

Nova Southeastern University NSUWorks

Biology Faculty Articles

Department of Biological Sciences

9-1983

Murine Retroviral Restriction Genes Fv-4 and Akvr-1 are Alleles of a Single Locus

Stephen J. O'Brien National Cancer Institute at Frederick, sobrien1@nova.edu

Eric J. Berman National Cancer Institute at Frederick

John D. Estes University of Southern California - Los Angeles

Murray B. Gardner University of California - Davis

Follow this and additional works at: https://nsuworks.nova.edu/cnso_bio_facarticles

Part of the Genetics and Genomics Commons, and the Zoology Commons

NSUWorks Citation

O'Brien, Stephen J.; Eric J. Berman; John D. Estes; and Murray B. Gardner. 1983. "Murine Retroviral Restriction Genes Fv-4 and Akvr-1 are Alleles of a Single Locus." *Journal of Virology* 47, (3): 649-651. https://nsuworks.nova.edu/cnso_bio_facarticles/223

This Article is brought to you for free and open access by the Department of Biological Sciences at NSUWorks. It has been accepted for inclusion in Biology Faculty Articles by an authorized administrator of NSUWorks. For more information, please contact nsuworks@nova.edu.

Murine Retroviral Restriction Genes Fv-4 and Akvr-1 Are Alleles of a Single Locus

STEPHEN J. O'BRIEN,^{1*} ERIC J. BERMAN,¹ JOHN D. ESTES,² AND MURRAY B. GARDNER³

Section of Genetics, Laboratory of Viral Carcinogenesis, National Cancer Institute, Frederick, Maryland 21701¹; Department of Pathology, University of Southern California, School of Medicine, Los Angeles, California 90032²; and Department of Pathology, University of California, School of Medicine, Davis, California 95616³

Received 22 April 1983/Accepted 9 June 1983

The two murine retroviral restriction genes, Fv-4 and Akvr-1, are very similar in their effects, distributions, ranges of action, and phenotypes. Akvr-1 has been shown to segregate independently in backcrosses with a variety of retroviral restriction loci, including Fv-1, Fv-2, Ril-1, and Ril-2. An allelism test cross of FRG $(Fv-4^R) \times LC^{RR} (Akvr-1^R)$ hybrids mated to AKR mice failed to produce any viremic offspring. These results suggested that $Akvr-1^R$ and $Fv-4^R$ are alleles of a single locus, Fv-4, on mouse chromosome 12.

In laboratory and feral mice, a number of genetic loci have been discovered which specifically delimit the replication and associated pathology of endogenous retroviruses (1, 5, 9, 12, 13). Two of these cellullar restriction genes, Akvr-1 and Fv-4, share a number of phenotypic characters, although they were originally discovered in different subspecies of Mus musculus (Akvr-1 in a California population of M. musculus subsp. domesticus and Fv-4 from a Japanese strain, FRG, of *M. musculus* subsp. molossinus) (1, 3, 8, 10, 13, 14, 16, 17). Both loci exert a strong restriction of ecotropic murine retrovirus in vivo and in vitro. Restriction is dominant, and F_1 hybrids between AKR and $Fv-4^R$ or Akvr- l^R are totally free of AKR viremia and the associated neoplastic disease characteristic of the AKR inbred strain (1, 8). In addition, both genes confer dominant resistance to leukemia, lymphoma, and splenomegaly which is induced by exogenous inoculation of newborn mice with NB-tropic Friend murine leukemia virus and NB-tropic Moloney murine leukemia virus. Both loci are polymorphic in modern feral mouse populations and both fail to restrict replication of amphotropic murine leukemia virus. Because of the phenotypic similarities of Akvr-1 and Fv-4, the possibility that the same cellular gene was responsible for both was investigated.

A strain of mice, LC^{RR} , homozygous for the restriction allele of Akvr-I has been derived. $Akvr-I^R$ dominantly restricts ecotropic viremia and leukemia in $AKR \times LC^{RR}$ hybrid mice and has been shown previously to segregate in backcross progeny as a single genetic locus (1). LC^{RR} mice and AKR mice differ in coat color genes and electrophoretically at a number of allelic isozymes previously mapped to individual chromosomal loci (11). We determined the recombination frequency between the Akvr-1 locus and eight such loci on different chromosomes of $(AKR \times LC^{RR}) \times AKR$ backcross progeny (Table 1). Sera were obtained from parental, F_1 , and backcross progeny at 6 to 8 weeks of age and assayed for infectious murine leukemia virus on wild mouse SC-1 cells by using an immunofluorescence assay as described previously (1, 4). Fifty percent of the progeny of this cross were viremic due to the expression of AKR endogenous ecotropic virogene loci and the presence of the Akvr-1s/Akvr-1s genotype. The remaining 50% were Akvr-1s/Akvr-1^R and thus virus negative. The observed virus restriction was due to the influence of Akvr-1 and not other restriction loci since AKR and LC^{RR} are isogenic at both Fv-1 and Fv-2 for a permissive genotype (Table 2). No linkage between Akvr-1 and each of these loci, which included genes closely linked to Fv-1 (Gpd-1) and Fv-2 (Mod-1), was detected.

The Fv-4 locus has been chromosomally mapped to murine chromosome 12 and found to be linked to Pre-1 and to Igh-1 by using Fv-4 alleles derived from both the FRG inbred strain and an outbred wild mouse allele, Fv-4w (2, 10, 15). We tested for allelism of Akvr-1 and Fv-4 by crossing LC^{RR} mice and FRG mice. LC^{RR} and FRG mice are also isogenic for the permissive alleles of Fv-1 and Fv-2 (Table 2). The F₁ animals were crossed to AKR mice to test for independent assortment of Fv-4 versus Akvr-1, using suppression of AKR viremia as our assay for restriction. The results of virus assay of crosses involving these strains are summarized

Locus ^a	Chromo- some	Genotype		No.	%			
		AKR	LC	of mice	Recombination gene versus Akvr-1	x*	Retrovirus loci on same chromosome (5–7)	
Id-1	1	b	a,c	70	51.4	0.06	Bxv-1, Ril-2, Mtv-7, 10	
а	2	а	A	42	43.7	0.1	Rec-1, Ril-1	
Gpd-1	4	b	a,b	68	51.5	0.06	Fv-1; end.MMTV, Ril-3, DBA-CSA	
с	7	c	С	87	52.4	0.02	Akv-1; Fgv-1, Gv-2, Mtv-1	
Gr-1	8	а	a,b	52	48.1	0.08	Ram-1, Bv, C58v-1	
Mod-I	9	b	a,b	48	60.4	2.1	Fv-2, Dbv, Sev-1	
Es-3	11	с	a,c	70	57.1	1.42	Mtv-3, Bbv	
Got-1	19	а	a,b	42	57.1	0.86	,	

TABLE 1. Segregation of Akvr- l^R in (AKR \times LC^{RR}) \times AKR backcross progeny

^a Isozymes were typed by electrophoresis (11) and viremia by the fluorescent-antibody test on SC-1 cells. ^b χ^2 with 1 df = 3.841 (P = 0.5).

Store in		Genotype at				
Strain	Fv-1	Fv-2	Fv-4	Akvr-1	Source	
AKR	N	S	S	S	Jackson Laboratories	
LC	Ν	S		R	Lake Casitas, M. B. Gardner	
FRG	Ν	S	R		M. Tanigawa, S. Suzuki	
AKR $(Fv-l^B)^b$	В	S	5	5	E. A. Boyse	

TABLE 2. Mouse strains used in this analysis^a

^a Genotypes determined in references 1, 10, and 12.

^b Congenic inbred mouse with $Fv-l^B$ on an AKR genetic background.

Cross no.	Maternal	Paternal	No. of litters	No. viremic/ no. tested	Frequency (%)
1	AKR	AKR	7	21/21	100
2	LC ^{RR}	LC ^{RR}	10	0/42	0
3	AKR	LC ^{RR}	5	0/32	0
4 ^a	FRG	AKR	ND ^b	0/23	0
5	FRG	LC ^{RR}	3	0/20	Ő
6	AKR	$AKR \times LC^{RR}$	5	19/41	46
7ª	AKR	$AKR \times FRG$	ND	31/72	43
8	AKR	AKR $(Fv-l^B) \times LC^{RR}$	5	4/25	16
9	AKR	$FRG \times LC^{RR}$	5	0/33	0

TABLE 3. Infectious murine leukemia virus in progeny of crosses involving Akvr-1 and Fv-4

^a From Odaka et al. (8).

^b ND, Not determined.

in Table 3. Crosses 1 through 5 demonstrate that both Fv-4 and Akvr-1 dominantly suppressed AKR-associated viremia and crosses 6 and 7 demonstrated the 1:1 backcross ratio characteristic of a single-gene locus. Cross 8 provided evidence for independent assortment of Fv-1versus Akvr-1, indicating lack of allelism for the two restriction genes. Cross 9 demonstrated that $Akvr-1^R$ and $Fv-4^R$ segregate from each other since no viremic progeny were obtained from 33 progeny. If the two genes were separate genes located on separate chromosomes, 25% of the offspring would be expected to be viremic. The significant departure from the expectation ($\chi^2 =$ 11.1; P < 0.001) strongly suggests that the genes are either two rather tightly linked genes or that they are alleles of a single locus. The physiological and phenotypic parallels in gene action (discussed above) of the two genes strongly support the latter interpretation. Within the limits of Vol. 47, 1983

these reservations, it is suggested that until evidence to the contrary demonstrates duality of these genes they be considered as members of an allelic series of a single locus, Fv-4.

LITERATURE CITED

- Gardner, M. B., S. Rasheed, B. K. Pal, J. D. Estes, and S. J. O'Brien. 1980. Akvr-1, a dominant murine leukemia virus restriction gene, is polymorphic in leukemia-prone wild mice. Proc. Natl. Acad. Sci. U.S.A. 77:531-535.
- Ikeda, H., H. Sato, and T. Odaka. 1981. Mapping of the Fv4 mouse gene controlling resistance to murine leukemia viruses. Int. J. Cancer 28:237-240.
- Kai, K., H. Ikeda, Y. Yuasa, S. Suzuki, and T. Odaka. 1976. Mouse strain resistant to N-, B-, and NB-tropic murine leukemia viruses. J. Virol. 20:436-440.
- Klement, U., and M. O. Nicolson. 1977. Methods for assays of RNA tumor viruses. Methods Virol. 6:59–108.
- Kozak, C. A. 1982. Retroviral and cancer associated loci of the mouse, p. 294–297. *In S. J. O'Brien (ed.)*, Genetic maps, vol. 2. National Cancer Institute, Frederick, Md.
- Lilly, F. 1970. Fv-2: identification and location of a second gene governing the spleen focus response to Friend leukemia virus in mice. J. Natl. Cancer Inst. 45:163–169.
- Meruelo, D., M. Lieberman, N. Ginzton, B. Deak, and H. O. McDevitt. 1977. Genetic control of radiation leukemia virus-induced tumorigenesis. I. Role of the major murine histocompatability complex, H-2. J. Exp. Med. 146:1079-1087.
- 8. Odaka, T., H. Ikeda, and T. Akatsuka. 1980. Restricted expression of endogenous N-tropic XC-positive leukemia virus in hybrids between G and AKR mice: an effect of the $Fv\mathcal{A}^r$ gene. Int. J. Cancer 25:757-762.

- Odaka, T., H. Ikeda, K. Moriwaki, A. Matsuzawa, M. Mizuno, and K. Kondo. 1978. Genetic resistance of Japanese wild mice (*Mus musculus molossinus*) to an NBtropic Friend murine leukemia virus. J. Natl. Cancer Inst. 61:1301-1306.
- Odaka, T., H. Ikeda, H. Yoshikura, K. Moriwaki, and S. Suzuki. 1981. Fv-4: gene controlling resistance to NB-tropic Friend murine leukemia virus. Distribution in wild mice, introduction into genetic background of BALB/c mice, and mapping of chromosomes. J. Natl. Cancer Inst. 67:1123-1127.
- Rice, M. C., M. B. Gardner, and S. J. O'Brien. 1980. Genetic diversity in leukemia-prone feral house mice infected with murine leukemia virus. Biochem. Genet. 18:915-928.
- Rowe, W. P., J. B. Humphrey, and F. Lilly. 1973. A major genetic locus affecting resistance to infection with murine leukemia viruses. Assignment of the *Fv-1* to linkage group VIII of the mouse. J. Exp. Med. 137:850-852.
- Suzuki, S. 1975. Fv-4: a new gene affecting the splenomegaly induction by Friend leukemia virus. Jpn. J. Exp. Med. 45:473-478.
- Suzuki, S., and S. Matsubara. 1975. Isolation of Friend leukemia virus resistant line from non-inbred mouse colony. Jpn. J. Exp. Med. 45:467–471.
- Suzuki, S., K. Tsuji, and K. Moriwaki. 1981. Friend murine leukemia virus resistance in Japanese wild mice: possible allelism with Fv-4 in FRG mice. J. Natl. Cancer Inst. 66:729-731.
- Yoshikura, H., Y. Naito, and K. Moriwaki. 1979. Unstable resistance of G mouse fibroblasts to ecotropic murine leukemia virus infection. J. Virol. 29:1078–1086.
- Yoshikura, H., and T. Odaka. 1978. Resistance of G mice to murine leukemia virus infection: apparent disparity in *in vivo* and in *in vitro* resistances. J. Natl. Cancer Inst. 61:461-463.