OPEN ACCESS
Saudi Journal of Biomedical Research
Abbreviated Key Title: Saudi J Biomed Res
ISSN 2518-3214 (Print) |ISSN 2518-3222 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: http://scholarsmepub.com/sjbr/

Original Research Article

Chromosomal Abnormalities of 1200 Patients in FEZ HASSAN II University Hospital

L. Bouguenouch[1, 3*], S. Trhanint1, I. Otmani[1], O. Kettani[1], M. Ahakoud[1], L. Qebibo1, FZ. Moufid1, S. Chaouki[2, 3], M. Hida[2, 3], K. Ouldim[1, 3]

[1]Medical Genetic and Oncogenetic Unit, University Hospital Hassan II Fez, Morocco
[2]Department of Medicine, University Hospital Hassan II Fez, Morocco
[3]Faculty of Medicine and Pharmacy of Fez, Morocco

***Corresponding author:** L. Bouguenouch
| **Received:** 09.05.2019 | **Accepted:** 16.05.2019 | **Published:** 30.05.2019
DOI:10.21276/sjbr.2019.4.5.5

Abstract

Background*:** The aim of this study is to identify the profile of patients being referred for cytogenetic analysis in the medical genetics and oncogenetics unit of FEZ Hassan II University Hospital, to determine the prevalence and type of chromosomal abnormalities in the different groups and to compare the results with those of similar studies done in other countries. ***Materials and Methods: We examined the analysis of 1,200 cases referred to the medical genetics and oncogenetics unit of FEZ, between September 2009 and June 2014. They were grouped according to the indications of the cytogenetic study. Frequencies of the different numerical and structural abnormalities were calculated. The relative frequency of cases with abnormal karyotypes was also determined in each group. ***Results and Discussion:*** 70,4% cases were referred from pediatric department and 54,4% are aged under 5 years old. Cytogenetic testing was essentially requested for Dysmorphism (25,6%), Mental Retardation (16%), Down syndrome (14%), girls' growth retardation (13,8%) and for recurrent miscarriage (12,6%). Of the 1200 cases studied, 79% had a normal karyotype and 21% had chromosomal abnormalities. The most common chromosomal abnormality was trisomy 21 (11,7%) followed by Turner syndrome (2,1%) and Klinefelter syndrome (1,5%). ***Conclusion:*** This study compares the results of cytogenetic analysis of chromosomal abnormalities in the north Moroccan population with other studies and research centers. This comparison will help Moroccan clinicians to determine the priority for requesting a cytogenetic analysis in individual cases.

Keywords: patients, Moroccan clinicians, medical genetics and oncogenetics.

INTRODUCTION

The cytogenetic analysis of children with suspected chromosomal aberration is important to uncover the contribution of chromosomal disorder in genesis of dysmorphisms, mental retardation, short stature, sexual ambiguity and congenital malformation in children and prevent further potentially unpleasant investigation being undertaken.

They actually describe 1000 differents chromosome syndroms that cause human morbidity and mortality [1]. Chromosomal abnormalities are present in 1/300 new born. Most chromosomal abnormalities are accidental (98%). However, some are related to a inherited chromosomal rearrangement (2%) [2]

6% of deformities, 2/3 of miscarriages at the first trimester of pregnancy are associated with a chromosomal abnormality and over 30% of children with a chromosomal aberration carry a severe malformation. .

Analyzing and comparing the results of this cytogenetic study of chromosomal abnormalities with other studies and research centers, will help moroccan clinicians to determine the priority for requesting a cytogenetic analysis in individual cases and will demonstrate the importance of cytogenetic evaluation in patients who show clinical abnormalities.

This study compares the results of cytogenetic analysis of chromosomal abnormalities in the north Moroccan population with other studies and research centers.

MATERIALS AND METHODS

1200 patients were referred to the department of medical genetics, of the University hospital

HASSAN II FEZ from September 2009 to June 2014, with a variety of clinical disorders such as congenital anomalies; intellectual disability; clinical features of Down syndrome, Turner's syndrome, and Klinefelter syndrome; ambiguous sex; sterility; amenorrhea; recurrent miscarriage; and chromosome breakage syndromes.

A detailed clinical observation and family tree were realized for all cases before cytogenetic analysis.

The age of the patients ranged from birth to 50 years and 54,4% are aged under 5 years old. Of the 1200 patients, 43,7 % were females and 48,9.1% were males and 5,4% had ambiguous sex. Clinical features are reported in Table-1.

Metaphase cells were prepared after treatment with colcemide (0.1 ug/ml media) for 60 min and 0.075 hypotonic KCL for 20 min, followed by fixation using standard 3:1 methanol-acetic fixative for 25 min, as previously described.

We choose R-banding after treatment with high temperature and EARL buffer and analyse 20 cells of each patient. In some cases of mosaicism, we must come up to approximately 30 metaphases. The best metaphases were photographed. The parents were also tested in cases of structural abnormalities. Fluorescence in situ hybridization (FISH) method was used to to diagnose microdeletion syndromes and numerical sex chromosome abnormalities.

The karyotypic descriptions were reported according to the International System for Human Cytogenetic Nomenclature recommendations [3].

The frequencies of the different types of numerical and structural abnormalities were determined, and the relative frequency of cases with abnormal karyotypes was calculated in each group.

Genetic counseling was systematically indicated for each patient having chromosomal abnormalities in our Department.

RESULTS

70,4% cases were referred from pediatric department and 54,4% are aged under 5 years old. Cytogenetic testing was indicated essentially for Dysmorphism (25,7%), Mental Retardation (16%), Down syndrome (14,6%), girls' growth retardation (13,8%) and recurrent miscarriage (12,6%) (Table-1).

Of the 1236 cases studied, 79% had a normal karyotype and 21% had chromosomal abnormalities. The highest frequencies of abnormal karyotypes found among cases were referred due to suspicion of Down syndrome (86,7%), following by Klinefelter's syndrome (27,6%) and Turner syndrome (15,3%) (Table-1). The other groups showed abnormal karyotypes followed by cases with amenorrhea, male infertility, ambiguous genitalia, intellectual disability, dysmorphic features, congenital anomalies and developmental delay, and repeated abortions.

Abnormal chromosomes were found in 21 % of the cases (Table-1), with 78% of these being numerical abnormalities; the remaining 22% were structural variants (Table-2). Of the 200 numerical abnormalities, 160 cases were in the form of trisomies, 22 cases of turner syndrome and 18 cases of Klinefelter's syndromes. The frequencies of the different forms of abnormal karyotype are shown in Table-2.

A total of 180 cases were referred for suspected Down syndrome. Of these, 142 had trisomy 21, and 14 cases had Robertsonian translocation (Table-4).

A largest group of referrals was for repeated abortions; both husband and wife were examined in 78 cases, only 6 cases had chromosomal abnormalities (Table-3).

Of the 318 cases referred for intellectual disability, dysmorphic features, congenital anomalies, developmental delay, and so forth, 27 cases had chromosomal abnormalities. These abnormalities include 18 trisomies, 2 isochromosomes, 1 inversions, 5 structural abnormalities, 2 Klinefelter's syndromes.

Of the 170 cases referred for Turner's syndrome, 26 (15.3%) were found to have abnormal chromosomes (Table 6). Of the 58 cases referred for Klinefelter's syndrome; 18 cases (27.6%) had 47,XXY (including mosaic) (Table-6).

Table-1: Distribution of chromosomal abnormalities according to the indication of cytogenetic study

Reason for referral	Total		Abnormal	
	N	%	N	%
AUTISME	52	4,2	2	3,9
Dysmorphic features congenital anomalies/developmental delay, and so forth	318	25,7	27	8,5
Klinefelter's syndrome	58	4,7	16	27,6
Repeated abortions	78	12,6	6	7,6
Intellectual disability	156	9,1	10	6,4

Turner syndrome	170	13,8	26	15,3
Ambiguous genitalia	80	6,4	10	12,5
Down syndrome	180	14,6	156	86,7
Miscellaneous	64	5,2		
Fanconi anemia	20	1,6	8	40
Total	1236	100	261	21

Table-2: Distribution of numerical and structural chromosomal abnormalities in 259 cases

Numerical	**No. of cases**
Trisomy 21 (including mosaic)	142
Trisomy 18	14
Trisomy 13	4
Klinefelter's syndrome (including mosaic)	18
Monosomy X	22
Total	**200**
Structural	
Isochromosome X	4
Unbalanced translocation	16
Markers	2
Balanced translocation	6
Inversions	1
46,XX male	4
46,XY female	6
Ring chromosome	2
Others	7
Derivative chromosome	3
Chromosomal instability	8
Total	**59**

Table-3: Chromosomal abnormalities in cases referred for suspicion of Down syndrome

Results	**No. of cases**
47,XY,+21	75
47,XX,+21	56
47,XX,+21/46,XX	6
47,XY,+21/46,XY	4
48,XXY,+21	1
46,XX,der(14;21)(q10;q10)	7
46,XY,der(15;21)(q10;q10)	5
46,XY,der(21;21)(q10;q10)	2

Table-4: Chromosomal abnormalities in cases referred for suspicion of repeated abortions

Results	**No. of cases**	**Abortions**
46,XX,t(1;3;18)	1	4
46,XY,t(8;18)	1	2
46,XX,t(15;22)	2	3
45,XX,der(15;21)(q10;q10)	1	1
45,XY,der(14;21)(q10;q10)	1	1

Table-5: Chromosomal abnormalities in cases referred for suspicion of intellectual disability, dysmorphic features, congenital anomalies, developmental delay, and so forth

Results	**No. of cases**
47,XY,+13	2
47,XX,+13	1
47,XX,+13	2
47,XX,+18	6
47,XY,+18	4
47,XY,+18/46,XY	2
47,XX,+18/48,XXX,+18	1

45,X,i(X)(q10)	2
47,XXY	2
46,XY,inv,(22)	1
47,XY,+mar	2
46,XY,r13	1
46,XX,der16	1

Table-6: Chromosomal abnormalities in cases referred for suspicion of Klinefelter's syndrome, Turner's syndrome, primary or secondary amenorrhea, ambiguous genitalia, and male infertility

Results	No. of cases
Klinefelter's syndrome	
47,XXY	15
47,XXY/46,XY	3
total	18
Turner's syndrome	
45,X	16
45,X/46,XX	4
46,X,i(X)(q10)	2
45,X/46,X,i(X)(q10)	1
45,X/46,X,i(X)(q10)/46,XX	1
45,X/46,XY	2
Ambiguous genitalia	
46,XX male	4
46,XY female	6

DISCUSSION

In this study, we evaluated the pattern of referral of cases for cytogenetic study in morocco, and we compared the distribution of referrals for our study and similar studies performed in morocco by Aboussair *et al*., [4], Turkey by Solak *et al.*, [5] and in Saudi Arabia by Al Husain and Zaki [6].

These studies were chosen for comparison because they apply a similar methodology to our study and cases were grouped into almost the same types of referrals.

In our study, we diagnosed 261 probands which represents 21% of chromosomal abnormalities in 1,200 cases. Similar frequencies have been reported previously in other studies, 31.7% [7], 29.3% [2], 28.6% [8] and 28.3% [1], although other below rates have been reported 17.5% [9] and 3.8% [10]. This wide variation in frequency of chromosomal aberrations may reflect variations in the inclusion criteria, indications of the Constitutional postnatal karyotype and cytogenetic methods used [4].

In the studies of patients referred for phenotypic abnormalities (dysmorphism, mental retardation, disorders of sexual differenciation, short stature ...), autosomal abnormalities (our series: 16.36%) are much more frequent than gonosome ones (4.65%), this percentage is coherent with previous inquests.

We found that here are statistically significant higher frequencies of two groups of people referred for examination (patients with Down syndrome and turner's syndrome). These variations may be explained by social and economical influences.

Down syndrome is the first chromosomal abnormalities in our study (59.4% of cases) followed by turner and klinfelter syndroms. The same ascertainment was reported [11].

This could be attributed to the simple clinical diagnosis. Only 1.42% of Down syndrome in our study had a mosaic.

We found two cases with double trisomy mosaic involving chromosome 21, 18 and a gonosome, Down- Klinefelter mos 47, XY, + 21 [10] / 48, XYY, + 21 [14] and trisomy 18-triple X 47 mos, XX, + 18 [16] / 48, XXX, + 18 [7].

The occurrence of two numerical chromosomal abnormalities in the same case (double aneuploidy) is relatively rare and the clinical presentation is variable depending on the predominant aneuploidy or the combination effect of the two [12, 13].

The trisomy 18 (13 cases) and trisomy 13 (5 cases) were the second and third group of trisomy syndromes in our study 3, 6%.

Among sexual chromosomal abnormalities, the Most frequent were Turner's syndrome (10%) and Klinefelter's syndrome (7%) in which, the classic karyotype (47, XXY) (83.5%) Was more common than

somatic mosaicism (46, XY / 47, XXY) (16.5%), and 75% of the cases showed the classic, well- defined phenotype.

Turner syndrome is characterized by total or partial chromosomal abnormality of the X chromosome. It affects 1/2,500 female newborns. Our study showed that the homogeneous monosomy 45, X was the most frequent. Other forms were either mosaics or structural abnormalities, including long arm iso chromosome (4 cases), deletion of the short arm (2 cases), deletion of the long arm (1 case), and the X chromosome ring (2 cases). These results are consistent with those reported in similar studies [14],

The prevalence of chromosomal abnormalities among repeated abortions was 2.31% per couple in our study. This value is Reported as 7.4% [15], 4.2% [5], and 7.4% [6].

Structural chromosomal abnormalities regroup autosomal translocation (22 cases including 16 balanced and 6 unbalanced) with reciprocal (8 cases) and Robertsonian translocation (14 cases) Then in order of frequency: chromosomal instabilities (8 cases), iso chromosome (4 cases), marker chromosome (3 cases) and ring chromosome (2 cases).

Identification of structural disorder helps in diagnosis, genetic counseling and also in gene mapping [16]. Supernumerary chromosomes (SMC: supernumerary marker chromosome) are known to be derived from chromosome 15, as inv dup (15) in half of studied cases [17-19]. In addition to the identification of chromosome markers, clinical correlation study of parents, and many other means are important for genetic counseling [20].

In this study three chromosomal markers (de novo) were found but we could not identify their origins. We also indicate that the karyotype plays an important role in identifying the gonadal sex of newborns with ambiguity.

Molecular cytogenetic techniques showed that a growing number of syndromes are due to micro deletions involved in the loss of only a few genes closely adjacent known as a contiguous gene syndromes [21].

In this study, we found 7 cases of Williams syndrome and 5 cases of the 22q11 deletion syndrome. In our study, 1,200 cases, about 79% of patients referred had normal karyotype. These results in agreement with other studies [4, 22] should challenge the management of these patients through syndromic clinical examination, radiological, electrophysiological and metabolic balance.

The high resolution studies comes only at the end of this diagnostic arsenal through the array CGH for syndromic mental retardation, targeted sequencing and high-throughput sequencing (NGS) to establish a precise genetic diagnosis, genetic counseling and even identify different mutations throughout the genome.

CONCLUSION

In conclusion, a high rate of chromosomal abnormalities (21%) found in our referred population demonstrates the importance of cytogenetic evaluation in patients who are clinically abnormal.

This study compares the results of cytogenetic analysis of chromosomal abnormalities in the north Moroccan population with other studies and research centers. It will provide a basis for determining the risks of recurrence and for deciding on clinical treatment and genetic counseling in our population.

REFERENCES

1. Goud, M. T., Al-Harassi, S. M., Al-Khalili, S. A., Al-Salmani, K. K., Al-Busaidy, S. M., & Rajab, A. (2005). Incidence of chromosome abnormalities in the Sultanate of Oman. *Saudi medical journal*, *26*(12), 1951-1957.
2. Duarte, A. C., Cunha, E., Roth, J. M., Ferriera, F. L., Garcias, G. L., & Martino-Roth, M. G. (2004). Cytogenetics of genetic counseling patients in Pelotas, Rio Grande do Sul, Brazil. *Genet Mol Res*, *3*(3), 303-308.
3. Shaffer, L. G., Slovak, M. L., & Campbell, L. J. (2009). ISCN (2009): International System of Human Cytogenetic. *Nomenclature S Karger AG, Basel*.
4. Aboussair, N., Jaouad, I. C., Dequaqui, S. C., Sbiti, A., Elkerch, F., Yahya, B., ... & Sefiani, A. (2012). Cytogenetic analysis of 5572 patients referred for suspected chromosomal abnormalities in Morocco. *Genetic testing and molecular biomarkers*, *16*(6), 569-573.
5. Solak, M., Fistik, T., Eser, B., & Söylemez, Z. (2007). Cytogenetic Analyses in Medical Genetic Laboratory of Medical Biology Department in Afyonkarahisar Kocatepe University. *Osmangazi J. Med*, *29*, 93-99.
6. Al Husain, M., & Zaki, O. K. (1999). A survey of 1,000 cases referred for cytogenetic study to King Khalid University Hospital, Saudi Arabia. *Human heredity*, *49*(4), 208-214.
7. Al-Awadi, S. A., Teebi, A. S., & Sundareshan, T. S. (1985). Complex chromosomal rearrangement involving chromosomes 11, 13, 14 and 18 resulting in monosomy for 13q32----qter. In *Annales de genetique*, 28(3):181-184.
8. Santos, C. B., Boy, R. T., Santos, J. M., Silva, M. P. S., & Pimentel, M. M. G. (2000). Chromosomal investigations in patients with mental retardation and/or congenital malformations. *Genetics and Molecular Biology*, *23*(4), 703-707.

9. Kim, S. S., Jung, S. C., Kim, H. J., Moon, H. R., & Lee, J. S. (1999). Chromosome abnormalities in a referred population for suspected chromosomal aberrations: a report of 4117 cases. *Journal of Korean medical science*, *14*(4), 373-376.
10. Kumar, P., Radhakrishnan, J., Chowdhary, M. A., & Giampietro, P. F. (2001, August). Prevalence and patterns of presentation of genetic disorders in a pediatric emergency department. In *Mayo Clinic Proceedings*, 76(8): 777-783
11. Mokhtar, M. M. (1997). Chromosomal aberrations in children with suspected genetic disorders. *Eastern Mediterranean Health Journal*, 3(1): 114-122.
12. Zaki, M. S., Kamel, A. A., & El-Ruby, M. (2005). Double aneuploidy in three Egyptian patients : Dow-Turmer and Down-Klinfelter syndromes. *Genet Couns*, 16(4):393-402.
13. Ratbi, I., Ouldim, K., & Natiq, A. (2006). Double trisomie en mosaïque 47, XY,+ 21/48, XXY,+ 21. A propos d'un cas et revue de la littérature. *Médecine du Maghreb*, *139*, 51-53.
14. Sybert, V. P., McCualey, E. (2004). Turner's syndrome. *N England Journal Med*, 351(12):1227-38.
15. Yuce, H., Tekedereli, I., & Elyas, H. (2007). Cytogenetic results of recurrent spontaneous abortions in Turkey. *Medical science monitor*, *13*(6), CR286-CR289.
16. Ouldim, K., Sbitti, A., & Natiq, A. (2004). Unexpected fertility in men with robertsonian translocation (22q; 22q) and a new paternal uniparental disomy 22. *Am J Hum Genet*, *75*(Suppl), A915.
17. Buckton, K. E., Spowart, G., Newton, M. S., & Evans, H. J. (1985). Forty four probands with an additional "marker" chromosome. *Human genetics*, *69*(4), 353-370.
18. Woo, H. Y., Cho, H. J., Kong, S. Y., Kim, H. J., Jeon, H. B., Kim, E. C., ... & Kim, S. H. (2003). Marker chromosomes in Korean patients: incidence, identification and diagnostic approach. *Journal of Korean medical science*, *18*(6), 773-778.
19. Ouldim, K., Natiq, A., Jonveaux, P., & Sefiani, A. (2007). Tetrasomy 15q11-q13 diagnosed by FISH in a patient with autistic disorder. *BioMed Research International*, *2007*.
20. Samri, I., Bouguenouch, L., Hamdaoui, H., Otmani, I. E., Omairi, N. E., Chaouki, S., ... & Ouldim, K. (2013). Marqueurs chromosomiques: à propos d'un cas. *Pan African Medical Journal*, *15*(1), 104.
21. Mueller, R. F., & Young, I. D. (1995). Chromosome disorders. In: Mueller, R. F., Young, I. D. (eds): Emery's Elements of medical genetics. Edinburgh: Churchill Livingstone, 126-142.
22. Verma, R. S., & Dosik, H. (1980). Incidence of major chromosomal abnormalities in a referred population for suspected chromosomal aberrations: a report of 357 cases. *Clinical genetics*, *17*(5), 305-308.