Recombination Suppression by Heterozygous Robertsonian Chromosomes in the Mouse

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ABSTRACT

Robertsonian chromosomes are metacentric chromosomes formed by the joining of two telocentric chromosomes at their centromere ends. Many Robertsonian chromosomes of the mouse suppress genetic recombination near the centromere when heterozygous. We have analyzed genetic recombination and meiotic pairing in mice heterozygous for Robertsonian chromosomes and genetic markers to determine (1) the reason for this recombination suppression and (2) whether there are any consistent rules to predict which Robertsonian chromosomes will suppress recombination. Meiotic pairing was analyzed using synaptonemal complex preparations. Our data provide evidence that the underlying mechanism of recombination suppression is mechanical interference in meiotic pairing between Robertsonian chromosomes and their telocentric partners. The fact that recombination suppression is specific to individual Robertsonian chromosomes suggests that the pairing delay is caused by minor structural differences between the Robertsonian chromosomes and their telocentric homologs and that these differences arise during Robertsonian formation. Further understanding of this pairing delay is important for mouse mapping studies. In 10 mouse chromosomes (*3, 4, 5, 6, 8, 9, 10, 11, 15* and *19*) the distances from the centromeres to first markers may still be underestimated because they have been determined using only Robertsonian chromosomes. Our control linkage studies using C-band (heterochromatin) markers for the centromeric region provide improved estimates for the centromere-to-first-locus distance in mouse chromosomes *1, 2* and *16*.

ROBERTSONIAN chromosomes are metacentrics formed by the joining of two telocentric chromosomes at their centromere ends (ROBERTSON 1916). In the mouse Robertsonian chromosomes have been used to assign linkage groups to chromosomes (CATTANACH and MOSELEY 1973; CATTANACH, WILLIAMS and BAILEY 1972; MILLER *et al.* 1971a,b; KLEIN 1971; NESBITT and FRANCKE 1971) and to determine the centromeric ends of mouse chromosomes (BEECHEY and SEARLE 1979; CATTANACH and MOSELEY 1974; LYON and NEWPORT 1973; LYON, BUTLER and KEMP 1968). Many Robertsonian chromosomes of the mouse, however, suppress genetic recombination near the centromere when heterozygous (CATTANACH 1978; DAVISSON 1985; DAVISSON and RODERICK 1975; NADEAU and EICHER 1982). This recombination suppression has important implications for the mouse genetic map. Robertsonian chromosomes have been used extensively as centromere markers in genetic mapping studies because no other centromere markers have been available. Yet, because we cannot predict which Robertsonian chromosomes will suppress recombination and to what extent, at least some centromere-to-first-locus distances are likely to be underestimated. The centromere-to-first-locus distances in ten of the mouse chromosomes (*3, 4, 5, 6, 8, 9, 10, 11, 15* and *19*) on the present composite mouse genetic map (GBASE 1992) may be underestimated because they have been estimated using only Robertsonian chromosomes.

The phenomenon of suppression itself is also of interest because it provides a potential system to analyze factors that influence genetic recombination. Since the suppression occurs in Robertsonian chromosome heterozygotes, it appears to result from differences between the Robertsonian chromosome and its telocentric homologs. Recombination suppression could be caused by (1) genic or minor structural differences between the Robertsonian chromosomes and their telocentric homologs or (2) physical interference with pairing during meiosis in Robertsonian chromosome heterozygotes. Genic or minor structural differences could result from differences between chromosomes of laboratory and wild-derived mice (most Robertsonian chromosomes studied have been found in wild *Mus musculus domesticus* populations) or between normal and translocated chromosomes. Identification and further analysis of these phenomena are important for mouse mapping studies because mice from wild populations are used increasingly to map mouse chromosomes. The studies we report here were designed (1) to answer the question of why Robertsonian chromosomes suppress recombination and (2) to determine whether there are any

consistent rules to predict which ones will suppress recombination. We show that mechanical interference in meiotic pairing between Robertsonian chromosomes and their telocentric partners is enough to account for the suppression in the Robertsonian chromosomes we analyzed and that pairing differences are specific to Robertsonian chromosome formation and not to interspecific differences. In addition our control linkage studies using C-band (heterochromatin) markers for the centromeric region provide improved estimates for the centromere-to-first-locus distance in mouse chromosomes *1*, *2* and *16*.

MATERIALS AND METHODS

To determine whether genic differences or meiotic pairing interference might be the basis of recombination suppression, we began by identifying some Robertsonian chromosomes that suppress recombination, and some that do not, using standard Mendelian backcross analysis. For each Robertsonian chromosome tested, we did simultaneous control linkage crosses using a pericentromeric heterochromatin (C-band) size variant to mark the centromere and the same marker loci whenever possible (see tables). The exceptions were Robertsonian chromosomes involving chromosomes *5* and *7*, for which we could not reliably identify scorable C-band polymorphisms. Chromosomes were prepared from bone marrow and G-banded according to our methods published previously (DAVISSON, EICHER and GREEN 1976; DAVISSON and AKESON 1987). Chromosomes to be scored for C-bands were stained initially by the G-band method (DAVISSON and AKESON 1987), destained in methanol for 10 min, and then restained using the same G-band procedure. This protocol gives preparations in which the C-bands are distinctly stained and the G-bands are faint but usually clear enough to identify individual chromosomes simultaneously.

We then analyzed meiotic pairing using synaptonemal complex (SC) preparations from mice heterozygous for the same Robertsonian chromosomes that we tested for recombination suppression. In most cases the males examined for meiotic pairing were the actual males used in the linkage analyses. Female SC preparations were made from 18-day fetuses produced by the same genetic cross as that used for linkage analysis. All SC preparations were made using the microspreading technique of MOSES (MOSES 1977; DRESSER and MOSES 1979). Preparations were silver stained according to previously published methods (DRESSER and MOSES 1979, 1980; HOWELL and BLACK 1980).

The mice were all reared and maintained in the Robertsonian Resource at The Jackson Laboratory. The linkage crosses, including genetic background, are described in the tables. The Robertsonian stocks used were those in which the Robertsonian chromosomes are maintained on their own inbred backgrounds, most of which are a combination of approximately 50% wild-derived *M. m. domesticus* and 50% laboratory mouse strain background. *Rb(1.3)1Ei* arose spontaneously in a laboratory mouse carrying *T(4;In8)36H*. Pedigrees for individual Robertsonian chromosome strains are on file in the Robertsonian Resource at The Jackson Laboratory.

The crosses for *Rb(1.3)1Bnr* and *Rb(16.17)7Bnr* were made using multiple Robertsonian chromosome stocks *RBF/Dn* and *RBD/Dn*. *RBF/Dn* is homozygous for *Rb(1.3)1Bnr*, *Rb(8.12)5Bnr* and *Rb(9.14)6Bnr*; *RBD/Dn* is homozygous for *Rb(5.15)3Bnr*, *Rb(11.13)4Bnr* and *Rb(16.17)7Bnr*. The degree of pairing delay, however, was probably not affected by additional Robertsonian chromosomes in these crosses since all the chromosome *1* Robertsonian chromosomes [*Rb(1.3)1Bnr*, *Rb(1.3)1Ei*, *Rb(1.2)18Lub*] suppressed recombination similarly whether or not there were other Robertsonian chromosomes segregating.

Recombination estimates for intercrosses and partial backcrosses were calculated using (GREEN's (1985) computer program based on Fisher's scores. Chi square analysis was used for all statistical comparisons, within and between crosses.

RESULTS

Our results confirm previous reports that many mouse Robertsonian chromosomes suppress genetic recombination in the centromere (or proximal) region of one or both of the chromosomes involved. We have also confirmed that recombination suppression is not common to all mouse Robertsonian chromosomes, since none of the three Robertsonian chromosomes involving chromosome *7* that we tested suppressed recombination in chromosome *7*.

Genetic analysis: We have completed genetic analysis of recombination for one chromosome arm of each of 10 Robertsonian chromosomes. Recombination between the centromeres and most proximal gene markers is suppressed by *Rb(1.3)1Bnr*, *Rb(1.3)1Ei* and *Rb(1.2)18Lub* in chromosome *1*, by *Rb(1.2)18Lub* in chromosome *2*, by *Rb(5.15)4Lub*, *Rb(5.15)3Bnr* and *Rb(5.15)15Rma* in chromosome *5*, and by *Rb(16.17)7Bnr* in chromosome *16*, respectively (see Tables 1–11, 19–21). Three different Robertsonian chromosomes, *Rb(1.7)1Rma*, *Rb(6.7)13Rma* and *Rb(7.18)9Lub*, do not suppress recombination in chromosome *7* (Tables 12–18).

Chromosome 1: The linkage data for *Rb(1.3)1Bnr*, *Rb(1.3)1Ei*, *Rb(1.2)18Lub* and chromosome *1* proximal loci are given in Tables 1–3. All three reduced recombination between the centromere and fuzzy (*fz*) to about 1% (Tables 1–3) as compared to 6% in the C-band control cross (Table 4). This difference was significant in all three cases (Table 5). For *Rb(1.3)1Bnr* and *Rb(1.2)18Lub* (in F_1 males only), this suppression extended as far distal as leaden (*ln*). *Rb(1.3)1Ei*, which arose spontaneously in a laboratory mouse, suppressed recombination between the centromere and *fz* as much as the two Robertsonian chromosomes derived from *M. m. domesticus* wild populations (although this suppression did not extend as far as the *ln* locus), showing that the suppression phenomenon in this case, at least, is not dependent on differences between wild- and laboratory-derived genomes, or between laboratory and pure *M. m. domesticus* chromosomes. The sex-related differences in recombination estimates for chromosome *1* (Tables 1–3) are similar to those observed in other studies of recombination in this area of chromosome *1* (GBASE 1992) and are probably

TABLE 1

Linkage data for chromosome *1*: *Rb(1.3)1Bnr* × C57BL/6J (B6)-*fz ln* backcross

Cross: *Rb* + + *Pep-3*^{c}/+ *fz ln Pep-3*^{a} × + *fz ln Pep-3*^{a}/+ *fz ln Pep-3*^{a}

Progeny phenotype							No. of progeny[a]		
							Sex of F_1 parent		
Rb		*fz*		*ln*		*Pep-3*	Female	Male	Combined
Rb		+		+		*ac*	15 (5)	42 (+4)	57 (+9)
+		*fz*		*ln*		*a*	25 (+17)	59 (+1)	84 (+18)
Rb	×	*fz*		*ln*		*a*	0	1	1
+	×	+		+		*ac*	0	0	0
Rb		+	×	*ln*		*a*	2 (+6)	27 (+1)	29 (+7)
+		*fz*	×	+		*ac*	13 (+9)	24 (+1)	37 (+10)
Rb		+		+	×	*a*	4	8	12
+		*fz*		*ln*	×	*ac*	9	16	25
Rb	×	*fz*		+		*ac*	0	1	1
+	×	+		+	×	*a*	1	0	1
Rb		+	×	*ln*	×	*ac*	1	2	3
+		*fz*	×	+	×	*a*	2	3	5
Totals							72 (+37)	183 (+7)	255 (+44)

Recombination percentages:

Interval	F_1 female	F_1 male	Combined
Rb-fz	1/109 = 0.9 ± 0.9	2/190 = 1.1 ± 0.8	3/299 = 1.0 ± 0.6
fz-ln	33/109 = 30.3 ± 4.4	59/190 = 31.1 ± 3.4	92/299 = 30.8 ± 2.7
ln-Pep-3	17/72 = 23.6 ± 5.0	29/183 = 15.8 ± 2.7	46/255 = 18.0 ± 2.4

To conserve space here and in following tables, double recombinant classes with no progeny in them are not shown. These data include the data published previously in DAVISSON and RODERICK (1975).

[a] Numbers in parentheses are additional mice scored for *Rb*, *fz* and *ln* but not typed for *Pep-3*.

not related to the presence of the Robertsonian chromosomes.

Chromosome 2: The linkage data for *Rb(1.2)18Lub* and chromosome 2 markers are given in Table 6 and the control C-band cross is given in Table 7. *Rb(1.2)18Lub* reduces the recombination estimate between the centromere and Danforth short tail (*Sd*) by nearly one half and this reduction is significant at the $P < 0.05$ level (Table 8). It should be noted that the C-band marker used for chromosome 2 is extra large and may itself affect recombination; thus, even the 11% recombination estimate for the centromere to *Sd* interval may be an underestimate of the true distance.

Chromosome 5: The linkage data for *Rb(5.15)3Bnr*, *Rb(5.15)15Rma*, *Rb(5.15)4Lub* and chromosome 5 markers are given in Table 9 and the control data are given in Table 10. These data are complicated by the lack of a reliable C-band marker, preventing a control cross for the *Rb-rl* (reeler) interval. The control data for chromosome 5 are for the interval between the first and second loci, *rl* and hammer-toe (*Hm*). The *rl-Hm* interval was measured only in the *Rb(5.15)15Rma* cross (cross 9b). The recombination estimate between *rl* and *Hm* appears to be enhanced by *Rb(5.15)15Rma*. We do not believe, however, this difference is real. In both cross 9b and control cross 10c, which are intercrosses for *Hm* as well as *rl*, there is a significant deficiency of the *Hm/Hm* classes. This suggests that in these crosses some *Hm/Hm* may be misclassified as *Hm/+*. When segregation of alleles is abnormal as in crosses b in Table 9 and c in Table 10, the maximum likelihood method used in GREEN's (1985) program cannot be applied. We calculated recombination estimates for the *rl-Hm* interval based on only the manifesting (*Hm/Hm*) mice. In cross 9b there are 19 of these, all *rl Hm/rl Hm*, which is 0/38 recombinant chromosomes or 0% recombination with 95% upper confidence limit of 7.6%. For the intervals between *Hm* and the codominant markers *Rb(5.15)15Rma* and *Pgm-1*, we treated *Hm* as a dominant and used GREEN's program. In cross c (Table 10), because there were only three mice in the manifesting class, we treated *Hm* as a dominant and used GREEN's program. There appears to be suppression in the centromere to *Hm* interval by *Rb(5.15)3Bnr* and Rb(5.15)4Lub, because recombination between the centromere (cen) and *Hm* in separate crosses with these two Robertsonian chromosomes is similar to the *rl-Hm* distance with *Rb(5.15)15Rma* present or in control crosses (Table 11) and much less than the cen-*Hm* distance in the composite map based on published data on all other loci in this region of chromosome 5 (GBASE 1992). The centromere-to-*rl* distance on the GBASE composite map is based on crosses between

TABLE 2

Linkage data from chromosome *1*: *Rb(1.3)1Ei* × C57BL/6J-*fz ln* backcross

Cross: *Rb* + *Idh-1*^{a} + *Pep-3*^{b}/+ *fz Idh-1*^{b} *ln Pep-3*^{a} × + *fz ln Idh-1*^{b} *ln Pep-3*^{a}/+ *fz ln Idh-1*^{b} *ln Pep-3*^{a}

Progeny phenotype									No. of progeny		
									Sex of F_1 parent		
Rb		*fz*		*Idh-1*		*ln*		*Pep-3*	Female	Male	Combined
Rb		+		*ab*		+		*ab*	12	26	38
+		*fz*		*b*		*ln*		*a*	31	21	52
Rb	×	*fz*		*b*		*ln*		*a*	0	0	0
+	×	+		*ab*		+		*ab*	0	0	0
Rb		+	×	*b*		*ln*		*a*	10	6	16
+		*fz*	×	*ab*		+		*ab*	15	12	27
Rb		+		*ab*	×	*ln*		*a*	4	1	5
+		*fz*		*b*	×	+		*ab*	10	3	13
Rb		+		*ab*		+	×	*a*	7	5	12
+		*fz*		*b*		*ln*	×	*ab*	5	1	6
+	×	+		*ab*	×	*ln*		*a*	0	1	1
+		*fz*	×	*ab*	×	*ln*		*a*	1	0	1
Rb		+		*ab*	×	*ln*	×	*ab*	1	0	1
+		*fz*		*b*	×	+	×	*a*	1	1	2
+	×	+		*ab*		+	×	*a*	1	0	1
Rb		+	×	*b*		*ln*	×	*ab*	2	0	2
+		*fz*	×	*ab*		+	×	*a*	3	0	3
Rb		+	×	*b*	×	+	×	*a*	0	0	0
+		*fz*	×	*ab*	×	*ln*	×	*ab*	1	0	1
Totals									104	77	181

Recombination percentages:

Interval	F_1 female	F_1 male	Combined
Rb-fz	1/104 = 0.96 ± 0.96	1/77 = 1.3 ± 1.3	2/181 = 1.1 ± 0.9
fz-Idh-1	32/104 = 30.8 ± 4.5	18/77 = 23.4 ± 4.8	50/181 = 27.6 ± 3.3
Idh-1-ln	18/104 = 17.3 ± 3.7	6/77 = 7.8 ± 3.1	24/181 = 13.3 ± 2.5
ln-Pep-3	21/104 = 20.2 ± 3.9	7/77 = 9.1 ± 3.3	27/181 = 15.5 ± 2.7
fz-ln	46/104 = 44.2 ± 4.9	24/77 = 31.2 ± 5.3	70/181 = 38.7 ± 3.6

Robertsonian chromosomes and markers distal to *Hm*. The recombination estimates for the intervals between *Hm* and phosphoglycerate mutase-1 (*Pgm-1*) and *Pgm-1* and buff (*bf*) for *Rb(5.15)15Rma* and *Rb(5.15)3Bnr* did not differ from published estimates for this interval (GBASE 1992).

Chromosome 7: The data for *Rb(1.7)1Rma*, *Rb(6.7)13Rma*, *Rb(7.18)9Lub* and chromosome 7 markers are given in Tables 12–16. The simultaneous control cross for chromosome 7 was a C57BL/6J × BALB/cJ backcross in which glucose-6-phosphate isomerase (*Gpi-1*) and more distal isozyme markers were segregating (Table 17). None of these three Robertsonian chromosomes significantly suppressed recombination between the cen and *Gpi-1*, as compared to the distance for the cen-*Gpi-1* interval determined by the ovarian teratoma method [Table 18; EPPIG and EICHER (1988)] or between *Gpi-1* and distal markers. The ovarian teratoma method is presumed to be the most accurate method to measure proximal distances in chromosomes because no chromosomal heteromorphisms, which might interfere with recombination, are needed to detect crossing over between the centromere and a proximal marker.

Chromosome 16: Linkage data for *Rb(16.17)7Bnr* and the chromosome *16* marker mahoganoid (*md*) are given in Table 19. Two additional crosses were done with *Rb(16.17)7Bnr* and the more distal locus dwarf (*dw*). In the first, a backcross of *Rb* +/+ *dw* (females) × + *dw*/+ *dw*, we recovered 27 recombinants between *Rb(16.17)7Bnr* and *dw* in a total of 114 progeny scored, for a recombination estimate of 23.7 ± 4.0. In the second, an intercross of F_1s of genotype *Rb* + +/+ *md dw*, we typed homozygous mutants only: 8 *md*/*md* mice were all +/+ for *Rb(16.17)7Bnr* (0/16 chromosomes); of 8 *dw*/*dw* mice typed 5 were +/+, one was *Rb*/+ and two were *Rb*/*Rb*. This gives 5/16 recombinant chromosomes for a recombination estimate of 31.3%. Combining the data from these two crosses and the cross in Table 19 gives the following: *Rb-md*, 0/97 (≤3.0, 95% upper confidence limit) and *Rb-dw*, 32/130 = 24.6 ± 3.8. Control data for the cen-*md* interval from a cross using a C-band variant are given in Table 20. There was significant malsegregation in

TABLE 3

Linkage data for chromosome *1*: *Rb(1.2)18Lub* × C57BL/6J-*fz ln*

Cross: *Rb + Idh-1*^{a} *+ Pep-3*^{b}*/+ fz b ln a* × *+ fz b ln a/+ fz b ln a*

Progeny phenotype										No. of progeny		
										Sex of F_1 parent		
Rb		*fz*		*Idh-1*		*ln*		*Pep-3*		Female	Male	Combined
Rb		+		*ab*		+		*ab*		2	28	30
+		*fz*		*b*		*ln*		*a*		16	23	39
Rb	×	*fz*		*b*		*ln*		*a*		0	0	0
+	×	+		*ab*		+		*ab*		0	0	0
Rb		+	×	*b*		*ln*		*a*		1	6	7
+		*fz*	×	*ab*		+		*ab*		7	3	10
Rb		+		*ab*	×	*ln*		*a*		1	2	3
+		*fz*		*b*	×	+		*ab*		7	5	12
Rb		+		*ab*		+	×	*a*		1	3	4
+		*fz*		*b*		*ln*	×	*ab*		3	0	3
Rb		+	×	*b*		*ln*	×	*ab*		2	0	2
+		*fz*	×	*ab*		+	×	*a*		1	0	1
+		*fz*	×	*ab*	×	*ln*	×	*ab*		0	1	1
Totals										41	71	112

Recombination percentages:

Interval	F_1 female	F_1 male	Combined
Rb-fz	0/41 = 0%	0/71 = 0%	0/112 = 0%
fz-Idh-1	11/41 = 26.8 ± 6.9	10/71 = 14.1 ± 4.1	21/112 = 18.8 ± 3.7
Idh-1-ln	8/41 = 19.5 ± 6.2	8/71 = 11.3 ± 3.8	16/112 = 14.3 ± 3.3
ln-Pep-3	7/41 = 17.1 ± 5.9	4/71 = 5.6 ± 2.8	
fz-ln	19/41 = 46.3 ± 7.8	16/17 = 22.5 ± 5.0	

TABLE 4

Control linkage data for chromosome *1*:
DBA/2J-Hc1*^{l} *+ +* × C57BL/6J-*Hc1*^{s} *fz ln

Cross *Hc1*^{s} *fz ln/Hc1*^{l} *+ +* × *Hc1*^{s} *fz ln/Hc1*^{s} *fz ln*

Progeny phenotype							No. of progeny typed		
Hc1		*fz*		*ln*			For three markers	Not typed for C-band	*fz-ln* interval (combined)
s		*fz*		*ln*			12	9	21
ls		+		+			16	16	32
s	×	+		+			1	1	2
ls	×	*fz*		*ln*			1	0	1
s		*fz*	×	+			9	7	16
ls		+	×	*ln*			11	9	20
s	×	+	×	*ln*			0	1	1
ls	×	*fz*	×	+			1	2	3
Totals							51	45	96

Recombination percentages

Interval		
Hc1-fz	3/51 = 5.9 ± 3.3	
fz-ln	40/96 = 41.7 ± 5.0	

Only F_1 females were used. These data are the data summarized in DAVISSON (1985). *l* = large C-band; *s* = small C-band.

TABLE 5

Recombination percentages in crosses involving chromosome *1*

Centromere marker	F_1 sex	Interval *cen-fz*	P^a	Interval *fz-ln*	P^a
R(1.3)Bnr	F + M	1.0 ± 0.6	<0.02	30.8 ± 2.7	<0.08
Rb(1.3)1Ei	F + M	1.1 ± 0.9	<0.02	38.7 ± 3.6	NS
Rb(1.2)18Lub	F	0^b	<0.02	46.3 ± 7.8	NS
	M	0	<0.02	22.5 ± 5.0	<0.01
Hc1^l	F	5.9 ± 3.3		41.7 ± 5.0	

^{a} Probability of Robertsonian value differing from control value by chance. Significance tests were done by chi-square analysis. NS = not significant.

^{b} The 95% upper confidence limit value for F & M combined = 3%.

the male F_1 cross, including deficiency of *md* and excess of the small (*s*) variant of the *Hc16* heteromorphism. This did not appear to affect the recombination estimate because male and female recombination frequencies did not differ significantly. Therefore, we combined male and female data for comparison to the *Rb(16.17)7Bnr* data. *Rb(16.17)7Bnr* significantly reduces the recombination estimate for the cen-*md* interval from 7% to 0 (Table 21) and the effect appears to extend as far distal as *dw* when the *Rb-dw* estimate is compared to the *Hc16-md* estimate plus data from previous crosses for the *md-dw* interval (Table 21).

SC analysis of meiotic pairing: Analysis of chromosomal pairing at meiotic pachytene using SC prep-

TABLE 6

Linkage data for chromosome 2: *Rb(1.2)18Lub* × C57BL/6-*Sd pa* only segregated in cross b

Cross: *Rb* + (+)/+ *Sd(pa)* × + + (*pa*)/+ + (*pa*)

Progeny phenotype					No. of progeny		
					Sex of F_1 parent		
					Female	Male	Combined
a. *Rb*		*Sd*					
Rb		+			13	12	25
+		*Sd*			33	15	48
+	×	+			1	0	1
Rb	×	*Sd*			1	1	2
Totals					48	28	76
b. *Rb*		*Sd*		*pa*			
Rb		+		+	5	32	37
+		*Sd*		*pa*	9	34	43
Rb	×	*Sd*		*pa*	0	1	1
+	×	+		+	3	3	6
Rb		+	×	*pa*	10	21	31
+		*Sd*	×	+	8	19	27
Rb	×	*Sd*	×	+	0	3	3
+	×	+	×	*pa*	1	0	1
Totals					36	113	149

Recombination percentages:

Cross	Interval	F_1 female	F_1 male	Combined
a	*Rb-Sd*	2/48 = 4.2 ± 2.9	1/28 = 3.6 ± 3.5	3/76 = 3.9 ± 2.2
b	*Rb-Sd*	4/36 = 11.1 ± 5.2	7/113 = 6.2 ± 2.3	11/149 = 7.4 ± 2.1
a + b	*Rb-Sd*	6/84 = 7.1 ± 2.8	8/141 = 5.7 ± 2.0	14/255 = 6.2 ± 1.6
b	*Sd-pa*	19/36 > 50	43/113 = 38.1 ± 4.6	62/149 = 41.6 ± 4.3

arations was completed in heterozygous male adults and female embryos for 7 of the 10 Robertsonian chromosomes examined. Only one of the three *Rb(5.15)* Robertsonian stocks was examined. Degree of pairing in the Robertsonian trivalents was assessed by scoring pachytene cells into the four classes of pairing illustrated in Figure 1. Those Robertsonian stocks for which both sexes have been analyzed had no apparent female/male difference in overall degree of pairing and there were no significant differences in recombination between male and female heterozygotes (except in the *fz-ln-Pep-3* interval in the cross in Table 3). Therefore, data for females and males is combined in Figure 2A to show the overall frequency of each pairing stage for each Robertsonian analyzed. Because progression through pachytene can be staged more accurately in males than in females by the appearance of the *XY* bivalent (see below), Figure 2B shows the frequency of each pairing stage at late pachytene for males only to illustrate the differences in the rate of pairing progress. Male cells were classified into early to late pachytene stages by the degree of pairing and lateral element thickening in the *XY* bivalent and the appearance of the pericentromeric heterochromatin (MOSES 1977). Robertsonian bivalents almost always initiated pairing at the telomeres and "zippered up" toward the centromere. Pairing was never observed to initiate in the centromere region, but occasionally interstitial initiation was seen. As the centromere segments of the telocentric homologs approached each other, they frequently associated with each other rather than the Robertsonian homolog (stage 2, Figure 1, c and d). This association sometimes progressed to nonhomologous pairing of these segments (stage 3, Figure 1, a, c and e). A summary of these data for all Robertsonian chromosomes studied at all stages is shown in Figure 2. Note that the number of cells with delayed pairing between proximal segments of telocentrics (as illustrated by stages 1 and 2) is greater in *Rb(1.3)1Bnr*, *Rb(1.2)18Lub*, *Rb(5.15)4Lub* and *Rb(16.17)7Bnr* than in the Robertsonian chromosomes involving chromosome 7.

DISCUSSION

Suppression of genetic recombination by heterozygous Robertsonian chromosomes in the mouse was

TABLE 7

Control linkage data for chromosome 2: MOLG/Dn-*Hc2^l* × C57BL/6-*Sd pa* segregated in the crosses b and c

Cross: *Hc2^l* + (+)/+ *Sd* (*pa*) × Hc2^n + (*pa*)/Hc2^n + (*pa*) or *Sd* +/+ pa × +pa/+ pa

Progeny phenotype					No. of progeny		
					Sex of F_1 parent		
					Female	Male	Combined
a. *Hc2*		*Sd*					
ln		+			51	39	90
nn		*Sd*			49	28	77
nn	×	+			10	3	13
ln	×	*Sd*			6	3	9
Totals					116	73	189
b. *Hc2*		*Sd*		*pa*			
ln		+		+	11	22	33
nn		*Sd*		*pa*	7	12	19
ln	×	*Sd*		*pa*	0	2	2
nn	×	+		+	2	1	3
ln		+	×	*pa*	3	10	13
nn		*Sd*		+	5	4	9
		×					
ln	×	*Sd*	×	+	0	1	1
nn	×	+	×	*pa*	1	1	2
Totals					29	53	82
c. *Sd*		*pa*					
Sd		+			14	—	
+		*pa*			23	—	
Sd	×	*pa*			11	—	
+	×	+			11	—	
Totals					59	—	

Recombination percentages:

Cross	Interval	F_1 female	F_1 male	Combined
a	*Hc2-Sd*	16/116 = 13.8 ± 3.2	6/73 = 8.2 ± 3.2	22/189 = 11.6 ± 2.3
b	*Hc2-Sd*	3/29 = 10.3 ± 5.6	5/53 = 9.4 ± 4.0	8/82 = 9.8 ± 3.3
a + b	*Hc2-Sd*	19/145 = 13.1 ± 2.8	11/126 = 8.7 ± 2.5	30/271 = 11.1 ± 1.9
b	*Sd-pa*	9/29 = 31.0 ± 8.6	16/53 = 30.2 ± 6.3	25/82 = 30.5 ± 5.1
c	*Sd-pa*	22/59 = 37.3 ± 6.3		
b + c	*Sd-pa*	31/88 = 35.2 ± 5.1	16/53 = 30.2 ± 6.3	47/141 = 33.3 ± 4.0

Hc2^l, only in crosses a and b. *l* = large C-band; *n* = normal C-band.

TABLE 8

Recombination percentages in crosses involving chromosome 2

Centromere marker	F_1 sex	Interval cen-*Sd*	*P*	Interval *Sd-pa*	*P*
Rb(1.2)18Lub	F + M	6.2 ± 1.6	<0.05	41.6 ± 4.3	NS
Hc2^l	*F + M*	11.1 ± 1.9	—	30.5 ± 5.1	—
None	F	—	—	37.3 ± 6.3	—

first reported by CATTANACH and MOSELEY (1973). Since then recombination suppression has been observed for various Robertsonian chromosomes in several different laboratories (CATTANACH 1978; CATTANACH and JONES 1979; CATTANACH and MOSELEY 1974; DAVISSON 1985; DAVISSON and RODERICK 1975; NADEAU and EICHER 1982; and PHILLIPS *et al.* 1980). Recombination suppression is not an obligatory feature of Robertsonian chromosome heterozygosity, because some Robertsonian chromosomes do not appear to alter recombination significantly (CATTANACH 1978; DAVISSON *et al.* 1991; LYON, BUTLER and KEMP 1968). We reasoned that understanding the differences between these two types of Robertsonian chromosomes might lead to an understanding of why certain heterozygous Robertsonian chromosomes suppress recombination. In the research reported here, we have studied genetic recombination and meiotic chromosomal pairing involving seven different heterozygous Robertsonian chromosomes to determine the mechanism of recombination suppression and to identify common features related to suppression that might be used to predict which Robertsonian chro-

TABLE 9

Linkage data for chromosome 5 loci and Robertsonian chromosomes

a. Cross: *Rb(5.15)4Lub* +/+ *rl* × *Rb* +/+ *rl*

Progeny genotype		
Rb	*rl*	No. of progeny
Rb/Rb	+/?	17
Rb/+	+/?	38
+/+	+/?	3
Rb/Rb	*rl/rl*	0
Rb/+	*rl/rl*	2
+/+	*rl/rl*	23
Total		83

Recombination estimate:[b]
Rb-rl: 5.6 ± 2.6

b. Cross *Rb(5.15)15Rma* + + *Pgm-1*^{a}/+ *rl Hm Pgm-1*^{b} × + + + *Pgm-1*^{b}/+ *rl Hm Pgm-1*^{b}. Intercross-backcross data include female and male data combined. *Pgm-1* was typed in only 88 of the 222 total mice scored.

Progeny genotype				No. of progeny		
Rb	*rl*	*Hm*	*Pgm-1*	*Pgm-1* typed	*Pgm-1* not typed	Total typed for *Rb-rl-Hm*
Rb/+	+/?	+/+	*a/b*	12	—	
Rb/+	+/?	+/+	*b/b*	4	—	
Rb/+	+/?	+/+	—	—	26	42
Rb/+	+/?	*Hm/+*	*a/b*	15	—	
Rb/+	+/?	*Hm/+*	*b/b*	1	—	
Rb/+	+/?	*Hm/+*	—	—	28	44
+/+	*rl/rl*	*Hm/Hm*	*b/b*	4	—	
+/+	*rl/rl*	*Hm/Hm*	—	—	15	19
+/+	+/?	*Hm/+*	*b/b*	21	—	
+/+	+/?	*Hm/+*	*a/b*	8	—	
+/+	+/?	*Hm/+*	—	—	44	73
+/+	*rl/rl*	*Hm/+*	*b/b*	14	—	
+/+	*rl/rl*	*Hm/+*	*a/b*	5	—	
+/+	*rl/rl*	*Hm/+*	—	—	18	37
+/+	+/?	+/+	*a/b*	4	—	
+/+	+/?	+/+	—	—	3	7
Totals				88	134	222

Recombination percentages:

Interval	Type of cross	RE + SE
Rb-rl	Backcross-intercross	0%
rl-Hm	Repulsion intercross	0%[c]
Hm-Pgm-1	Intercross-backcross	20.7 ± 7.8[d]
Rb-Hm	Backcross-intercross	9.5 ± 3.7[d]
Rb-Pgm-1	Backcross	25.0 ± 4.6

c. Cross: *Rb(5.15)4Lub* +/+ *Hm* × + +/+ +.

Progeny phenotype		Sex of F_1 parent		
Rb	*Hm*	Females	Males	Total
Rb	+	12	60	72
+	*Hm*	20	60	80
Rb	*Hm*	3	2	5
+	+	1	4	5
Totals		36	126	162

Recombination percentages:

	F_1 females	F_1 males	Combined
Rb-Hm	11.1 ± 5.6	4.8 ± 1.9	6.2 ± 1.9

d. Cross: *Rb(5.15)3Bnr* + *Pgm-1*^{b} +/+ *Hm Pgm-1*^{a} *bf*♀ × + + *Pgm-1*^{a} *bf*/+ + *Pgm-1*^{a} *bf*♂

Phenotype									No. of progeny
Rb		*Hm*		*Pgm-1*		*bf*	
Rb		+		ab		+			34
+		*Hm*		a		*bf*			22
Rb	×	*Hm*		a		*bf*			1
+	×	+		ab		+			2
Rb		+	×	a		*bf*			3
+		*Hm*	×	ab		+			5
Rb		+		ab	×	*bf*			4
+		*Hm*		a	×	+			11
Rb	×	*Hm*	×	ab		+			0
+	×	+	×	a		*bf*			1
Rb		+	×	a	×	+			4
+		*Hm*	×	ab	×	*bf*			1
Rb	×	*Hm*		a	×	+			1
+	×	+		ab	×	*bf*			2
Rb	×	*Hm*		ab	×	*bf*			1
+	×	+ cma	×	+		1			
Total									93

Recombination percentages:

Rb-Hm	9/93 = 9.7 ± 3.1
Hm-Pgm-1	16/93 = 17.2 ± 3.9
Pgm-1-bf	25/93 = 26.9 ± 4.6

[a] Recombination estimates (RE) and standard errors (SE) were calculated using GREEN's (1985) computer program.
[b] Recombination estimate based on using *rl/rl* homozygotes only: 23 + *rl/+ rl*, 2 *Rb rl/+ rl*, 0 *Rb rl/Rb rl* = 2/50 recombinant chromosomes = 4.0 ± 2.8.
[c] Calculated using manifesting class (*Hm/Hm*) only.
[d] Calculated using *Hm* at as a full dominant.

mosomes will suppress recombination. Unlike most previous work on Robertsonian chromosome suppression, we did simultaneous Robertsonian and control crosses using the same marker stock to keep the genetic background as similar as possible.

Although many different reports on Robertsonian

TABLE 10

Linkage data from control crosses for chromosome *5*

Progeny genotype		Cross:	a	b	c	d
		Female:	+ +/*rl* +	+ *Hm*/*rl* +	+ *Hm*/*rl* +	*rl* +/*rl* +
rl	*Hm*	Male:	+ *Hm*/*rl* +	++/*rl* +	+ *Hm*/*rl* +	+ *Hm*/*rl* +
+/?	*Hm*/*Hm*		—	—	2	—
+/?	*Hm*/+		16	6	22	9
+/?	+/+		9	0	0	1
rl/*rl*	+/+		11	1	9	5
rl/*rl*	*Hm*/+		1	0	2	0
rl/*rl*	*Hm*/*Hm*		—	—	1	—
Totals			37	7	36	15

Recombination percentages:

Cross	Type of cross	RE + SE
a	Intercross-backcross	8.3 ± 8.6
b	Intercross-backcross	0
a + b	Intercross-backcross	6.4 ± 7.1
c	Coupling intercross	9.5 ± 5.1
d	Backcross	6.7 ± 6.4

We were unable to identify a reliable C-band polymorphism for chromosome *5*. Combined estimate for *rl-Hm* interval is 8.0 ± 3.5, using MATHER's (1947) weighted average method and treating crosses a and b as one cross.

chromosome suppression of genetic recombination exist, it is difficult to make comparisons among them. Often different gene markers at quite varied distances from the centromere were used and early work often compared distances derived from Robertsonian crosses to summarized composite map distances or distances derived in crosses made in other laboratories using strains of different genetic backgrounds. Nevertheless, three consistent features emerge from a review of the existing literature and our work reported here.

Recombination suppression is Robertsonian-specific and cannot be predicted from one Robertsonian chromosome to another: In general, Robertsonian chromosomes that suppress recombination do so consistently in different experiments and on different genetic backgrounds. Out best evidence is for *Rb(1.3)1Bnr* and *Rb(16.17)7Bnr* (Tables 5 and 21), but data from at least two laboratories for several other Robertsonian chromosomes is consistent with this observation. Robertsonian chromosomes that consistently suppress recombination include *Rb(1.3)1Bnr* in chromosome *1* (CATTANACH 1978; CATTANACH and MOSELEY 1973; this paper), *Rb(4.6)2Bnr* in chromosome *4* (CATTANACH and MOSELEY 1974; NADEAU and EICHER 1982), and *Rb(16.17)7Bnr* in chromosome *16* (PHILLIPS and FISHER 1979; this paper). Robertsonian chromosomes that consistently do not suppress recombination include *Rb(9.14)6Bnr* in chromosome *14* (CATTANACH and MOSELEY 1974; LYON and NEWPORT 1973; EPPIG and EICHER 1983; WOMACK *et al.* 1977) and *Rb(16.17)7Bnr* in chromosome *17* (CATTANACH 1978; CATTANACH and MOSELEY 1974; FOREJT 1973; HAMMERBERG and KLEIN 1975).

The only exception so far appears to be *Rb(5.15)3Bnr*; it has suppressed recombination in all studies but the extent of suppression seems to vary between different crosses. For example, we were unable to detect suppression distal to *Hm* (Table 11), while others report suppression as far distal as rump white (*Rw*) (CATTANACH and MOSELEY 1974). CATTANACH (1978) suggests that *Rb(11.13)4Bnr* does not always suppress recombination because early reports of suppression were affected by misclassification of beige (*bg*). *Rb(11.13)4Bnr*, however, suppressed recombination significantly in several crosses in which *bg* was not the marker locus (CATTANACH, WILLIAMS and BAILEY 1972; PHILLIPS *et al.* 1980; M. T. DAVISSON, unpublished observations) when compared to the estimated distance using *T(10;13)199H*, a translocation with a breakpoint in the pericentromeric heterochromatin of chromosome *13* (LYON and GLENISTER 1974).

Suppression is restricted to the region near the centromere and gradually decreases distally: In general, in our work and most other published reports,

TABLE 11

Recombination percentages in crosses involving chromosome *5*

Centromere marker	F_1 sex	Crosses	Intervals				
			Rb-rl	*Rb-Hm*	*rl-Hm*	*Hm-Pgm-1*	*Pgm-1-bf*
Rb(5.15)4Lub	F + M	Table 9a	5.6 ± 2.6				
Rb(5.15)4Lub	F + M	T[a]	4.0 ± 2.8				
Rb(5.15)4Lub	F + M	Table 9c	—	6.2 ± 1.9			
Rb(5.15)15Rma	F + M	Table 9b	0	9.5 ± 3.7	≤7.6 U.C.L.	20.7 ± 7.8	
Rb(5.15)3Bnr	F	Table 9d	—	9.7 ± 3.1	—	17.2 ± 3.9	26.9 ± 4.6
None	F + M	Table 10	—	—	8.0 ± 3.5	—	—
None	F + M	Map[c]	—	—	10[c]	20	24

[a] T = tested chromosomes from cross in 9a, 2 recombinant/50 total chromosomes.
[b] Recombination percent from all published data [taken from the GBASE linkage map (GBASE 1992)].
[c] *Hm* and *rl* have never been mapped in the same cross previous to our data reported here; the map distance is based on positioning them each with respect to other loci.

TABLE 12

Linkage data for chromosome 7: *Rb(1.7)1Rma* × C57BL/6J

Cross: *Rb Gpi-1^b Hbb^s*/+ *Gpi-1^a Hbb^d* × + *Gpi-1^b Hbb^s*/+ *Gpi-1^b Hbb^s*

Progeny phenotype						No. of progeny		
						Sex of F_1 parent		
Rb		*Gpi-1*		*Hbb*		Female	Male	Combined
Rb		*b*		*s*		32	21	53
+		*ab*		*sd*		29	30	59
Rb	×	*ab*		*sd*		1	5	6
+	×	*b*		*s*		6	2	8
Rb		*b*	×	*sd*		10	10	20
+		*ab*	×	*s*		14	3	17
Rb	×	*ab*	×	*s*		2	0	2
+	×	*b*	×	*sd*		2	0	2
Totals						96	71	167

Recombination percentages:

Interval	F_1 female	F_1 male	Combined
Rb-Gpi-1	11/96 = 11.5 ± 3.2	7/71 = 9.9 ± 3.5	18/167 = 10.8 ± 2.4
Gpi-1-Hbb	28/96 = 29.2 ± 5.4	13/71 = 18.3 ± 4.6	41/167 = 24.6 ± 3.3

TABLE 13

Linkage data for chromosome 7: *Rb(6.7)13Rma* × C57BL/6J

Cross: *Rb Gpi-1^a Mod-2^a Hbb^d*/+ *Gpi-1^b Mod-2^b Hbb^s* × + *Gpi-1^b Mod-2^b Hbb^s*/+ *Gpi-1^b Mod-2^b Hbb^s*

Progeny phenotype								No. of progeny		
								Sex of F_1 parent		
Rb		*Gpi-1*		*Mod-2*		*Hbb*		Female	Male	Combined
Rb		*ab*		*ab*		*sd*		7	29	36
+		*b*		*b*		*s*		12	20	32
Rb	×	*b*		*b*		*s*		1	3	4
+	×	*ab*		*ab*		*sd*		1	3	4
Rb		*ab*	×	*b*		*s*		0	5	5
+		*b*	×	*ab*		*sd*		10	8	18
Rb		*ab*		*ab*	×	*s*		0	2	2
+		*b*		*b*	×	*sd*		0	6	6
Rb	×	*b*	×	*ab*		*sd*		0	1	1
+	×	*ab*	×	*b*		*s*		0	3	3
Rb		*ab*	×	*b*	×	*sd*		0	3	3
+		*b*	×	*ab*	×	*s*		1	1	2
Rb	×	*b*	×	*ab*	×	*s*		0	1	1
Totals								32	85	117

Recombination percentages:

Interval	F_1 female	F_1 male	Combined
Rb-Gpi-1	2/32 = 6.3 ± 4.3	11/85 = 12.9 ± 3.6	12/117 ± 10.3 ± 2.8
Gpi-1-Mod-2	11/32 = 34.4 ± 8.4	22/85 = 25.9 ± 4.8	33/117 = 28.2 ± 4.2
Mod-2-Hbb	1/32 = 3.1 ± 3.1	13/85 = 15.3 ± 3.9	14/117 = 14.5 ± 3.3
Gpi-1-Hbb	12/32 = 37.5 ± 8.6	25/85 = 29.4 ± 4.9	37/117 = 31.6 ± 4.3

Robertsonian chromosome recombination suppression does not extend more than 15–20 cM distal to the centromere (Figure 3). Exceptions are a few Robertsonian chromosomes described in early work by CATTANACH and MOSELEY (1973) and CATTANACH (1978) and *Rb(1.3)1Bnr* and *Rb(1.2)18Lub*, in which suppression was detected as far distal as *ln* at 41 cM from the centromere. The variability of expression in different crosses with *Rb(5.15)3Bnr*, and possibly *Rb(11.13)4Bnr*, suggests that genetic background may influence the extent or severity of suppression, perhaps via genes affecting pairing that differ among

TABLE 14

Linkage data for chromosome 7: *Rb(6.7)13Rma* × CBA

Cross: *Rb Gpi-1^a Mod-2^a*/+ *Gpi-1^b Hbb^b* × + *Gpi-1^b Hbb^b*/+ *Gpi-1^b Hbb^b*

Progeny phenotype					No. of progeny		
					Sex of F_1 parent		
Rb		*Gpi-1*		*Mod-2*	Female	Male	Combined
Rb		*ab*		*ab*	17	51	67
+		*b*		*b*	48	67	115
Rb	×	*b*		*b*	3	2	5
+	×	*ab*		*ab*	4	7	11
Rb		*ab*	×	*b*	13	31	44
+		*b*	×	*ab*	17	10	27
Rb	×	*b*	×	*ab*	2	0	2
+	×	*ab*	×	*b*	3	2	5
Totals					107	170	277

Recombination percentages:

Interval	F_1 female	F_1 male	Combined
Rb-Gpi-1	12/107 = 11.2 ± 3.0	11/170 = 6.5 ± 1.9	23/277 = 8.3 ± 1.7
Gpi-1-Mod-2	35/107 = 32.7 ± 4.5	43/170 = 25.3 ± 3.3	78/277 = 28.2 ± 2.7

TABLE 15

Linkage data for chromosome 7: *Rb(7.18)9Lub* × CBA

Cross: *Rb Gpi-1^a Hbb^s*/+ *Gpi-1^b Hbb^d* × + *Gpi-1^b Hbb^s*/+ *Gpi-1^b Hbb^s*

Progeny phenotype					No. of progeny		
					Sex of F_1 parent		
Rb		*Gpi-1*		*Hbb*	Female	Male	Combined
Rb		*ab*		*s*	8	12	20
+		*b*		*sd*	15	20	35
Rb	×	*b*		*sd*	1	1	2
+	×	*ab*		*s*	2	4	6
Rb		*ab*	×	*sd*	2	5	7
+		*b*	×	*s*	9	6	15
Totals					37	48	85

Recombination percentages:

Interval	F_1 female	F_1 male	Combined
Rb-Gpi-1	3/37 = 8.1 ± 4.5	5/48 = 10.4 ± 4.4	8/85 = 9.4 ± 3.2
Gpi-1-Hbb	11/37 = 29.7 ± 7.5	11/48 = 22.9 ± 6.1	22/85 = 25.9 ± 4.8

different strains or subspecies. The sex difference in extent of suppression in the *fz-ln* and *ln-Pep-3* intervals with *Rb(1.2)18Lub* (Table 3) is probably a sex difference in recombination frequency in this chromosome and not related to the Robertsonian chromosomes since males generally show less recombination than females in this region of chromosome *1* (GBASE 1992).

Finally, CATTANACH (1978) has suggested that enhancement occurs distally in chromosome arms where suppression occurs at the centromere. We have not seen enhancement in our crosses with chromosome *1* markers as far distal as *Pep-3* (at 49 cM from the centromere) (GBASE 1992) or chromosome *5* with markers as far distal as *bf* (at 58 cM from the centromere) (GBASE 1992), but our studies with distal markers are generally too limited to address this point. Such enhancement would result if heterozygosity for a Robertsonian chromosome actually shifted chiasma distally or if pairing delay decreased the number of proximal crossover events, thereby increasing the proportion of distal events recovered. JOHN and FREEMAN (1975) have reported chiasma shifting for some Robertsonian chromosome heterozygous bivalents in grasshoppers, but POLANI (1972) was unable to detect chiasma shift in *Rb(6.15)1Ald* heterozygotes even though proximal recombination is suppressed. Our

TABLE 16

Linkage data for chromosome 7: *Rb(7.18)9Lub* × C57BL/6J

Cross: *Rb Gpi-1^a Tam-1^a*/+ *Gpi-1^b Tam-1^c* × + *Gpi-1^b Tam-1^c*/+ *Gpi-1^b Tam-1^c*

Progeny phenotype					F$_1$ female progeny		F$_1$ male progeny		Combined progeny	
Rb		*Gpi-1*		(*Tam-1*)	♀	♂	♀	♂	♀	♂
Rb		*ab*		(*ac*)	22	10	9	13	31	23
+		*bb*		(*cc*)	45	37	6	12	51	49
Rb	×	*bb*		(*cc*)	10	8	3	1	13	9
+	×	*ab*		(*ac*)	3	2	1	0	4	2
Rb		*ab*	×	(*cc*)	—	11	—	2	—	13
+		*bb*	×	(*ac*)	—	4	—	0	—	4
Rb	×	*bb*	×	(*ac*)	—	1	—	0	—	1
−	×	*ab*	×	(*cc*)	—	1	—	0	—	1
		Totals			80	74	19	28	99	102

Recombination percentages:

Interval	F$_1$ female	F$_1$ male	Combined
Rb-Gpi-1	25/154 = 16.2 ± 3.0	5/47 = 10.6 ± 4.5	30/201 = 14.9 ± 2.5
Gpi-1-Tam-1	17/74 = 23.0 ± 4.9	2/28 = 7.1 ± 4.9	19/102 = 18.6 ± 3.9

Tamase-1 (*Tam-1*) was typed in male progeny only.

TABLE 17

Control linkage data for chromosome 7: (C57BL/6J × BALB/cJ) × C57BL/6J

Cross: *Gpi-1^a Tam-1^a Hbb^d*/*Gpi-1^b Tam-1^c Hbb^s* × *Gpi-1^b Tam-1^c Hbb^s*/*Gpi-1^b Tam-1^c Hbb^s*

Progeny phenotype			F$_1$ female progeny		F$_1$ male progeny		Combined progeny	
Gpi-1	*Tam-1*	*Hbb*	♀	♂	♀	♂	♀	♂
ab	*ac*	*sd*	14	15	7	15	21	30
b	*c*	*s*	11	18	5	9	16	27
ab	*c*	*s*	1	3	0	0	1	3
b	*ac*	*sd*	6	5	0	0	6	5
ab	*ac*	*s*	4	6	2	1	4	7
b	*c*	*sd*	2	7	0	4	2	11
ab	*c*	*sd*	0	2	0	0	0	2
b	*ac*	*s*	0	0	0	0	0	0
Totals			38	56	14	29	50	85

Recombination percentages:

Interval	F$_1$ female	F$_1$ male
Gpi-1-Tam-1	10/56 = 17.9 ± 5.1	1/29 = 3.4 ± 3.4
Tam-1-Hbb	15/56 = 26.8 ± 5.9	5/29 = 17.2 ± 7.0
Gpi-1-Hbb	34/94 = 36.2 ± 5.0	7/43 = 16.3 ± 5.6

Additional mice were typed for *Gpi-1* and *Tam-1* only.

observations are consistent with the second hypothesis.

There is a direct correlation between suppression and delayed meiotic pairing in all Robertsonian chromosomes in which both phenomena have been studied (Figure 3): The third common and most important feature that we describe in this paper is the correlation between genetic recombination suppression and delayed chromosomal pairing at meiotic pachytene. Four of the seven Robertsonian chromosomes in which SCs were analyzed showed pairing delay in the centromeric region and suppressed recombination; the remaining three showed very little pairing delay and did not alter genetic recombination. In addition, MAHADEVAIAH, SETTERFIELD and MITTWOCH (1990) observed 21 and 43% of pachytene trivalents with centromeric asynapsis (pairing delay) in *Rb(6.15)1Ald* and *Rb(4.6)2Bnr* heterozygotes, respectively; *Rb(6.15)1Ald* shows some recombination suppression in the chromosome 6 arm (CATTANACH

TABLE 18

Recombination percentages in crosses involving chromosome 7

Centromere marker	Genetic background	F_1 sex	Interval		
			cen-*Gpi-1*	*Gpi-1-Hbb*	*Gpi-1-Tam-1*
Rb(1.7)1Rma	B6	F + M	10.8 ± 2.4	24.6 ± 33.3	—
Rb(6.7)13Rma	B6	F + M	10.3 ± 2.8	31.6 ± 3.3	—
Rb(6.7)13Rma	DBA	F + M	8.3 ± 1.7	—	—
Rb(7.18)9Lub	B6	F + M	14.9 ± 2.5	—	18.6 ± 3.9
		F	16.2 ± 3.0	—	23.0 ± 4.9
		M	10.6 ± 4.5	—	7.1 ± 4.9
Rb(7.18)9Lub	CBA	F + M	9.4 ± 3.2	25.9 ± 4.8	—
None	C × B6	F + M	—[a]	29.9 ± 3.9	11.1 ± 3.1
		F	—[a]	36.2 ± 5.0	17.9 ± 5.1
		M	—[a]	16.3 ± 5.6	3.4 ± 3.4
—	OT[b]	F	11.7 ± 1.1	—	—

[a] Reported C-band difference turned out not to be reproducibly distinguishable.
[b] Ovarian teratoma data from EPPIG and EICHER (1988).

TABLE 19

Linkage data for chromosome *16*: *Rb(16.17)7Bnr* × C3H/HeJ-*md*

Cross: *Rb* +/+ *md* × + *md*/+ *md*

Progeny phenotype			No. of progeny		
			Sex of F_1 parent		
Rb		*md*	Female	Male	Combined
Rb		+	39	3	42
+		*md*	35	4	39
+	×	+	0	0	0
Rb	×	*md*	0	0	0
Totals			74	7	81

Recombination percentage: 0/81 ≤ 3.0%, 95% upper confidence limit

TABLE 20

Linkage data for chromosome *16*: MOLD/*Rk-Hc16*^{s} × C3H/HeJ-*md*

Cross: *Hc16*^{s} +/+ *md* × + *md*/+ *md*

Progeny phenotype			No. of progeny		
			Sex of F_1 parent		
Hc16		*md*	Female	Male	Combined
s		+	33	30	63
+		*md*	31	17	48
s	×	*md*	5	2	7
+	×	+	1	0	1
Totals			70	49	119

Recombination percentages:

F_1 female	F_1 male	Combined
6/70 = 8.6 ± 3.3	2/49 = 4.1 ± 2.8	8/119 = 6.7 ± 2.3

and MOSELEY 1974) and *Rb(4.6)2Bnr* strongly suppresses in both arms (CATTANACH and MOSELEY 1974; LYON and NEWPORT 1973; NADEAU and EICHER 1982). We suggest that our observations taken together with published information show that assessing pairing delay by SC preparations can be used to predict whether a given Robertsonian chromosome will suppress genetic recombination.

Hypotheses for Robertsonian chromosome suppression: It is clear from our studies and a review of the literature that simple heterozygosity in Robertsonian chromosome heterozygotes is not the sole cause of recombination suppression. Factors that may cause or influence recombination suppression include genic differences between the Robertsonian chromosome and its telocentric partners, aneuploidy and embryonic loss, meiotic nondisjunction, segregation or transmission distortion, Robertsonian chromosome arm ratio or size differences, or mechanical failure to pair during the critical crossing over period of meiotic pachytene (MOSES *et al.* 1982).

Early studies in which suppression of genetic recombination in mouse Robertsonian chromosome heterozygotes was detected involved crosses between wild-derived Robertsonian chromosome-carrying *M. m. domesticus* mice and laboratory mice. As a result, CATTANACH and MOSELEY (1973) hypothesized that minor genic or structural differences might exist between the chromosomes of wild *M. m. domesticus* mice and laboratory strains. If so, one would expect that Robertsonian chromosomes arising in laboratory strains would not affect recombination. Our data show that at least one laboratory-derived Robertsonian chromosome (*Rb(1.3)1Ei*) with the same chromosomal constitution as a wild-derived Robertsonian chromosome (*Rb(1.3)1Bnr*) suppresses recombination to the same extent.

It has been suggested that recombination suppres-

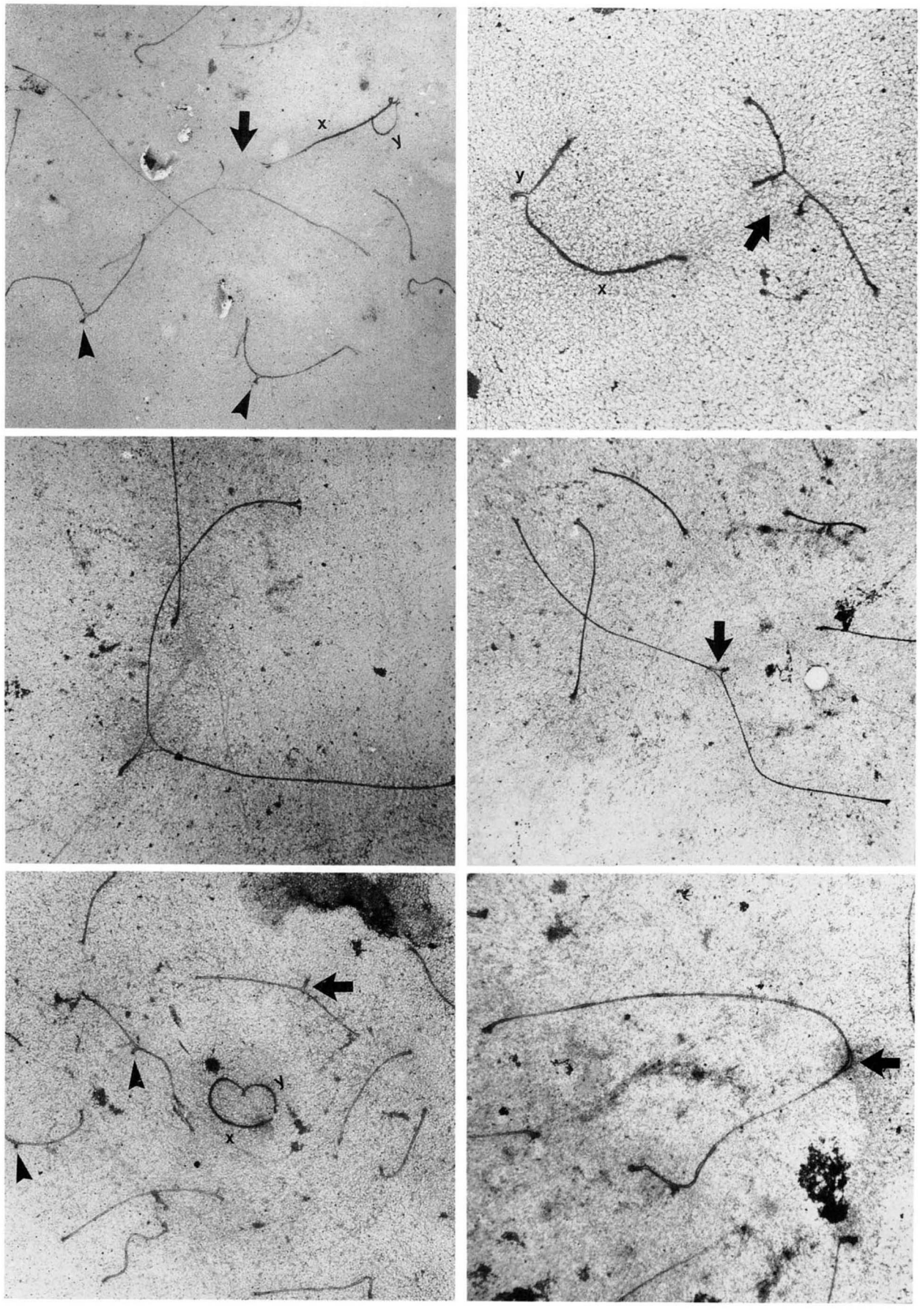
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TABLE 21

Recombination percentages in crosses involving chromosome *16*

Centromere marker	F_1 sex	Cross	Interval cen-*md*	*P*	*Rb-dw*	*md-dw*
Rb(16.17)7Bnr	F + M	BC	0	<0.03	—	—
Rb(16.17)7Bnr	F + M	IC	0	—	24.6 ± 3.8	—
Hc16[s]	F + M	BC	6.7 ± 2.3	—	—	—
None	F + M	C[a]	—	—	—	32.4 ± 1.9

[a] Data from four combined crosses (LANE and SWEET, 1979).

sion might be correlated with meiotic nondisjunction, which varies among Robertsonian chromosome heterozygotes (CATTANACH, MURRAY and TRACEY 1976; CATTANACH and MOSELEY 1974). A survey of the literature on Robertsonian chromosomes since 1970 shows that there are too few Robertsonian chromosomes for which both nondisjunction and recombination suppression have been determined to address this possibility. At least two Robertsonian chromosomes show relatively high nondisjunction rates and recombination suppression in one chromosome arm but not the other. *Rb(16.17)7Bnr*/+ trivalents show 12–20% nondisjunction (CATTANACH and MOSELEY 1973), and suppression in the chromosome *16* arm (our data) but not in the chromosome *17* arm (HAMMERBERG and KLEIN 1975; CATTANACH and MOSELEY 1974). *Rb(11.13)4Bnr* has the highest nondisjunction rate of any of the original seven *Bnr* Robertsonian chromosomes (CATTANACH and MOSELEY 1973) and suppresses recombination in the chromosome *13* but not the chromosome *11* arm. Thus, while pairing delay may lead to both nondisjunction and recombination suppression, there is no evidence for direct cause and effect relationship between the two.

We and others [*e.g.*, CATTANACH and MOSELEY (1973) and GROPP and WINKING (1981)] have observed that some Robertsonian chromosome heterozygotes produce significantly fewer Robertsonian chromosome-carrying than telocentric progeny; this discrepancy might distort linkage data and give the appearance of genetic recombination suppression. Our studies show that there is no correlation between transmission distortion and suppression. First, only females showed transmission distortion, yet recombination suppression for the same Robertsonian chromosomes occurred in both F_1 parents. Second, *Rb(6.7)13Rma* and *Rb(7.18)9Lub* showed transmission distortion but did not suppress recombination.

Trivial explanations for recombination suppression include correlations between recombination suppression and Robertsonian chromosome size or chromosomal arm ratio. Our data show that suppression occurred with both large and small Robertsonian chromosomes and with Robertsonian chromosomes with both equal and unequal arm ratio.

Our data are most consistent with the hypothesis that minor structural differences arise during the formation of the Robertsonian chromosomes that suppress recombination. The best argument for this hypothesis is that suppression is specific to individual Robertsonian chromosomes regardless of their origin. Our synaptonemal complex analysis of meiotic pairing confirms other observations that Robertsonian-telocentric trivalents in mice heterozygous for some Robertsonian chromosomes show delayed pairing in the centric region. Since we began this study, others have observed this phenomenon in mice (BROWN and BURTENSHAW 1980; MAHADEVAIAH, SETTERFIELD and MITTWOCH 1990), lemurs (MOSES, KARATSIS, and HAMILTON 1979), and human beings (NAVARRO *et al.* 1991). Our studies have now shown that this delayed pairing is correlated with recombination suppression.

MOSES *et al.* (1982) have postulated (that delayed or nonhomologous pairing in heterozygous inversion bivalents leads to recombination suppression by reducing the amount of time homologous segments are paired during the critical pachytene period when crossing over can occur. The observations presented here for Robertsonian chromosomes are consistent with this hypothesis and add additional support to the model that crossing over is limited to a critical period during pachytene. The observation that recombination suppression is restricted to intervals near the centromere and decreases distally along the chromosome is consistent with the delay in pairing as it progresses from the telomeres proximal, being most severe near the centromere (Figure 3).

Recent observations in *Saccharomyces cerevisiae* have

FIGURE 1.—Electron micrographs of synaptonemal complexes from pachytene cells of mice heterozygous for Robertsonian chromosomes, showing different stages of pairing in *Rb*/+ trivalents. (a) Top left, SCs from early pachytene cell, as shown by *XY* pair, from *RBF/Dn* male. Delayed stage 1 pairing in *Rb(1.3)1Bnr* (arrow) and stage 3 pairing in *Rb(8.12)5Bnr* and *Rb(9.14)6Bnr* (arrowheads); the unpaired end of the *X* is associated with the centromere end of one of the telocentrics in the *Rb(1.3)1Bnr* trivalent, 2500×. (b) Top right, early to mid-pachytene SCs from *RBD/Dn* male; *Rb(5.15)3Bnr*/+ trivalent is on the right and *XY* bivalent on the left, 3900×. (c) Middle left, stage 2 synaptonemal complex in an *Rb(1.7)1Rma*/+ trivalent, 3550×. (d) Middle right, *Rb(1.7)1Rma*/+ SC between stage 2 and 3 (arrow) from an early pachytene cell of a male heterozygous for this *Rb*, 2375×. (e) Bottom left, stage 3 trivalents from an *RBD/Dn* male heterozygous for *Rb(5.15)3Bnr* (arrow), *Rb(11.13)4Bnr* and *Rb(16.17)7Bnr* (arrowheads). Thickening of *XY* pair and density of sex vesicle show cell is at late pachytene, 2800×. (f) Bottom right, *Rb(1.7)1Rma*/+ trivalent showing complete pairing in the centromere region, 4350×.

led to the hypothesis that early events in meiotic recombination precede and are necessary for normal SC formation. This hypothesis is based on the temporal correlation between progressive stages of recombination and SC formation (PADMORE, CAO and KLECKNER 1991) and the observation that mutations that specifically disrupt meiotic recombination lead to delay or failure of SC formation (BISHOP *et al.* 1992). If this hypothesis is valid and holds true for mammalian meiosis, then our hypothesis must be revised. While the correlation of SC synapsis and meiotic recombination that we see is consistent with either order of SC and recombination events, this new hypothesis would say that some other factor inhibits recombination in the mouse Robertsonian heterozygotes and that inhibition in turn leads to delayed SC synapsis. The most likely possibility is that independent formation of independent Robertsonian chromosomes can result in small chromosomal deletions in some Robertsonian chromosomes and, when these occur, they interfere with homolog searching/pairing and reduce recombination. Only direct molecular analysis and comparison of the centromere regions of acrocentric and Robertsonian chromosomes would detect such differences. Until more information on mammalian meiosis is available, the alternative orders of recombination and SC formation can not be distinguished.

Formation of Robertsonian chromosomes: Robertsonian chromosomes can arise by either of two alternative mechanisms: centromeric fusion or whole arm reciprocal translocation (JOHN and FREEMAN 1975; LAU and HSU 1977). Both types have been observed in mammalian cells (COMINGS and OKADA 1970; LAU and HSU 1977; WOLFF and SCHWARTZ 1992). Since all mouse chromosomes except the *Y* have no short arm (are telocentric), centromeric fusion is possible (COMINGS and OKADA 1970; MOSES 1977). COMINGS and OKADA conclude from electron microscopic studies of mammalian Robertsonian chromosomes that many arise from such breakage-reunion within the centromeres themselves. Whole arm translocation by definition would lead to loss of one centromere. Breakage and reunion within the centromeres would lead to varying amounts of DNA within the centromeric region of the resulting Robertsonian chromosome, depending on the location of the break within each telocentric chromosome. It is unlikely that loss of material during centromeric joining extends into the pericentromeric heterochromatin, because neither COMINGS and AVELINO (1972) nor REDI *et al.* (1986) were able to detect loss of satellite (pericentromeric heterochromatin) DNA in mice homozygous for several Robertsonian chromosomes; however, only analysis of individual Robertsonian chromosomes is likely to detect small differences within single Robertsonian chromosomes.

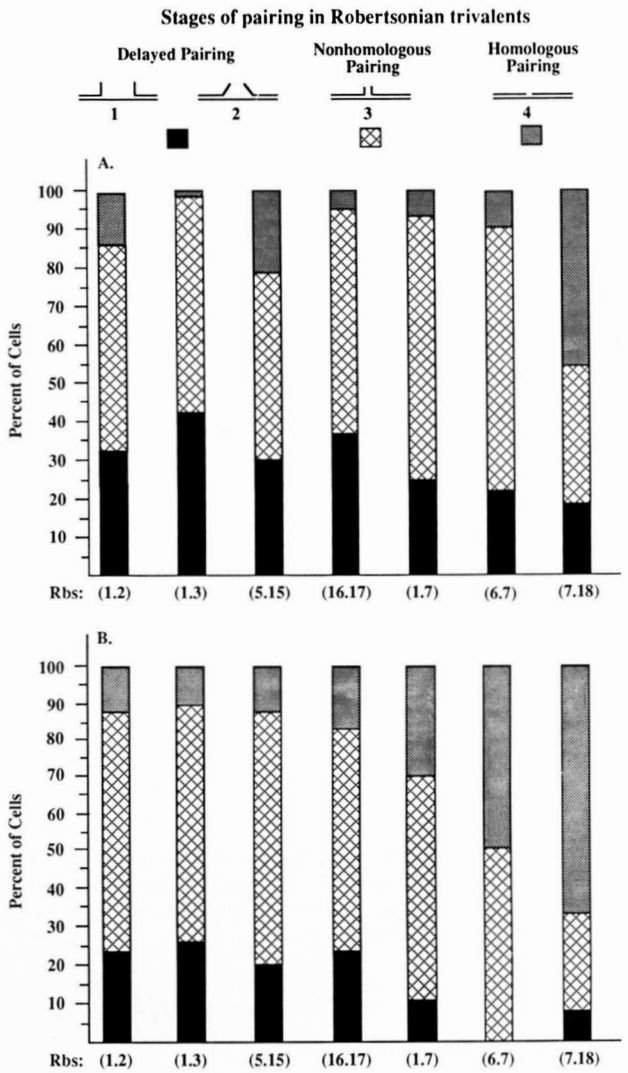

FIGURE 2.—Histograms showing (A) the frequency of the different stages of pairing at all stages of pachytene in Robertsonian trivalents from heterozygous females and males combined and (B) the frequency of pairing stages at late pachytene in heterozygous males only. The stages of trivalent pairing are numbered and depicted diagrammatically above the graphs. The total number of cells scored for each Robertsonian chromosome were *Rb(1.2)18Lub*, 68(54); *Rb(1.3)1Bnr*, 239(149); *Rb(5.15)3Bnr*, 48(31); *Rb(16.17)7Bnr*, 187(155); *Rb(1.7)1Rma*, 173(91); *Rb(6.7)13Rma*, 92(17); *Rb(7.18)9Lub*, 75(62). Numbers in parentheses are the number of cells scored in males, *i.e.*, for rate of progression through pachytene as well as frequency of different pairing stages.

The strongest evidence to support the hypothesis that small losses in centromeric DNA have occurred in some Robertsonian chromosomes is observation by us and others (MAHADAVAIAH, SETTERFIELD and MITTWOCH 1990; MOSES, KARATSIS and HAMILTON 1979) of nonhomologous synapsis between the centromeric regions of the telocentric chromosomes in the trivalents. Note in Figure 1, a, c and e, configurations in which the telocentric kinetochores and terminal

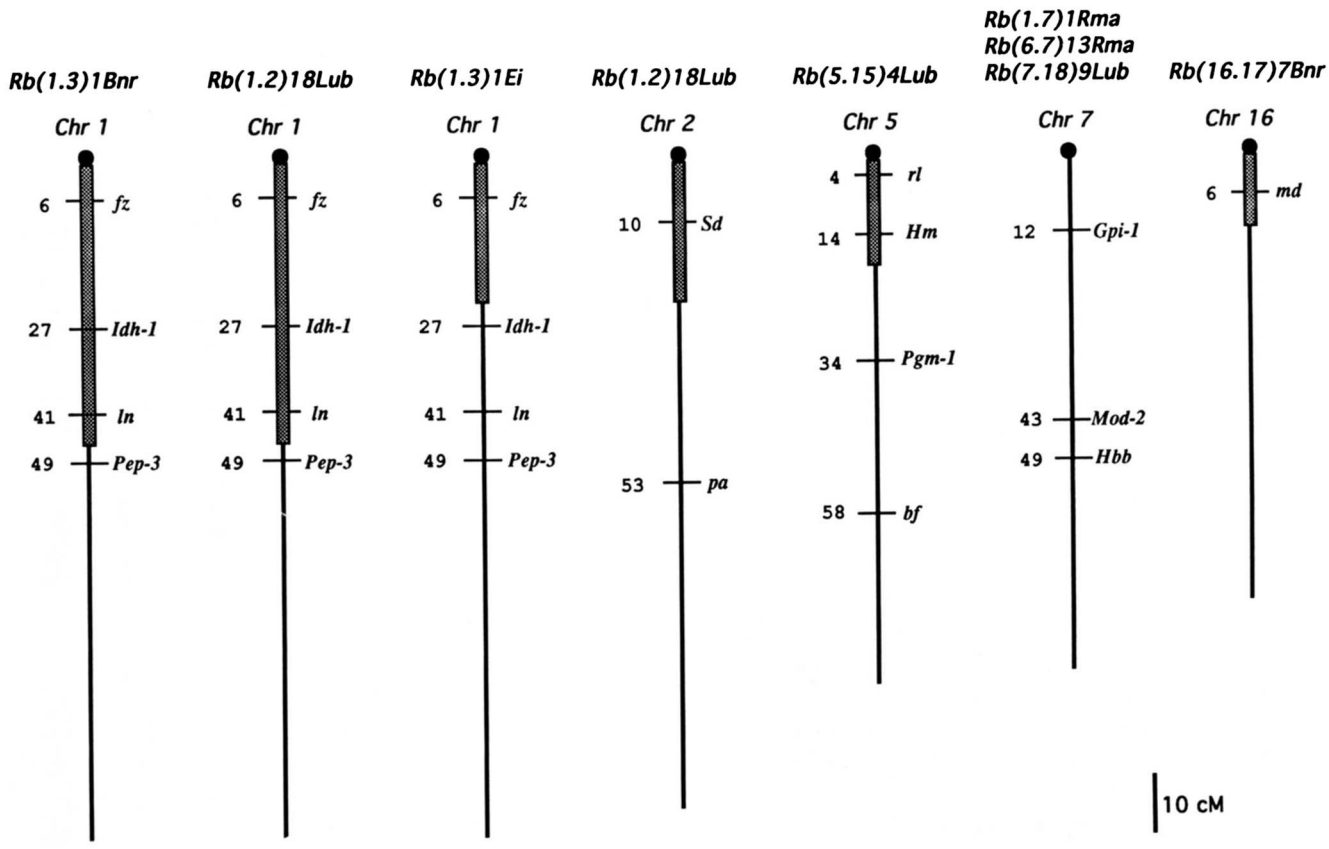

FIGURE 3.—Diagram showing the extent of recombination suppression in the Robertsonian chromosomes analyzed. The genes tested in linkage analyses are shown at the right of the chromosome bars; the centiMorgan distances from the centromere shown at the left of the chromosomes are based on our control crosses and the consensus map in GBASE (1992). Hatched boxes indicate the extent of suppression for each Robertsonian chromosome.

plaques project outward from the main axis of the telocentric-metacentric SCs. This nonhomologous synapsis between the two telocentric chromosomes suggests that those Robertsonian chromosomes that suppress recombination have small deletions near or within the centromeres. These deletions could be sufficient to delay either the pairing and recombination process or SC synapsis. In addition, electron microscopic studies have shown that some Robertsonian chromosomes formed in mouse cell lines have only one active kinetochore, that part of the centromere that is directly involved in spindle fiber attachment and chromatid separation during cell division (RATTNER and LIN 1985). This would also lead to structural differences in the centromeric region of Robertsonian-telocentric trivalents.

Value of Robertsonian chromosomes for mapping: To complete chromosomal maps, markers for the centromeric and telomeric ends must be used as boundary markers. When the data are handled with caution, Robertsonian chromosomes can be useful for genetic mapping until centromeric probes are available. They have been used effectively to assign linkage groups to chromosomes (CATTANACH and MOSELEY 1973; CATTANACH, WILLIAMS and BAILEY 1972; MILLER *et al.* 1971a,b; KLEIN 1971; NESBITT and FRANCKE 1971) and to determine centromere ends of linkage groups (BEECHEY and SEARLE 1979; CATTANACH and MOSELEY 1974; LYON and NEWPORT 1973; LYON, BUTLER and KEMP 1968). In 10 chromosomes (*3*, *4*, *5*, *6*, *8*, *9*, *10*, *11*, *15* and *19*) the distances from the centromeres to first markers may be underestimated because they have been determined using only Robertsonian chromosomes (GBASE 1992). Our data on chromosome 7 Robertsonian chromosomes, however, clearly demonstrate that one cannot assume this to be the case. Also, some of these distances have been determined using loci more distal than the most proximal locus on the chromosome, and it is clear from our data and that of others (GBASE 1992) that the extent of suppression can vary for different Robertsonian chromosomes even when they suppress recombination.

Robertsonian chromosomes are most valuable for detecting chromosomal linkage of new mutations, because Robertsonian chromosomes that significantly inhibit recombination will rapidly detect linkage of new loci that map within 20 cM of the centromere. For example, we have used this approach effectively to locate a number of new spontaneous mutations, *e.g.*, congenital polycystic kidneys (*cpk*) (DAVISSON *et*

al. 1991) and juvenile depilation (*jd*) (SWEET, BRONSON and DAVISSON 1991).

CONCLUSIONS

Our data correlating delayed meiotic pairing with suppression of genetic recombination provide strong evidence that the underlying mechanism of suppression is pairing delay. The pairing abnormalities most likely result from small structural differences generated during Robertsonian chromosome formation. These differences lead to delayed meiotic pairing which is sufficient to cause genetic recombination suppression. We have also demonstrated that analyzing SC preparations from an F_1 male for frequency and progression of pairing delay can reliably predict whether an untested Robertsonian chromosome will suppress recombination in a particular cross.

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