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# Original Article

# Cytogenetic Analysis of Referral Cases with Growth Failure and Clinical Suspicion of having Chromosomal Abnormality

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## ABSTRACT

***Background and Objective:*** **Failure to thrive (FTT) is a sign that describes a particular problem rather than a diagnosis and explain growth failure or more advanced failure to gain weight appropriately. The aim of this study was to determine the prevalence and type of chromosomal abnormalities in patients presented with FTT.**

***Materials and Method:*** **One hundred FTT cases with clinical impression of having chromosomal abnormality referred for cytogenetic study during a period of 5 years (2007-2011) with age range from 5 month to 15 years. Chromosomal analysis was carried out for them. The standard protocol for peripheral blood lymphocyte culture was followed by metaphase chromosome preparation and conventional analysis of G-banded chromosomes. All analyses were performed using the SPSS soft ware package, version 18.**

***Result:*** **Fifteen cases showed karyotypic abnormality. The most common karyotype abnormality was aneuploidy resulted from monosomy of the chromosome X in girls.**

***Conclusion:*** **Turner syndrome with various forms of chromosomal complement is the most common chromosomal abnormality causing growth failure in girls.**

***Keyword:*** **Failure to Thrive, Chromosomal Disorders**

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## Introduction

Failure to thrive (FTT) is considered as a sign denoting a particular problem rather than a diagnosis. This term describes infants and children who lose weight or failure to gain weight in accordance with standardized growth chart. Stature (linear growth) and head circumference may also be affected in severe cases of FTT (1).

Although newborn growth is dependent on intrauterine factors, growth during infancy is largely nutritionally driven. Under nutrition is believed to be the most common cause of growth failure. Most of referral cases with impression of growth retardation are presented with short stature, inappropriate weight for age or failure to gain weight in accordance with standardized growth chart. Delay in secondary sexual development may also is seen (2). Chromosomal derangement might also adversely affect fetal and postnatal growth (3). Down syndrome (DS) and Turner syndrome (TS) are the most common chromosomal abnormalities noted in cases with growth failure (3). Posture and interaction also may reflect growth retardation. Dysmorphic features suggest possible genetic and chromosomal abnormality. Recently the genetic and non environmental diseases are going to be important cause of morbidity and mortality (2,4-6). There are also several groups of disorders both medical and psychosocial that can affect growth pattern at any time both prenatally and postnatally (6). Standard karyotyping is used as the first step for diagnosis of cytogenetic abnormalities in suspected cases with growth retardation. The aim of this study was cytogenetic examination of referral cases who presented with FTT.

## Materials and Methods

In this cross sectional descriptive study, 100 patients during the period, 2007 to 2011 were examined. All of these children had evidence of growth failure based on history, physical examination and laboratory data and were referred by pediatricians in order to rule out any possibility of cytogenetic abnormality as the main cause of growth retardation. Patients with multiple congenital anomalies and mental retardation excluded from study.

All referral cases with age range above 15 years and those with typical gross abnormalities such as DS were excluded.

Standard karyotyping using cultured peripheral blood lymphocytes with subsequent G banding of metaphase spreads was carried out for the cases. Briefly, peripheral blood lymphocytes were cultured in RPMI 1640 basal medium containing 10% fetal calf serum (Gibco-Invitrogen-USA) for 72 hours in 35 Celsius degree, then treated with 0.1 microgram/ml of colcemid (Gibco-Invitrogen-USA) to stop the cells in metaphase of mitotic division. After harvesting, metaphase chromosomes were spread and stained using standard G-banding technique. For each case, 15 metaphase spreads were analyzed using Cytovision Chromosomal Karyotyping Automatic System (Genetix Company-USA). In case of mosaicism, at least 30 metaphases were examined. Cytogenetic analysis and report were based on ISCN 2009 (7).

We performed statistics comparing between cytogenetic subclasses and age groups using independent *t*-test. All analyses were performed using the SPSS soft ware package, version 18.The mean age of cases with abnormal karyotype and those with normal karyotype was analyzed by independent *t*-test method. All data were protected for purpose of anonymity.

## Results

There were 100 children with clinical manifestation of growth retardation referred from pediatricians for cytogenetic study. The subjects ranged from 5 months to 15 years with mean age

6.9 ±4.2 years. Most of them (85%) had normal karyotye (Fig.1). Fifteen percent of them had abnormal karyotype (Fig. 2). Pericentric inversion on chromosome 9 was noted in two cases which is usually considered as a normal variation of the chromosome 9.

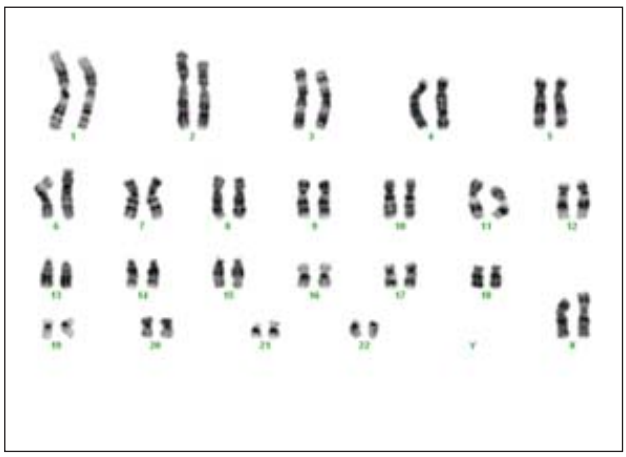

**Fig. 1-** Normal Karyotype, 46XX from referral cases

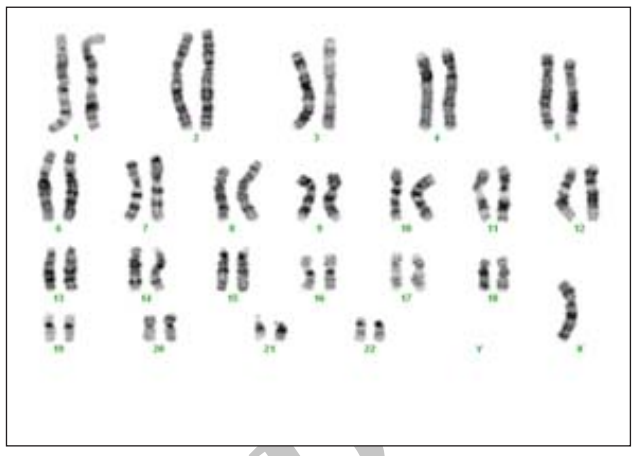

**Fig. 2-** Abnormal Karyotype from a referral case with Turner sydrome, 46xo

**Table 1-** Distribution of chromosomal abnormality in 100 referral cases with growth retardation

| Chromosomal Abnormality | Number of cases | Age Mean ±SD | Sex |
|---|---|---|---|
| 45,X | 8 | 8.8±2.7 | F |
| 45,X/46,X,i(X)(q10) | 3 | 8.8±3.8 | F |
| 46,X,i(X)(q10) | 2 | 11.5±4.5 | F |
| 45,X/46,XX | 1 | 9 | F |
| 45,X/46,XX/47,XXX | 1 | 11 | F |
| 46,XX,inv(9)(p13q12) | 2 | 11.25±4.4 | F |
| 46 XY | 14 | 2.17±1.36 | M |
| 46XX | 69 | 7.3±4 | F |
| Total | 100 | | |

The most common karyotypic abnormality was 45,X (a karyotype with one X chromosome) (Table 1). In addition to numerical abnormalities of chromosome X, two types of structural abnormality of chromosomes including isochromosome of the long arm of the X and pericentric inversion on the chromosome 9 were noted. Fourteen percent of the cases were male children presenting with failure to thrive, however, no abnormality was detected in cytogenetic analysis. Fifteen percent of the cases, all of whom were female children had abnormal chromosomal complement identifying Turner syndrome (Table 1). The mean age of females with Turner syndrome was 9.4±2.9 and the mean age of females with normal karyotype was 7.3±4. There was no significant correlation between chromosomal abnormality and age of the patients ($P$=0.053).

## Discussion

Although, undernutrition is the most common cause of growth failure, chromosomal abnormalities are also among common factors that adversely affect both fetal and postnatal growth (8-14). Of these, the most common is DS which

affect nearly 1:600 live born infants. In girls with short stature and growth retardation, Turner syndrome is a very common cause of short stature (linear growth failure) affecting 1:2000-5000 live born girls (15).

Other chromosomal abnormalities including trisomy 13 and 18, and monosomy 5 are associated with significant congenital anomaly, mental retardation and short stature. Furthermore, short stature is frequently associated with many other syndromes, both defined and undefined by specific genetic mutations.

Because of easily recognized typical phenotypic features, cases with significant congenital anomalies and mental retardation have been already excluded from our study. It is said that the most common features of Turner syndrome are pre- and postnatal growth retardation and gonadal dysgenesis. Girls with Turner syndrome have mild growth impairment at birth, grow slowly during infancy and at the onset of childhood and have delayed onset of secondary sex characteristics as well (16). Three percent of 555 children presented with FTT had Turner syndrome (17). Iravathy *et al.* studied 60 referral cases with suspected chromosomal abnormality and 10% had abnormal karyotype (18). The most frequent karyotypic abnormality in cases with primary amenorrhea was sex chromosome aneuploidy comprising monosomy of the X chromosome (19, 20). We found that 15% of cases had abnormal Karyotype who had cytogenetic finding in favor of Turner syndrome. While fourteen percent of our cases were male and had no karyotypic abnormality, 15 out of 86 female cases (17.4%) had abnormal karyotype.

Great majority of cases with chromosomal abnormality were pure or mosaic forms of Turner syndrome with different chromosome complements which constitute 88.2% of cases. Only two cases with pericentric inversion on chromosome 9 were detected. Although, this finding is usually considered as a normal variation of the chromosome 9, its probable effects and consequences remain to be studied. About 53% of cases with TS had the classic 45,X chromosome complement. The second most common karyotype in these cases is 45,X/46,X,I (X)(q10) a mosaic form of TS with relative frequency of 20%. Together with other mosaic forms shown in the Table1 about 34% of TS cases are mosaic. Accordingly, it may be concluded that post zygotic mitotic events in somatic cells derived from the fertilized egg, have significant role in giving rise to TS in present study. This finding disagrees with the frequencies reported for mosaic forms of TS (21-23). Literature review however, shows that the frequency of both classic and mosaic forms of TS is variable among studies (22). For example Iqbal *et al* .found that 40% of the girls were with ,45X karyotype and 32% were with45,X,46/XX chromosomal complement similar to our study .(8)We advise all girls with short stature (less than the3 rd percentile) should have a cytogenetic study if there are any features of Turner syndrome presented.

## Conclusion

We showed that a significant proportion of pediatric cases especially girls with unexplained growth retardation had karyotypic abnormality, most commonly Turner syndrome. We recommend cytogenetic study for such cases for early diagnosis and management. It is necessary that females with Turner syndrome be diagnosed as soon as possible so they may achieve the maximum benefit of growth hormone therapy. The lack of significant correlation between chromosomal abnormality and age of these cases might be due to limited samples therefore, the repetition of the study using a larger sample size is recommended.

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