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Mental Retardation Associated with "Balanced" Chromosome Rearrangements

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Breg et al. [1] postulated an increased incidence of balanced reciprocal translocations in mentally retarded individuals. Subsequently, Jacobs [2] reported the association of de novo balanced chromosome rearrangements with retardation. The data presented here, when pooled with reported studies, specifically associate de novo non-Robertsonian translocations with retardation.

METHOD AND RESULTS

Cytogenetic studies were carried out on 2,134 patients (ages 0 through 18 with a mean of 9 years) who visited the UCLA Child Psychiatric and Mental Retardation Clinic between 1968 and 1974. Mental retardation (IQ < 70) was found in 455 patients, and psychiatric disorders without retardation in the remaining 1,679. Patients with abnormal karyotypes detected by conventional stain were further evaluated by chromosome banding using quinacrine fluorescence or trypsin-Giemsa stains [3, 4]. Seven autosomal rearrangements were found among the 455 retarded patients, whereas only four were found among those 1,679 with psychiatric disorders ($P < .05$, table 1). These rearrangements were considered "balanced" as there was no detectable loss or excess of chromosome material. No Robertsonian translocations (i.e., centric-fusion rearrangements among D and G group chromosomes) were found in the entire sample. Among the seven patients with mental retardation and apparently balanced rearrangements, there were six non-Robertsonian translocations and one pericentric inversion; among the four patients with psychiatric disorders but no retardation, there were no translocations and four pericentric inversions (table 2). Four patients have been previously reported [5–8]. One retarded patient with an inherited pericentric inversion of the Y chromosome was not included in table 1 in order to compare the incidence from previous surveys reporting only the incidence of balanced autosomal rearrangements. Neither parent of three of the seven patients with retardation and balanced rearrangements were available for examination; therefore, no conclusion can be drawn about the incidence of de novo vs. familial chromosome rearrangements among the retarded in this study.

DISCUSSION

The reported incidence of balanced chromosome rearrangements from previous

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TABLE 1

"BALANCED" CHROMOSOME REARRANGEMENTS IN PATIENTS FROM THE UCLA CHILD PSYCHIATRIC AND MENTAL RETARDATION CLINIC

DIAGNOSTIC CATEGORY	No. PATIENTS	BALANCED REARRANGEMENTS			ORIGIN*	
		No.	Translocations†	Pericentric Inversions	Familial	De Novo
Mental retardation ...	455	7	6	1	2	2
Psychiatric disorders .	1,679	4	0	4	3	1

* Origin reported only when parental studies were complete.
† There were no Robertsonian translocations.

surveys of the mentally retarded was combined with that reported here (table 3). When compared with the incidence of balanced rearrangements from several large newborn surveys (table 4), a marked increase in non-Robertsonian translocations is evident among the retarded (table 5). There is a suggestion of an increase in pericentric inversions as well, but the sample is still too small to be of statistical significance. It is interesting that a high incidence of pericentric inversions was observed for the nonretarded, psychiatric patients reported in the current survey. The combined data also show an increase in de novo rather than familial rearrangements among the retarded. The increase in de novo rearrangements appears to be specifically for non-Robertsonian translocations. A less striking increase in familial rearrangements

TABLE 2

"BALANCED" CHROMOSOME REARRANGEMENTS IN PATIENTS FROM UCLA CHILD PSYCHIATRIC AND MENTAL RETARDATION CLINIC

Patient	Age at Exam (yrs.)	Karyotype	Origin	Clinical Features
Case 1	2	46,XX,inv(3p+q−)	Paternal	Normal development
Case 2*	9	46,XY,inv(15p+q−)	Maternal	Normal intelligence
Case 3*	16	46,XY,inv(15p+q−)	Paternal	Normal intelligence
Case 4*	13	46,XY,inv(4p+q−)	De novo	Normal intelligence
Case 5	6	46,XY,t(2q−;8q+)	Paternal	Moderate retardation
Case 6	7	46,XX,t(4p+;9q−)	De novo	Severe retardation; autism
Case 7*	17	46,XX,t(10q−;22p+)	De novo	Mild retardation; convergence insufficiency
Case 8*	10	46,XY,inv(Yp+q−)	Paternal	Moderate retardation; height < 3rd percentile
Case 9	9	46,XY,t(9p−;17p+)	Paternal†	Moderate retardation; narrow palpebral fissures; narrow palate; club foot
Case 10	10	46,XY,t(6q−;17q+)	N.C.	Moderate retardation; ptosis; facial asymmetry; short 4th metatarsals
Case 11	5	46,XY,t(1p−;8q+)	N.C.	Moderate retardation; club foot
Case 12	5	46,XY,inv(5p−q+)	N.C.	Moderate retardation; autism

NOTE.—N.C. = parental studies not complete.
* Previously reported [5–8].
† Personal communication, Raymond Teplitz, M.D., Los Angeles.

TABLE 3

SURVEYS OF MENTALLY RETARDED

REFERENCE	NO. PATIENTS EXCLUDING DOWNS	BALANCED AUTOSOMAL REARRANGEMENTS				FAMILIAL*			DE NOVO*		
		No.	R	N-R	Inv	R	N-R	Inv	R	N-R	Inv
[1]	1,000	4	...	4	...	...	...	...	...	...	...
[9]	50	1	...	1	...	...	1	...	...	...	...
[10]	50	2	1	1	...	1	...	...	...	...	...
[11]	264	3	2	...	1	1	...	...	...	...	1
[12]	83	2	...	2	...	...	...	...	...	2	...
[13]	44	...	...	...	...	...	...	...	...	...	...
[14]	85	...	...	...	...	...	...	...	...	...	...
[15]	537	1	...	1	...	...	...	...	...	...	...
[16]	54	...	...	...	...	...	...	...	...	...	...
[17]	2,426	12	3	8	1	1	2	...	1	3	...
Current report	455	7	...	6	1	...	1	...	...	2	...
Total	5,048	32	6	23	3	3	4	0	1	7	1
Incidence per 1,000	...	6.3	1.2	4.5	0.6		1.4			1.8	

NOTE.—R = Robertsonian translocations; N-R = non-Robertsonian translocations; Inv = inversions.

* Origin reported only when parental studies were complete.

TABLE 4

NEWBORN SURVEYS

REFERENCE	No. NEWBORNS	BALANCED AUTOSOMAL REARRANGEMENTS				FAMILIAL*			DE NOVO*		
		No.	R	N-R	Inv	R	N-R	Inv	R	N-R	Inv
[18]	11,680	22	10	10	2	6	6	2	1	4	...
[19]	13,939	24	13	11	...	11	8	...	...	1	...
[20]	5,049	16	8	7	1	8	6	1	...	1	...
[21]	2,081	1	1	...	...	1	...	...	...	...	...
[22]	4,400	6	3	3	...	1	1	...	1	2	...
[23]	3,543	8	3	2	3	3	1	2†	...	...	...
Total	40,692	77	38	33	6	30	22	5	2	8	0
Incidence per 1,000	...	1.9	0.93	0.81	0.15		1.4			0.25	

NOTE.—R = Robertsonian translocations; N-R = non-Robertsonian translocations; Inv = inversions.
* Origin reported only when parental studies were complete.
† Includes one familial inversion of a Y chromosome.

TABLE 5

POOLED DATA COMPARING INCIDENCE OF BALANCED AUTOSOMAL REARRANGEMENTS IN RETARDED AND NEWBORN

	TOTAL	FAMILIAL		DE NOVO	
		Robertsonian	Non-Robertsonian and Inversions	Robertsonian	Non-Robertsonian and Inversions
Retarded	5,048	3 (0.6)*	4 (0.8)	1 (0.2)	8 (1.6)
Newborn	40,692	30 (0.7)	27 (0.7)	2 (0.05)	8 (0.2)
χ^2 test (Yates correction) P value	...	N.S.	N.S.	N.S.	< .001

* Rate per 1,000.

could also be present among the retarded since studies were not done in both parents for a larger proportion of parents of the retarded than for parents of the newborns.

As previously suggested [2], the deleterious effect of balanced translocations may be due to: (1) a small deletion or duplication at the site of the chromosome break; (2) a gene mutation at the site of the chromosome break; or (3) a detrimental effect from rearrangement of gene position. Alternatively, the high proportion of de novo rearrangements among the retarded suggests that whatever agent(s) causes the chromosome rearrangement may, in addition, have a deleterious effect preconceptionally on the egg or sperm. One possible example in humans may be the increased abortions observed among nonexposed wives of male anesthetists [24].

If confirmed, the findings reported here could be of clinical importance in the interpretation of chromosome rearrangements detected prenatally. The data suggest a potential developmental vulnerability for individuals with apparently balanced non-Robertsonian translocations and possibly pericentric inversions. The extent of this risk to the developing fetus and child will become evident only after long-term follow-up of children with apparently balanced chromosome rearrangements detected during newborn screening surveys. Of 77 infants with balanced rearrangements reported from newborn surveys, seven manifested either poor growth or more than one congenital anomaly [19, 20]. Although five of these seven rearrangements were familial, it is interesting that only two were Robertsonian translocations, in keeping with the findings reported here of a high proportion of non-Robertsonian rearrangements among the mentally retarded.

SUMMARY

Balanced chromosome rearrangements were found in seven of 455 retarded children vs. four of 1,679 nonretarded, psychiatric children ($P < .05$). The combined incidence of non-Robertsonian balanced rearrangements from this and reported surveys of the mentally retarded was five times greater than that from newborn surveys, whereas Robertsonian translocations were not increased among the retarded. The combined data show an increase in de novo rather than familial rearrangements among the retarded; the increase in de novo rearrangements is specifically for non-Robertsonian translocations.

REFERENCES

1. Breg WR, Miller DA, Allerdice PW, Miller OJ: Identification of translocation chromosomes by quinacrine fluorescence. *Am J Dis Child* 123:561–564, 1972
2. Jacobs PA: Correlation between euploid structural chromosome rearrangements and mental subnormality in humans. *Nature* 249:164–165, 1974
3. Caspersson T, Zech L, Johansson C, Modest EJ: Identification of human chromosomes by DNA-binding fluorescent agents. *Chromosoma* 30:215–227, 1970
4. Seabright M: Rapid banding technique for human chromosomes. *Lancet* 2:971–972, 1971
5. Crandall BF, Carrel RE, Sparkes RS: Chromosome findings in 700 children referred to a psychiatric clinic. *J Pediatr* 80:62–68, 1972
6. Crandall BF, Carrel RE, Adams GL, Sparkes RS: Cytogenetic studies in a patient with a de novo t(Cq−;Gp+). *J Med Genet* 7:413–416, 1970
7. Crandall B, Sparkes RS: Pericentric inversion of a number 15 chromosome in nine members of one family. *Cytogenetics* 9:307–316, 1970

8. FRANCKE U: Quinacrine mustard fluorescence of human chromosomes: characterization of unusual translocations. *Am J Hum Genet* 24:189–213, 1972
9. SUMMITT RL: Cytogenetics in mentally defective children with anomalies: a controlled study. *J Pediatr* 74:58–66, 1969
10. DALY RF: Chromosome aberrations in 50 patients with idiopathic mental retardation and in 50 control subjects. *J Pediatr* 77:444–453, 1970
11. CHEN ATL, SERGOVICH FR, MCKIM JS, BARR ML, GRUBER D: Chromosome studies in full-term, low-birth-weight, mentally retarded patients. *J Pediatr* 76:393–398, 1970
12. THORBURN MJ, MARTIN PA: Chromosome studies in 101 mentally handicapped Jamaican children. *J Med Genet* 8:59–64, 1971
13. BROGGER A, MORH J, WEHN M, VISLIE H: Concerning translocation as a cause of mental retardation. International Copenhagen Congress Scientific Study of Mental Retardation, 1964, pp 128–131
14. YANAGISAWA S: Cytogenetic studies on the mentally retarded children. *Acta Paediatr Jpn* 10:30, 1968
15. IIVANAINEN M, GRIPENBERG U: Clinico-neurological findings in connection of three chromosomal aberrations: an extra chromosome in group E, a D/C translocation and an unusually long B group chromosome. *Acta Neurol Scand* [*Suppl*] 43(31):53–54, 1967
16. LUBS HA, LUBS ML: New cytogenetic techniques applied to a series of children with mental retardation, in *Nobel Symposia*, vol 23, edited by CASPERSSON T, ZECH L, New York, Academic Press, 1972, pp 241–250
17. JACOBS PA, BUCKTON KE, CUNNINGHAM C, NEWTON M: An analysis of the break points of structural rearrangements in man. *J Med Genet* 11:50–64, 1974
18. JACOBS PA, MELVILLE M, RATCLIFFE S: A cytogenetic survey of 11,680 newborn infants. *Ann Hum Genet* 37:359–376, 1974
19. HAMERTON JL, CANNING N, RAY M, SMITH S: A cytogenetic survey of 14,069 newborn infants. *Clin Genet* 8:223–243, 1975
20. FRIEDRICH U, NIELSEN J: Chromosome studies in 5,049 consecutive newborn children. *Clin Genet* 4:333–343, 1973
21. SERGOVICH F, VALENTINE GH, CHEN ATL, KINCH RAH, SMOUT MS: Chromosome aberrations in 2,159 consecutive newborn babies. *N Engl J Med* 280:851–855, 1969
22. LUBS HA, RUDDLE FH: Application of quantitative karyotypy to chromosome variation in 4,400 consecutive newborns, in *Human Population Cytogenetics*, edited by JACOBS PA, PRICE WH, LAW P, Baltimore, Williams & Wilkins 1970, pp 120–142
23. GERALD PS, WALZER S: Chromosome studies in normal newborn infants, in *Human Population Cytogenetics*, edited by JACOBS PA, PRICE WH, LAW P, Baltimore, Williams & Wilkins, 1970, 144–151
24. ASKROG V, HARVALD B: Teratogen effekt af inhalationsanaestetika. *Nord Med* 83:498–500, 1970