CYTOGENETIC STUDIES IN DOWN SYNDROME

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ABSTRACT

Cytogenetic studies were carried out in 645 patients with Down syndrome. Free trisomy of chromosome 21 was present in 600 cases (93%). Translocation karyotypes were observed in 26 cases (4%). Seventeen patients (2.6%) had mosaicism. Two (0.3%) patients had additional karyotypic abnormalities along with trisomy 21.

Key words: *Down Syndrome, Cytogenetics*

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Down syndrome is the most common genetic cause of mental retardation. It occurs with an overall frequency of 1 in 700 to 1000 newborns in the western populations(1). Data from eight hospitals in India on 75,103 births, shows the frequency of Down syndrome to be 1 in 920 births, *i.e.*, 1.09 in 1000 live births(2). Cytogenetic analysis of Down syndrome patients is useful in genetic counselling. It confirms the diagnosis and indicates the likely risk of recurrence. However, for genetic counselling to be accurate, it should be based on cytogenetic data from a large number of patients. In India, only a few studies have been reported on the cytogenetics of Down syndrome with large sample size(3-15). We report the cytogenetic analysis of 645 Down syndrome patients–the largest number so far from India and collate it with the previously available data. The implications of these results in genetic counselling are also discussed.

Material and Methods

Of 852 cases, in whom a clinical diagnosis of Down syndrome was made in the Genetic Clinic, 645 cases had a successful cytogenetic analysis. In the remaining cases (n=207), chromosomal analysis was either not done due to the parents having completed their reproduction or failing to turn up for the appointment for blood culture or the culture was not successful. The present sample also includes 150 patients reported by Verma *et al.* almost 10 years ago(7). Ages of the patients ranged from few hours after birth to 15 years.

Peripheral blood culture was done

using the microculture technique of Arakaki and Sparkes(16), with slight modifications. Briefly, 6 to 8 drops of whole blood was incubated at 37°C in 5 ml of Eagles minimal essential medium supplemented with 10% newborn calf serum, antibiotics and phytohemagglutinin P. The cells were harvested after 72 hours. The G and Q banding were done by standard techniques(17,18). A minimum of 11 metaphases were scored and one karyotype was made for each patient. In case of mosaicism, 50 or more metaphases were scored. Wherever possible, parents of translocation Down syndrome patients were also investigated for chromosomal abnormality.

Results

Cytogenetic analysis of 645 cases of Down syndrome is presented in *Table I*. Out of these, 600 (93%) cases had free trisomy of chromosome 21. Seventeen cases (2.6%) had mosaicism. Two (0.3%) rare karyotypes, involving chromosomal abnormalities in addition to trisomy 21 were also observed.

Translocation karyotypes (D/G and G/G) were observed in 26 (4.0%) cases.

TABLE I– *Cytogenetics of Down Syndrome Patients*

Karyotype	Number	%
Free trisomy 21	600	93.0
Translocation		
D/G	17	2.6
G/G	9	1.5
Mosaic	17	2.6
Additional abnormality	2	0.3
Total	645	100.0

Seventeen (2.6%) had D/G and nine (1.5%) had G/G translocations. Of D/G translocations eight were of t (14; 21) and 2 were of 15/21 translocation. G/G translocations involved 21/21 translocation in 3, and 21/22 translocation in one. In the remaining cases, identification of chromosomes were not possible, due to very old slides.

In two cases with translocation between chromosomes 14 and 21, mothers were carriers. In five cases (one D/G and four G/G translocation), parents were normal. Parental chromosomes were not studied in rest of the cases, for various reasons.

In the group with additional karyotypic abnormalities double aneuploidy (48, XXX +21) was seen in one patient. One girl had an extra small metacentric chromosome (smaller than G group chromosomes), in addition to chromosome 21. The specific origin of this metacentric chromosome could not be identified based on banding patterns. The parents did not show a similar metacentric chromosome or reciprocal translocation.

Analysis of the cytogenetic data, according to the maternal age, was possible only in 600 cases (*Table II*). Of 25 translocation karyotypes observed, 23 were children born to mothers who were equal to or less than 30 years of age at conception, whereas only two were born to older mothers (>30 years at conception). However, of all cases of Down syndrome born to mothers younger than 30 years in age at conception, 5% had a translocation karyotype. In older mothers (>30 years at conception) the frequency of translocation karyotypes was only 1.4%. Similarly free trisomy 21 karyotypes was observed in only 91.7% of cases born to younger mothers as compared to 97.2% among children born to older mothers. Significant differences

TABLE II—*Maternal Age at Birth of Down Syndrome (n = 600)*

Maternal age	<30 yr		>30 yr	
	No.	%	No.	%
Karyotype				
Free trisomy 21	422	91.7	136	97.2
Translocation	23	5.0	2	1.4
Mosaic	13	2.8	2	1.4
Unusual	2	0.4	0	–
Total	460	99.9	140	100.0

were observed in the frequency of free trisomy 21 and translocation cases between the two age groups (p = 0.016 and 0.041). Thirteen (2.8%) of mosaic Down syndrome children were born to young mothers (<30 years) as compared to two (1.4%) in older mothers. The difference was not statistically significant. Rare karyotypes were observed only in children who were born to young mothers.

Discussion

Cytogenetic data available on cases of Down syndrome from different parts of India are given in *Table III*. The frequency of free trisomy 21 ranged from 83.6% to 97.8% with a mean of 91.6%. Mosaic karyotytpes were observed only in some studies, varying in range from none to 11.76% with a mean of 4.1%. The frequency of translocation karyotypes varied from 2.2 to 13.7% with a mean of 4.1%. In the present study, the frequency of cases with translocation (4.0%) and mosaicism (2.5%) are within the range reported from India, and the means closely correspond to the mean values calculated by pooling the data from all over India. As our sample size is large, this may be used for purposes of genetic counselling in India.

The distribution of Down syndrome cases in India could not be analysed according to maternal age at conception, because most of the studies from India do not provide the breakup of data according to maternal age.

Frequency of rare (unusual) karyotypes in the present series is well within the frequency (upto 1.0%) reported around the world(19). Many cases with supernumarary marker chromosome have been reported in patients with mental retardation(20). In this series, one Down syndrome child with a metacentric marker chromosome was observed, which was of *de novo* origin.

The implications of these results in genetic counselling are clear. In younger mothers, free trisomy 21 karyotype is observed in only 91.7% of cases, while 8.3% of Down syndrome cases show other karyotypic abnormalities–either translocation, mosaicism or marker chromosomes. Therefore in such cases, chromosomal studies are required before proper genetic counselling can be offered. On the other hand, in older mothers 97.2% of the cases of Down syndrome had free trisomy 21 karyotypes. This indicates that in the older

TABLE III–*Comparative Cytogenetic Data from India*

Place	Total	Trisomy	Trans	Mosaic	Others	Reference
Ahmedabad	110	93.60	3.60	2.70	–	Murthy *et al.* 1989
Banaras	34	88.24	–	11.76	–	Bamezai and Hussain, 1988
Bangalore	70	88.57	7.14	2.86	1.43	ICMR study, 1984*
Bangalore	93	90.32	–	9.68	–	ICMR study, 1987**
Bangalore	275	87.64	6.55	5.82	–	Sayee and Thomas, 1988
Bombay	113	80.53	8.80	10.62	–	Krishna Murthy *et al.*, 1981
Bombay	146	83.60	6.80	9.60	–	Ambani *et al.*, 1984
Bombay	86	88.37	5.81	5.81	–	ICMR Study, 1984*
Bombay	73	84.92	13.69	1.37	–	Parikh and Bhanumathi, 1989
Calcutta	63	93.65	6.34	–	–	Chaudhuri and Chaudhuri, 1966
Delhi	150	92.00	5.33	2.00	0.67	Verma *et al.*, 1979
Hyderabad	240	92.08	2.92	5.00	–	Isaac and Reddi, 1988
Lucknow	32	100.00	–	–	–	ICMR Study, 1984*
Madras	92	97.83	2.17	–	–	Rafi and Marimuthu, 1977
Pondicherry	69	100.00	–	–	–	Puri *et al.*, 1977
Pune	136	97.79	2.20	–	–	Phadke *et al.*, 1975
Pune	133	97.74	–	2.26	–	ICMR study, 1987**
Delhi	645	93.00	4.10	2.60	0.30	Present study
Total	2410	91.64	4.12	4.12	0.10	(Mean)

* ICMR multicentric study on mental retardation (1981-1984).

**ICMR Multicentric Study on Genetic Counselling and Prenatal Diagnosis of Genetic Disorders in India (1984-87).

mothers chromosomal studies are not absolutely necessary, unless there is uncertainty about the diagnosis. Thus, based on the present study, we would recommend that chromosomal studies are mandatory in cases of Down syndrome born to younger mothers; while in mothers older than 30 years at the time of conception chromosomal studies can be avoided, if facilities are not available locally or in a nearby centre. That is, such a case need not be referred to a distant centre, thus avoiding the cost for the parents.

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NOTES AND NEWS

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