

Cytogenetic Analysis of Mentally Retarded Patients in Srikakulam

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ABSTRACT The present study is undertaken to analyze the frequency of chromosomal abnormalities in mentally retarded patients (mild, moderate and severe), and to determine the types of chromosomal abnormalities that play a major role in causing mental retardation. Thirty subjects of both gender in the age group of 05-50 years were selected for study from "Behara Manovikas Kendram" of Srikakulam. Peripheral blood samples were collected from the patients with the help of technicians from TRIMS, Visakhapatnam and the samples were subjected to chromosomal analysis. Physical features like microcephaly, seizures, status of retardation etc., were also noted. The metaphase studies clearly revealed 5p deletions, Mosaic Down syndrome, 5q additions. One case revealed translocation in 9 and 17 chromosomes which also showed blast cells in Blood Smear. Chromosomal abnormalities play a vital role in causing mental retardation and its frequency increases with severity of mental retardation. We concluded that chromosomal studies in mentally retarded patients help in accurate diagnosis and proper prognosis followed by genetic counseling and management rehabilitations.

INTRODUCTION

The incomplete development of mental capacities and associated behavioural abnormalities are referred to as Mental Retardation. At least 7.6 million children are born globally every year with severe congenital malformations. 90 percent of mentally retarded people are born in countries with low incomes (Kaur and J R Singh 2010). In India, it is difficult to collect precise data on Mental Retardation (MR), causes for disorders, because of diversified social and cultural factors. Many reports are available on mentally retarded patients at global level, such as Speed et al. (1976) reports on Scotland, Jacobs et al. (1978) report on North America, Sutherland et al. (1976) reports on South Australia, Kondo et al. (1980) reports on Japan. The first report from India on cytogenetic abnormalities was published by Moghe et al. (1981). Subsequently Isaac et al. (1985) reported a survey on Down syndrome in Hyderabad, Verma et al. (1998) reported cases from Delhi region, Modi et al. (1998) reported cases in Baroda region. Jain et al. (1998) screened 1206 children with MR and found 6.38 percent positive for fragile-

X syndrome. Sex anomalies were also established by many scientists which include Turner syndrome, Klinefelter's syndrome. Micro deletion syndromes were detected in 73 cases among 374 by Madon prochi et al. (2010). First report from Jammu and Kashmir on chromosomal anomalies was reported by Parvinder Kumar et al. (2010) and they reported 11.2 percent Turner syndrome cases and 6.8 percent Klinefelter syndrome cases. Rajasekhar et al. (2010) analyzed 1400 referral cases for cytogenetic analysis and reported karyotype 45X in 36.17 percent cases. Reports on congenital anomalies are also available from different parts of India. Mishra and Baveja (1989), Aggarwal et al. (1991), Kumar et al. (1994), Patel and Adhia (2005) assess overall incidence of malformations which include Neural Tube Defects, Microcephaly, Cleft lip / palate, Hydrocephalus and Heart diseases.

With reference to Andhra Pradesh (AP), very little information is available on the data on prevalence of Mental Retardation, except work by Jyothy et al. (2000), who recorded cytogenetic data obtained from 1001 patients of Down syndrome and their parents over a period of 20 years (Jan 1979 – Jan 1999) in Hyderabad area of AP.

The present study has been undertaken with an intent to determine the frequency and types of chromosomal abnormalities in mentally retarded patients of Srikakulam district of AP, India. Furthermore, this type of study from Srikakulam has not been reported. However, the number of individuals investigated was not sufficient

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to permit statistical analysis and patients who are not institutionalized have not been included.

SUBJECTS AND METHODS

In the Behara Mano Vikasa Kendram of Srikakulam, Andhra Pradesh, India, we have physically examined 50 subjects. Based on deformities we have selected 30 subjects of both sexes in the age group of 05-50 years for Karyotypic study. Peripheral blood samples were collected from the patients, with the help of the technicians from TRIMS, Visakhapatnam and chromosomal analysis was conducted. Peripheral blood samples were collected in sodium heparin vacutainers. Cultures were initiated using rpm 1640 including 15 percent serum, Glutamine, antibiotics and phytohemagglutinin. The cultures were terminated on 3rd day by adding colchicine. Metaphase preparations were made and GTG banding was done. Well spread metaphases were scored for chromosomal analysis. 30 metaphases were scored to estimate numerical abnormalities and 3 metaphases were karyotyped to analyze structural abnormalities. Physical features were also noted like Microcephaly, seizures and magnitude of retardation etc.

RESULTS

All 30 subjects are known mentally retarded patients, among them 66.66 percent were under weight (Table 1), 13.33 percent were dumb, 10 percent were suffering from dermatological disorders like dry skin, 16.60 percent were with skeletal deformities, 10 percent were microcephalic, 6.66 percent were suffering from seizures and 6.66 percent were with long faces.

Fifty percent of the subjects are categorized as Mild MR (Table 2), 30 percent are Moderate MR and 20 percent are suffering from severe Mental Retardation.

Out of 30 subjects, 9 showed chromosomal aberrations (30.0%) included 7 (23.3%) structural variations, 2 (6.66%) numerical anomalies (Table 3). Structural variations include Deletions, Inversions, Translocations and Additions. Numerical variations included Down syndrome. Surprisingly no sex chromosomal abnormalities were noticed.

Sex-wise 36.36 percent males (Table 4) and 12.5 percent females were suffering from chromosomal anomalies. Age showed no impact on chromosomal aberrations.

Table 1: Physical findings of sample population

| Finding | Sample size | Prevalence (N %) |
|--------------------------|-------------|---------------------------|
| | 30 | All are mentally retarded |
| <i>Weight</i> | | |
| Under weight | | 20 (66.6%) |
| Over weight | | 2 (6.6%) |
| Normal | | 8 (26.6%) |
| Dumb | 30 | 4 (13.33%) |
| Dermatological disorders | 30 | 3 (10.0%) |
| Skeletal disorders | 30 | 5 (16.66%) |
| Microcephaly | 30 | 3 (10.0%) |
| Seizures | 30 | 2 (6.66%) |
| Long face | 30 | 2 (6.66%) |

Table 2: Degree of MR among the patient groups (n=30)

| Abnormality | Age group | Males | Females | Total | % |
|-------------|-----------|-------|---------|-------|----|
| Mild MR | 6-50 yrs | 11 | 4 | 15 | 50 |
| Moderate MR | 6-50 yrs | 7 | 2 | 9 | 30 |
| Severe MR | 6-50 yrs | 4 | 2 | 6 | 20 |

Table 3: Different chromosomal anomalies found among the positive subjects in the present study (n=9) (Figs. 1 to 9)

| Case No. | Chromosomal abnormality | Sex | Age in years | Clinical status |
|----------|---------------------------|--------|--------------|-----------------|
| 1 | 47 XY + 21 | Male | 8 | MILD MR |
| 2 | 46 XY Del 5(p) | Male | 26 | MILD MR |
| 3 | 46 XX inv 9(p12-q13) | Female | 30 | MILD MR |
| 4 | 46 XY t(9q; 17q) | Male | 50 | MILD MR |
| 5 | 46XY t(15q; 17q) | Male | 40 | MILD MR |
| 6 | 46 XY Del (5p) | Male | 14 | MODERATE MR |
| 7 | 46 XY add(15q) | Male | 12 | MILD/SEVERE MR |
| 8 | 46 XY add(4q) | Male | 17 | MILD MR |
| 9 | 46 XY(10) / 47 XY +21(02) | Male | 09 | MILD MR |

Table 4: Influence of age and sex

| S. No. | Sex and age | Total cases | No. of abnormal cases | % |
|--------|----------------|-------------|-----------------------|-------|
| 1 | Female | 8 | 1 | 12.5 |
| 2 | Male | 22 | 8 | 36.36 |
| 3 | Below 15 years | 15 | 4 | 26.66 |
| 4 | Above 15 years | 15 | 5 | 33.3 |

Chromosomal study in individuals suspected to be suffering from genetic disorders has been carried out by Kanata (1986 a), Kanata (1986b), Latha (1996), Anderlid et al. (2002), Chethan et

al. (2007), Jeong et al. (2010), Kumar Parvinder et al. (2010), Rajasekhar et al. (2010), Yeshwanth (2010). These workers reported wide variations in the frequencies of chromosomal aberrations in their study. In the present study (Table 5) chromosomal aberrations were detected in 30.3 percent and as such this figure is higher than most of the previous reports except, 56.32 percent as reported by Kumar Parvinder et al. (2010).

Table 5: The percentage of chromosomal abnormalities reported previously by various authors in subjects with MR

| S. No. | Investigation | Year | Subjects studied (n) | Subjects with chromosomal anomalies (n) | % |
|--------|-------------------------|------|----------------------|---|-------|
| 1 | Kanata S | 1986 | 56 | 9 | 16.1 |
| 2 | Latha P | 1996 | 100 | 18 | 18.0 |
| 3 | Anderlid et al. | 2002 | 111 | 10 | 9.0 |
| 4 | G K Chetan et al. | 2007 | 100 | 12 | 12.0 |
| 5 | Radhakrishnan Yeshwanth | 2010 | 176 | 32 | 18.8 |
| 6 | Parvinder kumar et al. | 2010 | 161 | 91 | 56.32 |
| 7 | M Rajasekar et al. | 2010 | 1400 | 343 | 24.5 |
| 8 | Seon-Yong Jeong et al. | 2010 | 431 | 60 | 13.9 |
| 9 | Present Study | 2010 | 30 | 9 | 33.3 |

DISCUSSION

Abnormal Physical Features

The physical features of the subjects clearly showed symptoms of mild, moderate and severe Mental Retardation. 66.66 percent are under weight patients. This may be due to malnutrition and the inability of the subject to gulp food. This underweight condition coincides with their low red blood cell count and Hb levels (Oddbjorn Hove (2004).Jaya Kumari and Mythili (2010) worked on weight survey of MR patients and reported that patients with severe MR were more likely to be underweight and people with mild MR were more likely to be stout. Food refusal and self induced vomiting were present among persons who are underweight. Simila and Niskanen (2008) reported that 29.5 percent of the MR subjects of their study were underweight, an obvious consequence of the different feeding and dietary problems connected with their multiple disabilities. Al-Sharbati Marwan (2003) reported 20 percent of the patients of their study were

underweight. The subjects of the present study are living in a home organized by a social worker. Due to paucity of funds, they are not providing balanced diet to the MR patients.

The incidence of microcephaly is not known in India. Present study reported 10 percent microcephalic cases, with 3.3 percent abnormal karyotypes. This figure is higher than the 9 percent microcephalic cases reported by Kaur et al. (2003). Microcephalic condition in some cases is due to monogenic abnormalities, the others might have been due to injuries during delivery or infections like Rubella during early stage of pregnancy. Cases with apparently normal chromosomal complement may have some monogenic abnormality or complex structural rearrangements that are beyond the detection of G-banded chromosome analysis. Kaur et al. (2008) also reported 3 microcephalic cases with chromosomal aberrations like 2p deletion, 18p deletion and ring chromosomes.

Many reports are available on physical deformities of MR with skeletal disorder, seizures, but dumb cases are not yet reported. The cytogenetic analysis of 3 dumb patients of the present study was also normal.

Five patients (16.66%) were suffering from different skeletal disorders like spinal cord deformation, limb deformation. Among this, 2 karyotypes (40%) showed abnormality, one with translocation 46 XY t (15q: 17q) (Fig. 1) and one with addition 46XY (15q) (Fig. 2). Ventroto et al. (2005) reported that balanced reciprocal translocation 2:8(q:32;p:13) leads to multiple skeletal abnormalities. Emanuel Beverly et al. (2010) reported that patients with t8: 22 have some deformation of the fingers. Jung (2007) reported that 46 XY t(3:17) is associated with multiple muscular and skeletal abnormalities.

According to Peng-Cheng-Fang et al. (2008), MR patients are suffering from seizures. Steffenburg Ulf et al. (1996) also reported that 50 percent of the MR children had seizures. But present study reports only 6.6 percent of seizures among MR patients. Among these patients 50 percent showed trisomy for 21 chromosomes (Fig. 3).

Abnormal Karyotypes

Among 30 subjects, 9 showed abnormal karyotypes (30%) among them 6.6% are numerical abnormalities and 23.3 percent are structural abnormalities.

Only 2.6 percent cases related to Down syn-



Fig. 1.
 Karyotype: 46, XY, t(15q; 17q).
 IMPRESSION: Presence of t(15q; 17q) in 100% of metaphases.

drome and Down syndrome with mosaicism reported among numerical abnormalities among which one free trisomy was reported (Fig. 3)

and one had a mosaic cell line (80 percent of his cells are normal, the other cells being trisomic for chromosome no.21.) In the cytogenetic analy-

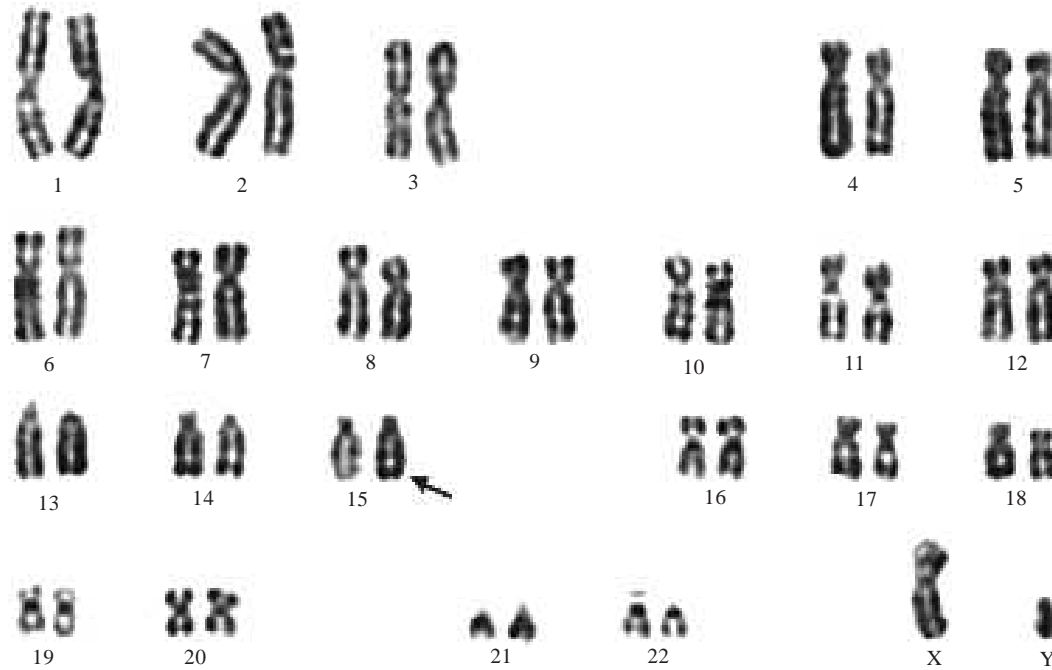


Fig. 2.
 Karyotype: 46, XY, add (15q).
 IMPRESSION: Presence of add (15q).

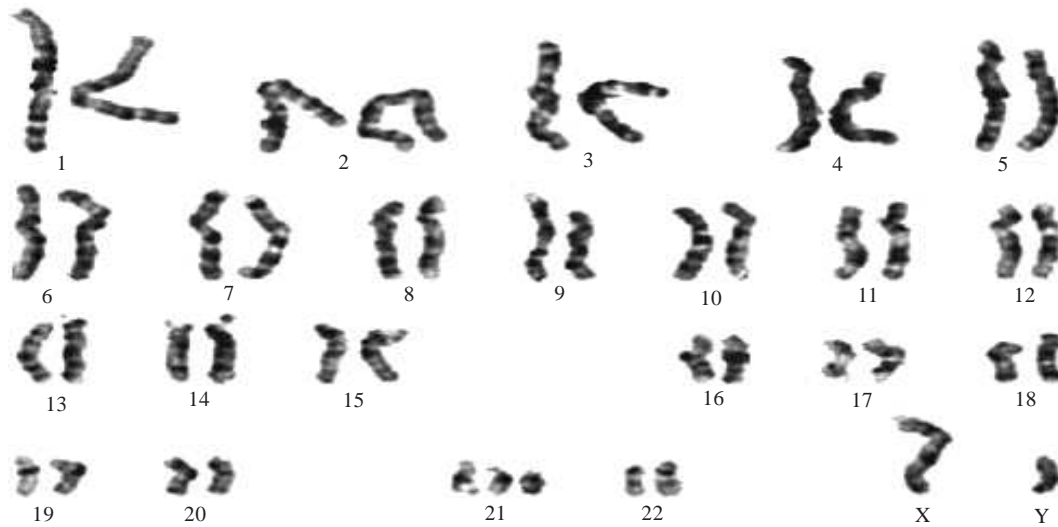


Fig. 3.
 Karyotype: 46, XY, +21.
 IMPRESSION: Down's syndrome.

sis, out of 40 metaphases counted, 8 metaphases revealed trisomy of chromosome no.21 (Fig. 4). This abnormality is less than 11.3 percent reported by Kaur and Singh (2010), 27 percent

reported by Thomas et al. (1992), 12.09 percent by M.Rajasekhar et al. (2010).

Prevalence of Down syndrome is more in India and many scientists worked on this elabo-



Fig. 4.
 Karyotype: 46, XY, [10] / 47, XY, +21[02].
 IMPRESSION: Presence of trisomy 21 in 20% of metaphases (Mosaic Down's syndrome).

rately. Hence more statistical data is available on Down syndrome with reference to India. Verma et al. (1998) reported a frequency of 0.81/1000 in Delhi region. Patel et al. (2005) reported incidence of trisomy 21 was 1 in 1200 in Mumbai region.

Rajgam et al. (1977) reported the associated malformation in cytogenetically confirmed Down syndrome patients and among them 5.52 percent are osteoarticular malformation. In the present study, the Down syndrome patients are not suffering from this malformation.

5p deletion is a rare abnormality and the estimated prevalence is about 1 in 50,000 live births. The prevalence among individuals with MR is about 1.5 in 1000. In the present study, among 9 positive subjects, 2 are (22.22%) with 5p deletions (Figs. 5 and 6) and they are males only. Dave Usha and Shetty Dhana lakshmi (2010) were reported 5.2 percent deletions of 7q, 18p, 16q and Xq. Rajasekher et al. (2010) were reported 18.75 percent of deletions in their study with two 5p deletions and one 18q deletions. Chetan et al. (2010) reported 33.33 percent deletions of three 15q and one Xq in their study on Idiopathic MR.

Translocation anomaly is the most common among structural deformities and vast literature

is available on it. The chromosomes involved in translocations reported were t(2;8) translocation by Ventruto et al. (2005), t(3;17) by Jung et al. (2007), t(8;22) by Emaneuel Beverly et al. (2010), t(3;10) by Chetan et al. (2010), t(11q;16q), t(12p;17q), t(3q;14q), t(Xq;10q), t(14p;21p) by Dave and Shetty (2010), t(9;22), t(14;7), t(16;22) by Rajasekher et al. (2010). In the present study, translocations are reported at t(9q;17q) (Fig.7) and t(15q;17q) (Fig.7) which are rare translocations. Nampoothiri et al. (2008) claimed that for the first time they have reported a translocation between q arms of chromosome 9 and 17. Lowwage et al. (1987) have reported one case of Philadelphia positive chronic myeloid leukemia which showed a high promyelocytic component associated with a variant t(15q-17q). In our study also patient with 15q-17q is suffering from leukemia as the blood smear showed blast cells. The other case of translocation is with microcephaly.

One female karyotype showed inv 9(p12-q13) (Fig. 8) which is a structural variant that has been found in both normal populations and patients with various abnormal phenotypes and diseases. Babu V Rao et al. (2006) and Balkan et al. (2010) reported high frequency of inv 9(p12-q13) and 9(p13 q13). Rajasekher et al. (2010) reported

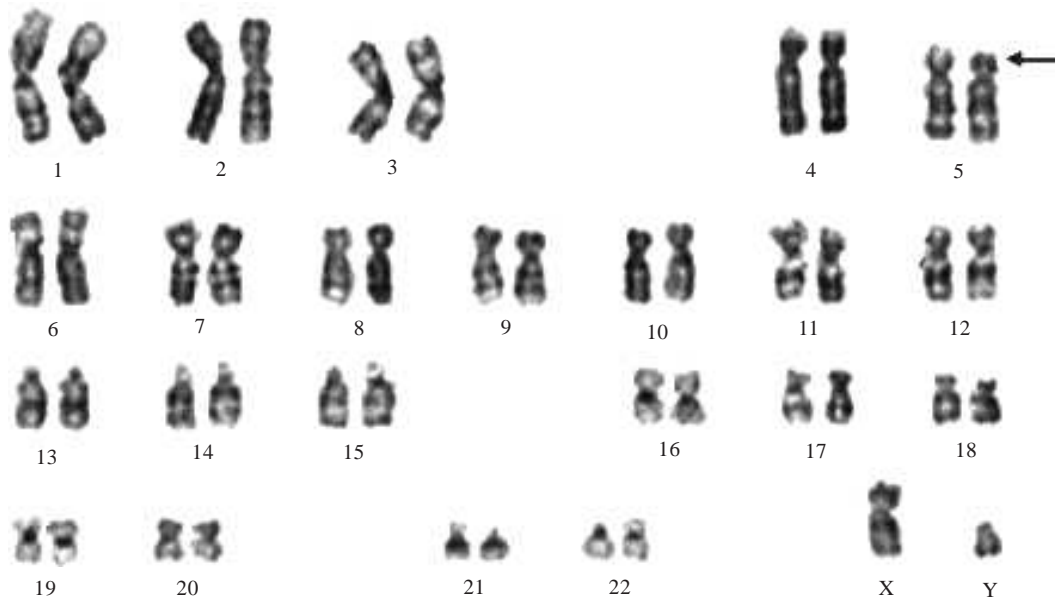
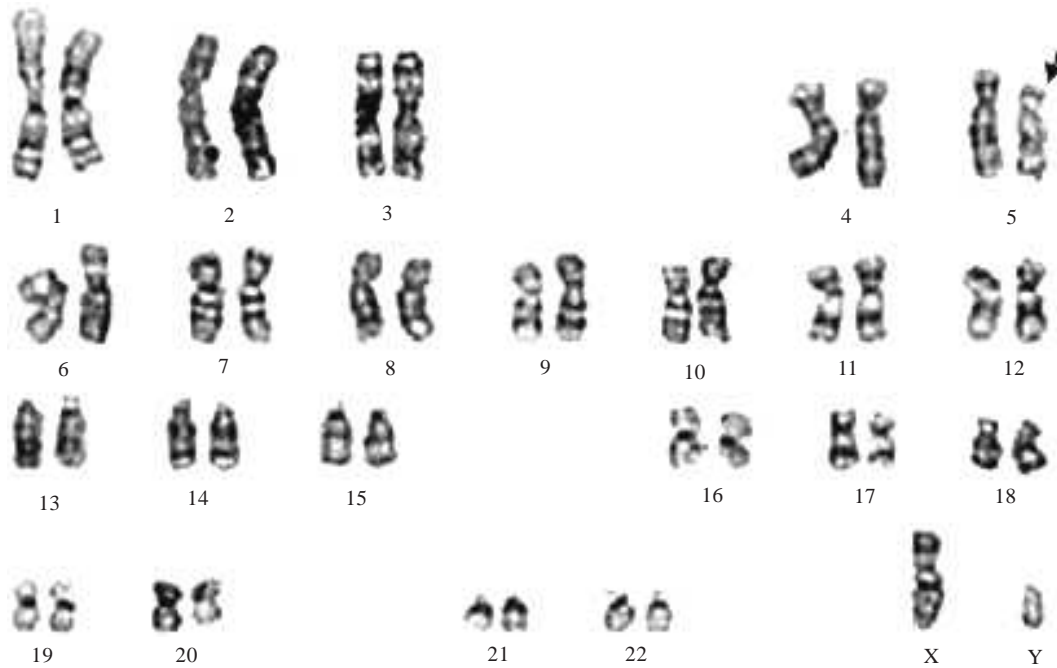


Fig. 5.

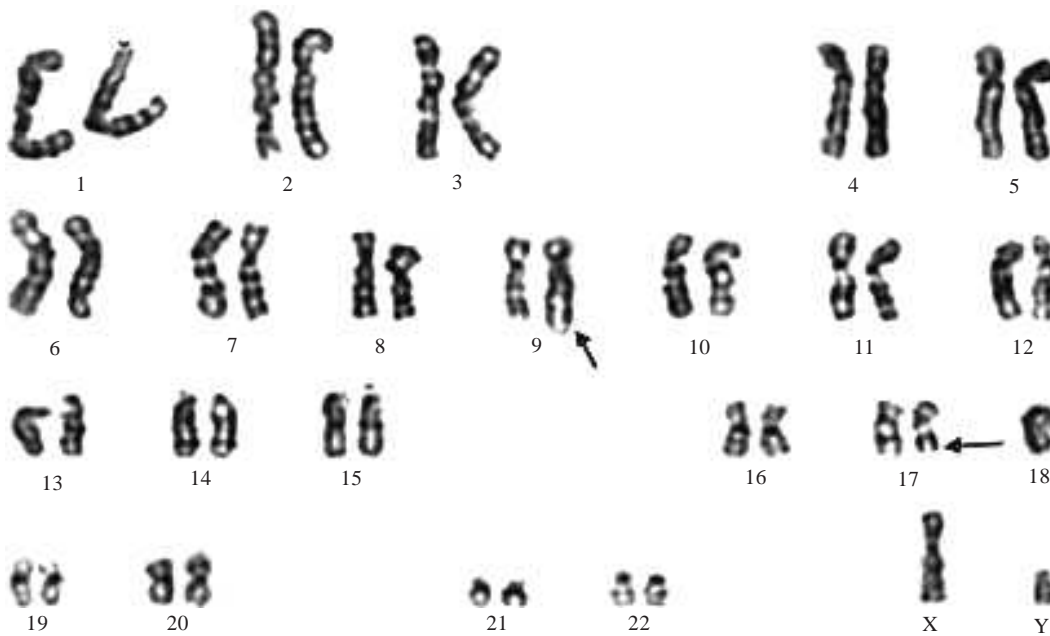
Karyotype: 46, XY, del(5p).

IMPRESSION: Presence of del(5p) in 100% metaphases.

**Fig. 6.**

Karyotype: 46, XY, del(5p).

IMPRESSION: Presence of del(5p) in 100% metaphases.

**Fig. 7.**

Karyotype: 46, XY, t(9q; 17q).

IMPRESSION: Presence of t(9q; 17q) in 100% metaphases.



Fig. 8.

Karyotype: 46, XY, inv 9(p12-q13).

IMPRESSION: Pericentric inversion of chromosome No.9 is a structural variant that occurs frequently in normal population. It is considered as a normal variant.

inversion of 7 and 8 chromosomes. Dave Usha and Shetty Dhanalaxmi (2010) also reported 7.2

percent of inversions of which 8, 9, 11, 17 and X chromosomes are involved. Jeong (2010) re-

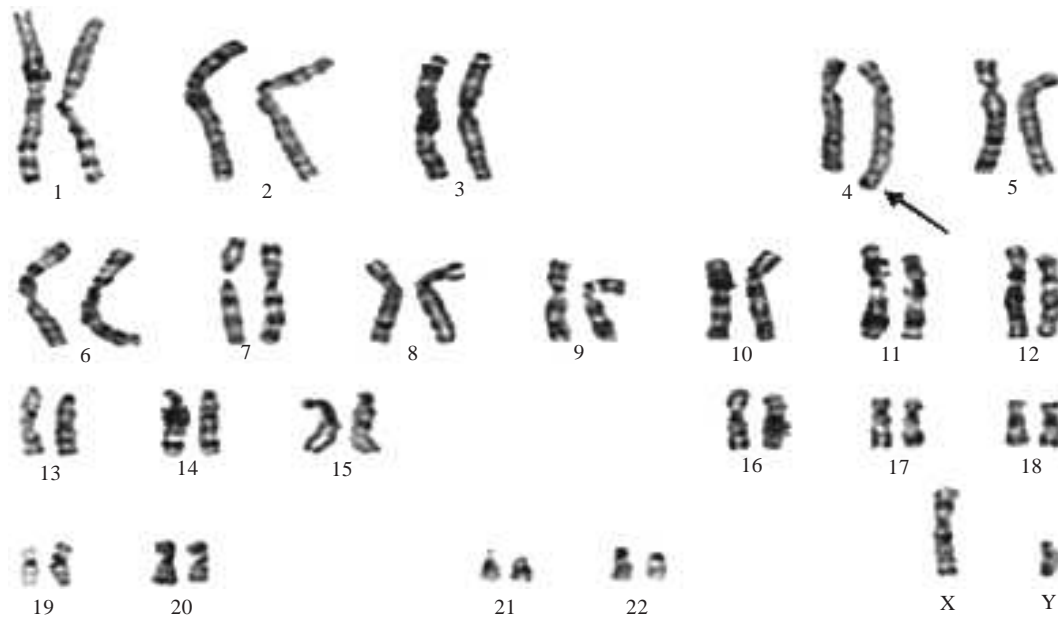


Fig. 9.

Karyotype: 46, XY, add(4q).

IMPRESSION: Presence of add(4q).

ported 13.3 percent inversion frequency of 9(p11-q13) with congenital anomalies. Gaber Khaled et al. (2010) for the first time reported phenotypically normal female carrying structural variant on both the chromosome 1 and 9 leading to recurrent miscarriages.

Two cases showed positive 4q and 15q additions (Figs. 9 and 2). Chromosome 4, partial trisomy of distal 4q is a rare disorder in which a portion of the 4th chromosome appears 3 times rather than twice in cells of the body. The common symptom of the disorder is MR, defects of the hand and feet. The patient of the present study had mild MR, long head and skeletal deformity. Patel et al. (2007) also reported clinical features including absence of right thumb and claw like fingers on both hands with duplication of majority of 4q. Rajasekher et al. (2010) reported duplication of 18, 14 chromosomes but Dave Usha and Shetty Dhanalaxmi (2010) reported 4q addition along with 5p,6q,9p,11p, and 16q.

15q addition is an extremely rare chromosomal disorder. A few reports are available on this as Ruggenbuck et al. (2004) reported this abnormality in 3 patients. The patient of the present study showed long upper lip and short neck.

CONCLUSION

1. 33.3 percent of the study population showed chromosomal abnormalities.
2. Males are suffering more in comparison with females.
3. Rare translocations are observed in the positive cases with Leukemic conditions t(9q 17q) and t(15q 17q).
4. Rare 4q, 15q Additions are reported in the positive subjects.

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