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Genetics

Akvr-1, a dominant murine leukemia virus restriction gene, is polymorphic in leukemia-prone wild mice

(murine leukemia virus regulation/retrovirus control gene)

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ABSTRACT **We describe a restriction gene (*Akvr-1*, for AKR virus restriction) that is polymorphic for two alleles, *Akvr-1*^{R} (restrictive) and *Akvr-1*^{r} (susceptible), in a feral population of mice (*Mus musculus domesticus*) at a squab farm near Lake Casitas (LC) in southern California. *Akvr-1*^{R} is a dominant allele that exhibits 100% penetrance in prevention of viremia of AKR endogenous retrovirus and of virus-mediated lymphoma in LC (*Akvr-1*^{RR}) × AKR F_1 hybrids. The restriction phenotype segregates as a single Mendelian locus in backcrosses to AKR mice. *Akvr-1*^{R} likewise is effective in restriction of NB-tropic Moloney murine leukemia virus-induced viremia and NB-tropic Friend virus-induced splenomegaly but fails to restrict expression or pathogenesis of LC-derived amphotropic retrovirus. Pleiotropic restriction of AKR, Friend, and Moloney ecotropic viruses, but not of amphotropic virus, suggests that the viral targets of *Akvr-1* in the three ecotropic viruses are similar to each other and distinct from the target in the LC-amphotropic virus. The relationship of *Akvr-1* to previously reported murine restriction loci *Fv-1*, *Fv-2*, and *Fv-4* is discussed.**

Inbred and wild mouse strains contain multiple DNA sequences in their chromosomal DNA that are homologous to type C RNA tumor viruses and that become expressed, spontaneously or after induction, in a genetically determined pattern (1–5). A number of classes of retrovirus have been isolated from leukemic and nonleukemic mouse tissues, and it is rapidly becoming apparent that endogenous retrovirus genes differ among themselves and in general occupy distinct chromosomal positions in the mouse genome (6–8). Endogenous viral genes differ from each other in competence and degree of expression, in inducibility in various strains, in host range of recovered virus, in immunologic determinants of encoded structural proteins, and in response to regulatory loci that govern expression of endogenous and exogenous retroviruses (9). The interaction of endogenous cellular virogenes and *trans*-acting restriction genes in the mouse is an intriguing area of mammalian genetics which promises to be of use in resolving the developmental progression of virus-associated murine leukemia.

The AKR mouse strain possesses two unlinked retrovirus structural loci, *Akv-1* and *Akv-2*, which are spontaneously expressed early in life as infectious ecotropic virus (6). In addition, a dual-tropic virus (MCF) has been detected in the thymus of late preleukemic AKR mice (10). The dual-tropic MCF virus is apparently an *in situ* genetic recombinant between endogenous ecotropic and xenotropic AKR virogenes (11). The developmental sequence of ecotropic and dual-tropic virus expression in AKR mice is clearly related to the onset of leukemogenesis and to the increased lymphoma incidence present in this strain (12).

Expression of AKR viremia and associated lymphoma is prevented by alleles of two previously described restriction genes, *Fv-1* (13) and *Fv-4* (14). We have discovered an additional restriction gene (*Akvr-1*) segregating in wild mice from the Lake Casitas (LC) area in rural southern California. The *Akvr-1*^{R} allele effectively prevents viremia and lymphoma in LC × AKR hybrids as well as the *in vivo* growth of both Moloney and Friend murine leukemia virus (MuLV). *Akvr-1*^{R} does not restrict the expression and tumor promotion of amphotropic virus indigenous in LC mice (15). The locus appears to be phenotypically distinct from *Fv-1* but cannot at this time be separated from the *Fv-4* locus described in Japanese mice (*Mus musculus molossinus*).

MATERIALS AND METHODS

Mice. Wild mice (*Mus musculus domesticus*) were trapped at a squab farm in southern California near LC. This population of mice is characterized by a high level of infectious MuLV expression and related splenic non-T-cell lymphoma (16, 17) and paralysis (18) occurring mainly after 1 year of age. In most LC mice the congenitally acquired MuLV leads to lifelong viremia and specific immunologic tolerance (19–21). The infectious MuLV show either a wide *in vitro* host range with growth in cells of both murine and heterologous species ("amphotropic") or their growth is restricted to murine cells ("ecotropic") (22–24). Only the ecotropic viruses register in the XC test and usually produce small plaques atypical of conventional murine ecotropic virus. In LC wild mice the amphotropic virus is by far the more prevalent and high-titered and is generally the only virus readily detected in sera of young healthy animals.

All amphotropic and ecotropic LC virus isolates tested have been N-tropic for mouse cells, and LC mice, whether infected or uninfected, appear to be monomorphic for *Fv-1*^{N} (refs. 22–24; unpublished data). Amphotropic virogenes are endogenous in LC and other wild and laboratory mice (5) but perhaps not in all wild mice (25). However, the virus has so far been recovered only from feral mice in southern California. About 10% of LC mice escape congenital infection and remain persistently nonviremic and free of lymphoma or paralysis until at least 18 months of age (20). By selective breeding we have produced separate laboratory colonies of infected and uninfected LC progeny. Eleven first-generation (F_1) laboratory-bred LC wild mice and seven LC mice trapped in the wild were typed for MuLV and bred to AKR inbred mice obtained from The Jackson Laboratory. In addition, seven wild mice from another trapping area, a squab farm in Bouquet Canyon (BC), CA, were also mated to AKR mice. BC wild mice are heavily infected with indigenous polyoma virus but show a low level

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Abbreviations: LC, Lake Casitas, CA; MuLV, murine leukemia virus; BC, Bouquet Canyon, CA; FA, fluorescent antibody; FFFU, fluorescent focus-forming units.

of natural MuLV activity and a low incidence of leukemia (26).

Assay for Infectious Endogenous MuLV. Sera were obtained, by retroorbital puncture, from parental mice and AKR × wild mouse hybrid progeny at 6–8 weeks of age, diluted 1:5 with phosphate-buffered saline, and assayed for infectious MuLV on wild mouse SC-1 cells (27) by a fluorescent antibody (FA) focus induction method (28). The borderline sensitivity of this assay is $10^{1.2}$ fluorescent focus-forming units/ml (FFFU/ml). The SC-1 cell detects total infectious virus, whether amphotropic or ecotropic. Amphotropic virus was detected by FA on the basis of growth for 6 days in rabbit cornea (SIRC) or human sarcoma (1080) cells; ecotropic virus was detected by the XC test from virus grown for 6 days in SC-1 cells. Compared to the AKR ecotropic virus, the wild mouse ecotropic viruses give small, atypical XC plaques. UV-irradiated virus-exposed SC-1 cells were overlaid with XC cells without serial passage *in vitro* (direct XC test). The level of sensitivity for detection of either MuLV class was the same—$10^{1.5}$ FFFU/ml. Sera were stored at −70°C for up to 6 months before testing.

Assays for Concordant Resistance to Exogenous NB-tropic MuLV. Offspring of mice previously typed for their *Akvr-1* genotype were inoculated intraperitoneally as newborns with 0.05 ml of a tissue culture pool of NB-tropic Moloney MuLV of titer $10^{4.7}$ and $10^{4.2}$ FFFU/ml on NIH Swiss and BALB/c 3T3 cells, respectively. Viremia was determined by the FA method in SC-1 cells at 2 months of age. Similarly, mice of known *Akvr-1* genotype were challenged at 5–6 months of age with NB-tropic Friend MuLV (a mixture of spleen focus-forming virus and Friend leukemia helper virus). Each mouse was inoculated intraperitoneally with 0.2 ml of a 1:100 dilution of a fresh 10% splenic tumor extract of titer $10^{5.3}$ and $10^{4.6}$ FFFU/ml on NIH Swiss and BALB/c 3T3 cells, respectively, and the spleen weight was determined after 9 days (29).

RESULTS

Evidence for a Dominant AKR Virus Restriction Gene Polymorphic in LC Wild Mice. Each of 18 LC wild mice was bred to a different AKR mouse, and each pair gave rise to one or more litters (Table 1). The LC parents were typed for the exogenous (non-germ-line) amphotropic retrovirus found in 85% of LC mice prior to breeding. Because this virus is transmitted maternally, only virus-negative LC females were used. Viremic males fail to transmit virus vertically, so all of their F_1 viremia would be expected to be of AKR origin (see below).

Three classes of LC phenotypes were evident from the results of the LC × AKR cross: (*i*) those that produced nonviremic F_1 mice (0 of 90 mice in 15 litters); (*ii*) those that produced ≈50% viremic F_1 mice (25 of 53 mice in 8 litters); and (*iii*) those that produced nearly 100% viremic F_1 offspring (71 of 74 mice in 15 litters). In viremic mice, the virus titer was consistently $10^{2.0}$–$10^{3.0}$ FFFU/ml with slight litter variation. The three observed LC phenotypes presumably represent three genotypic classes of a polymorphic restriction gene (here named *Akvr-1*)—namely, *Akvr-1*^{RR}, *Akvr-1*^{rr}, and *Akvr-1*^{Rr}, (*R* is the dominant allele for restriction of AKR virus induction or expression and *r* is the recessive permissive or susceptible allele).

Confirmation of the single dominant gene proposition comes from examination of LC (*Akvr-1*^{RR}) × AKR F_2 mice and backcrosses to AKR (Table 2). The F_1 hybrids selected for these matings were progeny of an LC male (24468 in Table 1) homozygous for this resistance allele (*RR*); thus, each F_1 would be heterozygous (*Rr*). Viremia of comparable titer (10^2–10^3 FFFU/ml) was detected in 14% (6 of 43 mice in 5 litters) of the F_2 mice and 46% (37 of 81 in 10 litters) of the backcross animals with no difference related to sex of the AKR parent (Table 2). A single dominant gene effect would predict 25% and 50% viremia, respectively, in these crosses. The differences between observed and expected numbers in a single dominant gene model in the backcross and F_2 hybrids were not statistically significant ($P = 0.63$ and 0.13, respectively). These results thus appear to be consistent with segregation, in LC mice, of a single dominant gene for suppression of AKR virus.

Table 1. MuLV viremia in LC × AKR F_1 hybrids

LC wild mouse no. and endogenous virus status*	Sex	No. of litters	No. viremic*/ no. tested at 2 months		*Akvr-1* genotype of LC parent
18732 (+)†	M	2	0/7		
24468 (−)‡	M	5	0/32		
27258 (−)‡	M	2	0/16		*RR*
27260 (−)‡	M	2	0/15		
27261 (−)‡	M	2	0/7		
27749 (−)§	F	2	0/13		
Total		15	0/90	(0%)	
24467 (−)‡	M	3	12/27		
25774 (+)¶	M	1	3/6		
27085 (−)	M	1	5/8		*Rr*
27746 (−)§	F	1	1/2		
27748 (−)§	F	2	4/10		
Total		8	25/53	(47%)	
17523 (+)†	M	2	8/8		
18733 (+)†	M	2	10/10		
24466 (−)‡	M	3	22/23		
25771 (+)¶	M	1	5/5		*rr*
25773 (+)¶	M	3	13/13		
24462 (−)‡	F	3	10/12		
27747 (−)§	F	1	3/3		
Total		15	71/74	(96%)	

* Viremia was determined in LC parental and AKR hybrid mice by the fluorescent focus induction method (28) on SC-1 cells at 6–8 weeks of age. (+) = viremic; (−) = nonviremic. The average titer of the positive sera was $10^{2.7}$ FFFU/ml. The borderline sensitivity of this assay was $10^{1.2}$ FFFU/ml.

† Viremic and presumably unrelated LC mice born and trapped in the wild and then bred to AKR mice.

‡ Nonviremic LC mice littermates born in the laboratory from uninfected parents trapped in the wild.

§ Three nonviremic LC mice were littermates born in the laboratory from uninfected parents trapped in the wild. The father of this litter (27085) was also bred to an AKR female.

¶ Viremic LC mice littermates born in the laboratory from infected parents trapped in the wild.

Table 2. Infectious MuLV in AKR × LC progeny segregating for the *Akvr-1*^{R} allele

Cross*		No. of litters	No. viremic/ no. tested	Frequency, %
Female	Male			
AKR	AKR	7	21/21	100
LC (+)	LC (+)	10	39/44	88
LC (−)	LC (−)	10	0/42	0
AKR	LC (24468)†	5	0/32	0
AKR	LC (24468)F_2	5	6/43	14
[AKR × LC (24468)]F_1	AKR	5	18/40	45
AKR	[AKR × LC (24468)]F_1	5	19/41	46

* (+) = viremic with endogenous amphotropic MuLV: (−) = nonviremic with endogenous amphotropic MuLV.

† Nonviremic LC mouse of *Akvr-1*^{RR} genotype (Table 1).

The Restricted Virus is AKR Ecotropic Virus. Viremic sera taken at 2 months of age from several AKR × LC F_1 hybrids were retested for host range and XC plaque properties. In crosses between AKR females and LC^{rr} (or LC^{Rr}) males, regardless of whether or not the LC males were infected with endogenous amphotropic virus, the serum virus in eight of eight F_1 hybrids grew only in SC-1 cells and gave large XC plaques typical of AKR ecotropic virus. This result was expected because it was previously shown that LC males do not transmit infectious amphotropic MuLV vertically (20). In crosses between AKR males and uninfected LC^{rr} females the virus in three of these progeny again grew only in SC-1 cells and gave large XC plaques typical of AKR virus. Thus, this virus was also of AKR origin, a finding consistent with our previous observation that uninfected LC females do not transmit infectious virus to their progeny (20). However, when viremic LC^{rr} (or LC^{Rr}) females were mated to AKR males, the virus in some (6 of 11) of the F_1 progeny gave AKR-type large XC plaques in SC-1 cells but grew in both SC-1 and SIRC cells, indicating a probable mixture of LC amphotropic and AKR ecotropic viruses. These results demonstrate that, except in crosses with viremic LC females, the virus present in the sera of the 2-month-old F_1 hybrids inheriting the recessive *Akvr-1*^{r} allele from their LC parent is solely of AKR origin.

Duration of Virus Repression and Prevention of Lymphoma in F_1 Hybrids. To determine if the AKR virus repressor effect was long-lasting and associated with prevention of lymphoma, the F_1 progeny of matings between AKR females and two LC males (24468 and 18732), homozygous for the resistance allele, were retested for viremia after 9 months and were observed for up to 18 months (Table 3). All of the mice tested (35 of 35 in seven litters) remained nonviremic and healthy at 9 months, and lymphoma has not occurred in 22 of these mice still living at 15–18 months of age. By contrast, the parental AKR mice were 100% viremic at weanling age (10 of 10) and developed the usual high incidence of thymic lymphoma (9 of 12) by 9 months of age. Viremic LC parental mice, as reported (30), had an increased incidence (17%) of nonthymic lymphoma, occurring mostly after 1 year of age. The same incidence and type of lymphomas occurred in F_1 progeny of viremic LC females and AKR males, suggesting that the *Akvr-1*^{r} allele present in AKR mice does not restrict LC amphotropic virus expression or pathogenesis.

Table 3. Incidence of lymphoma in AKR × LC hybrids and controls

Cross		No. of litters	No. of lymphomas/ no. of mice observed ≥9 months	%
Female	Male			
AKR	AKR	4	9/12*	75
LC	LC	83	73/417†	17
AKR	LC‡	7	0/35§	0
LC	AKR	9	6/36¶	17

* These were thymic lymphomas, typical of AKR mice, occurring at an average age of 9 months. All (10 of 10) AKR mice were viremic at 6–8 weeks of age.

† The lymphomatous mice were all viremic by 6 months of age, and the lymphomas were of splenic non-T-cell origin.

‡ LC *Akvr-1*^{RR} males 24468 and 18732 (Table 1).

§ These mice were all nonviremic at ≥9 months of age. At 12–17 months of age virus was not isolated in SC-1 cells from 10% spleen extracts of three of these F_1 mice.

¶ The LC female parents and all of the F_1 progeny were viremic early in life.

***Akvr-1*^{R} is Restrictive for NB-tropic Moloney and Friend MuLVs but Is Not Restrictive for LC Amphotropic MuLV.** Offspring of mice previously typed for their *Akvr-1* genotype were challenged at birth with NB-tropic Moloney MuLV and monitored for viremia at 2 months of age (Table 4). Homozygous *Akvr-1*^{rr} mice (Swiss or LC) became viremic (11 of 12) and homozygous *Akvr-1*^{RR} mice were resistant (0 of 10). A single exception was a viremic AKR × LC heterozygote (*Rr*) (1 of 5), raising the possibility of either leakiness of *Akvr-1* in Moloney MuLV restriction or possible variation in the *Akvr-1* target in this virus stock. Nonetheless, *Akvr-1* appears to exert a strong restriction of Moloney MuLV proliferation *in vivo*.

Additional LC × LC and AKR × LC crosses and backcrosses segregating for *Akvr-1*^{R} were challenged at 2–5 months of age with NB-tropic Friend MuLV (a mixture of spleen focus-forming virus and Friend leukemia helper virus). Spleens were removed and weighed 9 days later. In susceptible mice, the spleen focus-forming component of Friend MuLV produces erythroleukemia and splenomegaly within 7–10 days (29). The ratio observed of resistant (spleen weight < 0.5 g) to susceptible (spleen weight ≥ 0.5 g) mice was in close agreement with that expected on the basis of Mendelian segregation of a single dominant virus-restriction gene (Table 4). The susceptible hybrids were the same individual mice that had previously been typed as *Akvr-1*^{rr} based upon the detection of viremia, whereas the resistant hybrids were of *Akvr-1*^{Rr} genotype and were all nonviremic. The average spleen weight of the susceptible (*rr*) progeny was 6-fold greater than the average of the resistant (*Rr*) progeny (1.7 g versus 0.3 g), indicating *Akvr-1*^{R}-mediated restriction of Friend MuLV-induced splenomegaly.

The allele frequency of *Akvr-1*^{R} is 0.47 in LC mice, based upon the admittedly small sample presented in Table 1. The genotype frequencies in Table 1 do not vary significantly from expectations of the Hardy–Weinberg equilibrium ($\chi^2 = 3.6$; $P = 0.05$). Thus, the probable frequency of LC animals that contain at least one *Akvr-1*^{R} allele is 0.72; the observed value in our sample is 0.61. All these mice would be expected to be

Table 4. Concordant resistance to AKR ecotropic virus and to Friend and Moloney NB-tropic viruses

Cross*		*Akvr-1* genotype†	Resistance to MuLV	
Female	Male		Moloney‡	Friend§
NIH Swiss	NIH Swiss	*rr* × *rr*	0/6	0/10
LC	LC	*rr* × *rr*	1/6	NT¶
LC	LC	*RR* × *RR*	10/10	NT
AKR	LC	*rr* × *RR*	4/5	NT
LC	LC	*Rr* × *Rr*	2/6	8/9
(AKR × LC)F_1	(AKR × LC)F_1	*Rr* × *Rr*	NT	6/7
AKR	(AKR × LC)F_1	*rr* × *Rr*	NT	4/7
(AKR × LC)F_1	AKR	*Rr* × *rr*	NT	7/8
LC	AKR	*Rr* × *rr*	NT	2/6

* The LC mice in these crosses were nonviremic.

† The *Akvr-1* genotype of each LC parent was previously determined by the segregation of viremia in (AKR × LC)F_1 hybrids. The *rr* genotype was assigned to NIH Swiss mice on the basis of data in ref. 31.

‡ Newborn mice were challenged with 0.05 ml (intraperitoneally) of Moloney MuLV, and viremia was determined at 2 months of age by the FA test on SC-1 cells.

§ The Friend MuLV was a mixture of the spleen focus-forming virus and its helper virus serially passaged in NIH Swiss mice. At 2–5 months of age, mice were inoculated with 0.2 ml of 1:100 dilution of a 10% NIH Swiss splenic extract. Spleen weight was determined 9 days after inoculation. Susceptible mice had spleen weights >0.5 g; resistant mice had normal small (<0.5 g) spleens without tumor nodules. Erythroleukemia was confirmed microscopically in the enlarged spleens.

¶ NT, not tested.

capable of restricting AKR ecotropic virus expression. Nonetheless, approximately 90% of LC mice contain amphotropic virus, which has been implicated in generation of lymphoma in this feral mouse colony. It seems that *Akvr-1*^{R} fails to suppress the highly prevalent amphotropic virus of its natural host. This conclusion is supported by the finding of high amphotropic virus titers in animals both homozygous and heterozygous for *Akvr-1*^{R} (Table 1). In addition, when an uninfected LC male (24468), homozygous for *Akvr-1*^{R} (based upon absence of viremia in all of his AKR F_1 progeny), was mated with a viremic LC female, 100% (15 of 15 in three litters) of the weanling progeny became infected. Furthermore, when 7 nonviremic wild mice from the BC trapping area were mated to AKR females, 92% F_1 hybrids (47 of 51 in eight litters) were viremic at weanling age (i.e., *Akvr-1*^{rr} genotype), indicating that the strong control of amphotropic virus noted in this population of wild mice (26) could not be attributed to the *Akvr-1*^{R} allele. Thus, the target of *Akvr-1* found in endogenous AKR ecotropic retrovirus is distinct from the target in the LC amphotropic virus. Whether the same target of the LC ecotropic virus is restricted by *Akvr-1* remains to be determined.

DISCUSSION

The observations described here provide evidence for the genetic polymorphism, in feral LC mice, of a gene (*Akvr-1*) that can effectively restrict induction or expression of the endogenous virogene loci *Akv-1* and *Akv-2* in AKR mice (6) and thereby eliminate the progress of retrovirus-mediated lymphomagenesis in this strain (10, 11). Two alleles, *Akvr-1*^{R} (restrictive) and *Akvr-1*^{r} (susceptible), were detected in LC mice, but only the recessive allele (*Akvr-1*^{r}) was found in seven mice tested from the separate BC population. The dominant allele (*Akvr-1*^{R}) restricts three ecotropic viruses (AKR endogenous virus, Moloney MuLV, and Friend MuLV) but fails to restrict the wild mouse amphotropic virus indigenous in the LC mouse colony. The penetrance of *Akvr-1*^{r} is 100% in prevention of AKR retrovirus expression and lymphoma, but the restriction is leaky (penetrance = 93%) in prevention of Moloney MuLV.

The phenotypic properties of *Akvr-1* appear to preclude participation of previously described alleles of *Fv-1* in the restriction phenotype. First, AKR virus is an N-tropic virus and would be capable, by definition, of growth on cells derived from *Fv-1*^{N} mice. LC mice are monomorphic for *Fv-1*^{N} by virtue of permissive replication of the N-tropic amphotropic virus in viremic as well as nonviremic animals (by inoculation). Furthermore, embryo cultures of LC mice typed previously are all *Fv-1*^{N}. Second, *Akvr-1*^{R} has no restrictive effect on amphotropic virus (Table 1), which is strongly restricted by *Fv-1*^{B} (32). Third, *Akvr-1* restricts NB-tropic Moloney MuLV and Friend MuLV, whereas no known allele of *Fv-1* restricts these viruses. Fourth, *Fv-1* restriction is generally leaky and abrogated by high-multiplicity infection. This does not seem to hold with *Akvr-1*^{R}-mediated AKR virus restriction.

An additional *Fv-1* allele has been described in the RF inbred mouse strain (33). In crosses with AKR mice, this allele exerts a dominant restriction on lymphoma development associated with a restriction on thymic expression of both ecotropic and, especially, xenotropic viruses (33). However, in contrast to an absence of detectable viremia as we observed in the (AKR × LC)F_1 mice, this RF allele did not lower ecotropic virus titers in the spleen of (AKR × RF)F_1 mice compared to AKR mice. Therefore, it appears very unlikely that the AKR resistance gene in LC wild mice is identical to the *Fv-1* allele of RF mice.

It also seems unlikely that the AKR virus resistance gene in LC wild mice corresponds to certain of the other described genetic loci controlling resistance to MuLV in laboratory mice. The *Fv-2* locus restricts the spleen focus-forming portion of Friend virus and has no effect on leukemia or helper virus replication (34). Thus, unlike *Akvr-1*, *Fv-2* does not restrict AKR virus or Moloney MuLV replication in homozygous *Fv-2*^{r}/*Fv-2*^{r} animals. In addition, restriction is recessive in the *Fv-2* system, in contrast to *Akvr-1*.

The *Fv-3* gene regulates the *in vitro* susceptibility of lymphocytes to the suppressive action of Friend MuLV (35), and another non-*H-2* gene, called *Rfv-3*, apparently affects the recovery from Friend MuLV viremia by influencing the antiviral immune response (36). Neither of these genes has any known restrictive effect on AKR virus. Although *H-2*-linked *Ir* loci do affect leukemogenesis in AKR (34) and other laboratory mouse strains (37), this mainly reflects an enhancement of the autogenous immune response to infected or transformed cells rather than an effect upon activation or spread of infectious MuLV. However, it has been demonstrated in B10 congeneic mice that genes within the *H-2* region also regulate early virologic events before tumor development (38, 39).

Another MuLV restriction locus, called *Fv-4*, was recently described in the G inbred strain of Japanese laboratory mice (14) and, possibly, in several (four of eight) Japanese wild mice (*Mus musculus molossinus*) (40). The *Fv-4* resistance allele is defined by its dominant restriction of NB-tropic MuLV replication *in vivo* and in hematopoietic cells (41). Odaka *et al.* (40) have suggested that the *Fv-4*^{r} allele of G mice suppressed the expression of endogenous AKR virus, and Yoshikura *et al.* (42) reported that G mouse cells (*Fv-4*^{rr}) were fully permissive to wild mouse amphotropic virus.

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