Chromosomal Abnormalities in Selected Group of Individuals with Intellectual Disability/MR: A Preliminary Study from Himachal Pradesh

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Abstract

The present study was aimed to find out the etiology by evaluation of 30 patients with MR who were being selected stringently from inhabitants of Himachal Pradesh. The chromosomal study was done for every patient on lymphocyte culture, based upon conventional cytogenetic technique. X-linked recessive mode of inheritance was found to be predominant in familial cases of MR. The present study revealed that birth order and mother's age couldn't predict mental retardation of unknown etiology. Chromosomal abnormalities were found in18 individuals corresponding to a diagnostic yield of 60 percent. Chromosomal deviances found were trisomy-21(Down's syndrome) in 10 patients, deletions in 3 patients, in version in 1 patient, translocations in 2 patients, ring14 chromosome in 1 patient and marker chromosome in 1 patient. Cases with abnormal chromosomal complements had greater proportion of severe MR. Chromosomal studies in mentally retarded subjects help in diagnostic evaluation to assist in providing a restorative household for children with intellectual disabilities.

KEY WORDS: *Diagnostic yield, X-linked recessive, Trisomy-21, ring-14 chromosome, dicentric chromosome, mosaicism*

Introduction

Mental retardation is characterized by impaired cognitive, linguistic and social abilities which manifest in infancy or early childhood (1, 2). Non-uniformity in study designs, methodologies, age groups, and case definitions contributed to an array of prevalence estimates (0.05 to 1.55 %) (3). MR is present in about 2 to 3 percent of the population and increased acclaim has been given to innumerable biological factors, including chromosomal abnormalities but for approximately half of individuals diagnosed with MR, the etiological basis remains obscure. Person with an intelligence quotient(IQ) below 70 are considered mentally retarded; milder forms of mental retardation, with IQ between 50-70(overall prevalence 1.5%) are more common than moderate and severe forms with IQ below 50 (prevalence 0.4%) and its causative diagnosis also remains unknown up-to 80-90 percent of cases (4,5). Although, diagnosis might be established in up-to 65 percent of cases of moderate to severe mental retardation (6). Mental retardation can be caused by genetic and non-genetic (exogenous) factors such as infection or intoxication during pregnancy, complications of delivery or postnatal infection or trauma. According to an estimate 18.6 to 44.5 percent of cases have exogenous causes and 25 to 50 percent had genetic causes (7-10). Among them, chromosomal abnormalities accounted for 10 percent of total live births (11) and 17 percent children exhibiting chromosomal anomalies with congenital malformation are known syndrome (12). Notably, unraveling the causes of mental retardation is one of the greatest challenges for clinicians and scientists as the spectrum of possible underlying disorders is an enormous

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and extensive range of available other investigations (13). Although the information about etiology of mental retardation generally does not help in treatment but it can serve as a key element in disease management, acceptance of the disability and enduring emotional relief for the parents (14).

Objectives*:* The present investigation was undertaken to report a diagnostic yield of conventional karyotyping in 30 subjects with various degrees of MR and to document many parameters such as sex ratio, birth orders, maternal age effect, the frequency of MR, IQ testing and clinical evaluation.

Material and methods

For cytogenetic investigation 30 MR and 10 normal individuals (as a control group) belonging to different districts of Himachal Pradesh were selected based upon congenital abnormalities, which was performed in the Diagnostic Center for Genetic Disorders, Guru Nanak Dev University, Amritsar. All individuals were evaluated with regard to any genetic causes that might underlie these disorders of unknown etiology. Kamat's Binet test of intelligence was performed for assessing the intelligence quotient and all MR cases were classified into mild, moderate, severe and profound individuals. Age of the selected patients ranges between 1 to 22 years. A proforma, which incorporated clinical features, pedigrees as well as other useful information, was filled for each patient after consulting their parents. Blood samples were collected in sodium heparin vacutainer. Chromosomal preparations were made by using standard culture technique with modifications (15, 16). Slides were stained with Giemsa stain and well spreaded plates were selected for karyotyping. Images were taken by Leica Image analyzer and karyotypes were prepared manually. Karyotyping was done according to ISCN 'International system for human cytogenetic nomenclature 2016' classification and evaluated to find abnormalities.

Results

Pedigree analysis showed that frequency of MR children was found to be 13.6 percent. The majority of cases were of sporadic type (93.3%), only 6.7 percent mentally retarded children were of familial type. All familial cases showed X-linked recessive mode of inheritance (Fig. 1, 2). Majority of MR children were first born (63.3%) (Table 1).

Figure 1-2. Pedigrees of familial cases with X-linked recessive mode of inheritance

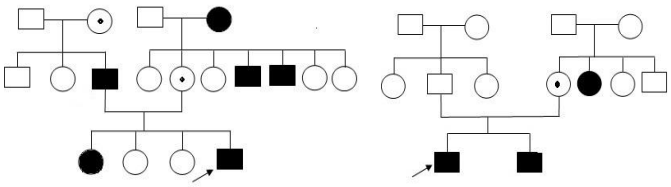


Table 1. Order in sibship in mentally retarded patients

Order in sibship	Total n=30
1	19(63.3%)
2	5(16.7%)
3	2(6.7%)
4	4(13.3%)

and most of them, born to the mothers in the age group 21-24 years (56.7%) (Table 2). Average maternal age was found to be 26 ± 5.7 years in 30 MR children. Average maternal age in male patients is 26± 5.0 years. Average maternal age in female patients is

25± 5.1 years. Only one case of consanguineous marriage (far cousins) was reported and had a child with Down's syndrome. Maternal illiteracy was found to be more (62%). Sex ratio was reported to be 2.3:1.

Table 2. Maternal age effect in mentally retarded patients

Maternal Age Group	Total n=30
<20	2(6.7%)
21-24	17(56.7%)
25-29	7(23.3%)
30-34	3(10%)
>=35	1(3.3%

IQ testing depicted that majority of individuals were mildly affected (40%) followed by severe (36.7%), moderate (16.7%) and profound (6.7%) (Table 3).

Table 3. Degree of MR in 30 mentally retarded individuals

Degree of MR	5-8	9-14	Above 14	%age
Mild	4	5	3	40%
Moderate	2	2	1	16.7%
Severe	2	7	2	36.7%
Profound	1	1	0	6.6%

MR was found to be associated with many clinical abnormalities e.g. speech disorders, mouth abnormalities (cleft palate, high arched palate, cleft lip, carp-shaped, thin lips etc.), eye abnormalities (strabismus, refractive errors etc.) (Table 4).

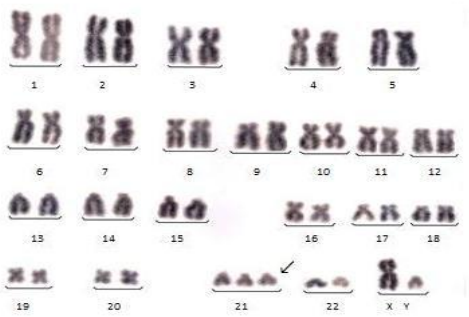
Table 4.Clinical features associated with mentally retarded cases in present investigation

S. No.	Clinical features	Present	Absent
1.	Speech disorders	18 (60%)	14(40%)
2.	Mouth abnormalities	8 (26.7%)	22 (73.3%)
3.	Eye Abnormalities	3 (10%)	27 (90%)
4.	Simian crease	6 (20%)	24 (80%)
5.	Obesity	3 (10%)	27 (90%)
6.	Ear abnormalities	8(26.7%)	22(73.3%)
7.	Under wt. after birth	2 (6.7%)	28 (93.3%)
8.	Premature birth	3 (10%)	27 (90%)
9.	High body temperature after birth	4 (13.3%)	26 (86.7%)
10.	High body temperature during pregnancy	1 (3.3%)	29 (96.7%)
11.	Neonatal jaundice	2 (6.7%)	28 (93.3%)
12.	Neonatal Pneumonia	3 (10%)	27 (90%)

13.	Epileptic seizures	8 (26.7%)	22 (73.3%)

The chromosomal investigation revealed that abnormalities were found in 18(60 %) of the subjected 30 MR patients and rest were compatible with normality. Among individuals with abnormal karyotypes, 14 were males and 4 were females and sex ratio was found to be 3.5:1. Numerical chromosomal abnormalities were reported in 10 patients with trisomy 21 (Table 4, 5, 6). The frequency of DS individuals was found to be 33.3 percent (Figure 3).

Figure 3. Karyotype of case no.1 with 47,XY, +21chromosomal constituition



Structural chromosomal abnormalities found in rest were i.e. deletions in 3 patients, inversion in 1 patient, translocations in 2 patients, ring 14 chromosome in 1 patient and marker chromosome in 1 patient (Table 5, 6) (Fig. 4-8).

Figure 4. Karyotype of case no.5 with 46,XX,8q$^-$ chromosomal constitution

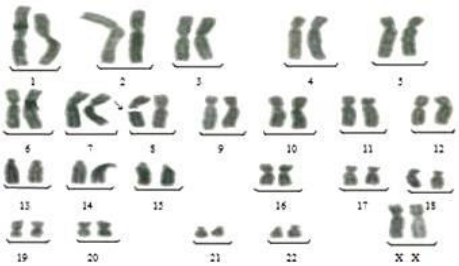
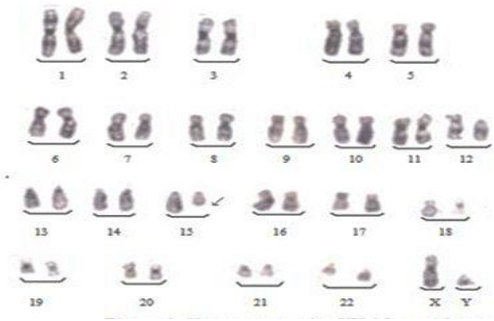


Figure 5. Karyotype of case no.6 with 46,XY,15q$^-$ chromosomal constitution



The cases of mosaics presented 46, XY, inv 9(p12;q13)(1%); 46 XY , 45,XX, tdic(2;21)(2%); 46,XX and 46, XY ,(+14r),-14, +M (1%); 46,XY karyotypes (Fig. 6,7,8).

Figure 6. Karyotype of case no.6 with 46,XY, inv 9(p12;q13) chromosomal constitution

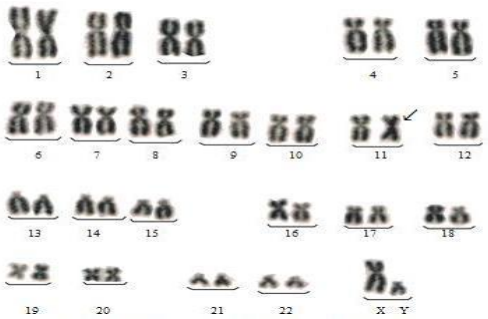


Figure 7. Karyotype of case no.11 with 45,XX, tdic(2;21) chromosomal constitution

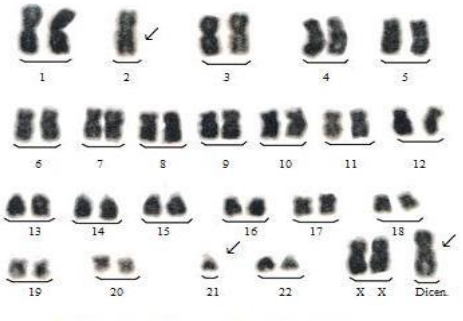


Figure 8. Karyotype of case no.14 with 46,XY, (+14r), -14,+M chromosomal constitution

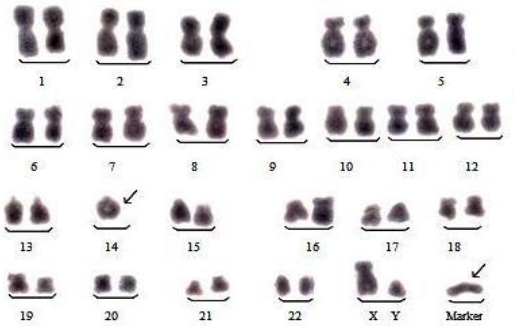


Table 5. Chromosomal abnormalities detected during screening

S. No	Abnormality	Total (n=18)
1.	Trisomy	10
2.	Deletions	3
3.	Inversion	1
4.	Translocations	2
5.	Ring Chromosome	1
6.	Marker chromosome	1

Table 6. Karyotype with constituition of MR individuals with chromosomal anomalies

S. No.	Sex	Age(yrs)	IQ	Karyotypic constitution
1.	Male	5	Severe	47,XY,+21
2.	Male	7	Severe	46,XY,t(15q ;17q)
3.	Male	9	Severe	47,XY,+21
4.	Female	14	Severe	46, XX,8q$^-$
5.	Male	6	Moderate	47,XY,+21
6.	Female	12	Severe	46,XX,15q$^-$
7.	Male	7	Moderate	46, XY, inv 9(p12;q13)(1%); 46 XY
8.	Male	11	Severe	47,XY,+21
9.	Male	7	Mild	47,XY,+21
10.	Male	16	Moderate	46,XY,-22,+M
11.	Female	13	Severe	45,XX, tdic (2;21)(2%); 46,XX
12.	Male	6	Mild	47,XY,+21
13.	Male	6	Mild	47,XY,+21
14.	Male	12	Severe	46, XY,(+14r),-14, +M(1%); 46,XY
15.	Male	10	Mild	47, XY, +21
16.	Male	13	Severe	46, XY,1pter$^-$
17.	Female	5	Mild	47,XX,+21
18.	Male	17	Mild	47,XY,+21

IQ scores of mentally retarded cases having chromosomal abnormalities were as 9 (50%) with severe mental retardation, 6(33.3%) with mild mental retardation, 3 (16.7%) with moderate mental retardation (Table 7). In mildly affected cases, causative diagnosis is unknown in 50 percent of cases. But in severe to moderate cases it is established in 81.8 and 60 percent of cases respectively.

Table 7. Degree of MR in 18 MR with chromosomal abnormalities

Degree of MR	5-8	9-14	Above 14	%age
Mild	4	1	1	33.3%
Moderate	2	0	1	16.7%
Severe	2	7	0	50%
Profound	0	0	0	0%

Discussion

In the present study, pedigree analysis resulted that majority of MR cases were of the sporadic type. Evidence of concordance, in familial cases, X-linked mode of inheritance is higher as compared to other (17,18). In present work, the majority of individuals were first in their order in sib ship. Likewise, three previous reports (19-21) found no association between birth order and abnormal karyotype. A study (22) has cited as support for the hygiene hypothesis, first born children are wide-open to fewer infection which

may undesirably affect neurodevelopment. Formerly it was held that risk of mental retardation increases with maternal age (23), but present study is in sharp contrast to previous ones, no maternal age effect was found in mentally retarded individuals. Majority of MR individuals were born to mothers in age group 21-24 years. This might be due to competing for nutritional needs of mother and the foetus, lack of family structure or lack of economic resources (24). Maternal education was found to be inversely related with MR. This finding corresponds well with various studies, which also demonstrated a strong inverse association between maternal education and prevalence of MR (23, 25).

In the present investigation, most of MR individuals were mildly affected, this information is contemporaneous with many previous reports (26-28). In the present study, the preponderance of male was found to be more towards mental retardation (29). Due to the accumulation of intelligence genes on X-chromosome, it can be speculated that the possibility of MR and exceptional intelligence is more frequent in males (30). In the present study, clinical diagnosis of 30 MR individual was done, it was found that mental retardation was found to be associated with speech disorders, mouth abnormalities, and abnormalities of eye, ear and other facial features. Other factors like seizures, neonatal jaundice, and neonatal pneumonia, the high body temperature of the child after birth and high body temperature of the mother during pregnancy were also found to be associated with mental retardation. This is in accordance with other studies published so far (31-36).

Chromosomal abnormalities were delineated in 18 individuals (60%). A previous work (37) has reported chromosomal anomalies in 15.3 percent individuals by the cytogenetic study of 173 individual. Another study (38) has observed genetic causes to be responsible in 31.5 percent cases with karyotypic anomalies. The reason behind this disparity is small sample size, variation in study design and stringent patient's inclusion criteria, which was followed here for the selection of MR patients to increase the detection yield of chromosomal abnormalities as recommended in a previous report (39). Some caution should therefore be implemented in interpretation of these differences**.**

Prevalence of syndromic MR was found to be greater as compared to non-syndromic MR. Most prevalent chromosome anomaly was found to be Down's syndrome, 10 (33.3%) and all patients have trisomy-21, cases with translocation and mosaicism were not reported. Our results were consistent with many previous studies carried by many investigators (40-42). In the present study, other autosomal anomalies e.g. deletions were observed in 3 patients. In this study, deletions were observed in 1 $pter^{-}$, $8q^{-}$, $15q^{-}$, chromosomes. Some of the most important deletion observed in human chromosomes are $4p^{-}$, $5p^{-}$, $9p^{-}$, $11p^{-}$, $11q^{-}$, $13q^{-}$, $18p^{-}$, and $18q^{-}$ (43). A report (44) detected an $8q^{-}$ subtelomeric deletion in an idiopathic mentally retarded subject. Terminal deletion in p arm of chromosome no 1 is most common deletion (45-48), which was found in 13 years old male with developmental and intellectual disabilities.

Ring (14) was observed along with an acentric fragment (marker chromosome), in a female patient with short stature, epileptic seizures and microcephaly. Many scientists have reported its presence in MR individuals (49-51). In a female MR patient, dicentric chromosome which is one of the rare abnormality, was observed. Dicentric autosomes are encountered exceptionally in cases with Robertsonian translocations. A dicentric formed from a translocation between chromosome 2 and 21 has not apparently been previously reported. We also observed marker chromosome in 1 patient, which was reported in MR patients in a study done so far (52). Inversion in chromosome 9 is also associated with genetic diseases (53-55). In this investigation, a 9 years old female with MR had this chromosomal abnormality. Of note, the majority of individuals having abnormal chromosomal complement were severely affected and this information is concomitant to fore-published reports (56-58). Diagnostic yield was found to be greater in severely

affected individuals as compared to other degrees of MR, this information is in line with previous studies done so far (59-60).

Conclusion

From the foregoing discussion, author concluded that there is a bewildering array of causes of MR, it can be caused by both genetic and non-genetic factors or it is a heterogeneous disorder. The concurrence of a number of minor anomalies and the probability of chromosomal abnormalities is proved to be an important modality for diagnosis of MR. The severity of MR and the presence of congenital abnormalities increase the diagnostic yield of chromosome anomalies. Those patients for whom etiology of MR is unknown; they might have other cryptic abnormalities which can't be ascertained by conventional karyotyping. These patients need reevaluations as new diagnostic techniques i.e. fluorescent in situ hybridization (FISH) or multiplex ligation-dependent probe amplification (MLPA) techniques and newer chromosome microarray or comparative genomic hybridization technique (array-CGH) are available nowadays.

The present work is a preliminary step towards revealing the subtle causes of mental retardation in population of Himachal Pradesh, which will help in specific diagnosis of these patients and will provide a better understanding of the possible reasons of pathogenesis, thus providing more true information to families on recurrence risk, prognosis, promising management options and prenatal diagnosis. This is ascribed to the fact that Indian subcontinent has relatively higher incidence of MR as compared to developed countries. It is customary to put more efforts to combat the incidences of mental retardation by using new techniques with high resolution for chromosomal analysis so that this problem can be diagnosed as earlier as possible.

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