Tests of Genetic Allelism between Four Inbred Mouse Strains with Absent Corpus Callosum

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Abstract:

Inbred mouse strains that lack the corpus callosum connecting the cerebral hemispheres in the adult differ from the C57BL/6J strain at several relevant but unknown loci. To identify at least one major locus that influences axon guidance, different strains showing phenotypically similar defects were crossed to test for allelism. It the F_1 hybrid between two strains with the same brain defect is phenotypically normal, it is much more likely that the two strains will differ at fewer loci than will an acallosal strain and C57BL/6J. This approach proved to be very informative. Five reasonable models of inheritance involving two or three loci were assessed, and the data justified rejection of all but one hypothesis. A total of 479 mice were obtained from tour inbred strains prone to absence of the corpus callosum (BALB/cWah 1, BALB/cWah2, I/LnJ, and 129/ReJ), one normal strain (C57BL/6J), and 11 F_1 hybrids among them. Because the size of forebrain axon bundles is generally greater in mice with larger brains, and because whole brain size is certainly polygenic, the phenotypically normal groups were used to derive a standard index of the degree of corpus callosum deficiency relative to brain size. Results demonstrated clearly that the hybrid between BALB/ cWah 1 and 129/ReJ is normal, whereas the crosses among the BALB/c substrains and I/LnJ yielded many mice with deficient corpus callosum. I/LnJ crossed with 129/ ReJ also produced some animals with callosal defects. The data were consistent with a model in which the difference between BALB/c and 129/ReJ involves two loci, whereas the defect In l/LnJ involves homozygosity at three loci, which impairs development more severely. Furthermore, severe deficiency of the hippocampal commissure occurred in I/LnJ mice but never In crosses with other strains. Collisions of the fornix and anterior commissure occurred only in the BALB/c substrains and their F_1 hybrid, and were independent of the CC defect.

Article:

Three inbred strains of mice and several of their substrains have a very similar defect of the corpus callosum (CC), which connects the cerebral hemispheres, Although they differ in the frequency and severity of the CC defect (see Table 1), when each is crossed with a normal strain such as C57BL/6J, inheritance is clearly recessive and polygenic in the adult (Wahlsten 1982b; Wahlsten and Smith 1989). Two findings suggest that the difference may involve relatively few loci. In fetuses where the CC is just beginning to form, the difference between BALB/c and C57BL/6J appears to involve two major loci (Wahlsten and Smith 1989), and, in successive backcrosses to l/LnJ, a high frequency of total CC absence occurs after only two generations (Lipp and Waanders, 1990). It is therefore plausible that certain of the strains prone to CC absence differ at only one or two relevant loci. If this is so, further genetic analysis comparing them should be much more likely to reveal a major locus effect than would crosses of a normal and abnormal strain. Of course, it could also happen that the same loci are involved in each abnormal strain and that they differ only in their alleles at each locus.

F_1 hybrids can be used to assess allelism among phenotypically similar strains, and, as the present study shows, they allow sensitive tests of several alternative models of the mode of inheritance. Given facts known about three of the strains (BALB/ cWah 1 or Wahl; 129/ReJ or 129; I/LnJ), five models involving two or three loci were considered plausible and testable with simple F_1 crosses. In the following models the alleles for the three strains are symbolized by W, 1, and L, respectively.

Model 1. Two loci involved, with different alleles at each.

Wahl	a^w/a^w	b^w/b^w
129	a^1/a^1	b^1/b^1
I/Ln	a^L/a^L	b^L/b^L

All F_1 hybrids (and backcrosses) should show CC detects at least as severe as the least affected parent.

Model 2. Two different loci involved for each strain.

Wahl	a^w/a^w	b^w/b^w	+/+
129	a^1/a^1	+/+	c^1/c^1
I/Ln	+/+	b^L/b^L	c^L/c^L

All F_1 hybrids should be normal or show improvement over the least affected parent.

Model 3. I/Ln has a third mutation, which exacerbates the defect,

Wahl	a^w/a^w	b^w/b^w	+/+
129	a^1/a^1	b^1/b^1	+/+
I/Ln	a^L/a^L	b^L/b^L	c/c
Wahl × 129	a^w/a^1	b^w/b^1	+/+
Wahl × I/Ln	a^w/a^L	b^w/b^L	+/c
129 × I/Ln	a^1/a^L	b^1/b^L	+/c

All hybrids should be abnormal and show defects similar to the least affected parent or between the two parents.

Model 4. I/Ln defective at three loci; 129 and Wahl differ at two loci.

Wahl	a^w/a^w	b^w/b^w	+/+
129	a^1/a^1	+/+	c^1/c^1
I/Ln	a^L/a^L	b^L/b^L	c^L/c^L
Wahl × 129	a^w/a^1	$b^w/+$	$+/c^1$
Wahl × I/Ln	a^w/a^L	b^w/b^L	$+/c^L$
129 × I/Ln	a^1/a^L	$+/b^L$	c^1/c^L

Wahl × 129 should be normal. Others should be abnormal.

Model 5. Wahl and I/Ln have different alleles at two loci; 129 has a defect at the third locus.

Wahl	a^w/a^w	b^w/b^w	+/+
129	a^1/a^1	+/+	c/c
I/Ln	a^L/a^L	b^L/b^L	+/+
Wahl × 129	a^w/a^1	$b^w/+$	+/c
Wahl × I/Ln	a^w/a^L	b^w/b^L	+/+
129 × I/Ln	a^1/a^L	$+/b^L$	c/+

Wahl × 129 and 129 × I/Ln should be normal. Wahl × I/Ln should be abnormal.

Table 1. Four mouse strains with defective CC

Strain	Defective CC (%)	Absent CC (%)	Inheritance
BALB/cWah2	16.7[a]	2[a]	polygenic
BALB/cWah1	54.8[a]	20[a]	polygenic
129/J	70[b]	16.67[c]	polygenic
I/LnJ	100[d]	100[d]	polygenic

[a] Wahlsten (1987).
[b] Wahlsten (1982a).
[c] Ward et al. (1987).
[d] Lipp and Waanders (1990).

In each of the models at least two loci must be homozygous recessive relative to the wild-type allele in order for a defect to occur. According to previous evidence, when only one locus Is homozygous recessive, the outcome should be a normal CC, although homozygosity at that one locus may have an effect on some part of the developing brain. These models are also pertinent to other defects seen in certain of the strains. Including severe

deficiency of the hippocampal commissure (Wahlsten 1987) and collisions between the columns of the fornix and the anterior commissure (Cassells 1988; Wahlsten 1974).

Methods

Five inbred strains and 11 of their F_1 hybrid crosses were used (Table 2), BALB/ cWahl and BALB/cWah2 were bred and raised at the University of Waterloo (Wahlsten 1989); the C57BL/6J, 129/ReJ, and I/LnJ mice were obtained from Jackson Laboratory, Bar Harbor, Maine, and bred at the University of Waterloo. The housing, feeding, and breeding protocols of the mice have been described previously (Wahlsten 1982a). There were at least two litters from each of the crosses except for the I/LnJ. Owing to their extremely poor breeding characteristics, the eight I/LnJ mice were all adults. Most reciprocal crosses were not performed because maternal effects have been shown not to be involved in the CC defect (Bulman-Fleming and Wahlsten 1988) and because of doubt about the breeding efficiency of some of the strains. BALB mice are noted poor breeders. I/LnJ mice are much worse, demonstrating high pup mortality due mainly to very poor maternal care. Although 129/.1 mice have been found to be poor breeders (Wahlsten 1982a), little has been reported about the 129/ReJ sub-strain. In this study they were reasonably proficient and demonstrated adequate maternal care. Most litter sizes were in the range of five to seven pups.

Table 2. Sample sizes, mean and standard deviation (in parentheses) for brain weights[a] at 28 days after birth for each mouse strain and F_1 hybrid cross

Strain	*N*	Brain weight
Wah1	109	0.427 (0.019)
Wah1 × Wah2	49	0.415 (0.024)
Wah1 × 129	28	0.432 (0.029)
Wah1 × I/Ln	13	0.468 (0.009)
Wah2	49	0.461 (0.026)
Wah2 × Wah1	44	0.443 (0.024)
Wah2 × 129	22	0.452 (0.019)
Wah2 × I/Ln	20	0.460 (0.019)
129	52	0.411 (0.025)
129 × I/Ln	11	0.472 (0.010)
I/Ln[b]	8	0.456 (0.030)
C57	10	0.427 (0.013)
C57 × Wah1	19	0.450 (0.011)
C57 × Wah2	18	0.458 (0.010)
C57 × 129	15	0.481 (0.007)
C57 × I/Ln	12	0.474 (0.020)

[a] Brain weight adjusted to a common body weight of 12.0 g using the equation BRWT − 0.008085(BDWT − 12.0) derived from the present data, which indicated that for every gram increase in body weight, brain weight increased by about 8.1 mg.

[b] Data for I/LnJ are for adults and are not corrected for body size.

One male was mated with one, two, or three females, and females were isolated in a fresh cage when they were visibly pregnant. The day of birth was designated day 0. Pups were raised by the mothers until 28 ± 1 days of age, at which time the CC is near the adult size (Wahlsten 1984). Each pup was then anaesthetized with sodium pentobarbital and perfused intracardially with one rinse of 5 mL 0.9% saline solution followed by 10 mL 10% neutral buffered formalin. Brains were extracted from the skull and submerged for 1 week in fresh fixative. After 1 week the brains were trimmed (Wahlsten 1983), weighed, encased in gelatin, and stored in 10% sucrose formalin. Frozen sagittal sections (25 µm) were stained with Sudan Black B to reveal phospholipids in myelin.

We measured tracings of the CC, HC (hippocampal commissure) and AC (anterior commissure) at the midsagittal plane at 33 × to determine their areas. When tracing the CC, we excluded the dorsal commissure of the fornix, as well as the superior fornix and the longitudinal striae, whenever possible. The anterior half of the anterior commissure stains much darker than the posterior half when using the Sudan stain, and thereby any abnormalities in AC development were easily seen.

Results

Index of Abnormality

CC size ranges along a continuum from acallosal, or absent, to clearly normal (Wahlsten 1982b), which makes it difficult to define abnormality in a population. Furthermore, among normal mice the cross-sectional area of

the CC and other forebrain commissures is larger in those animals with larger brains (Wahlsten 1982a). An index of abnormality was therefore devised using brain weight (BRWT) as a predictor of CC (as well as HC and AC) size for normal groups in the study (C57 and F_1 hybrids with C57), Weanling mice from the abnormal strains were then compared to this reference group. No sex differences in brain weight were found after correcting for variance in body weight ($P = .296$); therefore males and females were pooled within each strain.

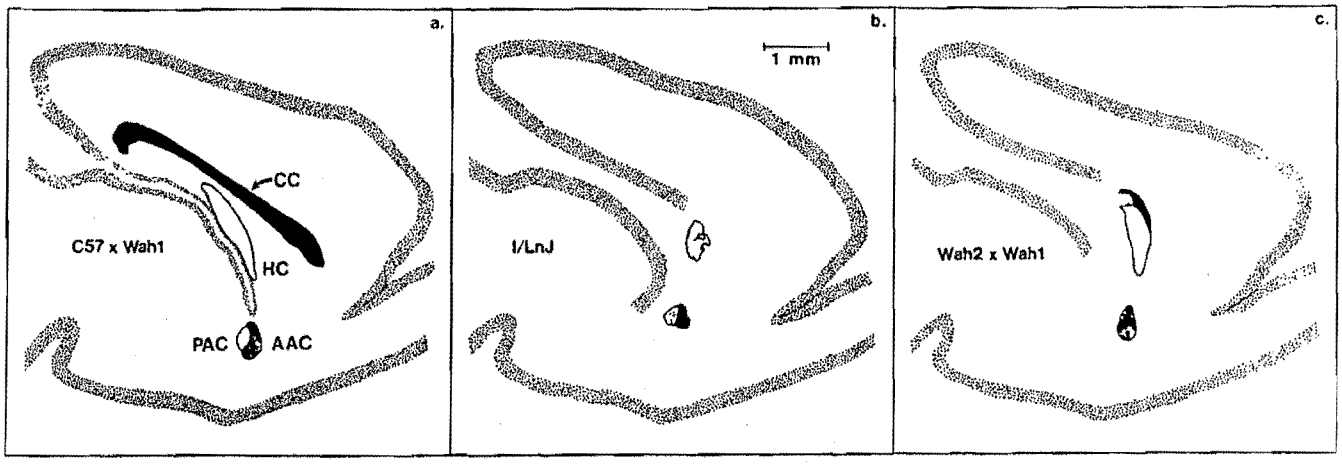

Figure 1. Diagram showing midsagittal sections of three different levels of CC defect. The CC (corpus callosum) is shown in solid black, the HC (hippocampal commissure) in white, and the AC (anterior commissure) in light (posterior part) and dark (anterior part) stipple: (a) Normal size and shape of all three commissures; (b) Absence of the CC; note the irregular shape and size of the HC; (c) CC is present but small; note the extensive mixing (code 6 in Figure 4) of AC fibers.

Abbreviations and their definitions are provided in Table 3. For the reference group, the best prediction of CC area (CCA) from BRWT was CCA = —0.429 + 2.80(BRWT) with an adjusted $R^2 = .672$. Dummy coding for strain in a second regression equation resulted in $R^2 = .706$, but the small increase in explained variance was not significant ($P > .05$), which justified combining the five normal groups into one reference group.

Knowing the CC area expected on the basis of brain size of a mouse, the standardized index is

$$CCZ = \frac{CCA - E(CCA)}{\text{SD of residuals}} = \frac{CCA - [-0.429 + 2.80(BRWT)]}{0.0413}.$$

The same procedure for total AC area (ACT) yielded

$$ACZ = \frac{ACT - [-0.0331 + 0.376(BRWT)]}{0.00772}.$$

HC area (HCA) in relation to BRWT was significantly smaller for C57 than for the F_1 hybrids with C57 ($P < .001$); therefore the four hybrids were used for the reference group:

$$HCZ = \frac{HCA - [0.144 + 0.406(BRWT)]}{0.0204}.$$

These indices are valid for the methods indicated. At other ages, the rates of development of body and brain will likely be different. Different histological techniques may produce differing amounts of tissue distortion, limiting the applicability of this scale.

Corpus Callosum

Diagrams of the midsagittal sections of three different levels of CC defect severity (Figure 1) show a normal (a), absent (b), and abnormally small CC (c). The distributions of brain weights, CC areas (CCA), and standardized CC areas (CCZ) (Figure 2) demonstrate the effectiveness of the index in removing the variability due to brain weight differences, Relative to the reference population, the CCZ means of all the abnormal strains were significantly different from $z = 0$, except for Wah2, which had only a marginal difference (Mann-Whitney U test, $P = .168$; t test, $P < .001$), The F_1 hybrids among the abnormal strains all had means significantly lower than $z = 0$ except for Wahl × 129 and Wah2 × 129. This is Interesting because the parent strains of these hybrids

are defective, yet the hybrids are not.

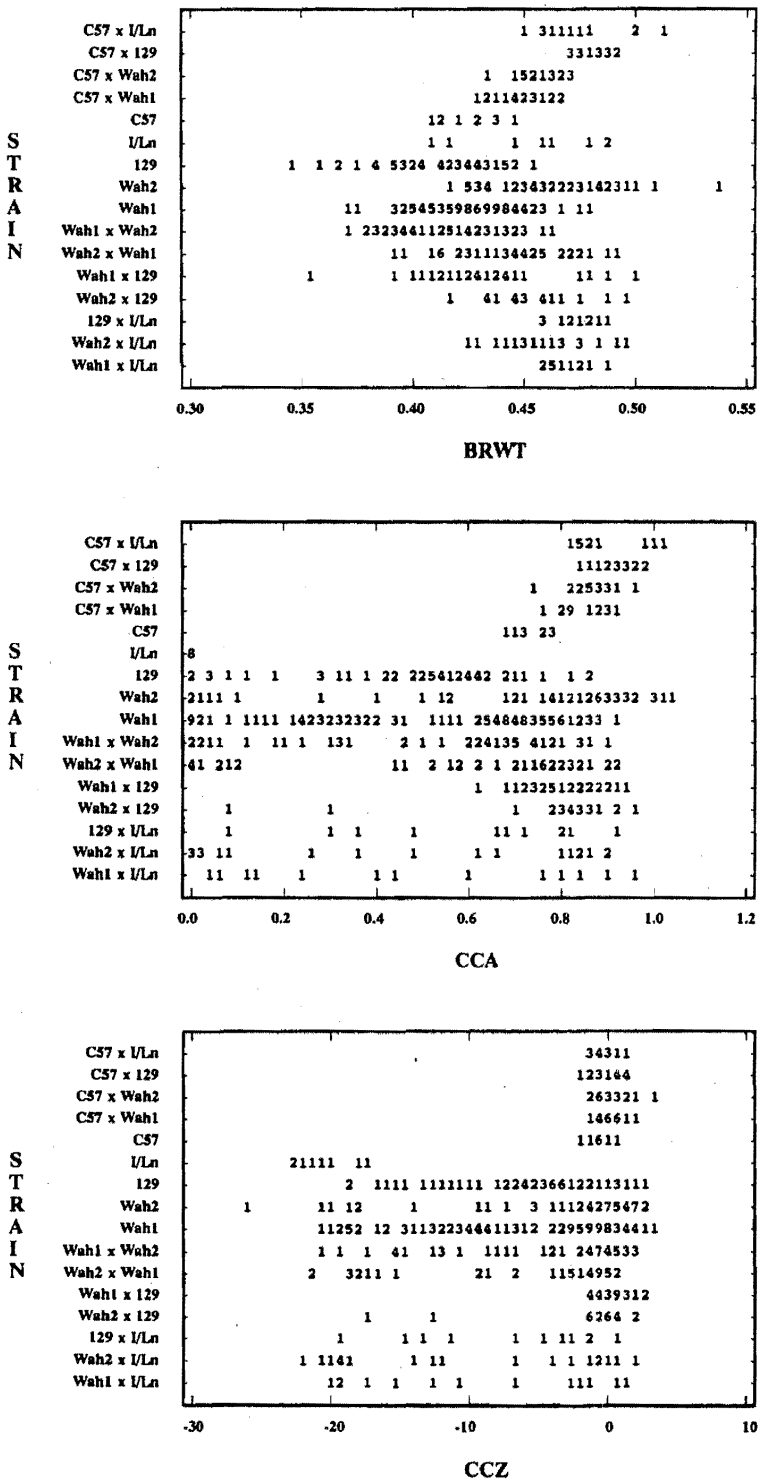

Figure 2. *Distribution of brain weights (BRWr), measured CC areas (CCA), and standardized CC areas (CCZ) for each strain, Numbers refer to the number of animals with that value. The number "9" refers to nine or more. Note the alignment of the CCZ scores after removal of brain weight variability from the CCA values. Of course, variability was increased for animals completely lacking the CC.*

Comparisons of CCZ values between each hybrid cross and the least affected parent were made using a Kolmogorov-Smirnov two-sample test and a Mann-Whitney *U* test. The Wahl × 129 mean was significantly greater than the 129 mean ($P < .0001$). However, Wah2 × 129 did not exceed Wah2 ($P = .076$) because of the extreme variability in the Wah2 scores. Wahl × I/Ln was not significantly different from Wahl, nor was 129 × I/Ln different from 129. This suggests that both 129 and Wahl display complete dominance over the I/Ln. The

Wah2 × I/Ln mean was significantly lower than the Wah2 mean, indicating that any possible factors contributing to the dominance of Wahl and 129 over I/Ln are not expressed in the same way by Wah2. Wah2 was less affected than Wah2 × Wahl, but Wahl × Wah2 showed the same level of defect as Wah2. A comparison between the two hybrids revealed no difference ($P = .389$). Because all previous research indicates that there should be no difference between the reciprocal crosses (Bulman-Fleming and Wahlsten 1988), the differences relative to Wah2 may be a result of small sample size.

A CC was considered abnormally small or defective if CCZ was at least 2.33 SD below normal ($P < .01$). Although some of the samples are too small to say much about absent CCs, more can be said about the frequencies of defective CC (Table 4). Immediately obvious are the low penetrance levels of Wahl × 129 and Wah2 × 129. Wahl × 129 mice showed no CC defects. Only two animals from Wah2 × 129 had a defect In the CC. The penetrance level of Wahl × Wah2 did not differ from either of the parent strains, and the same was true for Wah2 × Wahl.

Table 3. Abbreviated terms and their definitions

Abbreviation	Definition
BRWT	Brain weight
CCA	Area of the corpus callosum
CCZ	Standardized area of the corpus callosum
HCA	Area of the hippocampal commissure
HCZ	Standardized area of the hippocampal commissure
ACT	Total area of the anterior commissure
ACZ	Standardized area of the anterior commissure
ACC	Anterior commissure collision severity code

Table 4. Frequency of CC absence and defect

Group	Complete absences (%)	Defective (%)[a]
Wahl	8.3	56.9
Wahl × Wah2	4.1	42.9
Wahl × 129	0	0
Wahl × I/Ln	0	69.2
Wah2	4.1	32.7
Wah2 × Wahl	6.8	50
Wah2 × 129	0	9.1
Wah2 × I/Ln	15	70
129	1.9	76.9
129 × I/Ln	0	72.7
I/Ln	100	100

[a] A defective CC was defined as one with a z score less than −2.33.

Hippocampal Commissure

Figure 3 shows the distribution of HCZ scores for each strain, Only two strains appear to be different from the normal population, C57 and the I/Ln. Wahl and Wah2 have two and three animals, respectively, which were quite low, but most of the animals were close to the normal group. As well, most of the F_1 hybrids between abnormal strains had no HC deficiencies. One Wah2 x l/Ln mouse had a severe defect of the HC, and this animal also had an absent CC. In fact, all animals with an HCZ score lower than —5 also had an absent CC, except for one Wah2 mouse that had a severe defect at midline, which made it very difficult to distinguish between HC and CC. In I/LnJ, most HC areas were smaller than normal and about half of them had a more irregular HC shape, sometimes with short finger-like projections off the main HC mass (see Figure 1 b).

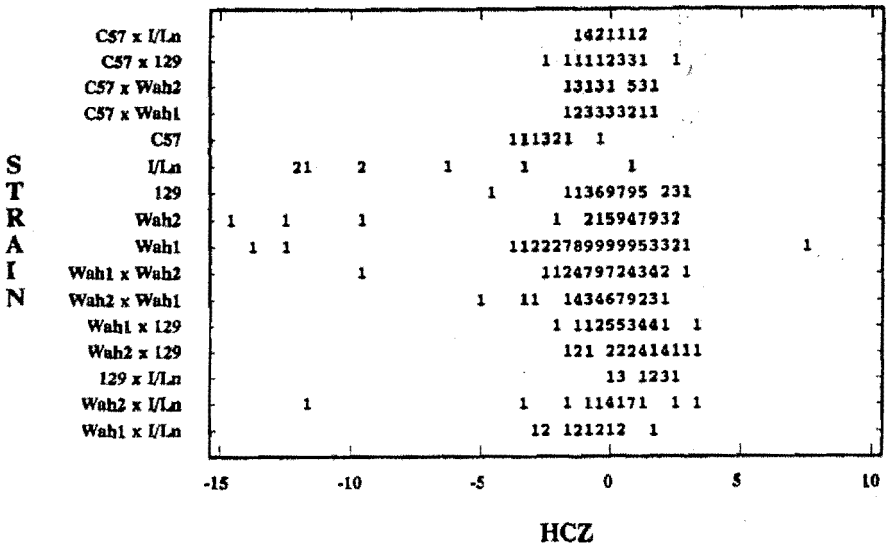

Figure 3. Distribution of standardized HC areas (HCZ) for each strain. Numbers refer to the number of animals with that value. The number "9" refers to nine or more. I/Ln is most severely affected, although one animal is in the normal range. C57 inbreds are lower than the normal group, which may indicate an effect of hybrid vigor on HC size.

Anterior Commissure

All the abnormal inbreds had a lower ACZ score than the normal group; Wahl, Wah2, and their reciprocal F_1 hybrids were the most severely affected. The other F, hybrids were all fairly close to normal, although the three crosses with I/Ln were slightly lower. Wahl × 129, Wah2 × 129, and 129 × I/Ln showed higher means than their parent strains. A measurement scale was devised to rate the severity of any defect in the AC development, to observe differences between strains and to correlate these defects with abnormalities in CC development (Figure 4). Major departures from the normal appearance of the AC (Figure 4, Type 0) were caused by prenatal collisions between the embryonic AC and the columns of the fornix (Cassells 1988; Wahlsten 1974). The distributions of ACC scores are shown for each strain in Figure 5. The strains most affected by collisions were Wahl, Wah2, and their reciprocal F_1 hybrids, Wah2 being affected more than Wahl (Mann-Whitney *U* test, $P = .006$). A few of the F_1 hybrids with C57 did have mild defects, and relatively low scores were found in the I/Ln and their crosses.

Correlations

Spearman correlations were obtained within each inbred strain to determine if any relationship existed between the severity of collisions in the AC (ACC scores) and the severity of the defect in the CC. The correlation was —0.076 for Wahl, —0.306 for Wah2, 0.109 for 129, and 0,025 for I/Ln. The only correlation significantly different from 0 was for Wah2, although the relationship was of marginal significance ($t = 2.206$, df = 47, $P < .05$).

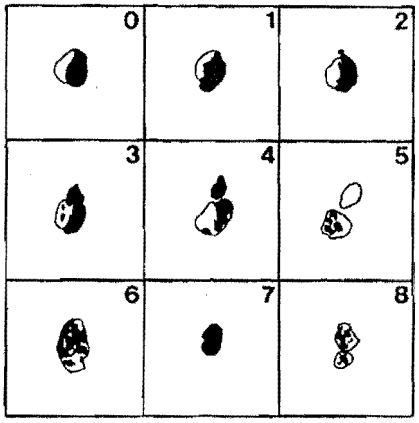

Figure 4. Diagrams representing the nine levels of collision severity seen in the anterior commissure. The anterior half of the AC is shown in black and the posterior half in white. A brief explanation of the collision severity codes follows: (0) Distinct, smooth border between anterior and posterior halves; (1) Border distinct but has interdigitations between the two halves; (2) Distinct border; external satellite bundles near parent bundle; (3) Distinct border; small satellite bundles within main mass; satellites are intermixed close to the border or off on their own; (4) Small external satellite bundles near parent bundle; internal satellites mixed within main mass; border still apparent; (5) More extensive mixing within main mass; more, or larger, satellite bundles, away from parent bundle; difficult to identify border; (6) Severe mixing within main mass; no identifiable border; external bundles close to main mass; labeled as "moonscape"; (7) Appears to be single mass of one color, usually dark; assumed to be complete mixing of the fibers from both halves; (8) Severe collisions; main mass separated into two or three large bundles; may be some fibers in vicinity of the hippocampal commissure.

Discussion

The results clearly indicate support for Model 4 as representative of the relationship between Wahl, 129, and I/Ln for the corpus callosum defect. The critical result is the improvement seen in the Wahl × 129 over both its parent strains. The normal CC found in Wahl × 129 eliminated Model I, which hypothesized that all F_1s should have no recovery; Model 2, which proposed that all F, hybrids should be normal; and Model 3, which proposed no recovery for Wahl × 129. Model 5 hypothesized that Wahl x 129 would be normal and that Wahl × I/Ln would be like Wahl, both of which occurred. However, 129 × I/Ln was not normal but rather demonstrated the same degree of CC defect as 129.

In contrast, Model 4 met all conditions established for the F, hybrids. Wahl × 129 displayed improvement over both parent strains, and Wahl × I/Ln and 129 × I/Ln were both similar to the non-1/Ln parent. The model maintains the assumption of a two-locus difference between BALB and normals suggested previously (Wahlsten and Smith 1989), and it proposes a similar mode of inheritance for 129. The difference in severity between these two inbreds could simply be due to the differences in strength of the second locus. For example, the locus may be more important in terms of CC development: because 129 is homozygous recessive at that locus, its development may be more severely affected. The involvement of three loci in 1/Ln is a reasonable assumption, considering the severity of the defect in I/Ln. Backcross results between C57 and I/Ln have suggested the involvement of a difference at two or three loci (Lipp and Waanders, 1990).

The results cannot be explained by overall genetic similarity among BALB/c, I/LnJ, and 129/ReJ. From the data given by Roderick (1980), BALB/cJ (the ancestor of BALB/cWah 1) and I/LnJ differ at 32% of 31 tested loci and BALB/cJ and 1290 differ at 29% of 66 loci, whereas 129/J and I/LnJ differ at 28% of 29 loci. Furthermore, there was no heterosis for crosses of BALB/ cWah I and BALB/cWah2 for any measure, but crosses of BALB/c with I/LnJ indicated moderate heterosis for body and brain size. If two strains are closely related, one would not expect heterosis for polygenic characteristics.

During normal CC development, CC fibers cross midline when fetal body weight is about 0.5 to 0.6 g (Wahlsten and Bulman-Fleming 1990) using a layer of subependymal cells called the "sling"(Hankin and Silver 1986; Katz et al. 1983). Caudal to the sling, the dorsal surface of the hippocampal commissure is used to cross (Silver et al, 1982). Mice with abnormal development have a fluid-filled gap present at mid-line that prevents CC fibers from crossing (Wahlsten 1987). If the hippocampal commissure development is not delayed, the CC axons may exclusively use the dorsal surface of the HC to cross, allowing some CC axons to cross midline. It is reasonable to assume that a defect severe enough to eliminate the CC could also affect HC development. This is supported by the finding that almost all animals with an HCZ score below -5.0 SD also had an absent CC. C57 and 1/Ln were the only two strains to show an abnormally small HC size. C57 inbreds had smaller HC sizes than the hybrids with C57, but none were markedly abnormal to the extent seen In 1/Ln.l. This result may indicate an effect of hybrid vigor on HC size. All I/Ln inbreds but one displayed an abnormally small HC. This was likely due to a delay in the crossing of midline by the HC axons. One reason for this delay could be the large deflection of the HC axons under the longitudinal cerebral fissure during their travel to mid-line. However, the irregular shape of the HC may indicate a problem with the actual crossing of the axons to the contralateral side during the time when the HC is being filled in. Such delays could result in the HC not attaining a normal size in sufficient time to allow recovery of any of the CC fibers.

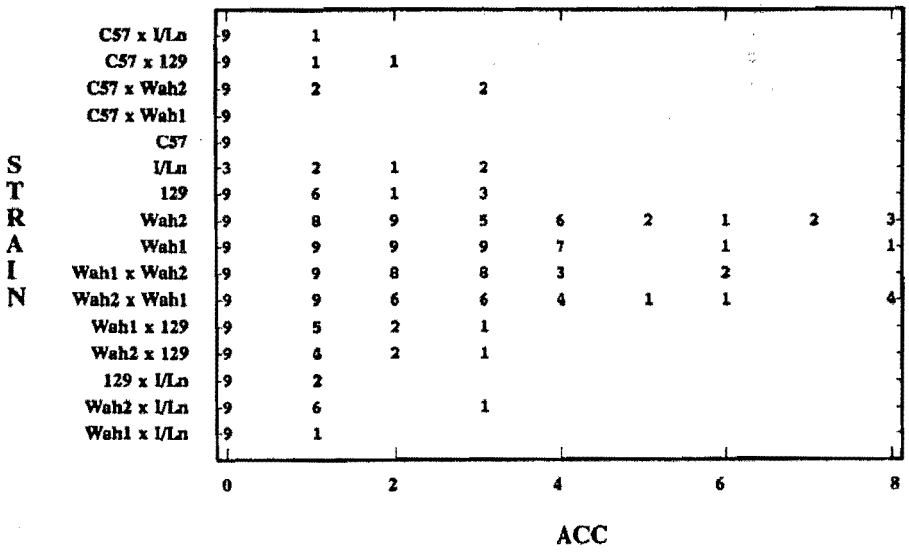

Figure 5. Distribution of the anterior commissure collision severity (ACC) scores for each strain. Numbers refer to the number of animals with that value. The number "9" refers to nine or more. Most strains are close to 0 (normal development). Most severely affected are Wah1, Wah2 and their reciprocal F_1 hybrids. These are the only strains with the more severe collisions (greater than code 4).

The size of the anterior commissure in all of the inbred strains and most of the hybrids was smaller than the normal group. Small AC areas may result from collisions during AC development, which may cause bundles of fibers to split from the main bundle and become "lost," as seen in Wahl, Wah2, Wahl × Wah2, Wah2 × Wah 1 , and 129, However, in I/Ln and 129 × I/Ln AC size was small but no collisions were observed, and in Wahl x 129 collisions were seen but AC size was normal. It should be noted that collisions may have occurred some distance away from midline and therefore were not observed. The largest effects of collisions in the AC were seen in Wahl, Wah2, and their reciprocal F_1 hybrids. This was to be expected because the anterior commissure and columns of fornix in BALB mice come rather close to each other and arrive in the same area at about the same time (Wahlsten 1974). The frequency of minor collisions seen in the AC supports the suggestion that this is a normal developmental process and not necessarily an abnormality (Wahlsten 1974). The lack of a correlation between the AC collisions and the CC defect indicates that their developments are independent of each other.

The results clearly support a model that involves three unlinked, autosomal loci, but further evidence will he needed to confirm this. In particular, backcrosses involving BALB/cWahl and l29/ReJ should reveal a bimodal distribution of CC size in fetuses (Wahlsten and Smith 1989). Recent results of a separate experiment also indicate that the strain ddN, which shows a low frequency of CC defects (Ozaki et al. 1984), yields abnormal hybrid mice when crossed with BALB/cWahl or l/LnJ.

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