Mode of inheritance of deficient corpus callosum in mice

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Abstract:

Many mice of the Inbred strain BALB/cCF have deficient corpus callosum, and a few of them have total absence of this large forebrain commissure. Reciprocal F_1 hybrid crosses with the inbred strains A/J, C57BL/6J, and DBA/2J revealed that Inheritance of the defect Is completely recessive. Reciprocal backcrosses to BALB/cCF revealed that Inheritance is not attributable to a single Mendelian locus with the same degree of pens-trance as In the parent strain. The ac locus has not been rediscovered, Instead, there Is good reason to withdraw ac from current listings of Mendelian loci in the mouse.

Article:

Single-locus Mendelian inheritance of absence of mouse corpus callosum was first reported by Keeler[8] and was subsequently assigned the gene symbol ac by Snell[19]. However, subsequent work by King[9] using the same stock of mice revealed a more complicated situation. Unfortunately, the stock of mice became extinct before the necessary experiments could be done to establish the mode of inheritance unequivocally.

A very similar brain defect was later discovered by R. E. Wimer (personal communication) in the BALB/cJ and 129/J inbred strains, and investigation of hereditary aspects was undertaken by Wahlsten[21]. In crosses involving the strains BALB/cJ and A/1, the frequencies of the defect in F_2 hybrids and backcrosses were significantly lower than expected if the difference between BALB/cJ and A/J were a manifestation of an allelic difference at a single autosomal locus. Interpretation of that study was rendered difficult by three problems that have now been solved.

First, the extremely poor reproductive performance of female BALB/cJ mice in the author's laboratory at the University of Waterloo made it impractical to try to obtain sufficient F_1 hybrid and backcross mice with a BALB/cJ mother. Thus, the possibility remained that inheritance in a BALB/cJ maternal environment might be monogenic. This problem was addressed by assessing the brains and reproductive performances of BALB/c substrains from seven different suppliers[22]. Mice from Carworth Farms and Charles River Breeding Laboratories were found to have a moderate frequency of defective corpus callosum but reasonably good breeding qualities, and the CF substrain was used for further studies.

Second, only a fraction of the BALB/cJ and BALB/cCF inbred mice showed partial or total absence of corpus callosum. This raised the possibility that there might be continuing genetic segregation within a strain at a locus influencing brain development, a situation that would reduce substantially the expected frequencies of defective offspring in various crosses. Fortunately, several breeding tests (Wahlsten, ms.) involving different families within the BALB/cCF strain in the author's laboratory contradicted the hypothesis of genetic segregation and made it plausible to assume that BALB/cCF mice used in the present study of crosses with other inbred strains were genetically homozygous and homogeneous.

Third, BA L B/c mice are closely related to the A/1 strain, which was derived from a cross of the Bags albino and Cold Spring Harbor albino stocks by Strong in 1921[7]. Consequently, the difference between BALB/c and A

mice is likely to reflect allelic differences at fewer loci than the difference between BALB/c and more remotely related strains. For this reason, crosses involving BALB/cCF mice also were done with other inbred strains to extend the generality of the findings.

The present study was therefore done to assess the mode of inheritance of defective corpus callosum in BALB/CCF mice using reciprocal F_1 hybrid crosses and reciprocal backcrosses to three different inbred strains: A/1, C57BL/6J and DBA/2J.

Methods

The BALB/cCF mice were procured in 1976 and 1977 from Carworth Farms, which had maintained the strain by full-sib matings since it obtained pedigreed BALB/c mice in 1968 from the Laboratory Animals Centre in the United Kingdom. The Laboratory Animals Centre had in turn obtained BALB/cJ mice at F_{61} of inbreeding from The Jackson Laboratory in 1955. Although the 3ALB/ cCF substrain was liquidated when Carworth Farms was recently acquired by the Charles River Breeding Laboratories, a large colony is maintained by full-sib matings at the University of Waterloo, and breeding pairs are available from the author upon request. The inbred strains A/J, C57BL/6J, and DBA/2J were obtained in 1977, 1978, and 1979 from The Jackson Laboratory and then propagated in the author's laboratory using full-sib matings. The data reported in the present study are taken only from mice bred at Waterloo, because it was found[24] that sizes of corpus callosum, whole brain, and body varied substantially between mice bred commercially and their progeny bred at Waterloo.

In 1979 the numbers of generations of full-sib matings of strains A/J, C57BL/6J, and DBA/2J at the Jackson Laboratory were 180, 134, and 133, respectively[7], and the same figures apply to mice obtained from the Jackson Laboratory and described in this report. When Charles River Breeding Laboratories acquired Carworth Farms, precise information on the number of generations of inbreeding of the BALB/c mice since 1955 was not available, although it was known that the Laboratory Animal Centre and Carworth Farms used full-sib matings (G. J. Pucak, personal communication). If three generations per year were bred, by 1977 there would have been 63 generations added to the 61 accumulated by the Jackson Laboratory. This figure may be somewhat high, but it is safe to say that at least 100 generations of inbreeding had been completed, and that the BALB/cCF strain was inbred more than 20 generations at Carworth Farms.

All mice were maintained in two large colony rooms on a 12-hour light-12-hour dark schedule at 22° ± 1°C with free access to tap water and non-autoclaved Master MLM rodent food from Maple Leaf Mills, Toronto. They were housed in 29 cm × 18 cm × 13 cm opaque plastic mouse cages with Betta-Chip ,hardwood bedding (Northeastern Products Corp., Warrensburg, NY) and a few sheets of toilet tissue for nesting material. One male was mated with one to three females in a single cage, and each female was isolated when she became visibly pregnant. In most cases the male was remated with the same female to obtain a second litter after the first litter was weaned at one month of age.

The various crosses and sample sizes are listed in Table I. Reciprocal F_1 hybrids and backcrosses were included to control for maternal, cytoplasmic, and sex chromosome influences. The brains of adult mice of each inbred, F_1 hybrid, and backcross group were removed and processed as described in detail elsewhere[24]. Two measures of size of corpus callosum were made at the mid-sagittal plane, cross-sectional area (mm2) and maximum length (mm^2). Brain and body weights also were taken.

Results

Correction for changes with age

Almost all mice in the backcross groups were tested within a relatively narrow range of age-70-110 days after birth, but inbred and F_1 hybrid animals varied widely in age at testing because many were used for breeding. Sizes of corpus callosum, whole brain, and body changed substantially across age in these latter groups, so a method was devised to correct for differences in age. Linear and quadratic changes of each variable with age were assessed separately for males and females of each inbred strain, reciprocal F_1 hybrid cross, and reciprocal

backcross group using a hierarchical regression procedure that has been described in detail elsewhere[24]. Where the change was significant at the $\alpha = 0.05$ level, the regression equation was then used to transform each mouse's score to a value it would have had at 100 days of age. A listing of the numerous regression equations used for this purpose is available from the author on request.

Criteria for deficient corpus callosum

In a previous study[24] comparing inbred strains of mice, it was found that both cross-sectional area and length of corpus callosum (CC) must be considered to establish criteria for deficient CC. In the inbred strains A/J, C57BL/6J, and DBA/2J the area of CC was sometimes small because the structure was of normal anterior-posterior length but rather thin, whereas in BALB/c mice a short CC sometimes had a relatively normal area because it was rather thick. In that study and a subsequent study (Wahlsten, unpub. ms.) of genetic segregation in BALB/cCF mice, all scores had been transformed to their equivalents at 250 days of age, and deficient CC was defined as one with area less than 0.85 mm^2, and length less than 3.0 mm, Area and length of CC for inbred mice in the present study transformed to 100 days of age are shown in Figure I. It is evident that no mouse of the strain A/J, C57BL/6J, or DBA/2J ever had CC shorter than 2.9 ram. Area of CC was clearly a continuous measure, so the criterion for deficiency was derived from the quadratic regression equation for BALB/cCF mice to yield the same proportion of mice with deficient CC at 100 days as at 250 days, which was 0.82 mm^2 instead of 0.85 mm^2. Thus, deficient CC at 100 days of age for a mouse was defined as CC with area less than 0.82 mm^2, and length less than 2.9 mm. These criteria were used to determine the numbers of abnormal animals in the various F_1 hybrid and backcross groups; but because they were somewhat arbitrary, other criteria for abnormality also were considered.

Table I. Observed frequencies of abnormal (Ab) and total (n) mice in each cross, and comparison to single-locus model*

		Males		Females		Pooled reciprocal backcrosses				
							observed	expected		
Dam	Sire	n	Ab	n	Ab	Ab/n	%A	%A	z	P
Crosses involving A/J										
B	A	36	0	32	0					
A	B	27	0	25	0					
B	B × A	45	1	52	1					
B	A × B	41	1	56	1					
B × A	B	30	3	43	3	10/329	3.0	6.9	−2.59	0.010
A × B	B	25	0	37	0					
Crosses involving C57BL/6J										
B	C	23	0	11	0					
C	B	26	0	28	0					
B	B × C	28	0	30	0					
B	C × B	32	0	56	1					
B × C	B	44	1	37	0	3/265	1.1	8.5	−4.14	0.000004
C × B	B	19	0	19	1					
Crosses involving DBA/2J										
B	D	19	0	10	0					
D	B	2	0	5	0					
B	B × D	41	0	56	0					
B	D × B	21	1	25	0					
B × D	B	30	4	24	0	5/235	2.1	8.3	−3.31	0.001
D × B	B	14	0	24	0					

* Abbreviations of strains: A = A/J; B = BALB/cCF; C = C57BL/6J; D = DBA/2J. Criteria for abnormality (Ab) are CC area less than 0.82 mm^2 and CC length less than 2.9 mm, as discussed in the text. Probabilities (*P*) are derived from a two-tailed test of the single-locus model

Frequencies of deficient CC

The numbers of mice in each group found to have deficient CC are shown in Table I separately for males and females. Clearly, there was no sex difference in frequency of the defect, and inheritance was completely recessive in all F_1 hybrid crosses. No substantial differences among reciprocal backcross groups were evident, although frequencies of deficient CC were generally so low that the tests of reciprocal effects lacked power. Data of both sexes and all four backcross groups were pooled for the tests of single-locus inheritance, yielding observed frequencies of deficient CC ranging from 3.0 percent for backcrosses involving A/J to 1.1 percent for those involving C57BL/6J.

Derivation of expected frequencies of deficient CC was complicated by two surprising features of BALB/cCF mice. The strain was maintained as several distinct inbred lines derived from different male-female pairs beginning in 1977, During the first four generations of inbreeding there were significant differences in frequency of deficient CC between these lines, although the lines with highest and lowest frequencies eventually converged in the fifth generation. Furthermore, all lines tended to fluctuate synchronously across generations (Wahlsten, unpub. ms.), suggesting the influence of colony-wide environmental factors. For example, 10.0 percent of the 560 mice in the third generation of inbreeding at Waterloo showed deficient CC, whereas 18,8 percent of the 303 mice in the fourth generation were defective.

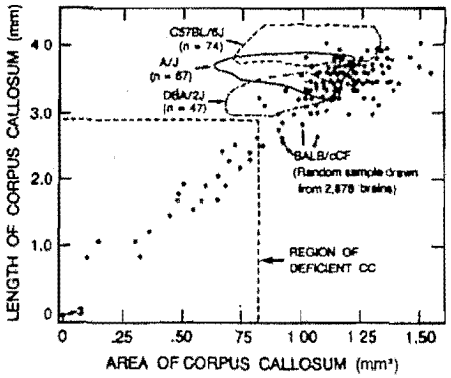

FIGURE 1 Scatterplots of CC length and CC cross-sectional area at the mid-sagittal plane of four inbred strains. The solid line encloses the data for every A/J mouse, and other lines enclose all data for C57BL/6J and DBA/2J mice as indicated. Variability is obviously much greater for CC area than CC length, which reflects both the greater accuracy of measurements of length and genuine individual differences in CC size. Black dots give individual values for a random sample of 5 percent of 2,878 BALB/cCF mice bred at Waterloo over a period of seven generations. To be considered abnormal, a mouse must have CC area less than 0.82 mm^2 and CC length less than 2.9 mm.

The expected frequencies for the various backcross groups could not be estimated using a single percentage figure for the BALB/cCF parent strain because different backcross litters were derived from BALB/cCF mice of different lines and were born at different times covering a span of three years. Instead, the expected frequency of deficient CC was determined for each backcross litter using one-half the observed frequency of deficient CC in the line and generation of BALB/cCF mice that corresponded to the BALB/cCF parent line and time of birth of the backcross litter. These expected frequencies were then summed across all litters to obtain the expected frequency for the entire backcross group, as given in Table I. The expected frequencies in backcrosses involving the A/J, C57BL/6J, and DBA/2J inbred strains differed slightly because the parental lines and times of birth of backcross litters differed to a small extent.

Two-tailed z tests revealed that in all three groups of backcrosses, the observed frequencies of deficient CC were significantly different from expected frequencies derived from the hypothesis of single-locus recessive Mendelian inheritance with incomplete penetrance. Frequencies of deficient CC did not differ significantly among the backcross groups derived from the strains A/J, C57BL/6J, and DBA/2J ($\chi^2 = 2.59$, df = 2, $P > 0.10$).

To assess the importance of the specific criteria chosen for deficiency of CC, the entire analysis was repeated using three other criteria: a) CC area less than 0.82 mm^2, b) CC length less than 2.9 mm, and c) CC area less than 0.82 mm^2 or length less than 2.9 mm. In each case with a less stringent criterion, the observed frequency of mice with deficient CC in the backcross groups was elevated, but so was the observed frequency in corresponding BALB/cCF groups. The net result was that the discrepancy between observed frequencies and those expected from single-locus inheritance was even greater than that evident in Table I.

CC size as a continuous measure

If two Strains differ at a locus that exerts a major influence on CC development, not only should the frequencies of overt deficiencies correspond closely to Mendelian ratios (which they do not in this study), but the distribution of CC size in a backcross should show signs of bimodality. As shown in Figure 2, there clearly is no bimodality of CC area in backcrosses. However, in the present instance where CC size in homozygous BALB/cCF mice is unimodal with mode in the normal range, distinct bimodality in a backcross is not likely. Nevertheless, continuous distributions can yield useful information about mode of inheritance[2,5]. If BALB/cCF Mice are homozygous at a relevant locus and F_1 hybrids are heterozygous, and if no epistatic interaction is involved, then the expected frequency distribution of CC size in the backcross to BALB/cC F can be estimated by adding half the BALB/ cCF distribution and half the appropriate F_1 hybrid distribution.

Comparing cumulative frequency distributions for backcross groups indicated in Figure 2 to expected distributions using the Kolmogorov-Smirnov one-sample test, each of the three backcross groups had significantly fewer instances of CC deficient in length ($P < 0.01$) than expected from the hypothesis of single-locus inheritance with incomplete penetrance. For CC area the discrepancy was significant for backcross groups involving A/J ($P < 0.01$), and only marginally significant for those involving DBA/2J ($P = 0.05$), but not significant for those involving C57BL/6J. The lack of a significant difference in the latter case appeared to reflect the low power of the statistical test owing to the lower precision of measures of CC area than CC length. These results show clearly that rejection of the hypothesis of single-locus Mendelian inheritance of deficient CC does not occur only at a particular choice of criteria for deficient CC.

Analysis of mean size of CC was done for F_1 hybrids using analysis of variance to corn-pare the effects of strain to which the BALB/cCF mice were crossed, the reciprocal effect of having a BALE mother or father, and sex differences. A similar but separate analysis was done on data from the 12 backcross groups. Results are summarized in Table II.

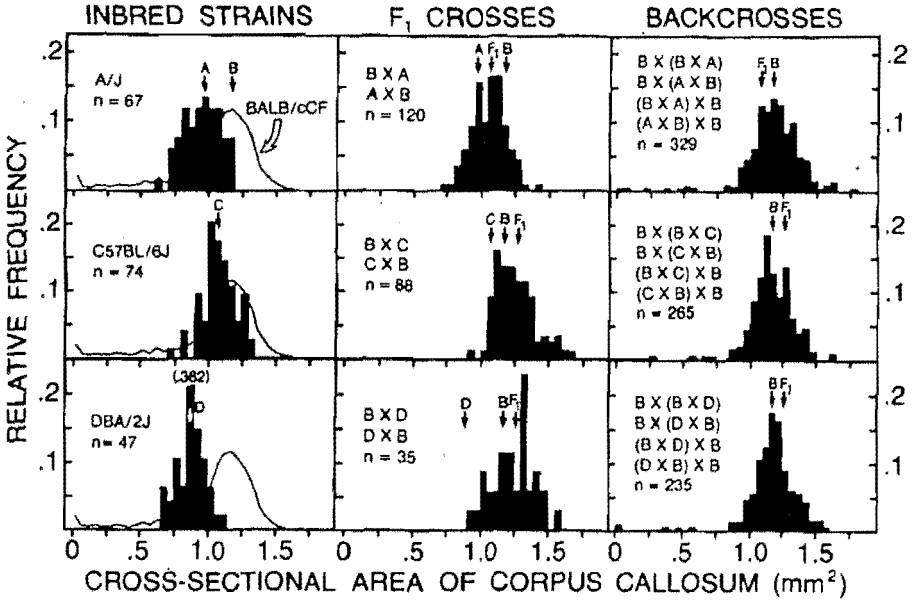

FIGURE 2 Frequency histograms of CC area for three inbred strains, the F_1 hybrids between each strain and BALB/cCF, and the backcrosses of each F_1 hybrid to BALB/cCF. The data for reciprocal F_1 hybrids and reciprocal backcrosses are pooled as indicated for each histogram. A frequency polygon for CC area of BALB/cCF is superimposed on the histogram of each inbred strain. Arrows indicate the mean values for the three inbred strains (A, C, D) and F_1 hybrids, whereas the arrow at B points to the mode of BALB/cCF approximating the mean for that strain when mice with deficient CC are omitted from the calculation.

Among the F1 hybrids, crosses with A/J showed intermediate inheritance (see Figure 2), whereas those with C57BL/6J and DBA/2J showed dominance of the BALB heredity with a tendency towards overdominance. This pattern is not surprising in view of the fact that the A/J strain is rather closely related to BALB. Dominance and especially overdominance arc generally more likely when distantly related strains differing at a large number of loci arc crossed[17].

The situation was complicated by substantial reciprocal effects. There were larger CC and whole brain size for F_1 hybrids with a BALB mother than those with a BALB father. Analysis of the ratio of CC area to brain weight showed that a substantial portion of these group differences in CC size reflected differences in whole brain size. The effect of parental strain was much larger for CC area than the ratio score; and the significant reciprocal effect was not present at all for CC area/brain weight ratio.

Among backcross groups all effects were much smaller. There was no effect of strain of grandparent on CC area, which suggests dominance of the BALB heredity. The variation in CC area among reciprocals was closely related to variation in whole brain size, as shown by the ratio measure. Sex differences were not evident in any measure of the brain.

Discussion

The results of this study show clearly that deficiency of corpus callosum in BA LB/cCF mice is completely recessive, is unrelated to sex of the mouse, but does not exhibit single-locus Mendelian inheritance in backcrosses involving the strains A/J, C57BL/6J or DBA/2J. Although the anatomy of the brain of affected BA L B/c mice is similar to that described by King[9], there is no basis to assert that the locus y ac has been rediscovered. On the contrary, King's own words indicate that designation of a single locus was premature and that ac should be withdrawn from lists of Mendelian genes in mice. He wrote: "The genetic aspects are at present under investigation by Dr. Clyde E. Keeler of Harvard University, and will be reported separately at a future date." He noted that different types of CC defect "do not breed absolutely true" and that two parents with defective CC sometimes give rise to "perfectly normal mice". He concluded his paper with this sentence: "The genetic aspects have not as yet been fully worked out." Keeler's report never appeared in print.

Absence of corpus callosum was first described in a stock of mice with rodless retina, which had a common origin with the Bagg; albino strain, but King and Keeler[10] concluded that the Bagg albino strain was "true-breeding for the normal structure" after assessing only 11 mice. Thus, it is possible that the defect arose before the two stocks were separated and that the hereditary factors causing CC agenesis are the same by descent in BALB/c and the stock of mice studied by King[9] and Keeler[8]. It also is possible that the defect had separate origins, but the fact that it appears in the BALB/cBy substrain[22] whose ancestors were separated from the strain that gave rise to the J substrain[1] in 1935 suggests that it arose relatively long ago. If so, this reveals something about the narrow vision of many investigators who over the years have studied BALB/c mice, especially the brain and behavior, without realizing that the largest commissure in the brain is often not present. To see how easily this can happen, one need only glance at Figure 2 of a study of the amygdala[4], where the BALB/cJ brain obviously has no corpus callosum.

Table II. F ratios for effects of three factors and their interactions derived from separate analyses of variance for reciprocal F_1 hybrids and reciprocal backcrosses

	Reciprocal F_1 hybrids					Reciprocal backcrosses				
Measure: Effect	*df*	CC area	CC length	brain weight	area/ weight ratio	*df*	CC area	CC length	brain weight	area/ weight ratio
Strain	2	70.4*	168.6*	229.5*	11.1*	2	—	6.6*	14.2*	5.7*
Reciprocals	1	7.9*	49.7*	44.8*	—	3	3.6	6.4*	12.7*	—
Sex	1	7.0*	—	—	8.6*	1	—	—	—	—
Strain × reciprocals	2	—	—	—	—	6	4.8*	—	6.2*	2.7
Strain × sex	2	3.9	—	3.5	—	2	—	—	—	—
Reciprocals × sex	1	—	—	—	—	3	—	—	—	—
Three-way	2	—	—	—	—	6	—	—	—	—
Residual	231					788				

* $P < 0.01$; other F ratios shown are significant only at the $P = 0.05$ level; those not shown are not significant at even the 0.05 level

Agenesis of corpus callosum also is known in humans[13], and autosomal recessive inheritance has been reported for a syndrome that occurs in one region of Quebec in Canada[15]. However, this syndrome includes not only CC agenesis but also progressive neuromuscular degeneration that clearly is not present in affected BALB/c mice. Many other human cases of CC agenesis are known that cause remarkably little impairment of mental and motor function[3,11], although virtually nothing is known about the fine details of brain structure. Whether the BALB/c mouse will prove to be a useful model for hereditary disorders of corpus callosum in humans remains to be seen.

The defect in BALB/c mice is obviously not monogenic, but it would be unwise to label it polygenic, Analysis of CC size in the normal range demonstrated significant differences among reciprocal crosses and revealed the presence of maternal environment effects. Other studies[23,24] (Wahlsten, unpub. ins.) documented substantial environmental influences on frequency of deficient CC in BALB/c mice. To argue that a gene or group of genes has a low level of penetrance is simply to say that unknown factors exert a powerful influence on CC development[16].

Several reasonable hypotheses about mechanisms of inheritance arc consistent with the present findings. I) There may be two autosomal loci with two alleles each, where a fraction of mice that are homozygous recessive at both loci have deficient CC. 2) There may be a large number of relevant loci segregating in backcrosses, and mice homozygous recessive at enough loci may exceed a threshold for expression of the defect. 3) There may be one major locus exerting a strong influence on CC development but the effects of the homozygous recessive genotype may be apparent only when developmental homeostasis has been impaired by inbreeding; fetuses with sufficient heterozygosity at other loci may be buffered against maldevelopment of CC. Discrimination between the first two alternatives is beset with difficulties[6], and research on heterotic effects also presents serious problems[12]. The relatively low frequency of deficient CC will make this work especially perilous "because there is presently no way to tell which living animals have deficient CC.

Whatever the case may be, the defect of CC development in BALB/c mice should be useful in brain research. Silver et al.[18] have identified a population of glial cells, which normally migrate to the midline of the fetal brain before the axons arrive and serves as a glial sling to guide axons to the opposite hemisphere; they have found that this glial structure is malformed in some BALB/cCF mice. However, it is not yet known why the structure is aberrant in only some of the mice. Development of corpus callosum must be exquisitely sensitive to mild environmental influences in the BALB/c strain. Perhaps there is something about the local uterine environment of certain fetuses that impairs the growth or migration of glial cells before they approach the longitudinal cerebral fissure, Recent studies[14,20] of the uterine location of fetuses have revealed much about within-litter variation in behavior and hormonal function, and similar research on forebrain anatomy also may be fruitful.

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