Segregation Patterns of Endogenous Mouse Mammary Tumor Viruses in Five Recombinant Inbred Strain Sets

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We identified mouse mammary tumor proviral loci in the AKR/J, C3H/HeJ, C57BL/6J, C57L/J, DBA/2J, and SWR/J inbred mouse strains and determined their segregation patterns in the AKXD, AKXL, BXD, BXH, and SWXL recombinant inbred strain sets. Two new *Mtv* loci, *Mtv-29* and *Mtv-30*, were identified. *Mtv-30* was genetically mapped to chromosome 12. Additionally, two previously identified *Mtv* loci, *Mtv-14* and *Mtv-23*, were genetically mapped to chromosome 4 and chromosome 6, respectively.

Sequences related to endogenous mouse mammary tumor viruses (MMTVs) are present in multiple copies dispersed throughout the murine genome. These sequences represent MMTV proviral loci (*Mtv*) that are integrated into the germ line and segregate as Mendelian loci. A variety of inbred mouse strains have been characterized for their *Mtv* content; standard molecular genetic techniques, such as analysis of somatic-cell hybrids, congenic strains, and backcross panels, as well as comparison of strain distribution patterns (SDP) within recombinant inbred (RI) strain sets, have been successfully used to assign a number of *Mtv* loci to specific chromosomes (Chr) (2, 6, 8-11, 13, 16). Problems have been encountered in coordinating results between studies because different MMTV-related sequences (including full-length cDNA) have been used as probes, varied electrophoretic techniques have produced what appear to be MMTV-related fragments of different sizes, and *Eco*RI fragments of similar size can be associated with more than one MMTV proviral locus. Recent studies in which 5' and 3' MMTV-specific flanking sequences were used to define the *Eco*RI fragments of each *Mtv* locus (10), coupled with the adoption of a standardized nomenclature for endogenous MMTVs (4), have facilitated the interpretation and coordination of most of the earlier published data.

During a study to define the MMTVs present in the NZB/BINJ and SM/J inbred strains and a set of RI strains derived from these strains (3a), we used the BXD and BXH RI strain sets as a control to aid us in correct MMTV identification. Unexpectedly, our results conflicted with the published data for *Mtv-1*, *Mtv-6*, *Mtv-7*, *Mtv-9*, *Mtv-11*, and *Mtv-14* in the BXD RI strains and for *Mtv-6*, *Mtv-9*, and *Mtv-14* in the BXH RI strains (16). By using both MMTV long terminal repeat (LTR)-specific and MMTV *env*-specific probes to identify the 5' and 3' *Eco*RI fragments associated with each MMTV proviral locus, we were able to determine the correct SDP of MMTV loci in these strains. We report here the SDP of MMTV proviral loci for the BXD and BXH RI strains, as well as those for the AKXD, AKXL, and SWXL RI strains. Although the MMTV proviral content has been characterized for various substrains of the AKR, C3H, C57BL, and DBA inbred strains, we also defined the MMTV proviral content of the AKR/J, C3H/HeJ, C57BL/6J, C57L/J, DBA/2J, and SWR/J strains, as they are the progenitor strains of the RI strains listed above. To our knowledge this

is the first description of the MMTV proviral content of strains C57L/J and SWR/J.

Identification of MMTV proviral loci. Genomic DNA extraction, digestion with *Eco*RI, gel electrophoresis, blotting to nylon membranes, hybridization, and autoradiography were performed as previously described (3a). Hybridization probes used were MMTV 8-29, a 1.4-kilobase pair (kb) *Pst*I fragment derived from a 5' LTR, and MMTV 8-21, a 1.7-kb *Pst*I fragment derived from the *env* region (7). At least two DNA samples from each inbred and RI strain were typed for MMTV proviral content. Because our data disagreed with published results for several of the BXD RI strains (16) and because the BXD-31 strain was contaminated in 1984 (B. A. Taylor, Mouse Newsl. 80:167, 1988), four mice of each BXD RI strain, two of which were born prior to 1984, were analyzed. Southern blots containing *Eco*RI-digested DNAs were first hybridized with ³²P-labeled MMTV LTR probe to identify 5' and 3' *Eco*RI fragments. The blots were then stripped of LTR probe and hybridized to ³²P-labeled MMTV *env* probe to provide confirmation of the 3' derivation and fragment size of each locus. Segregation patterns for *env*-specific fragments were matched to segregation patterns of LTR-specific fragments to obtain an SDP for each locus. This approach provided clear and consistent results as to the derivation, size, and segregation pattern of each *Eco*RI fragment defining an MMTV proviral locus. Because *Eco*RI was the only restriction endonuclease used in this study, DNA fragments will usually be referred to by size only.

Figure 1 shows the distribution and size of the MMTV LTR and *env*-hybridizing fragments present in the five RI progenitor strains. Table 1 defines each MMTV proviral locus with respect to fragment size, chromosomal assignment, and distribution among the RI progenitor strains. Also included for comparison are the generally accepted MMTV proviral *Eco*RI fragment sizes (4). Tables 2 through 6 present the SDP for each MMTV proviral locus segregating in the RI strain sets analyzed.

By using the criteria presented above, the following MMTV proviral loci were readily identified: *Mtv-1*, *Mtv-6*, *Mtv-7*, *Mtv-8*, *Mtv-9*, *Mtv-11*, *Mtv-13*, *Mtv-14*, *Mtv-17*, and *Mtv-23*. Because the characteristics, distribution, and history of MMTV proviral loci have been well described by Kozak et al. (4), we will not comment per se on each MMTV locus identified.

Some comments concerning the identification and strain distribution of the *Mtv-6*, *Mtv-7*, and *Mtv-11* loci are relevant. *Mtv-6* is defined by a 16.7-kb *Eco*RI fragment that

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FIG. 1. Southern blot of *Eco*RI-digested DNA hybridized to ³²P-labeled MMTV LTR (A) and ³²P-labeled MMTV *env* (B). RI progenitor strains C3H/HeJ (H), C57BL/6J (B), DBA/2J (D), AKR/J (A), C57L/J (L), and SWR/J (S) are shown. The sizes (in kilobases) of the 5' *Eco*RI fragments identified with the MMTV LTR probe are indicated at the right of panel A. Note that the sizes of the 3' fragments identified by the LTR probe are not labeled but are identical to the sizes given in panel B. Sizes of the 3' *Eco*RI fragments identified with the MMTV *env* probe (and LTR probe) are indicated at the right of panel B. Distributions of the MMTV LTR and MMTV *env* fragments among the RI progenitor strains are listed in Table 1. Fragment sizes were calculated on the basis of migration distance in 1% agarose gels compared with that for lambda (λ) *Hind*III fragments. Both panels were exposed for 3 days with intensifying screens.

hybridizes strongly to the MMTV LTR and weakly to MMTV *env* sequences (3). *Mtv*-7, also defined by a 16.7-kb LTR-specific fragment, can be distinguished from *Mtv*-6 by the presence of a 12.0-kb *env*-specific fragment and the absence of a 16.7-kb *env*-specific fragment. The first report of *Mtv* loci in the BXD RI strains did not correctly identify

the *Mtv* origin of the DBA/2J-derived 16.7-kb *Eco*RI fragment because a cDNA probe was used (16). We were able to identify the *Mtv*-6 origin of the 16.7-kb fragment in each BXD and AKXD strain by using the MMTV *env* probe, which does not detect the similar-size 5' cell-virus junction fragment of *Mtv*-7.

TABLE 1. MMTV proviral loci in RI progenitor strains

Locus and Chr ^a	Fragment size(s) (kb) from this study		Presence ^b of locus in strain:						Standardized fragment size (kb) ^c	
	LTR	<i>env</i>	SWR/J	C57L/J	AKR/J	DBA/2J	C57BL/6J	C3H/HeJ	5'	3'
<i>Mtv</i> -1, 7	6.0, 4.2	4.2				X		X	6.5	4.5
<i>Mtv</i> -6, 16	16.7	16.7				X		X	16.7 ^d	
<i>Mtv</i> -7, 1	16.7, 12.0	12.0	X		X	X			16.7	11.7
<i>Mtv</i> -8, 6	7.7, 6.3	6.3	X	X	X	X	X	X	7.8	6.7
<i>Mtv</i> -9, 12	7.4, 9.7	9.7		X	X		X		7.8	10.0
<i>Mtv</i> -11, 14	15.6, 5.4	5.4		X		X		X	15.0	5.8
<i>Mtv</i> -13, 4	9.0, 5.4	5.4				X			9.0	5.8
<i>Mtv</i> -14, 4	1.7		X			X		X	1.7 ^e	
<i>Mtv</i> -17, 4	9.9, 7.9	7.9	X	X	X	X	X		10.0	8.3
<i>Mtv</i> -23, 6?	12.3, 4.4	4.4			X				11.8	4.6
<i>Mtv</i> -29, ?	13.1, 5.3	5.3		X					13.0	5.3
<i>Mtv</i> -30, 12	~27.0	~27.0			X					
<i>Mtv</i> -, ?	~27.0	~27.0					X			

^a ?, Chr assignment unknown or questioned.

^b Presence is indicated by an X.

^c Standardized *Eco*RI fragment sizes (4).

^d Subgenomic provirus that hybridizes with MMTV LTR, *env*, and *gag* probes but not with a *pol* probe (3).

^e Fragment contains only LTR sequences.

TABLE 2. SDP of MMTV proviral loci in the AKXD RI strain set^a

Locus and Chr	AKXD strain																										
	1	2	3	6	7	8	9	10	11	12	13	14	15	16	17	18	20	21	22	23	24	26	27	28			
<i>Mtv-1</i> , 7	A	A	D	A	D	D	D	A	D	D	A	A	A	A	D	A	A	A	A	A	A	A	D	D			
<i>Mtv-6</i> , 16	D	D	A	D	D	A	A	A	A	A	A	A	A	A	D	A	D	D	D	A	D	A	D	D			
<i>Mtv-9</i> , 12	D	A	D	A	A	A	D	A	D	A	D	A	A	D	D	A	A	D	A	A	A	D	A	D			
<i>Mtv-11</i> , 14	D	D	A	D	A	D	A	D	A	D	A	A	D	A	D	D	A	A	A	A	D	D	A	D			
<i>Mtv-13</i> , 4	D	D	A	D	D	D	D	A	D	A	D	A	D	D	D	D	D	A	D	D	A	D	D	D			
<i>Mtv-14</i> , 4	A	A	D	D	A	A	A	A	A	D	A	A	A	A	D	D	A	A	A	D	A	A	D	A			
<i>Mtv-23</i> , 6	D	A	A	D	D	A	A	D	D	D	D	D	D	D	A	A	D	D	D	A	D	A	A	D			
<i>Mtv-30</i> , 12	D	D	A	A	D	D	A	D	D	A	A	A	A	D	A	D	A	A	A	A	D	D	D	D			

^a Strain symbols: A, AKR/J; D, DBA/2J. Our data agree with the results of Blank et al. (1) for the *Mtv-9* typing of the AKXD RI strains. Traina et al. (16) referred to *Mtv-1* as Unit V, *Mtv-6* as Unit 1, *Mtv-9* as Unit III, *Mtv-11* as Unit VII, and *Mtv-14* as Unit IX.

The segregation pattern of C3H/HeJ-derived *Mtv-6* in the BXH RI strain was also misinterpreted in an earlier study because of the inability to distinguish the *Mtv-6*-derived 16.7-kb fragment and the *Mtv-11*-derived 15.6-kb 5' fragment (16), a problem that was not encountered in this study.

Peters and co-workers (10) reported that AKR/J contains a provirus, provisionally designated *Mtv-22* (4), that is composed of a 5' 17.0-kb *Eco*RI fragment and a 3' 11.3-kb *Eco*RI fragment. We identified similar-size AKR/J-derived fragments of 16.7 and 12.0 kb that comigrated with the *Mtv-7*-derived fragments in DBA/2J mice (Fig. 1). Analysis of the AKXL RI strains indicated that the AKR/J-derived fragments cosegregated as a single proviral locus, and analysis of the SDP with other typed loci indicated that this provirus was located on Chr 1 in the region known to contain *Mtv-7*. Data from the AKXD RI strains indicated that the AKR/J-derived and DBA/2J-derived fragments were either allelic or closely linked, since each strain contained a 16.7- and a 12.0-kb fragment. We conclude from these results that the AKR/J provirus previously designated *Mtv-22* is, in fact, *Mtv-7*.

At least two new MMTV proviral loci were identified in this study. In the C57L/J RI progenitor strain, we identified two MMTV LTR-related fragments, 13.1 and 5.3 kb, that cosegregated in AKXL and SWXL RI strains. The MMTV *env* probe hybridized to the 5.3-kb fragment, indicating that it was derived from a 3' cell-virus junction fragment. Although these fragment sizes are almost identical to those previously reported for *Mtv-20*, which was found in only one substrain of C57BL (17), without further study we cannot determine whether the C57L/J-derived provirus is the same as *Mtv-20*. For this reason, we provisionally designate this a new proviral locus, *Mtv-29*.

A second new MMTV proviral locus, characterized by a single *Eco*RI fragment estimated to be at least 27 kb in size, was detected in the AKR/J strain with both MMTV LTR and

env probes (Table 1). A similar-size fragment was also detected in the C57BL/6J (Table 1) and NZB/BINJ (3a) inbred strains. Analysis of the SDP in RI strains derived from the AKR/J strain indicated that this 27-kb fragment was located on Chr 12 (see below); however, the C57BL/6J- and NZB/BINJ-derived 27-kb fragments were clearly not located in this region of Chr 12. It is possible that more than one provirus is represented by this large MMTV-related fragment in the C57BL/6J and NZB/BINJ strains or that these strains contain a single 27-kb fragment derived from an MMTV proviral locus other than the one carried by the AKR/J strain. We suggest that the locus identified by the 27-kb AKR/J-derived MMTV proviral fragment be designated *Mtv-30*. Until further clarification is possible, we have designated the locus (loci) defined by the 27-kb C57BL/6J-derived fragment(s) as *Mtv-?* (Table 1).

Linkage analysis of MMTV proviral loci. To confirm previous chromosomal assignments of known *Mtv* loci or to obtain evidence of linkage of previously unassigned MMTV proviral loci, the SDP of each *Mtv* locus was compared with those of other typed loci within each RI strain set by using data compiled by Taylor (15) or more recent information obtained from the literature. The results were consistent with the previous chromosomal assignments and locations for *Mtv-1*, *Mtv-6*, *Mtv-9*, *Mtv-7*, *Mtv-11*, *Mtv-13*, and *Mtv-17* (4, 15). New linkage information was obtained for *Mtv-14*, *Mtv-23*, *Mtv-29*, and *Mtv-30*. Genetic distances for RI strain data, obtained from tables provided by Silver (14), are presented as percent recombination (95% confidence interval), and those for backcross data are presented as percent recombination $\pm$ standard error.

Mtv-14 was originally assigned to Chr 6 by Traina et al. (16) by using data obtained from the BXD and BXH RI strains. However, analysis of the revised SDP for the BXD RI strains and the new SDP in the AKXD RI strains

TABLE 3. SDP of MMTV proviral loci in the AKXL RI strain set^a

Locus and Chr	AKXL strain																		
	5	6	7	8	9	12	13	14	16	17	19	21	24	25	28	29	37	38	
<i>Mtv-7</i> , 1	L	L	L	A	A	L	L	L	L	A	L	L	L	A	A	A	A	A	
<i>Mtv-11</i> , 14	A	A	A	L	L	A	A	A	L	L	L	A	A	L	L	L	A	A	
<i>Mtv-23</i> , 6	L	L	L	L	L	L	A	A	L	A	L	A	L	L	A	A	L	L	
<i>Mtv-29</i> , ?	A	L	L	L	L	L	A	A	L	A	L	A	L	A	A	A	L	L	
<i>Mtv-30</i> , 12	A	L	L	A	A	L	L	A	L	A	L	L	A	L	A	A	L	L	

^a Strain symbols: A, AKR/J; L, C57L/J. Traina et al. (16) referred to *Mtv-7* as Unit Ia and *Mtv-11* as Unit VII.

TABLE 4. SDP of MMTV proviral loci in the SWXL RI strain set^a

Locus and Chr	SWXL strain						
	4	7	12	14	15	16	17
<i>Mtv-7</i> , 1	S	S	L	S	L	S	L
<i>Mtv-9</i> , 12	L	L	L	S	L	S	L
<i>Mtv-11</i> , 14	L	S	S	S	S	L	L
<i>Mtv-14</i> , 4	S	S	S	S	S	L	L
<i>Mtv-29</i> , ?	L	L	L	S	L	S	S

^a Strain symbols: L, C57L/J; S, SWR/J. Our data agree with the results of Blank et al. (1) for the *Mtv-9* typing of the SWXL RI strains. Traina et al. (16) referred to *Mtv-7* as Unit Ia, *Mtv-9* as Unit III, *Mtv-11* as Unit VII, and *Mtv-14* as Unit IX.

TABLE 5. SDP of MMTV proviral loci in the BXD RI strain set^a

Locus and Chr	BXD strain																																	
	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								
<i>Mtv-1</i> , 7	B	D	B	B	B	B	B	D	B	D	D	B	B	B	B	D	B	B	D	B	B	B	B	D	D	D	D	D	D	D	D	D	D	D
<i>Mtv-6</i> , 16	B	B	B	B	D	B	D	B	B	B	D	D	B	D	D	B	B	D	D	D	D	D	B	D	D	B	D	D	D	D	D	D	D	D
<i>Mtv-7</i> , 1	B	D	D	B	D	D	D	B	B	B	B	B	B	B	B	D	B	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
<i>Mtv-9</i> , 12	B	B	B	B	D	B	B	D	B	B	D	B	D	D	D	B	B	D	B	D	D	D	B	B	D	D	D	D	D	D	D	D	D	D
<i>Mtv-11</i> , 14	B	D	B	D	D	D	D	B	B	D	D	D	B	D	B	B	D	B	B	D	B	B	D	B	D	B	D	D	D	D	D	D	D	D
<i>Mtv-13</i> , 4	D	B	D	B	B	D	B	D	B	D	D	D	D	D	B	D	D	D	B	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
<i>Mtv-14</i> , 4	D	B	B	D	B	B	D	B	D	B	B	B	D	D	B	B	D	B	D	D	D	D	B	B	D	D	D	D	D	D	D	D	D	D

^a Strain symbols: B, C57BL/6J; D, DBA/2J. Traina et al. (16) referred to *Mtv-1* as Unit V, *Mtv-6* as Unit I, *Mtv-7* as Unit Ia, *Mtv-9* as Unit III, *Mtv-11* as Unit VII, and *Mtv-14* as Unit IX.

suggested linkage of *Mtv-14* to loci on Chr 4, and unpublished data from Christine Kozak indicated that *Mtv-14* was linked to the Chr 4 locus *Mtv-17*. To verify the assignment of *Mtv-14* to Chr 4, we analyzed 43 backcross mice obtained from the mating of (C57BL/6J × DBA/2J)F₁ females to C57BL/6J males. Each individual was typed for *Mtv-14* and the two Chr 4 loci, *Mos* (12), which is located at the proximal end, and *Mup* (5), which is more centrally located. *Mos* typing was accomplished by using the pMSH probe (12) to identify a *TaqI* restriction fragment length polymorphism between C57BL/6J and DBA/2J. In a like manner, *Mup* typing was accomplished by using the p1057 probe (5) to identify an *EcoRI* restriction fragment length polymorphism between these two strains. The results indicate that *Mtv-14* is located on Chr 4; the gene order and genetic distances (given as percent recombination ± standard error) are as follows: *Mos* (7.0 ± 3.9)–*Mtv-14* (20.9 ± 5.4)–*Mup* (Table 7).

Analysis of the SDP in the AKXD and AKXL RI strains indicated that the AKR/J-derived *Mtv-23* locus is linked to two loci on Chr 6, *Myk-103*, a sequence flanking a transgenic insert, and *Tcrb*, T-cell receptor beta chain. Analysis of the 18 AKXL strains identified 2 strains (AKXL-25 and AKXL-29) that were recombinant between *Mtv-23* and *Myk-103*, indicating a genetic distance of 3.3% recombination (0.4 to 18.1%), and 3 strains (AKXL-19, AKXL-25, and AKXL-29) that were recombinant between *Mtv-23* and *Tcrb*, indicating a genetic distance of 5.6% recombination (1.0 to 27.3%). No linkage was detected in the AKXD RI strain set between *Mtv-23* and *Igk*-related loci, which are located distal to *Myk-103* and *Tcrb*. We conclude that *Mtv-23* is located on Chr 6 proximal to the *Myk-103* and *Tcrb* loci.

It should be noted that *Mtv-29* may also be located on Chr 6, since 3 of the 18 AKXL strains were recombinant between *Mtv-23* and *Mtv-29* (Table 3). However, if *Mtv-29* is located on Chr 6, it is proximal to *Mtv-23*.

TABLE 6. SDP of MMTV proviral loci in the BXH RI strain set^a

Locus and Chr	BXH strain												
	2	3	4	6	7	8	9	10	11	12	14	19	
<i>Mtv-1</i> , 7	H	H	H	H	B	H	B	H	H	H	H	H	
<i>Mtv-6</i> , 16	B	B	H	H	B	H	B	B	H	H	B	H	
<i>Mtv-9</i> , 12	B	B	B	B	H	B	H	H	B	H	H	H	
<i>Mtv-11</i> , 14	H	B	H	B	B	B	B	B	H	H	H	H	
<i>Mtv-14</i> , 4	B	B	B	H	H	H	B	B	H	H	B	B	
<i>Mtv-17</i> , 4	B	H	B	H	H	H	B	H	B	H	H	B	

^a Strain symbols: B, C57BL/6J; H, C3H/HeJ. Traina et al. (16) referred to *Mtv-1* as Unit V, *Mtv-6* as Unit I, *Mtv-9* as Unit III, *Mtv-11* as Unit VII, and *Mtv-14* as Unit IX.

TABLE 7. Analysis of backcross offspring segregating for *Mtv-14* and the Chr 4 markers *Mos* and *Mup*

Region of recombination ^a	Gene allele ^b			No. of backcross offspring
	<i>Mos</i>	<i>Mtv-14</i>	<i>Mup</i>	
None	B	B	B	14
	D	D	D	17
<i>Mos</i> – <i>Mtv-14</i>	B	D	D	1
	D	B	B	2
<i>Mtv-14</i> – <i>Mup</i>	B	B	D	3
	D	D	B	6
<i>Mos</i> – <i>Mtv-14</i> – <i>Mup</i>	B	D	B	0
	D	B	D	0

^a Percent recombination ± standard error: *Mos* (7.0 ± 3.9)–*Mtv-14* (20.9 ± 5.4)–*Mup*.

^b B, Allele inherited from strain C57BL/6J; D, allele inherited from strain DBA/2J.

The SDP of the AKR/J-derived *Mtv-30* locus in the AKXD and AKXL RI strains indicated that it is closely linked to *Apob* (apolipoprotein B), proximally located on Chr 12, as discord was noted between *Mtv-30* and *Apob* for only 1 strain (AKXD-3) among the 42 RI strains analyzed, indicating a genetic distance of 0.6% recombination (0.02 to 3.8%). As mentioned above, a similar-size MMTV-related fragment identified in the C57BL/6J and NZB/BINJ strains showed no linkage to loci located in the proximal region of Chr 12.

The more complete MMTV proviral profile reported here increases the number of markers available in each of the five RI strain sets analyzed and thus will aid in locating new genes in the mouse genome. For example, the *Mtv-11* proviral locus provides the first marker for Chr 14 in the AKXD and SWXL RI strain sets, and the *Mtv-6* and *Mtv-9* proviral loci occupy regions of Chr 16 and Chr 12, respectively, that were previously lacking in molecular markers for AKXD, BXD, and BXH RI strain sets.

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