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Cytogenetic Abnormalities in 772 Patients with Mental Retardation (MR) in Southern Region of Turkey: Report and Review

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Abstract

Mental retardation (MR) is a heterogeneous condition, affecting 1-3% of general population. Identification of chromosomal abnormalities (CAs) associated with mental disorders may be especially important given the unknown pathophysiology and the probable genetic heterogeneity of MR. In this study, we aimed to evaluate karyotype results of 772 MR cases, retrospectively. For karyotyping, standard lymphocyte culturing and GTG banding methods were done. For analysis, cytovision software was used. In result, out of 772 MR cases, 87 cases showed abnormal chromosomal constitutions (11.3%), and normal karyotype results were detected in 88.7% of all patients. Numerical and structural CAs were detected in 2.6% (20 of 772) and 8.7 (67 of 772) of cases, respectively. This study revealed Down syndrome as the most common chromosomal abnormality (1%). The ratio of X chromosome monosomy was 0.6%. In conclusion, patients with MR should be routinely karyotyped. Interesting CAs we found, may harbor important genes for MR and give important tips for linkage in possible genome scan projects.

Keywords: Chromosomal abnormalities, GTG-banding, karyotype, MR

1 Introduction

MR is the most frequent cause of serious handicap in children and young adults with an estimated prevalence up to 1-3% of the population, and is one of the more important topics in medical science [1,2]. MR can be caused by genetic or non-genetic factors. Genetic abnormalities are the most common identifiable cause of unexplained MR [3]. Genetic

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defects including chromosomal and single gene abnormalities are one of the known causes of MR [4]. Chromosomal and genetic disorders account for 30–40% of cases of moderate to severe MR [5-8]. CAs are one of the most important causes of MR. Some 15% of all mentally retarded persons harbor CAs that can be detected under the light microscope [9]. CAs include numerical CAs, partial CAs and microdeletions. Numerical and structural abnormalities are responsible for about 4-28% of all MR [10]. and are found in about 40% of severe MR and 10% of mild MR.[11] In addition to the severity of MR, the presence of congenital anomalies increases the diagnostic yield of CAs [12,13]. Numerical anomalies affect autosomes more often than sex chromosomes, with a median frequency of 6.5% vs. 0.4%. Numerical anomalies of the sex chromosomes occur foremost in borderline to mild MR, while numerical anomalies of the autosomes are mostly detected in patients with more severe MR. Unbalanced structural anomalies are also present more often in patients with moderate to profound MR than in those with a milder MR and affect the autosomes more often than the sex chromosomes [14]. Because CAs are so common, all patients with MR of unknown cause should undergo chromosomal analysis.
Here, we present the results of the postnatal prevalence of CAs in 772 cases with MR, in the scope of the long-term retrospective study in South Region of Turkey.

2 Materials and Methods

During the period 1992-2009, total 772 cases were referred to Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University with age ranging from 1 to 45 years (x=7.4 years) for chromosomal analysis, who had mental retardation and/or motor delay, language, speech and communication disorders and behavioral problems. The patients were referred to our laboratory from the pediatrics and the neurology departments. Metaphase chromosome preparations from peripheral blood were made according to the standard cytogenetic protocols. Twenty metaphases were analyzed in all the patients, but in cases of abnormalities and mosaicism the study was extended up to 50 metaphases. All the CAs were reported according to the current international standard nomenclature (ISCN, 2009).N

3 Results

Totally, 772 karyotypes are consisting of 478 (61.9%) males and 294 (39.1%) females (sex ratio = 1.6). These karyotype results were normal (46,XX and 46,XY) in 88.7% of all patients. However, major and minor CAs was detected in 11.3% of all patients (87 of 772). Numerical CAs to be 2.6% (21), out of which autosomal abnormalities were 1.7% and sex CAs were 0.9%. The structural CAs were detected in 8.7, out of which autosomal abnormalities were 7.7% and sex CAs were 1%. The incidence of Down syndrome was found to be 1% in MR cases. The ratio of X chromosome monosomy was 0.6% (45,X and 45,X/46,XX). Klinefelter syndrome (XXY) was found in one case. The most frequently encountered structural CAs were the fragile sites (7.1%, 41 cases): fra(3p22); fra(6q24)x2; fra(8q22); fra(12q24)x2; fra(1q21); fra(10q24); fra(17p); fra(16q24); fra(12q22). The ratio of autosomal fragilities were recorded as 6.1 % (33 cases) (Table 1). The fragile X syndrome (FXS) (46,XY/46,XX,fragXq27.3) was found in 1% (8 cases). Translocations

were seen in three cases (0.4%) [46,XY,t(5;12)(p12;q34); 45,XY,t(10;18)(p15;q11); 46,XX,t(1;10)(q42;q24)]. There were various other structural abnormalities as observed on Tablo 1: deletions (0.6%, 5 case) [46,XY,del(5)(p12); 46,XX,del(15)(p11-ter); 46,XY,del(15)(p13-ter); 46,XX,del(18)(q-) and 46,XY,del(21)(q)], ring chromosomes (1 case) [46,XX,rin(22)], inversion (1.4%, 11 cases): 46,XY,inv(4)(p16;q31); 46,XX or 46,XY,inv(9)(p11;12) or (p11;13) and 46,XX,inv(12)(q42;q24). Other variations/ abnormalities were also seen in the patients, namely 1qh+ (1 case), 16qh+ (2cases), 9qh+ (3 cases), Yqh+ (1 case) and 13s++ (1 case) (Table 1).

Table 1: Frequencies and distributions of the karyotypes in 772 patients with mental retardation.

Cytogenetic Category	Karyotype	No.of cases	Frequency in all cases (%)
Normal	**46,XX or 46,XY**	**685**	**88.7**
Abnormal	**Numerical and structural abnormalities**	**87**	**11.3**
	Sex		
Male		**478**	**61.9**
Female		**294**	**39.1**
NUMERICAL CHROMOSOME ABNORMALITIES			
Sex abnormalities			
Pure Turner **(**Monosomy X)	**45,X**	**3**	
Turner with mosaic	**45,X/46,XX**	**2**	0.7
Klinefelter	**47,XXY**	**1**	1.0
Autosomal abnormalities			
Down syndrome (Trisomy chromosome 21)	**47,XX or 47,XY,+21**	**7 (**3/3)*	0.8
Down syndrome with mosaic	**47,XY,+21/46,XY**	**1**	
Otosomal anöploidy	**46,XX or 46,XY (10-8%)**	**6 (**3/3)	
Total		**20**	2.6
STRUCTURAL CHROMOSOME ABNORMALITIES			
Translocations	**46,XY,t(5;12)(p12;q34)** **45,XY,t(10;18)(p15;q11)** **46,XX,t(1;10)(q42;q24)**	**3**	0.4
Deletions			
	46,XY,del(5)(p12) **46,XX,del(15)(p11-ter)** **46,XY,del(15)(p13-ter)** **46,XX,del(18)(q-)** **46,XY,del(21)(q)**	**5**	**0.7**
Ring chromosomes	**46,XX,rin(22)**	**1**	
Inversions	**46,XY,inv(4)(p16;q31)**	**1** **9**	

FRAGILITIES	**46,XX or 46,XY,inv(9)(p11;12) or (p11;13) 46,XX,inv(12)(q42;q24)**	**1**	1.0
Sex chromosomal fagilities Fragile-X syndrome	**46,XX or 46,XY,fra(X)(q27.3)**	**8**	
Autosomal fragilities			
Different chromosomal autosomal fragilities	**46,XX or 46,XY (6-30%) 46,XY,fra(3p22) 46,XX,fra(6q24)x2 46,XX,fra(8q22) 46,XY,fra(12q24)x2 46,XY,fra(1q21),fra(10q24) 46,XX.fra(16q24) 46,XY,fra(12q22) 46,XX,fra(17p),1qh+**	**22** (16/14)	4.1
The other structural variations	**46,XX,16qh+ 46, XX or XY, 9qh+ 46,XY,Yqh+ 46,XX,13s++**	**10 2 3 1 1** (5/2)	0.9
Total		**67**	8.7
General total		**87**	

4 Discussion

The etiology of MR is complex; the cause remains unknown in about 50% of cases. Identification of CAs associated with mental developmental disorders may be especially important given the unknown pathophysiology and the probable genetic heterogeneity of MR. It is generally assumed that severe forms of MR are thought to be due to larger CAs or defects in single genes. Numerical and structural CAs are responsible for about 4-28% of all MRs [10]. In the present study, the CAs in MR patients was 11.3% (Table 1). This ratio is similar to those described in literature, that is; 13.3% [14], 15.03% [15], 15% [16] and 16% [17], but lower than that observed in the other studies; 28.3% [18], 26% [19], 32% [20] and 32.2% [21]. These differences in the frequencies of CAs among the studies are probably due to variations in the criteria for inclusion of patients and the cytogenetic methodology applied. The higher incidence of CAs demonstrated the importance of cytogenetic evaluation in every MR patient with/without dysmorphic features and congenital anomalies [22].

The prevalence of MR is significantly higher in boys than in girls, with a sex ratio of 1.4:1 for severe MR and 1.9:1 for mild MR [23]. The higher prevalence in boys is partly due to X-chromosomal genetic defects, which, according to current estimates, are the cause of MR in about 10% of affected boys [24]. We also observed an increase in the sex ratio (1.6:1) in male patients compared with female patients (Table 1). This suggests that the males are more sensitive to MR. According to results of molecular studies in literature, individual genes on X chromosome are also important in terms of MR in males. Recently, a pathological duplication of MECP2 and L1CAM genes has been described in males with severe MR and progressive neurological symptoms. But, other duplications on the X chromosome at Xp22.3, Xq22.3 and Xq26.3 have also been described with no pathological

significance [25,26]. This suggests that in males there is a general predisposition to MR where genetic predisposing alleles need to be identified.

We found that numerical CAs are the second most common (2.6%) cause of MR after structural CAs. Numerical autosomal CAs are more common than numerical sex CAs. Turner syndrome (45,X) and Klinefelter syndrome (XXY) patients may be intellectually normal. However, once the number of X chromosomes exceeds two, such as in the triple X syndrome, patients are always mentally retarded. Missing or extra sex chromosome affects sexual development and may cause infertility, growth abnormalities, behavioral and learning problems. We also have reported Turner syndrome in three patients, Klinefelter syndrome in one patient and Turner mosaicism in two patients. Most of the genes along the X chromosome are expressed in the brain. The first gene identified was FMR1 that causes fragile X syndrome and still remains the commonest single gene abnormality identified [27]. A systematic but limited search of brain expressed genes within Xp11 region that included 50 genes, revealed only three new genes [28]. related to brain development. Mutations in any of these genes hinder normal brain development and function, and they are potential causes of the X-linked MR.

Trisomy 21 (Down syndrome) is the most frequent cause of MR. We have described trisomy chromosome 21 in seven patients (0.9%), one patient having also 46,XY/47,XY,+ 21 mosaicism and one patient have 21(q22-ter) deletion syndrome. So, DS are the most common otosomal anoploidy cause of MR. In our previous study with schizophrenia population, we also have described deletion 21q22 in four patients (2.9%), one patient having also 46,XX/47,XX,+ 21 mosaicism and two patients with 47,XX,+ 21 in one metaphase [29]. This band (21q22) has been called the Down syndrome region. The mosaic trisomy was found more (8%) than those reported in the literatüre [30]. Dave and Shetty [31] also reported 45% DS with MR children in Indian. Additionally, we identified six patients (0.8%) with otosomal anoploidies of different chromosomes in 8-10% of metaphases. There may be an association between these different autosomal CAs in the some person and MR. The reason for this might be that these anomalies increase risk for mental development in a relatively nonspecific way, such as contributing to disruption of normal embryogenesis of the nervous system.

Chromosomal fragile sites (FSs) have been instrumental in identifying disease genes that may be helpful in finding candidate regions for linkage studies. The FS may play an important role in the genetics of mental deficiency. In the present study, the different FS was significantly higher (4.2%) than the frequency of other CAs in MR patients. The some of FS regions include fra(3p22), fra(6q24)x2, fra(8q22), fra(12q24)x2, fra(1q21), fra(10q24), fra(16q24), fra(12q22) and fra(17p),1qh+ bands. Particularly, sites fra(6q24) and fra(12q24) sites were expressed in 4 patients. These two regions may be hot spots for this patients group, and may harbor important genes for mental development. Also in literature, the presence of FS on chromosomes 3, 9, 17, 18 and 19 in schizophrenic patients has been reviewed by Bassett [32] Thus, these findings represent a broad exploration of evidence for common susceptibility genes for mental developmental disorders that may help us to understand the biological bases of complex MR.

FXS (Xq27.3) is the most common X-chromosome linked type of MR and the second most frequent cause of MR after DS. On chromosome spreads of cells grown under specific cell culture conditions, fragile X patients show a gap or break on the X chromosome, the so-called fragile site FRAXA. X-linked forms of MR are estimated to cause 10-20% of all inherited cases of MR. We also identified abnormalities of FXS in 1% of patients. FXS shows varied incidence pattern ranging from 5-19% [33]. It is a disorder characterised by

MR and typical physical and behavioural abnormalities. Adult patients suffer from mild to severe MR in addition to very specific phenotypic features. At the molecular level, the disorder is due to a dynamic mutation caused by the expansion of a CGG repeat located in the promotor region at the 5' end of the FMR1 gene [34].

Pericentric inversion of chromosome 9 [inv(9)] is the most common reciprocal translocation in the general population and the prevalence of inv(9) varies with ethnicity. It could be estimated that the incidence in Asian populations is approximately 1.5%. Structural and numerical aberrations involving both paracentric and pericentric inversion of chromosome 9 is well known among subjects with MR [35] and reported to be 7.2% in MR cases. However, some studies indicated that the pericentric regions of chromosome 9 may be etiologically linked to schizophrenia [36]. In the present study, chromosome 9 seems to be involved more often than the other chromosomes, and were involved in 1.2% of the patients (three patients had 9qh+). Most of inv(9)s observed do not give rise to any specific phenotypic abnormalities. However, inv(9) has been found to be associated with infertility, repeated fetal loss, congenital anomalies and MR, possibly as a predisposing factor for non-disjunction and inter-chromosomal effect [37]. The localization of breakpoints on chromosome 9 may lead to the cloning of MR- susceptibility genes. Polymorphic inversion of the 9qh+ region is considered to be a normal variation. Possible clinical effects of 9qh+ are certainly unknown, but Liu et al [38] suggested that inv(9) and 9qh+ were associated with various diseases and appear to be unfavorable for human reproduction. This may indicate that the effect of qh region on the development of MR would not be major one, but it may be a risk-increasing factor. Undoubtedly, further studies are necessary to understand the role of inv(9) and 9qh+ in MR.

In the present study, two patients also had inv(4)(p16;q31) and inv(12)(q42;q24). The localization of breakpoints on chromosome 4 and 12 may lead to the defects of MR-susceptibility genes. There are varying symptoms of minor anomalies and of developmental status in patients with deletions in the short arm of chromosome 4 in the literature. Vincent et al [39] discussed two brothers with autism and neonatal seizures who had paracentic inversions of 4p (p12p15.3), which directly interrupted the GABRG1 gene, one of the g-aminobutyric acid (GABA) receptor subunit genes. Interstitial deletions of 4p12 to 4p15 also have been described in few cases in the literature [40]. The main clinical features in the previously reported cases were mild-to-moderate MR and multiple minor dysmorphic features. Two cases have been reported with a similar de novo interstitial deletion of band 12q24.31 [41,42]. Both had developmental delay, dysmorphic facial features, heart malformations and foot anomalies. The presence of above two breakpoints in our patients are permit us to establish any clear genotypeephenotype correlations.

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. Translocations can remain without clinical consequences as long as they are balanced, without loss or gain of genetic material and do not interrupt an important gene. Association of translocations with bad obstetric history, fertility failure, amenorrhea, ambiguous genitalia, MR with multiple congenital anomaly or Down syndrome is well documented by many investigators. 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 are noted whereas translocations in MR is hardly dealt and there appears only few reports. We also noticed three novel translocations [t(1;10)(q42;q24), t(5;12)(p12;q34) and t(10;18)(p15;q11)] in MR patients.

These translocations in our patients are new and not known to have any linkage to MR. However, these translocations 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 of MR.

We have detected five deletions at 5(p12-ter), 15(p11-ter), 15(p13-ter), 18(q-) and 21(q22-ter). Deletions may cause diverse phenotypes, depending on both the size and location of the deletion, but almost invariably including MR. The child observed (5p12 deletion) here had the clinical characteristics of the syndrome, including MR after birth. As a general rule, deletions spanning more than 2% of the total genome are not viable. The breakage occurred in the 5p15.2 region contains a gene which, when appearing as a single copy, is responsible for the cri-du-chat syndrome, whereas the genes responsible for the facial features and motor delay are located in the 5p15.2 region. In the present study, 15p deletions were identified in two patients. The overall incidence of 15q13.3 microdeletion syndrome is about 0.3% in patients with idiopathic MR, considering it comparable to William and Angelman syndromes [43]. But the deletions at 15p11 and 15p13 were newly observed in the present study, and these sites may be specific hot spots for MR. Here, we also describe a first case of a terminal deletion of 18q-. Deletions and duplications of chromosome 18 rank among the most common autosomal anomalies with abnormalities of chromosome 18q being the most frequent and deletions of 18q being reported in 1/40,000 live births [48]. Distal deletions of 18q are particularly frequent and appear to cause a variable phenotypic spectrum including growth deficiency, microcephaly, midface hypoplasia, congenital aural atresia, genitourinary malformations, myelination disorders, hypotonia and MR [44]. We found terminal deletion 18q- which may be related to MR.

Ring chromosomes are formed by breakage in both arms of a chromosome with fusion of the points of fracture and loss of the distal fragments. In the present study, we identified a ring chromosome 22 [r(22)] in one patient. Ring(22) is a rare cytogenetic finding, and it has been reported in conjuction with DiGeorge syndrome. Survival into adulthood is common [45]. Clinical findings of children with ring(22) mostly overlap with the features of 22q13 deletion syndrome, which shows MR, delayed motor development, hypotonia, growth retardation and many minor and major dysmorphic features. The significant change in the r(22) with concomitant loss of a sizeable amount of genomic material is undoubtedly the principal factor in the etiology of the patient's phenotype, which was consistent with the known features of our patients with terminal deletions of 22q13 and r(22). All these findings suggest that there is an association between the MR and this chromosomal anomalies.

5 Conclusion

We conclude that patients with MR should be routinely karyotyped. In general, a routine chromosome analysis should be used as a starting point for any cytogenetics investigation of MR. Genetic diagnosis by cytogenetic screening thus proved to be crucial in counseling of parents, and special education and management of MR children. Knowledge of the critical regions in chromosomes is very useful in correlating the genotype and the phenotype. The positioning of the genes responsible for MR could be gained from the studies of phenotypic effects of human CAs. Therefore, further molecular mutational studies are necessary to define the abnormality.

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