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Chromosomal Abnormalities in Mental Retardation: Indian Experience

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ABSTRACT At a Tertiary Genetic Centre, children with mental retardation (MR) (also referred as intellectual disability) and associated developmental disabilities were investigated for genetic diagnosis which is important in prevention and genetic counseling while offering the risk of recurrence to the family. A prospective and retrospective cytogenetic study was conducted on 1760 MR cases for chromosomal abnormalities using routine GTG and high resolution banding methods of karyotyping. Out of 1760 MR cases, 555 cases showed abnormal chromosomal constitution (31.5%), and males were more than females (2.1: 1). Numerical chromosomal abnormalities were detected in 40.4% (224 of 555), out of which autosomal abnormalities were 36% (199 of 555) and sex chromosomal abnormalities were 4.5% (25 of 555). Structural chromosomal abnormalities were detected in 52% (289 of 555), out of which autosomal abnormalities were 28.6% (159 of 555) and sex chromosomal abnormalities were 29.5% (164 of 555), with some having both numerical-structural (7.6%) and autosomal-sex abnormalities (1.4%). The chromosomal study revealed Down syndrome as the most common chromosomal abnormality i.e. 45% (250 of 555). The children varied from mild to severe mental retardation with and without multiple congenital anomalies and dysmorphism. A few genetic syndromes with characteristic clinical features were also confirmed due to chromosomal aberrations. Genetic counseling was provided to the family members explaining the importance of recurrence risk, the need for prenatal diagnosis in subsequent pregnancies, along with the management of MR children in Indian set-up.

INTRODUCTION

Genetic disorders have been a great burden on the society since the beginning of the civilization and with the human genome project completed, the genetic services are being integrated with the other health care services. Mental retardation (MR), also referred as 'Intellectual Disability', 'Mental Deficit', 'Mental Subnormality' or 'Mental Handicap' means delay in mental development; it means an impairment of the intellectual processes of the mind, making it difficult for the person to cope with environment in which they find themselves. In 1992, the American Association on Mental Retardation (AAMR) revised the definition as significantly sub average intellectual functioning (defined as an I.Q. score below 70) existing concurrently with limitations in two or more of the following adaptive areas like communication, self care, home living, social skills, self direction, health and safety, leisure, work and functional academics (Grossman 1977; Epstein 1996).

Despite extensive studies in area of mental retardation the overall prevalence of MR is still not known with certainty. It is approximately 1-3% (Munro 1986; DeVries et al. 2005) and in India too it is estimated to be 2 – 3% of the population (Kaur et al. 2003).

Chromosome abnormalities are visible alteration of chromosomes. Alternatively these are produced by specific chromosomal mechanism. Errors in mitosis and meiosis may result in chromosomally abnormal daughter nuclei containing either the wrong number of chromosomes or structurally altered chromosomal complement (Hamerton 1971). Most aberrations are produced by mis-repair of broken chromosomes, improper recombination or improper segregation of chromosomes. Chromosome complements are subject to two kinds of changes-(1) numerical and (2) structural and they may affect either sex chromosomes or autosomes. In rare cases both kinds of chromosomes are affected.

There are over 100 chromosomal syndromes, which have been reported. While, on the individual basis many of these are rare, together they make a major contribution to human

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morbidity and mortality (Mueller and Young 1995). The impact of chromosomal abnormalities is greatest during fetal life with highest frequency (Seashore and Wappner 1996), and cause 50–60% of fetal wastage in 1st trimester (Purandare 2002). The frequency of various chromosomal abnormalities is quite different in neonates (0.7%) as compared to abortuses (about 50%), since some aneuploidies are lethal in utero (Thompson et al. 1991). The major autosomal abnormalities share a number of phenotypic features like mental retardation, cardiac malformation and growth deficiency. While there is variability within every cytogenetic syndrome, neonatal death and serious congenital malformations are frequent manifestations. Chromosomal abnormalities occur in 6% of all recognized congenital malformation. It also accounts for 30-40% of severe mental retardation, and 10% of mild mental retardation (Raynham et al. 1996; Ahuja et al. 2005). Most of the cytogenetic syndromes due to distinguished features allow the clinician to suspect the condition (Seashore and Wappner 1996).

The present study was undertaken to investigate the different types of chromosomal aberrations and their relative frequencies in a group of MR cases with suspected genetic disorders in Indian population, and to identify precisely the role of cytogenetic investigation in confirming the diagnosis, thus allowing the proper genetic counseling.

MATERIALS AND METHOD

During the period 1992-2006, total 1760 cases were referred to CREMERE with age ranging from 1 to 30 years for chromosomal analysis who had mental and/ motor delay, language, speech and communication disorders and behavioral problems. A genetic team comprised of pediatric neurologists, geneticists, clinical psychologists, research personnel and special educators. The psychological evaluation revealed mental retardation (IQ<70). Dysmorphic features, congenital anomalies, or recognizable clinical genetic syndromes were recorded.

Assessment of MR: It is important to confirm whether the IQ is below 70 to identify the child as a mentally retarded according to DSM IV criteria (APA 1994). The clinical psychologist evaluated all cases using the standard battery of tests which included: Infant Bayley Scale for Development, Vineland Social Maturity Scale, Wechsler Intelligence Scale for Indian children or Kamat's Binet Test of Intelligence for assessing development quotient (DQ), intelligent quotient (IQ), social quotient (SQ) and were classified into below average, mild, moderate or severe retardation according to the guidelines given by American Psychiatric Association (AAMR 1992).

Cytogenetic Method: Phytohemaglutinin stimulated lymphocyte cultures for G-banding method of karyotyping were set up using the peripheral blood using 2 ml sodium heparinized intravenous blood; harvested and the slides for metaphase study were prepared (Moorehead et al. 1960); the slides were stained using Giemsa stain, (Hungerford 1965; Seabright 1971). The separate lymphocyte cultures were also set up for High Resolution Banding using Ethidium bromide method (Rybak et al. 1982), which shows more chromosomal bands (about 400-600), in comparision with the routine G-Banding Method (about 250- 300). It helped in studying structural variations better than G- banding. Metaphases were studied under oil immersion lens (100 X) in Zeiss microscope and were captured using KaryoImager Version V 1.0. For each sample, 40-50 metaphases were screened for abnormal chromosomal changes (about 100 metaphases in case of suspected Fragile-X syndrome), which were designated according to the International Standard Nomenclature (ISCN 2005). The length of Y chromosome was measured using the Y/F index ratio.

RESULTS

The cytogenetic analysis of both GTG and high resolution banding metaphases was conducted. Out of total 1760 karyotype cases consisting of males- 1071(60.8%) and females-689 (39.2%), 555 cases (31.5%) (Table 1) showed major and minor chromosomal abnormalities where 377 were males (67.9%) and 178 were females (32.1%). Further analysis revealed numerical chromosomal abnormalities to be 40.4% (224 of 555), out of which autosomal abnormalities were 36% (199 of 555) and sex chromosomal abnormalities were 4.5% (25 of 555). The structural chromosomal abnormalities were detected in 52% (289 of 555), out of which autosomal abnormalities were 28.6% (159 of 555) and sex chromosomal abnormality were 29.5% (164 of 555), which consisted of more of Y chromosome variations (long Y/ short Y/ inv Y).

Table 1: Chromosomal aberrations –31.53% (n=555 of 1760 MR cases)

Chromosomal abnormality	*Numerical*	*Structural*	*Numerical and structural*	*Total*
Sex	25 (4.5%)	164(29.5?%)		189(34%)
Autosomal	199(36%)	159 (28.6%)		358(64.6%)
Sex and Autosomal				8(1.4%)
Total	224(40.4%)	289(52%)+34*	42(7.6%)	555

*34 cases are involved in both sex/ autosomal and numerical/structural

Fig. 1(a). Two brothers with Fragile-X syndrome

A few cases had both numerical- structural (7.6%) and autosomal -sex abnormalities (1.4%).

The chromosomal study revealed Down syndrome as the most common chromosomal abnormality i.e.45% (250 of 555). There were 144 males (57.6%) and 106 females (42.4%). The incidence of Down syndrome was found to be 1 in 2.2 MR cases.

Free trisomy was found in 88.8% (222 of 250), mosaic cell line was found in 8% (20 of 250) and translocation was seen in 3.2% (8 of 250). Other variations/ abnormalities were also seen in the Down syndrome patients namely 9qh+(9 cases),

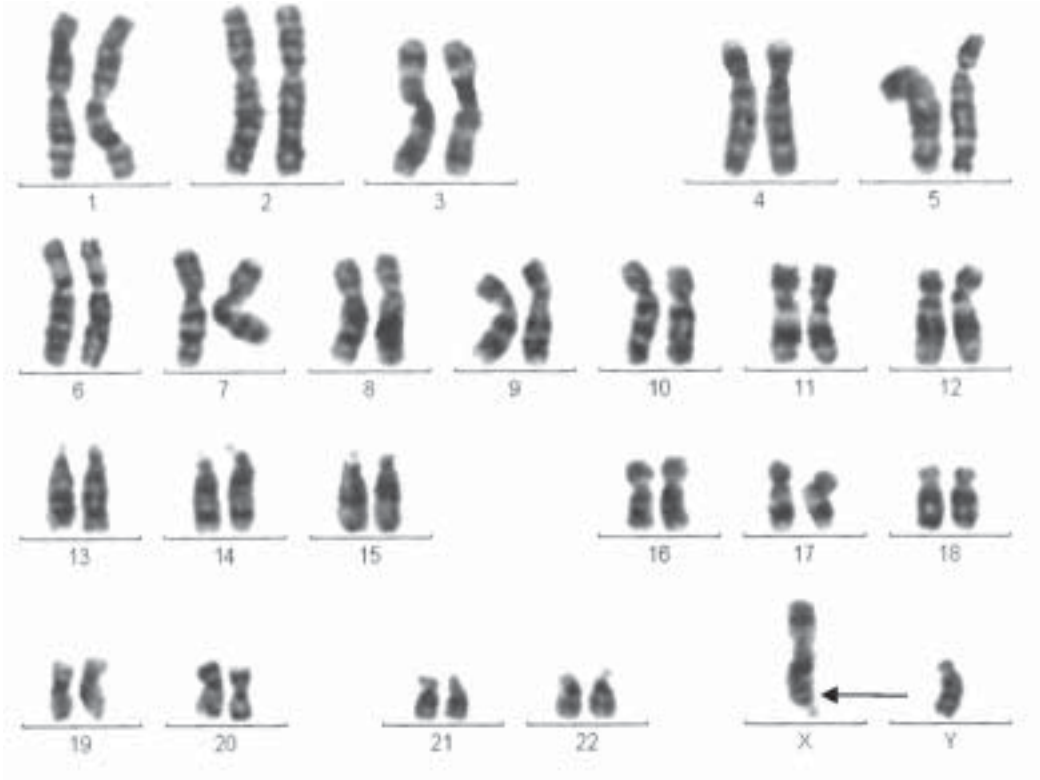

Fig. 1(b). Karyotype 46,XY/46, fragXq27.3 Y(14%) with a Fragile site in X (arrow).

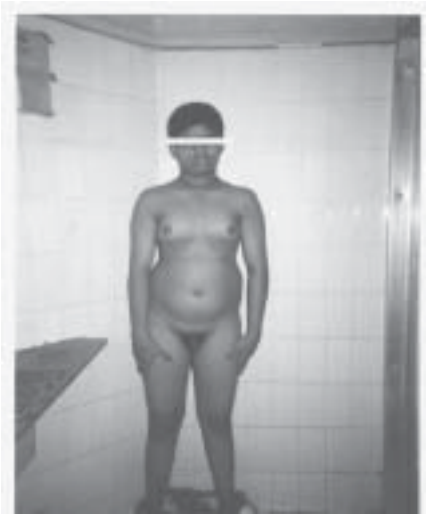

Fig. 2(a) A patient with Klinefelter syndrome showing breast development.

15p+ (3 cases), 14p+(2 cases), 13p+(1case), 22pstk +(1 case), inv9(2 cases), t(1q;5q) (1 case), small Y(6 cases), long Y(4 cases) and inv Y(2 cases).

Among the other genetic syndromes, the precise diagnosis could be achieved due to well known specific chromosomal abnormality that is, Fragile-X syndrome (46,XY/46, fragXq27.3 Y) found in 2.7% (Fig. 1-a and b), Klinefelter syndrome (46,XXY) (Fig.2-a and b), Turner syndrome (45,X), Cri-du –Chat syndrome (46,XX, del 5p), XYY syndrome (46,XYY), XXX syndrome (46,XXX), Angelman syndrome (46,XY, del 15p), WAGR syndrome (46,XY, del 11p13), Trisomy 9p syndrome (47,XX, +9p), and 46 XY female. A few other genetic syndromes showed chromosomal variants that is, Coffin Lowry syndrome (46,X, invY), CATCH Syndrome, Cornelia de Lange syndrome (46,X, invY) (Fig. 4-a and b), Lowe syndrome (46,X, smallY), Noonan syndrome (46,XX,14p+,15p+), Rubinstein Taybi syndrome (46,XY,15p+), Russel Silver syndrome (46,X, smallY); and Sotos syndrome (46,X,small Y).

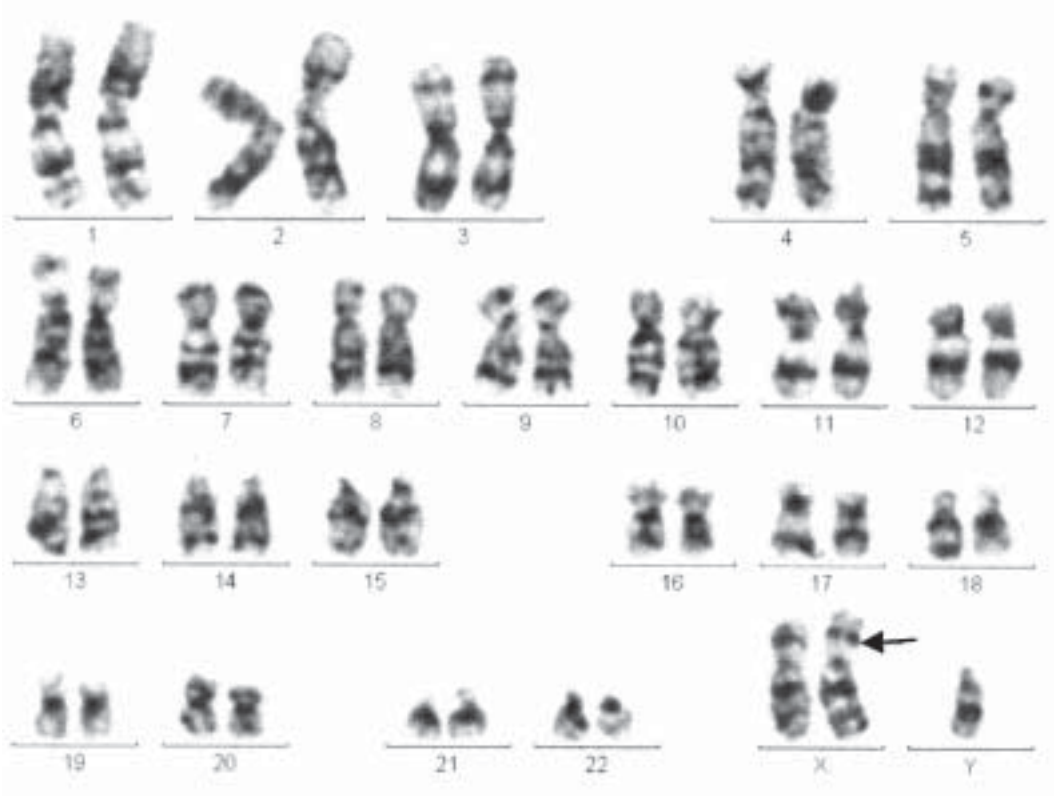

Fig. 2(b) Karyotype of the same patient showing - 47,XXY (arrow).

Fig. 3(b)

Fig. 3(a). A patient with CATCH –22 syndrome with dysmorphic facial features.

Important findings of this study were the rare chromosomal aberrations found in the phenotypically described rare genetic syndromes: i.e. Treacher–Collin syndrome [46,XY,t (12p;17q)? dup12p], CATCH –22 syndrome (46,XX,3p+) (Fig. 3a and b), Robinhow syndrome (46,XX,11p+), Trichodent Osseous syndrome/ Killian Teschler Nicholas syndrome [46,XXt (3p;12q)].

Mosaic cell line was found in 6.1% of the cases (34 of 555) showing various chromosomal abnormalities. A few of them were single cell abnormality (Table 2). Turner syndrome mosaic cell line was found in 6 cases, Klinefelter mosaic cell line and XYY syndrome mosaic cell line were found in 1 case each. The most common mosaic cell line observed was with t(7;14) in 7 cases.

Further analysis revealed translocation in 5.7% cases (34 of 555) of which 8 cases were of translocation trisomy 21. Robertsonian translocation was found in 13 of 34 cases (38.2%), whereas the other 21 cases (61.8%) revealed

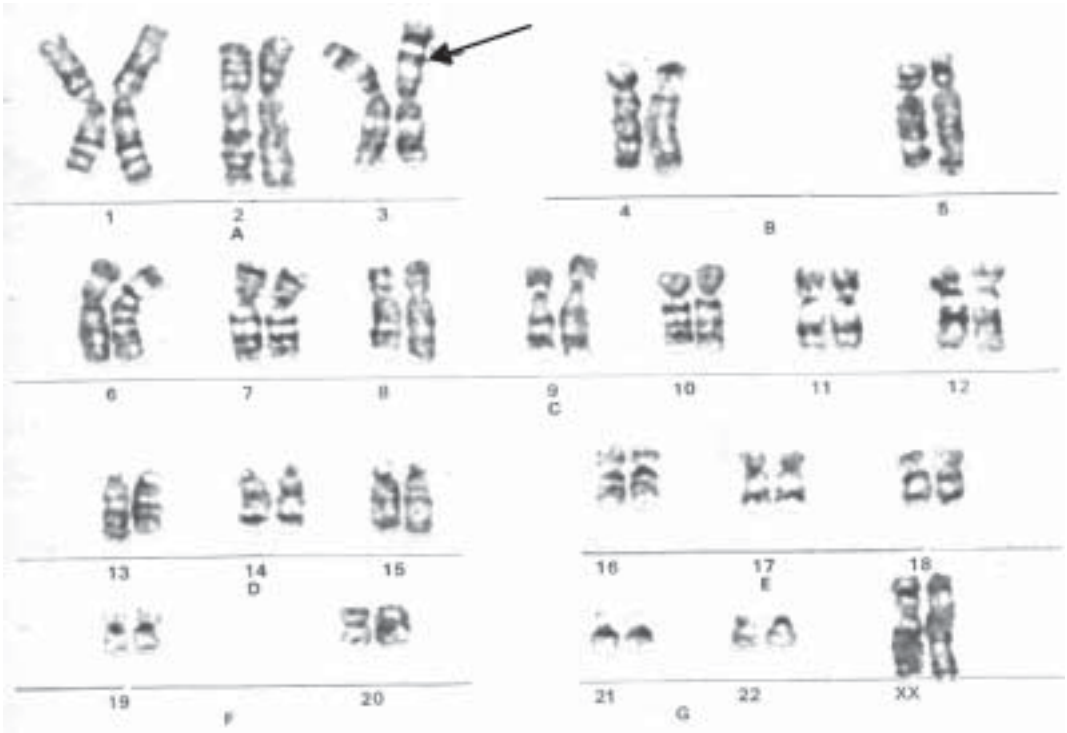

Fig. 3(b). Karyotype of him showing 46,XX,3p+ (arrow).

Fig. 4(a). A patient with Cornelia de Lange syndrome showing characteristic bushy eyebrows, crowding of facial features, microcephaly, thin upper lip-line.

reciprocal translocation (Table 3). The most common chromosomes involved in translocations were chromosome 21 and 14 among acrocentric chromosomes, and 3, 10, 11, 12 and X among others. In Down syndrome too, there was 3.2% translocation seen and the common was t(14;21) followed by t(13;21) and t(21;21).

There were various other structural abnormalities observed as listed below:

1) *Deletions* - (5.2%)(15 of 289): del 7q, del 18 p, del 16q12.2(6 cases), del Xq (2 cases), del 22q, del 2p, del 12p, del5p (2 cases).

2) *Additions*-(2.1) (6 of 289): 4q+, 5p+, 6q+,9p+,11p+,16q+

3) *Breaks*-(1.7%)(5 of 289): brk 2q, brk 5q, brk 7q, brk 12p, brk 14q

4) *Insertion*- (0.3%) (1 of 289): ins 2p

5) *Inversion*- (7.2%)(21 of 289):inv 8(2 cases), inv 9(16 cases), inv11, inv 17, inv X

6) *Fragile Sites*- (6.5%) (19 of 289): frag Xq(15 cases), frag 2q, frag6q, frag Xp, frag 8q

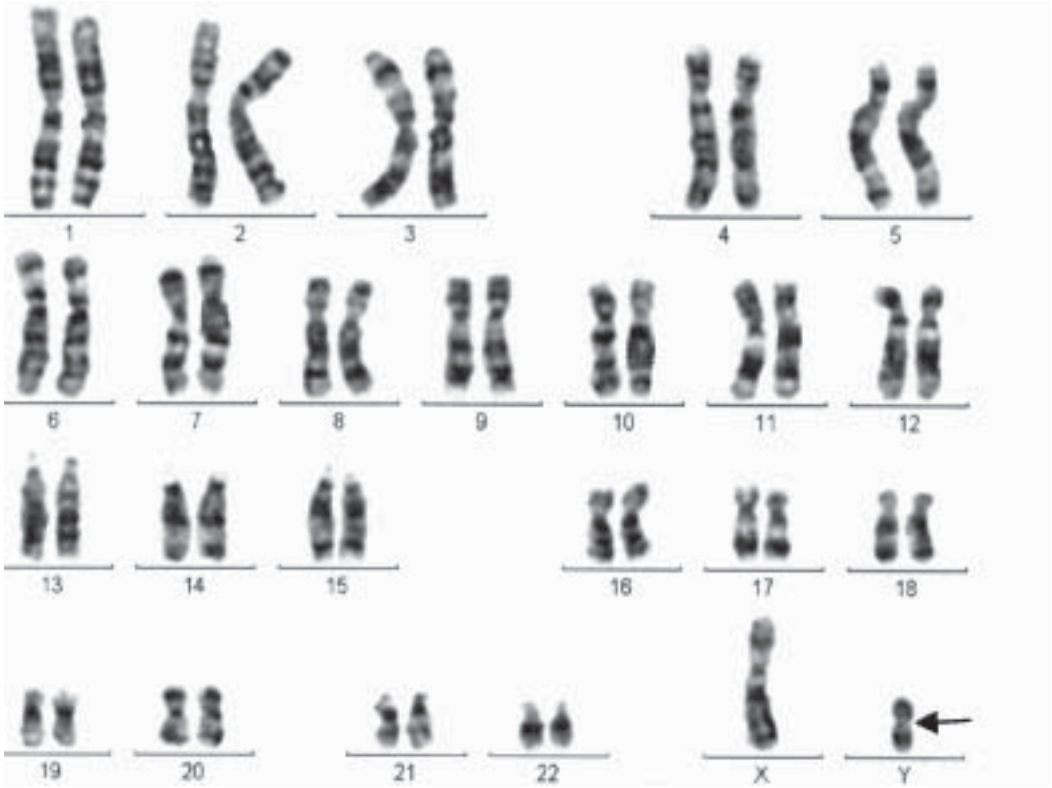

Fig. 4(b). Karyotype of the same patient showing-46,X, invY (arrow).

Table 2: Chromosomal aberrations with Mosaic cell line-6.1%(n=34 of 555cases)

46,XX/46,X frag Xp(9%)/ 46,X, del Xq25(4%)/ 46,XX, frag 6p & 6q (4%)	46,X, small Y/46,X, small Y, frag 15q(4%)/ 46,delXq small Y(2%)
46,XY/ 46,XY,frag 5p(4%)/46,XY, brk 3p(6%)	46,XY,9qh+/46,XY,9qh+, inv8p(9%)
46,XX/46XX, brk 3p(12%)	46,XY,9qh+/45,XY,9qh+ der(15;20)(43%)
46,XX/46,XX,16q+(15%)	46,XX/46,XX, t(7q;14q) (2%)
46,XX/46,XX,del 12p (6%)	46,XX/46,XX, t(7q;14q) (2%)
46,XY/46,XY del 15q (15%)	46,XY/46,XY,t(7p;14q)(4%)
46,XX/47,Xxy(2%)	46,XY/46,XY,t(7p;14q)(4%)
46,XX/ 46,XX,del 10q25 (10%)	46,XY/46,XY,t(7q;14q) (2%)
46,XX/46,XX brk 3p (4%)	46,XY/46,XY,t(7q;14q)(2%)/46,XY,t(13q;17q)(2%)
46,XY/46,XY, frag9p22(2%)	46,XY/46,XY,t(7q;14q)(6%)/46,XY,t(18q;21q)(2%)
46,XY/46,XYfrag6qter(2%)/46,XY,del 9q(2%)	46,XY,inv 8p/46,XY,inv 8p,t(3q; 14q) (2%)
46,XX/46,XX, brk 19(2%)	46,XX/46,XX,t(14p;22q)(2%)
46,XY/47,XYY (6%)	46,XX/45,X(4%)
46,XX/46,X del Xq27 (26%)	46,XY(45,X(8%)
46,XY, inv9p/46,X Ys+,inv 9p(10%)	46,XX,/45,X(4%)
46.XX/46,XX, del 16q12.2(30%)/ 46,X, del Xq (6%)	45,X /46,X,ring (X)(2%)
46,X,small Y/45,X(2%)	46,X, small Y /45,X(8%)
46,XX/46,X frag Xp(9%)/ 46,X, del Xq25(4%)/ 46,XX, frag 6p & 6q (4%)	46,X, small Y/46,X, small Y, frag 15q(4%)/ 46,delXq small Y(2%)
46,XY/ 46,XY,frag 5p(4%)/ 46,XY, brk 3p(6%)	46,XY,9qh+/46,XY,9qh+, inv8p(9%)
46,XX/46XX, brk 3p(12%)	46,XY,9qh+/45,XY,9qh+ der(15;20)(43%)
46,XX/46,XX,16q+(15%)	46,XX/46,XX, t(7q;14q) (2%)
46,XX/46,XX,del 12p (6%)	46,XX/46,XX, t(7q;14q) (2%)
46,XY/46,XY del 15q (15%)	46,XY/46,XY,t(7p;14q)(4%)
46,XX/47,Xxy(2%)	46,XY/46,XY,t(7p;14q)(4%)
46,XX/ 46,XX,del 10q25 (10%)	46,XY/46,XY,t(7q;14q) (2%)
46,XX/46,XX brk 3p (4%)	46,XY/46,XY,t(7q;14q)(2%)/46,XY,t(13q;17q)(2%)
46,XY/46,XY, frag9p22(2%)	46,XY/46,XY,t(7q;14q)(6%)/46,XY,t(18q;21q)(2%)
46,XY/46,XYfrag6qter(2%)/46,XY,del 9q(2%)	46,XY,inv 8p/46,XY,inv 8p,t(3q; 14q) (2%)
46,XX/46,XX, brk 19(2%)	46,XX/46,XX,t(14p;22q)(2%)
46,XY/47,XYY (6%)	46,XX/45,X(4%)
46,XX/46,X del Xq27 (26%)	46,XY(45,X(8%)
46,XY, inv9p/46,X Ys+,inv 9p(10%)	46,XX,/45,X(4%)
46.XX/46,XX, del 16q12.2(30%)/ 46,X, del Xq (6%)	45,X /46,X,ring (X)(2%)
46,X,small Y/45,X(2%)	46,X, small Y /45,X(8%)

Table 3: Chromosomal Translocations – 5.7% (n=24 of 555 MR cases)

46,XX,t(11p14;16q23)	46,XY,t(1p;2q)	46,XX,t(3q 21;12q24.1)
46,XX,t(11q;16q)	46,XX,t(2p;4q)	46,XX,t(3p21;12q24.1)
46,XY,t(3q26.1;11q24.1)	46,XY,t(11q24; 22q12)	46,XX,t(3p21;12q24.1)
46,XY,t(10q23.1;13q34)	46,XY,t(3q;14q)	45,XY,t(14p;21p)
46,XY,t(10q22;13q10)	46,XY,t(12q24;14q24)	45,XY,t(14p;21p)
46,XY,t(5p15.1;18q11.1)	46,XY,t(12q24;14q24)	45,XX,t(14p;21p)
46,XY,t(Xp;9q)	46,XX,t(Xq;10q)	45,XY,t(15p;21p)
46,XY,t(12p;17q)	46,XX,t(Xq22;1p22)	45,XY,t(13q;14q)

Table 4: Degree of Mental Retardation –n=232 of 555 MR cases

Degree of Mental Retardation	*Intelligence Quotient (I.Q.)*	*No. of patients (41.8 %)n= 232 (of 555)*
Severe mental retardation	Less than 35	66 (%)
Moderate mental retardation	35-55	62 (%)
Mild mental retardation	55-70	86 (%)
Dull normal/ Borderline	70-90	16 (%)

7) *Multiple Breaks*- (1.4%) (4 of 289):1,3,9,11(1 case), 6,20,Y(1 case),1,4,6,9,16,Y (1 case)

8) *Increase in heterochromatin region/ satellite/stalk*-9qh+(10 cases), 22ps+(7 cases), 22pstk+(1 case), 15ps+(3 cases), 21ps+(3 cases),13ps+(1 case).

The structural abnormalities were found to be predominant due to variation in the length of Y chromosome (142 of 289) being 49% when Y/F index ratio was used. Abnormalities consisted of 56.3% small Y (80 of 142), 30.3% long Y (43 of 142) and 13.4% metacentric /inversion Y (19 of 142).

The psychological evaluation could be conducted only in 41.8%of the cases (232 of 555) which showed mild to severe mental retardation (Table 4).

DISCUSSION

About 1 in 200 babies are born with chromosomal abnormality (March of Dimes 2001), but in only 30% of cases a specific diagnosis can be identified. Greater the degree of MR (moderate-severe as compared to mild), the more likely are cases of genetic, and chromosomal, disorder (Agostoni 2000). However, the mild retardation had revealed 86% chromosomal abnormality as compared to 66% in severe retardation in the present analysis indicating the need of karyo-typing in all types of MR cases.

The most single and important prerequisite for genetic counseling is accurate diagnosis. The critical region in the chromosomes is very useful in correlating the genotype-phenotype and defining a particular genetic syndrome. High resolution banding was found essential to depict these critical regions.

A positive family history of stillbirths, or multiple spontaneous abortions, congenital anomalies/ birth defects and mental retardation was found to be a strong indicative factor for cytogenetic investigations. Various congenital malformations observed were correlated with chromosomal anomaly. In the present 14 year study, the chromosomal aberration in mentally retarded children was 31.5%; more than the other reported studies possibly due to HRB technique, that is, 15% (Rauch et al. 2006), 16% (Navsaria et al. 1993) and 28.3% (Goud et al. 2005). A similar high frequency (40%) of chromosomal abnormalities was reported among 120 patients (Kenue et al. 1995). The higher incidence of chromosomal abnormalities demonstrated the importance of cytogenetic evaluation in every MR patient with/without dysmorphic features and congenital anomalies (Narahara 1981). The characteristic dysmorphic features noted in Down syndrome were mongoloid slant, Simian crease, epicanthal folds, flat facies, low set small ears and hypotonia.

The frequency of Down syndrome (DS) was 45% amounting to 1 in every 2.2 MR children reflecting higher frequency and need for prevention by prenatal diagnosis. Its well defined phenotypic features and congenital anomalies made it easier to diagnose this syndrome clinically. Presence of trisomy 21 in 88.8%, translocation in 3.2% and mosaic cell line in 8% was supportive of the published literature (Murthy et al. 2007). The mosaic trisomy was found more (8%) than those reported in the literature, e.g. Even Kava et al. (2004) reported 95% free trisomy, 3.2% translocation and 1.8% mosaic cell line among Down syndrome patients, possibly due to large number of samples.

Missing or extra sex chromosome (X and Y) affects sexual development and may cause infertility, growth abnormalities, behavioral and learning problems. The sex chromosome related syndromes were common with numerical abnormalities like Turner syndrome, Klinefelter syndrome, XYY syndrome and XXX syndrome, and there was one case of 46, XY female wherein genetic counseling was found very crucial while advising on special training, future recurrence risk and fertility aspects as such patients are often referred for lack of secondary sexual characteristics, behavioral and learning disabilities and not for mental retardation.

The structural abnormalities largely consisted of Fragile-X syndrome patients in 2.7%, this being the next common (second to Down syndrome) genetic cause for mental retardation, representing 30% of X-linked MR (Hagerman and Cronister 1996) and causing a broad spectrum of learning and behavioral problems. They had mental deficiency, mild connective tissue dysplasia, macro-orchidism, prognathism and large ears. A few reports from India on Fragile-X syndrome showed varied incidence pattern ranging from 5-19% (Chetan et al. 2002). The early detection in a family becomes important as it is maternally inherited due to expansion of CGG repeats. The other female sibs, carriers of premutation in the family, also need screening for which the family requires appropriate genetic counseling. Often, males show autism, ADHD, hyperactivity and learning disability whereas the girls show anxiety disorder and social phobia. The screening of all MR boys for Fragile X syndrome opted in some countries is to reduce the burden of MR with a thrust on early detection and prevention. This is a vital message to physicians in Indian scenario who often know three generations of the family history, including disability.

The high resolution banding method used was helpful in the detection of many more deletion syndromes and genotype-phenotype

correlation was possible. A few rare syndromes showed new, previously not reported chromosomal abnormalities which could be due to single gene defects or mutations at the gene level. Since chromosomal rearrangements (loss or gain) appear very small from a cytogenetic perspective, these involve multiple genes that independently contribute to the phenotype and MR. Mosaic cell lines observed in 6.1%; many with major abnormalities and a few with chromosomal variants, especially mild mental retardation.

Translocations seen in 5.7% cases were either robertsonian or reciprocal and were either balanced or unbalanced. Association of translocations with bad obstetric history, fertility failure, amenorrhea, ambiguous genitalia, mental retardation with multiple congenital anomaly or Down syndrome is well documented by many investigators. The finding of a translocation in a parent is an indication for prenatal diagnosis in all the future pregnancies with possible rare exception of 21;21 translocation. No balanced zygote can be produced by the carrier of this translocation, and the possible outcome of pregnancy is either 21 monosomy (probably lethal with early abortion) or 21 trisomy. Clinically the most important single Robertsonian translocation involves chromosome 14 and 21 and 2% to 3% of Down syndrome are affected as a result of this translocation. If Robertsonian (centric fusion) translocation involves homologous chromosomes, the prognosis is hopeless. All liveborns resulting from t(13;13) or t(21;21) are abnormal, with either trisomy 13 or trisomy 21, and all other conceptions (for example monosomies) terminate in spontaneous abortion. Homologous translocations involving numbers 14, 15 and 22 result in abortion only (Simpson and Golbus 2003).

The other most common Robertsonian translocation involves chromosome 14, less commonly chromosome 22, occasionally two 21 chromosomes translocate onto each other (Harper 1988) which was seen also in our study. Robertsonian translocations between chromosomes 14 and 21 are of particular clinical relevance. An individual with this translocation could have a child with three copies of chromosome 21, resulting in Down syndrome (trisomy 21). Women who carry this translocation have approximately 10% risk of giving birth to a baby with Down syndrome; men who carry this translocation have 1-3% risk. Down syndrome due to a translocation shows no relation to age, but a parent with a balanced Robertsonian translocation who already has Down syndrome child has a relatively higher risk (10-30%) of having abnormal affected children (Simpson and Biscchoff 2002; Scriven et al. 2001). The acrocentric translocations were also found in 38.2% patients who were not affected with Down syndrome, here too t(14;21) was common along with one case of t(15;21) and t(13;14).

When chromosome abnormalities present in parents is balanced or otherwise clinically silent form, they also have the potential of producing live-borns with unbalanced karyotypes and birth defects. Therefore when a translocation is found in a pregnancy loss, parental karyotypes must be done to determine whether it is inherited or *de novo* in origin.

Chromosomal abnormality in a single cell is considered important and reported by some cytogeneticists when more metaphase spreads are analysed on suspicion of the abnormality. Translocation t(7;14) was the most frequently noticed reciprocal translocation. Translocations may lead to repositioning of genetic material and in some instances can change the cell behavior or function in some unexplained manner and may lead to variable phenotypic expressions (Hecht et al. 1975). These isolated translocations may be indicators of mosaicism and a need of analyzing other tissues like fibroblasts or gonads is stressed (Rao and Kar 1999). A relatively higher incidence of translocation 7;14 in the present study may explain the location of the breakpoints and the size of the translocation segment of the chromosome, probably playing a role in determining the phenotypic expression. Reddy and Thomas et al. (1985) reported that increased chromosome breakage of t(7;14) in individuals not known to have any malignancy or predisposition suggest that this may be seen in routine cytogenetic procedures due to the influence of viral aetiological agents or alteration in DNA repair mechanism or extraneous factors like PHA involved in the *in vitro* culture. The reciprocal translocations may have no relation to the phenotype if the translocation is apparently balanced, except mental retardation. Sometimes, the abnormal phenotypes may be due to the loss of a few genes or unrelated balanced rearrangement (Sasikala 1989).

Various investigators have studied the possible mechanisms involved in the production of

spontaneous chromosomal mutations. Tharapel et al. (1985) supported the view that majority of chromosomal mutations arise *de novo* from the errors occurring during male and female gametogenesis. Hamerton (1971) opined that spontaneous chromosomal breakage may occur at random. The time taken for the restitution of these may vary in different chromosomal regions. If the ends of two different chromosomes are in close proximity, then such regions may be susceptible to exchange, a process by which the breaks are healed more rapidly. Second possibility may be the presence in one of the parents of an undetected cell line for the translocation, which was not restricted to gonadal tissue (Niebuhr 1974).

The other common translocations found similar to that reported in the literature were t(11;22), t(11;16),t(1;2) but showed variable phenotypes. Other common translocation seen were t(12;14), t(10;13) and (3;12) with hardly any published reports. Translocations related with male infertility (Guichaoua et al. 1992) and recurrent spontaneous abortions (Thanemozhi et al. 1997) are noted whereas translocations in mental retardation is hardly dealt and there appears only few reports. We noticed a few novel translocations with mental retardation along with dysmorphic features.

Structural abnormalities of Y- chromosome do not lead to specific mental retardation syndrome but are of great significance in male infertility. Y chromosome microdeletions occur in 10-20% of men with oligospermia (Purandare 2002). Hou and Wang (1999) in their study of human Y chromosome polymorphism in Taiwan demonstrated that there are no indications that Yq+, inv Y and Yq- are connected to any deviation in intelligence or with an increased risk of physical malformation or other chromosomal disorders. Conversely, Salo and co-workers (1995) reported 46,X, small Y in MR patients with dysmorphic features such as small chin and mouth, high-arch palate or cleft palate, downward slanting eyes, palpebral fissures, high nasal bridge and malformed ears. Interestingly, in our study a large number of MR children showed small Y(56.3%), long Y(30.3%) and inv Y (13.4%) and a true significance of which can only be understood by the latest molecular techniques like array CGH.

Structural and numerical aberrations involving both paracentric and pericentric inversion of chromosome 9 is well known among subjects with mental retardation (Sasikala 1990) and reported to be in 7.2% MR cases. Most of the pericentic inversions observed do not give rise to any specific phenotypic abnormalities. However, pericentric inversion has been found to be associated with infertility, repeated fetal loss, congenital anomalies and mental retardation, possibly as a predisposing factor for non-disjunction and inter-chromosomal effect (Gardner and Sutherland 1996; Krishna et al. 1992). Many of the chromosomal aberrations especially related to the heterochromatin region, namely, p+/q+ are considered as normal variants, which may or may not lead to mental retardation.

Knowledge of the critical regions in chromosomes is very useful in correlating the genotype and the phenotype. Karyotyping determines these critical regions and thus various congenital malformations can be observed for the chromosomal aberrations. The positioning of the genes responsible for human malformations could be gained from the studies of phenotypic effects of human chromosomal aberrations. Therefore, further molecular mutational studies are necessary to define the abnormality.

Genetic diagnosis by cytogenetic screening thus proved to be crucial in counseling of parents, and special education and management of MR children. The karyotype of parents with chromosomally abnormal children could help to establish the inheritance or recurrence risk in the family, and proved significant in prevention and genetic counseling.

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