Incidence of chromosome abnormalities in the Sultanate of Oman

Mallana T. Goud, *PhD,* ***Salma M. Al-Harassi,*** *MSc,* ***Shafiya A. Al-Khalili,*** *BSc,* ***Kamla K. Al-Salmani,*** *Diploma in MLS,* ***Suleiman M. Al-Busaidy,*** *BVMS, PhD,* ***Anna Rajab,*** *MD (Paed), PhD.*

ABSTRACT

Objectives: To evaluate the cytogenetic findings in Omani children referred for suspected chromosomal anomalies that caused a variety of clinical disorders. Secondly, to study the frequency of chromosomal abnormalities in these patients and to compare our results with those reported elsewhere.

Methods: We performed chromosomal analysis on 1800 consecutive pediatric patients referred to the Cytogenetics section between June 1999 and May 2004 at Central Public Health Laboratories, Sultanate of Oman. Indication for referrals for exclusion of chromosomal rearrangements was multiple congenital anomalies, dysmorphic features, unclassified mental retardation, developmental delay, growth, and endocrine disorders. We carried out the lymphocyte culture according to standard methods.

Results: We found various types of chromosomal anomalies in 510 (28.3%) children and showed abnormal karyotypes in the form of trisomy 21 (391; 21.7%), trisomy 18 (32; 1.8%), trisomy 13 (20; 1.1%), sex chromosome aberrations (50; 2.8%) and other types of abnormalities (17; 0.95%). There was a considerable phenotypic-cytogenetic heterogeneity. We found a high rate of chromosomal abnormalities in the present study, and we observed variations in the frequency of chromosomal aberrations reported by different investigators.

Conclusion: The higher incidence of the chromosomal abnormalities demonstrates the importance of cytogenetic evaluation in patients with dysmorphic features and congenital anomalies. Our findings suggest that chromosome analysis is a useful tool in the investigation of children with genetic disorders of unknown origin for confirmation of clinical diagnosis and proper medical care followed by genetic counseling and management.

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Chromosome analysis is an important component in the diagnosis and evaluation of genetic disorders. To date, reports include approximately 1000 chromosome syndromes, and while on an individual basis most of these are rare, together they make a major contribution to human morbidity and mortality.[1] The impact of chromosomal abnormalities during fetal life is at its highest frequency and represents a major cause of fetal loss.[2] The frequency of various chromosomal abnormalities is quite different in neonates (0.7%), pregnancies in women over 35 years (2%) as compared to abortuses (50%) since some aneuploidies are lethal in utero[3] and a few full trisomies are not necessarily lethal in utero, and many partial chromosomal aneuploidies are associated with survival through to the birth of an infant. One in every one hundred live born child can have a chromosomal abnormality, and half of the

From the Department of Public Health Laboratories (Goud, Al-Harassi, Al-Khalili, Al-Salmani, Al-Busaidy) Central Public Health Laboratories and the Department of Pediatrics (Rajab) , Directorate General of Health Services, Ministry of Health, Muscat, *Sultanate of Oman.*

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Address correspondence and reprint request to: Dr. Mallana T. Goud, Cytogenetic Section, Central Public Health Laboratories, Darseit, Directorate General of Health Services, Ministry of Health, Muscat, Post Box # 393, Postal Code # 113, *Sultanate of Oman.* Tel. +968 24788250. Fax. +968 24788250. E-mail: tmgoud_99@yahoo.com / cytolab@omantel.net.om

first trimester spontaneous abortions can be due to chromosomal abnormalities.[4] Changes in the number or the structure of chromosomes, which affect the autosome, as well as the sex chromosome[5,6] form major causes of mental retardation (MR), multiple malformations, cancer, infertility and spontaneous abortions.[7,8] It is agreed that autosomal aberrations are the single most common cause of severe MR,[9] and that abnormalities in the number of sex chromosomes, generally have less devastating effects than aneuploidies in the autosomes.[6] Hence, we designed the present study to investigate the frequency and types of chromosomal abnormalities in Omani children with suspected genetic disorders to identify precisely the role of cytogenetic investigation in confirming the clinical diagnosis, thus allowing proper genetic counseling to be offered.

Methods. One thousand, eight hundred cases (cancer patients excluded), referred to the cytogenetics unit, Central Public Health Laboratories, Ministry of Health from various hospitals in Oman over 5 years between June 1999 to May 2004 were investigated. The study included mostly newborn children, age range newborn to 13 years, with various phenotypic abnormalities such as genetically uncertain syndromes, multiple congenital anomalies, developmental delay, growth and endocrine disorders, dysmorphic features, unclassified MR and known syndromes. Cytogenetic analysis was carried out on all the patients. The study included peripheral blood lymphocyte culture using the conventional Geimsa-banding (GTG banding)[10] technique. For routine cytogenetic analysis, 0.6 ml-0.8 ml of peripheral blood was incubated in complete lymphocyte culture medium (20% fetal bovine serum in RPMI – 1640 with 0.3% Phytohemagglutinin and pen-strep) in 5% CO_2 incubator at 37°C for 3 days. Metaphases were harvested by adding karyomax colcemid solution (final concentration of 0.10 ug/ml) for 45 minutes followed by hypotonic Kcl (0.075 M) treatment for 15 minutes and fixation using standard 3:1 methanol and glacial acetic acid fixative. A high–resolution study was carried out by synchronization technique by adding thymidine solution (15 mg/ml) for 16 hours before harvesting.[11] At least 20 metaphases were scored for each patient. Three cells were karyotyped, and usually the total chromosome count was determined in 10-15 cells. If mosaicism was suspected 30 or more cell counts were undertaken,[12] microscopic photography and karyotype were carried out for documentation of abnormal cases.

Results. Of the 1800 cases studied, 510 (28.3%) patients revealed obvious chromosomal abnormalities; of these, 460 (25.55%) involved autosomes, while only 50 (2.8%) involved sex chromosomes. **Table 1** summarizes the category and frequency of the identified chromosome abnormalities, and **Table 2** indicates the genetic disorders in patients referred for cytogenetic studies. Four hundred and forty-three patients had autosomal trisomy, trisomy 21 was detected in 76.7% of the cytogenetically abnormal cases, forming the majority. Forty patients (7.8% of cytogenetically abnormal cases) had sex chromosome aberrations (**Tables 2 & 3**). Klinefelter's syndrome (KFS)/ Variant KFS was detected in 18 male patients. One male patient had Double Trisomy (48, XXY+18). Triple X syndrome was detected in one patient with 48, XXX. Fourteen female patients (2.7%) were monosomic X (45, X), one was mosaic with 45X/ 46XX and 2 were mosaic variants with 45,X/46,X, i(X)(q10)/46,XX; and 45,X/46,X,i(X)(q10). Eighteen cases were referred because of dysmorphic features/ developmental delay and multiple congenital anomalies. The cytogenetic findings in these cases are listed in **Table 3**. Two patients (11.1%) had partial trisomy: one infant referred with dysmorphic features? +18 syndrome had 46, XX der(21) t(8;21) (p11.2;p11) with partial trisomy of # 8p [as a consequence of paternally inherited balanced translocation carrier t(8;21)(p11.2;p11)]. The second patient had partial trisomy of 7q, mother was carrier for a balanced translocation (7;14) (q22;p10). Five patients (27.77%) had supernumerary marker chromosome. One patient and his father showed marker chromosome. The precise origin of the markers could not be determined using available techniques, as they were smaller than G-group chromosomes. Three patients (16.66%) had reciprocal translocations one with developmental delay with 46,XX, t(X;2)(p;p), one with short stature and subtle features had 46,XX, t(14;20) (q11.2;q12.1)the other with dysmorphism with 46,XX, t(3;22)(q21;q13).

Table 4 shows the distribution of numerical and structural chromosomal abnormalities in 510 cases. Fifty-nine patients (3.3%) showed normal variants, of which 30 had 15p+, 9 patients with inv (9), 17 male patients with short Y, 2 male patients with long Y and one patient with 13p+.

Discussion. Several surveys have reported the frequency, and types of chromosomal abnormalities in patients suspected to have genetic disorders.[13-20] Among consecutive newborn surveys, autosomal abnormalities are usually as common as sex chromosome abnormalities.[21] In the present study, sex chromosomal abnormalities accounted for 2.8% and autosomal 25.55%, and this finding is in concordance with reported studies.[22,28] This is mainly due to the fact that sex chromosome

Table 1 - Categories and frequency of the chromosome abnormalities identified.

Category	No. of cases	(%)
Trisomy 21(Down syndrome) (including mosaic + R.T*)	391	(21.8)
Trisomy 18 (Edwards syndrome)	32	(1.8)
Trisomy 13 (Patau syndrome) (one RT*)	20	(1.1)
47, XXY (Klinefelter's syndrome) (includes mosaic and variant types)	18	(1)
Monosomy X (Turner's syndrome) (includes mosaic and variant types)	14	(0.8)
Ambiguous (having opposite genetic constitution) (true hermaphrodite)	11	(0.6)
Testicular feminization syndrome	3	(0.2)
69, XXY / 69, XXX (triploidy)	2	(0.1)
Marker chromosome	5	(0.3)
47, XXX (triple X syndrome)	1	(0.1)
Dysmorphic features / mental retardation / congenital anomalies / developmental delay, and so forth	13	(0.7)
Normal variants	59	(3.3)
Normals	1178	(65.4)
Failure	53	(2.9)
Total	**1800**	**(100)**

RT - Robertsonian translocation

Table 2 - Genetic disorders in patients referred for cytogenetic studies.

Karyotype	Phenotype	No. of cases
47, XY, / 47, XX +21	Down syndrome	372
46, XX/XY, t(13;21)(q10; q10)	Down syndrome	12
46, XX/XY, t(14;21)(q10; q10)	Down syndrome	
46, XX/XY, t(15;21)(q10; q10)	Down syndrome	
46, XX/XY, t(21;21)(q10; q10)	Down syndrome	
46, XY/XX / 47,XY/XX (mosaic)	Down syndrome	5
47, XY, +del(21)(q12)	? Down (dysmorphic)	1
47, XX, 5p+, +21	Down syndrome	1
47,XXY	Klinefelter syndrome	14
47, XXY/46,XY	Mosaic klinefelter syndrome	1
48,XX YY; 49, XXXXY; 48,XXXY	Variant klinefelter syndrome	3
47, XY / XX +18	Edward syndrome	30
48,XXY, +18 (double Trisomy)	Klinefelter and Edward syndrome	1
47, XX, +1mar (smaller than # 18)	? +18 syndrome	1
47, XY/XX, +13	Patau syndrome	19
46, XY, +13, t(13;14)(q10;q10)	Patau syndrome	1
45, X	Turner syndrome	11
45,X / 46XX	Mosaic turner syndrome	1
45, X / 46, X, i(X) (q10) / 46, XX	Mosaic variant turner syndrome	1
45, X / 46, X, i(X) (q10)	Mosaic variant turner syndrome	1
46,XY/XX (having opposite genetic constitution to the phenotype)	Ambiguous genitalia	10
46,XY (female phenotype with 46, XY)	True hermaphrodite	1
46,XY	Testicular feminization syndrome	3
47, XXX (triple X syndrome)	Soft dysmorphism / clinodactyly	1
69, XXY (triploidy)	Grossly dysmorphic	1
69, XXX (triploidy)	? Trisomy # 18, preterm dysmorphic	1

imbalance has a much less devastating effect on the phenotype than autosomal aneuploidy.[17,21] The overall incidence of major chromosomal abnormalities is 0.5-0.55% in surveys of unselected populations.[15,16] We detected a high rate of chromosomal abnormalities (28.3%) in the present study from a total of 1800 cases. **Table 5** illustrates the wide variations observed in the frequency of chromosomal aberrations from 13.4 to 43.0 in individuals suspected of having genetic disorders reported by different investigators.[13,17,19,20,22-29]

Down syndrome (DS) is the archetypal chromosome disorder. It was the first medical condition shown to result from a chromosome abnormality. In the present study, we found the frequency of DS to be 76.7%, a value similar to other surveys,[18,30,31] and lower than a study observed in Saudi Arabia.[24] We can attribute this to its easy detection at the clinical level. Some authors postulate a direct relationship of consanguinity with a higher incidence of DS,[32] and consanguinity is common in Oman, like other Middle Eastern countries. The distribution of different anomalies associated with DS in the present study is very similar to earlier reports.[33,34] Regular trisomy 21 in 95.7%, Robertsonian translocation of 21 in 3.1% and mosaic trisomy 21 in 1.3%. Frequency of regular trisomy 21 was 95.7%, agreeing with other surveys, which range from 84.6-95%.[21] The frequency of translocation DS was 3.1%, which is less when compared with previous reports of 8.3%,[28] 5.6%,[35] 5.2%,[36] and 6.8%.[37] 47, +21/46, N mosaicism accounted for 2-3%, but we found only 1.3% in the present study (**Table 2**).

In the present study, Trisomy 18 and Trisomy 13 formed the 2nd and 3rd largest Trisomy groups (**Table 1**). As with trisomy 21, a beginning has been made in the correlative phenotypic mapping of certain segments of chromosomes 18 and 13,[38,39] Ninety-three percent of Edward's syndrome had regular trisomy; one double aneuploidy, one with marker smaller than 18 was recorded in this study, other surveys showed 80% with full Trisomy.[40] Approximately 10% of cases are caused by mosaicism or unbalanced rearrangements, particularly Robertsonian translocations in cases of Patau's syndrome,[1] one patient had Robertsonian translocation with 46,XY,+13, t(13;14)(q10;q10) in the present study (**Table 2**).

Infertility is almost inevitable in Klinefelter syndrome, but remarkable exceptions exist. The frequency of the sex chromosomal aneuploidy in the newborns is 0.2%. Among which one in 500 to 1000 newborn males may have the karyotype of Klinefelter syndrome (KFS).[41] The frequency of the KFS with 47, XXY karyotype in this study, was higher than the reported range in the literature (**Table 1**). We observed rare variants and mosaicism (one case) with 46, XY/47, XXY, and 3 male patients with more than 2 X-chromosomes 48, XXYY, 48,XXXY and 49, XXXXY. These patients are usually quite severely retarded as reported in a previous study.[1] Thompson et al[3] reported the incidence of Turner syndrome in consecutive neonates to be 0.04%. The present study included 14 (2.7%) infants with Turner syndrome. Their chromosomal patterns were variable; 45, X (7 cases), one patient was mosaic with 45X/46,XX and, 2 patients were mosaic variant type, 45,X/46,X,i(X)(q10)/46,XX (one case), and 45,X/46,X,i(X)(q10) (one case). The frequency is in correlation with Mokhtar,[28] but lower than that reported by Guera[42] at 18%.

Triploidy is a common finding in spontaneously aborted products of conception, but rare in live born infants.[15] We found in our study 2 newborn infants had triploidy (69,XXX and 69,XXY) but they died within 5 days of birth. Such a child will usually show severe intra-uterine growth retardation with other dysmorphic features, these triploid cases with a double maternal contribution survive for longer, but rarely beyond the early neonatal period.[1] We reported a case of double trisomy involving chromosome 18 and the sex chromosomes (48,XXY, +18) (Klinefelter/Edward syndrome) in a child. Although non-disjunction is the most common cause of chromosome abnormalities, we rarely observe the presence of 2 numerical abnormalities in a single conceptus. From a careful review of the literature, reports show only a few cases of double trisomy so far.[43]

Of the total cytogenetically abnormal cases, we detected 1% of partial autosomal aneuploidies from our study, which is less reports in other studies (3.6%),[28] and higher than that of Al Awadi et al[18] (0.3%). We presume that gain or loss of several contiguous genes along the chromosome involved will explain the phenotypes of these conditions. A small accessory chromosome of unknown origin is often referred to as a marker chromosome (mar).[44] In the present study, we detected a marker chromosome in 5 patients who had dysmorphism. We define marker chromosomes as abnormal chromosomes that we cannot be fully characterize based on standard cytogenetic analysis.[45] Reports have found the incidence of marker chromosomes to be 0.024% among neonates,[46] and estimated as 0.4-1.5 in 1000 pregnancies in prenatal conditions.[47] Most of the pericentric inversions, 15p+, short 'Y' and long 'Y', which we report in this study, are observed in humans but do not in themselves give rise to any specific phenotypic abnormalities. Another study[48] reports that break points in alpha, beta, and satellite III DNA sequences of chromosome 9 result in a variety of pericentric inversions. However, pericentric inversion has been found to be associated with infertility, repeated fetal loss, congenital anomalies and mental retardation.[21]

Table 3 - Chromosomal abnormalities in cases of dysmorphism, developmental delay/MCA and so forth.

Referral diagnosis	Karyotype	Comment
Dysmorphic,? +18	46,XX, der(21)t(8;21)(p11.2;p11)	Partial trisomy of chromosome 8p
Dysmorphic,? deletion	46XX, del(4)(p15)	Wolf-Hirchhorn syndrome
Dysmorphic	46, XX del(5)(p13)	Cri du-chat syndrome
Developmental delay	46, XX, t(X; 2)(p; p)	Reciprocal translocation
Dysmorphic	46, XX, del (X)(p21)	Short arm deletion of chromosome X
Child's father had inv(Y)	46, X; inv(Y)	Pericentric inversion of Y
Dysmorphic	46, XY, add(18)(q23)	Possibility of 18q syndrome
Dysmorphic	46, XX, del(10)(p12 or 13–ter)	Short arm deletion of chromosome 10
Dysmorphic	47, XX, +1mar / 46, XX	Marker chromosome
Antenatal diagnosis – bilateral hydronephrosis	47, XY, +1mar	Marker chromosome
Dysmorphic child	47, XX, +1mar	Marker chromosome
Dysmorphic child	47, XX, +1mar	Marker chromosome
Dysmorphic/MCA	46, XX, 18(q+)	Partial trisomy of chromosome 18q
Short stature with subtle features	46,XX, t(14;20)(q11.2;q12.1)	Reciprocal translocation
Dysmorphism /MCA/CHD	46, XX, t(3;22)(q21;q13)	Reciprocal translocation
? Trisomy # 18	46, XY, der(14), t(7;14)(q22;p10)	Partial trisomy of 7q
? Downs syndrome	46, XY (a small chromosomal fragment without centromere)	-
Dysmorphic	46, XY, del(18)(pter→ p11.2) or t(15;18)(p11;p11.2)	Short arm deletion of chromosome 18

t - translocation, del - deletion, add - addition, der - derivative, mar - marker chromosome, inv - inversion, MCA - multiple congenital anomaly, CHD - congenital heart disease.

Table 4 - Distributions of numerical and structural chromosomal anomalies in 510 cases.

Chromosomal aberration	n (%)
Numerical	
Trisomy 21 (including mosaic)	377
Trisomy 18	32
Trisomy 13	19
XXY	15
XXX	1
XXYY	1
XXXY	1
XXXXY	1
48, XXY, +18	1
Monosomy X (including mosaic)	12
69,XXX / 69, XXY (triploidy)	2
Total	**462 (90.6)**
Structural	
Iso chromosome X	2
Additions	3
Deletions	6
Reciprocal and robertsonian translocations	15
Marker chromosome	5
Inversions	1
Unbalanced derivative chromosome	2
Total	**34 (6.7)**
Others	
Ambiguous genitalia (having opposite genetic constitution to the phenotype)	10
True hermaphrodite	1
Testicular feminization syndrome	3
Total	**14 (2.7)**

Table 5 - Comparisons of the frequencies of chromosomal aberrations of present study with other similar studies reported by different investigators.

Name of the investigator	Total patients examined	Frequency of chromosomal aberration found (%)
Berry et al[17] (1991)	–	– (15.8)
Navasaria et al[26] (1993)	1000	166 (16.6)
Al Arrayed[19] (1991)	–	– (27.0)
Verma and Dosik[20] (1980)	–	– (27.2)
Winter et al[27] (1980)	140	60 (43)
Mokhtar[28] (1997)	137	53 (38.7)
Shah et al[13] (1990)	–	– (39.6)
Singh[29] (1977)	451	130 (28.8)
Al-Awadi et al[22] (1985)	1550	434 (31.7)
Mitra et al[23] (1988)	325	77 (23.6)
Hussain and Zaki[24] (1999)	1000	134 (13.4)
Hatem and Jamil[25] (2002)	747	152 (20.3)
Present study (2004)	1800	510 (28.3)

In conclusion, these findings suggest that we should view a request for chromosomal analysis in the newborn period as an important step in syndrome identification and is useful in the investigation of various genetic disorders of unknown origin for confirmation of clinical diagnosis, and has a significant contribution in the genesis of genetic diseases, and abnormal sexual development. The most common chromosome abnormality was trisomy 21 followed by trisomy 18 and 13, as seen in other similar surveys. A high rate of chromosomal abnormalities (28.33%) found in our referred population demonstrates the importance of cytogenetic evaluation in patients who are clinically abnormal. The present study also indicates that karyotyping still plays an important role in gender assignment of ambiguous genitalia infants. Hence, the karyotyping service is a diagnostic tool for children with multiple congenital anomalies, mental retardation, dysmorphic features, developmental delay, growth and endocrine disorders, which in turn will facilitate proper genetic counseling thereby assisting physicians in Oman by increasing awareness and usefulness of cytogenetic investigation in different diagnostic groups.

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