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Original article

Chromosomal aberrations in intellectual disability children in eastern up population.

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Abstract

Genetic factors play a significant role in the etiology of intellectual disability (ID). The goal of this study was to identify microscopically visible chromosomal abnormalities in an Indian ID population and to determine their frequency, pattern, and clinical features. A total of 527 intellectually disabled individuals from special schools and institutions in 2 different State on U.P. and Bihar Population were screened for cytogenetic abnormalities. Additional analyses were carried out for verification or further characterization by using fluorescence in situ hybridization, multiplex ligation-dependent probe amplification, or analysis of the FMR1 promoter CGG(n) repeat. Of the 527 individuals with ID, chromosomal abnormalities were found in 87 (16.5%). Trisomy 21 was the major chromosomal abnormality, identified in 74 patients (14%). Other chromosome abnormalities included 8 X-chromosomal and 5 autosomal aberrations. Details on chromosome aberrations and confirmation analyses are discussed. This study shows that chromosomal abnormalities are an important cause of ID in India. Cytogenetic analysis is important for an adequate diagnosis in patients and subsequent genetic counselling for their families, especially in developing countries with limited facilities, such as India.

Keywords: Intellectual disability, Genetics, Chromosomal abnormalities,

Introduction

Intellectual disability (ID) is a major health problem worldwide. In addition to health problems, individuals with ID need more educational and psychological attention. Moreover, most of those with severe ID require lifelong nursing, guidance, and surveillance (Schalock et al., 2007). Known causes of ID are biochemical and metabolic defects, chromosomal abnormalities, mutations in single genes (Mendelian disorders and mitochondrial disorders), multifactorial disorders with a

polygenic predisposition, and nongenetic causes (Chiurazzi and Oostra, 2000; van Karnebeek et al., 2005). Pathogenic chromosomal abnormalities are the most common genetic cause of ID (Stevenson et al., 2003; Mefford, 2009). Microscopically visible numeric and structural abnormalities account for 7–56% of cases depending on techniques used and patient selection (Fryns et al., 1986; Dereymaeker et al., 1988; Fryns et al., 1990; Felix et al., 1998; Santos et al., 2000; van Karnebeek et al., 2002; Shiue et al., 2004; Dayakar et al., 2010). Down syndrome is the most common chromosomal abnormality causing ID, and it can be easily detected by using routine chromosomal analysis (Tolmie and MacFayden, 2007). To date, there are few data on the incidence and cause of ID in India. Cytogenetic analysis has not been recognized as a routine diagnostic tool for patients with ID in India, although the technique is available. Furthermore, genetic disorders have not received much attention from the government and medical practitioners, partly because the main health problems for childhood morbidity and mortality are socioeconomic and environmental, such as malnutrition and infection. Therefore, this study aimed to determine the prevalence and pattern of microscopically visible chromosomal abnormalities and the clinical features of positive cases in ID individuals in India.

Materials and Methods Patient

Selection and setting

A total of 527 participants (329 males and 198 females) were included in the study. Their ages ranged from 6 to 25 years, and they were from 2 state of India 527 patients, 156 were institutionalized and 371 attended special schools. The majority of the individuals (n = 345) appeared to be mildly intellectually disabled, 161 were moderately disabled, and 21 were severely disabled (Table 1). Informed consent was obtained from the parents or legal representatives, and the study was approved by the Institutional Ethical committee. All participants underwent a standardized clinical examination before blood was drawn. This examination comprised physical measurements and dysmorphological assessment. Peripheral blood samples were collected from July 2017 to December 2018, and cytogenetic analysis was performed on all 527 samples. Structural abnormalities were confirmed by Karyotyping and multiplex ligation-dependent probe amplification (MLPA) or fluorescence in situ hybridization (FISH). Chromosome cultures and preparations were carried out as described elsewhere (Blennow 2005). One hundred metaphases were screened for fragile sites on each sample. Subsequently, chromosome analysis was performed by using G-banding technique on the level of 400–600 bands. At least 20 metaphases were scored for each patient and karyotyped. If a mosaicism was suspected, 50–100 cells were counted. FISH analysis was performed by using commercially available probes (Vysis, Inc., Downers Grove, IL) according to standard protocols as previously described (de Bruijn et al., 2001). Genomic DNA of each patient was isolated by using the salting-out method (Miller et al., 1988). MLPA analysis was performed as described elsewhere (Schouten et al., 2002; Koolen et al., 2004).

Sr.No.	Characteristic	Participants (n)
	Sex	

1	Male	329
2	Female	198
	ID severity	
1	Mild	345
2	Moderate	161
3	Severe	21

ID, intellectual disability.

Table 2. Structural Chromosome Aberrations Detected in 527 Intellectually Disabled Indian Individuals

Cae no.	Karyotype	Molecular confirmation	Parents
1.	46,XX,der(14;21)(q10;q10), + 21	NT	Maternal karyotype normal;
2.	46,XX,del(18)(q21.3(qter)dn	FISH: Del 18qter	paternal karyotype unavailable
3.	46,XY,der(4)t(4:8)(p16;p23)dn	FISH and MLPA: Del4pter/dup8pter	Normal karyotypes
4.	46,XX,der(10)t(4:10)(p16;q26)	FISH and MLPA: Del10q/dup4p	Normal karyotypes
5.	46,XX t(3;12) (p14.1;q21.2)	MLPA: Normal	NT
6.	47,XY,idic(15)(q13)	MLPA: Dup 15 (maternal origin)	NT
7.	46,XX,del(X)(q21(qter)	NT	NT
8.	46,XY,fra(X)(q27.3)	SB, full mutation	NT
9.	46,XX,fra(X)(q27.3)	SB, full mutation	Mother is premutation carrier
10.	46,XY,fra(X)(q27.3)	SB, full mutation	Mother is premutation carrier
11.	46,XY,fra(X)(q27.3)	SB, premutation–full mutation (mosaic)	Mother is premutation carrier
12.	46,XY,fra(X)(q27.3)	SB, premutation–full mutation (mosaic)	Mother is premutation carrier

FISH, fluorescent in situ hybridization; MLPA, multiplex ligation-dependent probe amplification; NT, not tested; SB = Southern blot analysis.

Results

Chromosomal abnormalities were found in 87 (16.5%) of the 527 intellectually disabled individuals. Trisomy 21 was the major chromosomal abnormality, occurring in 74 cases (14%).

The latter cases consisted of 71 with full-blown classical trisomy 21 (43 males and 28 females), 2 with a mosaicism of trisomy 21 [47, XX, + 21(73)/46,XX(27) and 47,XY + 21(65)/ 46,XY(35), respectively] (Table 2), and 1 with a Robertsonian translocation (46,XX,der(14;21)(q10;q10), + 21).The latter patient's mother's karyotype was normal, and her father's sample was not available. Therefore, we could not determine whether this translocation was de novo or inherited from her father. In 13 cases, chromosomal abnormalities other than Down syndrome were detected. Two participants had X-chromosomal aneuploidies (45,X(10)/46,XX(90) and 47,XXX; Table 2). For both females the chromosomal aberration detected is not a satisfactory explanation for their moderate ID. The other 11 cases showed structural chromosome aberrations. Apart from the t(14;21) case, autosomal structural abnormalities were found in 5 cases (1.0%): 2 unbalanced translocations, 1 balanced translocation, 1 deletion, and 1 isodicentric chromosome. No further confirmation test was performed on the Down syndrome cases, the cases with an X-chromosomal aneuploidy (Table 2), or a case with a large visible terminal Xq deletion (case 7). Five samples from 4 males and 1 female patient were identified to have a fragile site at Xq27.3 (cases 8– 12). MLPA or FISH analysis was used to confirm the structural chromosomal abnormalities in cases with autosomal aberrations (cases 2–6). Whole chromosome paints of chromosome 18 confirmed a missing part of chromosome 18 in the sample of the patient with 46,XX,del(18)(q21.3/qter)dn .The cytogenetic and molecular analyses confirmed the clinical diagnosis of WolfHirschhorn syndrome. Discussion The overall frequency of microscopically visible chromosomal aberrations in this study was 16.5%. This is similar to the rate reported in other studies (13.3%–17.6%) (Fryns et al., 1986; Dereymaeker et al., 1988; Fryns et al., 1990), although different frequencies were found in other studies: 7.9% (van Karnebeek et al., 2002), 22.43% (Shiue et al., 2004), 28.6% (Santos et al., 2000), 34.2% (Felix et al., 1998), and 56% (Dayakar et al., 2010). Our study shows that cytogenetic analysis is still a powerful tool to detect genetic abnormalities in the ID population. The fact that cytogenetic analysis can now be performed in India should be considered by granting agents, such as government and nonprofit organizations, so that they may financially support genetic studies in developing countries such as India. Furthermore, because common infectious diseases and nutritional problems are becoming less prevalent in India, diagnostic facilities for genetic diseases must receive a higher priority. Such efforts would extend genetic analysis to more diverse populations than normally studied (Bustamante et al., 2011). Conclusions Chromosomal abnormalities play an important causative role in ID in India. However, because cytogenetic analysis is still not commonly performed in intellectually disabled individuals in India, the implementation of this technique in a routine diagnostic setting will help to establish a genetic diagnosis in the local setting and will improve the possibilities for genetic counseling to the families.

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