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Nonrandomness of Translocations in Man: Preferential Entry of Chromosomes into 13-15/21 Translocations

Abstract. *Lymphocytes from 20 individuals with Down's syndrome due to 13-15/21 centric-fusion translocations were studied by autoradiography after continuous late labeling with tritiated thymidine. In no case was chromosome 13 involved; chromosome 14 was involved in 18 cases, and chromosome 15 in two cases. These results are similar to those from 13 previously studied cases and indicate that the entry of chromosomes 13-15 into translocations is nonrandom. This nonrandomness is not a simple function of chromosome size or shape, since chromosomes 13-15 are acrocentrics of similar size.*

Translocations in the general population and in criminal populations (*1*) nonrandomly involve acrocentric chromosomes (Nos. 13, 14, 15, 21, and 22). This tendency is also apparent in trisomy 21 (Down's) syndrome (*2*) and in trisomy 13 (D_1) syndrome (*3*). Translocations in patients with these syndromes tend to involve chromosome 21 or chromosome 13 in centric-fusion with other acrocentric chromosomes (*3*). The tendency for any chromosome to be observed in translocations can reflect either the preferential entry of that chromosome into the translocation event or selection for individuals receiving the translocation with that chromosome (or selection against individuals receiving translocations involving other chromosomes).

The present investigation was designed to provide information as to whether the entry of chromosomes 13-15 into a translocation is nonrandom. The translocation chosen for study was the 13-15/21 centric-fusion translocation in Down's syndrome. All patients studied had the same abnormal phenotype (Down's syndrome), the same chromosomal abnormality (13-15/21 centric-fusion translocation), and presumably the same chromosomal imbalance (triplication of the long arm of chromosome 21). As far as is known, loss of the short arm of chromosomes 13, 14, or 15 does not have phenotypic effects upon the individual (*4*). Differences between the frequencies of 13/21, 14/21, and 15/21 translocations in Down's syndrome should therefore reflect different tendencies on the part of chromosomes 13, 14, and 15 to enter into centric-fusion translocations with chromosome 21.

Twenty patients with Down's syndrome with 13-15/21 translocation were studied to determine the identity of the chromosome from the 13-15 group. These patients were ascertained in Washington, Oregon, Idaho, southern California, and Michigan. They included all such patients available to us. To our knowledge, the patients were not related to each other.

Peripheral blood lymphocytes were cultured for 48 to 72 hours and continuously labeled with tritiated thymidine (specific activity 2.0 c/mmole at a concentration of 1 μc/ml medium) beginning 6 hours before harvest. Well-spread metaphases were photographed before and after autoradiography with Kodak AR-10 stripping film, as described by Schmid (*5*).

Although pairs 13, 14, and 15 are morphologically very similar, they have been shown to be distinguishable by autoradiographic analysis of their DNA replication patterns (*5, 6*). Chromosomally normal cells labeled late in their DNA synthetic period have been found to show a pair of chromosomes (Nos. 13) with heavy label over the middle and distal portions of the long arms, a pair of chromosomes (Nos. 14) with heavy label over the centromere and short arms, and a pair of chromosomes (Nos. 15) with very light or no label. Individuals with Down's syndrome due to a 13-15/21 translocation have been shown to have five free chromosomes in the 13-15 group, which on autoradiography consist, as would be expected, of two pairs of chromosomes and one unpaired chromosome (*5, 7*). The results of the autoradiography are given in Table 1. In 12 cases all cells analyzed were consistent with the missing chromosome's being No. 14 and in one case with its being chromosome 15. In six cases 90 percent or more of cells were consistent with the missing chromosome's being No. 14, although in each case one or two cells showed discordant labeling patterns. The same was noted in one case with chromosome 15 missing. Similar minor discrepancies in labeling patterns have been observed by other workers (*6, 7*).

The results in our 20 patients thus indicate that chromosome 13 was not involved in any case, chromosome 14 was involved in 18 cases, and chromosome 15 in two cases (Table 1). The

Table 1. Autoradiographic analysis of 13-15/21 translocations in Down's syndrome.

Patient's laboratory No.	Parents' karyotype*		No. of Total cells scored	Unpaired chromosome						Chromosome in translocation
	Father	Mother		13	13 or 14	14	14 or 15	15	13 or 15	
171/66	T	N	11	0	0	6	5	0	0	14
255/66		N	27	0	2	8	15	1	1	14
45/67	N	N	19	0	2	8	8	1	0	14
94/67	N	N	5	0	0	4	1	0	0	14
131/67	N	T	13	0	3	5	5	0	0	14
167/67			41	0	3	15	22	0	1	14
183/67	N	N	25	2	2	17	4	0	0	14
184/67	N	N	15	0	0	9	6	0	0	14
193/67			16	0	1	8	7	0	0	14
194/67	N	N	14	0	2	2	10	0	0	14
230/67	N	N	21	0	0	1	10	9	1	15
235/67	N	N	20	0	5	8	7	0	0	14
247/67			19	0	1	10	8	0	0	14
258/67			9	0	1	8	0	0	0	14
2/68			12	0	0	10	2	0	0	14
3/68			18	0	2	7	8	1	0	14
6/68			45	0	0	0	37	8	0	15
8/68			20	1	4	5	9	1	0	14
24/68	N	N	24	0	2	18	4	0	0	14
60/68	N	N	25	0	3	15	7	0	0	14

* Key: N, normal karyotype; T, translocation carrier; blank, unstudied.

Table 2. Autoradiographic studies of 13-15/21 translocations in Down's syndrome.

Reference	No. of cases with translocation involving chromosome No.		
	13	14	15
This study	0	18	2
Schmid (*5*)	0	2	0
Yunis *et al.* (*7*)	0	2	0
Mikkelsen (*7*)	0	5	1
Bloom and Gerald (*7*)	0	3	0
Total	0	30	3

results of previous autoradiographic studies of 13-15/21 translocations in Down's syndrome are similar: no case with chromosome 13, 12 cases with chromosome 14, and one case with chromosome 15 in the translocation (*5*, *7*). Combining these data, we find that there were no translocations with chromosome 13, 30 with chromosome 14, and three with chromosome 15 (Table 2). If the expectation had been that the participation of chromosomes 13, 14, and 15 is random, one would have expected chromosome 13 to have been found in 11 cases, chromosome 14 in 11 cases, and chromosome 15 in 11 cases. The differences between these expectations and the observed data are statistically very highly significant (*8*), indicating that the entry of chromosomes 13-15 into centric-fusion translocation with chromosome 21 is nonrandom (*9*).

The factors underlying this nonrandomness are not yet defined. It cannot be related simply to differences in size or shape of chromosomes 13-15, since, as mentioned, these chromosomes are all acrocentrics of similar size. The nonrandomness might reflect different tendencies for broken chromosomes 13, 14, and 15 to fuse with chromosome 21, perhaps because of spatial relationships within the nucleus. The nonrandomness may also reflect differences in the frequencies with which chromosomes 13, 14, and 15 break near the centromere, due perhaps to differences in molecular organization, as suggested by the late replication of the area around the centromere in chromosome 14 and the early replication of that area in chromosomes 13 and 15 (*5*, *6*).

Twelve of the translocations in Table 2 were known to be familial. In no case was a 13/21 translocation demonstrated. As Mikkelsen has noted (see *7*), 13-trisomies have not been observed ". . . in the quite numerous families with 13-15/21 translocations that have been published. 13/21 translocations may not occur at all and therefore not give rise to the occurrence of 13 trisomy cases. . . ."

It could be argued that chromosome 13 enters into centric-fusion translocations with chromosome 21, but the resultant translocations are not observed in individuals with Down's syndrome. However, in trisomy 13 syndrome a deficiency of 13/21-22 translocations compared to 13/13-15 translocations has been found (*3*), providing further evidence that 13/21 translocations tend not to form.

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8. The chances are as follows for finding no case with chromosome 13 (chi-square 16.5, $P < .001$, 1 d.f.), 30 cases with chromosome 14 (chi-square 49.2, $P < .001$, 1 d.f.), and 3 cases with chromosome 15 (chi-square 8.7, $P < .005$, 1 d.f.).
9. The entry of chromosomes 13-15 into centric-fusion translocation with other chromosomes in the 13-15 group may also prove to be nonrandom. Autoradiographic analysis by several laboratories of five cases show all to be 13/14 translocations (G. E. Bloom and P. S. Gerald, Meeting of Society for Pediatric Research, 3–4 May 1968, Atlantic City, N.J.).
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Rhapidosomes: 2′-O-Methylated Ribonucleoproteins

Abstract. *Methylation of the RNA component from seven flexibacterial rhapidosomes varied in extent, distribution along the RNA chain, and distribution between nucleotides. Flexibacterial soluble and ribosomal RNA had normal (low) methylation.*

Rhapidosomes were first observed in flexibacterial cultures by Lewin (*1*). They are cylinders, approximately 225 nm long and 33 nm in diameter, from which a "wick-like" process, 15 nm in diameter, may extend for various distances up to 1600 nm (*1*, *2*). Rhapidosomes from *Saprospira grandis* WH have been reported to contain RNA, the nucleotides of which were at least 85-percent 2′-*O*-methylated (*2*). Such a high level of *O*-methylation has not been reported for RNA from any other source. Particles having rhapidosome morphology have been described from such diverse sources as *Archangium violaceum* (*3*), *Proteus mirabilis* (*4*), and *Actinomyces streptomycini* (*5*). However, only rhapidosomes from *S. grandis* WH have been isolated and chemically examined.

Seven strains of flexibacteria (*6*) were cultured in aerated carboys of enriched sea-water medium, and the rhapidosomes were isolated by a reported (*2*) method. Ribonucleic acid was extracted by modified phenol procedures from rhapidosomes (*2*) and from cells of *S. grandis* WH harvested by centrifugation during the early part of the growth curve (*7*). When the procedure used for extraction of cells was tested on isolated rhapidosomes, it failed to extract that RNA. All RNA fractions were first chromatographed on columns (2.5 by 35 cm) of diethylaminoethyl-cellulose (DEAE-cellulose) (*7*).