GENETIC MAPPING OF ECOTROPIC MURINE LEUKEMIA VIRUS-INDUCING LOCI IN SIX INBRED STRAINS

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Chromosomal DNA of inbred and wild mice contains multiple copies of DNA sequences homologous to the RNA genomes of the murine leukemia viruses (MuLV). Some of these chromosomal sequences represent complete viral genomes that can be expressed as infectious virus (V loci). These endogenous V loci differ from one another in their patterns of induced and spontaneous expression and in the host range type of the recovered virus.

Genetic crosses between inbred mice with different patterns of expression have shown that V loci segregate as classical mendelian genes. High ecotropic virus, high leukemic strains generally carry multiple (two to four) unlinked V loci (1-3). The AKR mouse has been described as carrying two independently segregating V loci for ecotropic virus (1, 4, 5). One of these genes, Akv-1, was mapped to chromosome 7 (6), and, more recently, Akv-2 has been mapped to chromosome 16 (7). Low virus, low leukemic mice such as BALB/c, C3H/He, and C57BL/10, produce virus spontaneously only late in life and carry single, poorly inducible genes for virus induction (8, 9). The induction of ecotropic virus in BALB/c is controlled by a V locus, Cv, which was mapped to chromosome 5 (10, 11). This locus is not unique to BALB/c, being allelic with the ecotropic V locus defined serologically in C3H/HeJ, a low leukemic inbred strain derived from the same mouse stocks as BALB/c (11).

Genetic studies on the induction of the xenotropic class of MuLV have mapped a single site for virus inducibility, Bxv-1, present in many of the older inbred strains. Bxv-1 has been positioned on chromosome 1 and has been identified in five strains (AKR, C57BL, C57L, C58, and BALB/c) (12).

A number of V loci have now been bred onto the NFS genetic background to develop a series of congenic strains (3; W. P. Rowe, unpublished data). The generation of NFS.Akv-1 congenics together with knowledge of the chromosomal map position of Akv-1 has proven useful in defining the nature of this locus (13) and in documenting the occurrence of germ line reintegrations (3). The further analysis of isolated V loci should help resolve other questions on their nature, stability, regulation, and functional interactions.

In this paper, we describe the genetic mapping of ecotropic V loci in six additional mouse strains. We identify four new loci for ecotropic virus and extend previous data indicating that Cv represents an ancestral V locus in inbred strains originally derived from Bagg albino stocks.
Materials and Methods

Mice. The parental strains used in the genetic crosses are given in Table I. The NIH Swiss inbred line NFS/N was obtained from the Small Animal Section, Veterinary Resources Branch, Division of Research Sciences, National Institutes of Health, Bethesda, Md. NFS.HxSN is partially congenic for a dominant hemimelic extra-toe mutation on chromosome 5, arising in our colony and shown to be allelic with $H_m$. The $H-2$ congenic strain B10.BR/SgLi was obtained from Dr. F. Lilly, Albert Einstein College of Medicine, New York; these mice carry endogenous V loci for both N- and B-tropic virus (14). C3H/FgLw and C58/Lw mice were obtained from Dr. L. Law, NIH, Bethesda, Md. All other mice were from The Jackson Laboratory, Bar Harbor, Maine. RSV/Le is a linkage testing stock that carries the dominant locus $Rex$ ($Re$) on chromosome 11; $Re$ is expressed as a ruffled coat and curly whiskers. $E^{sk}$ is a linkage stock carrying the dominant mutation for somber (black) coat color; this locus is allelic with the recessive yellow locus ($e$) on chromosome 8.

Hybrid mice were bred in our laboratory. Genetic analysis of strains with single V loci was based on data from first backcross mice; analysis of strains carrying multiple loci required the initial separation of individual V loci into congenic lines. Four such congenic strains were developed in our laboratory carrying high expression V loci from C58 (NFS.C58V-1, NFS.C58V-2) or C3H/Fg (NFS.Fgv-1, NFS.Fgv-2). V loci in B10.BR mice were mapped through the analysis of backcrosses from B10.BR and from a partial congenic, SIM.R.Bev, carrying only the B-tropic V locus.

Virus Induction and Assay. The patterns of virus inducibility characteristic of the different V loci examined in this study are given in Table I. The efficiency of ecotropic virus expression varies considerably for different V loci, and the methods used to analyze hybrid mice for high and low expression V loci were chosen to maximize detection of appropriate loci.

The congenic mice carrying C58V-1 or Fgv-1 showed the high virus phenotype characteristic of the parental strains. Cell-free extracts were prepared from tail biopsy tissue of adult hybrid

| Table I |
| --- |

| Strain | $Fo$-1 type | Ecotropic MuLV |
| --- |
| Tail extracts | Inducibility in cultured cells* |
| A/HeJ | b | — | + |
| SWR/J | n | — | — |
| NFS/N | n | — | — |
| SEA/GnJ | n | Positive, late in life | ++ |
| RSV/Le | NT$\dagger$ | — | + |
| NFS.C58V-1 | n | High | +++ |
| B10.BR/ | b | Moderate-high | ++ |
| SgLi | | | |
| C57BL/10J | b | — | (+) |
| MA/My | n | — | (+) |
| C57L | n | — | — |
| SIM R | b | — | — |
| NFS.Fgv-1 | n | Moderate-high | +++ |
| NFS.HxSN | n | — | — |
| $E^{sk}$ | NT | NT | + |

* ++++, XC-detectable virus in uninduced cell cultures; ++, XC plaques after one passage after induction; +, XC-detectable plaques after multiple passages after induction; (+), few XC plaques after multiple passages, best detected in embryo rather than adult cell cultures; —, no XC-positive virus. All induced viruses are N-tropic except for one of the two loci of B10.BR/SgLi.

$\dagger$ Not tested.
mice and inoculated into cultures of SC-1 cells (15). Virus was detected by the XC test 6 d later (16).

Ecotropic virus expression at all other loci was determined by induction of cultured cells. Tissue cultures were prepared from the tail biopsy tissue of weanling mice (17) or from individual embryos. When the cultures were in subconfluent growth, 20 μg/ml of 5-iododeoxyuridine (IdU) was added for 48 h. The cultures were then fluid changed and overlaid with SC-1 cells to amplify viral titers. The mixed cell cultures were fluid changed twice weekly with minimum essential medium containing 3% fetal calf serum. 12 d after addition of SC-1 cells and at weekly intervals thereafter, the mixed cultures were passaged and monitored for virus production by the XC test. In some crosses involving inefficiently inducible V loci, cell cultures that were negative by the XC test were also examined by immunofluorescence (18). Ecotropic viruses isolated in B10.BR crosses were typed as N- or B-tropic, depending on their efficiency of replication on NFS or BALB/c embryo fibroblasts.

Isozyme Typing. The isozyme phenotypes of individual backcross mice were determined by vertical starch gel electrophoresis of clarified extracts of adult kidneys or fetal liver tissue. The following eight isozyme markers, mapped to five mouse chromosomes (Fig. 1), were used in linkage testing: esterase-1 and esterase-3 (Es-1, Es-3; E.C. 3.1.1.1); malic enzyme (Mod-1; E.C. 1.1.1.40); mannose phosphate isomerase-1 (Mpi-1; E.C. 5.3.1.8); glutathione reductase (Gr-1; E.C. 1.6.4.2); glucose phosphate isomerase (Gpi-1; E.C. 5.3.1.9); glutamate-oxaloacetate transaminase-2 (Got-2; E.C. 3.2.1.31); and phosphoglucomutase-1 (Pgm-1; E.C. 2.7.5.1). Methods for the electrophoretic separation of alleles at these loci are given by Nichols and Ruddte. Hbb typing was kindly done by Dr. T. Bremner.

Results

C3H/FgLw. C3H/Fg, a subline of C3H/St established by Dr. F. Figge in the 1940's, was observed by Dr. Figge to have an unexpectedly high incidence of leukemia. These mice were subsequently carried by Dr. L. Law, who confirmed the high incidence of spontaneous hematopoietic neoplasms (19). We analyzed the C3H/FgLw subline and its hybrids for endogenous virus expression and observed that these mice expressed high levels of N-tropic ecotropic MuLV (Table I). A single male, obtained in 1972 of the 45th inbred generation, was selected for analysis by sexual genetics. In tests of 165 NIH × (NIH × C3H/FgLw)F1 mice, 137 (83%) were positive for virus in tail extracts, indicating the presence of three independently segregating high-virus loci. Two of these loci, designated Fgv-1 and Fgv-2, were subsequently bred into NIH Swiss and then NFS.

In the initial backcross generation, it was apparent that one of the C3H/Fg loci was located on chromosome 7 because 83 (91%) of 91 non-albino mice were virus positive as compared to 54 (73%) of 74 albino segregants (P < 0.01). This locus, Fgv-1, was carried into NFS in coupling with C (color) and was positioned on chromosome 7 by means of a three point cross with C and Hbb (Table II). The gene order is C, Hbb, Fgv-1. Because Fgv-1 was not fully penetrant in this three-point cross, the best linkage estimates are those based on virus-positive mice, and these place Fgv-1 3 units from Hbb. Consistent with this position, weak linkage was observed with Gpi-1 (r = 34/91 = 37 ± 5).

The Fgv-2 locus has not been mapped, but preliminary data show that this locus is not allelic with the V locus of C3H/HeJ on chromosome 5.

C58/Lw. C58 is a high leukemic high virus mouse that has been shown to carry up to four ecotropic V loci (2). We carried out a segregation analysis of ecotropic virus expression in NIH × (NIH × C58)F1 mice, using a C58/Lw mouse obtained in 1972 at F133. Of 127 mice tested, 109 (86%) were positive in tail extracts for ecotropic virus, confirming that C58 carries three or four high expression V loci. Two of these
TABLE II
Linkage Analysis of \( \text{Fgv-1} \) and Markers on Chromosome 7

| Virus | C | Number of mice | Virus | Hbb | C | Number of mice |
|-------|---|---------------|-------|-----|---|---------------|
| +     | + | 238           | +     | +   | + | 28            |
| +     | − | 14            | +     | −   | + | 0             |
| −     | + | 33            | +     | +   | − | 2             |
| −     | − | 210           | +     | −   | − | 1             |

Recombination Total
\( \text{Fgv-1} -- \text{Hbb} \) \( r = 8/78 = 10 \pm 3.3 \) 1/31 = 3 ± 3
\( \text{Fgv-1} -- \text{C} \) \( r = 58/573 = 10 \pm 1.2 \) 17/283 = 6 ± 1.4
\( \text{Hbb} -- \text{C} \) \( r = 3/78 = 4 \pm 2.2 \)

The two-point cross data were obtained from a series of backcrosses in which \( \text{C} \) and \( \text{Fgv-1} \) were carried in coupling from C57L/Fg into NFS. Segregation of both \( \text{C} \) and \( \text{Hbb} \) was monitored in the three-point cross, NFS × (C57L × NFS.Fgv-I)\( \text{F1} \), in which the NFS.Fgv-I mouse was an albino.

TABLE III
Linkage Analysis of \( \text{C58v-1} \) and Three Markers on Chromosome 8

| Chromosome 8 markers | Inheritance of marker from virus-positive grandparent* | Recombination |
|----------------------|------------------------------------------------------|---------------|
|                      | \( \text{V}^+ \) mice | \( \text{V}^- \) mice | Total | Virus-positive mice only |
| \( \text{E}^\text{o} \) | 23/24 (96) | 6/30 (20) | 7/54 = 13 ± 4.6 | 1/24 = 4 ± 4 |
| \( \text{E}-1 \) | 31/42 (74) | 11/71 (15) | 22/113 = 19 ± 3.7 | 11/42 = 26 ± 6.8 |
| \( \text{Gr}-1 \) | 18/36 (50) | 22/63 (33) | 40/99 = 40 ± 4.9 | 18/36 = 50 ± 8.3 |

Segregation of \( \text{E}-1 \) and \( \text{Gr}-1 \) was monitored in the cross NFS × (C57L × NFS.C58v-1). Linkage with \( \text{E}^\text{o} \) was established in a separate cross; \( \text{E}^\text{o} \) mice were crossed with NFS, and virus-negative backcross segregants were selected for mating with NFS.C58v-1. Black males of this cross were mated with NFS females. Linkage estimates were calculated for total backcross mice as well as virus-positive segregants because the preponderance of virus-negative mice suggests incomplete penetrance of \( \text{C58v-1} \) in these crosses.

* Number with marker per number in group (%).

loci were bred into NIH and then into NFS mice and subsequently were tested for linkage. The \( \text{V} \) locus designated \( \text{C58v-1} \) showed linkage to markers on chromosome 8, with gene order \( \text{C58v-1}, \, \text{Es}-1, \, \text{Gr}-1 \) (Table III); the locus is relatively close to \( \text{E}^\text{o} \), but the gene order was not established.

The \( \text{V} \) locus carried by the second congenic family (\( \text{C58v-2} \)) showed no linkage to markers on chromosome 8, nor to markers on other chromosomes known to carry \( \text{V} \) loci, i.e., chromosomes 1, 5, 7, or 11.

\( \text{C57BL/10} \). The \( \text{C57BL/10} \) mouse carries a single ecotropic provirus that was shown to be nonallelic with that of C3H/HeJ (9). The efficiency of XC-detectable virus induction from this locus is poor, particularly with tail cultures. Therefore, inductions were carried out on cultured cells derived from individual embryos, and
fetal livers were used for isozyme tests. Of 123 backcross embryos tested, 49 (39%) were virus positive, consistent with the segregation of a single gene characterized by poor inducibility. This locus showed linkage to markers on chromosome 8 (Table IV). Because of the poor efficiency of induction at this locus, the best estimate of its recombinational distance from Got-2 is that obtained from virus-positive animals only ($r = 26.5 \pm 0.3$). Although this locus shows close proximity to C58c-1, the marked difference in phenotypic expression prompted us to consider this C57BL locus as a distinct proviral integration, which we designate $Bv$.

$B10.BR/sgL$. Adult mice of the $H-2^b$ congenic C57BL/10 subline B10.BR/sgL carry endogenous N- and B-tropic retroviral genomes (14). Genetic crosses with NFS or A strain mice confirmed that B10.BR carries the same endogenous N-tropic ecotropic viral locus, $Bv$, as its strain of origin (Table V).

Unlike C57BL, B10.BR mice of this subline show a high level of expression of B-
tropic ecotropic leukemia virus, and cultured cells can be induced to produce B-tropic virus. This unusual pattern of virus expression is presumably due to the germ line reinsertion of the B-tropic viral genome that in other $Fv-1^b$ mice typically appears only as a de novo recombinant in older animals.

$(A/J \times B10.BR)F_1$ males were crossed to NFS or $A/J$ mice. B-tropic virus induction segregated as a single gene and showed linkage to $Er-3$, a marker at the distal end of chromosome 11. Partially congenic SIM.R mice carrying this locus, designated $Btv$, were mated to mice carrying the $Re$ locus, and virus-positive offspring were mated to SIM.R. The combined data from both crosses gives the gene order $Re, Btv, Es-3$ (Table VI).

$SEA/GnJ$. The $SEA/GnJ$ strain was derived from a cross between BALB/c and $P/J$ mice (20). This mouse is rarely used in studies of viral oncogenesis, and the incidence of spontaneous disease has not been documented. $SEA/Gn$ shows high ecotropic virus expression. Cultured adult cells constitutively produce virus, and it can be detected at high titers in spleens and tail extracts of adult mice and their hybrids.

$SEA/Gn$ mice were mated with MA/My or NFS mice and backcrossed to NFS. Induction of XC-detectable virus was scored in tail cultures 2 wk after treatment with IdU. Virus expression as assayed in this manner showed single gene segregation (Table VII). This gene, designated $Sev-1$, showed linkage to the $Mod-1$ locus on chromosome 9 in a two-point cross. Analysis of a three-point cross provided the gene order $Mpi-1, Mod-1, Sev-1$.

$A/J$. $A/J$ is a low leukemic, low virus strain. Spontaneous expression of virus occurs rarely and only in older animals. Similarly, ecotropic virus can be induced from cultured cells with IdU, but the efficiency of induction is poor (Table I).

| Cross | Chromosome 9 marker | Inheritance of marker from SEA/GnJ* | Recombination | Total |
|-------|---------------------|------------------------------------|---------------|-------|
| NFS $\times (SEA \times NFS) F_1$ | $Mod-1$ | 29/38 (76) | 10/34 (29) | 19/72 = 26 ± 5.2 | 28/141 = 20 ± 3.4 |
| NFS $\times (MA \times SEA) F_1$ | $Mod-1$ | 31/40 (78) | 0/29 (0) | 9/69 = 13 ± 4.1 |
|        | $Mpi-1$            | 26/40 (65) | 4/29 (13) | 18/69 = 26 ± 5.3 |

* Number with marker per number in group (%).

| Inheritance of $A/J$ alleles | Number of animals |
|-----------------------------|-------------------|
| Virus inducibility $Pgm-1$   |                   |
| +                           | 31                |
| +                           | 6                 |
| -                           | 9                 |
| -                           | 25                |

Recombination: virus $(C_{st}) = Pgm-1/1; r = 15/71 = 21 ± 4.8.
A/J males were mated with females of the SWR inbred line, and F1 animals were crossed to NFS females. Because of the poor inducibility of virus in hybrid mice, all cultures that were XC-negative at 6 wk were tested by immunofluorescence. 2 of the 36 XC-negative cultures were shown to be positive for viral antigen. A total of 37 (52%) of 71 animals were virus positive by these criteria, consistent with single gene control of ecotropic virus. Comparison of the segregation of this locus and various isozyme markers showed that virus inducibility was linked to the Pgm-1 locus on chromosome 5 (Table VIII).

A second cross was used to position this locus. A/J males were crossed with NFS.Hx2N mice and backcrossed to NFS. All 11 Hx2N backcross mice were virus negative and all six wild-type mice were positive. Because Hx is 24 units proximal to Pgm-1, the V locus can be positioned at the centromeric end of chromosome 5.

The low efficiency of virus inducibility and the chromosomal position of this locus relative to Pgm-1 are comparable to those described previously for two related strains, BALB/c and C3H/HeJ (10, 11). Preliminary data suggests that the BALB/c locus Cv and Hx2N are very closely linked. The A/J locus is therefore assumed to be allelic with Cv.

Discussion

We have now mapped nine ecotropic viral loci of various mouse strains to seven positions on five different chromosomes. A summary of our accumulated data on the chromosomal distribution of ecotropic and xenotropic V loci in the mouse is given in Fig. 1.

![Fig. 1. Mouse linkage map of endogenous V loci and linked marker genes. Numbers along the lengths of the chromosomes represent recombinational distances between loci and were taken from the most recent mouse gene map (26) or from data presented in this paper. Brackets enclose loci for which the gene order is not known. Ecotropic V loci are boxed by solid lines; the single xenotropic V locus by a jagged line. Strains known to carry each V locus are given next to the locus name.](image-url)
Little is known of the precise origin of the common inbred strains of laboratory mice. Most of the older strains originated from animals provided early in this century by private dealers in North America; many of the mice were probably hybrids between fancy mice of western Europe (*Mus musculus domesticus*) and Japan (*Mus musculus molossinus*). The introduction of V loci into inbred strains can probably be traced to this Japanese ancestry. Only wild *M. m. molossinus* and other Asian mice are known to carry endogenous ecotropic and xenotropic MuLV, and molecular techniques cannot distinguish ecotropic viruses of inbred and Japanese origin (21, 22). The mendelian studies presented here describe the chromosomal distribution and genetic stability of these loci in the older virus-positive strains in laboratory mice.

Our genetic mapping data have identified at least one low expression ecotropic V locus that was evidently present in mouse stocks before inbreeding. This ecotropic locus on chromosome 5, *Cv*, is carried by three inbred strains: BALB/c, C3H, and A/J. These mice have been maintained as separate stocks for over 60 yr, but they share a common ancestry (23). A strain mice were derived from crosses of the Cold Spring Harbor albino and Bagg albino (the progenitor of BALB/c). C3H mice were similarly derived from hybrids of Bagg albino and DBA. All three strains show similar patterns of virus inducibility, although Ihle has reported (11) that inheritance of the C3H locus results in the earlier appearance of antibody than that observed in BALB/c. It remains to be determined whether this difference can be attributed to differences at the site of integration or to other genetic factors that affect V gene expression.

A fourth related strain, SEA/GnJ, was developed from a cross between BALB/c and P/J mice (20) but shows a distinct pattern of virus expression. We did not determine whether SEA/Gn carries the poorly inducible *Cv* locus; however, high virus expression in this mouse is inherited with a novel locus on chromosome 9 not found in BALB/c. This gene may have been inherited from P/J or may represent a novel insertion generated during inbreeding.

The final strain examined in this study that can trace its ancestry to Bagg albino stocks is the high virus C3H/Fg subline of C3H. This mouse clearly carries multiple (three or more) high expression V loci in contrast to C3H/HeJ, and our mapping studies show that two of these loci are nonallelic with *Cv*. The determination of whether C3H/Fg also carries proviral sequences at *Cv* and the characterization of this locus as high or low expression may provide some insight into the events responsible for the development of this high leukemic subline.

The low virus C57BL mouse represents a different line of descent and carries a single, poorly inducible V locus clearly distinct from *Cv*. However, our genetic crosses show that both C57BL and C58 mice carry ecotropic V loci at the distal end of chromosome 8. The possibility that these loci may, in fact, be allelic is underscored by the close relationship of these strains, which were derived from offspring of the same male by two different sisters (23). These two strains show striking differences in the natural history of disease and virus expression; therefore, the possibility that these V loci represent an allelic pair with high and low expression patterns is particularly interesting. These strains may provide a unique opportunity to study the molecular and genetic basis of regulation.

The high leukemic strains AKR, C3H/Fg, and C58 carry multiple V loci, consistent with the phenomenon of germ line reinsertions observed in high virus congenics (3). Four of these loci have been mapped to nonallelic sites on chromosomes 7, 16, and 8.
The remainder of these high expression loci remain unmapped, but it is clear that Fge-2 and C58v-2 as well as several of the reinsertion loci in AKV congenics are not allelic with mapped V loci. Thus, the stable integration of these V genes into the germ line can occur at many sites. This observation of heterogeneity among mice of different high virus strains can now be extended; recent biochemical and genetic studies suggest that individuals within the same strain may differ from one another in the number and chromosomal sites occupied by proviral sequences (D. Steffen, personal communication; Moore, Buckler, Chan, Staal, Rowe, and Martin, in preparation). Thus, the complement of endogenous V loci in a high virus strain may change because newly acquired V loci can become fixed during inbreeding, and a locus that was present as a heterozygote can be lost. The individual mice from the high virus strains C3H/Fg and C58 used in our crosses may not be representative of the same strains now. Further analysis of the heterogeneity of these loci might result in information on the generation of this diversity and the identification of factors that might restrict the number and phenotypic expression of V loci.

Several of the endogenous proviral sequences appear to be closely linked with cellular genes involved with sensitivity or resistance to retroviral infection or affecting lymphoid differentiation. Among the possibly coincidental linkage associations that warrant further study are (a) the proximity of Sev-1 and Fv-2 on chromosome 9; (b) Bxv-1 and a complex of lymphoid cell surface markers on chromosome 1 (24); and (c) Cv and a chromosome 5 locus for resistance to MCF viruses (J. Hartley, personal communication). It may also be relevant that the cell receptor for ecotropic virus is coded for by a locus on chromosome 5 (25).

Finally, the identification and separation of individual V loci aids in their characterization and makes it possible to identify DNA fragments carrying biologically defined proviruses. Combined use of classical and molecular technologies will greatly simplify identification of common V loci in related inbred populations and wild mice. Further studies might provide insight on the origin of these sequences in the germ line of inbred mice, on the different regulatory controls of high and low V loci, and on the fine structural arrangement of these sequences in mouse chromosomes.

Summary

Mendelian segregation analysis was used to map chromosomal genes for the induction of endogenous N- and B-tropic ecotropic retroviruses (V loci) in high and low leukemic mouse strains. Patterns of virus expression were determined for mice of various inbred strains, congenic lines carrying single V loci, and the linkage testing stocks used in mapping studies. Segregation analysis resulted in the genetic mapping of V loci from six inbred strains to five mouse chromosomes. The V locus of A/J was mapped to chromosome 5 and shown to be allelic with that of BALB/cJ and C3H/HeJ (Cv); this suggests that Cv represents a stable ancestral V locus present in Bagg albino stocks before the separation of inbred lines. The single, poorly inducible V locus of C57BL/10J and one of the four high virus loci of C58/Lw were mapped to the same region of chromosome 8 and may represent an allelic pair with different patterns of expression. An N-tropic V locus of the SEA/GnJ mouse was mapped to chromosome 9, and one of the three V loci of C3H/FgLw was mapped to chromosome 7. The endogenous B-tropic virus of B10.BR/SgLi was mapped to chromosome 11. These studies provide further evidence that endogenous ecotropic V loci are present
at different chromosomal sites in unrelated mouse strains and emphasize the role of germ line reinfections in the generation of this diversity.

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