The Putative Oncogene *Pim-1* in the Mouse: Its Linkage and Variation Among *t* Haplotypes

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ABSTRACT

*Pim-1*, a putative oncogene involved in T-cell lymphomagenesis, was mapped between the pseudo-alpha globin gene *Hba-4ps* and the alpha-crystallin gene *Crya-1* on mouse chromosome 17 and therefore within the *t* complex. *Pim-1* restriction fragment variants were identified among *t* haplotypes. Analysis of restriction fragment sizes obtained with 12 endonucleases demonstrated that the *Pim-1* genes in some *t* haplotypes were indistinguishable from the sizes for the *Pim-1* allele in BALB/c inbred mice. There are now three genes, *Pim-1*, *Crya-1* and *H-2 I-E*, that vary among independently derived *t* haplotypes and that have indistinguishable alleles in *t* haplotypes and inbred strains. These genes are closely linked within the distal inversion of the *t* complex. Because it is unlikely that these variants arose independently in *t* haplotypes and their wild-type homologues, we propose that an exchange of chromosomal segments, probably through double crossingover, was responsible for indistinguishable *Pim-1* genes shared by certain *t* haplotypes and their wild-type homologues. There was, however, no apparent association between variant alleles of these three genes among *t* haplotypes as would be expected if a single exchange introduced these alleles into *t* haplotypes. If these variant alleles can be shown to be identical to the wild-type allele, then lack of association suggests that multiple exchanges have occurred during the evolution of the *t* complex.

Genes affecting a variety of developmental and genetic processes including male fertility, embryonic development and meiotic transmission are located within the *t* complex (Bennett 1975; Lyon 1981; Silver 1985). These genes are distributed over a 15 centiMorgan (cM) segment of chromosome (Chr) 17 representing about 1% of the genome. One of the exceptional features of the *t* complex is that variant alleles of genes affecting each of these properties are usually inherited together as a single Mendelian unit rather than assorting through recombination (Dunn and Caspari 1945; Dunn and Gluecksohn-Schoenheimer 1950). Maintenance of this unique combination of alleles results from recombination suppression (Lyon and Phillips 1959; Hammerberg and Klein 1975a; Lyon et al. 1979; Nadeau, Phillips and Egorov 1985). Although the basis for suppression was poorly understood for many years, it is now well-established that at least two paracentric inversions are responsible for suppressing recombination in mice heterozygous for a *t* haplotype and its wild-type homologue (Silver and Artzt 1981; Artzt, Shin and Bennett 1982; Pla and Condamine 1984; Herrmann et al. 1986; Herrmann, Barlow and Lehrrach 1987). Although suppressed, however, very rare recombination between the *t* complex and its wild-type homologue does occur (Lyon and Phillips 1959; Lyon and Meridith 1964a-c). Crossovers producing these partial *t* haplotypes usually occur within the proximal inversion or between the proximal and distal inversions; crossovers within the distal inversion have not been described (Herrmann et al. 1986; Herrmann, Barlow and Lehrrach 1987; Schimenti et al. 1987). Mice with these partial *t* haplotypes usually lose some but not all of the properties associated with complete *t* haplotypes (Lyon and Phillips 1959; Lyon and Meridith 1964a-c; Lyon 1984, 1986). Loss of properties essential for the maintenance of *t* haplotypes in natural populations (Lyon 1984; Silver 1985) probably accounts for the absence of partial *t* haplotypes in wild mice (M. Erhart, S. J. Phillips and J. H. Nadeau, unpublished data).

One of the most important consequences of recombination suppression is that the combination of alleles producing the various phenotypic properties of the *t* complex and variant alleles of other genes within the *t* complex are preserved. Surveys of genetic variation among *t* haplotypes and their wild-type homologues have demonstrated that, with the exception of the *t* lethal genes, alleles are usually shared among all *t* haplotypes and that alleles associated with *t* haplotypes are either not found in mice that do not have a *t* complex or do not vary among wild mice, regardless of whether they have a *t* haplotype (Hammerberg and Klein 1975b; Hammerberg et al. 1976; Levinson and McDevitt 1976; Hauptfeld, Hammerberg 1987a; Hauptfeld, Hammerberg 1987b; Hauptfeld, Hammerberg 1987c).

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subject
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not be limited to genes within the H-2 complex
T-cell lymphomagenesis
showing this pattern of variation are located exclu-
and
haplotypes but to have indistinguishable alleles asso-
necting intron (CUYPERS et al. 1984; SELTEN et al. 1986).

MATERIALS AND METHODS

**Mice:** Mice were obtained from the research and produc-
tion colonies of the Jackson Laboratory.

**Genomic DNA:** Most of the DNAs from inbred, con-
genic, and recombinant inbred strains were purchased from
the Mouse DNA Resource of the Jackson Laboratory. Other
 genomic DNAs were prepared from spleen by using meth-
ods described by PHILLIPS and NADEAU (1984) and NADEAU,
PHILLIPS and EGOROV (1985).

**Pim-1 probe:** Probe A is a 923-bp BamHI genomic frag-
ment containing portions of exons 5 and 6 and the interven-
ing intron (CUYPERS et al. 1984; SELTEN et al. 1986).

**Southern analysis:** DNA (4 µg/lane) was digested with a
10-fold excess of restriction endonuclease for 3–6 hr under
conditions recommended by the enzyme supplier (Bethesda
Research Labs, Gaithersburg, Maryland). DNAs were elec-
trophoresed in horizontal 1%
agrose gels at 35 V for 18–
20 hr using E electrophoresis buffer (E buffer is 0.04 M
Tris, 0.02 M sodium acetate, 0.001 M Na2EDTA, pH 7.2).
Two gels were run simultaneously in long-bed gel boxes
(Dankar Corporation, Reading, Massachusetts). Gels were
prepared for transfer by soaking in 0.2 M NaOH, 0.6 M
NaCl, 0.15% thymol blue for 1 hr, followed by neutraliza-
tion in 1 M Tris, pH 7.4, 0.6 M NaCl for 1 hr. Transfer to
Zetabind nylon membranes (AME-Cuno, Stamford, Con-
necticut) was overnight in 10XSSC as described previously
(SOUTHERN 1975). Membranes were blotted dry for 5 min
at room temperature and UV irradiated for 30 sec by using
a 254 nm UV transilluminator.

**Preparation of probes and hybridization:** Total plasmid
DNA (200 ng) was linearized and labeled using random
hexamers (Pharmacia, Piscataway, New Jersey) as described
previously (FEINBERG and VOGELSTEIN 1983). Newly pre-
pared filters were prewashed in 0.1XSSC, 0.5% SDS at 65°
for 1 hr, followed by soaking in 1X Denhardt’s solution,
3XSSC for 2–24 hr at 65°. Filters were hybridized in
6XSSC, 1% Denhardt’s solution, 0.5% SDS in S256 (S256
is 8 µg/ml poly(A), 8 µg/ml poly(C), 200 µg/ml yeast RNA,
10 µg/ml Echerichia coli DNA, and 50 µg/ml salmon sperm
dNA in 3 mM Tris, pH 8.1) with 1–5 x 10⁶ cpm/ml of
probe overnight at 70°. Filters were then washed exten-
sively in 0.1XSSC, 0.05% SDS at 52°, dried, and exposed to
Kodak XAR film using DuPont Lightening-plus intensi-
fying screens at −70° for 1–5 days.

**Statistical analysis:** The maximum likelihood method
described by BISHOP (1985) was used to identify the most
likely gene order and to calculate the LOD score for order.
Maximum likelihood methods described by HALDANE and
WADDINGTON (1931) and by TAYLOR (1981) were used to
calculate recombination frequencies.

**RESULTS**

**Pim-1 restriction fragment variation among in-
bred strains:** Three restriction endonucleases, BamHI, HincII
and TaqI, were used to examine re-
striction fragments among selected inbred strains.
Three additional endonucleases, EcoRI, HindIII
and Mspl, were used to examine restriction fragments
among progenitors of recombinant inbred (RI)
strains. Variation was detected with BamHI, HincII
and TaqI, but not with any other endonuclease tested.
The six combinations of restriction fragments ob-
served define six alleles of Pim-1 (Table 1).

**Analysis of recombinant inbred and congenic
strains:** Restriction fragment variants involving 69
strains from 3 sets of recombinant inbred strains were
used to map Pim-1 (Table 2). Maximum likelihood
methods (BISHOP 1985) were used to identify the most
likely gene order and to calculate the LOD score for
order (Table 3). The gene order Hba-4ps-Pim-1-H-2
was 43 times more likely than alternative orders and
the order Pim-1-Crya-1-H-2 was 729 times more
likely than alternative orders (Table 3). Analysis of
genetic strains support this order (Table 4). Results
for the B6.TC2/Rn and B6.TC3/Rn strains (RINCHIK
and AMOS 1985) suggest that Pim-1 is located proximal
to Crya-1 and results for the LT.MA-Glo-1 strains
suggest that Pim-1 is located proximal to H-2, whereas
results for the B10.D2 strain suggest that Pim-1 is
located distal to D17Leh54. Recombination percent-
ages were Hba-4ps-4.4 ± 2.1–Pim-1-1.1 ± 0.8–Crya-
1. Because both Hba-4ps and Crya-1 are located within
the t complex (D’ESTACHIO et al. 1984; FOX, SILVER
and MARTIN 1984; Skow and DONNER 1985; Skow et
al. 1987), Pim-1 must also be located within the t
complex.
Variation of Pim-1 among inbred and wild mice and among t haplotypes

<table>
<thead>
<tr>
<th>Pim-1 allele</th>
<th>BamHI</th>
<th>HincII</th>
<th>TaqI</th>
<th>Strain, species or t haplotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pim-1*</td>
<td>0.9</td>
<td>10.2</td>
<td>2.8</td>
<td>BALB/cBy, BALB/cJ, C57BL/KsJ, C57BR/cdJ, C57L/J, C58/Bl, DBA/2J, FS/Ei, LP/J, LT/Sv, SEA/GnJ, SEC/1ReJ, TF/GnLe, 129/Sv, tα, tβ, tγ, tα32, tβ32</td>
</tr>
<tr>
<td>Pim-1*</td>
<td>5.1, 12.0</td>
<td>10.2</td>
<td>2.8</td>
<td>NZB/BINJ, RI11S/J</td>
</tr>
<tr>
<td>Pim-1*</td>
<td>2.2</td>
<td>10.2</td>
<td>2.8</td>
<td>AEJ/GnRJ, BDP/J, BUB/BnJ, C57BL/6J, C57BL/6By, C57BL/10J, IS/CamEi, MA/MJ, P/J, SF/CamEi, SJL/J, Sk/CamEi, SM/J, ST/J, SWR/J</td>
</tr>
<tr>
<td>Pim-1*</td>
<td>2.2</td>
<td>13.8</td>
<td>3.0</td>
<td>CAST/Ei, MOLF/Ei, RF/J</td>
</tr>
<tr>
<td>Pim-1*</td>
<td>2.2</td>
<td>18.0</td>
<td>3.4</td>
<td>Mus spretus, tα, tβ, tγ32</td>
</tr>
</tbody>
</table>

Inheritance of Pim-1 and other Chr 17 genes in the AKXD, AKXL, and BXD RI strains

<table>
<thead>
<tr>
<th>Gene</th>
<th>AKXD strain</th>
<th>AKXL strain</th>
<th>BXD strain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pim-1</td>
<td>A D A A A D D A A D A A D D A A D D A A A A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crys-1</td>
<td>A D A A A D D A A D D A A D D A A A A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-2</td>
<td>A D A A A D D A A D D A A D D A A A A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Hba-4ps</th>
<th>Pim-1</th>
<th>H-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hba-4ps</td>
<td>L L L A L L L L L L A A A A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pim-1</td>
<td>L A L A A L L L L L A A A A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-2</td>
<td>L A L A A L A A A A A L L L L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Pim-1 variation among t haplotypes: To determine whether Pim-1 varies among t haplotypes, 10 independently derived t haplotypes were each digested with BamHI, BanII, BclI, EcoRI, HincII, HindIII, PstI, PvuII, SacI, StuI, TaqI or XbaI. The tα, tβ and tγ32 haplotypes had a combination of BamHI, HincII, and TaqI restriction fragment variants (Figure 1) not found in other t haplotypes or inbred or wild mice tested (Table 1). The 2.2-kb BamHI fragment in the Pim-1 allele associated with these three t haplotypes was indistinguishable from that found in C57BL/6J and other inbred strains with the Pim-1* allele. By contrast, the 18-kb HincII and the 3.4-kb TaqI fragments were found only in the Pim-1 allele associated with these three t haplotypes.
TABLE 3
Maximum likelihood analysis of gene order for *Hba-4ps*, *Pim-1*, *Crya-1*, and *H-2* in RI strains

<table>
<thead>
<tr>
<th>RI strain</th>
<th><em>Hba-4ps</em> - <em>Pim-1</em> - <em>H-2</em></th>
<th><em>Hba-4ps</em> - <em>H-2</em> - <em>Pim-1</em></th>
<th><em>Pim-1</em> - <em>Hba-4ps</em> - <em>H-2</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>AKXL</td>
<td>-6.41</td>
<td>-8.04</td>
<td>-8.04</td>
</tr>
<tr>
<td>LOD score for order: 1.63</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comment: The most likely order is 43 times more likely than the order with the next largest likelihood

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-8.29</td>
<td>-11.15</td>
<td>-11.15</td>
</tr>
<tr>
<td>LOD score for order: 2.86</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comment: The most likely order is 729 times more likely than the order with the next largest likelihood

<table>
<thead>
<tr>
<th>BXD</th>
<th><em>Hba-4ps</em> - <em>Pim-1</em> - <em>Crya-1</em></th>
<th><em>Hba-4ps</em> - <em>Crya-1</em> - <em>Pim-1</em></th>
<th><em>Pim-1</em> - <em>Hba-4ps</em> - <em>Crya-1</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-10.42</td>
<td>-11.04</td>
<td>-12.03</td>
</tr>
<tr>
<td>LOD score for order: 0.62</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comment: The most likely order is 4 times more likely than the order with the next largest likelihood

TABLE 4
Mapping of *Pim-1* in congenic strains

<table>
<thead>
<tr>
<th>Strain</th>
<th><em>D17Leh54</em></th>
<th><em>Hba-4ps</em></th>
<th><em>Pim-1</em></th>
<th><em>Crya-1</em></th>
<th><em>H-2</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>C57BL/10J</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>B10.D2</td>
<td>B</td>
<td>x</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>DBA/2J</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>L.T/Sv</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>L.T.MA-Glo-1†</td>
<td>?</td>
<td>M</td>
<td>M</td>
<td>x</td>
<td>?</td>
</tr>
<tr>
<td>MA/Mj</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>C57BL/6J</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>B6.TC2/Rn</td>
<td>—</td>
<td>—</td>
<td>C</td>
<td>x</td>
<td>B</td>
</tr>
<tr>
<td>B6.TC3/Rn</td>
<td>—</td>
<td>—</td>
<td>C</td>
<td>x</td>
<td>B</td>
</tr>
<tr>
<td>BALB/c</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

* B, D, L, M and C are used as generic terms for alleles inherited from C57BL/10J, C57BL/6J, DBA/2J, L.T/Sv, MA/Mj and BALB/c, respectively. References for typing data are the following: *D17Leh54* (M.-B. TCHETGEN and J. H. NADEAU, unpublished observations), *Hba-4ps* (D'EUSTACHIO et al. 1984), except B10.D2 and L.T.MA-Glo-1† which is D. BURKART and J. H. NADEAU (unpublished observations), *Crya-1* (KLEIN, FIGUEROA and DAVID 1983).

with the *t*, *t*6 and *t*62 haplotypes. This *Pim-1* allele, which was defined by the unique *HincII* and *TagI* restriction fragments, represents a seventh allele of *Pim-1* and is designated *Pim-1t*. *Pim-1* variants among the 10 *t* haplotypes were not detected with any of the other endonucleases tested.

**Organization of the *Pim-1* gene associated with *t* haplotypes:** Restriction fragment sizes observed in the previous analysis for each of the 10 *t* haplotypes were compared to the fragment sizes predicted by a sequence analysis of the *Pim-1* gene in BALB/c mice (SELTEK et al. 1986). Results of this comparison are presented in Figure 2. The only restriction fragments that were unique to the *t* complex were *BanHI*, *HincII* and *TagI* fragments observed in the *Pim-1nt* gene associated with the *t*, *t*6 and *t*62 haplotypes. Other fragments observed in these and the other seven haplotypes analyzed were indistinguishable from predicted fragment sizes for the *Pim-1nt* allele (Table 1, Figure 2). These results suggest that the *Pim-1* genes in certain *t* haplotypes and inbred strains were indistinguishable.

**Lack of association between variant alleles among *t* haplotypes:** The occurrence of *Pim-1nt* variants among a panel of *t* haplotypes was compared to the occurrence of alleles of other genes known to vary among *t* haplotypes (Table 5). It is readily apparent that there is no association between alleles of any of these genes. Lack of association suggests that a single exchange is not a sufficient explanation for the pattern of variation of these genes among *t* haplotypes.

**DISCUSSION**

Restriction fragment sizes suggested that the *Pim-1* genes in *t* haplotypes and their wild-type homologues are organized in very similar ways. Analysis of genomic DNAs with endonucleases such as *BamHI*, *PstI*, *PvuII*, *SacI*, and *Stul* revealed fragments whose sizes were indistinguishable from those predicted by analysis of the DNA sequence of the *Pim-1* gene from BALB/c mice (Figure 2). Although Probe A recognizes a relatively small portion of the *Pim-1* gene, the analysis of *Pim-1* organization extended well beyond the limits of the 923 bp homologous to the probe. For example, *BglII*, *EcoRI*, *HindII* and *XbaI* restriction fragments extended beyond the 5', 3' or both boundaries of the *Pim-1* gene (Figure 2). There was no evidence that deletions, insertions or other structural
Figure 1.—(A) Inbred strains. BamHI restriction fragments in C3H/HeJ (Pim-Ia), BALB/cJ (Pim-I*), and NZB/BINJ (Pim-1') mice are illustrated. Fragment sizes (kb) are also given. (B) t haplotypes. The Pim-1' and Pim-1b alleles associated with the t" and t' haplotypes are illustrated. The t" haplotypes belong to the t" and t' complementation groups, respectively (Bennett 1975; Silver 1985). C3H-Tfl+/fl was included as a control. Genomic DNAs were digested with TaqI. Fragment sizes (kb) are also given.

rearrangements of Pim-1 were responsible for the variation observed. Thus for all haplotypes except t", t' and t" haplotypes, the Pim-1 genes in t haplotypes and those in wild-type chromosomes were indistinguishable.

The organization of the Pim-1 gene associated with the t", t' and t" haplotypes was very similar to the Pim-1b allele in BALB/c mice. Base substitutions probably account for the variable restriction sites. For example, gain (or loss) of a BamHI restriction site at position 5639 (Selten et al. 1986) accounts for the difference between the 0.9 kb and the 2.2 kb fragments (Figure 2). Similar arguments apply to the HindII and TaqI variants (data not shown). Although the variable HindII restriction site was probably located distal to the 3' end of the gene, the BamHI restriction site occurred in the translated portion of the last exon and the TaqI restriction site occurred in the 3' untranslated portion of the Pim-1 gene (Figure 2) (S. J. Phillips and J. H. Nadeau, unpublished observations).

Three patterns of variation of genes among t haplotypes and their wild-type homologues can now be recognized. The two previously identified patterns are either variants unique to the t complex and shared by all t haplotypes or genes that vary among t haplotypes but with variants in all cases unique to the t complex. Examples of the former are t complex proteins-1–9 (Tcp-1–Tcp-9) (Silver, White and Artzt 1980; Silver et al. 1983), glyoxalase-1 (Glo-1) (Nadeau 1986), Hba-4ps (Fox, Silver and Martin 1984), and several randomly selected genomic sequences within the t complex (Rohme et al. 1983; Fox, Silver and Martin 1984; Herrmann et al. 1986; J. H. Nadeau, M. Erhart, D. Burkart, S. J. Phillips and M.-B. Tchetgen, unpublished observations), and examples of genes with unique alleles that vary among t haplotypes are the t lethal genes (Bennett 1975), complement component4 gene C4 (Golubic et al. 1984), and other class I and class II genes within the H-2 complex (Hammerberg and Klein 1975b; Levinson and McDevitt 1976; Silver 1982; Shhn et al. 1982).

The third pattern consists of genes that vary among t haplotypes and that have indistinguishable alleles associated with t haplotypes and some wild-type chromosomes. These alleles include Pim-1" (Table 1 and Figure 2), Cya-1a and Cya-1b (Skow et al. 1987), and I-E" (Dembic, Singer and Klein 1984; Dembic et al. 1985). Extensive restriction fragment analysis for each of these alleles failed to reveal any differences between the allele associated with some t haplotypes and the corresponding alleles in inbred strains. These variant alleles are the only exceptions to the complete gametic disequilibrium associated with the t complex (Hammerberg and Klein 1975b; Nadeau 1986).

Three hypotheses could account for variation of Pim-1 and other genes among t haplotypes: (a) t haplotypes (and therefore Pim-1 and other variants) could have independent origins, (b) indistinguishable Pim-1 variants in t haplotypes and their wild-type homologues could have arisen independently through mutation and convergent evolution after t haplotypes originated, or (c) Pim-1 and other alleles could be exchanged between t haplotypes and their wild-type homologues. The first hypothesis does not seem very likely for two reasons. Although independent origins would account for the Pim-1 variants associated with the t", t' and t" haplotypes, it would not account for the numerous variants of other genes such as Tcp-1–9 (Silver et al. 1983) that appear to be unique to and shared by all t haplotypes. Similarly, the second hy-
Figure 2.—(a) Structure of the Pim-1 gene in BALB/c mice (after Cuypers et al. 1984; Selten et al. 1986). Open boxes illustrate transcribed but not translated sequences, closed boxes transcribed and translated sequences. The arbitrary scale (kb) corresponds to the DNA sequence provided by Selten et al. (1986). The location of several viral integration sites are indicated by vertical arrows. The 932 BamHI fragment representing Probe A is also illustrated. (b) Restriction fragments expected after digestion of genomic DNA with the endonucleases indicated are presented. Fragment sizes detected in the 10 t haplotypes surveyed are also presented. Vertical ticks indicate the location of the restriction site in the sequence of the Pim-1 gene in BALB/c mice (cf. Selten et al. 1986). Fragments detected by Probe A are illustrated by a solid line; other fragments are illustrated by a broken line. An arrow is used to indicate expected (or observed) fragment whose size extends beyond the limits of the sequence.
table 5

<table>
<thead>
<tr>
<th>t haplotype</th>
<th>tcl</th>
<th>Pim-1</th>
<th>Crya-1</th>
<th>H-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>t^b</td>
<td>0</td>
<td>t</td>
<td>a</td>
<td>w29</td>
</tr>
<tr>
<td>t^s</td>
<td>0</td>
<td>t</td>
<td>a</td>
<td>w30</td>
</tr>
<tr>
<td>t^12</td>
<td>4</td>
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<td>ND</td>
<td>Wild type</td>
</tr>
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<td>b</td>
<td>ND</td>
<td>w30</td>
</tr>
<tr>
<td>t^w1</td>
<td>w1</td>
<td>b</td>
<td>t</td>
<td>w30</td>
</tr>
<tr>
<td>t^w1+w5</td>
<td>w1 + w5</td>
<td>b</td>
<td>t</td>
<td>w31</td>
</tr>
<tr>
<td>t^w5</td>
<td>w5</td>
<td>b</td>
<td>a</td>
<td>w31</td>
</tr>
<tr>
<td>t^a</td>
<td>SL</td>
<td>b</td>
<td>t</td>
<td>w29</td>
</tr>
</tbody>
</table>

*Sources of data for genes other than Pim-1 are the following: tcl (Bennett 1975), Crya-1 (Skow et al. 1987), and H-2 (Klein, Figueroa and David 1983). ND indicates not done and SL indicates semilethal, i.e., no lethal gene. Pim-1, Crya-1, and H-2 are listed in order. Because t lethal genes are nonallelic (Artzt, McCormick and Bennett 1982; Artzt 1984; Shin, Bennett and Artzt 1984), they are listed here regardless of their location in each haplotype.

Although heterozygosity for inversions associated with t haplotypes strongly suppresses recombination (Lyon and Phillips 1959; Hammerberg and Klein 1975a; Lyon et al. 1979; Nadeau, Phillips and Egorov 1985; Herrmann et al. 1986; Herrmann, Barlow and Lehrach 1987; Schimenti et al. 1987), rare crossovers do occur and invariably produce partial t haplotypes that have lost some but not all of the properties of the t complex (Lyon and Phillips 1959; Lyon and Meredith 1964a-c; Lyon 1984, 1986). These rare crossovers occur either within the proximal inversion or between the proximal and distal inversions (Herrmann et al. 1986; Herrmann, Barlow and Lehrach 1987; Schimenti et al. 1987). Recombination involving the distal inversion has not been observed. Because double crossingover within inverted segments in inversion heterozygotes can produce viable progeny, however, recombination could exchange alleles of Pim-1 and other genes between the t complex and its wild-type homologue. Because t haplotypes in wild mice are usually heterozygous with wild-type homologues rather than with other complementing t haplotypes (Bennett 1981), there are many opportunities for recombination, even though recombination is strongly suppressed. We therefore propose that recombination between the t complex and wild-type homologues is responsible for the Pim-1, Crya-1, and some of the H-2 variation among t haplotypes. Dembic et al. (1985) proposed a similar argument to account for identical deletions involving the I-E gene in t haplotypes and wild-type homologues.

If exchange is responsible for wild-derived alleles associated with t haplotypes, then we might expect to find reciprocal exchanges with t-derived variants among wild-type chromosomes. Such t-derived variants have yet to be described for wild or inbred mice. Several properties of the t complex readily account for the absence of these variants in wild-type chromosomes. Although variants introduced into t haplotypes are preferentially preserved because of recombination suppression and transmission ratio distortion, variants resulting from reciprocal exchange will experience the same fate as mutations and most will be lost.

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LITERATURE CITED


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