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Cytogenetic Profiles of 1213 Children with Down Syndrome in South Region of Turkey

Osman Demirhan*, Nilgun Tanrıverdi, Dilara Suleymanova and Nesrin Cetinel

Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University, Balcali-Adana, Turkey

***Corresponding author:** Osman Demirhan, Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University, 01330 Balcalı-Adana, Turkey, Tel: 90-322-3387140; Fax: 90-322-3386572; E-mail: osdemir@cu.edu.tr

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Abstract

Down syndrome (DS) is a complex disorder characterized by well-defined and distinctive phenotypic features. Different karyotypes are associated with varying phenotypic expression of DS. The type of karyotypes in the children with DS plays an important role in genetic diagnosis and family counselling. This study describes the characteristics of karyotypes leading to phenotypic Down syndrome in 1213 cases diagnosed between 1992 and 2009 in South Region of Turkey. The frequency of occurrence of the different karyotypes was analyzed. The karyotype results were normal in 9.1% of all cases. However, chromosomal abnormalities (CAs) were detected in nearly 91% of all cases. The free trisomy 21 was the most common karyotype (nearly 93% of all cases). The ration of mosaic trisomy 21 was 2.5%. The CAs in addition to trisomy 21 was present in 1.5% of cases. The ratio of Robertsonian and reciprocal translocations in these variants were 2.3% and 0.3%, respectively. The ration of other variants was nearly 1%. This study showing the frequency and distribution of karyotypes causing DS, are the great value to be gleaned from studies of DS patients in furthering our understanding of the atypical clinical features associated with DS. These cytogenetic investigations carried out greatly helped in the management of these children and for counseling the affected families.

Keywords: Down syndrome; Chromosome; Karyotype

Introduction

Down syndrome (DS) or trisomy 21 is one of the most common CAs, with numerous clinical manifestations. The frequency in the general population is approximately 1 in 700 [1]. In 93-96% of the individuals the chromosome consistency is an extra chromosome 21, whereas 2-3% occurs due to mosaicism. In the remaining 2-5% the DS occurs due to Robertsonian translocation or rarely reciprocal translocation [2]. While it is frequently assumed that the extra chromosome 21 in mosaic DS patients arises from mitotic non disjunction in a chromosomally normal zygote, evidence from maternal ages [3] suggests that a large proportion of such cases arise from meiotic non disjunction. Mosaicism often arises as a post zygotic error [4]. Several patients of mosaicism in DS with rob (14;21) and der (21;21) [5], t (13;21) and t (21;21) [6] have been reported. In addition, few patients with mosaic trisomy 21 and monosomy 21 have also been reported [7]. Several patients involving autosome and/or sex chromosome aneuploidy, such as double autosomal trisomy and autosomal trisomy with sex chromosome monosomy or trisomy though rare in live borns have also been reported [8]. Constitutional mosaicism consisting of sex chromosome aneuploidy and autosomal trisomy is a rare finding. Most of the reported cases involve X monosomy and trisomy 21 [9] but only a few reports exist with the mosaic DS and Y chromosome abnormality [10]. In this report we present the frequencies and distributions of the postnatal prevalence of CAs in children and newborns with DS physical features, and the relation between the karyotypes and phenotypes in a large group of cases in South Region of Turkey.

Method

The patients in this study are retrospectively evaluated children and newborns for suspicion of DS, postnatally. Participants comprised 1213 cases, showing clinical features such as dysmorphic facial features, flat facial features, with a small nose, developmental delay, absent speech, mental retardation, the nasal bridge, small and abnormally shaped ears, single deep crease across the center of the palm, and family history. The 5.4% of the families had one or two children with DS. Firstly, patients have been seen and diagnosed by the Departments of Pediatrics, and the neonatal unites and then they were referred to Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University for cytogenetic analyses. Study group was comprised of children and newborns had been referred to our laboratory between 1992 to 2009, postnatally. The age of the analyzed population ranged between 2 days and 20 years and the average age was 3.2 years. Nearly 73% of the DS cases were children less than one year old. The sex ratio (male/female) was 1.5. The mothers and fathers of children with DS-suspicion were healthy and 27.6% of their was relatives. The mean age of the mothers were 35 years (range 18-52), and that of the fathers 38 years (range 26-60 years). Standard techniques for the cultivation of lymphocytes from peripheral blood of patients were used and the preparations were treated with trypsin to obtain G-banding. The analyses were performed on 50 cells. Evaluation of karyotypes was done according to ISCN (2005) standards.

Results

Cytogenetics was performed for 1213 children for suspicion of DS. Karyotype results were divided into six categories: normal karyotypes, free trisomy 21, mosaic trisomy 21, CAs in addition to trisomy 21,

translocations and the other variants are shown in Table 1. The karyotype results were normal in 110 (9.1%) of all cases. However, CAs were detected in 1103 (90.9%) of all cases. Specifically, free trisomy 21 was the most common karyotype (92.5% and 1020 cases) among CAs. The ration of mosaic trisomy 21 was 2.5% (28 cases). In 17 cases (1.5%), regular trisomy 21 was associated with structural or numerical CAs, followed by 47, XX,+21, aneoploidy. The ratio of Robertsonian and reciprocal translocations among these variants were 2.6% (28 cases) and 0.2% (2 cases), and the ration of other variants was 1% (10 cases).

Cytogenetic types of Down syndrome	Karyotypes	No. of cases	Frequency in anomalies (%)	Frequency in all cases (%)	Clinical features
Normal	46,XX or 46,XY	110		9.1	dysmorphic facial features, flat facial features, with a small nose, developmental delay, absent speech, mental retardation, the nasal bridge, small and abnormally shaped ears, single deep crease across the center of the palm
	Free trisomy 21 and the others	1103		90.9	
	Total	1213			
Types of Down Syndrome					
Free trisomy 21	47,XX,+21 or 47,XY,+21	1020	92.5		
Mosaic trisomy 21	46,XX/47,XX,+21 or 46,XY/47,XY,+21	28	2.5		
Chromosomal aberrations in addition to trisomy 21	46,XY,+21,t(14q,7p) 47,XY,+21,t(5p;6q) 47,XY,+21,t(12;16)(q24;q24) 47,XY,+21, t(11,21)(q23;31.1) 46,XX,+21,t(13q;14q) 46,XX,+21,t(18q;21q) 47,XY,+21/47,XY,t(13q:19p),+13 47,XX,+21,inv(2)(p11;q21) 47,XY,+21,inv(9)(p12;q21) 47,XX,+21,inv(9)(p11;q13) 47,XX,+21,fra(6q) 47,XY,+21 (25%), CA (15%) 47XY,+21,CA (%10) 47,XX,+21, aneoploidy (20%)	1 1 1 1 1 1 1 1 1 1 3 2 1 1			
	Total	17	1.5		
Translocations Robertsonian translocation 13;21 translocation 14;21 translocation 15;21 translocation 21;21 mosaic translocation 21;21	46,XY,t(13q-21q) 46,XY,t(14q-21q) 46,XY,t(15q-21q) 46,XY,t(21q-21q) 47,XY,+21/46,XY,t(21q,21q)	2 7 2 14 1			
	Total	26	2.4		
Resiprocal	46,XY,t(6;12)(q21;p11) 46 XX,t(16;19)	1 1			
	Total	2	0.2		
The other variants	46,XX,dup(9)(p22-p24) 46,XY,inv(9)(p11:q13) 46,XY,inv(9)(p11;q12) 47,XXY	1 3 4 2			
	Total	10	1		

Table 1: Frequencies and distributions of the karyotypes in children for suspicion of Down syndrome.

Discussion

The data reported here represent the largest national consecutive series of trisomy 21 diagnoses known to us. We comment below on features of particular interest, and evaluated the pattern of referral of cases for cytogenetic study in south region Turkey, and compared the distribution of referrals for our study and a similar study performed in Southeast Turkey by Balkan et al. [11]. In study of these researchers, trisomy 21 was observed in 88.7% of 557 children for suspicion of DS, whereas 0.9% occurs due to mosaicism. In the remaining 4.3% the DS occurs due to Robertsonian translocation. Whereas among the patients, the frequency of free trisomy, mosaicism and Robertsonian translocation was 92.5, 2.5 and 2.4 percent, respectively (Table 1). The differences among these studies may be due to the size of the samples and reflect variations in criteria for inclusion of the patients. In the present study, males accounted for 59.8% of the Down's cases, and the sex ratio was 1.50. This shows that indicated more males with DS were born, and an excess of males in the referred population. Previous studies were observed the gender ratio as 0.82-1.7 males in children that have DS [11-13]. This discrepancy was due to the size of the samples. Nearly, 73% of the DS cases were children less than one year old in our cases. This increase in the frequency of the cases of DS in our study might be the result that a low percentage of mothers have gone for follow-ups at a health institution to have prenatal diagnosis during pregnancy.

Since the free trisomy 21 is the most common genetic cause of birth of children with DS, and it is of great importance to undertake preventive measures in order to reduce the disorder incidence among human population. In the present study, the free trisomy 21 was significantly more frequent (92.5%) than the other types of trisomy 21. The distribution of different anomalies associated with DS is very similar to that in earlier reports. They indicated high occurrence of free trisomy 21 (92-97%) in children that have DS [13-16]. It shows that this CA is presented equally as frequent as in rest of the world. The mosaic trisomy 21 was the second most frequent distinct chromosome abnormality in DS occurring in some 2.5% of our cases. Whereas, previous studies are observed the mosaics ratio in 0.7-1% of children with DS [13,17,18]. There was considerable karyotypic variability in individuals with DS between our study and those studies previously reported. This discrepancy may be due to the size of the samples. In addition, these observations emphasize the importance of cytogenetic confirmation in cases of DS.

We detected surprisingly two hearing loss patients with DS in our study. An increased risk of hearing loss in DS due to altered anatomy and related otolaryngology diseases and disorders is known [19]. However, previous prevalence studies performed in children with DS used varying definitions of hearing loss and reported impairment ranging from 34% to 81% [19-21]. The children with DS examined in this study were underdiagnosed. We also found three acute lymphoblastic leukemia (ALL) patients with DS. Children with DS have an increased risk of developing leukemia, including acute myeloid leukemia and ALL [22,23]. At the same time, children with DS have a 10- to 30-fold increased risk of leukemia. DS cases are more likely to have B-cell precursor ALL, and their leukemic cells lack adverse genetic abnormalities [24]. Leukemia cells with either i(21q10) or trisomy 21 have the potential for basophil formation [25]. Worth et al. [26], has reported a transient leukemic condition in a phenotypically normal newborn bearing i(21q10) clones, suggesting that the q arm of chromosome 21 contains sufficient genetic information for the development of transient leukemia. The study also showed identified novel prognostic groups that predicted clinical outcome and hence may be used for stratification in future treatment protocols.

In the present study, all translocations were found in 35 cases (3.2%). In 17 cases (1.5%), which secondary aberrations were found along with free trisomy 21; these anomalies were t(14q;7p); t(5p;6q); t(12;16)(q24;q24); t(11;21)(q23;31.1); t(13q;14q); t(18q;21q); inv(2)(q21;p11); inv(9)(p12;q21); inv(9)(p11;q13); fra(6q); CA; aneoploidy (20%), and concluded that these variants of translocation and inv (2) may be associated with a typical molecular break points which ultimately leads to Down's phenotype development in an early stage, thus it may be a diagnostic criteria for DS. Chromosome 21 most frequently creates translocations with acrocentric chromosomes than to other non-acrocentric autosomal chromosomes. Our findings conclusively argue that as well, where Robertsonian translocation between chromosome 21 and another acrocentric chromosome have been found in 26 (2.5%) children. The most frequent type of translocation were the Robertsonian translocation 21q; 21q. The second most frequent translocation type was the Robertsonian translocation 14q; 21q. Other Robertsonian translocation types were less present in our study cases (Table 1). These results are exactly similar to the results of Kolgeci et al. [13]. There has been reported that in 75% of all translocation cases it may occur de novo, while in 25% of cases, it can be inherited from one carrier parent, but more frequently by the mother side [27]. To prevent the birth of children with DS in translocation affected families the early detection of parent's carriers with Robertsonian translocation involving chromosome 21 is of the great importance. The couples which are carriers of Robertsonian translocation involving translocation 21q; 21q have reported 100% risk of having a child with DS and unable to have healthy baby [28,29].

In our study, the frequency of inv(9) in DS patients was observed to be 1.1%. Pericentric inversion of chromosome 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%. This inversion is usually considered as a polymorphism, and its clinical consequences remain unclear [17]. 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 [30]. This may indicate that the effect of inv(9) on the development of MR would not be major one, but it may be a risk-increasing factor. Several patients involving autosome and/or sex chromosome aneuploidy, such as double autosomal trisomy and autosomal trisomy with sex chromosome monosomy or trisomy though rare in live borns have also been reported [8]. There have been some reports of individuals with Klinefelter syndrome (KS) who also have other chromosome abnormalities, such as DS [31]. We also describe two males with features of DS, and resulting from an 47,XXY karyotype. In contrast to DS, KS cannot be identified in infancy, after karyotyping is performed as part of a routine evaluation for hypospadias, small phallus, or cryptorchidism. Not all infants with DS present with every feature; the phenotype is variable. DS also should be suspected in a phenotypically infant with 47,XXY. This showed that there is a similarity between features of KS and features of DS. So, our study has important clinical implications in that it calls attention to the different symptoms in DS.

Conclusions

This results support that trisomy 21 has a universal genetic etiology across different human populations. Free trisomy 21 karyotype is more frequent in DS cases than translocation and mosaic karyotypes in southern Turkey. DS among Turkish population was more frequent in males than females. These findings can be highly informative for the segregation behavior of Robertsonian and reciprocal translocations and determination of the imbalance products in the progeny of the carriers of translocation. These findings can be used in clinical genetics and may be used as an effective tool for reproductive guidance and genetic counseling. Most children with DS are under the care of specialists. It has been proposed that adults should also be followed in multidisciplinary specialty clinics.

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