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ORIGINAL ARTICLE

Cytogenetic status of patients with congenital malformations or suspected chromosomal abnormalities in Turkey: a comprehensive cytogenetic survey of 11,420 patients

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Abstract
Cytogenetic analysis is helpful in diagnostic workup of patients having prenatal or early postnatal medical problems and provides a basis for genetic counseling or deciding on clinical treatment options. Chromosomal abnormalities (CAs) constitute one of the most important category of genetic defects which have the potential to cause irreversible disorders. In this study, chromosome analysis results of 11,420 patients having congenital malformations or suspected of having chromosomal abnormalities, who were referred to Çukurova University Research and Training Hospital Cytogenetic Laboratory over a 16-year period, were investigated, retrospectively. Of all patients analyzed, CAs were found in 1768 cases, accounting for 15.5% of all cases. It was observed that 1175 (15.5%) of CAs were numerical (10.3%) and 593 (5.2%) were structural chromosome abnormalities. Among numerical CAs, Down syndrome (DS), Turner syndrome (TS) and Klinefelter syndrome (KS) constituted common categories which were observed in 7, 1.1 and 0.9% of all cases, respectively. Among the structural CAs, translocations, inversions, fragilities, deletions,, and others were the most common categories and constituted 2.2, 0.9, 0.9, 0.7, 0.3, and 0.3% of all cases, respectively. The sex ratio (male/female) of all cases was 1.01 and of DS cases was 1.6. Our results further confirmed that cytogenetic analysis is necessary in terms of making definite diagnosis of genetic disorders, providing proper genetic counseling and clinical treatment, assessing the recurrence risk, and preventing the hereditary genetic diseases and disorders. Besides, such studies will greatly assist in constituting national and international databases or records of genetic disorders.

Keywords Cytogenetic analysis · Chromosomal abnormalities · Genetic counseling · Turkey

Introduction

Chromosomal abnormalities, as the causes of chromosome-level human genetic diseases, are conventionally divided into two main categories, numerical and structural abnormalities. Genetic diseases are a category of syndromes and conditions that includes infertility, amenorrhea, recurrent pregnancy loss, developmental delay, sexual development disorder, congenital abnormalities and dysmorphic features. Numerical or structural chromosome aberrations can cause various syndromes and conditions, including mental retardation, primary amenorrhea, irregular menstruation, recurrent pregnancy losses, male infertility, sexual development disorders, KS, TS, DS, Edward syndrome (ES), congenital abnormalities, and dysmorphic features. CAs occur around 0.5–1% of overall live births, and the frequency may increase to up to around 2% in live births to women over 35 years old (Theisen and Shaffer 2010; Kim et al. 2013). CAs affect at least 7.5% of all pregnancies, with most of these abnormalities resulting in spontaneous abortion. Studies show that approximately 50% of pregnancies with spontaneous abortion in the first trimester are due to CAs (Flynn et al. 2014; Pylyp et al. 2018; Santos et al. 2000). CAs can cause genetic diseases and disorders in pregnancies which reach the term and result in the delivery of live births. Therefore, the cytogenetic analysis of children with suspected genetic disorder is important for establishing the proper diagnosis and providing information about prognosis and recurrence risk for subsequently born siblings. Variations in the frequencies of genetic diseases and disorders may be linked to

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populations and geographic variations. Therefore, this retrospective study reveals the cytogenetic profile of children and adults with suspected genetic disorders referred to a genetic unit in Turkey, and our findings will help to identify the most common CAs in the region, thus making an important contribution to more accurate genetic counseling for a wide variety of genetic disorders.

Materials and methods

The present study compiled and analyzed the chromosome analysis results of 11,420 children and adults who had a suspected genetic disease and referred to the Genetics Laboratory at Cukurova University Medical Faculty Hospital with purpose of routine karyotyping over a period of 16 years (from 1998 to 2003). The age of the analyzed population ranged between 1 day and 70 years, and the average age was 3.2 years. The male-to-female ratio of all patients was 1.01; accordingly, the proportions of men and women among 11,420 cases were 50.2% and 49.8%, respectively. The total number of cases analyzed also included the karyotype results of cord blood samples obtained from 52 cases. In each case, after obtaining the detailed history of the patient and the informed consent form, cytogenetic analysis was performed. Patients were referred to cytogenetics laboratory due to having clinical findings compatible with DS, KS, and TS or due to having one or more of following conditions: infertility, amenorrhea, recurrent pregnancy loss, ambiguous genitalia, congenital abnormalities, dysmorphic features, mental retardation, growth retardation, hematological cancers, lymphoma, breast cancer, and psychiatric disorders. For chromosome analysis, a 2 mL of heparinized peripheral blood was obtained from each patient and lymphocyte cultures were established according to laboratory-standardized method. Lymphocyte cultures were harvested, and slides were prepared following the conventional procedure. The chromosomes were stained by using the Giemsa-Trypsin-Giemsa (GTG) banding method. In each case, at least 30 metaphases were analyzed; in cases of mosaicism, the number of metaphases analyzed was increased to approximately 100 metaphases. The karyotypic descriptions were reported according to the International System for Human Cytogenetic Nomenclature recommendations (ISCN, 2005).

Statistical analysis

The total number of events and the percentages of each group were recorded. The comparison of percentages was performed using the exact Fisher test. *P* values less than 0.05 were considered as statistically significant. All statistical analyses were performed using the R programming language.

Results

Chromosomal abnormalities were found in 1768 out of 11,420 cases, constituting 15.5% of all cases (Table 1). Of the 1768 cases with chromosomal abnormalities, 1175 (10.3%) showed numerical CAs, and 593 (5.2%) showed structural CAs. Among all numerical CAs, Down syndrome was represented with the highest frequency of 7%, which was followed by Turner (1.1%) and Klinefelter (0.9%) syndromes. Among the structural CAs, translocations (1.9%), inversions (0.9%), fragilities (0.7%), deletions (0.6%), and other constituted common categories (Table 1).

A total of 805 children who had DS and accordingly were carriers of trisomy 21 were analyzed over the 16-year study period (Table 1). These patients showed phenotypic findings such as dysmorphic facial features, flat facial features, small nose, developmental delay, speech deficiency, mental retardation, nasal bridge, small and abnormally shaped ears, congenital heart defects, and a single deep fold in the middle of the palm. The age of the analyzed population ranged between 1 day and 17 years, and the average age was 2.9 years. Nearly 75% of the DS cases were children less than 1 year old. The sex ratio (male/female) in this group of patients was 1.6, which is significantly higher than the population mean ($p = 0.006$). Out of a total of 805 cases who were referred for suspected DS, 742 cases (92.2%) had trisomy 21, 4 cases (0.5) had trisomy 21 along with an inversion of chromosome 9, 4 cases (0.5%) had trisomy 21 together with reciprocal translocation, and 4 cases (0.5%) had trisomy 21 together with deletion (Table 2). Specifically, free trisomy 21 was the most common karyotype, which was observed in 739 cases (92.0%). Besides, mosaic trisomy 21 and translocation type trisomy 21 were observed in 30 cases (3.7%) and 17 cases (2.1%), respectively. Structural irregularities of the long and short arms of chromosome 21 were observed in 8 (3.1%) cases.

As of numerical CAs, monosomy X (TS) karyotype was reported in 132 cases. In these cases, the clinical findings such as short stature, gonadal insufficiency, pterygium, sphinx face, primary/secondary amenorrhea, infertility, micrognathia, cubitus valgus, abnormal ears, low posterior hairline, short neck, short fourth metacarpal, webbed neck, spina bifida, kyphoscoliosis, nevus pilosus, lymphedema of the hands and feet, nail dysplasia, scoliosis, mental retardation, hypothyroidism, developmental concerns, and gastrointestinal and nutritional problems were observed. The age of this group of patients ranged between 5 months and 36 years, and the average age was recorded as 14.4 years. The TS karyotype (45,X) was found in 132 cases and accounted for 7.5% of all anomalies, of which 83.3% were pure, 4.5% were mosaic, and 12.1% were structural

Table 1 Distribution of numerical and structural chromosomal abnormalities in 11,420 patients with congenital malformations or suspected chromosomal abnormalities

	Karyotypes	No. of Cases	Freq. in all cases (%)	Freq. in all anomalies (%)
Abnormal Karyotypes	Normal Karyotypes (46,XX or 46,XY)	9652	**84.5**	
	(Numerical and structural chromosome abnormalities)	1768	**15.5**	
	Total	**11420**	**100**	
Abnormal Karyotypes				
Numerical				
Trisomy 21(including mosaics and structural abnormality)		**805**	**7.0**	**45.5**
Trisomy 18		**12**	**0.1**	**0.7**
Trisomy 13		**7**	**0.06**	**0.4**
Mosaic trisomy 8		**1**	**0.009**	**0.06**
Autosomal chromosome aberrations (including mosaic numerical aberrations,10%-60%)		**94**	**0.8**	**5.3**
Other (marker etc. including mosaics)		**6**	**0.05**	**0.6**
Monosomy X (including mosaics and structural abnormality)				
Klinefelter's syndrome (including mosaics)		**130**	**1.1**	**7.4**
		107	**0.9**	**6.1**
Other X and Y numerical deviations		**10**	**0.09**	**0.6**
Intersex (X and Y dependent numerical and structural deviations)		**6**	**0.05**	**0.3**
Total		**1175**	**10.3**	**66.5**
Structural				
Resiprocal translocations (including mosaics, derivative chromosomes and Ph+)		**216**	**1.9**	**12.2**
Robertsonian translocations [including rob(21)]		**40**	**0.4**	**2.3**
Inversions [inv(9) and others]		**99**	**0.9**	**5.6**
Deletions (including mosaics)		**73**	**0.6**	**4.1**
Duplications		**29**	**0.3**	**1.6**
Fragilities		**78**	**0.7**	**4.4**
Fragile-X		**20**	**0.2**	**1.1**
Isochromosomes (including mosaics and X chromosome)		**20**	**0.2**	**1.1**
Insertions		**1**	**0.009**	**0.06**
Ring chromosomes		**2**	**0.02**	**0.1**
Quadriradial chromosomes		**15**	**0.1**	**0.8**
Total		**593**	**5.3**	**33.5**

The number and precentage of cytogenetic abnormalities that are considered important were provided in boldface

variants. The frequencies of karyotypes showing numerical CAs are provided in Table 3. The second most prevalent karyotype category among numerical CAs was the KS karyotype (47,XXY), which were found in a total of 114 cases. These patients were referred to us due to the complaints such as tall status, narrow shoulders, broad hips, sparse body hair, gynecomastia, small testis, androgen deficiency, and normal to slightly decreased verbal intelligence. KS karyotypes accounted for 6.4% of all abnormal karyotypes, of which 93.9% were pure and 2.6% were mosaic karyotypes. Other sex chromosome aneuploidies constituted 3.5% of all anomalies (Table 3).

Structural chromosomal abnormalities were observed in 593 cases, which constituted 5.2% of all cases and 33.5% of all anomalies. The most common type of structural abnormalities was found to be translocations, which were found in 256 cases, constituting 14.5% of all anomalies and 43.2% of all structural anomalies. Reciprocal translocations were found in a total of 216 cases, which accounted for 12.2% of all anomalies and 84.4% of all translocations. This category of translocations was followed by Robertsonian translocations, which were found in 40 cases constituting 2.7% of all anomalies and 15.6% of all structural abnormalities. The second most common type of structural abnormalities were inversions, which were found in

Table 2 Frequencies and distributions of karyotypes in children with Down syndrome

Karyotypes		No. of cases	M/F (%)
	47,XY,+21 (Male)	493	61.3
	47,XX,+21 (Female)	312	38.7
	The male–female ratio (sex ratio, SR)		**1.6**
	Total	**805**	**100**
	Types of Down Syndrome		**% (n = 805)**
Free trisomy 21 (47,XX,+21 or 47,XY,+21)		741	**92.0**
48,XXX,+21		1	**0.1**
Mosaic trisomy 21		31	**3.9**
46,XY,+21,rob(21;21)(q10;q10)		6	**0.6**
46,XX,+21,rob(21;21)(q10;q10)		4	**0.5**
46,XX,+21,rob(14;21)(q11;q11)		4	**0.5**
46,XY,+21,rob(21;22)(q10;q10)		3	**0.4**
46,XY,+21,rob(14;7)		1	**0.1**
47,XY,+21,t(12q;16p)		1	**0.1**
47,XY,+21,t(11;21)(q23;q11)		1	**0.1**
47,XX,+21,t(3;21)(p11;p11)		1	**0.1**
47,XY,+21,der(22)t(9;22)(q34;q11)		1	**0.1**
47,XY,+21/47,XY,t(13q;19p),+13		1	**0.1**
47,XY,+21,inv(9)(p12;q21)		3	**0.4**
47,XX,+21,inv(9)(p12;q21)		1	**0.1**
46,XX,del(21q21 or q22)		4	**0.5**
46,XX,dup(21q)		1	**0.1**
46,XY/46,XY,ace(21p),del(21p11.2–cen–qter)		1	**0.1**
	Total	**66**	**8.2**

The number and precentage of cytogenetic abnormalities that are considered important were provided in boldface

99 cases, constituting 5.6% of all anomalies and 16.7% of all structural abnormalities. Fragile regions, deletions, and duplications were found in 78, 67, and 27, respectively (Table 4).

Discussion

In the present study, the prevalence of CAs was found to be 15.5% in all cases analyzed. This overall ratio of CAs was similar to the ratio which was found in a study conducted in the south of Turkey (16.1%) (Balkan et al. 2010). Besides, some studies in other countries found similar frequencies of overall CAs (12.2%, 13.4%, 14.3%, 17.5%, 18.6%) (Butler and Hamill 1995; Al Husain and Zaki 1999; Kim et al. 1999; Pal et al. 2020; Mao et al. 2015), and some studies even reported higher frequencies (21% and 29.3%) (Bouguenouch et al. 2019; Duarte et al. 2004). Alterations in the ratio of overall CAs between these studies may have resulted from differences in physicians' knowledge and interest in genetic diseases, patient selection and classification criteria, regional differences in the frequency of genetic diseases, and cytogenetic methods. In this study, the ratios of numerical chromosome abnormalities (66.5%) were found to be higher than structural abnormalities (33.5%). The numerical aberrations were divided into two groups according to their involvement in autosomal or gonosomal chromosomes. Consequently, it was found that the highest frequency of numerical aberrations involved autosomal chromosomes (45.5%), and this group of cases were mostly referred with suspicion of trisomy 21 (DS), which was followed by trisomy 18 (ES) (0.7%) and trisomy 13 (Patau syndrome, PS) (0.4%).

DS is the most common and best-known chromosome disorder in humans and its frequency in the general population is estimated to be 1 in 700 live births. The presence of extra 21 chromosome in the chromosome constitution of DS patients causes abnormal chromosome dosage and thus abnormal gene dosage, which causes the features defining the syndrome to develop. However, as of yet, the individual dosage-sensitive genes underlying each phenotype remain largely unknown. The most obvious defects observed in DS patients are mental retardation, characteristic facial features, hand anomalies, and congenital heart defects. Advanced maternal age at conception is a major risk factor for DS, as is true for all other human autosomal trisomies. This risk is associated with non-disjunction of homologous chromosomes or chromatids, which may occur during female meiosis or oogenesis. Environmental factors also influence the risk of non-disjunction (Pal et al. 2021).

Table 3 Distribution of chromosomal abnormalities in patients who were referred for chromosome analysis on suspicion of Turner syndrome, Klinefelter syndrome, and other sex chromosome anomalies

Karyotypes	No. of cases	Frequ. in all anomalies (%)
45,X (monosomy X)	**132**	**7.5**
47,XXY	**114**	**6.4**
Other sex chromosome anomalies	**10**	**0.6**
Turner syndrome		**(n = 132)**
Pure Turner 45,X	**110**	
Mosaic Turner (45,X/46,XX)	**6**	**4.5**
Mosaic Turner with isochromosome Xp abnormalities		
46,XX/46,X,i(Xp)	**2**	**1.5**
45,X/46,X,i(Xp)		
Mosaic Turner with isochromosome Xq abnormalities		
46,X,i(Xq)		
46,X,i(Xq)		
46,X,i(Xq)		
45,X/46,XX/46,X,i(Xq)		
45,X/46,X,i(Xq)		
45,X/46,X,i(Xq)		
45,X/46,XX/46,Xi(Xq)	**14**	**10.6**
45,X/46,XX/46,Xi(Xq)		
46,XX/46,X,i(Xq13)		
46,XX/46,X,i(Xq13)		
44,X,rob(14;15)		
45,X,del(Xq13)		
46,X,del(Xq25)		
45,X/46,X,del(Xq13)		
Klinefelter syndrome		**(n = 114)**
47,XXY	**107**	**93.9**
46,XY/47,XXY		
46,XY/47,XXY	**3**	**2.6**
46,XY/47,XXY, del(13q22)		
48,XXYY		
48,XXXY	**4**	**3.5**
49,XXXXY × 2		
Other X chromosome anomalies		**(no = 10)**
47,XXX		
47,XXX		
47,XXX		
46,XX/47,XXX	**10**	**0.6**
46,XX/47,XXX		
46,XX/47,XXX		

The number and precentage of cytogenetic abnormalities that are considered important were provided in boldface

In this study, the majority (72.4%) of child cases with karyotypically confirmed DS were younger than 1 year old in the present study. In other comparable studies, similar values of average age have been reported in patients with DS (Balkan et al. 2010; Thillainathan et al. 2015). In our study, another important difference found in DS cases was the sex ratio (male/female). In DS cases, the sex ratio was found to be 1.6 (510 males; 329 females), which was significantly higher than the sex ratio in the general population (1.01) (p=0.005). This finding showed that DS occurred mostly in boys. In another study conducted in Turkey, it was reported that 53.1% of DS cases were male (Balkan et al. 2010). Other comparable studies similarly reported that sex ratio was biased in favor of males in DS patients (Kovaleva

Table 4 Frequencies and distributions of structural chromosome anomalies in patients with congenital malformations or suspected chromosomal abnormalities

	Karyotypes	No. of cases	Freq. in all anomalies (n = 1768,%)	Freq. in all structural anomalies (n = 593,%)
Translocations		**(n = 256)**	14.5	43.2
Resiprocal translocations				
46,XX or XY,der(22),t(9;22)(q34;q11), Philadelphia chromosome (Ph+)		**140**	**7.9**	**23.6**
Others; (including mosaics)				
t(1;9)(p34.2;q34.3); t(5;9)(q35;q22); t(12;22)(p11;p11); t(13p;21p); t(Dp;Dp); t(2q;p22);+21,t(Dp;Gp); t(14p;21p); t(6;12)(q21;p11); t(6;11)(q25;q23); t(16;19)(q24;p11); t(5;12)(q34;p12); t(18;?); t(2;12)(q36;p12); t(15;17)(p22;q24); t(6;12)(q21;p11); t(6;11)(q25;q23); t(16;19)(q24;p11); t(5;12)(q34;p12); t(9;11)(p22;q23); t(11;?); t(2;8); t(11;16); t(3;9); t(3;13)(q23;q32); t(4;5)(q31;p15); t(9;13); t(16;19); t(12;?); t(16;19)(p24;q12); t(9;15)(q34;p12); t(3;6); t(7;1); t(2;3); t(10p;11q); t(11;21)(q23;q311); t(8;7); t(3;11); t(15;17); t(13;X)(q22;q28); t(9;11)(p22;q23); t(6;9); t(7;15); t(7;15); t(2;18); t(11;18)(q23;p12); t(8;X); t(7q;?); t(15;17); t(4;9); t(1;4); t(11:22); t(10;11)(q25;q25); t(11;22); t(9;22)(q34;q11); t(2;14)(q27;q22); t(4q;8p); t(4;11); t(3;12)(p25;q23); t(2;14)(q37;q26); t(1;12)(p36;p12); t(8;10)(q24;q24); t(12q;16p); t(6p;15q); t(2p;15q); t(3p;16q); t(6;11);		**76**	**4.3**	**12.8**
t(3;12); t(3p;7q); t(11;17) t(1;13); t(9p;22q); t(14;15); t(7;14)(p22;q22); t(2q;13q); t(5;8)(q23;p23); t(12;13)(p13;q14);		**40**	**2.7**	**6.7**
Robertsonian translocations				
including rob(21); rob(13;13)(p11;q11);rob(13;21);rob(13;14);rob(14;21); rob(14;21); rob(21p;21p); rob(14p;21p);rob(13;14); rob(14;15;),+mar; rob(15;14); rob(13;14); rob(13;14); rob(13;14); rob(14;7); rob(13;14); rob(14;21); rob(13;14); rob(13;14); rob(13;14); rob(15;22); rob(13;14); rob(13;14); rob(14;15)(including mosaics)				
Deletions		**67**	**3.8**	**11.3**
46,XX or 46,XY,del(1p15); del(3p); del(3p); del(3p?); del(4p-); del(4p-); del(4p); del(5)(p12;p13); del(5p1.3); del(5p13); del(5q34); del(5p13); del(5p12); del(5p-); del(5p); del(6p24); del(6q16); del(7q32); del(7q-?); del(7q-); del(7); del(7q34); del(7p); del(7q21); del(8q21); del(9)(q11;q13); del(9q13); del(11)(q12-q23); del(11q24); q15); del(11q23); del(11q23); del(11q24); del(l1p); del(11q); del(11q23);del(13);del(18p-); del(12p12); del(12q11); del(12p); del(12); del(13q22); del(13p); del(14p11); del(15q22); del(17); del(17p); del(18q); del(18p13); del(18); del(18p-); del(21q-); ace(21); del(21q22); del(21q21); del(21q); del(22q12); del(22q12); del(22); del(22q12); del(Xq25); del(Xq13); del(Yq) (including mosaics)				
Duplications		**27**	**1.5**	**4.6**
46,XX or XY, dup(15)(q11;q13); dup(5)(q22→cen→p22);				

Table 4 (continued)

	Karyotypes	No. of cases	Freq. in all anomalies (n = 1768,%)	Freq. in all structural anomalies (n = 593,%)
dup(2q23); dup(7p); dup(8q12); dup(8q24); 1qh+; 2qh+; 3q+; 4q+; 5q+; 6q+; dmin; 9p+; 9qh+×18; 13q+; 13 ps+; 14 ps+; 15 ps+×10; 16qh+×18; 16qh+, Ph+; 17p+×2; 18q+; 20q+; 21 ps+; 22 ps+×8; 21 ps+×6; Yqh+×15 (including mosaics)				
Inversions		**99**	**5.6**	**16.7**
46,XY or XX, inv(1)(p13;q32); inv(1)(p22;q23); inv(2)(p12;q13); inv(4)(q22;q34); inv(5)(q12;q25); inv(7)(p13;q21); inv(7)(p11;q22); inv(7)(p22;q22); inv(9)(p11;q13)×45; inv(9)(p11;q12)×12; inv(9)(p12;q21)×9; inv(9)(p12;q13)×11; inv(9)(p11;q21)×2; inv(10); inv(Xq13); inv(11)(p11;q13); inv(11)(q23;q13); inv(11)(p11;p15); inv(11)(p11;p14); inv(11)(p11;q13); inv(11),t(1;13); inv(12)(q12-q11); inv(14)(q13;q24); inv(X)(q22;q21); inv(Y)(q12-q11) (including mosaics)				
Fragile sites		**78**	**4.4**	**13.2**
fra(1q35); fra(1q21); fra(1p13); fra(1q21); fra(1q43); fra(1p36); fra(1q43); fra(1q35); fra(1); fra(1q2); fra(1p13); fra(2q35); fra(3p23); fra(3p2); fra(4); fra(5q32); fra(5q24); fra(5q31); fra(5q),(10q); fra(6q24); fra(7q36); fra(8p23); fra(8q24); fra(8q24); fra(8p23); fra(11q24); fra(11q23); fra(11q24); fra(11q23); fra(12q24); fra(12q24); fra(12q24); fra(12q24); fra(12q2); fra(13q32); fra(15q26); fra(16q24); fra(16q24) (including mosaics)				

The number and precentage of cytogenetic abnormalities that are considered important were provided in boldface

and Butomo 2002; Duarte et al. 2004). All these studies showed that the male-to-female ratio was higher in patients with DS in comparison with sex ratio in the general population, although there were significant differences between the sex ratios these studies reported (Kovaleva and Butomo 2002; Duarte et al. 2004). Publications reporting the cytogenetic profile of DS in the world revealed that carrying regular trisomy 21 or sporadic/hereditary translocation type trisomy 21 did not make difference between patient groups in terms of showing high male prevalence. The reason for the increase in the sex ratio in favor of males is not exactly known. However, it is hypothesized that the increased sex ratio in DS patients is due to a failure in chromosome segregation during spermatogenesis and that environmental factors might be considered important in terms of their effects on the chromosome segregation process. It is already known that the predominance of males in patient groups with DS is largely due to meiotic missegregation of the 21 and Y chromosomes (Kovaleva et al. 2001; Mikkelsen et al. 1989; Petersen et al. 1993; Savage et al. 1998). However, it has been suggested that segregation errors involving only chromosome 21 commonly occur during the second meiotic division of oogenesis, whereas segregation errors involving chromosomes 21 and Y frequently occur during spermatogenesis (Kovaleva and Butomo 2002). It has also been reported that the high frequency of sexual intercourse might lead to chromosomal segregation errors in spermatogenesis and these errors, in turn, might cause DS males (Kovaleva and Butomo 2002; Kovaleva and Butomo 1996). It has been suggested that there is a relationship between parental age and sex ratio in DS patients; accordingly, a study reported that males were not predominant among children with DS born to younger mothers, but the percentage of males were higher in children born to mothers older than 44 years (Iselius and Lindsten 1986). On the contrary, another study reported a predominance of male gender in DS children born to mothers younger than 35 years old, while elderly mothers had a high proportion of males (Verma and Hug 1987). The most common genetic cause of DS is complete or partial trisomy 21. In general, it is known that free/regular trisomy 21 is responsible for 95% of DS cases, translocations are responsible for ~5% of cases, and mosaicism is responsible for ~2% of cases. In the present study, complete trisomy 21 was observed in 92.2%, translocation type trisomy 21 in 2.2%, mosaicism in 3.9%,

and partial structural irregularities in 3.1% of DS cases. To our knowledge, the data presented in this report represents the largest national series of trisomy 21 cases. In the present study, DS cases comprised 7.0% of all cases analyzed and 45.5% of all abnormalities detected. Besides, in addition to chromosome 21, trisomy X was observed in one case. In support of our results, another routine cytogenetic study conducted in the southern region of Turkey reported that clinical phenotype or suspicion of DS was cytogenetically verified in 84.8% of cases which were referred for chromosome analysis, and the 88.7% of cases cytogenetically verified showed complete trisomy 21 and 0.9% of cases showed mosaic forms (Balkan et al. 2010). In another study, it has been reported that in Scandinavia, 90% of DS patients were complete trisomy 21, about 6% were translocation type trisomy 21, about 3% were mosaics, and less than 1% of DS cases carried abnormalities involving chromosome 21 (Mikkelsen 1988). Other studies also reported high ratios of free trisomy 21 (92–97%) in DS children (Kolgeci et al. 2013; Mutton et al. 1996; Owens et al. 1983; Mulcahy 1979; Pankaj et al. 2015). Our results seemed to be compatible with the results of other studies. In one case, we detected a double chromosome nondisjunction resulting in trisomies of chromosomes 21 and X (48,XXX,+21). Double trisomy is a rare event, possibly because in most cases, double nondisjunction causes death during the early stages of embryo development. A previous study reported a similar case of 48,XXX,+21. Molecular analyses in this study have shown that the origin of extra chromosomes is maternal meiosis I for chromosome 21 and maternal meiosis II for chromosome X (Güzel et al. 2009). Likewise, multiple aneuploidies (most often aneuploidy of the sex chromosomes combined with trisomy 13, 18, or 21) have been described in different studies (Jaruratanasirikul and Jinorose 1994; Tsukahara et al. 1994; Park et al. 1995; Kovaleva and Mutton 2005). An earlier report also described a case showing 48,XXY,+21 karyotype, where the origins of additional chromosomes were maternal meiosis II and paternal meiosis I for chromosomes 21 and X, respectively (Lorda-Sanchez et al. 1991). In the present study, 3.9% DS cases (31 out of 805 cases) showed mosaic karyotypes involving trisomy 21, an incidence rate which was found to be higher than the incidence rate of 0.7% reported in a recent study (Pankaj et al. 2015). Further confirming our result, it has been reported that mosaic aneuploidy is observed in 2-4% of DS cases worldwide (Mikkelsen 1977). Partial structural chromosome 21 defects occur very rarely. In the present study, structural irregularities were observed in chromosome 21 (3.1%), particularly in the long arm, in 2.9% of DS cases (23 cases). These structural irregularities included translocations, deletions, and duplications. The most common (2.1%) form of structural irregularities was found to be Robertsonian translocations. The rob(21q;21q) translocation occurred most commonly and was detected in 9 cases, followed by the rob(14;21) translocation which was detected in 4 cases.

Some investigators have also reported partial trisomies in the terminal portion of the long arms of chromosome 21 in DS patients (Aula et al. 1973). This shows that chromosome 21 is very sensitive to both anaphase segregation defects and breakages. These breakages can cause translocations or translocation type trisomy 21. Translocation carriers have a high risk of aneuploid offspring in every pregnancy. Although they cause no phenotypic abnormalities, balanced translocations can still have effects on the offspring of carrier parents. We found that chromosome 21 was transferred to chromosomes 3 and 11 in two DS cases. This shows that chromosomes 21 transfer not only among themselves and, to D- and G-group chromosomes, but also can transfer to other autosomal chromosomes. A very unusual and rare reciprocal translocation involving chromosomes 9 and 21 was noted in one DS patient in our study. However, we also reported a long arm duplication of chromosome 21. We detected a deletion in the long arm of chromosome 21 in four cases (0.5%). The 21q22.1-q22.3 region contains the genes responsible for the typical physical phenotypes observed in DS. The breakpoints of deletions reported in DS patients in the present study were within the 21q21-q22 region. These breakpoints were found to be in agreement with the breakpoints reported in other studies.

Following trisomy 21, in agreement with literature data, trisomy 18 and 13 were the second and third most commonly reported autosomal trisomies in the present study. The prevalence of ES and PS are highly dependent on maternal age. Both syndromes affect multiple systems and have a high risk of fetal death and short postnatal survival (Springett and Morris 2014). We found a small fragment of an unidentified chromosome (marker chromosome) in 6 children with Waandalay syndrome, dysmorphogenesis, developmental delay, and unable to speak, walk, and sit. The marker chromosome is a small extra chromosome which occurs in addition to the standard chromosome number. It may consist of inactive genetic material that has little or no effect on the phenotype, or it may carry active genes that affect the phenotype (Jafari-Ghahfarokhi et al. 2015).

We also found mosaic forms of autosomal aneuploidies involving autosomes other than chromosomes 21, 18, 13 at a very high rate of 5.3%. The cases with mosaic forms of autosomal aneuploidies showed mosaicism rate ranged from 10 to 60%. The aneuploidy rate in mosaic cases is an important determinant causing pathogenesis. Most cases of aneuploidy involving autosomes result in miscarriage. Autosomal aneuploidies which are more dangerous than sex chromosome aneuploidies, almost always cease embryonic development and cause death. Tumor tissues are typical in terms of containing a high rate of aneuploid cells, and accordingly, it has been shown that approximately 68% of human solid tumors carry aneuploidy (Sen 2000).

We detected a case showing mosaic trisomy 8 karyotype and dysmorphogenesis. Mosaic trisomy 8 is a rare genetic condition. Unlike complete trisomy 8, which develops as a result of a chromosome segregation error during gamete formation in meiosis and frequently causes first trimester loss, patients with mosaic trisomy 8 can survive. Mosaic trisomy 8 causes a wide spectrum of phenotypic features which include central nervous, ocular, cardiac, gastrointestinal, genitourinary, and musculoskeletal abnormalities (Datta et al. 2010). In relation to trisomy 8 condition, we found 47,XY,+del(8q12) and 46,XX,del(8p) karyotypes in two umbilical cord blood samples which referred to our laboratory due to suspected prenatal anomaly. In addition, we reported mosaic deletions in two regions of the long arm of chromosome 8 (q21 and q24) in two cases with developmental delay and dysmorphogenesis. These findings further confirm that an increase or loss of chromosome 8 material can cause phenotypic abnormalities or even death.

In the present study, the second most common category of aneuploidies were gonosomal aneuploidies. Accordingly, in this study, the 2.2% of all cases and 14.3% of all chromosomal abnormalities involved sex chromosome abnormalities. TS (45,XY), KS (47,XXY), other sex chromosome aneuploidies, and intersexes were found in 7.4%, 6.1%, 0.6%, and 0.3% of all abnormalities, respectively. Aneuploidies of the sex chromosomes are found in the general population at a frequency of approximately 1 in 1000. The effects of sex chromosome aneuploidies are milder than the effects of autosomal aneuploidies, and the prognosis of those cases is variable. They are often hard to recognize at birth and may not be diagnosed until puberty. Some individuals show mild symptoms, while others show more marked physical, endocrine, cognitive, and psychological symptoms. Complete TS is most commonly caused by the loss of an entire X chromosome. The Turner phenotype can also be produced by various partial X deletions or other structural abnormalities involving the loss of genetic material from any copy of X-chromosome. The root causes which are responsible for chromosome non-disjunction leading to the TS karyotype have not so far been identified. TS affects every 1:2500 live-born female. At least 99% of pregnancies with TS result in spontaneous abortion during the early period of gestation (Elsheikh et al. 2002). The physical phenotype which identifies almost all TS patients was also observed in our cases with TS. So, common phenotypic features associated with TS in the present study were short stature, mental retardation, growth retardation, primary and secondary amenorrhea, hyperthyroidism, and primary infertility. TS cases in this study included cases showing pure karyotype (45,X) (83.3%), somatic mosaicism (45,X/46,XX,4.5%), and other structural abnormalities involving the loss of genetic material from X-chromosome copies (12.1%). Structural abnormalities involving (87.5%) the long arm of X-chromosome were more common than those involving the short arm (12.1%), and there were complex TS karyotypes in 5.3% of cases which were denoted as [45,X/46,X,i(Xq), 45,X/46,XX/46,X,i(Xq), 45,X/47,XX,+i(Xq), 46,XX/46,X,i(Xq13)]. Three cases had deletions of the long arm of the X chromosome [45,X,del(Xq13), 46,X,del(Xq25), 45,X/46,X,del(Xq13)]. The X-chromosome deletions are usually sporadic, although some familial cases have been reported so far (Demirhan et al. 2016)

In this study, KS was found in 114 cases constituting 6.4% of all abnormalities. Classical KS karyotype (47,XXY) and mosaics (46,XY/47,XXY) and Klinefelter variants constituted 93.9%, 2.6%, and 3.5% of all KS cases, respectively. Literature data shows that about 80% of KS patients have a classical KS karyotype of 47,XXY, and 20% have other numerical sex chromosome abnormalities including mosaicism, or structurally abnormal sex chromosomes. The XXY aneuploidy is the most common disorder of sex chromosomes in humans. In these cases, the extra X chromosome is sporadically retained in the gametes due to the failure of X-chromosome copies to separate during the first or second meiotic division in the spermatogenesis process or due to mitotic missegregation in the developing zygote (Fryns 1982; Lanfranco et al. 2004). It was supposed that unknown reasons triggered the mechanisms causing KS karyotype in our cases, as well. Males with KS may present with a variety of subtle clinical signs that are age-related. Most cases showed the classic, well-defined phenotype, while others had various sexual behavior problems, mental retardation, and developmental delay. The KS cases in this study presented with complaints of long legs and arms, developmental delay, mental retardation, speech and language deficits, learning disabilities, hypogonadism, and behavioral problems (Fryns 1982; Lanfranco et al. 2004). In this study, three KS cases showed mosaic karyotypes of 45,X/46,XX, 46,XX/47,XXX, or 46,XY/47,XXY. Although major medical problems were not present in these cases, some mild medical conditions seen in our cases may have stemmed from trisomy X. Four KS cases (3.5% of all KS cases) showed Klinefelter variants, which were represented by 48,XXXY, 48,XXYY, and 49,XXXXY karyotypes. Extra copies of genes on the extra X and Y chromosomes contribute to the signs and symptoms seen in these cases. The incidence of 49,XXXXY is 1 in 85,000 to 100,000 male births, and these cases are severely affected from this extreme type of aneuploidy (Linden et al. 1995). Our cases presented with moderate mental retardation and advanced developmental delay. The extra X chromosomes in these variants accrue during maternal meiosis I and II and should be the product of a double nondisjunction event (Simsek et al. 2009).

Structural chromosomal aberrations (SCAs) are usually caused by chromosomal breaks and abnormal recombination of broken chromosomes, and many of these do not result in gain or loss of DNA. As seen in Table 4, we reported very significant SCAs in our cases. The balanced and unbalanced

SCAs were observed in 593 cases accounting for 33.5% of all abnormalities and 5.2% of all cases. The balanced translocations rate was 14.5% in all anomalies. The balanced SCAs involved mostly translocations and some inversions. Although balanced rearrangements include inverted or translocated chromosomal regions, these types of chromosomal rearrangements may not lead to phenotypic manifestations or cause disease, because the full complement of DNA material is still represented in the relevant genome. Therefore, in general, carriers of balanced translocations have a normal phenotype but are at higher reproductive risk. Accordingly, in this study, most balanced translocations were detected in couples with a history of miscarriage and the most common reciprocal translocation of t(9;22)(q34;q11), Philadelphia chromosome, was found in 140 cases with chronic myeloid leukemia (23.6% of all structural anomalies). In general, no genetic material is lost in reciprocal translocations; but as seen in the Philadelphia chromosome, a disease can also arise as a result of a balanced rearrangement. If breaks in the chromosomes occur within the genes, then the fusion of chromosomal segments may result in a hybrid gene, which is formed from the fused parts of two previously separate genes and produces a new protein product that damages the cell. Therefore, 6% of the prenatally detected de novo balanced reciprocal translocations have been associated with a risk of important congenital abnormalities (Gardner and Sutherland 2012; Kim and Shaffer 2002; Warburton 1991). An overwhelming majority of reciprocal translocations in the present study appear to have occurred between autosomal chromosomes. The most common autosomes involved in these types of rearrangements included chromosomes 15, 21, and 22. The pericentromeric regions of these chromosomes are predisposed to pairing with the X chromosome. We found X-autosome translocations in two cases; however, they involved autosomes other than chromosomes 15, 21, and 22.

In the present study, the number of cases with Robertsonian translocations corresponded to 15.6% of cases carrying overall translocations, 2.3% of cases having chromosome abnormalities, and 0.4% of all cases. Robertsonian translocations have an estimated incidence rate of 1/1000 births, which makes this type of rearrangement the most prevalent structural chromosomal abnormalities among the general population (Kim and Shaffer 2002; Zhao et al. 2015). Robertsonian translocations do not have phenotypic consequences as acrocentric chromosomes lose only their short p-arms containing ribosomal RNA. But, unbalanced gametes of heterozygous carriers give rise to a monosomic or trisomic fetuses, which are spontaneously aborted during the early stages of pregnancy (Kim and Shaffer 2002; Zhao et al. 2015).

Unbalanced rearrangements include deletions, duplications, or insertions of any chromosomal segment and can be de novo or familial. Deletion is a type of chromosomal rearrangement which involve the loss of genetic material. Cytogenetically visible deletions occur in 1 in approximately every 7,000 live births (Brewer et al. 1998). Deletions can often cause severe congenital anomalies and significant mental and physical disabilities. The range and severity of symptoms varies, greatly depending on the location and size of the missing genetic material. In this study, deletions were detected in 67 cases, which comprised 3.8% of all abnormalities and 11.3% of all structural abnormalities. In general, cases carrying deletions were referred to our laboratory with the complaints of growth retardation, acute lymphoblastic leukemia, chronic myeloid leukemia, myelodysplastic syndrome, retinoblastoma, breast cancer, spina bifida, dysmorphogenesis, spontaneous abortion, secondary amenorrhea, mental retardation, gait disturbance, and cleft palate. In this study, deletions were most frequently detected in chromosome 11 followed by chromosomes 5, 22, and 18, respectively. Chromosome 11q deletion is a rare chromosomal disorder, and the exact cause of this type of deletion was not fully understood. The cases carrying deletions involving chromosome 11 were referred to our laboratory due to complaints of a bad obstetric history, mental retardation and growth retardation, acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, and spina bifia. Accordingly, structural rearrangements in the chromosome 11q23 region have been previously reported to be involved in hematological diseases; particularly rearrangements involving 11q23/MLL locus were frequently encountered in acute leukemia, and rearrangements involving 11q23/MLL were observed in therapy-related AML (Rowley 1993; Pui et al. 1994). In addition to confirming previous findings, our results showed that partial monosomy 11q could be associated with symptoms such as abnormally slow growth, moderate to severe delay in mental and muscle activity, bleeding due to head, face, hands, feet, ear defects, platelet abnormalities, and immunological defects. We reported del(5p) in seven cases showing clinical manifestations of delayed gait and speech and hematological malignancy. Cri du chat syndrome, which is seen in one out of every 50,000 live births, is caused by a deletion in the short arm of chromosome 5 and is characterized by mental retardation and a number of physical defects. The deletion occurs very early in the development of an embryo. In general, the severity of the symptoms is determined by the size and location of the deletion on chromosome 5 (Chen et al. 2004). We have also reported 18q deletion in four cases presenting with spontaneous abortion and prenatal fetal abnormalities.

Chromosome 18q- deletion is a rare chromosomal disorder, which describe a deletion on the long arm of chromosome 18, and the deletion usually results from spontaneous mutations occurring very early during embryonic development. The syndrome-associated symptoms and the severity of symptoms may vary greatly; however, characteristic

features include short stature, mental retardation, hypotonia, malformations of the hands and feet, and craniofacial anomalies. Some affected individuals may also have visual abnormalities, hearing impairment, genital malformations, structural heart defects, and/or other physical abnormalities (Budisteanu et al. 2010; Bohîlţea et al. 2020). We reported 22q12 deletion in four cases presenting with complaints such as chronic myeloid leukemia, cleft palate, and growth retardation. 22q11.2 deletion or syndrome, which is caused by the deletion of a small piece of chromosome 22, has a prevalence of approximately 1 in 4000 live births. This syndrome shows a wide range of signs and symptoms that can affect almost any part of the body. So, the 22q11.2 deletion syndrome is commonly associated with congenital heart abnormalities, recurrent infections, distinctive facial features, submucosal cleft palate, genitourinary abnormalities, mild short stature, and abnormalities of the spinal bones (Swillen and McDonald-McGinn 2015).

In the present study, the second most common type of structural CAs was found to be inversions which detected in 0.9% of all cases and in about 6% of all abnormalities. Inversions affecting the pericentromeric region of chromosome 9 were found far more frequently than inversions affecting other chromosomes. The pericentric inversion of chromosome 9 is considered as one of the most common structural chromosome variants or a normal population variant, and accordingly, it does not cause any specific phenotypic abnormality in most cases. However, carriers of large pericentric inversions are at risk for meiotic recombination within the inverted segment, resulting in duplication or deletion of relevant parts of chromosomes in the gametes. Gametes carrying a duplication or deletion as a result of inversion 9 may cause spontaneous fetal death or malformed offspring. In line with this reasoning, many studies have reported that inversion 9 was closely associated with recurrent spontaneous miscarriage, infertility, congenital anomalies, schizophrenia increased risk of offspring with DS, and idiopathic reproductive failure (Elkarhat et al. 2019; Jeong et al. 2010; Demirhan et al. 2008; Sipek et al. 2015). In agreement with literature findings, in our cases with inversion 9, there were complaints of mental and developmental delay, spontaneous abortus, amenorrhea, poor obstetric history, risky pregnancy, irregular menstruation, and cryptorchidism.

Chromosomal duplication defines the presence of one or more extra copies of any chromosomal region in the genom, meaning that the genes located in the boundaries of this chromosomal region are represented by three or more copies in the genome. Duplications may affect phenotype by altering gene dosage (Clancy and Shaw 2008). Children born to parents carrying duplications often survive, but they may exhibit physical and mental abnormalities (D'Angelo et al. 2014). We found the important duplications in 27 cases, which account for 1.5% of all anomalies and 4.6% of all structural anomalies. These cases were referred to our laboratory due to complaints of spontaneous abortus, amenorrhea, poor obstetric history, and risky pregnancy.

Fragile sites (FSs) are considered have a role in the genetics of disorders and might be accepted as potentially informative endpoints in the investigation of clinical disorders. Thus, identification of FSs may be especially important because of their unknown etiology and function (Bassett 1992). In this study, FSs were found in 78 cases who were diagnosed with developmental and speech retardation, mental retardation, anemia, chronic myeloid leukemia, spontaneous abortion, risky pregnancy, poor obstetric history, lymphoma, low ears, short neck, and fragile-X syndrome. These FSs accounted for 4.4% of all anomalies and 13.2% of all structural anomalies. The FSs detected in chromosome analysis may also serve as a starting point for gene-level analyses, which will contribute to a better understanding of the pathophysiology of any accompanying disorder.

Conclusion

This comprehensive study, which is based on retrospective screening of karyotype results of a vast number of patients (11,420 patients) presented with various clinical findings, provided the rates of chromosomal abnormalities in a huge group of patients and so constituted an extensive database of common chromosomal abnormalities in Turkey. The results of this study were found to be in general agreement with the results of previous studies. This study concludes that chromosomal defects are significantly associated with both isolated and multiple congenital defects. Therefore, it is recommended that chromosomal analysis should be done in all patients with congenital malformations and/or suspected chromosomal abnormalities, and chromosome analysis should be considered as a basic requirement for better management and proper counseling of those patients. In such patients, when any chromosomal abnormality cannot be detected, other possible causes of defects, e.g., single gene defects, and multifactorial or environmental factors must be probed in order to find possible management strategies.

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Author contribution Osman Demirhan conceived study, analyzed data, and wrote the paper. Erdal Tunç analyzed data and wrote the paper. All authors read and approved the final manuscript.

Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Competing interests The authors declare no competing interests.

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