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Inheritance of Susceptibility to Friend Mouse Leukemia Virus

V. Introduction of a Gene Responsible for Susceptibility in the Genetic Complement of Resistant Mice

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Based on the previous observation that a single major autosomal gene controls susceptibility to Friend leukemia virus in mice, an attempt was made to place the gene for susceptibility, Fv^s, from susceptible DDD mice into the genetic complement of resistant C57BL/6 mice. The backcross system was adopted for this purpose, the heterozygotes being selected by progeny test at each generation. During successive backcrosses, the effect of gene Fv^s was not diluted out, and progeny were almost always obtained as expected from the single-gene hypothesis, with respect to both genotype and phenotype. With the eighth backcross generation, brother-sister mating was done between the heterozygotes, and it produced mice homozygous for gene Fv^s. These susceptible homozygotes and their progeny produced by incross could be assumed congenic with C57BL/6 mice except for susceptibility to Friend leukemia virus. The results indicate that the appearance of early splenomegaly in Friend virus-infected mice is under the control of a single major autosomal gene.

Friend leukemia virus (FLV) shows different degrees of leukemogenicity in various strains of mice, as do other strains of mouse leukemia virus (7). Among those tested, C57BL mice are the most resistant to infection with FLV (5, 7). Furthermore, this mouse strain has been shown to be resistant to several viruses such as polyoma (4), mammary tumor (10), leukemias (12, 14, 20), and ectromelia (23).

These characteristics of C57BL mice prompted us to undertake genetic studies on their innate resistance to FLV, which led to the conclusion that the resistance of C57BL/6 was under the control of a single major autosomal gene (17, 18). This finding was confirmed and extended by Axelrad (1), Lilly (11; Abstract, Genetics, p. 198, 1968), and Franker and Quilligan (6).

Such single-gene control of susceptibility has been reported in some viral diseases: arbo B virus-mouse (22), hepatitis virus-mouse (3), influenza virus-mouse (13), and Rous sarcoma virus-chicken (19). It was of interest to study the innate resistance of mice to FLV, because both virus and cell growth in a mammal are involved in this system.

For studying the control mechanism of the gene responsible for innate resistance, information based on comparative studies on resistant and susceptible mice might be misleading, because the effects of other genes which play no essential role in pathogenesis could be considered significant. A pair of congenic strains which have common genetic complement except for the gene of interest are useful for this purpose. Furthermore, the establishment of the congenic strain itself should be conclusive evidence for the single-gene hypothesis. Since 1964, an attempt was made to place the gene of susceptibility from FLV-susceptible DDD mice into the genetic complement of resistant C57BL/6 mice. This report is concerned with the matings which resulted in establishment of a congenic strain.

MATERIALS AND METHODS

Virus. Since 1960, FLV has been passed in our laboratory in random-bred ddD and subsequently in inbred DDD mice (17, 18). On repeated checks, the virus was shown to be accompanied by Riley virus (lactate dehydrogenase-elevating agent; 21). The virus stocks used in the present experiment were prepared on several occasions from spleens of DDD mice in early splenomegalic phase as 20% suspension in either saline or phosphate-buffered saline (*p*H 7.4). To some preparations, skimmed milk powder (3 to 5%) or heat-inactivated calf serum (2%) was added. Freshly harvested pooled spleens were homogenized with a blendor and centrifuged at 4,000 × *g* for 30 min. The

supernatant fluids were stored in sealed ampoules at −78 C in a Revco refrigerator. Before use, it was thawed and diluted twofold with saline; 0.2 ml was injected intraperitoneally into mice 20 to 30 days old. The inoculum contained $10^{3.75}$ to $10^{6.0}$ MID_{50} (mouse infective dose as determined by the incidence of splenomegaly in young DDD mice within 1 month after inoculation).

Mice. Mice of DDD and C57BL/6 strains were previously described (16). The former is highly susceptible to FLV, whereas the latter is highly resistant. When challenged after weaning, no C57BL/6 mice developed splenomegaly, even with the highest dose of available virus preparations. Only when infected in the first half of the suckling stage did they develop splenomegaly after an unusually long latent period (15). Both strains have been maintained in our laboratory as inbred colonies. The DDD mice used for the production of F_1 hybrids were in the 26th generation; C57BL/6 was in the ? + 29th generation of brother-sister inbreeding. Animals were given commercial chows and water ad libitum. Peanuts, millet seeds, and wheat were given occasionally.

Test for susceptibility of individual mice (determination of phenotype). As previously reported (17), occurrence of splenomegaly within 3 weeks after FLV inoculation into 20- to 30-day-old mice served as the criterion for determining susceptibility or resistance of individual mice. Inoculated mice were examined at various intervals for splenomegaly. When spleens were noticeably enlarged, mice were killed and spleens were weighed. Other animals were submitted to autopsy on day 21 of infection; those with spleens weighing less than 0.6 g were considered resistant. The reason for assuming 0.6 g as the borderline between susceptible and resistant was previously discussed (17). Sometimes spleens weighing less than 0.6 g had focal lesions on their surface. This response suggested susceptibility. For the sake of simplicity, however, these animals were considered resistant except when specified.

Designation of genes. In previous papers (17, 18), symbols *S* and *s* were tentatively used for the gene of susceptibility and its allele controlling resistance, respectively. Hereafter, these symbols will be replaced, respectively, by Fv^s (abbreviated as *S*) and Fv^r (*R*). The locus at which the alleles are located will be called *Fv*. Another locus controlling susceptibility and resistance to FLV has been found by Lilly (Abstract, Genetics, p. 198, 1968). According to this designation, the genotype of susceptible DDD mice is *S*/*S*, whereas that of resistant C57BL/6 mice is *R*/*R*.

Determination of genotype. Genotypes for each mouse were determined by the results of progeny tests (Table 1). Mice to be tested were mated to C57BL/6 mice, and the phenotypes of their offspring (at least six in number) were determined as described above. There were three expected categories of response to FLV in the progeny tests: (i) all of the infected progeny susceptible, (ii) half susceptible and half resistant, and (iii) all resistant. From the single-gene hypothesis, the genotypes of the mice which produced the progeny of categories i, ii, and iii were determined as *S*/*S*, *S*/*R*, and *R*/*R*, respectively.

Mating system. To introduce the gene for susceptibility, *S*, from susceptible DDD mice into the genetic complement of C57BL/6 mice, successive backcrosses with C57BL/6 mice were carried out, heterozygotes with *S*/*R* genotype being selected at each generation. Since heterozygotes become diseased upon challenge of FLV, those to be used for breeding had to be selected without direct inoculation of FLV, namely, by progeny test. At BC_8 to BC_{10} generations, male and female mice were tested for their genotypes, and the heterozygotes which were found among offspring from the same parents were intercrossed to produce the next generation. In each family, homozygous *S*/*S* mice of both sexes were sought and crossed to produce congenic lines with *S*/*S* genotype. If susceptible homozygotes were not found, heterozygotes were used for breeding until the *S*/*S* homozygotes were obtained.

TABLE 1. *Progeny test for determination of genotype*

Mating	Susceptibility of progeny to FLV	Genotype of tested mice
Test mouse × C57BL/6	Susceptible only	*S*/*S*
Test mouse × C57BL/6	Susceptible and resistant in expected ratio 1:1	*S*/*R*
Test mouse × C57BL/6	Resistant only	*R*/*R*

RESULTS

Successive backcrosses. Results up to BC_1 generation were reported in a previous paper (18). The mice described here were progeny of these animals.

Successive matings were begun with two pairs of male DDD and female C57BL/6 mice. All of 34 F_1 hybrids developed splenomegaly upon challenge of FLV. Of 34 BC_1 hybrids produced by mating F_1 to C57BL/6 mice, 13 susceptible and 21 resistant mice were found. This was referred to as the ratio of phenotypic segregation in BC_1 generation (Table 2). Ten uninoculated mice from this generation were mated to C57BL/6 mice and progeny tests were carried out to determine their genotypes. Among those tested, three were of *S*/*R* and seven of *R*/*R* genotype. The mice which were challenged with FLV in these progeny tests were in BC_2 generation. Therefore, the numbers of susceptible and resistant mice in the progeny tests of these three *S*/*R* BC_1 mice were scored as the ratio of phenotypic segregation in BC_2. Mice of *R*/*R* genotype were discarded. The heterozygous BC_1 animals were crossed again with C57BL/6 mice to obtain the next generation, and the genotypes of their progeny were determined. Crosses were done successively in this way. The results of successive

backcross generations are summarized in Table 2. The genotypes of 114 mice were determined; 55 were shown to have *S/R* genotype and 59 were *R/R*. Only two mice gave ambiguous results. As expected from the mating system, mice of *S/S* genotype were never observed. In inoculated mice of BC_1 to BC_{11} generation, 227 were phenotypically susceptible and 284 were resistant. Except for BC_{10}, both phenotypic and genotypic segregation ratios in each generation were compatible with a single-gene hypothesis. This was also true for phenotypic segregation in progeny produced by mating individual heterozygotes to C57BL/6 mice. A pedigree chart of the lines is shown in Fig. 1, in which mice are individually represented with their genotypes.

TABLE 2. *Genotypic and phenotypic segregations in successive backcross generations*

Generation	Segregation in				
	Genotype			Phenotype	
	S/R	*R/R*	*S/R*?	Susceptible	Resistant
BC_1[a]	3[b]	7	0	13	21
BC_2	6	6	0	15	16
BC_3	4	5	0	13	23
BC_4	5	5	0	16	21
BC_5	6	4	0	25	40
BC_6	8	4	0	19	20
BC_7	5	7	0	34	37
BC_8	11	15	2	18	18
BC_9	3	2	0	47	47
BC_{10}	4	4	0	9	25
BC_{11}				18	16

[a] Phenotypes of BC_{n+1} generation were determined on the mice produced by mating heterozygous BC_n mice to C57BL/6. The results on the progeny of *R/R* and *S/R*? were omitted.

[b] Figures indicate number of mice.

Brother-sister mating after successive backcrosses. Two independent lines were successively backcrossed with C57BL/6 mice, male heterozygotes being used for advanced backcrosses (Fig. 1). At BC_8 to BC_{10} generations, mice of both sexes were tested for their genotypes. Two groups of mice belonged to BC_8 generation of line A; the third and fourth groups belonged to BC_9 and BC_{10} generation, respectively, of line B. As expected, half of the tested mice were heterozygous (18 of 36 mice). In all groups of mice, heterozygotes were found in both sexes (Table 3). Male and female heterozygotes originating from the same parents were intercrossed with the expectation that mice of three different genotypes, *S/S*, *S/R*, and *R/R*, would be produced in the ratio of 1:2:1. These generations which were produced by the intercross of BC_n were designated by the symbol $N_{n+1}F_1$. Genotypes were determined on individual mice of these generations. Figure 2 shows the results of individual progeny tests of N_9F_1 generation in which all mice to be tested came from the same parental pair ($BC_8 \times BC_8$, cross no. 1); the responses could be clearly classified into three types. The first

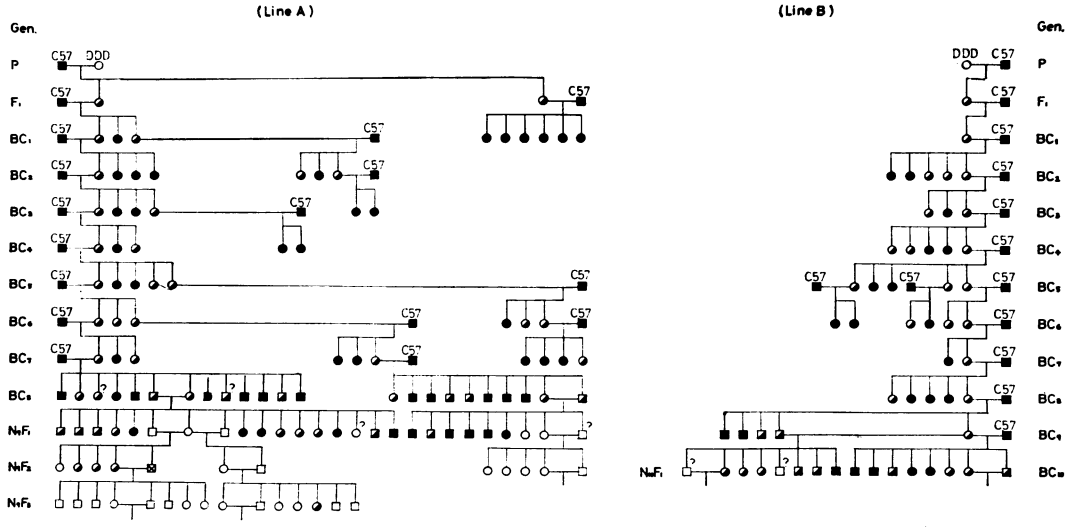

FIG. 1. *Pedigree chart of backcross and congenic lines. Mice without strain name are hybrids which are individually represented with their genotype. Symbols: open = S/S, half shadowed = S/R, shadowed = R/R, ? = genotype uncertain, × = not determined, circle = male, square = female.*

TABLE 3. *Appearance of heterozygotes in both sexes of BC_8 to BC_{10} generations*

Parents (♀ × ♂)	Cross no.	Generation	Genotype of offspring			
			S/R		*R/R*	
			♀	♂	♀	♂
C57BL/6 × BC_7[a]	1	BC_8	3[b]	3	6	1
C57BL/6 × BC_7	5	BC_8	3	2	5	0
C57BL/6 × BC_8	19	BC_9	2	1	2	0
C57BL/6 × BC_9	1	BC_{10}	2	2	2	2

[a] All male mice mated to C57BL/6 females are of genotype *S/R*.

[b] Figures indicate number of mice

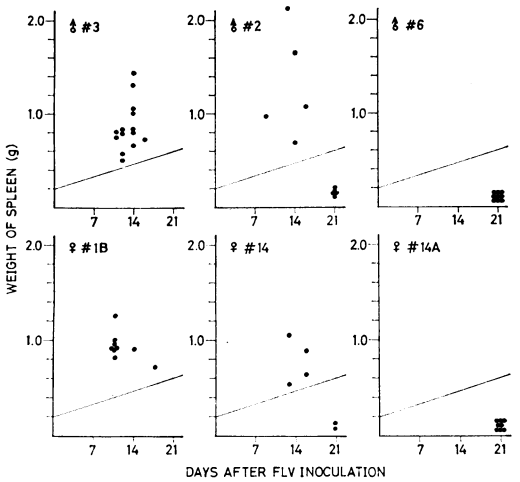

FIG. 2. *Response of individual mice to FLV in progeny tests on N_9F_1 generation. Progeny produced by mating the numbered mice of N_9F_1 generation to C57BL/6 were challenged with FLV when 20 to 30 days old.*

group of mice (no. 3, no. 1B) gave rise to only susceptible progeny, the second (no. 2, no. 14) to both susceptible and resistant, and the third (no. 6, no. 14A) to exclusively resistant. As deduced from Table 1, the mice of the first, second, and third groups were considered to have *S/S*, *S/R*, and *R/R* genotypes, respectively. Mice of *S/S* genotype appeared for the first time in these successive crosses; 9 *S/S* (including 4 *S/S*?), 14 *S/R*, and 11 *R/R* mice were found in these generations (Table 4).

Brother-sister inbreedings were carried out with homozygous *S/S* mice found in N_9F_1 generation and their descendants. However, no male mouse of *S/S* genotype was found in $N_{10}F_1$ generation. Therefore, a male *S/R* mouse was

TABLE 4. *Appearance of mice with three different genotypes in generations produced by intercrosses of heterozygotes*

Parents (♀ × ♂)	Cross no.	Generation	Genotype of offspring					
			S/S		*S/R*		*R/R*	
			♀	♂	♀	♂	♀	♂
BC_8 × BC_8[a]	1	N_9F_1	2[b]	2 (1)	4	4	1	4
BC_8 × BC_8	2	N_9F_1	1 (1)	2	1	0	4	1
BC_9 × BC_9	1	$N_{10}F_1$	2 (2)	0	2	3	1	0

[a] Heterozygotes belonging to the same family (Table 3) were intercrossed and their progeny were grouped according to their genotypes and sexes.

[b] Number of mice. Figures in parentheses indicate the number of mice with *S/S*? genotype.

crossed with an *S/S*? female, expecting *S/S* mice in the following generations. The pedigree chart of these congenic lines is included in Fig. 1. Although some of the congenic mice were classified as *S/R*, most mice were confirmed as having *S/S* genotype.

Reliability of the progeny test. It seemed worthwhile to examine the reliability of the progeny tests carried out on successive generations. During the present experiment, 139 mice of BC_1 to BC_{10} generations and 69 mice of NF generations were submitted to progeny tests. Among them, 32 mice were discarded, because of the shortage in number of their offspring, without determination of their genotypes. The genotypes of six other mice could not be determined with certainty. Two of the mice belonged to BC_8 generation, and one (no. 1 of BC_8 in Table 5) gave rise to 25 offspring when mated to a C57BL/6 mouse. Only five of them developed typical splenomegaly and four showed focal lesions on their spleens weighing less than 0.6 g. If the latter ones were not considered susceptible, the ratio of segregation was 5:20, a considerable deviation from the expected ratio of 1:1. The other one (no. 27 of BC_8 in Table 5) gave 1 susceptible and 16 resistant mice in progeny tests. This ratio is also unusual. Because these two mice, though not typical, could be considered to have *S/R* genotype, they were specified as *S/R*? (Table 2). Another four mice (e.g., no. 7C and no. 9 of N_9F_1 in Table 5) were classified as *S/S*?. In progeny tests, spleens of some of their progeny were found with focal lesions which weighed less than 0.6 g. However, since no progeny were completely resistant, they were classified as *S/S*?.

The remaining 170 mice were classified according to their genotype without difficulty (Fig. 2). On some of them, progeny tests were repeatedly

TABLE 5. *Repeated progeny tests on succeeding litters*

Mice to be tested		Litter							Total	Deduced genotype
Generation	Mouse no.	1st	2nd	3rd	4th	5th	8th	9th		
BC_1	3	0/8[a]	0/8						0/16	*R/R*
	4	0/8	0/7						0/15	*R/R*
BC_4	2	0/7 (1/7)	2/6		4/8	5/7			11/28 (12/28)	*S/R*
	7	1/6	0/3	3/6	5/8				9/23	*S/R*
BC_5	2	4/6	0/4	3/6					7/16	*S/R*
	6	3/6		6/7					9/13	*S/R*
	9	2/6		4/8					6/14	*S/R*
BC_6	3	4/6		5/7					9/13	*S/R*
	8	2/6		6/8					8/14	*S/R*
BC_8	1	2/6	0/5 (1/5)	2/6			1/2	0/6 (3/6)	5/25 (9/25)	*S/R*?
	4	0/6	0/10						0/16	*R/R*
	9	3/7		5/7					8/14	*S/R*
	13	2/8		4/8					6/16	*S/R*
	27	1/7	0/6	0/4					1/17	*S/R*?
N_9F_1	3	8/8	6/6						14/14	*S/S*
	7C	5/7 (7/7)	9/9						14/16 (16/16)	*S/S*?
	9	7/8 (8/8)	4/7 (7/7)						11/15 (15/15)	*S/S*?
	17	8/8	9/9						17/17	*S/S*

[a] Number of susceptible mice/total number of infected mice. Figures in parentheses include mice whose spleens weighed less than 0.6 g but showed focal lesions.

done by inoculating the virus into succeeding litters produced by mating to C57BL/6 mice. The tests were reproducible, allowing an unequivocal determination of genotypes if more than six progeny mice were available for testing (Table 5). Furthermore, the fact that mice with the genotype hoped for could be obtained as expected indicates that the progeny test is reliable.

DISCUSSION

The present study was designed (i) to present conclusive evidence for the single-gene hypothesis for the susceptibility to FLV in mice (17, 18) and (ii) to establish congenic mouse lines for future studies on genetic control of susceptibility. Starting with F_1 hybrids between susceptible DDD and resistant C57BL/6 mice, successive backcrosses were done with C57BL/6 mice (Fig. 1). Heterozygotes selected by progeny tests were used for advanced crosses. It was shown that the results of most progeny tests were clear-cut and reproducible even in advanced generations if sufficient numbers of mice were used (Table 5 and Fig. 2). This fact indicates that the effect of the selected gene, *Fv*^{s}, was not diluted out during successive backcrosses.

The adopted mating system depended on the consideration that unrelated genes introduced from DDD mice could be diluted out on successive backcrosses, placing the selected gene *Fv*^{s} into the genetic complement of C57BL/6 mice. In the present study, successive backcrosses were done up to generation BC_8 to BC_{10}, followed by brother-sister mating. At this level, it is expected that the genes of DDD mice which have no strong linkage relation with the locus *Fv* are almost completely replaced by those of C57BL/6 mice, and the gene *Fv*^{s} and adjacent ones originating in DDD mice are placed into the genetic complement of C57BL/6 mice (8). These congenic lines might be useful for studies on the locus *Fv*, as successfully demonstrated in studies on histocompatibility genes in mice (24). Among several examples of genetically controlled susceptibility to virus, only one, that of arbovirus B, can be studied in congenic mouse lines (9). Independently of us, Axelrad is also attempting to establish a congenic line with respect to susceptibility to FLV (*personal communication*).

Since heterozygotes are less susceptible to FLV than are DDD mice (18), care was taken to use only high-titered virus in susceptibility tests. However, stock preparations were found to have a 10- to 100-fold decreased titer after prolonged storage in a Revco freezer. There is, therefore, a possibility that some tests performed with such partially inactivated preparations did not detect all susceptible mice, and this may have been the cause of some errors in phenotype determination. Furthermore, it has been experienced, though rarely, that even the mice of genetically susceptible strains did not develop

disease upon inoculation with FLV. The reasons for this have not been analyzed.

Another factor which must be mentioned is the criterion in determining phenotype. Although the phenotypes of most mice could be clearly determined, some inoculated animals did not show typical response to FLV; their spleens showed focal lesions similar to those reported by Axelrad and Steeves (2) and weighed less than 0.6 g on the final day of the observation. These mice could be considered susceptible, but for the sake of simplicity they were scored resistant. This may have resulted in underestimation of the number of phenotypically susceptible mice (Table 2) and, in turn, in a decrease of recognized S/S and S/R genotypes.

The appearance of S/R mice in N_9F_2 and N_9F_3 generations (Fig. 1) is best explained by assuming that an error was made in determining the genotype of these mice or the genotype of their parents. Most of these mice were classified as S/R because there was only one resistant mouse in the progeny tests and, in fact, the titer of the virus preparation used at that time was exceptionally low. Furthermore, the genotype determination depends on a statistical consideration. When the number of mice is small, it is possible that all progeny animals of S/R mice are susceptible or resistant and their genotype is mistaken for S/S and R/R.

The results reported agree well with the hypothesis that a single gene or a group of closely linked genes controls the susceptibility of mice to FLV. However, this does not exclude the possibility that several minor genes also influence the manifestation of Friend leukemia. The present study indicates only that, under these conditions, the effect of a single major gene is clearly predominant.

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