

RETINAL DEGENERATION IN THE MOUSE

Location of the *rd* Locus in Linkage Group XVII

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OUR INTEREST in inherited neurological diseases in mice prompted this linkage study of the retinal degeneration (*rd*) gene. A practical motive for the study is that the assignment of one mutant locus to a position on the linkage map increases the prospect of assigning another, and in turn increases the opportunity to use marker genes in the analysis of a mutant disease mechanism. A less immediate motive is that some understanding of mammalian gene interrelationships might result from detailed linkage mapping.

An inherited retinal abnormality, later named retinal degeneration, *rd*, was recognized by Bruckner in 1951³ in wild mice caught near Basle, and was studied almost simultaneously in England^{35,36,39} and France^{18,19}. T. B. Dunn¹⁰ found, incidental to a radiation study, that inbred C3H mice have the same condition; these widely used mice had not previously been recognized as blind. The C3H mutant was shown to be allelic with *rd* by Lucas²⁷. A gene similar or identical to *rd* is found in many inbred mouse strains (Table III).

Noell²⁹ and Karli¹⁸ have reviewed the pathophysiology of *rd*. In animals homozygous for *rd*, photoreceptor cells appear to develop normally until about 10 days after birth, when the rod outer segments have just begun to form. Rods attain no more than a fraction of their normal length and then the whole photoreceptor cell degenerates progressively so that by 20 days the retina has intact

ganglion cell and bipolar layers but virtually no photoreceptor layer. Electroretinographic studies²⁹ indicate that some visual function is attained in the second postnatal week and then is lost as the photoreceptor cells degenerate. Caravaggio and Bonting⁴ found that affected animals begin to make normal rhodopsin in the second week after birth and then lose rhodopsin as the rod outer segments degenerate later in that week. Tissue culture studies suggest that the disease is intrinsic to the eye²⁸ and is not modified *in vitro* by addition of vitamin A (retinol) or the corresponding aldehyde (retinal) to the culture medium^{22,34}.

Linkage between *rd* and glucuronidase deficiency (*g*) was found by Paigen and Noell²¹, but neither locus had been shown to be associated with a known linkage group. In this paper we report the results of linkage tests which show that *rd* is located in linkage group XVII.

Materials and Methods

The C3H/HeJ strain (*rd g/rd g*) was the source of the *rd* and *g* genes in all crosses. The dominant marker genes white (*Mi^w*, linkage group XI), oligosyndactylism (*Os*, linkage group XVIII), and viable dominant spotting (*W^s*, linkage group XVII, formerly part of linkage group III, see *Mouse News Letter* No. 32, 1965) were available in a single stock maintained at The Jackson Lab-

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oratory. The C57BL/6J-*lxW^s* strain was used as the source of luxate (*lx*) and *W^s* in the four-point cross. This strain is wild type at the *rd* and *g* loci. Luxate was used as a dominant gene, recognizable in the heterozygote by a heteromorphic great toe on one or both hind feet. In this cross the penetrance of *lx* was about 25 percent.

Animals homozygous for *rd* were recognized by histological criteria¹⁸. Eyes were removed under anesthesia or at death. Five to seven eyes were embedded in each wax block, and were identified by an asymmetrical arrangement within the block.

Animals homozygous for *g* were recognized at death by a semi-quantitative spot test for liver glucuronidase activity (kindly suggested by Paigen, personal communication). The test is based on the enzymatic hydrolysis of phenolphthalein glucuronide followed by measurement of the color of the liberated phenolphthalein at an alkaline pH. Liver was homogenized in ten volumes of acetate buffer, pH 4.5, and centrifuged. One drop of the supernatant enzyme extract was placed in a white spot plate and two drops of 0.01M phenolphthalein glucuronide (Sigma Chemical Company, St. Louis) diluted with acetate buffer (1:8 v/v) at pH 4.5 were added. The spot plate was incubated at 37° C for two hours and then

two drops of alkaline glycine reagent were added to visualize the color of free phenolphthalein. A pink to strong lavender color in the spot test was interpreted as high glucuronidase activity (+/+ or +/g); a yellow to pale pink color was interpreted as low glucuronidase activity (g/g). The analytical procedure and reagents are described more fully by Fishman and Green¹⁴ and Paigen³⁰.

Results

The results of crosses with the three dominant marker genes are given in Table I, lines 1 to 3. There is no evidence for linkage of *rd* with *Mi^{wh}* or *Os*. Linkage with *W^s* (linkage group XVII) appeared likely after classification of the first seventeen animals (Table I, line 3), and further attention was focused on this linkage. Additional data (Table I, line 4) confirmed the initial result and gave a recombination of 15.5 ± 2.9 percent based on classification of 155 animals (Table I, line 5).

Paigen and Noell³¹ found close linkage between the *rd* and *g* loci. Recombination between *W^s* and *lx* in linkage group XVII is known to be 18 percent⁶. A four-point cross to determine the order of the four loci was therefore made by backcrossing male heterozygotes of the type *lx W^s + +/+ + rd g* to quadruple

TABLE I. Numbers of offspring produced in tests for linkage of the *rd* locus with dominant markers (*M*).

Parents	Offspring				Total	% recombination
	+ +	<i>M</i> +	+ <i>rd</i>	<i>M rd</i>		
1. $\frac{Mi^{wh} +}{+ rd} \times \frac{+ rd}{+ rd}$	5	8	4	8	25	52.0 ± 10.0
2. $\frac{Os +}{+ rd} \times \frac{+ rd}{+ rd}$	5	5	2	4	16	56.2 ± 12.4
3. $\frac{W^s +}{+ rd} \times \frac{+ rd}{+ rd}$	1	5	9	2	17	17.6 ± 9.2
4. Same as 3	12	64	53	9	138	15.2 ± 3.1
5. 3 + 4	13	69	62	11	155	15.5 ± 2.9

recessive female C3H/HeJ mice. The progeny were classified for the sixteen phenotypes at about 31 days of age.

The results are given in Table II. Of the 254 offspring in the test mating, only 32 were recognized as $lx/+$ on the basis of a heteromorphic great toe. Classification of these 32 animals for W^o , rd , and g gave sufficient data for the following map: $lx-15.6-W^o-18.8-rd$. This conclusion is based on the assumption that penetrance of lx is not influenced by the other loci in the test. Evidence in favor of this assumption is the fact that the observed recombination between lx and W^o (15.6 ± 6.4 percent) is reasonably close to the published value (17.7 ± 1.2 percent)⁶.

The order of W^o , rd , and g was determined by classification of all 254 animals for the eight possible phenotypes (Table II, third line). The numbers are clearly consistent with the interpretation that W^o++ and $+rdg$ are the non-crossover (parental) phenotypes, that W^ordg , $+++$, W^o+g , and $+rd+$ are the single crossover phenotypes, and that W^ord+ and $+++g$ are the rare double-crossover phenotypes. The only linear order which fits these data, with the calculated recombination values, is: $W^o-12.2-rd-15.4-g$.

The value of 12.2 percent for recombination between W^o and rd was determined from male heterozygotes. In cross 3, Table I, the heterozygous

parents were females. In cross 4 about 60 percent of the offspring were from heterozygous females and the remainder from heterozygous males, but the records were not kept in such a way as to show which offspring came from which parents. In both cross 3 and cross 4 recombination is greater than the value determined in males alone. While the data do not allow a reliable comparison of the sexes, they at least suggest that for this region of linkage group XVII recombination is no greater in males than in females. Recombination between W^o and rd based on the total data (Table I, line 5 plus Table II) is 13.4 ± 1.7 percent.

The recombination between rd and g recorded in Table II (15.4 ± 2.3 percent) is significantly greater than that obtained by Paigen and Noell (5.1 ± 2.9 percent, $\chi^2 = 4.35$, d.f. = 1, $P < 0.05$). Since in our cross heterozygous males were used, and in Paigen and Noell's cross heterozygous females, the difference may be due to sex. If so, the difference between the sexes in this region is in the opposite direction from the usual sex difference in the mouse and is an addition to the small number of cases of greater recombination in the male than in the female. The two crosses were made in different laboratories and with different stocks, however, and the difference in recombination values may be due to unknown

TABLE II. Numbers of offspring of the four-point cross: $lx W^o + + / + + rd g \delta \times + + rd g / + + rd g \varphi$

Phenotypes	$W^o + + + rd g$	$W^o rd g + + +$	$W^o + g + rd +$	$W^o rd + + + g$	Total				
Abnormal toe (lx)	20	5	5	0	1	0	1	0	32
Normal toe	79	81	8	17	19	18	0	0	222
Total	99	86	13	17	20	18	1	0	254

	Interval	Recombinants	Total	% recombination
lx classes only	$lx - W^o$	5	32	15.6 ± 6.4
	$lx - rd$	11	32	34.4 ± 8.4
	$W^o - rd$	6	32	18.8 ± 6.9
Total	$W^o - rd$	31	254	12.2 ± 2.1
	$rd - g$	39	254	15.4 ± 2.3
	$W^o - g$	70	254	27.6 ± 2.8

factors unrelated to sex. An additional small intercross in coupling using C3H/HeJ (*rd g/rd g*) and C57BL/6J (+ +/+ +) as the parental stocks gave 19 + +, 2 *rd* +, 1 + *g*, and 4 *rd g* offspring. From this cross the estimated recombination, which is an average of the values for the two sexes, is 13.3 ± 7.7 percent (estimated using table 3 of Finney¹²).

The map for the segment of linkage group XVII from *lx* to *g* (Carter⁶, Paigen and Noell³¹, and Tables I and II) is:

$$lx-18-W^e-13-rd-\overset{\sigma}{15} \underset{5-g}{\varnothing}$$

Discussion]

A recurrent theme in the published studies on inherited retinal degeneration has been the possible relationship of retinal degeneration (*rd*) to the mutant rodless retina (*r*) described by Keeler in 1924¹⁹ and thought to have become extinct before *rd* was found²⁰. Many investigators have considered it probable that *r* and *rd* are different mutations^{8, 30}.

The first *r/r* mice described by Keeler^{19, 20} had retinas indistinguishable histologically from retinas of present day *rd/rd* mice. Rod outer segments were absent and photoreceptor cell nuclei were reduced from more than ten rows to about one row. The disorder was not recognized in the first week after birth but was apparent at thirteen days, so that Keeler²⁰ interpreted the disease as "a postnatal inhibition of differentiation in the nervous tissue ordinarily destined to produce the sensory receptor mechanism of the eye." Outcrosses produced some mice with retinas containing intermediate numbers of photoreceptor cells^{20, 21}. The mice had an average of about 6 rows, 3 rows, or the previously described one row of photoreceptor cell nuclei. These intermediate forms were thought to have arisen through modifying factors introduced in the outcrosses²¹. The intermediate forms appeared to give further support to Keeler's interpretation of the disorder as an arrested developmental condition.

Keeler obtained his original animals in 1923 from Bagg's albino stock, in which the mutation apparently was already prevalent^{19, 21, 22}. In addition to the mutant animals in New York and Boston, Keeler brought affected animals to Paris and he recognized similar mice in Cold Spring Harbor, Sweet Briar, Evanston, Berlin, Munich and Riga²². Crosses between Keeler's affected mice and unrelated Berlin-Dahlem mice with abnormal retinas gave 100 percent rodless offspring of the "one-row" type in both F₁ and F₂ generations²³.

The histological argument for a difference between *rd* and *r* is not convincing. Tansley²⁹ properly emphasized that *rd* is a degenerative disorder. Degeneration is first recognizable after the photoreceptor cells have formed and while their outer segments are differentiating. Mature form and function are not attained^{4, 29, 35}. The disorder clearly involves both arrested development and subsequent degeneration of photoreceptor cells and may be classified as an *aplasia*³⁶. If, by contrast, *r* was purely an arrested developmental condition, the arrest must have occurred during the first week after birth, now recognized to be the time when cell divisions take place for formation of most of the photoreceptor cells³³. Such an arrest should have been easily noted by the sixth day after birth, but abnormalities were not described at this stage. Thus it now seems unlikely that rodless was purely an arrested developmental condition. The two mutations cannot be equated or distinguished on the available histological evidence.

Keeler^{20, 21} obtained intermediate manifestations of the rodless disorder when non-inbred *r/r* mice were outcrossed. If *r*, like *rd*, was a degenerative disorder, the pace of the degenerative process might have been slowed in certain outcrosses. Sorsby *et al.*³⁵ likewise obtained intermediate manifestations of disease in non-inbred *rd/rd* mice. Intermediate expressions were not found by other investigators of *r*¹⁵ or *rd*³. The presence or absence of intermediate forms do not distinguish *rd* and *r*. Inability to distinguish the two mutants by histological

criteria does not, however, rule out the possibility that they are genetically different.

The formal genetic argument for a difference between *rd* and *r* is stronger than the histological argument. DiPaolo and Noell⁸ showed that *rd* (derived from C3H) and silver (*si*) are independent (recombination = 48.5 ± 3.5 percent) whereas *r* and *si* are linked (recombination = 14.9 ± 5.8 percent, recalculated from Keeler²⁴). Although *si* is an unsatisfactory gene for linkage because the phenotype is variable and often difficult to recognize, it is very likely that Keeler's "silver" and the Jackson Laboratory "silver" used by DiPaolo and Noell⁸ were both derived from the original mutant described by Dunn and Thigpen⁹.

Before Keeler recognized linkage between *r* and *si* he tested *r* with a number of other loci. A test of *r* and *W* (an allele of *W*^{*}) gave a recombination value of 41.9 ± 7.5 percent, based on 42 ani-

mals²¹. This is significantly different from the value for *rd* and *W*^{*} (13.4 ± 1.7 percent).

The apparently different linkage relations of *r* and *rd* point to the conclusion that the two conditions are due to mutations at different loci. The only aspect of the subject which casts doubt on this conclusion is that the *r* gene, known to have been present by genetic test in Cold Spring Harbor, Boston and Berlin-Dahlem, should have become extinct and been replaced by *rd*, now known to be widely distributed in non-inbred and inbred mice (Table III). If *r* and *rd* are different it seems likely that *r* must still be in existence and will be recognized when enough stocks of different origin with absent retinal photoreceptor cells have been crossed.

If there are two loci it seems curious that all the tests so far made have shown allelism. It is possible, though unlikely, that the double heterozygote of the two mutants (*+r +rd*) may have the

TABLE III. Stocks and inbred strains of mice with recessive inherited retinal disease

A. Strains with disease proved identical by 100% affected F ₂ offspring: CBA/J × C3H/HeJ (present report); Keeler rodless × Berlin-Dahlem stock ²² .					
B. Strains with disease proved identical by 100% affected F ₁ offspring:					
CBA/J × Bruckner ¹⁰	C3H/HeJ × P/J				(Sidman, unpublished)
BDP/J × Bruckner ³⁶	C3H/HeJ × PL/J			" "	" "
P/J × Bruckner ³⁹	C3H/HeJ × SJL/J			" "	" "
C3H/CaH × Bruckner ²⁷	C3H/HeJ × ST/J			" "	" "
C3H/Ca × P/J ³⁷	C3H/HeJ × SWR/J			" "	" "
C. Stocks with histological changes indistinguishable from <i>rd</i> :					
BUB/Bn	C3HeB/FeJ	DA/Hu		Albino-Blühm ¹³	
C3H/An ⁸	C3HeB/Hu	FL/Re		Basle waltzing stock ^{3,3}	
C3H/Di	C3HfB/Hu	WB/Re		Basle and Zurich wild mice ³	
C3H/Ha ³¹	C3H/St ³¹	WC/Re		NIH wild stock ¹¹	
C3H/HeHu - S1J	CFW ³¹	WH/Re		Swiss albino stocks ¹⁰	
				Vienna stock ¹	
D. Stocks with histologically normal retinas:					
A ³¹	BALB/cJ	C57BL/10Gn	DE/WyDi	LaA ³¹	2-Prunt ³¹
A/G ³⁹	BSL/Di	C57BL/10J	F ³¹	LG/Rr	5-Prunt ²
A/HeJ	BrS ³¹	C57BR/cd	FZ/Di	LOW ³¹	RF/J
A/J	C/St ²¹	C57L/J	H ³¹	LP/J	R11 ¹ /AnJ
A/WySn	CBA/Ca	C58/J	HALB/Hu	MA/J	SM/J
A2G ²⁷	CBA/St ³¹	DBA/1J	HD/Hu	MA/MyHu	WK/Re
AK ³¹	CE/WyDi	DBA/1fHu	HG/Hu	MY/Hu	129/J
AKR/J	CH ³¹	DBA/1oHu	I ³¹	MYA/Hu	129/Rr
B1 + ³¹	C57 ³¹	DBA/2 ³¹	IPBR ³¹	N ³¹	
AU/Ss	C57BL/Ks	DBA/2DeJ	JB/Di	PBR ³¹	
BALB/cGn	C57BL/6J	DBA/2WyDi	JK ³¹	PIN ³¹	

Wherever specific references are not given, the data were obtained at The Jackson Laboratory (Staats³⁷ and unpublished data).

mutant phenotype and thus lead to a diagnosis of allelism from the occurrence of mutant-type F_1 offspring when in fact the mutants are not alleles. There is very little precedent for this in the mouse. The nearest example is that of the double heterozygote of shaker-1 and waltzer ($+/sh-1 +/v$). These mice have an abnormality of the inner ear but it is much less severe and of later onset than that of either single homozygote^{7,28}. The mutant-type F_1 offspring described in tests for allelism made with r and rd have all had retinas as severely affected as those of the parent strains^{8,23,27,35,39} (and Sidman, unpublished). While it is therefore unlikely that tests for allelism based only on the phenotype of the F_1 have led to false conclusions, tests carried to the F_2 generation make the diagnosis more secure. If the mutants are not alleles, recombination should produce some F_2 mice with normal eyes. The only tests carried to the F_2 generation have been Keeler's²³ demonstration that the retinal mutant was identical in his Bagg albino-derived stock and the Berlin-Dahlem stock (eight out of eight F_2 mice had retinal disease), and a cross by us between the CBA/J and C3H/HeJ strains (twenty-one out of twenty-one F_2 mice had retinal disease).

Table III summarizes the information known to us on retinal disease in existing mouse stocks and inbred strains. It is clear that there are a number of stocks with retinal disease which have not been adequately tested for allelism with each other. Tests with these strains might establish whether more than one retinal mutation now exist. If negative, such tests would cast some doubt on the validity of the conclusions from the linkage results and would favor the conclusion that one inherited degenerative disorder of photoreceptor cells is known in mice and probably is identical to the disorder described in the 1920's.

Summary

The mutant retinal degeneration, rd , is linked to W^c in linkage group XVII with recombination of 13.4 ± 1.7 percent.

Recombination between rd and low glucuronidase, g , another locus in this linkage group, is 15.4 ± 2.3 percent in males. This estimate is significantly different from that previously found for rd and g in females. The order of these three loci and luxate, lx , is: lx , W^c , rd , g . The very similar mutant, rodless retina, r , was previously shown not to be closely linked to the W locus. Therefore r and rd are probably not alleles. A diligent search for r , long thought to be extinct, might uncover its presence among the many stocks of different origin known to be lacking retinal photoreceptor cells.

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