Chromosome abnormality rate among Iranian patients with idiopathic mental retardation from consanguineous marriages

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Abstract

Introduction: Mental retardation (MR) has heterogeneous aetiology mostly with genetic causes. Chromosomal aberrations are one of the most common causes of MR. Reports on chromosome abnormality rate among consanguineous families are sparse. In order to identify the chromosome abnormality rate in idiopathic mental retardation from consanguineous marriages, a total of 322 Iranian families with positive family history for MR were investigated in the Genetics Research Center.

Material and methods: In the majority of families (92%) at least two sibs were affected with MR and none had specific chromosomal syndromes such as Down syndrome. Standard cytogenetic techniques using high resolution GTG banding were carried out on all the patients.

Results: The overall chromosome abnormality rate contributing to mental retardation was 1.24% (4 cases), which comprised 46,XY,der(18)t(4;18)(q31.1;q23)mat; 45,XY,-21,-22,+der(22)t(21;22)(q21.1;q13.33)mat; 46,XY,rec(2)dup(2p)inv(2)(p25.1q37.3)pat, and 46,XY,der(11)t(10;11)(q25.2;q25)pat.

Conclusions: Although the most likely genetic cause of mental retardation in patients with consanguineous parents is autosomal recessive, the fact that 1.24% of our patients had chromosomal abnormalities emphasizes the importance of cytogenetic investigation as the first laboratory genetic tests for all MR patients. To our knowledge, this is the first report on the rate of chromosome abnormality among patients with idiopathic mental retardation from consanguineous marriages.

Key words: chromosome abnormality, consanguineous marriage, idiopathic mental retardation, Iranian patients.

Introduction

Mental retardation (MR), with a prevalence of 2-3% in the population, is a heterogeneous disorder defined by an intelligence quotient (IQ) of less than 70 [1]. Specific aetiological factors of MR are found in only half of the

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patients [2]. Genetic defects including chromosomal and single gene abnormalities are one of the known causes of MR [3] and account for approximately 60% of cases, mainly with IQ less than 50 [4]. So far a large number of different gene mutations are known to be associated with mental retardation [5].

Chromosomal aberrations are one of the most important causes of MR. Numerical and structural abnormalities are responsible for about 4-28% of all mental retardation [6], and are found in about 40% of severe MR and 10% of mild MR [7]. In addition to the severity of MR, the presence of congenital anomalies increases the diagnostic yield of chromosome abnormalities [6]. 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. Structural chromosome anomalies [8], usually not smaller than 5 Mb, are detectable using cytogenetic studies with > 400 bands per haploid (bph) quality [9]. 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 [8]. Reports about the rate of chromosome abnormalities in MR patients with consanguineous marriage are very sparse. Hamamy *et al.* [10] in a report on the rate of genetic disorders in consanguineous marriage from Jordan did not observe any difference between the rate of dominant, X-linked and chromosomal conditions in the consanguineous and non-consanguineous patients with genetic syndromes, congenital anomalies or mental retardation. However, they observed that autosomal recessive disorders were strongly associated with consanguinity. In a report by Mosayebi *et al.* [11] from Kashan city in Iran, the rate of congenital malformations was much higher among neonates from consanguineous marriages (7%) compared with non-consanguineous marriages (2%).

In this study, chromosome investigation was carried out on 322 MR patients from consanguineous marriages referred to the Genetics Research Center during the last 5 years. This study was carried out within a comprehensive project on the genetic causes of hereditary mental retardation in our centre. As consanguineous marriage is common in Iran, it is important to evaluate the contribution of chromosome abnormality among patients with mental retardation in such families.

Material and methods

Cytogenetic investigation was carried out on 322 mentally retarded patients referred to the Genetics Research Center, during 2003 and 2007. All the work was carried out following the guidelines provided by the ethical council of the university of Social Welfare and Rehabilitation Sciences. The subjects were identified by experienced clinical geneticists. The criteria for selecting patients were to have idiopathic MR (excluding all known genetic syndromes), positive family history of MR and consanguineous parents. The IQ was assessed using the Wechsler test. The main clinical features of the patients are presented in Table I. Blood

Table I. Clinical information of patients with chromosome abnormality

Patient	Sex	Age [years]	Number of affected individuals	MR severity	Main clinical features
1	F	17	3	Moderate	Keratoconus, keratitis and primary amenorrhea
2	M	10	2	Profound	Long face, Marfan habitus, thick eyebrows
3	F	25	3	Moderate	Masculine phenotype, female genitalia, intra-abdominal genitalia
4	M	26	4	Severe	Microcephaly, short stature
5	M	22	2	Severe	Microcephaly
6	M	20	2	Severe	Microcephaly
7	M	54	4	Profound	Broad metatarsus, short toes, coarse face
8	M	18	2	Severe	Short toes, bulbus nose, strabismus, thick lips
9	M	7	4	Severe	Strabismus, ptosis, short toes, open mouth, long philtrum
10	M	24	1	Moderate	Prominent supraorbital ridge, contracture deformity of PIP, thick and malformed auricles

samples were collected from all patients in sterile heparinized test tubes. Cytogenetic analysis was performed on cultured peripheral blood lymphocytes stimulated with phytohaemagglutinin M, using standard techniques [12]. Karyotype was determined in all patients by high resolution GTG banding and, when necessary, CBG and NOR staining [12] were carried out. At least 15 cells were analysed, and in cases of mosaicism this number was increased to 100 metaphases.

Results

Ten patients (3.10%) showed chromosome abnormalities. A list of chromosome abnormalities is presented in Table II. Partial karyotype of each affected parent is presented in Figure 1.

The abnormalities included the following groups: 1) Abnormalities involving the sex chromosomes, 2) presence of high percentage of pro-metaphase/prophase chromosome spreads, with twisted, curly, and poor banding quality, and 3) autosomal structural abnormalities.

Abnormalities involving the sex chromosomes

Three patients (cases 1-3) showed sex chromosome abnormalities (0.93%). These patients are described as follows:
– case 1: this patient had moderate MR and her karyotype was mosaic for three cell lines involving the X chromosome, described as 45,X/46,XX/ 47,XXX; the patient had a mentally retarded sister with a normal karyotype;
– case 2: the patient had profound MR and his karyotype was 47,XYY; he had a mentally retarded brother with a normal karyotype;
– case 3: a female phenotype with 46,XY karyotype; the patient had 2 MR sisters, one of whom showed a 46,XY karyotype, but the other had a normal karyotype; the MR in the proband was moderate.

Presence of high percentage of pro-metaphase/prophase chromosome spreads, with twisted, curly, and poor banding quality

Three patients (cases 4-6) had normal karyotype (0.93%). The patients were from different families and from different provinces of Iran, all with severe MR and microcephaly. However, the chromosomes were twisted, curly, with poor banding quality (< 400 bph) and a high percentage of pro-meta-phase/prophase (80%) chromosomes compared to normal controls (13%). All these three patients using linkage analysis were linked to MCPH1 [13].
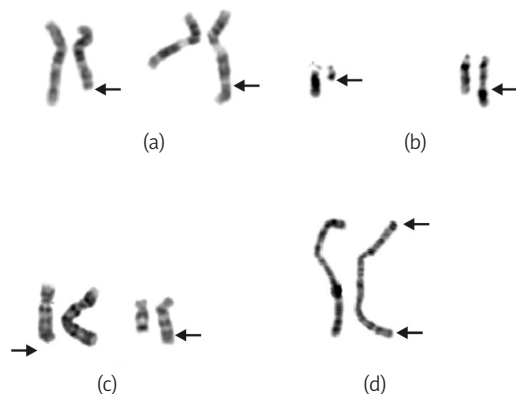
Autosomal structural abnormalities

Four patients (cases 7-10) had unbalanced structural chromosome abnormalities (1.24%), all of which were the unbalanced segregation products of parental balanced rearrangements. These patients are described as follows:
– case 7: this was a large family with 8 children, 4 of whom were mentally retarded; the patient had profound MR; the proband showed the following chromosome abnormality: 46,XY,der(18) t(4;18)(q31.1;q23)mat; the mother was the carrier of the balanced translocation described as 46,XX,t(4;18)(q31.1;q23);
– case 8: there were three affected sibs, one expired girl with two MR brothers; the proband had severe MR; the proband's karyotype was 45,XY,-21,-22,+der(22)t(21;22)(q21.1;q13.33)mat; the mother was the carrier of a balanced translocation described as 46,XX,t(21;22)(q21.1;q13.33);
– case 9: there were five affected step sibs (different mothers), two stepbrothers and two stepsisters, and one expired affected stepbrother; the proband had severe MR and his karyotype was

Table II. Karyotype results for 10 patients with consanguineous marriage and chromosomal abnormalities

Patient	Karyotype
Case 1	45,X[4]/47,XXX[1]/46,XX[25]
Case 2	47,XYY
Case 3	46,XY with a female phenotype
Cases 4-6	Twisted and curly chromosomes with high percentage of prophase
Case 7	46,XY,der(18)t(4;18)(q31.1;q23)mat
Case 8	45,XY,-21,-22,+der(22)t(21;22)(q21.1;q13.33)mat
Case 9	46,XY,der(11)t(10;11)(q25.2;q25)pat
Case 10	46,XY,rec(2)dup(2)inv(2)(p25.1q37.3)pat

Figure 1. The partial karyotypes of the affected parent for the patients with chromosome abnormalities: (a) father of case 9: 46,XY,t(10;11)(q25.2;q25); (b) mother of case 8: 46,XX,t(21;22)(q21.1;q13.33); (c) mother of case 7: 46,XX,t(4:18)(q31.1;q23); (d) father of case 10: 46,XY, inv(2)(p25.1q37.3)

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46,XY,der(11)t(10;11)(q25.2;q25)pat; the father was found to have a balanced reciprocal translocation described as 46,XY,t(10;11)(q25.2;q25);

– case 10: the proband was the only child with moderate MR; his karyotype was 46,XY,rec(2) dup(2p)inv(2)(p25.1q37.3)pat; the father was found to have a pericentric inversion for chromosome 2 described as 46,XY,inv(2)(p25.1q37.3), with the proband having the recombinant product of this abnormality.

Discussion

Iran is situated in the Middle East [14] with a high rate of consanguineous marriage [15]. In a report by Saadat *et al.* [16], the overall rate of consanguineous marriage in the Iranian population was given as 38.6%. However, reports on the rate of chromosome abnormalities following consanguineous marriage are very limited. In a report by Mosayebi *et al.* [11] from Kashan city in Iran, the rate of congenital malformations was much higher among neonates from consanguineous marriage (7%) compared to non-consanguineous marriage (2%).

In this study (Table I), three cases (cases 1-3) showed sex chromosome abnormalities comprising one case with numerical abnormality, one with mosaicism and the third case a female with 46,XY karyotype. However, all three patients had sibs with MR, but with normal karyotypes. It is therefore assumed that the sex chromosome anomalies were not the cause of MR in the affected patients. Cases 4-6 showed a high percentage of pro-metaphase/prophase chromosomes. These patients however demonstrated linkage to MCPH1. The presence of a high rate of prophase stage chromosomes in these patients is due to premature chromosome condensation (PCC) as a result of mutation in the MCPH1 gene [13, 17]. Therefore, the cytological finding of PCC is the manifestation of mutation in the MCPH1 gene. On the other hand, 4 patients (cases 7-10) demonstrated chromosome structural abnormalities, all of which had been inherited from one of the parents. The presence of an unbalanced autosome chromosome with partial monosomy/trisomy is the most likely cause of MR in the probands and their affected sibs [18]. Therefore one could suggest that in our study the only group of chromosome abnormalities which are the actual cause of mental retardation is the unbalanced autosome chromosomes (the last group). The rate of chromosome abnormality reported by other authors is mostly for MR patients with both consanguineous and non-consanguineous parents. The frequency of abnormal chromosomes, other than Down syndrome, in the study carried out on severely mentally retarded patients by Lantigua-Cruz *et al.* [19] was 3.7%. In the study performed by Schreppers-Tijdink *et al.* [20], this frequency was 6.1%. In the investigation of Rasmussen *et al.* [21], the frequency of chromosomal autosomal anomalies other than Down syndrome was 2.4% and sex chromosome aberrations were 1.8% (4.2% in total). The results obtained by Sutherland *et al.* [18] were 2.04% and 0.85% for autosomal abnormalities (except Down syndrome) and sex chromosome abnormalities, respectively (2.89% in total). In the study performed by Santos [22] the frequency of chromosome abnormalities other than known autosomal syndromes was 6%.

In a study carried out in our centre on the rate of chromosome abnormality in 89 patients with idiopathic MR from non-consanguineous parents, the rate of chromosome abnormality was 4.5% (unpublished data).

In our project, within a comprehensive study on the hereditary causes of mental retardation in Iranian patients, the selection criteria were MR patients with positive family history of MR, mostly with at least two affected sibs, from consanguineous marriage. The overall rate of chromosome abnormality in this study, contributing to mental retardation, is 1.24%. This is much smaller than other reported cases. This is probably due to biased referral, as all of our cases had consanguineous parents. Since the rate of autosomal recessive disorders increases in patients from consanguineous marriage, the aetiology of mental retardation in most of our patients is probably due to autosomal recessive conditions as opposed to chromosome abnormality. This has also been suggested by other investigators. In a report by Hamamy *et al.* [10] on a Jordanian population with a first cousin marriage rate of 20-30%, autosomal recessive conditions were significantly raised in patients with genetic disorders and consanguineous marriage compared to non-consanguineous marriage and the general population. In a study from Baghdad, Iraq, with a first cousin marriage rate of 29%, in a genetic counselling clinic, 31% of all referrals were categorized as autosomal recessive in aetiology [23]. Reports by Najmabadi *et al.* [24] and Kuss *et al.* [25] suggest an increased rate of autosomal recessive aetiology for hereditary mental retardation in Iranian patients from consanguineous marriages.

To our knowledge, this is the first report on the rate of chromosome abnormality among patients with idiopathic mental retardation from consanguineous parents. Although the most likely genetic cause of mental retardation in patients with consanguineous parents is autosomal recessive conditions, the fact that 1.24% of our patients had chromosomal abnormalities emphasizes the importance of cytogenetic investigation as the first laboratory genetic tests for all MR patients.

Acknowledgments

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