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Chromosomal mapping of the mink cell focus-inducing and xenotropic *env* gene family in the mouse

(retroviruses/recombination/polymorphism/xenotropic cell-surface antigen/leukemia induction)

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ABSTRACT **Chromosomal locations of members of the xenotropic-related *env* gene family in the mouse genome have been determined. Endonuclease restriction site polymorphisms detected by molecular hybridization were used to study the inheritance of mink cell-focus inducing and xenotropic *env* gene-related sequences in recombinant inbred strains of mice. Some of the endogenous *env* sequences appear to be closely linked to genes determining leukemia virus induction and to genes involved in the immune response, such as the heavy and light chains of the immunoglobulin molecules or allotypic determinants on B and T lymphocytes. The use of probes that detect restriction fragment length polymorphisms in a small family of dispersed sequences promises to yield a large number of markers that can be used together with recombinant inbred strains for efficient mapping of the mouse genome.**

The expression of specific retroviral functions is inherited in a stable fashion in inbred strains of mice. Some of these functions have been attributed to integrated ecotropic proviruses and others to xenotropic viral sequences. Ecotropic viruses can proliferate in murine cells, whereas xenotropic viruses primarily infect heterologous cells. Genetic loci associated with ecotropic virus induction and with stably integrated proviruses have been mapped in the mouse genome by following levels of virus expression or induction in different strains (1, 2). More recently DNA–DNA hybridization has been used to follow the pattern of segregation of restriction fragment length polymorphisms to map integrated viral sequences (3, 4).

All mice strains have sequences related to xenotropic viruses and these sequences are stable components of the mouse genome (5, 6). They appear to be comprised of a family of dispersed genes. Three xenotropic-virus-associated functions have been mapped by following the induction of virus in inbred mouse strains (7–9), and hybridization with envelope (*env*)-specific probes suggests that there are more than 15 sites at which these sequences reside (5, 6). The resident xenotropic sequences, and particularly those related to the *env* gene, appear to be associated with a variety of important functions in the mouse. They have been implicated in the immune response (10) and the appearance of differentiation-specific cell-surface antigens (11), and they play a role in the formation of leukemogenic viruses. The onset of leukemia is associated with the appearance of a new class of viruses, the dualtropic mink cell focus-inducing (MCF) viruses (12). Analysis of the structure of the MCF viruses suggests that they arise by a recombination event that substitutes an endogenous xenotropic-like sequence for the murine leukemia virus (MuLV) *env* gene (13–15). To further characterize the xenotropic-like *env* sequences and their relationship to the immune system, cell-surface antigen formation, and specific gene rearrangement, we sought to identify their locations on the mouse chromosomes.

We were able to determine chromosomal locations for some of the endogenous MCF *env* gene sequences by following endonuclease restriction site polymorphisms in DNA of recombinant inbred (RI) strains of mice. This approach has been applied to map a number of genes (3, 4). The B × D RI strains were derived by crossing the C57BL/6J (B) and DBA/2J (D) strains, followed by systematic inbreeding of the progeny, beginning with chosen pairs from the F_2 generation (16, 17). These strains are now highly inbred and have been used extensively for gene mapping (3, 18, 19). The probability of recombination occurring between any two loci in the course of inbreeding is related to the map distance between them (16). In using RI strains to map DNA-level variants, polymorphic patterns are first determined in the parental strains B and D. The DNA restriction pattern of each one of the B × D RI strains is then screened for resemblance to either parental pattern (B or D). The result of this analysis is summarized as the strain distribution pattern (SDP) for a given locus and is then compared with SDPs derived from previously mapped genes. Closely linked genes will have similar SDPs.

Using this method and probing with a MCF xenotropic-specific *env* gene clone, we were able to assign map positions to 15 *env* gene sequences in the mouse genome. Some of these were closely linked to genes involved in the immune response and others appeared to be linked to genes involved in virus induction.

MATERIALS AND METHODS

Mice. Mice were purchased from The Jackson Laboratory (3).

Restriction Endonuclease Digestion. Digestion of high molecular weight liver DNA was carried out in a 4- to 6-fold enzyme excess. The enzymes *Eco*RI, *Pst* I, and *Bgl* II were prepared in our laboratory. Other enzymes were purchased from Bethesda Research Laboratories.

Southern Blot and Hybridization Analysis. Digested DNA was electrophoresed through 0.8% agarose gels (5–10 μg per lane) and transferred to nitrocellulose as described (20). A recombinant pBR322 plasmid subclone that contains a 700-base pair *Bam*HI–*Eco*RI fragment of the *env* gene clone of Moloney-MCF virus pMo-MCF_1-16 (21) was used as probe. The sub-

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Abbreviations: MuLV, murine leukemia virus; MCF, mink cell focus-inducing; RI, recombinant inbred; SDP, strain distribution pattern; cM, centimorgan(s); kb, kilobase(s); MLC, mixed lymphocyte culture; LPS, lipopolysaccharide.

clone was isolated by Candy Haggblom. The probe was labeled with [^{32}P]dCTP by nick-translation (22) and hybridized at 37°C in 50% formamide. Because a large number of bands were apparent on the hybridization pattern, only polymorphisms consisting of the presence of a specific band in one parent and absence in the other were analyzed. Each RI strain was then scored as either plus or minus for the specific band and the SDP determined. Each band and each SDP is referred to as *env* n.

The Algorithm for Linkage Analysis by Using the RI Strains. The SDP of a new locus is compared with SDPs of previously mapped genes. The estimation of recombination frequency between two loci (r) is obtained by the equation $r = R/(4 - 6R)$, where R is the observed ratio of recombinant strains relative to the total number of RI strains (n) (16). The accuracy of this method is expressed by the SEM of the estimate of r, which is given by $[r(1 + 2r)(1 + 6r)^2/4n]^{1/2}$ (16). Analyzing 25 RI strains, as was usually done in this study, the following SEMs are obtained for the following recombination frequencies in centimorgans (cM): 1 ± 1.0, 2 ± 1.6, 3 ± 2.1, 4 ± 2.6, 5 ± 3.0, 6 ± 3.5, 7 ± 4.0, 8 ± 4.5, 9 ± 5.0, and 10 ± 5.5.

RESULTS

Copy Number and Organization of MCF and Xenotropic-Like Sequences in the Mouse Genome. It is clear from Fig. 1 that the *env* probe used detects a multimember family of sequences in the mouse genome. Most DNA fragments that hybridize to the *env* probe are common to all four mouse strains, but specific polymorphic patterns are readily detected. These variations may be due to restriction site polymorphisms or to the absence of particular integration sites in specific strains of mice.

Using *Eco*RI, *Hin*dIII, and *Bam*HI, we obtain heterogeneous patterns of DNA fragments containing *env* sequences, which give information on the cellular sequences that flank the *env* genes. In contrast, the hybridization patterns obtained with DNA restricted by *Pst* I, *Bgl* II, and *Pvu* II primarily show a few dense bands, which are common to all of the mouse strains analyzed, suggesting that these restriction sites fall within identical sequences adjacent to *env*-like sequences. Counting the number of bands suggests that there are at least 30 copies of xenotropic *env* sequences in the mouse genome. The strain distribution pattern of each polymorphic band was followed independently. The number of polymorphisms that can be mapped by screening a pattern derived from one restriction enzyme varies from three (with *Eco*RI) to seven (with *Hin*dIII). A total of 40 SDPs termed *env*-1 to *env*-40 (of which 16 are shown in Table 1) was derived by screening 20 hybridized Southern blots (2 representatives are depicted in Fig. 2). In addition, SDPs of five different groups are identical as follows: (*i*) *env*-1 and *env*-4 (both with *Eco*RI) identical to *env*-11 (*Bgl* II); (*ii*) *env*-9 (*Bgl* II) identical to *env*-14 (*Pst* I) and to *env*-20 (*Pvu* II); (*iii*) *env*-12 (*Pvu* II) identical to *env*-16 (*Pst* I), to *env*-28 (*Xba* I), and to *env*-32 (*Hin*dIII); (*iv*) *env*-17 (*Pst* I) identical to *env*-38 (*Bam*HI); and (*v*) *env*-34 (*Hin*dIII) identical to *env*-39 (*Bam*HI). These data provide us with internal confirmation of our strain distribution patterns for the segregation of the alleles in the B × D system, which is the basis for our mapping technique.

Chromosomal Localization of the Polymorphic Endogenous *env* Sequences. env *sequences on chromosome 1.* Three different polymorphic patterns led to the mapping of three *env*

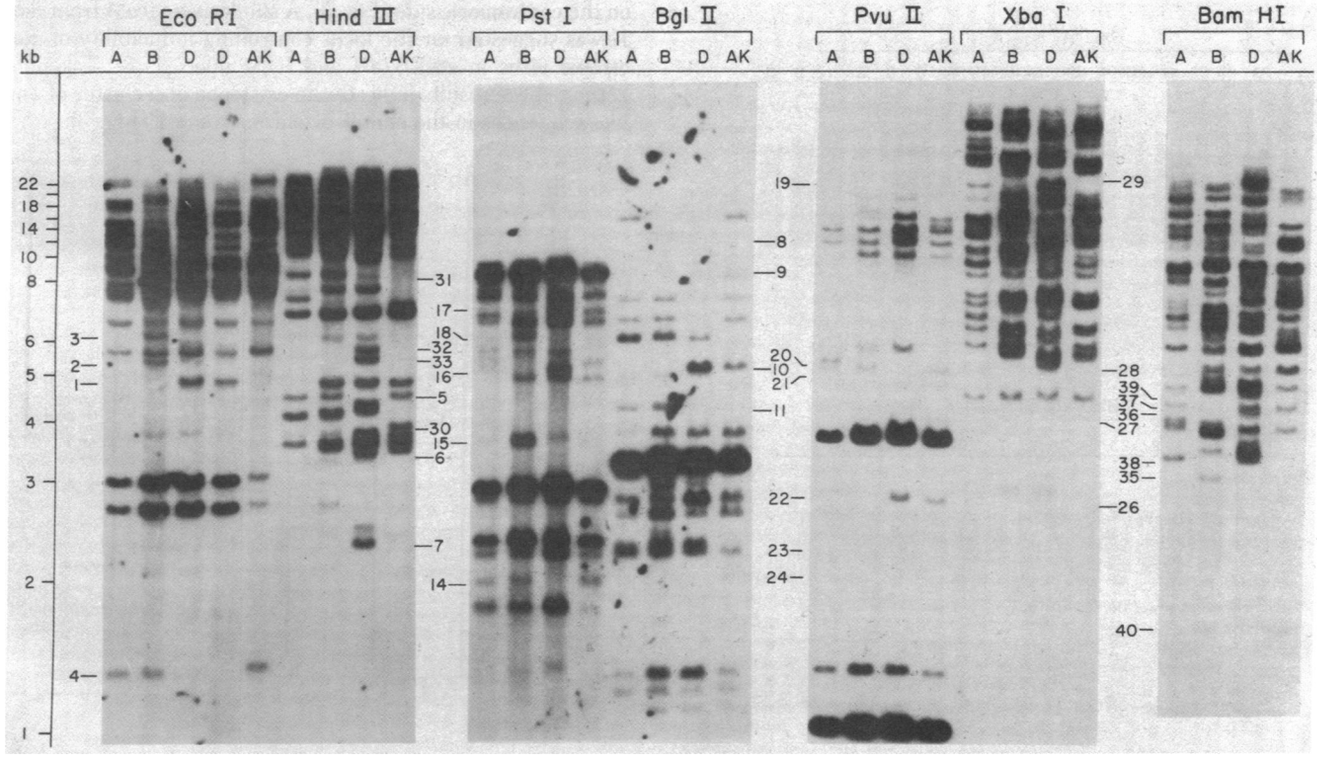

FIG. 1. Hybridization of the *Bam*HI–*Eco*RI fragment of MCF *env* probe to mouse DNA of four inbred strains: A-A/J, B-C57BL/6J, D-DBA/2J, and AK-AKR/J. The polymorphic patterns detected in the DNA of B and D strains are numbered as *env*-1 to *env*-40 and are shown in the spaces between the gels. Liver DNA was used except for the second D lane restricted with *Eco*RI, in which spleen DNA was used. The size of the fragments was determined by using *Eco*RI- and *Hin*dIII-digested phage DNA electrophoresed in the same gel containing the *Eco*RI-, *Hin*dIII-, *Pst* I-, and *Bgl* II-digested mouse DNAs. The other gels were run separately. Detection of some *env* sequences needed shorter or longer exposures than those depicted here. kb, Kilobases.

Table 1. Strain distribution patterns of *env*-specific sequences in the B × D RI strains for which map positions were determined

	B × D RI strains																								
Gene	1	2	5	6	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	27	28	29	30	31	32
env-2	B	D	B	B	D	D	B	D	B	D	B	D	D	D	B	D	B	D	D	D	B	D	D	D	B	D
env-3	B	D	D	B	B	D	B	D	B	D	D	D	B	D	D	D	D	B	B	B	B	B	D	B	B	D
env-5	B	D	D	B	B	B	D	B	B	B	B	D	B	D	D	D	D	B	D	B	D	D	B	D	D	D
env-6	B	B	D	B	D	D	D	B	B	B	B	B	D	B	B	B	D	B	D	D	D	D	D	D	B	D
env-8	D	B	B	B	B	B	B	B	D	B	B	B	B	D	B	D	D	B	D	D	B	B	B	D	B	D
env-9	B	B	D	B	B	D	D	B	D	B	D	B	B	B	B	B	D	D	D	D	D	D	D	D	B	D
env-15	D	D	D	*	B	B	B	B	B	B	B	B	B	D	B	B	B	B	*	B	B	D	B	B	B	D
env-21	B	B	B	*	D	B	D	B	B	B	D	D	B	D	D	B	B	B	D	D	D	B	D	D	B	D
env-23	D	B	B	*	D	B	B	D	D	D	D	B	D	B	B	D	B	D	B	D	B	D	B	D	B	D
env-25	B	B	B	*	D	B	D	B	B	B	D	D	B	D	D	B	B	B	B	B	B	B	B	B	D	D
env-27	D	B	D	*	D	B	D	B	D	B	B	*	B	D	B	D	D	D	D	D	D	D	B	B	B	B
env-29	D	B	D	*	D	D	D	B	B	B	D	*	B	D	D	D	B	B	D	D	D	B	D	B	D	D
env-31	B	D	B	B	B	B	B	B	B	B	B	B	B	B	B	B	D	B	B	D	B	B	B	B	D	B
env-34	B	B	B	D	B	D	D	D	D	*	D	D	B	B	D	B	B	B	D	D	D	D	B	D	D	D
env-35	B	D	B	*	B	B	B	D	B	D	B	B	B	B	B	B	B	B	B	B	B	B	B	B	D	D
env-36	B	B	D	*	D	D	D	B	B	B	B	B	B	B	B	B	D	B	D	D	D	D	D	D	B	D

* Not determined.

sites on chromosome 1. First, *env*-6 is a 3.4-kb *Hin*dIII fragment present in DBA/2J and absent in C57BL/6J. Linkage analysis to other markers on chromosome 1 locates *env*-6 to 1 cM from *Eph-1* (epoxide hydratase-1), 2 cM from *Mtv-7* (mammary tumor virus-7), 3 cM from *Mtv-10*, 5 cM from *Ltw-4* (liver 20,000–30,000 M_r protein-4), and 6 cM from *Mls* [mouse minor mixed lymphocyte culture (MLC)-stimulating] (23, 24). We suggest that *env*-6 may be allelic to a gene termed *Bxv-1*, which influences the inducibility of xenotropic-related viruses by either 5-iododeoxyuridine or by lipopolysaccharide (LPS). *Bxv-1* was previously mapped by linkage to two genes on chromosome 1: *Pep-3* (peptidase-3) and *Lp* (loop-tail) (7). Our results, obtained by using an *env* probe, suggest that the locus *Bxv-1* represents proviral sequences that play a role in viral induction. The second site on chromosome 1 is *env*-36 (*Bam*HI), which is located adjacent to *Eph-1* (no recombination observed among 25 RI strains), and is 1 cM away from *env*-6 and 2 cM from *Mtv-10*. The third site mapped to chromosome 1 is *env*-9 (Fig. 1, *Bgl* II). The *env*-9 polymorphism is located 1 cM from *Ltw-4*, 5 cM from *Eph-1* and *env*-36, 6 cM from *env*-6, and 8 cM from *Mls* on the distal side and 7 cM from *Pep-3* and *Rnr* (renin regulator) on the centromeric side (Fig. 3). A similar site, 9 cM from *Bxv-1*, was suggested for the locus controlling inducibility of xenotropic virus in BALB/cN and F/St mice (7, 8). Taken together, these results indicate the existence of a cluster of *env*-like sequences in the center of chromosome 1 (Fig. 3).

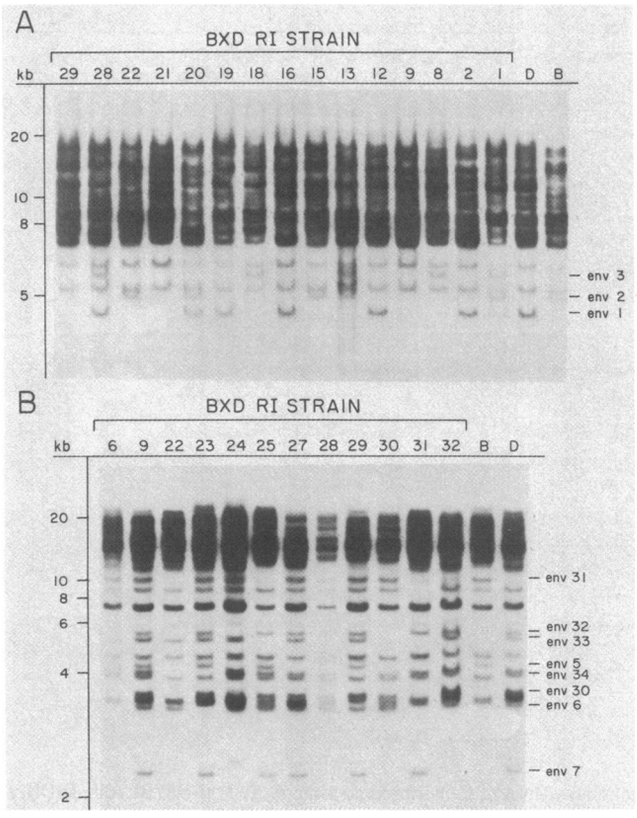

FIG. 2. Hybridization of the MCF *env* probe to the parental (B and D) and to the B × D RI strains DNAs. (*A*) DNA digested with *Eco*RI. (*B*) DNA digested with *Hin*dIII.

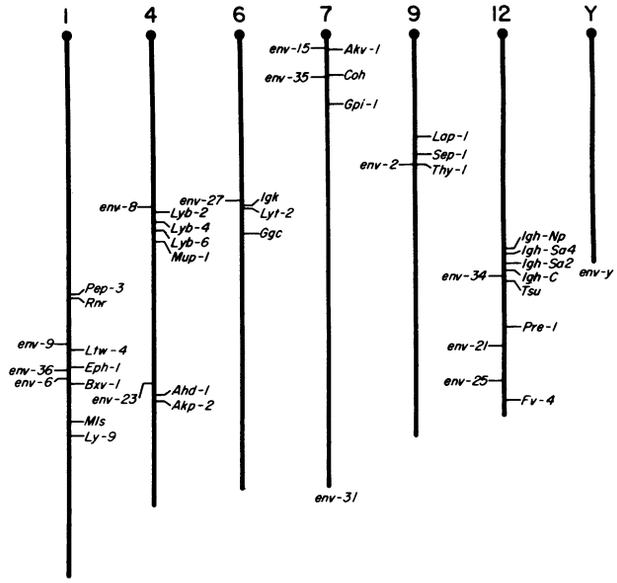

FIG. 3. A scheme representing localization of MCF *env* sequences on mouse chromosomes relative to neighboring genes (25, 26). The exact positions for *env*-31 and *env* sequences on chromosome Y were not determined. A few more *env* sequences were assigned to chromosomes 5 and 8 (see *Results*), but their localization is not yet clear and they were not included in this figure.

env *sequences on chromosome 4.* Two *env* polymorphisms are located on chromosome 4. The first, *env*-8 (*Bgl* II), shows tight linkage to a unique region of genes specifying B-lymphocyte alloantigens. *env*-8 maps 1 cM from *Lyb-2*, 1 cM from *Lyb-6*, 4 cM from *Lyb-4*, and 5 cM from *Mup-1* (major urinary protein-1) (23, 24). The *Lyb* genes apparently control antigenic determinants on cells of the B-lymphocyte lineage. *Lyb*-2 may represent a cell-surface marker for very early B cells (27). *Lyb-4* is an alloantigen that appears to be involved with lymphocyte-activating determinants in MLC reactions (27), and antiserum to *Lyb-6* determinants was shown to be mitogenic for B cells (28). Therefore, it is not surprising to find *Lps*, a gene for LPS responsiveness, in close association with the above genes (23). Our linkage data suggest that *env*-8 is located either among these genes, between *Lyb-2* and *Lyb-6*, or on the centromeric side of the cluster, 1 cM from *Lyb-2* (Fig. 3).

The second site for an *env* sequence on chromosome 4 is *env*-23 (*Pvu* II), which is located 2 cM from *Akp-2* (alkaline phosphatase-2) and *Ahd-1* (aldehyde dehydrogenase-1), 7 cM from *Gpd-1* (glucose phosphate dehydrogenase-1), and 11 cM from *Fv-1* (Friend virus susceptibility-1) (Fig. 3). This *env* sequence may be close to or overlap with a gene controlling the level of expression of xenotropic cell-surface antigen (24, 29).

env *sequences on chromosome 5.* Several *env* sequences show loose linkage to markers on chromosome 5. For example, *env*-5 (*Hin*dIII) maps 7 cM from *Pgm-1* (phosphoglucomutase-1) (23) and 11 cM from *Afp* (α-fetoprotein) (unpublished data) and is tentatively placed between these two genes. The polymorphism represented by *env*-3 (*Eco*RI) could be located 9 cM from *Afp*, but it does not show significant linkage to *Pgm-1* (14 cM) or *Ric* (Rickettsia resistance) (15 cM).

env *sequences on chromosome 6.* Restriction with *Xba* I gives rise to *env*-27, which maps 2 cM from *Lyt-2* (T-lymphocyte alloantigen-2) (24). The distance of 8 cM from *Ggc* (γ-glutamyl cyclotransferase) places *env*-27 on the centromeric side of *Lyt-2* and close to *Igk*, the gene coding for immunoglobulin light chain κ (23, 24).

env *sequences on chromosome 7.* The centromeric part of chromosome 7 includes at least two *env* sequences. *env*-35 (*Bam*HI) maps to the locus of *Coh* (coumarin hydroxylase) (no recombination among 23 mice tested) and 4 cM from *Gpi-1* (glucose phosphate isomerase-1) (23). The second locus, *env*-15 (*Pst* I), is located 6 cM from *Coh*. Lack of significant linkage to *Gpi-1* suggests that *env*-15 is close to the centromere and very near to *Akv-1*, a locus influencing inducibility of AKR leukemia virus (1, 23). A third locus is *env*-31 (*Hin*dIII), which shows linkage of 8 cM to *Coh*, 7 cM to *Tam-1* (tosyl arginine methylesterase-1), and 14 cM to *Gpi-1*. Thus, the exact position of *env*-31 is not clear.

env *sequences on chromosome 8.* The results of digestion with *Xba* I define *env*-29, which shows linkage to *Blv-1* (4 cM) on chromosome 8. The locus *Blv-1* designates an integration site of ecotropic MuLV in the DNA of C57BL/6J (4, 24).

env *sequences on chromosome 9.* The hybridization pattern of the *env* probe with *Eco*RI fragments of mouse DNA led to the mapping of *env*-2 on chromosome 9, 2 cM from *Sep-1* (serum protein-1) and 8 cM from *Lap-1* (leucine arylamino-peptidase-1) (23). These results locate *env*-2 very near or at the locus defined for *Thy-1* (θ antigen) (30).

env *sequences on chromsome 12.* Further analysis of SDPs led to the finding that *env*-34 (Fig. 2*B*, *Hin*dIII) and *env*-39 (Fig. 1, *Bam*HI) are identical and map to the region coding for the heavy chain of the immunoglobulin molecule on chromosome 12. This site is located 3 cM from *Igh-Sa2* and 4 cM from *Igh-Sa4* and *Igh-c* on the centromeric side and 7 cM from *Pre-1* (prealbumin component-1), which is on the distal side of chromosome 12 (23) (Fig. 3). The locus suggested for *env*-34 is also the site suggested for a cluster of T-cell alloantigens *Tsu* and *Tind* (31, 32). A second site on chromosome 12 is derived from the SDP of *env*-21 (*Pvu* II). This site is located 4 cM from *Pre-1*. A third *env* gene sequence, *env*-25 (*Pvu* II), is linked to *Lyb-7* (B-lymphocyte alloantigen-7) [no recombination was observed for the eight RI lines scored for *Lyb-7* (23)] and is loosely linked to *env*-21 (9 cM) and to *Pre-1* (12 cM). Lack of linkage to the immunoglobulin genes suggests that *env*-21 and *env*-25 may be located on the distal part of chromosome 12.

env *sequences on chromosome Y.* Three DNA fragments of strains A/J and C57BL/6J restricted with *Bgl* II hybridize with the *env* probe but are missing from DNA of DBA/2J mice (Fig. 1). These DNA fragments segregate in concordance with the Y chromosome in DNA of 40 males and females representing RI strains derived from A/J and C57BL/6J (data not shown).

Fifteen other SDPs were derived from the polymorphic patterns observed, but significant linkage with other markers (<10 cM) was not detected. However, as more genes are assigned to specific loci, we will be able to localize these 15 *env* gene sequences, whose SDPs contribute to the expansion of the linkage map of the mouse genome.

DISCUSSION

Recombinant inbred strains of mice have been used to map restriction length polymorphisms, including polymorphisms associated with ecotropic viral insertions in the mouse germ line (4). Using this technique we were able to look at the chromosomal distributions of sequences that correspond to a gene family—i.e., the MCF and xenotropic *env* gene sequences. The technique requires that the xenotropic sequences exist in a stable configuration in the parental and the RI mice. Hoggan *et al.* (6), using a probe similar to the one we used, concluded that there was minimal polymorphism of *env* sequences between inbred mouse strains. Corroboration for the chromosomal assignments reported here comes from studies in our laboratory with another set of RI strains (A × B and B × A), in which some of the same map positions have been found. Furthermore, using six other RI strains, Wejman *et al.* also found some of the same map positions with a similar *env*-specific probe (J. Wejman, B. A. Taylor, N. Jenkins, and N. Copeland, personal communication).

The resolution of the RI mapping technique establishes linkage to within 1 cM of a known marker. On the molecular level, 1 cM corresponds to hundreds of thousands of base pairs. Nonetheless, the RI method allows us to develop testable hypotheses about the relationships between MCF sequences and adjacent functions. For example, the polymorphisms *env*-6, *env*-9, and *env*-36 appear to cluster near the site of the *Bxv*-1 locus, which has been shown to be involved in the induction of xenotropic virus (7). A second cluster of polymorphisms associated with *env* map on chromosome 7 adjacent to the *Akv-1* locus, which is involved in ecotropic MuLV induction. The association of structural *env* gene sequences with loci determining virus inducibility suggests that molecular cloning and sequence analysis of these specific genomic DNA fragments may help to establish the relationship between MCF sequences and the mechanisms involved in the regulation of leukemia virus induction.

Another group of polymorphisms associated with *env* sequences map at or very close to loci that express genes involved directly in the immune response. The sequence *env*-34 is tightly linked to immunoglobulin heavy chain genes on chromosome 12, whereas *env*-27 is linked to the light chain gene on chromosome 6 (Fig. 3). Recently, it has been shown that specific

translocations into the immunoglobulin regions on chromosome 6 or 12, involving endogenous oncogenes such as c-*myc* or c-*mos*, were associated with plasmacytomas in mice (25, 26, 33). Our data suggest close linkage between endogenous *env* sequences and the immunoglobulin genes and raise the possibility that MCF sequences may play some role in the specific translocations that are frequently found in B-cell tumors.

It is interesting to note that the *env* loci on chromosomes 6 and 12 are also closely linked to genes that have been related to T-cell surface markers. In particular, *env*-27 is located 2 cM from *Lyt-2* and *Lyt-3* on chromosome 6, which are specifically expressed by cytotoxic and suppressor T cells. The *env* sequence on chromosome 12, *env*-34, is adjacent to the genes that have been associated with T-cell alloantigens *Tsu* and *Tind*, which are apparently involved in suppression or augmentation of the immune response (31, 32). In addition, *env*-2 appears to be adjacent to *Thy-1*, the θ antigen on chromosome 9, which is also a marker expressed on thymocytes. Furthermore, *env*-8 is linked to a cluster of *Lyb* genes on chromosome 4, which are involved in the expression of B-cell alloantigens. Howe *et al.* (25) suggested that the *Lyb-4* locus may reflect a viral integration site in order to account for a different chromosomal location for *Lyb-4* in C3H mice. The close association of a number of *env* sequences with loci involved in the immune response may be fortuitous, or the presence of these genes in a region of the chromosome that is activated in the immune response may lead to their gratuitous coexpression with immune-specific functions. Nevertheless, there is evidence to suggest that the viral envelope glycoprotein gp 70 is a constituent of the surface of normal cells (34–36). Its expression appears to be restricted mainly to lymphoid and epithelial cells and it could play a role in differentiation and development (34). Work by Moroni *et al.* (10) has documented the synergistic induction or inhibition of xenotropic *env* gene products and immune functions. The close chromosomal linkage between MCF *env* gene sequences and genes involved in various functions of the immune response may reflect a functional interaction between them. The cell-surface localization of xenotropic *env* gene products suggests that they may function as membrane receptors on some cells. Alteration of such receptors (36, 37) resulting from *env* gene recombination could play a role in cellular differentiation and oncogenesis. Alternatively, the genetic linkage may be adventitious. A closer analysis of the degree of linkage and the details of gene expression in specific regions involved in the immune response should resolve this question.

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