Journal of Genetic Syndromes & Gene Therapy
ISSN: 2157-7412

Belmokhtar et al., J Genet Syndr Gene Ther 2016, 7:1
DOI: 10.4172/2157-7412.1000280

Research Article Open Access

Cytogenetic Study of Down Syndrome In Algeria: Report and Review

Fayza Belmokhtar[1]*, Rahma Belmokhtar[1] and Ahmed Kerfouf[2]

[1]Faculty of Natural and Life Sciences and Sciences of Earth and the Universe, Abou Bekr, Belkaid University, Tlemcen, Algeria
[2]Department of environmental Sciences, Faculty of Natural and Life Sciences, Djillali Liabes University, Sidi Bel Abbes, Algeria

Abstract

Background: Down syndrome (DS) is the most common type of chromosomal trisomy found in new-born. It's associated with mental retardation and characteristic facial features. A clinical diagnosis of Down syndrome may be unconfirmed in one third of cases.

Objective: This study was conducted to confirm the clinical diagnosis of suspected cases with Down syndrome by a cytogenetic analysis and to evaluate several risk factors associated with trisomy 21 in a group of patients from West region of Algeria, Tlemcen.

Materials and method: Karyotype analysis was carried out for 22 patients with the clinical diagnosis of Down syndrome. GTG- band and RTG-band have been made according to the standard protocols.

Results: Among the 22 cases with Down syndrome, Free trisomy 21 was presented in 20 cases (91%). One case (4.5%) had translocation Down syndrome. One other case had mosaic Down syndrome. There was an excess of male than female; sex ratio was 1.75:1. The mean maternal age at birth of the affected children was 36.27 ± 7.59 years. It was significantly higher than this of mothers of non-trisomic children (27.83 ± 6.34 years; p=0.0002). Higher parity was an important risk factor associated with trisomy 21, 81% of affected children were of last or second last birth order. Paternal age and consanguinity had no effect.

Conclusion: The identification of specific types of chromosomal abnormalities in Down syndrome children is very significant. It greatly helped in the management of these children and to make aware the affected families about the recurrence risk and the options available.

Keywords: Cytogenetic analysis; Down syndrome; Karyotype; Maternal age; Algeria

Introduction

Down syndrome (DS) is the most common autosomal abnormality and is the most genetic cause of mental retardation, appearing in about 1 of every 700 newborns [1,2]. Down syndrome can be caused by three types of chromosomal abnormalities: trisomy 21, translocation or mosaicism [2]. Trisomy 21 is characterized by the presence of three copies of chromosomes 21, generally resulting from non-disjunction during maternal meiosis, while the extra chromosome 21 in mosaic Down syndrome arises from mitotic non-disjunction in a chromosomally normal zygote [3]. For Down syndrome by translocation, the extra chromosome 21 translocated to other chromosomes or to the acrocentric chromosomes of D and G group that is, 13, 14, 15, 21 and 22 [4].

The cause of the non-disjunction error is not known, but there is a definite connection with maternal age. Advanced maternal age remains the major well documented risk factor for maternal meiotic non-disjunction. The incidence of trisomy 21 conceptions increases with maternal age [1-5]. Subsequently, maternal parity was established as an additional independent risk factor and genetic predisposition as third independent risk factor [6-8]. An increased risk for Down syndrome may be the result of an autosomal recessive gene mutation, particularly in the Middle East where the rate of consanguinity is increasing [9].

Karyotype analysis by chromosome banding remains the standard method to identify the cytogenetic variants of Down syndrome and to provide appropriate genetic counselling. Most cytogenetic studies in the world indicate that the most frequent type of chromosomal abnormalities in Down syndrome is Free trisomy 21 with a frequency ranges from 93% to 96%, mosaic Down syndrome presents a frequency between 2% and 3% and translocation Down syndrome presents a frequency ranges from 2% to 5% [10]. However, these values show a geographical variation from the Eastern to the Western countries. In Algeria, the number of children with Down syndrome is about 80.000 cases [11]. No data is yet available about cytogenetic variants of Down syndrome in the Algerian population.

The aim of this study was to describe the cytogenetic profile of children with Down syndrome in the west region of Algeria, Tlemcen. Study the impact of maternal age and other risk factors associated with this disorder. Then review and compare the findings of previous international studies with our results.

Materials and Method

Sample

The study was carried out on 42 children (22 with Down syndrome, 20 control subjects) aged between 1 year to 19 years old. They were recruited from the Pediatric Department of Maghnia hospital and from the Psychomotor Center for Mentally Handicapped Children of Maghnia during a period of 8 months (2013-2014). Information on age, birth order, parity parental age, parental consanguinity and

***Corresponding author:** Fayza Belmokhtar, Abou Bekr Belkaid University, Tlemcen, 13000, Algeria, Tel: +21343507960; E-mail: fayza_belmokhtar@yahoo.fr

Received October 27, 2015; **Accepted** December 22, 2015; **Published** January 04, 2016

Citation: Belmokhtar F, Belmokhtar R, Kerfouf A (2016) Cytogenetic Study of Down Syndrome In Algeria: Report and Review. J Genet Syndr Gene Ther 7: 280. doi:10.4172/2157-7412.1000280

family history of Down syndrome at presentation were documented using a questionnaire. All tested individuals were voluntary donors which parents gave consent in compliance with ethical norms get by international conventions.

Karyotype analysis

Chromosome preparation was carried out from 2-5 ml of peripheral blood collected in Sodium Heparin in all cases with clinical features of Down syndrome. Chromosomal culture was done according to standard protocol [12]. Peripheral blood lymphocytes were stimulated for 72 hours in incubator at 37°C with phytohaemagglutinin-M (5 ng/l). Then, metaphases are harvested by adding colcemid (10 mg/l) for 120 min, followed by hypotonic KCl (0.075 M) treatment for 30 min and fixation using stand 3:1 methanol-acetic acid. Finally, cells obtained were dropped on distinct slides.

The karyotype of each patient was determined by direct staining with Giemsa or by G-banding using Banding trypsin solution and Giemsa for staining (GTG) or by R-banding using phosphate buffer heated to 87°C then Giemsa for staining (RTG) [13,14].

In each case, 25-50 metaphases were examined and 3-5 cells were photographed and karyotyped. In cases of mosaicism, 50 to 100 metaphases were scored. Karyotype description was done according to the international nomenclature guidelines (*ISCN* 2013) (*International Standard Committee on Human Cytogenetics Nomenclatue*) [15].

Statistical analysis

Data were analyzed using the software SPSS, version 17 (SPSS Inc. Chicago ILL, USA). Categorical variables were presented as the number and percentage, when the quantitative variables were presented as mean ± standard deviation. Student's T test was used for comparison of means. $P \leq 0.05$ was considered statistically significant.

Results

A total of 42 children were included in this study. Twenty-two patients with Down syndrome, among them, 14 (63.3%) were males and 8 (36.4%) were females, with male to female ratio of 1.75:1. The mean age at referral was 11.2 years. About 81% of cases were of the last or second last birth orders. Parental consanguinity was reported in 22.7% of the cases. Only 1 patient has a similar case in his family (Table 1).

Mean maternal age at first birth was significantly higher in (1990-2005) (27.2 ± 5.24 years) than in (1974-1989) (22.7 ± 3.92 years) (p=0.016) in our studied population. The age at first parity increase in these last years (Table 1).

For the mean maternal age of mothers at birth of Down syndrome children was 36.27 ± 7.59 years (ranges 21-52 years) of which 54.5% were in the advanced age group (≥ 35 years). This mean was significantly higher than the maternal age of mothers of non-trisomic children, whose age was around 27.83 ± 6.34 years (p=0.0002) (Figure 1).

The chromosomal analysis were undertaken in 22 cases, out of which 20 (91%) cases had free trisomy 21, 1 case had trisomy 21 with translocation (46, XY,+21, rob (21; 21) (q10; q10)), and 1 case had mosaic trisomy 21 (47,XY,+21/46,XY) (Table 2).

A comparison of the frequencies of trisomy 21, mosaicism and translocation Down syndrome of the current study with results of previous international studies was carried out. The frequencies of different countries, including Algeria are summarized in Table 3.

Age of children (years)	
Minimum-maximum	5-19
Mean ± SD	11.23 ± 4.12
Sex	
Male	14 (63.6%)
Female	08 (36.4%)
Sex ratio	1.75:1
Birth order	
First and second	04 (18.2%)
Third and more	18 (81.8%)
Maternal age at first birth (years)	
Minimum-maximum	16-39
Mean ± SD	25.18 ± 5.13
Years of birth: 1974-1989	
Mean maternal age ± SD	22.7 ± 3.92
Years of birth; 1990-2005	
Mean maternal age ± SD *P value	27.2 ± 5.24 0.016
Maternal age at birth of DS child (years)	
Minimum-maximum	21-52
Mean ± SD *P value	36.27 ± 7.59 0.0002
Paternal age at birth of DS child(years)	
Minimum-maximum	27-62
Mean ± SD	41.45 ± 8.09
Consanguinity	
Consanguineous	05 (22.7%)
Not consanguineous	17 (77.3%)
Similar case in the family	
No	21 (95.4%)
Yes	01 (04.6%)

* Student's T-test, **SD:** Standard Deviation, **DS:** Down Syndrome

Table 1: Sociodemographic features of Down syndrome cases.

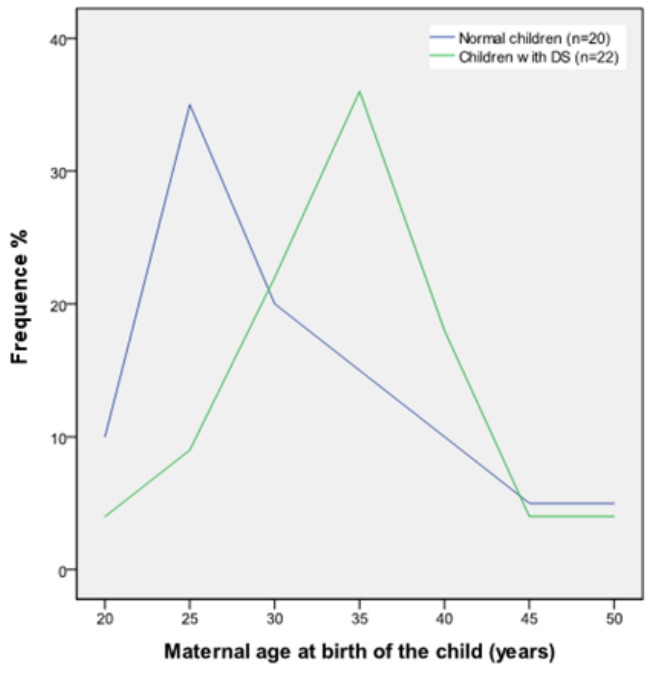

Figure 1: Prevalence of normal and trisomic newborns according to maternal age at term.

Karyotype	No	%
Regular trisomy 21		
47,XY,+21	12	54.6
47,XX,+21	8	36.4
Translocation DS		
46, XY, +21, rob (21; 21) (q10; q10)	1	4.5
Mosaic DS		
47,XY,+21/46,XY	1	4.5
Total	**22**	**100**

No: Number, **DS:** Down Syndrome

Table 2: Karyotype analysis of 22 Down syndrome cases.

Discussion

Trisomy 21 is a common birth defect and can be diagnosed easily on the basis of clinical features. However, karyotyping is necessary for the confirmation of free trisomy 21, mosaicism and translocation in Down syndrome children, to determine the recurrent risk and to provide genetic counseling. The data reported in this study represent the first work of Down syndrome in Tlemcen, Algeria. All cases were diagnosed postnatally, where a karyotype analysis was done for all studied cases.

In this study, the overall sex ratio was 1.75:1. The excess of males to be universal and was reported in many studies in different countries.

Country	Author	Total No.	Regular T21		Translocation DS		Mosaic DS		Non classical	
			No	%	No	%	No	%	No	%
North Africa										
Algeria	Current study	22	20	91.0%	01	04.5%	01	04.5%	-	-
Morocco [5]	Jaouad et al. 2010	852	820	96.2%	27	03.1%	05	00.6%	-	-
Tunisia [29]	Chaabouni et al. 1999	500	456	91.2%	20	04.0%	24	04.8%	-	-
Libya [23]	Verma et al. 1990	150	144	96.0%	04	2.67%	01	0.67%	01	0.67%
Sudan [50]	Ellaithi et al. 2008	05	04	80.0%	01	20.0%	-	-	-	-
Egypt [22]	El-Gilany et al. 2011	712	684	96.1%	22	03.1%	06	00.8%	-	-
Middle East										
Saudi Arabia [28]	Qahatani et al. 2011	72	68	94.4%	03	04.1%	01	01.5%	-	-
Yemen [51]	Al-Maweri et al. 2015	50	50	100%	-	-	-	-	-	-
Oman [44]	Al Harasi, 2010	680	640	94.1%	20	2.94%	19	2.79%	01	0.15%
UAE [19]	Murthy et al. 2007	141	138	97.9%	01	00.7%	01	00.7%	01	0.7%
Qatar [52]	Abdul Wahab et al. 2006	146	143	98.0%	-	-	03	02.0%	-	-
Bahrain [53]	Al-Arrayed, 1999	89	86	97.0%	01	1.12%	01	1.12%	01	1.12%
Kuwait [54]	Al-Awadi et al. 1991	1024	985	96.2%	24	02.3%	09	00.9%	06	0.6%
Iraq [39]	Al-Mefraji, 2012	39	33	84.6%	01	2.56%	05	12.8%	-	-
Jordan [17]	Amayreh et al. 2012	80	74	92.5%	02	02.5%	03	03.8%	01	1.3%
Turkey [10]	Demirhan et al. 2015	1103	1020	92.5%	28	02.5%	28	02.5%	27	2.4%
Iran [40]	Mehdipour et al. 1996	150	132	88.0%	01	0.63%	17	11.3%	-	
Asia										
China [45]	Wang et al. 2010	86	80	93.0%	03	03.5%	03	03.5%	-	-
Malaysia [26]	Azman et al. 2007	149	141	94.6%	01	00.7%	07	04.7%	-	-
India [36]	Verma et al. 1991	2410	2207	91.6%	98	04.1%	98	04.1%	07	0.3%
India [55]	Mandava et al. 2010	1572	1400	89.1%	111	07.1%	29	01.8%	32	2.0%
India [38]	Chandra et al. 2010	1020	855	83.8%	51	05.0%	110	10.8%	04	0.4%
India [56]	Poddar et al. 2012	45	42	93.3%	-	-	03	06.7%	-	-
India [4]	Jayalakshama et al.2010	870	756	86.9%	77	08.8%	37	04.3%		-
Pakistan [57]	Ahmed et al. 2005	295	282	95.6%	11	03.7%	02	00.7%	-	-
Europe										
France [46]	Stoll et al. 1990	391	368	94.1%	14	03.6%	09	02.3%	-	-
England and Wales [27]	Mutton et al. 1996	5737	5411	94.4%	220	03.8%	66	01.2%	40	0.7%
Danemark [47]	Zhu et al. 2013	987	932	94.4%	29	02.9%	26	02.6%	-	-
Ireland [58]	Delvin and Morrison, 2004	208	197	94.7%	03	01.4%	08	03.8%	-	-
Bosnia and Herzegovina [41]	Mačkić-Đurović et al. 2014	73	60	82.1%	05	06.9%	08	11.0%	-	-
Kosovo [16]	Kolgeci et al. 2013	305	285	93.4%	17	05.6%	03	01.0%	-	-
America										
Brazil [43]	Trevisan et al. 2014	644	598	92.9%	26	04.0%	20	03.1%	-	-
Mexico [48]	Garduño-Zarazúa et al. 2013	510	445	87.3%	15	02.9%	43	08.4%	07	1.4%
Chile [37]	Astete et al. 1991	83	68	81.9%	-	-	15	18.1%	-	-
Australia										
Australia [42]	Staples et al. 1991	635	596	93.9%	26	04.1%	13	02.0%	-	-

No: Number, **T21:** Trisomy 21, **DS:** Down Syndrome

Table 3: Karyotype frequencies among studied Down syndrome cases and pooled data from worldwide surveys.

Our results are similar to those found by Kolgeci, et al. in Kosovo (1.72:1) [16] and near to those of Amayreh, et al. in Jordan (1.61:1) [17].

The higher male sex ratio may be the inherent tendency of Y belonging to the G group chromosome to be closer to its other members, 21 and 22, especially the smallest acrocentric, the 21. The reasons for the excess of male Down syndrome associated to the paternal errors are not yet clearly known [18].

The birth order of children with Down syndrome ranged from 1 to 10. Overall, 81% of them were of the last or second last birth orders. This result agrees with previous studies in UAE and Dhaka [19,20]. Several studies suggest an increased risk of Down syndrome with increasing parity that is the same as our result, but at the same time other studies reported that is no increased risk with increasing parity [6,21].

In this last years, Age of marriage became higher than the age in the earliest years, so the age at the first birth became higher. This increase the maternal age for the last births and for consequence, the age at birth of Down syndrome children became higher in our results where, 54.5% of births were over 35 years old.

The mean maternal age at birth of all studied Down syndrome children was 36.27 ± 7.59 years, this result agrees with the study of El-Gilany, et al. in Egypt [22], where the mean maternal age was 36.8 years, and the study of Jaouad, et al. in Morocco [5]; the mean maternal age was 35.39 years. Also agrees with the result found by Verma, et al. in Libya (35.62 years) [23].

Advanced maternal age remains the principle risk factor for trisomy 21. It was reported in many previous studies in different countries: India, Turkey, Malaysia, England and Wales, Jordan, Saudi Arabia, Tunisia and Dubai [17,19,24-29].

Many other studies had shown increased number of Down syndrome babies born to the young mothers, like the study of Kava and his collaborators in India, the maternal age at birth of affected children was 26.8 years [24]. Other study in the same country reported a mean of 24.95 years [30].

For older mothers, the maternal age effect may be due to differential selection and accumulation of trisomy 21 oocytes in the ovarian reserve of older women [31].

For younger mothers, the mechanism behind the non-disjunction is not well understood. One of the reasons could be that the ovaries of young women are biologically older than their chronological age which may lead to increased incidence of non-disjunction [32].

Parent's consanguinity was observed in 22.7% of the effected children with Down syndrome. This result agrees with those of literature where about 17% of patients were products of consanguineous marriages in Egypt [22]. However, the effect of consanguinity on non-disjunction of chromosome 21 has not been clearly defined [33-35].

In the current study, the frequency of non-disjunction (free trisomy 21), mosaicism and translocation was 91%, 4.5% and 4.5% respectively. Our results are similar to a study performed in Tunisia by Chaabouni et al. [29] where the frequencies were 91.2%, 4.8% and 4% respectively and another study in India by Verma et al. [36] the frequencies were 91.6%, 4.1% and 4.1% respectively.

The frequency of non-disjunction in previous international studies in North Africa countries ranged from 91%-96% (Table 3). In Tunisia, we noted (91.2%), Libya (96%), Egypt (96.1%), Morocco (96.2%) [5,22,23,29]. However, in Middle East, Asia, Australia and America countries the frequency ranged from 81%-98%. The lowest frequencies were noted in Chile (81.9%), India (83.8%), Iraq (84.6%), Iran (88%) [37-40]. While for European countries, the value of free trisomy 21 was around 94%, except in Bosnia and Kerzegovina, where the frequency was lower than found in other European countries (82.1%) [41].

Previous studies have reported that the frequency of translocation Down syndrome varied from 0.67% to 8.8%, where the lowest frequency was noted in Iran, UAE and Malaysia and the highest frequency was reported in India (8.8%) [4,19,26,40]. The frequencies around 4% were noted in Tunisia (4.1%), Saudi Arabia (4.1%), India (4.1%), Australia (4.1%) and Brazil (4%) [28,29,36,42,43].

For mosaic Down syndrome, the frequency in previous studies varied from 0.6% to 18.1%. 0.6% was noted in Morocco and Libya, while 18.1% was noted in Chile [5,23,37]. Our frequency (4.5%) is similar to those found in Tunisia, Malaysia and India [4,26,29]. But it's higher than other reports in Egypt (0.8%), Oman (2.79%), Jordan (3.8%), China (3.5%), France (2.3%), Denmark (2.6%) and Brazil (3.1%) [17,22,43-47]. In contrast, it is lower than that reported in Iraq (12.8%), Iran (11.3%), India (10.8%), Bosnia (11%), Mexico (8.4%) and Chile (18.1%) [37-41,48].

Among all studied cases here and in previous studies, the frequency of translocation and mosaicism was very much lower than the frequency of free trisomy 21. This could be attributed to the high fertility rate and trends towards reproduction even at an advanced maternal age [49].

For non-disjunction trisomy 21, the most common error is maternal non-disjunction in the first meiotic division, with meiosis I error occurring three times as frequently as meiosis II errors. Most mosaic cases result from a trisomic zygote with mitotic loss of chromosome 21. The Down syndrome cases with unbalanced translocation usually are de *novo* and nearly 25% result from familial transmission [26].

Various studies have reported the frequency of free trisomy 21 associated with structural and /or numerical anomalies of other chromosomes (non-classical type of Down syndrome) to be 0.15%-2.4%. 0.15% was noted in Oman, 0.67% in Libya, 0.7% in England and Wales, 1.2% in Egypt and 2.4% in Turkey [10,23,27,44,49]. Whereas, we did not find this type of Down syndrome in our results.

Conclusion

In this study, a cytogenetic analysis by karyotyping was done for all cases that have clinical features of Down syndrome, in order to confirm the clinical diagnosis and to determine the frequency of different types of Down syndrome. Our results suggest that free trisomy 21 karyotype is more frequent in Down syndrome cases than translocation and mosaic karyotypes. These results were comparable to many international studies in the world. Of the various factors analyzed during the present study, advanced maternal age, and higher parity were the major influencing factors contributing to Down's syndrome. These should be considered as important factors while genetic counselling of the parents and families to make them aware of recurrence risk and the options available.

Funding

There is no funding of any type granted for this publication.

Conflict of Interest

The authors have no conflicts of interest to declare.

References

1. Mégarbané A, Ravel A, Mircher C, Sturtz F, Grattau Y, et al. (2009) The 50th anniversary of the discovery of trisomy 21: the past, present, and future of research and treatment of Down syndrome. Genet Med 11: 611-616.

2. Newberger DS (2000) Down syndrome: prenatal risk assessment and diagnosis. Am Fam Physician 62: 825-832.
3. Kovaleva NV, Mutton DE (2005) Epidemiology of double aneuploidies involving chromosome 21 and the sex chromosomes. Am J Med Genet A 134A: 24-32.
4. Jayalakshamma MM, Margaret M, Amudha S, Tilak P, Devi R, et al. (2010) Cytogenetic analysis in Down syndrome. Int J Hum Genet 10: 95-99.
5. Jaouad IC, Cherkaoui Deqaqi S, Sbiti A, Natiq A, Elkerch F, et al. (2010) Cytogenetic and epidemiological profiles of Down syndrome in a Moroccan population: a report of 852 cases. Singapore Med J 51: 133-136.
6. Doria-Rose VP, Kim HS, Augustine ET, Edwards KL (2003) Parity and the risk of Down's syndrome. Am J Epidemiol 158: 503-508.
7. Farag TI, Teebi AS (1988) Possible evidence for genetic predisposition to nondisjunction in man. J Med Genet 25: 136-137.
8. Mokhtar MM, Abdel-Fattah M (2001) Major birth defects among infants with Down syndrome in Alexandria, Egypt (1995-2000): trends and risk factors. East Mediterr Health J 7: 441-451.
9. Zlotogora J, Shalev SA (2010) The consequences of consanguinity on the rates of malformations and major medical conditions at birth and in early childhood in inbred populations. Am J Med Genet A 152A: 2023-2028.
10. Demirhan O, Tanriverdi N, Suleymanova D, Cetinel N (2015) Cytogenetic Profiles of 1213 Children with Down Syndrome in South Region of Turkey. J Mol Genet Med 9: 157.
11. ANIT (Association Nationale de l'Insertion des Trisomiques 21) (2012) 80.000 enfants trisomiques, en Algérie. Santé-Mag-actualité 4:1p (Article in French).
12. Ferguson-Smith MA (1974) Techniques of human chromosome analysis. La Ricerca in Clinica and in Laboratorio 4: 297-335.
13. Seabright M (1971) A rapid banding technique for human chromosomes. Lancet 2: 971-972.
14. Dutrillaux B, Lejeune J (1971) A new technic of analysis of the human karyotype. C R Acad Sci Hebd Seances Acad Sci D 272: 2638-2640.
15. ISCN (2013) An International System for Human Cytogenetic Nomenclature, Shaffer LG, McGowan-Jordan J, Schmid M (eds), (S Karger, Basel 2013).
16. Kolgeci S, Kolgeci J, Azemi M, Shala-Beqiraj R, Gashi Z, et al. (2013) Cytogenetic study in children with down syndrome among kosova Albanian population between 2000 and 2010. Mater Sociomed 25: 131-135.
17. Amayreh W, Al Qa'qa' K, Al Hawamdeh A, Khashashneh I (2012) Clinical and Cytogenetic Profile of Down Syndrome at King Hussein Medical Centre. Journal of the Royal Medical Services 19: 14-18.
18. Petersen MB, Antonarakis SE, Hassold TJ, Freeman SB, Sherman SL, et al. (1993) Paternal nondisjunction in trisomy 21: excess of male patients. Hum Mol Genet 2: 1691-1695.
19. Murthy SK, Malhotra AK, Mani S, Shara ME, Al-Rowaished EE, et al. (2007) Incidence of Down syndrome in Dubai, UAE. Med Princ Pract 16: 25-28.
20. Munsi AS, Hussain M, Rima R, Biswas R, Mahmud S, et al. (2014) Pattern of congenital heart diseases among clinically diagnosed Down's syndrome children. Northern International Medical College Journal 6: 18-20.
21. Chan A, McCaul KA, Keane RJ, Haan EA (1998) Effect of parity, gravidity, previous miscarriage, and age on risk of Down's syndrome: population based study. BMJ 317: 923-924.
22. El-Gilany AH, Yahia S, Shoker M, El-Dahtory F (2011) Cytogenetic and comorbidity profile of Down syndrome in Mansoura University Children's Hospital, Egypt. Indian J Hum Genet 17: 157-163.
23. Verma IC, Mathews AR, Faquih A, el-Zouki AA, Malik GR, et al. (1990) Cytogenetic analysis of Down syndrome in Libya. Indian J Pediatr 57: 245-248.
24. Kava MP, Tullu MS, Muranjan MN, Girisha KM (2004) Down syndrome: clinical profile from India. Arch Med Res 35: 31-35.
25. Alp MN, Oral D, Budak T (2007) Cytogenetic analysis of 584 cases with clinical diagnosis of Down syndrome (Article in Turkish) Dicle Tip Dergisi 34:283-289.
26. Azman BZ, Ankathil R, Siti Mariam I, Suhaida MA, Norhashimah M, et al. (2007) Cytogenetic and clinical profile of Down syndrome in Northeast Malaysia. Singapore Med J 48: 550-554.
27. Mutton D, Alberman E, Hook EB (1996) Cytogenetic and epidemiological findings in Down syndrome, England and Wales 1989 to 1993. National Down Syndrome Cytogenetic Register and the Association of Clinical Cytogeneticists. J Med Genet 33: 387-394.
28. Qahatani MH, Faridi WA, Iqbal LM, Nazia N, Riaz A (2011) Environmental, Maternal and Cytogenetic Analysis of live Born Infants with Down's Syndrome. Journal of US-China Medical Science 8: 143-149.
29. Chaabouni H, Smaoui N, Maazoul F, Ben Jemaa L, M'Rad R (1999) [Epidemiologic and genetic study of trisomy 21 in Tunisia]. Tunis Med 77: 407-414.
30. Sheth F, Rao S, Desai M, Vin J, Sheth J (2007) Cytogenetic analysis of Down syndrome in Gujarat. Indian Pediatr 44: 774-777.
31. Hultèn MA, Patel SD, Tankimanova M, Westgren M, Papadogiannakis N, et al. (2008) On the origin of trisomy21Down syndrome. Mol Cytogenet 1: 21-31.
32. Schupf N, Kapell D, Lee JH, Ottman R, Mayeux R (1994) Increased risk of Alzheimer's disease in mothers of adults with Down's syndrome. Lancet 344: 353-356.
33. Naguib KK, Al-Awadi SA, Moussa MA, Farag TI, Teebi AS (1989) Effect of parental age, birth order and consanguinity on nondisjunction in the population of Kuwait. Journal of the Kuwait Medical Association 23: 37-43.
34. Hamamy HA, al-Hakkak ZS, al-Taha S (1990) Consanguinity and the genetic control of Down syndrome. Clin Genet 37: 24-29.
35. Hamamy H, Alwan A (1994) Hereditary disorders in the Eastern Mediterranean Region. Bull World Health Organ 72: 145-154.
36. Verma IC, Mathew S, Elango R, Shukla A (1991) Cytogenetic studies in Down syndrome. Indian Pediatr 28: 991-996.
37. Astete C, Youlton R, Castillo S, Be C, Daher V (1991) Clinical and cytogenetic analysis of 257 cases of Down's syndrome. Rev Chil Pediatr 62: 99-102.
38. Chandra N, Cyril C, Lakshminarayana P, Nallasivam P, Ramesh A, et al. (2010) Cytogenetic evaluation of Down syndrome: A review of 1020 referral cases. Int J Hum Genetics 10: 87-93.
39. Al-Mefraji S (2012) Is any Relation between cytogenetic types of Down's syndrome and congenital heart disease. Iraqi J Comm Med 4: 304-307.
40. Mehdipour P, Saadat M, Noori-Daloii MR (1996) Down's syndrome: cytogenetic studies in 150 cases in Tehran. Med J Isla Rep Iran 10: 47-52.
41. MaÄ kiÄ‡-Ä uroviÄ‡ M, ProjiÄ‡ P, Ibrulj S, Cakar J, MarjanoviÄ‡ D (2014) A comparative analysis of the effectiveness of cytogenetic and molecular genetic methods in the detection of Down syndrome. Bosn J Basic Med Sci 14: 94-98.
42. Staples AJ, Sutherland GR, Haan EA, Clisby S (1991) Epidemiology of Down syndrome in South Australia, 1960-89. Am J Hum Genet 49: 1014-1024.
43. Trevisan P, Moraes FN, Mattos VF, Graziadio C, Rosa RF, et al. (2014) Cytogenetic profile of patients with Down syndrome in southern Brazil. Sao Paulo Med J 132: 253-254.
44. Al Harasi SM. Down Syndrome in Oman: Etiology, Prevalence and Potential Risk Factors. A Cytogenetic, Molecular Genetic and Epidemiological Study. Thesis from Freie Universität Berlin, 2010.
45. Wang YF, Lin L, Chen ZY (2010) Cytogenetic study of Down syndrome cases in southern Hainan Province and report of a rare case of abnormal karyotype. Nan Fang Yi Ke Da Xue Xue Bao 30: 2592-2593, 2595.
46. Stoll C, Alembik Y, Dott B, Roth MP (1990) Epidemiology of Down syndrome in 118,265 consecutive births. Am J Med Genet Suppl 7: 79-83.
47. Zhu JL, Hasle H, Correa A, Schendel D, Friedman JM, et al. (2013) Survival among people with Down syndrome: a nationwide population-based study in Denmark. Genet Med 15: 64-69.
48. Garduño-Zarazúa LM, Giammatteo Alois L, Kofman-Epstein S, Cervantes Peredo AB (2013) Prevalence of mosaicism for trisomy 21 and cytogenetic variant analysis in patients with clinical diagnosis of Down syndrome: a 24-year review (1986-2010) at the Servicio de Genética, Hospital General de México "Dr.Eduardo Liceaga". Bol Med Hosp Infant Mex 70: 29-34.
49. Mokhtar MM, Abd el-Aziz AM, Nazmy NA, Mahrous HS (2003) Cytogenetic profile of Down syndrome in Alexandria, Egypt. East Mediterr Health J 9: 37-44.
50. Ellaithi M, Nilsson T, Elagib AA, Fadl-Elmula I, Gisselsson D (2008) A First Cytogenetic Study of Down Syndrome in Sudan. Journal on Developmental Disabilities 14: 54- 60.

51. Al-Maweri SA, Tarakji B, Al-Sufyani GA, Al-Shamiri HM, Gazal G (2015) Lip and oral lesions in children with Down syndrome. A controlled study. J Clin Exp Dent 7: e284-288.

52. Wahab AA, Bener A, Sandridge AL, Hoffmann GF (2006) The pattern of Down syndrome among children in Qatar: a population-based study. Birth Defects Res A Clin Mol Teratol 76: 609-612.

53. al-Arrayed SS (1999) Review of the spectrum of genetic diseases in Bahrain. East Mediterr Health J 5: 1114-1120.

54. Al-Awadi SA, Farag TI, Teebi AS, Naguib KK, El-Khalifa MY, et al. (1991) Cytogenetic profile of Down syndrome in Kuwait: A decade of experience. J Egypt Public Health Assoc 16: 259-269.

55. Mandava S, Koppaka N, Bhatia V, Das BR (2010) Cytogenetic analysis of 1572 cases of Down syndrome: a report of double aneuploidy and novel findings 47,XY, t(14;21)(q13;q22.3)mat,+21 and 45,XX,t(14;21) in an Indian population. Genet Test Mol Biomarkers 14: 499-504.

56. Poddar G, De A, Adhikari A, Haldar A, Banerjee J, et al. (2012) Cytogenetic, socioeconomic status and biological study of Down syndrome patients. Int J Hum Genet 12: 171-176.

57. Ahmed I, Ghafoor T, Samore NA, Chattha MN (2005) Down syndrome: clinical and cytogenetic analysis. J Coll Physicians Surg Pak 15: 426-429.

58. Devlin L, Morrison PJ (2004) Accuracy of the clinical diagnosis of Down syndrome. Ulster Med J 73: 4-12.