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Chromosomal Assignment of Two Endogenous Ecotropic Murine Leukemia Virus Proviruses of the AKR/J Mouse Strain

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The AKR/J mouse strain is genetically fixed for three different ecotropic murine leukemia virus genomes, designated *Akv-1*, *Akv-3*, and *Akv-4* (*Emv-11*, *Emv-13*, and *Emv-14*). With recombinant inbred strains and crosses with linkage-testing stocks, *Akv-3* and *Akv-4* were placed on the mouse chromosome map. *Akv-3*, which encodes a replication-defective provirus, maps near the agouti coat color locus, *a*, on chromosome 2. *Akv-4*, which is replication competent, maps near the neurological mutant gene locus trembler, *Tr*, on chromosome 11. *Akv-1* and *Akv-2* (*Emv-12*), an ecotropic provirus carried by AKR/N but not AKR/J, have previously been mapped to chromosome 7 and 16, respectively. Thus, the four *Akv* proviruses mapped to date are on four different chromosomes. *Akv-3* is the second ecotropic murine leukemia virus provirus to be mapped near the agouti locus. The results are discussed in relation to possible nonrandomness of viral integration.

The AKR mouse strain is the prototype strain for the study of spontaneous thymoma. Endogenous proviruses found in various AKR substrains are known to play a crucial role in the etiology of the disease (19, 22, 23). These proviruses confer a viremic state to their hosts unless there are genetic restrictions to the cell-to-cell spread of infectious murine leukemia virus (MuLV). After mice reach 6 months of age, xenotropic virus and recombinant mink cell focus-forming viruses begin to appear. It is the latter that appear to have the greatest potential for inducing early T-cell lymphomas. By classical genetic crosses and monitoring viral expression, it was shown that both AKR/J and AKR/N sublines carry two ecotropic proviruses which encode infectious MuLV. One of these was designated *Akv-1* and mapped to chromosome 7 (24). The application of Southern blotting techniques produced an unexpected result. Although all AKR substrains share a single provirus (*Akv-1*), the number and sites of integration of other *Akv* loci show considerable variability. In particular, while the AKR/N and AKR/J sublines share two *Akv* loci (*Akv-1* and *Akv-3*), each carries an additional *Akv* locus denoted *Akv-2* (present in AKR/N) and *Akv-4* (present in AKR/J) (3, 21, 25). *Akv-2* has been mapped to chromosome 16 (16). In this study we describe the mapping of *Akv-3 and Akv-4*.

MATERIALS AND METHODS

DNA isolation, restriction enzyme analysis, DNA transfers, and hybridization. DNAs were prepared from frozen spleens that had been stored at −70°C (14). DNAs (10 μg per lane) were digested to completion with an excess of restriction enzyme under reaction conditions described by the manufacturer (Bethesda Research Laboratories, Inc., Bethesda, Md.). The digested DNAs were electrophoresed in 0.6% agarose gels and transferred to nitrocellulose filters as described previously (14). Filters were hybridized with the ecotropic virus-specific probe isolated by Chattopadhyay et al. (4) that had been labeled with ^{32}P (>2 × 10^8 cpm/μg of DNA) by nick translation. Filters were washed, air dried, and autoradiographed at −70°C with Kodak XAR-5 film and Du Pont Lightning-Plus intensifying screens (14).

Typing mice for biochemical variants. Mouse saliva was collected and typed for the parotid secretory protein electrophoretic variant (*Psp*) by previously described methods (20). Mature male mice were typed for the seminal vesicle protein-1 variant (*Svp-1*) by polyacrylamide electrophoresis of seminal vesicle fluids (21). Glucose phosphate isomerase-1 (Gpi-1) and β-hemoglobin (Hbb) phenotypes were determined by cellulose acetate electrophoresis of erythrocyte lysates (7, 9). Esterase-1 and -3 (Es-1 and Es-3) phenotypes were determined on kidney homogenates by electrophoresis in a 5% polyacrylamide gel at 250 V for 2 h. Staining for esterases with α-napthyl butyrate as substrate was by the method of Ruddle et al. (25). Phenotypes for serum protein-1 (Sep-1) and serum prealbumin protein-1 (Pre-1) were determined by electrophoresis of serum on cellulose acetate plates and polyacrylamide gels, respectively (8, 28).

RESULTS

Linkage between *Akv-3* and *Psp* locus. Linkage between *Akv-3* and *Psp* (20) was detected when the AKXD recombinant inbred (RI) strains, derived from crossing AKR/J and DBA/2J, were typed with respect to *Psp*. The *Psp* locus controls an elecrophoretic variant of a protein secreted into mouse saliva by the parotid gland. This locus had previously been mapped to chromosome 2 near the agouti coat color locus (*a*). Typing 27 AKXD RI strains for *Psp* revealed close linkage with the *Pvu*II restriction fragment associated with *Akv-3*. The assignment of *Akv* proviruses by Southern analysis of *Pvu*II-digested DNA was done as previously described (14, 15). Of the 27 strains typed (two of these are now extinct), only one crossover strain (AKXD-13) was detected. This strain inherited *Akv-3* from AKR/J and the Psp^a allele (fast electrophoretic form) from DBA/2J. The distribution of ecotropic proviruses among the AKXD RI strains has been described previously (14). Since unlinked genes are expected to reassociate randomly in RI strains, the great excess (26:1) of parental-to-recombinant genotypes is strong evidence for linkage between *Psp* and *Akv-3*. Based on the equation used for estimating recombination frequencey from RI strain data (28), we estimate recombination frequency to be 0.01 ± 0.01. The 95% confidence limits of recombination frequency (com-

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TABLE 1. Segregation of chromosome 2 markers in C57L/J × (AKXL-8 × RSV/Le)F_1 test cross (cross I)

Progeny class	Gametes from F1 parent				No. of progeny (males)	
	Sd	*a*	*Akv-3*	*Svp-1*	Total	Non-*Va*/+[a]
1	+	*a*	+	*b*	11	5
2	*Sd*	+	−	*a*	8	6
3	+	+	−	*a*	14	7
4	*Sd*	*a*	+	*b*	11	5
5	+	*a*	−	*a*	2	0
6	*Sd*	+	+	*b*	1	0
7	+	*a*	+	*a*	1	0
8	*Sd*	+	−	*b*	1	0
9	+	+	+	*b*	1	0
10	*Sd*	*a*	−	*a*	1	0

[a] Because of the effect of the varitint (*Va*) gene on coat color, the scoring of agouti (*a*) is considered reliable only in the nonvaritint (+/+) progeny.

puted from a table of binomial confidence limits) are 0.0002 and 0.066.

Genetic cross to map *Akv-3* with respect to other chromosome 2 loci. In an attempt to determine the position of *Akv-3* in the chromosome 2 linkage map, a four-point test cross was analyzed. The cross selected was C57L/J × (AKXL-8 × RSV/Le)F_1 (referred to as cross I). C57L/J was chosen as the test cross parent because it carries no ecotropic proviruses. An RI strain derived from the cross between AKR/J and C57L/J, AKXL-8, was used as the source of the *Akv-3* provirus rather than AKR/J for two reasons. Firstly, in addition to the three AKR proviruses inherited from AKR/J, AKXL-8 carries a new provirus reinsertion (27), and secondly, it has inherited the *b* allele from C57L/J at the *Svp-1* locus, which is situated approximately 10 map units distal to the agouti locus. The RSV/Le strain is a linkage-testing stock which carries three dominant visible markers: *Re* (rex) on chromosome 11, *Sd* (Danforth short tail) on chromosome 2, and *Va* (varitint waddler) on chromosome 3. RSV/Le had been shown previously to have the *Svp-1*[a] allele. It also carries the wild-type (+) allele at the agouti locus, in contrast to AKXL-8 and C57L/J, which each carry the recessive nonagouti (*a*) allele. The cross could also be scored with respect to two biochemical markers on chromosome 7, *Hbb* and *Gpi-1*, and thus, we could glean further data about the position of *Akv-1*. The *Sd* mutation, which marks the proximal region of chromosome 2, shows relatively free recombination with distal markers and was not expected to be helpful in pinpointing the position of *Akv-3*. Finally, it should be noted that RSV/Le carries the ecotropic provirus designated *Cv* (or *Emv-1*) found in BALB/c and related strains which maps to chromosome 5. Males were used since *Svp-1* can only be scored in males. The segregation of the chromosome 2 markers is shown in Table 1. Difficulty was encountered in scoring the *Va*/+ test cross progeny with respect to the agouti locus. The aberrant distribution of *a*–*Akv-3* crossovers among the *Va*/+ and the +/+ classes reinforced our misgivings; five crossovers were scored among the 26 *Va*/+ progeny, while none was scored among the 23 nonvaritint (+/+) progeny (heterogeneity chi-square test: $\chi^2_1 = 4.9$; $P < 0.05$). Thus we are only confident in the agouti scoring of the 23 nonvaritint progeny. On the basis of the complete linkage between *a* and *Akv-3* in the 23 nonvaritint progeny, we can say that the linkage to chromosome 2 is confirmed and that the 95% upper confidence limit of the recombination frequency is 0.15. Among the 49 progeny scored for *Akv-3* and *Svp-1*, only two crossovers were detected, for an estimated recombination frequency of 0.041 ± 0.028 (95% confidence limits, 0.005 and 0.135). Thus *Akv-3* shows close linkage to both *a* and *Psp*, but the data do not permit a determination of gene order.

Linkage of *Akv-4* to *Re* on chromosome 11. The choice of the C57L/J × (AKXL-8 × RSV/Le)F_1 cross permitted testing for linkage between *Akv-4* and each of the three dominant markers *Re*, *Va*, and *Sd*. This proved to be a fortuitious choice, as strong linkage was observed between *Akv-4* and the chromosome 11 marker *Re*. Of the 49 test cross progeny scored, 21 were *Re Akv-4*$^-$, 22 were + *Akv-4*$^+$, 1 was *Re Akv-4*$^+$, and 5 were + *Akv-4*$^-$, for an estimated recombination frequency of 0.12 ± 0.05. These results deviate significantly from independent assortment ($\chi^2_1 = 28.8$; $P < 0.0001$). In an effort to more precisely locate *Akv-4* on chromosome 11, the following matings were made: (AKR/J × C57BL/6Ei-*Re Tr*^{J})F_1 females were mated to C57L/J males, and (C57BL/6ei-*Re Tr*^{J} × AKR/J) F_1 females were mated to C57BL/6J males. (The data from these matings were combined and are referred to as cross II data.) The trembler locus (*Tr*) is near the middle of chromosome 11, and *Re* is 20 centimorgans (cM) distal to *Tr*. The mice were also typed with repect to the *Es-3* electrophoretic marker. The *Es-3* locus is about 19 cM distal to *Re*. The results are tabulated in Table 2. Among the 49 progeny analyzed, only two crossovers were observed between *Akv-4* and *Tr*, for an estimated recombination frequency of 0.041 ± 0.028 (95% confidence limits, 0.005 and 0.135). Linkage with *Re* was relatively loose (18 recombinants among 49 progeny), with an estimated recombination frequency of 0.37 ± 0.07. This estimate of the *Akv-4* to *Re* recombination frequency was significantly different at the 1% level (as judged by the χ^2 test for heterogeneity) from the frequency obtained in cross I. This difference might be accounted for by sex differences in recombination frequency or unidentified genetic factors. Since one of the two *Tr*–*Akv-4* crossovers must be a double crossover with respect to *Re*, the data from this cross do not discriminate between the two possible gene orders: *Akv-4-Tr-Re-Es-3* and *Tr-Akv-4-Re-Es-3*.

Other ecotropic proviral loci. Additional linkage data were collected with respect to other ecotropic proviruses segregating in these crosses. Thus, the linkage of *Akv-1* with respect to the *Gpi-1* and *Hbb* loci was confirmed and further quantified (Table 3). The recombination frequency between *Akv-1* and *Gpi-1* in cross I (hybrid male) was 0.163 ± 0.053. In cross II (hybrid female), the frequency was 0.128 ± 0.049. The combined estimate, 0.146 ± .036, agrees well with the previous estimate 0.121 ± 0.028 (22) based on recombination

TABLE 2. Four-point test cross mapping of *Akv-4* on chromosome 11[a]

Progeny class	Gametes from F1 parent				No. of progeny
	Akv-4	*Tr*	*Re*	*Es-3*	
1	+	+	+	*c*	11
2	−	*Tr*^{J}	*Re*	*a*	15
3	+	*Tr*^{J}	*Re*	*a*	1
4	+	+	*Re*	*a*	8
5	−	*Tr*^{J}	+	*c*	8
6	+	+	+	*a*	3
7	−	*Tr*^{J}	*Re*	*c*	1
8	+	*Tr*^{J}	+	*c*	1
9	+	+	*Re*	*c*	1

[a] The cross involved mating (C57BL/6Ei-*Re Tr*^{J} × AKR/J)F_1 females (or the reciprocal F_1 females) to C57L/J (or C57BL/6J) males.

TABLE 3. Segregation of *Akv-1* and other chromosome 7 markers in crosses I and II

Progeny class[a]	Gametes from F1 parent			No. of progeny
	Akv-1	*Gpi-1*	*Hbb*	
Cross I				
1	+	*a*	*d*	13
2	−	*b*	*s*	13
3	+	*b*	*s*	3
4	−	*a*	*d*	5
5	+	*a*	*s*	7
6	−	*b*	*d*	8
Cross II				
1	+	*a*	*d*	11
2	−	*b*	*s*	13
3	+	*b*	*s*	2
4	−	*a*	*d*	3
5	+	*a*	*s*	7
6	−	*b*	*d*	10
7	−	*a*	*s*	1

[a] Cross I, C57L/J × (RSV/Le × AKXL-8)F_1; cross II, (AKR/J × C57BL/6Ei-*Tr*^{J} *Re*)F_1 × C57L/J or (C57BL/6Ei-*Tr*^{J} *Re* × AKR/J)F_1 × C57BL/6J.

in males. Recombination between the ecotropic provirus of C57BL/6J (designated *Bv* or *Emv-2*) and the *Es-1* locus on chromosome 8 was estimated to be 0.39 ± 0.10, based on 23 progeny from the (AKR/J × C57BL/6Ei-*Re Tr*^{J})F_1 × C57L/J cross. This compares with a previously published (17, 18) frequency of 0.26 ± 0.05 and also with our own unpublished data from another cross [(C57BL/6J × C3H/HeJ)F_1 × C57L/J], in which a frequency of 0.20 ± 0.06 was obtained. A combined estimate is 0.261 ± 0.035. No linkage was detected between the newly acquired provirus of AKXL-8 and any of the other markers scored in the (AKXL-8 × RSV/Le)F_1 × C57L/J cross. These included (number of recombinants per number of progeny): chromosome 2, *Sd* (26 of 49), *a* (23 of 49), and *Svp-1* (26 of 49); chromosome 3, *Va* (24 of 49); chromosome 5, *Cv* (29 of 48); chromosome 7, *Akv-1* (24 of 49) and *Hbb* (22 of 49); chromosome 9, *Alp-1* (28 of 49); chromosome 11, *Akv-4* (28 of 49) and *Re* (27 of 49); and chromosome 12, *Pre-1* (22 of 49). Thus, this germ line reinsertion, which evidently occurred during the inbreeding of AKXL-8, is not integrated near any other AKR/J proviruses or the BALB/c provirus *Cv*.

Segregation of *Akv-3* and *Akv-4* in AKXL RI strains. Previously published data on the strain distribution patterns of *Akv-3* and *Akv-4* in the AKXL RI strains failed to reveal significant linkage with any other genetic markers (27). In retrospect, one can see that the *Akv-3* segregation is consistent with chromosome 2 linkage [4 of 18 recombinants with β-2-microglobulin (*B2m*) and 6 of 18 recombinants with *Svp-1*],while the *Akv-4* segregation is consistent with linkage to *Es-3* on chromosome 11 (5 of 18 recombinants with *Es-3*) (Table 4).

DISCUSSION

The results presented permit chromosomal assignment and localization of two (*Akv-3* and *Akv-4*) of three ecotropic MuLV proviruses characteristic of the AKR/J substrain. The *Akv-1* provirus, which is thought to have been the original germ line provirus of AKR mice, had been previously mapped to chromosome 7 (24). Many individual AKR/J mice have been reported to carry one or more additional *Akv* proviruses in either heterozygous or homozygous states (11). New proviruses have become fixed in the germ line of various sublines of the AKR strain at a rate of one per 15 years of inbreeding (27). One of these proviruses, *Akv-2*, which is present in AKR/N mice but absent from AKR/J mice, has been mapped to chromosome 16 (16). Thus, four different *Akv* proviruses map to four different chromosomes, a finding consistent with random reintegration. It is of interest, however, that *Akv-3* is the second ecotropic provirus to map near the agouti locus. Previously, a unique ecotropic provirus was described which is closely linked to the agouti locus and found in association with the lethal yellow (A^y) coat color mutation (6). Because of difficulties in classification, our data do not permit a precise placement of *Akv-3* with respect to agouti. Nonetheless, such data as there are suggest that *Akv-3* and *a* are within 5 cM of each other. A germ line reinsertion in the B10.BR/SgLi strain, designated *Bbv*, has been mapped to chromosome 11, (17). However, it would appear that *Bbv* is at least 20 cM distal to *Akv-4*. The C57BL/6 provirus *Bv* (*Emv-2*) maps in the same vicinity of chromosome 8 as does one of the proviruses of strain C58, *C58v-1* (17). Thus, there may be some tendency for germ line reinsertions to occur preferentially in certain chromosomal regions.

Not all proviruses are infectious; mice bearing *Akv-3* as their only ecotropic provirus never express infectious ecotropic virus (1, 12). However, the defectiveness of *Akv-3* can be complemented with the *Dbv* (*Emv-3*) provirus, which is itself apparently defective (5). The tissue-specific expression of Moloney MuLV in mouse strains transfected with Moloney MuLV appears to be very dependent on chromosomal position (13). Comparable differences in tissue specificity of expression have not been observed for different *Akv* reinsertions. Thus, expression of *Akv* proviruses appears to

TABLE 4. Segregation of *Akv-3* and AKV-4 with linked markers in AKXL RI strains

Locus	AKXL RI strain																	
	5	6	7	8	9	12	13	14	16	17	19	21	24	25	28	29	37	38
B2m	L[a]	L	L	A[a]	L	A	L	L	L	A	L	L	A	A	A	L	A	L
					×[a]				×	×	×							
Akv-3	L	L	L	A	A	A	L	L	A	L	A	L	A	A	A	L	A	L
	×	×	×	×			×				×							
Svp-1	A	A	A	L	A	A	A	L	A	L	L	L	A	A	A	L	A	L
Akv-4	A	A	A	A	L	L	A	A	L	A	A	L	A	L	L	L	A	A
		×	×				×	×					×					
Es-3	A	L	L	A	L	L	L	L	L	A	A	L	L	L	L	L	A	A

[a] The letters A and L are used as generic symbols for alleles inherited from progenitor strains AKR/J and C57L/J, respectively. The symbol × is used to denote crossover regions.

be a function of the integrity of the proviral sequence rather than chromosomal position.

As additional polymorphic loci are mapped in RI strains derived from AKR/J (the AKXL and AKXD RI sets), it should be possible to localize *Akv-1*, *Akv-3*, and *Akv-4* more precisely in the mouse linkage map. The *Akv-4* provirus provides a marker for the middle of chromosome 11 in the RI strains and extends the portion of the mouse genome covered by mapped loci. The *Akv-3* provirus and flanking cellular sequences have been molecularly cloned (5), and subclones of the latter may prove useful for the molecular analysis of the agouti region of chromosome 2.

Our *Akv-1* linkage data confirm the placement of *Akv-1* proximal to *Gpi-1* on chromosome 7. When we combine our cross I data with previously published data (24), there are 22 crossovers among 162 progeny, for an estimated recombination frequency (males) of 0.136 ± 0.027. The estimated frequency in cross II (female recombination), 0.128 ± 0.049, does not differ significantly from the estimate for male recombination. Since the centromere to *Gpi-1* interval has been estimated to be 11.3 ± 1.2 cM, based on the frequency of *Gpi-1* allelic segregation in ovarian teratomas (10), the *Akv-1* locus must be near the centromere. However, there is no basis for assignment of *Akv-1* to a particular band of chromosome 7.

The placement of *Akv-3* near agouti probably means that *Akv-3* is located within the lightly staining (Giemsa) band H3 near the distal end of chromosome 2 (26). *Akv-4* may lie near the breakpoint of the T30H reciprocal translocation, which has the lightly staining Giemsa band B1 as its chromosome 11 breakpoint (2). This would place *Akv-4* near the middle of the chromosome. Since the location of both *Akv-4* and the T30H breakpoint in the chromosome 11 linkage map are both rather tentative, the assignment of *Akv-4* to the B1 band is only provisional. Thus, additional genetic and cytogenetic mapping data are needed to address the question whether AKV proviral insertions tend to be nonrandom relative to the Giemsa-banding patterns of chromosomes.

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