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DOWN'S SYNDROME: CYTOGENETIC STUDIES IN 150 CASES IN TEHRAN

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ABSTRACT

Cytogenetic studies were performed on 150 cases of Down's syndrome (DS) in Iran. The standard trisomy 21 was found in 132 (88%) and translocation-trisomy 21 (+21) in 18 (12%) patients, i.e., t(21,21) in 1(0.63%) and mosaicism in 17(11.33%) cases.

The comparison of the frequencies for mosaicism between different populations such as Denmark, Hungary, Egypt, Iraq, India, Australia and Iran demonstrated a difference in geographic distribution. There was a high incidence in the north of Europe towards Egypt and Iraq which decreased towards Iran and further towards the eastern region in the Indian ocean and India and further decreased towards Australia. Statistical analyses demonstrated significant differences between the data in Iran and Copenhagen, Hungary and Australia for mosaicism and translocation +21, and India, for translocation +21. The occurrence of translocation +21 decreased significantly from Denmark towards Egypt in Africa and Iraq in southwest Asia, then it increased from Iran towards Australia in the Pacific ocean.

The comparison of cells having satellite associations (SA), significantly indicated the involvement of two and three SAs in DS cases.

The study on the position of chromosomes in the metaphase plate, the occurrence of chromatid breaks and endoreduplication did not present any significance in DS cases.

Keywords: Down's syndrome, Cytogenetics, Geographic distribution, Iran

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INTRODUCTION

The history of cases with Down's syndrome (DS) reflects a long-standing background in the field of medical genetics.[6] Since then numerous reports have been published by many investigators, either in relation to the clinical and diagnostic approaches, or to the correlative phenomena and factors including mosaicism, other cytogenetic events and geographic distribution.[2,6,8,9,13,15-17,20,23]

The clinical examination revealed a frequency of 1/814 for DS cases in Iran.[7] DS is also considered as one of the most common chromosomal genetic disorders in Iran. However, the purpose of the present investigation is to reflect the studies of geographic distribution and cytogenetics of DS cases from northern Europe to southern Asia including Iran.

MATERIAL AND METHODS

Chromosomal analysis was performed on 150 cases with DS. Chromosome culture was carried out according to the usual criteria[1], using peripheral blood. The chromosomes were stained on the basis of conventional staining and Giemsa banding technique. Fifteen to twenty and fifty cells were analysed in the cases with standard trisomy 21 and in the mosaics, respectively.

The occurrence of satellite association (SA), the rate of chromatid breaks and endoreduplication were also studied in different sexes and compared with the control group by the X^2-test.

In order to find the specific pattern of the frequencies of trisomy 21, mosaicism and translocation in relation to geographic distribution, a comparative study was also carried out in different populations from northern Europe towards south Asia and the Pacific ocean.

RESULTS

The cytogenetic findings on 150 cases of DS were as follows:

1. Trisomy 21 due to non-disjunction was found in 132 cases (88%), translocation-trisomy 21(t21/21) in 1(0.63%) and 17 cases (11.33%) were mosaics. The frequencies of trisomy 21 and mosaicism relative to sex are presented in Table I.

2. Satellite association (SA): a total number of 2310 cells were analysed in order to study the occurrence of SA in four groups of DS cases and control. The findings are summarized in Table II.

Regarding the control group in both sexes, the cells lacking SA were found to be the most common. In the DS group, the cells containing two and three SAs were shown to have higher values than expected ($P < 0.01$). The number of SAs are given in Table III.

Concerning the involvement of specific acrocentric chromosomes, no significant differences were found (Table II). However, the different combination of SA between two acrocentric chromosomes in either sexes of DS cases and controls are given in Table V.

The present data and expected values revealed a statistically significant difference in DS cases ($P < 0.001$) and in the control group ($P < 0.001$). The association of chromosome 13/13 and 14/14 was less common and the association of 13/14 and 13/21 more common in DS cases.

3. Distribution of chromosomes in the metaphase plate: the analysis of three factor variance in order to find the effect of three factors was classified as follows:

1. Sex was considered as factor "A".

Table I. Distribution of mosaicism in males and females with DS.

Sex	Standard +21	Mosaics	Total
Male	82(81.5)*	10(10.5)	92
Female	50(50.4)	7(6.5)	57
Total	132	17	149

* ( ): Expected value
$X^2 = 0.0703$; $P > 0.05$

Table II. Distribution of the type of SA combination in DS cases and control.

Karyotype	0	1	2	3	Total
46,XY	132(110.6)	44(51.1)	3(15.7)	1(2.57)*	180
46,XX	102(92.2)	43(43.6)	4(13.1)	1(2.1)	150
47,XY +21	738(746.9)	337(34.50)	121(105.7)	19(17.4)	1215
47,XX +21	448(470.3)	232(217.2)	73(66.6)	12(10.9)	765
Total	1420	656	201	33	2310

* ( ): Expected value
$X^2 = 29.7472$; $P < 0.01$

Table III. The number of SAs in control and DS cases.

Karyotype	Number of SA	Number of cells
46 , XY	53	180
46 , XX	54	150
47 , XY +21	637	1215
47 , XX +21	414	765

Table IV. The frequency of acrocentric chromosomes involved in SA (controland DS cases).

Karyotype	Acrocentric Chromosomes					Expected Frequency	X^2
	13	14	15	21	22		
46 , XY	26.72 31*	15.52 18	9.48 11	27.59 32	20.69 21	20.00	13.569
46 , XX	28.07 32	25.44 29	13.16 15	25.44 29	7.89 9	20.00	18.1053
47 , XY +21	24.5 332	22.95 311	11.07 150	31.44 426	10.04 136	18.18**	132.5155
47 , XX +21	26.75 229	25.58 219	5.84 50	27.45 235	14.37 123	18.18	138.9624

* The number of chromosomes involved in SA
** The expected frequency for G21 is 27.27

Table V. The comparison of different SA-combinations.

Different combinations of SA	Control	DS cases
13/13	2 (7.9)*	9 (50.1)
13/14	21 (11.4)	166 (103.6)
13/15	5 (6.2)	47 (43.4)
14/14	1 (4.1)	17 (53.6)
14/15	9 (4.5)	49 (44.9)
15/15	- (1.2)	3 (9.4)
21/21	4 (6.0)	69 (87.1)
21/22	12 (5.9)	69 (59.1)
22/22	- (1.4)	4 (10.1)
13/21	18 (13.8)	159 (132.0)
13/22	6 (6.8)	34 (44.9)
14/21	5 (10.0)	131 (136.6)
14/22	2 (4.9)	59 (46.4)
15/21	4 (5.4)	62 (57.2)
15/22	3 (2.6)	20 (19.5)

* ( ) : Expected values

2. Health of the cases (normal and patients) was considered as factor "B".

3. The seven chromosome groups, i.e., A to G were considered as factor "C", with 20 repeats which were studied according to the position of the chromosome and it's distance from the center of the metaphase plate.

However, no effect of the three factors and no corresponding effects in the distance of chromosomes were obtained.

4. Chromatid breaks: in the DS cases, a total of 33 cells (1.66%) and in the control only 3 cells (0.91%) with one chromatid break, on the basis of conventional staining, were observed. However, no significant difference existed. The number of chromatid breaks in the seven chromosome groups is presented in Table VI.

The small chromosomes were seen to have less predisposition to be affected by breaks. Chromosomes of the A group showed more breaks while the G group had no break at all.

The comparison of the frequencies of trisomy 21, mosaicism and translocation-trisomy 21 in different populations, as a mixed selection, was carried out. The frequencies from different populations, including Iran are summarized in Table VII.

DISCUSSION

The most common chromosome aberrations in DS cases are, in order of frequency, the standard trisomy 21 (92-95%), translocation-trisomy 21 (4-6.3%) and mosaicism (1-4%) which have been reported by previous investigators.[8,9,18,21,24] The present data also revealed standard trisomy 21 as the most common aberration in 150 DS cases.The comparison of the mosaic rate between different populations has been carried out previously[10] showing a higher incidence of mosaic cases in Egypt.

In the present investigation, the comparison was done on the basis of findings from Denmark[19], Hungary[21], Egypt[10], Iraq[11], India,[23]Australia[18]and Iran (Table VII).

The comparison of the frequencies of mosaicism among the mentioned populations revealed a high incidence in the north of Europe, i.e., Denmark (Copenhagen), which increased towards Egypt and Iraq but decreased towards Iran and further towards more eastern regions in the Indian Ocean (India) and finally towards Australia (Fig. 1).

Statistical analysis demonstrated significant differences between Iran and the data in Copenhagen, Hungary and Australia for the frequencies of mosaicism and translocation, and in India for translocation. The data from Denmark and Australia also revealed significant differences concerning translocation between the two countries, but no significant differences in the frequency of mosaicism between them (Table VII, Fig. 1).

In contrast, the occurrence of translocation +21

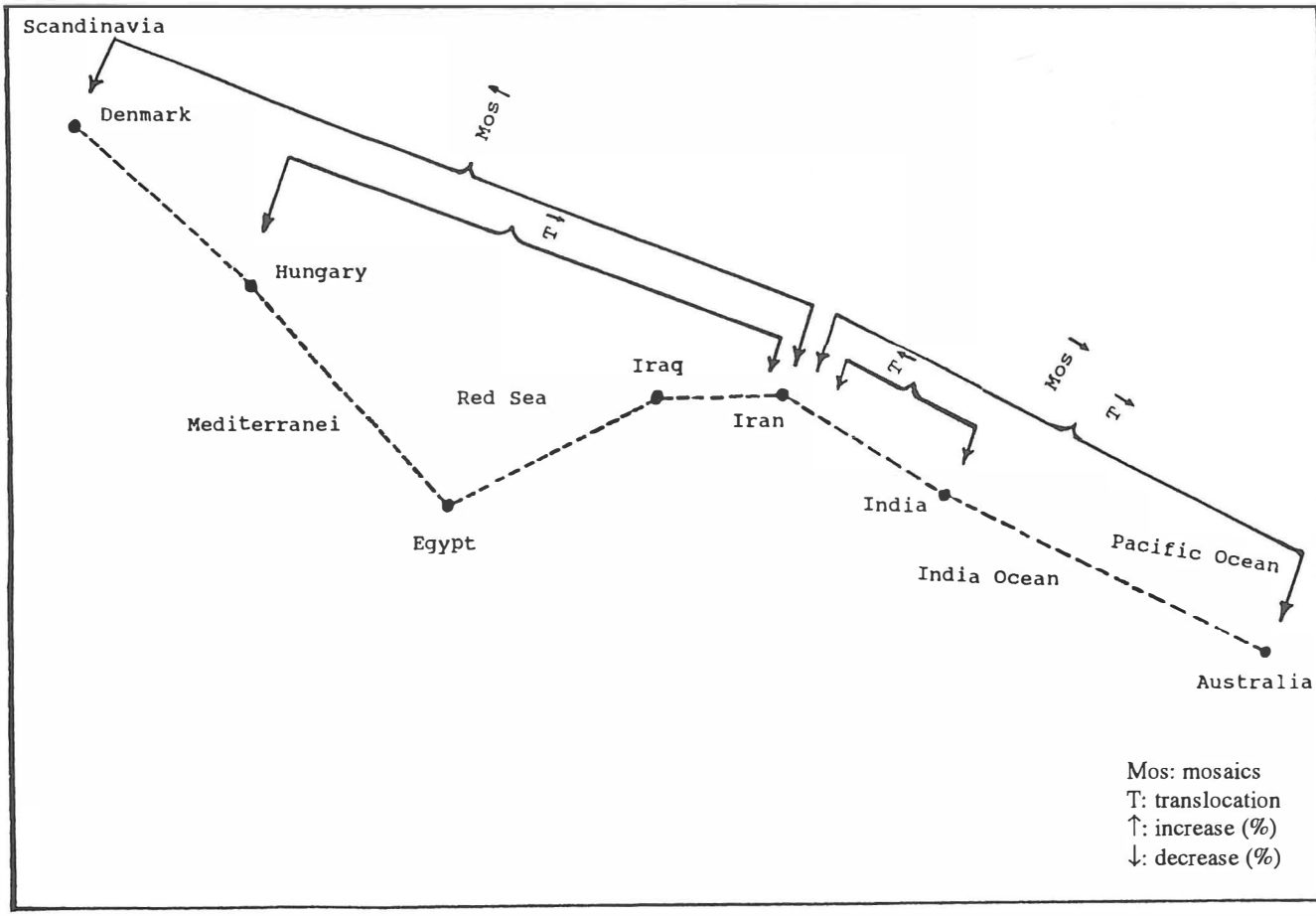

Fig. 1 Geographic distribution of the mosaics and translocated DS cases from northern Europe towards south Asia and Australia with significant differences. Statistical test: comparing two proportions test

Table VI. The number of chromatid breaks (ctb) relative to the chromosome group in DS cases.

Chromosome group	A	B	C	D	E	F	G
Number of ctb	15	7	5	4	1	1	0

decreases statistically from Copenhagen (Denmark) in northern Europe towards Egypt and Iraq and then increases from Iran towards the Pacific ocean and Australia (Fig. 1).

The differences found in the occurrence of mosaicism and translocation might be related to environmental factors and ethnic influences which could be considered as important factors in the studies on geographic and ethnic distributions of DS cases throughout the world. However this matter requires more extensive investigation.

Concerning satellite associations (SA), the literature presented evidence of differences between normal and abnormal cases that supports the role of SA events in the etiology of chromosomal aberrations.[2,5,14,16,17,20,22]

In the present study, the comparison of cells involved in SA, according to the number of SAs in males and females of both DS cases and controls,

Table VII. Frequency of trisomy 21 (+21), mosaics (Mos) and translocation (T) in DS cases among different populations.

Source	No.of DS cases	Standard +21 (%)	Mos(%)	T(%)	|P1-P2| > A Comparison of each population with Iran
Denmark (Mikkelson et al, 1976)	177	89.8	4	6.2	Mos: 0.073>0.058 T: 0.055>0.037
Hungary (Papp et al, 1977)	362	91.7	4.4	3.9	Mos: 0.069>0.054 T: 0.032>0.023
Egypt (Hafez et al, 1984)	236	85.16	13.55	1.29	Not Significant
Iraq (Hammy et al, 1990)	83	81.92	18.08	0	Not Significant
India (Sayee, 1993)	390	89.48	5.76	4.76	T: 0.040>0.024
Australia (Mulcahy, 1979)	235	95	4	1	Mos: 0.073>0.056 T: 0.07>0.058
Iran (Present Investigation)	150	88	11.33	0.67	

indicated an increase in the number of cells lacking any SA or containing one SA in normal males and females, and significantly indicated the involvement of two and three SAs in DS cases (Table II).

The cells containing two and three SAs in DS cases were shown to contain more SA than the control. This finding is similar to a previous report[25] on a mosaic case and may reflect the effective presence of the extra chromosome 21 in the event of SA.

Concerning the position of chromosomes in the metaphase plate, previous data reflected that the larger chromosomes tend to lie around and the smaller ones in the middle and inner part of the metaphase plate.[12-15] However, our present findings did not reveal any significant differences.

The occurrence of chromatid breaks (ctb) and endoreduplication in DS cases revealed the random involvement of chromosomes in ctb and did not present any significance either in ctb or in endoreduplication.

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