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Location of the gene for theta antigen in the mouse

II. Three-point crosses place *Thy-1* in proximal region of chromosome 9

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SEROLOGICALLY detectable variants of theta (Thy-1) cell surface antigens[33] are determined by codominant alleles at the *Thy-1* locus on chromosome 9 of the mouse[20]. Quantitative variations in the levels of these antigens, which are expressed by thymus-derived lymphocytes and brain, epidermal, and fibroblastic cells[28,32,38,42], reflect developmental processes in the nervous system as well as in the immune system[30,35]. Because Thy-1 antigens are genetically polymorphic, antibodies against them can be induced by reciprocal immunizations between *Thy-1*^{a}-homozygous mouse strains, which express the antigen Thy-1.1, and *Thy-1*^{b}-homozygous strains which express Thy-1.2. Some donor-recipient strain combinations give rise to stronger antibody responses than do others, since both the ability of the recipient to respond to Thy-1[45,46] and the capacity of the donor's thymus cells to induce an anti-Thy-1 response (Lake and Mitchison[23] and T.C. Douglas, unpublished results) are genetically controlled.

The gene sequence: theta antigen (*Thy-1*)—coat color dilution (*d*)—cytoplasmic malic enzyme (*Mod-1*)—transferrin (*Trf*) on chromosome 9 has been established by combining the results of two three-point backcrosses[2,21]. While these results have shown that *Thy-1* and *Trf* could not both be distal to *d*, as had been thought previously on the basis of two-point recombination data, they have not made possible an unambiguous decision as to which of these two markers is actually on the proximal (centromeric) side. Three-point data from subsequent crosses involving the fur deficiency gene *fd* have indicated that *Thy-1* is at the proximal end of this gene group[17]. In the present study we have undertaken an independent confirmation of this assignment using the gene curly whiskers (*cw*) as a centromeric marker[6,13,26,27]. Recombination frequencies for the intervals *cw*—*Thy-1* and *cw*—*Mod-1* also have been measured.

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Materials and Methods

Inbred mice were purchased from Gl. Bomholtgaard Ltd., Ry, Denmark (AKR/ABom); Cumberland View Farms, Clinton, Tennessee (AKR/Cum); and the Jackson Laboratory, Bar Harbor, Maine (AKR/J and C3H/HeJ). Mice homozygous for curly whiskers (*cw*) and dilute (*d*) were the generous gift of Dr. Margaret C. Green. The latter stock was derived from *cw*/*cw* mice obtained from Harwell that were crossed to DBA/2J and subsequently inbred for approximately six generations (Dr. Margaret C. Green, personal communication).

Antisera against Thy-1 antigens were produced using the optimal immunization schedule of Reif and Allen[34]. Additional bleedings also were taken 5 to 9 days following subsequent antigen boosts. AKR/Cum anti-AKR/J[1,39] and AKR/J anti-C3H/HeJ antisera provided reagents specific for Thy-1.1 and Thy-1.2, respectively.

Mice to be typed for *Thy-1* were thymectomized under nembutal anesthesia[3]. Thymocytes were suspended by mincing in Dulbecco's Modified Eagle Medium, washed, and used as target cells in complement-dependent cytotoxic assays as previously described[11]. Control tests with noncytotoxic AKR/Cum normal serum and complement were included for thymocytes from each animal.

Kidneys, which served as the source for cytoplasmic malic enzyme (*Mod-1*), were removed from mice that had been killed by cervical dislocation. Aqueous homogenates (3 ml water per gram kidney weight) were prepared using a loose-fitting Potter-Elvehjem tissue grinder and were clarified by centrifugation at 12,000 *g* for 10 minutes at 4°C. *Mod-1* typing was performed by thin-layer isoelectric focusing in polyacrylamide gels[9].

Results

Two male mice homozygous for *cw*, *Thy-1*^{b} and *d* were mated to AKR/ABom females (+,*Thy-1*^{a},+). Thirty-nine of the resulting F_1 females were backcrossed to the same *cw*, *Thy-1*^{b}, *d* males. Members of the 33 backcross litters obtained were visually typed for *cw* and *d* when weaned at 3-4 weeks of age. *Thy-1* typing was per-

formed as soon as possible thereafter. Recombination data for these three markers are presented in Table I.

The low frequencies of the last two classes in Table I indicate that these animals are double recombinants, so *Thy-1* must be located between *cw* and *d*. Allowing for these double recombinants, the calculated map distance between *cw* and *d* is therefore 40.8 ± 3.3 percent. Segregation ratios for the individual markers *cw*, *Thy-1*, *d*, and sex did not deviate significantly from 0.5.

In agreement with the genetic data of Krog[22], electrofocusing of kidney homogenates from several AKR/ABom animals showed this subline to be homozygous for the *b* allele at the *Mod-1* locus. Four F_1 males sired by each *cw d*/*cw d* male were tested and found to be heterozygous for *Mod-1*, thus indicating that the *cw d*/*cw d* males were both homozygous for the *Mod-1*^{a} allele.

In order to observe the segregation of *Mod-1* in this cross, members of the first 11 backcross litters analyzed above were additionally typed for cytoplasmic malic enzyme. These results are shown in Table II. Recombination frequencies measured for *cw—Thy-1*, *Thy-1—d*, and *cw—d* do not differ significantly from those shown in Table I. Consideration of these markers taken three at a time indicates the gene orders: *cw—Thy-1—d*, *Thy-1—d—Mod-1*, *cw—Thy-1—Mod-1* and *cw—d—Mod-1*. These are consistent only with the overall order: *cw—Thy-1—d—Mod-1*. The individual segregation ratio for each of these markers as well as that for sex did not deviate significantly from 0.5.

Discussion

The gene curly whiskers (*cw*), first found in 1958, was shown to be fully penetrant, easily typed, fully viable, and linked with tail kinks (*tk*) in linkage group II (chromosome 9)[13]. Subsequently, the more precise location of *cw* was made possible by genetic studies of three different translocations involving this chromosome.

Table I. Recombination data for *cw*, *Thy-1*, and *d*

<table>
<tr><th colspan="3">Gamete inherited from hybrid parent*</th><th>Frequency</th></tr>
<tr><td>cw</td><td>Thy-1^{b}</td><td>d</td><td>67</td></tr>
<tr><td>+</td><td>Thy-1^{a}</td><td>+</td><td>73</td></tr>
<tr><td>cw</td><td>|Thy-1^{a}</td><td>+</td><td>26</td></tr>
<tr><td>+</td><td>|Thy-1^{b}</td><td>d</td><td>30</td></tr>
<tr><td>cw</td><td>Thy-1^{b}|</td><td>+</td><td>12</td></tr>
<tr><td>+</td><td>Thy-1^{a}|</td><td>d</td><td>7</td></tr>
<tr><td>cw</td><td>|Thy-1^{a}|</td><td>d</td><td>4</td></tr>
<tr><td>+</td><td>|Thy-1^{b}|</td><td>+</td><td>4</td></tr>
</table>

Recombination percentages:		Significance of linkage**
cw–Thy-1	64/223 = 28.7 ± 3.0%	$P < 0.001$
Thy-1–d	27/223 = 12.1 ± 2.2%	$P < 0.001$
cw–d	75/223 = 33.6 ± 3.2%	$P < 0.001$

* The positions of recombinations are marked by vertical bars
** Using χ^2 test with one degree of freedom

Lyon et al.[26] were able to demonstrate linkage (1.8 percent recombination) between *cw* and the point of rearrangement for the translocation *Rb(9.19)163H* (abbreviated *Rb163*). Assuming that the submetacentric *Rb163* chromosome represents a simple centromeric fusion between the acrocentric chromosomes 9 and 19, the two recombinations observed between *cw* and *Rb163* indicate that the centromere is on the opposite side of *cw* from *se* and *tk* (Table IV).

The positioning of *cw* at the centromeric end of the chromosome was confirmed by nondisjunction studies of the reciprocal translocation *T(9; 17)138Ca* (abbreviated *T138*). The gene *se* behaved as if distal to the *T138* breakpoint whereas *cw* was found to be proximal[27].

Cattanach and Moseley's segregation data[6] for a second centromeric-fusion chromosome, *Rb(9.14)6Bnr* (abbreviated *Rb6*) are also in good agreement with those obtained for *Rb163*. The single *Rb6—cw* recombinant observed by those authors is consistent with the placement of the centromere to the left of *cw* at a distance of 2.5 map units (Table IV).

We have used *cw* as a centromeric marker to check the polarity of the *Thy-1—d—Mod-1—Trf* group. Our data clearly indicate the gene order: *cw—Thy-1—d—Mod-1*, thus confirming the placement of *Thy-1* at the proximal end of this group.

Of the six recombination intervals that we examined (Table II), four also have been measured in other experi-

Table II. Recombination data for *cw*, *Thy-1*, *d*, and *Mod-1*

<table>
<tr><th colspan="4">Hybrid gamete*</th><th>Frequency</th></tr>
<tr><td>cw</td><td>Thy-1^{b}</td><td>d</td><td>Mod-1^{a}</td><td>16</td></tr>
<tr><td>+</td><td>Thy-1^{a}</td><td>+</td><td>Mod-1^{b}</td><td>17</td></tr>
<tr><td>cw</td><td>Thy-1^{b}</td><td>d</td><td>|Mod-1^{b}</td><td>1</td></tr>
<tr><td>+</td><td>Thy-1^{a}</td><td>+</td><td>|Mod-1^{a}</td><td>2</td></tr>
<tr><td>cw</td><td>Thy-1^{b}|</td><td>+</td><td>Mod-1^{b}</td><td>4</td></tr>
<tr><td>+</td><td>Thy-1^{a}|</td><td>d</td><td>Mod-1^{a}</td><td>0</td></tr>
<tr><td>cw</td><td>|Thy-1^{a}</td><td>+</td><td>Mod-1^{b}</td><td>5</td></tr>
<tr><td>+</td><td>|Thy-1^{b}</td><td>d</td><td>Mod-1^{a}</td><td>12</td></tr>
<tr><td>cw</td><td>Thy-1^{b}|</td><td>+</td><td>|Mod-1^{a}</td><td>0</td></tr>
<tr><td>+</td><td>Thy-1^{a}|</td><td>d</td><td>|Mod-1^{b}</td><td>0</td></tr>
<tr><td>cw</td><td>|Thy-1^{a}</td><td>+</td><td>|Mod-1^{a}</td><td>0</td></tr>
<tr><td>+</td><td>|Thy-1^{b}</td><td>d</td><td>|Mod-1^{b}</td><td>0</td></tr>
<tr><td>cw</td><td>|Thy-1^{a}|</td><td>d</td><td>Mod-1^{a}</td><td>2</td></tr>
<tr><td>+</td><td>|Thy-1^{b}|</td><td>+</td><td>Mod-1^{b}</td><td>0</td></tr>
<tr><td>cw</td><td>|Thy-1^{a}|</td><td>d</td><td>|Mod-1^{b}</td><td>0</td></tr>
<tr><td>+</td><td>|Thy-1^{b}|</td><td>+</td><td>|Mod-1^{a}</td><td>0</td></tr>
</table>

Recombination percentages:		Significance of linkage**
cw–Thy-1	19/59 = 32.2 ± 6.1%	$P < 0.01$
cw–d	21/59 = 35.6 ± 6.2%	$P < 0.05$
cw–Mod-1	24/59 = 40.7 ± 6.4%	$0.1 < P < 0.2$
Thy-1–d	6/59 = 10.2 ± 3.9%	$P < 0.001$
Thy-1–Mod-1	9/59 = 15.3 ± 4.7%	$P < 0.001$
d–Mod-1	3/59 = 5.1 ± 2.9%	$P < 0.001$

* The positions of recombinations are marked by vertical bars
** Using χ^2 test with one degree of freedom

ments. For purposes of comparison we have taken as standards recombination frequencies for those studies reporting typing results for the largest number of backcross offspring of heterozygous females (Table III). Our results for the intervals *Thy-1*—*d*, *d*—*Mod-1*, and *Thy-1*—*Mod-1* do not differ significantly from those shown in Table III. In addition, our value for *cw*—*d* does not differ significantly from that given for *cw*—*se*. These latter two intervals are expected to be essentially equivalent because of the very close linkage between *d* and *se* [18].

Recombination frequencies for the markers *cw*—*Thy-1* and *cw*—*Mod-1*, which have not been reported previously, were found to be 28.7 ± 3.0 percent and 40.7 ± 6.4 percent, respectively. The size of the genetic region under study is illustrated by the latter value: in the absence of additional data the degree of linkage observed between *cw* and *Mod-1* would not be significant at the 5 percent level.

Three limitations of this study should be noted. First, the heterozygous parents are all females. This is significant because sex-specific differences in recombination frequencies for chromosome 9 genes are known to occur [2,12,36]. While this phenomenon may affect individual recombination frequencies, it should not alter gene orders deduced from the relative frequencies of single- versus multiple-recombinant classes. Second, our matings have all been constructed with *cw*, $Thy\text{-}1^b$, *d*, and $Mod\text{-}1^a$ in the coupling phase. This limitation is probably not serious because there is no evidence of inviability or distorted segregation for any of these markers. Third, the fact that the *cw d*/*cw d* stock is not fully inbred precludes a precise repetition of the present experiment. However, the agreement of the recombination frequencies observed in this study with those measured previously does not suggest any serious difficulty due to this factor.

While it is often possible to determine the order of linked genes by comparing two-point recombination frequencies measured in different crosses, gene orders based on multiple-point crosses tend to be more reliable. In the latter case gene orders can be deduced for the relative numbers of single- versus multiple-recombinants as well as from the comparative recombination frequencies for each pair of loci. The number of multiple-point crosses involving markers on chromosome 9 is now large enough that we have found a compilation of them to be useful (Table IV). Each line in this table represents the result of one such cross. Intervals in which informative recombinations occurred are signified by dashed lines connecting the symbols for the loci concerned.

One feature, which can be seen immediately from this table, is that the genes *d* and *se*, because of the frequency with which they have been used, play a key role in defining the structure of this linkage group. In fact, all of the markers involved in the crosses shown can be placed unequivocally either to the right or left of *d* and *se* solely on the basis of these data. Further ordering within the proximal and distal groups is also possible. The remaining structure of the linkage group, which must be based on data from other sources, has been filled in according to the linkage map prepared by Womack [43]. Further information and references regarding individual chromosome 9 markers is available in references 15 and 41, and much of the supporting two-point recombination data not discussed here has been reviewed by Robinson [36].

Table III. Literature values for recombination frequencies measured in this study

Interval studied	References	Recombination percentage for heterozygous female parent
Thy-1–*d*	17,20*,21,25	12.8 ± 3.6% (11/86)
d–*Mod-1*	7,17,19*,21,29,31,44	10.1 ± 2.9% (11/109)
Thy-1–*Mod-1*	2*,21	21.4 ± 4.1% (21/98)
cw–*se*	6,13*,26	40.1 ± 2.7% (130/324)

* Source of cited recombination percentage

Summary

Males of a partially inbred mouse stock homozygous for *cw* and *d* were crossed to AKR/ABom females. Progeny obtained by backcrossing heterozygous F_1 females to *cw d*/*cw d* males were analyzed for the markers *cw*, *Thy-1*, *d*, and *Mod-1*. Three- and four-point recombination data are consistent with the map: *cw*—29—*Thy-1*—12—*d*—5—*Mod-1*, in which *cw* is nearest to the centromere. These recombination data are discussed in relation to previous multiple-point recombination studies of chromosome 9.

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Table IV. Multiple-point recombination studies of chromosome 9

Centromere	*cw*	*T138*	*Lap-1*	*Thy-1*	*lu*	*Mpi-1*	*sg*	*d*	*se*	*sv*	*tk*	*Mod-1*	*fd*	*Trf*	*Fv-2*	*du*	*Bgs**	*sch*	Ref.
Rb6	*cw*								*(se*		*tk)*†								6
Rb163	*cw*								*se*		*tk*								26
	cw								*se*		*tk*								13
								d			*tk*		*fd*						24‡
								d				*Mod-1*	*fd*						17
				Thy-1				*d*					*fd*						17
	cw			*Thy-1*				*d*				*Mod-1*							this study
				Thy-1				*d*				*Mod-1*							21
				Thy-1				*d*							*Fv-2*				25
				Thy-1								*Mod-1*		*Trf*					2
												Mod-1		*Trf*			*Bgs*		8
								d				*Mod-1*					*Bgs*		7,31
			Lap-1					*d*				*Mod-1*							44
						Mpi-1		*(d*	*se)*			*Mod-1*							29
		T138						*d*			*tk*								16
		T138						*d*	*se*§										5
								d§	*se*							*du*			40
								d			*tk*					*du*			16
					lu			*(d*	*se)*							*du*			14
					lu				*se*	*sv*									10
					lu		*sg*	*(d*	*se)*										16

* The additional closely-linked loci *Bgt*[31] and *Bge*[4], which also affect β-galactosidase expression, have also been described
† No recombination was observed between markers enclosed in parentheses
‡ Also, personal communication from H. O. Sweet and P. W. Lane
§ In each of these two cases the indicated gene order is based on a single recombinant between *d* and *se*; these results, though individually inconclusive, are in agreement with each other and with those of Russell[37], who analyzed a series of deficiencies involving *d*, *se*, and *sv*

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