

Cytogenetic Analysis of Down Syndrome in Gujarat

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During 1995 to 2006, 382 cases clinically suspected for Down syndrome were investigated for cytogenetic study. Free trisomy 21 constituted 84.8% of cases, translocation 8.9%, mosaic 3.9% and in 2.4% cases regular T21 was associated with structural or numerical changes. Translocation was parentally inherited in 26.5% cases and maternal transmission was twice as common as paternal. Males were more pronounced to be affected than females in all the groups. 91.6% of DS babies were born to younger mothers (20-35 yr) compared to 8.4% in elderly mothers (>35 yr).

Key words: Down syndrome, Trisomy 21.

Down syndrome (DS) with trisomy (T21) is one of the most common aneuploidy in humans associated with mental retardation and developmental delay with the incidence of 1 per 920 births in India(1,2). The extra copy of chromosome 21 in DS children occurs as a free chromosome, part of Robertsonian (RT) fusion chromosome or in rare instances as a part of reciprocal translocation. The present study is aimed to document the types of cytogenetic abnormality in DS children and their relation to maternal age.

Subjects and Methods

The study included 382 children in the age range of 2 days to 14 yr. They were referred between the periods of 1995 to 2006 for cytogenetic analysis to confirm the clinical diagnosis of DS.

Chromosome preparation was carried out from 3-4 mL of peripheral blood collected in sodium heparine in all subjects. Routinely, Giemsa (GTG) banding technique was performed to identify the chromosomes. Additional banding techniques like Centromeric (CGB) and NOR were used to confirm the structurally alerted chromosomes. 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. Parents of children having structural anomalies were investigated to rule out the origin of altered chromosome.

Results

The abnormal karyotypes are listed in *Table I*. Translocation accounted for 34 (8.9%) cases; maternal and paternal inheritance was seen in 6 and 3 cases, respectively; parental karyotype was normal in 12 cases suggesting *de-novo* origin. Parents of remaining 13 cases denied investigations. The overall male: female (M : F) sex ratio in this study was 2.3 : 1. There was no marked difference in the mean maternal age of either group. The birth frequency of DS babies in younger mothers (<35 yrs) is 91.6% compared to older mothers (>35 yrs) (*Table II*).

Discussion

The frequency of free T21 observed in the present study is the most common and seen in 84.8% of cases which is consistent with Jacob et al. (84.6%) (3) and near to 87.9%(4).

RT is the second most and comprises of 8.9% and remain the highest among the larger series reported till date *i.e.*, 3.8%(5) and 4.4%(4) from India. Familial inheritance in RT is seen in one quarter whereas in remaining it arises as a *de-novo* (6). In the present study, 3/13 cases with t(14; 21) showed maternal inheritance. In one of these, mother was subjected to CVS in her subsequent pregnancy and the karyotype was T21 in translocated form. This shows that mother

TABLE I—Karyotype Analysis of 382 Down Syndrome Cases

Karyotype	No.	%	Mean maternal age
Regular trisomy 21 (M : F= 2.21)	324	84.8	24.7
47,XY,+21	223	58.4	
47,XX,+21	101	26.4	
Translocation (M : F = 1.43)	34	8.9	24.3
46,XX,der(13;21)(q10;q10),+21	1		
46,XY,der(14;21)(q10;q10),+21	7		
46,XX,der(14;21)(q10;q10),+21	6		
46,XY,der(21;21)(q10;q10),+21	9		
46,XX,der(21;21)(q10;q10),+21	3		
46,XX,der(21;21)(q22.3;q22.3),+21	1		
46,XX,der(21;22)(q10;q10),+21	1		
46,XX,der(15;21)(q10;q10),+21	2		
46,XY,der(15;21)(q10;q10),+21	1		
46,XY,idup(21;21)(q22.3;q22.3),+21	1		
47,XY,t(11;21)(q13.3;p13),+21	1		
46,XY,inv(9)(qh),der(21;21)(q10;q10),+21	1		
Mosaic (M:F = 2.0)	15	3.9	25.0
47,XY,+21/46,XY	8		
47,XX,+21/46,XX	5		
46,XY/46,XY,der(21;21)(q10;q10),+21	1		
47,XY,der(21;21)(q10;q10)/47,XY,+21	1		
Non-classical (M:F= 3.50)	9	2.4	25.8
47,XY,inv(9)(qh),+21	2		
47,XX,+21/48,XXY,+21	1		
46,XY,der(13;14)(q10;q10),+21	1		
47,X,inv(Y),+21	4		
47,XX,der(11;22)(q13;q11),+21	1		
Total	382	100	

transmitted the translocation in an unbalanced state to the offspring. The recurrence risk is <1% if the translocation is *de-novo*. In case of familial RT DS, the genetic risk for female carrier to have a live born child with translocation DS is about 10%, which increases to 15% at amniocentesis. For male carrier the recurrence risk to have a child with translocation DS is about 1%(7).

The homologous translocation (21q21q) is one

of the most common chromosomal rearrangements in DS. An interesting observation was seen in one case where karyotypic analysis showed a “mirror” duplication of #21 which confirmed to be of paternal origin. This confirms that most de-novo rearrangements (21q21q) are isochromosomes derived from a single parental #21 and only small proportion is consistent with true RT(8,9).

Thus in DS, free T21, RT and mosaicism are the classical anomalies. Nonetheless in the last few years, non-classical DS karyotype have been reported in major DS studies with frequency ranging from 0-1.2% (5,10). Our data of 2.4% is higher than that previously reported. It is important to consider such non-classical DS cases in genetic counseling and provide precise recurrence risk for such distinct groups.

Though the advance maternal age is an established risk factor for DS, present study has shown increased number of DS babies born to the young mothers as more number of pregnancies occurs in this reproductive age group. This could either be due to MTHFR gene polymorphism(11) and/or nutritional factor(12). Higher incidence of free trisomy in the elderly mother reflects the meiotic error as the common cause in the present study (93 vs 84%). On the other hand, translocation DS was more common in younger mother in contrast to elder mothers (10 vs 4%) reflecting likely cause of parental origin that provides important information for genetic counseling to the family.

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What this Study Adds?

- Translocation and non-classical DS are higher in Western India and majority of them are born to younger mother.

TABLE II—Effect of Maternal Age on Down Syndrome

Maternal age	Free trisomy % (FT)	Translocation % (T)	Mosaicism % (M)	Total %	FT:T:M %	
<35	76.9	der(13;14)	0.3	5.4	91.6	84:10:6
		der(14;21)	3.3			
		der(15;21)	0.8			
		der(11;21)	0.3			
		der(11;22)	0.3			
		der(21;22)	0.3			
		der(21;21)	3.7			
		der(13;21)	0.3			
		TOTAL	9.3			
>35	7.8	der(13;14)	0	0.3	8.4	93:4:3
		der(14;21)	0			
		der(15;21)	0			
		der(11;21)	0			
		der(11;22)	0			
		der(21;22)	0			
		der(21;21)	0.3			
		der(13;21)	0			
		Total	0.3			
Total	84.7	9.6	5.7	100.0		

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