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Immunology

Evidence for a major cluster of lymphocyte differentiation antigens on murine chromosome 2

(mapping of *Ly-11/Ly-6*/viral integration/radiation leukemia)

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ABSTRACT **The region of chromosome 2 between *H-13* and *H-3* has been shown to contain loci coding for a variety of other alloantigens, including *Ly-4* and the locus coding for β_2-microglobulin. Herein we show that Ly-6 and Ly-11 are coded for by genes in a segment of chromosome 2 adjacent to the *H-3–H-13* region and that this segment of chromosome also contains the tightly linked loci coding for antigens Ala-1, DAG, H9/25, H-30, Ly-8, and ThB. In addition, at least one locus (and probably more) affecting susceptibility to leukemia induction is found within this gene cluster.**

The region of murine chromosome 2 adjacent to the locus coding for β_2-microglobulin (1–3) has been shown to contain loci coding for the minor histocompatibility antigens H-3 (4) and H-13 (5); an immune response gene, *Ir-2* (6), an alloantigen, Ly-4, expressed on B (7) and T (8) cells; an alloantigen, Lym-11, perhaps identical with H-3 (9); and a major surface glycoprotein, Pgp-1, expressed on macrophages (10). Various other lymphocyte cell surface antigens have been shown to be coded for by loci closely linked to the previously unmapped gene coding for lymphocyte determinant Ly-6. Among these are Ala-1 (11), DAG (12), H9/25 (13), Ly-8 (14), and ThB (15). We report herein that Ly-6, the lymphocyte antigen Ly-11 (16), and the minor histocompatibility locus *H-30* map in the region of chromosome 2 to the left of *H-3*. Therefore Ala-1, DAG, H9/25, Ly-8, and ThB must also be encoded in this segment of chromosome 2.

With the exception of the chromosomal segment encompassing the *H-2* complex (17th chromosome) (17, 18), no other genomic segment has been shown to code for so many alloantigens or loci affecting lymphocyte differentiation. Although it is possible that some of these alloantigens are merely different determinants on the same molecule(s), recombination has been shown to occur between several of these loci and thus a trivial explanation cannot account for the linkage of loci coding for these many alloantigens. Furthermore, similarities and dissimilarities exist in the tissue and lymphocyte subpopulation distribution of most of these alloantigens, again suggesting that each antigen represents a unique entity.

This segment of chromosome may assume additional importance because there appears to be coordinate expression of its gene products and those of *H-2* on the 17th chromosome. For example, the obligatory interreaction between β_2-microglobulin and H-2 has been known for some time (19). Recently Croce *et al.* (20) provided strong evidence for the coordinate regulation of the transcription of *H-2* and β_2-microglobulin genes. Additional studies have shown that *H-2* gene(s) influence the expression of chromosome 2 loci *Ly-4*, *Ly-11*, and *Ly-6* (refs. 21 and 22; unpublished data).

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MATERIALS AND METHODS

Mice. CXB recombinant inbred (RI) mice were the kind gifts of Julia Phillips-Quagliata and Mary Clare Walker (New York University Medical Center). Mice purchased from The Jackson Laboratory included BXH and SWXL RI strains, courtesy of Ben A. Taylor, and chromosome linkage testing stocks C57BL/6J-*ma*, C57BL/6-*lnfz*, C57BL/6J-*Va*^{J}, C57BL/6J-*bg*, C57BL/6-*Ca*, C3H/HeJ-*md*, and C3H/HeB-*Sy*^{JB} through Priscilla Lane. All other mice were bred in our own colony at New York University Medical Center.

The alleles and antigens of the various strains used are as follows: *A/J*: Ly-1.2, Ly-2.2, Ly-4.1, Ly-6.1, Ly-11.1, Ly-22.2, H-2^a, Thy-1.2, *c* (albino), *b* (brown), Fv-2^s (virus susceptible); *C57BL/6 or C57BL/10 (B10)*: Ly-1.2, Ly-2.2, Ly-4.2, Ly-6.2, Ly-11.2, Ly-22.2, H-2^b, Thy 1.2, black, Fv-2^r; *C3H*: Ly-1.1, Ly-2.1, Ly-4.1, Ly-6.1, Ly-11.1, H-2^k, Thy-1.2, agouti, black, Fv-2^s. Mutant mice C57BL/6-*lnfz*, C57BL/6-*ma*, C57BL/6-*Va*^{J}, C57BL/6-*bg*, and C57BL/6-*Ca* have identical genotype to C57BL/6 mice except they carry a visual trait not carried by the latter mice. The loci coding for the distinguishing traits have been mapped to chromosomes 1, 3, 3, 13, or 15, respectively (23). C3H/HeJ-*md* and C3H/HeB-*Sy*^{JP} carry visual markers on the C3H background. *md* codes for mahogonoid (coat color) and is found on chromosome 16 (23). *Sy*^{JP}, fused phalange, is located on chromosome 18 (23). B6.Ly-1.1 and B6.Ly-2.1 are congeneic with C57BL/6, differing only at loci coding for Ly-1.1 (chromosome 19) and Ly-2.1 (chromosome 6) (23). A$^{Thy1.1}$ mice are congeneic with A mice but differ at Thy-1 (chromosome 9) (23). B10.*PaH-3*^{eat} mice differ from B10 mice at the pallid locus, *pa* (coat color), on chromosome 2 (23).

Cell binding radioimmunoassay (to measure Ly-11.2, Ly-6.2, Ly-22.2, H-2^d, H-2^b, Ly-1.1, Ly-2.1, Thy-1.2, and Thy-1.1), virus susceptibility test (to score mice for susceptibility or resistance due to *Fv-2*), isoenzyme assay (for peptidase 3), and leukemogenic-fractionated irradiation have been previously discussed (16).

Antisera. Monoclonal anti-Ly-6.2 was graciously provided by U. Hämmerling (Sloan Kettering Institute, New York). Anti-mouse-γ2a and -γ2b (monospecific) were purchased from Litton Bionetics, Bethesda, MD. Anti-γ2a was required as a second-step antibody prior to the staphylococcal protein A step (see below) for peripheral blood typing of mice for their Ly-6.2 phenotype. Anti-γ2b also had allotype specificity and was used in the segregation analysis to detect chromosome 12 linkage. Alloantiserum Ly-4.2 was kindly provided by John G. Ray, Jr. (Research Resources Branch, National Institutes of Health). Some aliquots were absorbed to remove contaminating activities but others were used as provided. Anti-Ly-11.2 [(A.AL × BALB.B)F$_1$ anti-B10.A(4R)] was defined and described in detail by us previously (24). Anti-H-2 and anti-Ly-22 alloanti-

Abbreviation: RI, recombinant inbred.

sera were produced by us by similar immunization procedures. Other monoclonal antibodies were obtained commercially or produced by us.

Estimates of Recombination Frequencies. Much of the methodology used to determine recombination frequencies is described in the text or table legends. The methods for analysis of F_2 matings are fairly complex as compared to backcross matings. However, F_2 crosses were preferred in the present analysis because antisera were available to Ly-4.2, Ly-6.2, and Ly-11.2 but not to Ly-4.1, Ly-6.1, and Ly-11.1. F_2 analysis requires only discernable differences between the homozygous offspring (e.g., 11.1/11.1 vs. 11.2/11.2). Although we can clearly distinguish quantitatively the heterozygote (e.g., 11.1/11.2) from either homozygote, the contrast is never as marked as that between the positive and negative homozygotes.

RESULTS

Ly-11 Maps to Chromosome 2. Table 1 lists the results of linkage analysis for *Ly-11* and 23 loci mapping in 15 different murine chromosomes. The recessive, dominant, or codominant nature of each trait is given in Table 1. Ly-4.2, Ly-6.2, and Ly-11.2 are all codominantly expressed. χ^2 analysis was performed for every cross. Values below 5.81 were taken to indicate lack of linkage. As shown in Tables 1 and 2, linkage between *Ly-11* and agouti (coat color; *A*) allowed the assignment of the former locus to chromosome 2. With the exception of chromosome 2 markers, the highest χ^2 value obtained with any trait was 2.32. The recombination frequency between *A* and *Ly-11* computed from data in Table 2 is approximately 27 ± 4%. To determine the centromeric position of *Ly-11* with respect to agouti, a separate linkage analysis was performed by using pallid (*pa*) as a marker for *Ly-11* localization. *pa* has been shown to map 16.7 ± 1.3 recombination units away from *A* (26). In (A/J × B10.*PaH-3*^{eat})F_2 mice, *Ly-11* is found 18 ± 5 recombination units away from *pa* (Table 2). Thus the most consistent interpretation of the data is that *Ly-11* maps to the left of *pa* and *A*, as shown in Fig. 1.

Once *Ly-11* was located, the position of *Ly-6* was determined

Table 1. Linkage relationship of *Ly-11* to known loci on various murine chromosomes

Chromosome no.	Strain combination tested	Marker locus	Nature of trait*	No. mice tested	Recombination distance†
1	(A/J × C57BL/6-*lnfz*)F_2	*ln*	r	149	0.49 ± 0.05
		fz	r	149	0.53 ± 0.05
	(A/J × B10)F_2	*Pep-3*	c	77	0.47 ± 0.06
2	See Table 2	*A*	d	396	0.27 ± 0.04
		pa	r	111	0.18 ± 0.05
3	(A/J × C57BL/6-*ma*)F_2	*ma*	r	97	0.50 ± 0.06
	(A/J × C57BL/6-*Va*^{J})F_2	*Va*^{J}	c	108	0.48 ± 0.05
4	‡	Brown	r	394	0.48 ± 0.03
	‡	Black	d	394	0.49 ± 0.03
	(A/J × B10)F_2	*Ly-22*	c	111	0.43 ± 0.05
6	(A/J × B6/Ly-2.1)F_2	*Ly-2*	c	97	0.47 ± 0.05
7	§	*c*	r	394	0.48 ± 0.03
9	(B10 × 1$^{Thy.1.1}$)F_2	*Thy-1*	c	72	0.50 ± 0.06
	(A/J × B10)F_2	*Fv-2*	r	50	0.43 ± 0.09
12	(A/J × B10.*PaH-3*^{eat})F_2	*γ2b*	c	53	0.46 ± 0.07
13	(A/J × C57BL/6-*bg*)F_2	*bg*	r	97	0.47 ± 0.06
15	(A/J × C57BL/6-*Ca*)F_2	*Ca*	d	100	0.42 ± 0.06
16	(B10 × C3H/HeJ-*md*)F_2	*md*	r	122	0.50 ± 0.06
17	(A/J × B10)F_2	*H-2*	c	136	0.50 ± 0.04
18	(B10 × C3H/HeB-*Sy*^{JP})F_2	*Sy*^{JP}	r	101	0.49 ± 0.06
19	(A/J × B6/Ly-1.1)F_2	*Ly-1*	c	115	0.44 ± 0.05
Y	¶	Y chromosome	d	219	0.49 ± 0.03

* c, Codominant; d, dominant; r, recessive.
† Computed as described in the footnotes for Table 2; results are presented ±SEM.
‡ (A/J × C57BL/6-*ma*)F_2, (A/J × B6/Ly-1.1)F_2, (A/J × C57BL/6-*Ca*)F_2, (A/J × B10)F_2, excluding white mice.
§ (A/J × C57BL/6-*ma*)F_2, (A/J × B6/Ly-1.1)F_2, (A/J × C57BL/6-*Ca*)F_2, (A/J × B10)F_2, including white mice.
¶ (A/J × C57BL/6-*bg*)F_2, (B10 × C3H/HeJ-*md*)F_2.

Table 2. Calculation of recombination frequency between *Ly-11* and *A* and *pa* as well as between *Ly-6* and *pa* in various test intercrosses

Cross	Trait 1	Trait 2	Score*	$N^{\dagger}$	$NS^{\ddagger}$	Table score§	$n \times$ table score	$r^{\P}$	$\chi^{2\|\|}$
(AKR × C3H/DiSn)F_2	*11.2/11.2*	*AA* or *Aa*	4/3	62	82.67	0.9524	59.05		
(AKR × C3H.Q)F_2	*11.2/11.2*	*aa*	−4	34	−136.00	−0.3704	−12.59		
(B10 × C3H/HeJ-*md*)F_2	*11.1/11.1*	*AA* or *Aa*	−4/3	82	−109.33	−0.3704	−30.37	0.27 ± 0.04	29.71
(BALB/c × C57BL/6)F_2	*11.1/11.1*	*aa*	4	16	64.00	5.5820	89.31		
				$n = 396$			$\Lambda = 105.40$		
							$ip = 1.455$		
(A/J × B10.*PaH-3*^{eat})F_2	*11.2/11.2*	*pa/pa*	−4	14	−56	0.3733	5.23		
	11.2/11.2	+/+	4	3	12	3.6806	11.04		
	11.1/11.1	*pa/pa*	4	1	4	3.6806	3.68	0.18 ± 0.05	34.97
	11.1/11.1	+/+	−4	10	−40	−1.9216	−19.22		
				$n = 111$			$\Lambda = 0.73$		
							$ip = 3.118$		
(A/J × B10.*PaH-3*^{eat})F_2	*6.2/6.2*	*pa/pa*	−4	5	−20	0.3535	1.7675		
	6.2/6.2	+ +	4	1	4	5.4040	5.4040		
	6.1/6.1	*pa/pa*	4	0	0	5.4040	0	0.28 ± 0.12	8.30
	6.1/6.1	+ +	−4	6	−24	−1.5404	−9.2424		
				$n = 35$			$\Lambda = -2.010$		
							$ip = 4.798$		

* Scores of maximum likelihood when two traits are codominant or dominant and offspring from an intercross mating are being examined (25).
† *N*, number of F_2 offspring in the phenotypic class shown; *n*, total number of offspring in all phenotypic classes, including those not used in the calculations because their score value is zero.
‡ The values of *NS* are those required for the initial calculation of recombination frequencies according to the formulas in ref. 25. $P = 0.5 \pm D/Ip$, in which $D = \Sigma NS$ and $Ip = (8/3)n$ for *Ly-11–A* and $4n$ for *Ly-11–pa* and *Ly-6–pa*.
§ According to Green (25), when large recombination frequencies are being measured it is necessary to use the initial P_o values (*Ly-11–A* = 0.41; *Ly-11–pa* = 0.32; and *Ly-6–pa* = 0.21) to obtain a second, more exact estimate of *P*. This can be achieved by using the initial P_o values in conjunction with table 21 provided by Green (the appropriate table scores are shown). The formulas $D = \Lambda - P_o Ip$ and $Ip = ipn$ replace those given in footnote ‡; $P = 0.5 + D/Ip$ as before. Recomputation of *P* is valid only when χ^2 values associated with P_o are significant; i.e., $\chi^2 \geq 5.81$.
¶ The recombination frequencies calculated by the formulas of footnotes ‡ and § are given. The standard error = $1/(Ip)^{1/2}$ (25).
‖ $\chi^2 = D^2/Ip$ (25).

by its distance from *Ly-11* and *pa*. *Ly-6* maps 22 ± 12 units away from *pa* (Table 2) and 10 ± 2 units away from Ly-11 (16). The close genetic linkage of *Ly-6* with *Ly-11* has been previously established by several criteria, including linkage analysis and the strain distribution pattern among recombinant inbred mouse strains (24). It should be noted that several investigators have previously reported absence of linkage between *Ly-6* and *A* (14, 27). This is not surprising in view of our current results, which indicate that *Ly-6* is approximately 45 recombination units away from *A* (*Ly-6–pa* = 28 ± 5; *pa–A* = 16.7 ± 1.3). A very extensive genetic analysis would have been required to detect such linkage and the number of mice tested was generally too few in each case (14, 27) to provide evidence of linkage. Of greater concern, however, is the recent report by Horton and Hetherington (27) demonstrating linkage between *Ly-6* and *Thy-1* on chromosome 9. These workers used large numbers of mice and provided evidence of very close linkage (15.7 ± 2.1 recombination units). Using monoclonal antibodies to Ly-6.2, Thy-1.1, and Thy-1.2 and strain crosses similar to those used by these authors [e.g., (B10 × A.Thy-1.1)F_2], we had been unable to confirm their findings (data not shown). Lack of linkage between *Ly-11* and *Thy-1* is shown in Table 1. Furthermore, another chromosome 9 marker, *Fv-2*, a locus governing absolute resistance to the spleen focus-forming component of Friend virus (28), was also found to be unlinked to *Ly-11* (Table 1). Therefore, we conclude that Horton and Hetherington's anti-Ly-6.2 reagent [(CBA/Ca × A-Thy-1.1)F_1 anti-AKR/Crc thymocytes] probably contains contaminating antibodies reactive with antigen(s) coded for by chromosome 9.

Analysis of the *Ly-11* and *Ly-6* linkage to chromosome 2 was extended by examination of RI mouse strains. Such strains have been used by numerous investigators (22, 29, 30) to verify suspected linkage of various genetic loci. RI strains are developed by inbreeding F_2 generation offspring of dissimilar mouse strains. Alleles at all loci tend to become homozygous in the RI strains after 15–20 generations, and those that are linked tend to stay in the parental combination in which they initially occurred (29).

As shown in Tables 3, 4, and 5, the segregation of alleles of *Ly-11* with alleles of other loci on chromosome 2 in the BXH and SWXL and CXB RI strains (29, 31) also indicates linkage. Among the 11 BXH (Table 3) and 7 SWXL RI (Table 4) strains, there are six recombinants (including the three double recombinants) between *A* and *Ly-11*. There are also two recombinants

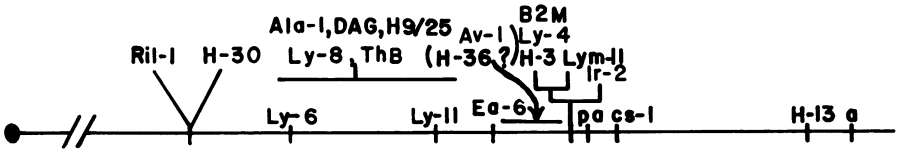

FIG. 1. Map of the *H-30*–agouti region of chromosome 2 as determined from studies reported here. Markers shown are primarily loci coding for lymphocyte and erythrocyte differentiation antigens. Only selected unrelated loci have been included in the map.

Table 3. Segregation of chromosome 2 markers and *Ly-11.2* and *Ly-6.2* in BXH RI strains

Strain	Loci			
	A	*Ly-4*	*Ly-11*	*Ly-6*
Parental				
C57BL/6	B	B	B	B
C3H/HeJ	H	H	H	H
RI				
BXH-2	B	–	B	B
BXH-3	H	B	H	H
BXH-4	B	B	B	B
BXH-6	H	B	B	B
BXH-7	B	B	H	H
BXH-8	H	H	H	H
BXH-9	H	H	H	H
BXH-10	B	H	B	B
BXH-11	B	H	B	B
BXH-12	H	H	H	B
BXH-14	H	H	H	B

Vertical bars indicate crossover location.

between *Ly-11* and *Ly-6* in the BXH RI strains (Table 3). In the SWXL (Table 4) there is one recombinant between *Ly-11* and *Ly-4* and four recombinants between *Ly-11* and *Hc*, a locus coding for hemolytic complement quite distant from *A* (42.9 ± 5.6 recombination units) (32). In the CXB series (Table 5), there are five recombinants (including double recombinants) between *A* and *Ly-11*, and none between *Ly-11* and *Ly-6*. These data may be used to estimate recombination frequency (*r*) (29, 33). The recombination frequency is estimated by the equation $r = R/(4 - 6R)$, in which *R* is the observed fraction of RI strains with recombinant genotypes. The standard error of the estimate of *r* is given by $[r(1 + 2r)(1 + 6r)^2/4N]^{1/2}$, in which *N* is the number of RI strains. Using these formulas, one obtains distances between *A* and *Ly-11* of 0.32 ± 0.21; between *Ly-11* and *Ly-6*, 0.06 ± 0.05; and between *Ly-11* and *Ly-4*, 0.15 ± 0.08. These values are within range of those obtained in the conventional segregation studies described above, although the value for *Ly-11–A* computed in this fashion is much less precise. The RI approach is not as desirable when such large recombination distances are involved (29).

A minor histocompatibility locus, *H-30*, has been shown to be tightly linked to *Ly-11* and *Ly-6* (24). The *H-30* locus is shown in Fig. 1 to the left of *Ly-6*. Several observations establish this location. First, the strain distribution pattern of *H-30* among Bailey's RI lines had been shown to be identical to that of *Ly-6* and *Ly-11* (24), indicating that *H-30* is tightly linked to these loci. Second, a mouse strain congeneic with C57BL/6, B6.C-*H-30*^{c}, has been generated by Bailey (31) by replacing the C57BL/6 *H-30*^{b} allele with the BALB/c *H-30*^{c} allele. Despite this substitution, B6.C-*H-30*^{c} and C57BL/6 are identical at *Ly-11* and *Ly-6* (24). Thus the chromosomal segment replaced (*H-30*) does not encompass *Ly-11* or *Ly-6*. *H-30* is therefore located adjacent (on either side) to *Ly-11* and *Ly-6* and represents a distinct locus. A third locus, *Ril-1*, conferring susceptibility to leukemia induction by fractionated irradiation has been previously shown to map to the left of *Ly-6* and *Ly-11*, 11 ± 2 and 20 ± 4 recombination units, respectively (16). This locus must be very close to *H-30* because, as shown in Fig. 2, the B6.C-*H-30*^{c} and C57BL/6 congeneic mouse strains differ markedly in their susceptibility to leukemia induced by fractionated irradiation. Therefore *H-30* must also map to the left of *Ly-6* and *Ly-11*.

It is actually surprising that B6.C-*H-30*^{c} mice are resistant to leukemia induced by fractionated irradiation because, as shown in Fig. 2, there is only a slight difference in susceptibility to this leukemia between C57BL/6 and BALB/c mice. However, we have shown elsewhere (34) that control of susceptibility to leukemia in C57BL/6 and BALB/c is under two-gene control and that B6.C-*H-30*^{c} mice carry the resistance allele at both loci by virtue of the replacement of the C57BL/6 *H-30* region with BALB/c genetic material. Table 5 gives the strain segregation pattern for *H-36*, a minor histocompatibility locus. This pattern suggests that this locus maps to the region of chromosome 2 to the left of *H-3*. *H-36* is the location of the Abelson virus-related oncogene, c-*abl* (unpublished data).

Table 4. Segregation of chromosome 2 and *Ly-11* markers in SWXL RI strains

Strain	Loci			
	A	*Ly-4*	*Ly-11*	*Hc**
Parental				
SWR	S	S	S	S
C57L/J	L	L	L	L
RI				
SWXL-4	S	S	S	L
SWXL-7	L	L†	S	S
SWXL-12	L	L	L	S
SWXL-14	L	L	L	S
SWXL-15	L	L	L	L
SWXL-16	S	S	S	S
SWXL-17	L	L	L	S

Vertical bars indicate crossover location.
* Data from R. Riblet and B. A. Taylor (personal communication).
† Despite numerous attempts, typing is unsure, but SWXL-7 appears to carry the C57L allele at *Ly-4*. One explanation for difficulties in typing the strain is that it is still segregating for *Ly-4* (because some SWXL-7 mice typed positive and some typed negative).

Table 5. Segregation of chromosome 2 and *Ly-11* markers in CXB RI strains

Strain	Loci*							
	A	*Cs-1*	(*Ly-4*, *β2M*, *H-3*)	*H-36*	*Ea-6*	*Ly-11*	*Ly-6*	*H-30*
Parental								
C57BL/6	B	B	B	B	B	B	B	B
BALB/c	C	C	C	C	C	C	C	C
RI								
CXBD	C	C	C	C	C	B	B	B
CXBE	C	B	B	B	B	B	B	B
CXBG	C	C	B	B	C	C	C	C
CXBH	B	B	C	C	B	C	C	C
CXBI	B	B	B	B	B	B	B	B
CXBJ	B	B	B	C	C	C	C	C
CXBK	B	B	B	B	B	B	B	B

Vertical bars indicate crossover location.
* Except for *Ly-11* and *Ly-6*, data have been taken from ref. 22. The H-30 data in ref. 22 are incorrect and have been taken from the original reference.

DISCUSSION

As stated in the Introduction, the region of chromosome between *H-3* and *H-13* has already been shown to contain loci coding for a variety of alloantigens, among which are H-3, H-13, Ly-4, Lym-11, β_2-microglobulin, and Pgp-1. The findings reported herein show that lymphocyte determinants H-30, Ly-6, and Ly-11 are also encoded by genes in the vicinity of *H-3* and therefore that this region of chromosome contains the tightly linked loci coding for Ala-1 (11), DAG (12), H9/25 (13), Ly-8 (14), and ThB (15).

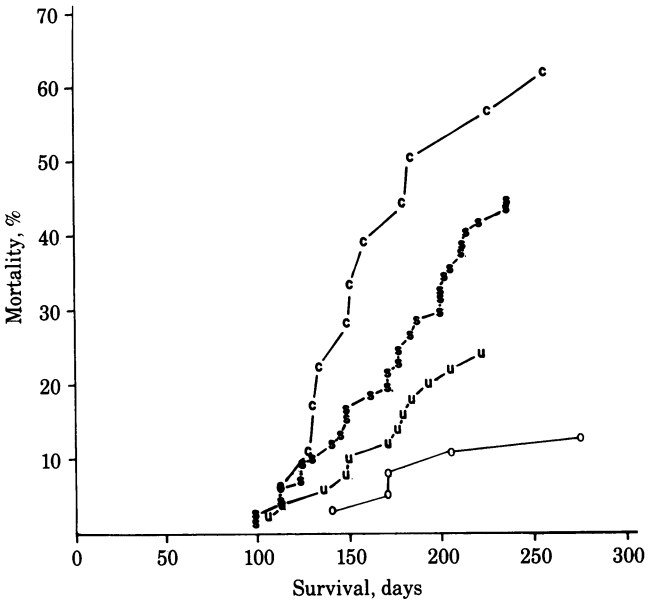

FIG. 2. Evidence that *Ril-1* and *H-30* are tightly linked. Susceptibility to fractionated irradiation by B6.C-*H-30*^{c} ($a^r a^r b^r b^r$) (o—o) is markedly less than that of C57BL/6 ($a^s a^s b^r b^r$) (c—c). While B6.C-*H-30*^{c} mice derived *H-30*^{c} from BALB/c ($a^r a^r b^s b^s$) (s—s), which are only slightly less susceptible than C57BL/6, this substitution renders B6.C-*H-30*^{c} resistant because two genes are involved in susceptibility to fractionated irradiation. The genotypes at both loci for each strain are given in parentheses. (C57BL/6 × BALB/c)F_1 ($a^r a^s b^r b^s$) (u—u) are also resistant.

There are several questions raised by these findings, but the most important, perhaps, is whether the clustering of these loci has any special significance. Relevant to this issue is the finding of several virus susceptibility loci in this section of chromosome. A locus affecting susceptibility to radiation leukemia virus (*RLVil-1*) also maps here (34), and a cellular oncogene (c-*abl*) related to a virus oncogene maps in this chromosome (35, 36). It may be speculated that this segment of chromosome plays a special role in viral infections because of the multitude of lymphocyte differentiation loci found therein.

At the present time the best approach to ascertain the significance of the clustering of these loci will come from biochemical, functional, and cellular characterization of the antigens encoded by these genes. Some similarities and dissimilarities have been noted thus far in the tissue and lymphocyte subpopulation distribution of most of these alloantigens. For example, Ly-8, Ly-6, H9/25, ThB, β_2-microglobulin, Ly-4, and Ly-11 have all been found on plaque-forming cells (13, 37–39). Ly-6, Ly-8, DAG, Ala-1, and H9/25 have been described as markers on mature T lymphocytes, but ThB is present on immature thymocytes (38), Ly-6 and Ala-1 are on helper and killer cells (22); H9/25 is found on killer but not on helper lymphocytes (13). Ly-11 is found on natural killer cells, but not on helper, suppressor, or cytotoxic T cells (37). In addition some of these alloantigens are found on virtually 100% of lymphocytes (i.e., β_2-microglobulin, H-3, H-13) whereas others (i.e., Ly-6, Ly-11, Ala-1, DAG, and H9/25) are expressed in only a small percentage of lymphocytes (13, 24, 31, 37).

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