Percentages may not sum to 100 due to rounding.

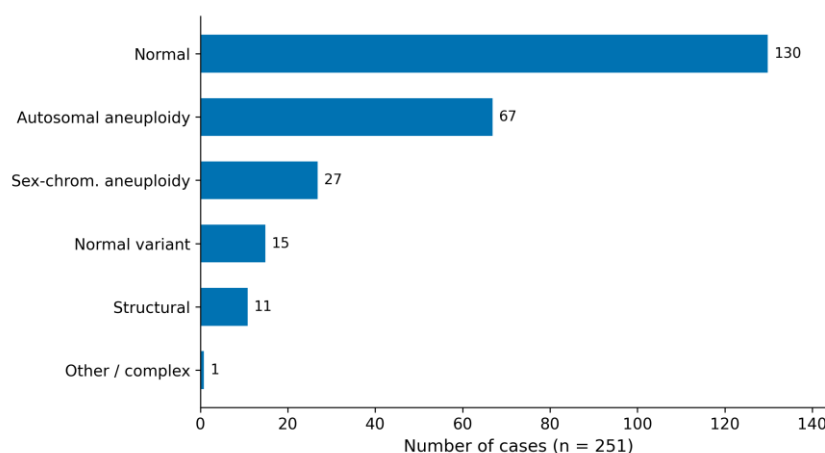


Figure 2. Distribution of cytogenetic findings among 251 karyotyped patients

Specific chromosomal abnormalities

Down syndrome was the single most common diagnosis, present in 58 patients (23.1% of the cohort and 54.7% of all abnormal results). Free trisomy 21 accounted for 54 of these (93.1%), with 3 translocation cases (5.2%) and 1 mosaic case (1.7%) (Figure 3). Turner syndrome and its mosaic variants were identified in 19 patients (7.6%), and the Klinefelter spectrum, including one 49, XXXXY case, in 8 (3.2%). Trisomy 18 was found in 7 patients (2.8%) and trisomy 13 in 2 (0.8%). Eleven patients (4.4%) carried structural rearrangements, including deletions [for example, del(9p) with del(16q); del(16q23)], an inv(X)(q23q27), reciprocal translocations, a ring chromosome 13, and a fragile-site finding; these are enumerated in (Table 3 and Figure 4).

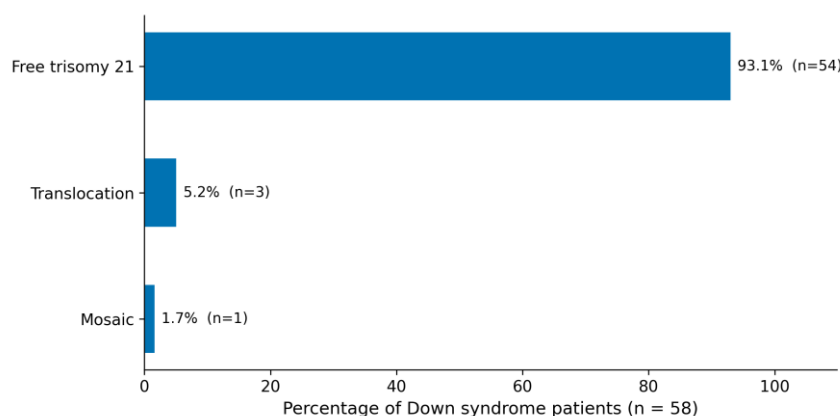


Figure 3. Mechanisms of Down syndrome among 58 affected patients

Table 3. Frequency of specific chromosomal abnormalities (n = 251)

Abnormality	n	% of cohort
Down syndrome (trisomy 21)	58	23.1
Free trisomy 21	54	21.5
Translocation	3	1.2
Mosaic	1	0.4
Turner syndrome (45, X spectrum)	19	7.6
Klinefelter spectrum	8	3.2
Trisomy 18 (Edwards)	7	2.8
Trisomy 13 (Patau)	2	0.8
Structural rearrangements	11	4.4

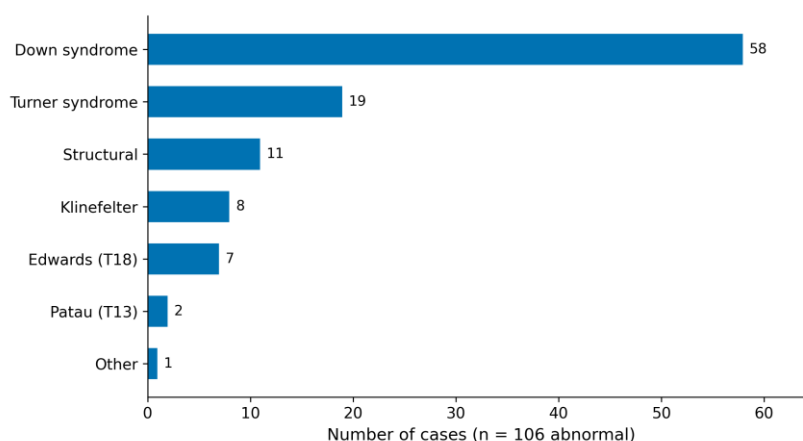


Figure 4. Relative frequency of specific abnormalities among the 106 abnormal karyotypes

Diagnostic yield by age and sex

The abnormality detection rate declined markedly with increasing age at referral: 80.4% in neonates (37/46), 57.9% in infants (33/57), 36.6% in children (15/41), 22.2% in adolescents (4/18), and 15.1% in adults (11/73) (Figure 5). This pattern reflects the referral indications characteristic of each age band, suspected aneuploidy and dysmorphism in the newborn period versus short stature, delayed puberty, amenorrhea, and infertility in older patients. The detection rate did not differ between males (44.1%, 52/118) and females (40.0%, 52/130; chi-square = 0.27, $p = 0.60$) (Table 4).

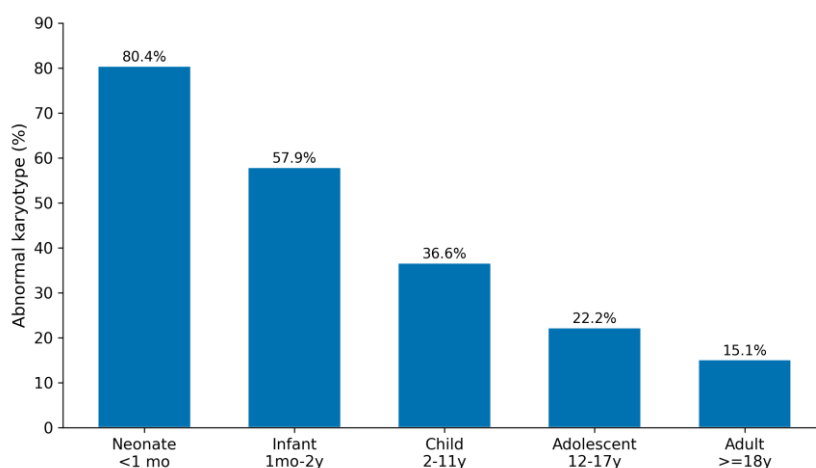


Figure 5. Diagnostic yield by age at referral

Table 4. Abnormality detection rate by age at referral and by sex

Subgroup	Abnormal/total	Rate (%)
Age at referral		
Neonate (<1 mo)	37 / 46	80.4
Infant (1 mo–<2 y)	33 / 57	57.9
Child (2–11 y)	15 / 41	36.6
Adolescent (12–17 y)	4 / 18	22.2
Adult (≥18 y)	11 / 73	15.1
Sex ($p = 0.60$)		
Male	52 / 118	44.1
Female	52 / 130	40.0

Maternal age (exploratory)

Maternal age was recorded for 106 patients (42.2% of the cohort). Among the 29 mothers of children with Down syndrome, the median maternal age was 37.0 years (IQR 31–41), compared with 31.0 years (IQR 27–37) among the 77 mothers of other referred children (Mann–Whitney U test, $P = .008$). This difference is consistent with the well-established association between advanced maternal age and trisomy 21 [4]. Because maternal age was missing for more than half of the cohort,

the comparison is underpowered and exploratory; it is examined in detail, with appropriate adjustment, in a companion analysis of the Down syndrome cohort.

Discussion

In this five-year, laboratory-based series from eastern Libya, a clinically significant chromosomal abnormality was found in 42.2% of successfully karyotyped patients. This high yield is characteristic of a selected referral population rather than the general population, and should be read as the probability of a positive result given referral, not as a community prevalence estimate. Because this laboratory was, to the authors' knowledge, the principal karyotyping provider for eastern Libya throughout the study period, the cohort likely captures most clinically referred cytogenetic cases in the region, which strengthens the regional representativeness of the referral-based findings reported here; this remains distinct from population prevalence, since referral itself selects for individuals with a clinical indication for testing. Comparison with other series is limited by differences in referral criteria and case mix. Our findings complement the recent Benghazi series that examined the subtypes of Down syndrome over an overlapping period [20]. That study focused on one condition and was reported from First International Laboratory, the organization into which the Genome Laboratory was administratively merged in 2023; the present analysis instead describes the full spectrum of chromosomal findings among cytogenetic referrals captured under the Genome Laboratory's own records.

Because the two laboratories shared common ownership and referral infrastructure from 2023 onward, we cannot exclude the possibility that some patients referred during 2023–2025 are represented in both reports; no patient-level identifiers were available to test this directly, and the two analyses should therefore not be treated as fully independent confirmations of one another. Down syndrome was the dominant finding, comprising more than half of all abnormal results, with free trisomy 21 accounting for over nine in ten Down syndrome cases, a distribution consistent with the international literature, in which free trisomy typically represents about 95% of cases and translocation and mosaic forms the remainder [1,2,5]. The relative excess of autosomal over sex-chromosome aneuploidies mirrors the newborn- and infant-weighted referral pattern, in which dysmorphic and syndromic presentations predominate. The most striking finding was the steep inverse gradient between age at referral and diagnostic yield, from over 80% in neonates to 15% in adults. Two forces plausibly drive this.

First, neonatal referrals are strongly enriched for clinically obvious aneuploidy, so the pre-test probability is high. Second, the lower but non-trivial yield in adolescents and adults, referred for short stature, primary amenorrhea, delayed puberty, and infertility, indicates that sex-chromosome and structural disorders such as Turner and Klinefelter syndromes are frequently recognized late. In settings without newborn karyotype or hormonal screening, these conditions may go undiagnosed until the failure of puberty or fertility prompts investigation, delaying growth-promoting, hormonal, and fertility-preserving interventions [8,10,11,12,13]. This supports a lower threshold for cytogenetic referral of children with short stature or dysmorphism and of adolescents with pubertal delay. The absence of a sex difference in overall detection is expected, given that the major autosomal syndromes affect both sexes and that sex-specific referral streams (Turner in females, Klinefelter and azoospermia in males) roughly balance. The older maternal age among Down syndrome cases reproduces the best-characterized risk factor for trisomy 21 and, in a population with later childbearing, has direct implications for counseling and for the potential value of maternal-age-based prenatal screening [4,17].

Limitations

This retrospective, single-laboratory series reflects referral practice rather than the population, so its frequencies are not prevalence estimates. For 68 of 319 records, the result field was blank in the source registry (it is unknown whether these reflect test failures, tests not performed, or unrecorded results); their exclusion may introduce selection bias if unrecorded cases differed systematically from those analyzed. Maternal age, consanguinity, and place of origin were also missing for roughly half of the patients, rendering those subgroup analyses exploratory; consanguinity is examined in detail in a companion study. Karyotyping cannot detect submicroscopic copy-number changes or single-gene disorders, which may underlie some normal results. Because the Genome Laboratory was administratively merged into First International Laboratory in 2023, unquantifiable case overlap with a separate report from that organization covering an overlapping period and region [20] cannot be excluded, since the absence of patient identifiers precluded deduplication. Finally, referral indications were recorded too inconsistently to serve as a denominator.

Conclusion

Cytogenetic testing in eastern Libya identifies a chromosomal abnormality in more than four of every ten referred patients, with free trisomy 21 the predominant diagnosis. The sharp fall in diagnostic yield with increasing age at referral, together with the recognition of Turner and Klinefelter syndromes largely in adolescence and adulthood, indicates that sex-chromosome and structural disorders are commonly diagnosed late. Earlier clinical suspicion, wider availability of karyotyping, and structured genetic counseling, particularly in a population with later maternal childbearing and a cultural background of frequent consanguinity, would improve timely diagnosis and care.

Authors' Contributions.

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

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Conflict of interest

The authors declare no conflicts of interest.

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Availability of data.

The anonymized dataset supporting this study is available from the corresponding author on reasonable request.

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