Survey of 21 inbred mouse strains in two laboratories reveals that BTBR T/+ *tf/tf* has severely reduced hippocampal commissure and absent corpus callosum

By: Douglas Wahlsten, Pamela Metten, John C. Crabbe

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Abstract:

A morphometric survey of brain size and forebrain commissures of 21 inbred mouse strains from the Jackson Laboratory was done with animals tested in two laboratories as part of the Mouse Phenome Project. Strain BTBR T / + *tf*/*tf* was found to have 100% total absence of the corpus callosum as well as severe reduction of the hippocampal commissure in almost every animal, the most severe commissure defect observed to date in any commercially available mouse strain. The strain 129S1/SvImJ had a milder defect with incomplete penetrance. Crosses of BTBR mice with inbred strains BALB/cWah1, 129P1/ReJ, and the recombinant strain 9XCA/Wah having a severe commissure defect supported a two-locus model of the genetic defect in these strains. Brain size varied greatly among strains but for any one strain was almost identical in mice housed for 5 weeks in the two laboratories. Sex differences in brain weight and forebrain commissure sizes were not statistically significant.

Theme: Disorders of the nervous system

Topic: Genetic models

Keywords: Inbred strain; Morphometry; Mouse Phenome Project; Complementation test; Incomplete penetrance; Brain weight

Article:

1. Introduction

Hereditary absence of the corpus callosum (CC) was first documented in laboratory mice by King and Keeler [6] in a stock that later became extinct, and it was rediscovered by Wimer [27] in the inbred strains BALB/ cJ, 129P3/J, and I/LnJ [5]. Every BALB/c and 129- derived strain examined to date shows incomplete penetrance for the CC defect, whereas all I/LnJ mice suffer absent CC. About half of I/LnJ mice also exhibit severe reduction of the size of the hippocampal commissure (HC), a defect that is only seen in individuals lacking the CC [8]. The recombinant inbred strain 9XCA/Wah derived from the progenitors 129P1/ReJ and BALB/cWah1 has 100% total absence of the CC and severe reduction of the HC [23]. We now report that the inbred strain BTBR T/ + *tf*/*tf* has a phenotype more severe than I/LnJ and similar to 9XCA/Wah, which amounts to the most severe and consistent forebrain commissure defect known in commercially available strains. This discovery should facilitate the study of the genetics, developmental origins, and behavioral consequences of commissure defects.

The present study was done as part of the Mouse Phenome Project (MPP; http://wwwjax.org/phenome), an extensive and intensive effort by more than a dozen laboratories to phenotype 40 inbred strains maintained at the Jackson Laboratory [12]. The 40 strains are divided into priority groups A, B, C, and D with ten strains each [20], chosen to represent a wide diversity of mouse genotypes. At the outset of the MPP in 1999, the highest priority group A included the little known strain BTBR T / + *tf*/*tf*, but that strain was later moved by MPP staff to the lowest priority group D. Our work with behavioral tests in two laboratories began in 2000 with the original group A, and we found some interesting behavioral differences in the BTBR mice, especially their superior performance on the accelerating rotarod [14,15]. Consequently, when we expanded our study in 2002

to include the 20 strains in priority groups A and B, we included BTBR from group D and assessed brain size and commissure anatomy of 21 inbred strains.

2. Materials and methods

2.1. Mice

The inbred strains listed in Table 1 were obtained from the Jackson Laboratory, Bar Harbor, ME, at 7 weeks of age, tested for several behaviors at 10–12 weeks of age, and then examined for brain defects at ~12.5 weeks. The mice were sent in five simultaneous shipments to the laboratories in Edmonton and Portland, with each shipment usually providing two or three mice per strain per laboratory. For any one shipment to a laboratory, all mice of a given strain were the same sex and could have been littermates. If males of a strain were sent to one laboratory in a shipment, females were usually sent to the other laboratory. Thus, no more than four or five mice per strain could have come from the same litter, and the total sample of about ten males and ten females must have been taken from at least five litters. The complement of strains in a single shipment was not identical for the two laboratories, but the net result of the five shipments was nearly equal sample sizes in the two laboratories.

Conditions in the colony rooms were similar at the two sites. Animals were housed two or three per cage in plastic shoe box cages with Bed-o-cob bedding. They had free access to Purina 5001 laboratory chow and local tap water. Colony room lights went on at 06:00 h and off at 18:00 h. Certain wild-derived strains (MOLF/Ei, PERA/Ei, SPRET/Ei) were maintained in Edmonton with filter tops on the cages because they came from colony rooms at the Jackson Laboratory that housed mice known to carry *Pasturella pneumotropica.* All cages in Portland had filter tops.

The BALB/cWah1 and 9XCA/Wah strains were maintained in the colony of D.W. at the University of Alberta by full-sib mating and had undergone 63 and 32 generations of inbreeding, respectively, at the time this study was done. After we discovered the brain defects in strain BTBR, F1 hybrid crosses were obtained by mating BTBR T/ + *tf*/*tf* with 9XCA/Wah, BALB/cWah1 and 129P1/ReJ.

Table 1
Strain means±S.D. and number with abnormal (Abn) CC and HC

Strain	*n*	Brain weight (g)	CC area (mm^2)	HC area (mm^2)	AC area (mm^2)	Abn CC	Abn HC
129S1/SvImJ	20	0.484±0.019	0.672±0.421	0.294±0.056	0.113±0.027	6	1
A/J	18	0.419±0.013	0.762±0.049	0.289±0.025	0.126±0.012	0	0
AKR/J	17	0.485±0.014	0.924±0.070	0.311±0.042	0.121±0.011	0	0
BALB/cByJ	20	0.447±0.020	0.835±0.258	0.311±0.042	0.129±0.021	1	0
BTBR T/ + *tf*/*tf*	18	0.473±0.018	0±0	0.120±0.071	0.148±0.020	18	15
C3H/HeJ	18	0.457±0.019	0.873±0.106	0.359±0.025	0.119±0.009	0	0
C57BL/6J	18	0.493±0.017	1.036±0.089	0.309±0.033	0.149±0.013	0	0
C57L/J	18	0.452±0.015	0.961±0.076	0.260±0.020	0.136±0.012	0	0
C58/J	19	0.437±0.017	0.934±0.069	0.280±0.034	0.139±0.010	0	0
CAST/Ei	18	0.388±0.011	0.699±0.066	0.255±0.028	0.081±0.015	0	0
DBA/2J	18	0.424±0.019	0.699±0.075	0.221±0.033	0.103±0.012	0	0
FVB/NJ	21	0.490±0.014	1.076±0.076	0.310±0.022	0.129±0.012	0	0
MOLF/Ei	14	0.320±0.009	0.503±0.035	0.162±0.011	0.086±0.010	0	0
NOD/LtJ	24	0.549±0.020	1.126±0.087	0.416±0.037	0.149±0.015	0	0
NZB/B1NJ	18	0.513±0.016	0.720±0.066	0.331±0.034	0.119±0.014	0	0
PERA/Ei	22	0.415±0.020	0.685±0.053	0.182±0.021	0.086±0.011	0	0
PL/J	20	0.506±0.014	0.952±0.056	0.331±0.021	0.135±0.009	0	0
SJL/J	20	0.434±0.027	0.799±0.102	0.347±0.033	0.178±0.018	0	0
SM/J	24	0.485±0.016	1.094±0.132	0.364±0.033	0.178±0.018	0	0
SPRET/Ei	7	0.377±0.021	0.576±0.026	0.210±0.019	0.095±0.007	0	0
SWR/J	20	0.439±0.015	0.875±0.068	0.321±0.031	0.121±0.011	0	0
Multiple R^2		0.886	0.765	0.806	0.729		

The multiple R^2 value is the unbiased estimate adjusted for degrees of freedom; it expresses the proportion of total variance that is attributable to the differences among strain means.

2.2. Behavioral testing

Following a previous report of lab-specific results of certain behavioral tests [3,25], the Mouse Phenome Project recommended that all phenotypes be assessed at more than one site. Each mouse in this study was subjected to a series of six behavioral tests simultaneously in our two laboratories, the results of which have been or will be presented elsewhere. On Monday there was a 5-min trial in the open field, followed by 5 min on an elevated plus maze on Tuesday. On Wednesday there were ten acquisition trials on the accelerating rotarod [14,15], followed by rotarod trials before and after a saline injection on Thursday and before and after an ethanol injection (2 mg/kg) on Friday. The next week there was 1 day of pretraining and then 4 days of training on a hidden platform water escape task [20]. Finally, food consumption and body size were monitored over a weekend and then mice were deprived of food for 24 h and given a test of food eating on Tuesday. They were returned to free feeding, and 2–7 days later their brains were removed.

Table 2
Analysis of variance of strain, sex and laboratory site effects on the brain

Measure	df_{within}	Strain (df 19)	Sex (df 1)	Site (df 1)	Strain×Sex (df 19)	Strain×Site (df 19)	Multiple R^2
Body weight	305	F=100.1 P<0.000001 est ω^2=0.853	F=526.8 P<0.000001 est ω^2=0.631	NS	F=4.4 P<0.000001 est ω^2=0.166	F=2.2 P=0.003 est ω^2=0.066	0.90
Brain weight	305	F=166.8 P<0.000001 est ω^2=0.906	NS	NS	F=2.1 P=0.005 est ω^2=0.060	F=2.1 P=0.004 est ω^2=0.060	0.91
AC area	305	F=57.5 P<0.000001 est ω^2=0.768	NS	F=6.5 P=0.011 est ω^2=0.018	NS	NS	0.80
HC area	291	F=74.3 P<0.000001 est ω^2=0.811	NS	NS	NS	NS	0.84
CC area	284	F=63.6 P<0.000001 est ω^2=0.785	NS	F=8.3 P=0.004 est ω^2=0.023	NS	NS	0.82

NS denotes P>0.05. Strain SPRET/Ei not included in any analysis, and strain BTBR T/+ *tf*/*tf* not included in analysis of CC or HC areas (df for strain, 18). Analysis of CC area does not include six mice in strain 129S1/SvImJ and one mouse in strain BALB/cByJ with absent or abnormally small CC. The partial effect size est ω^2 estimates the proportion of variance attributable to the differences among groups when only that one effect is compared with variation within groups.

2.3. Histology

Each mouse was euthanized with carbon dioxide gas. The brain was rapidly removed and immersed in 10% neutral buffered formalin for at least 1 week prior to staining. Brains extracted and fixed in Portland were shipped to Edmonton for histology. All fixed brains were coded for blind scoring and processed in Edmonton. Each brain was trimmed to a standard configuration [19], weighed, bisected at the midsagittal plane, and stained with gold chloride to reveal myelin [18,19]. Gray scale images at 640×480 pixels were obtained with a CCTV camera on a Wild M3Z stereoscope, and commissure lengths and areas were measured with ImageJ from NIH (http://rsb.in-fo.nih.gov/ij/index.html). The area of the CC did not include the dorsal commissure of the fornix or the superior fornix [22].

3. Results

The Portland laboratory was able to test only females of the wild-derived strain SPRET/Ei, and a full three-way analysis of variance (ANOVA) involving strain, sex, and site was possible only for 20 of the 21 strains (Table 2). The analyses revealed a significant sex main effect only for body weight (males 4.3 g heavier). The site main effect for body weight (mean body weight 0.1 g heavier in Portland than Edmonton) was not significant (P=0.43). Although there was a significant strain×site interaction for body size, the effect was very small and the multiple R^2 decreased trivially from 0.90 to 0.89 when site was removed from the ANOVA model. Males were larger than females in every strain, but, as indicated by the moderate strain by sex interaction, the sex difference in body size was larger for some strains than others. The sex difference was particularly small for the

diminutive MOLF/Ei strain (males 14.0 g, females 13.0 g) as well as the much larger NZB/B1NJ strain (males 30.0 g, females 27.6 g).

For brain weight, there was large variation among strain means (Tables 1 and 2), no sex or site main effects ($P>0.4$), and small strain×sex as well as strain×site interactions (Fig. 1). Brain weights averaged 0.3 mg heavier for females than males and 0.4 mg heavier in Edmonton than Portland. The correlation between means of the 20 strains in Edmonton and Portland was very high ($r = 0.975$). Because the multiple R^2 for the model with strain, sex and site decreased minimally from 0.91 to 0.89 when sex and site were omitted from the analysis, strain means in Table 1 based on data pooled over sex and site provide good portrayals of genetic effects.

It was visually obvious that every mouse in strain BTBR T/+ *tf*/*tf* lacked a CC (Fig. 2). For the other strains, abnormality was more difficult to judge because commissures tended to be smaller in mice with smaller brains, and certain strains had unusually small brains, especially the wild-derived strains (Fig. 1). Thus, abnormality was best judged relative to brain size. As shown in Fig. 3, areas of all three commissures were strongly and linearly related to brain weight [2]. Because this study included such a wide range of strains, linear regression equations were based on the 368 mice that clearly had normal commissures, rather than using equations from a previous study done in Edmonton [9]. To determine whether the CC in any particular mouse was abnormally small for its brain size, commissure area in mm^2 was divided by the area expected from the animal's brain weight, using equations in Fig. 3. The resulting ratio, an index of abnormality, was close to 1.0 for a perfectly normal brain and 0 for one lacking the commissure. Because CC size exists on a continuum in mice and any value is possible [9,22], no true dichotomy between normal and abnormal exists. Nevertheless, previous studies found that normal hybrid and C57BL/6J mice never have a CC area less than 60 or 65% of the values expected from brain size [21,22] and there is a minimum in the size distribution for BALB/c mice at about this value; therefore, an index less than 0.6 or 0.65 denotes a CC that is abnormally small. By this criterion, four mice of strain 129S 1 / SvImJ had no CC and another two had abnormally small CC. One BALB/cByJ mouse had no CC.

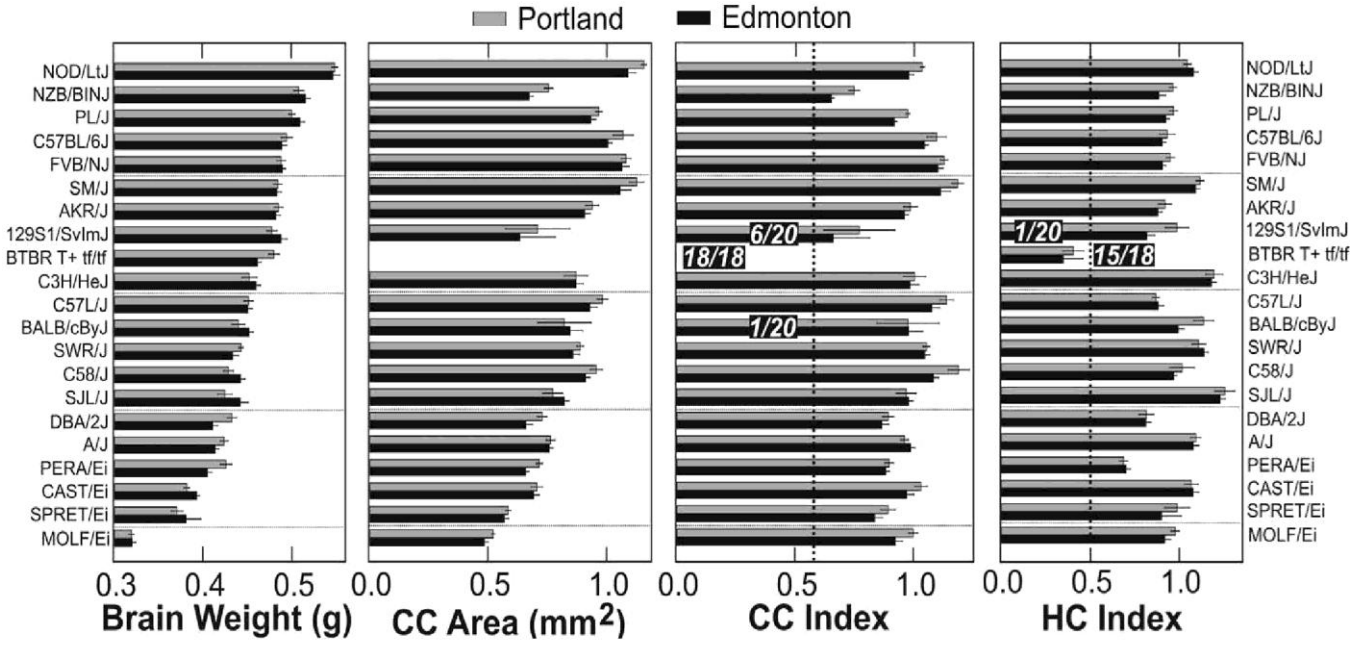

Fig. 1. Strain means in Portland and Edmonton for brain weight, CC area, and commissure indices of abnormality. Strains are arranged by rank order of brain size. The CC index was obtained by dividing the actual CC area by the area expected from brain weight using the regression equation given in Fig. 3. Ratios in boxes give the number of mice with abnormally small commissure size, as judged by the index of abnormality shown by dotted lines (0.6 for CC, 0.5 for HC), over sample size. Standard error of the mean is shown for each group. Horizontal dashed lines are provided to align strains across graphs and have no importance for the data.

For the HC, there is also a size continuum but an index of abnormality less than 0.5 or 0.6 indicates an unusually small structure (Figs. 2 and 3). By this criterion, 15 of 18 BTBR T/ + *tf*/*tf* mice and one of 20 129S1 /SvImJ mice had an abnormally small HC (Table 2). In an additional sample of ten BTBR T / + *tf*/*tf* mice from a separate study in Edmonton, all ten showed abnormally small HC, and our best estimate of the penetrance of the

HC defect in this strain is 25/28. Most mice of the strain PERA/Ei had HC index values in the range 0.55–0.75, relatively small for the brain size but not markedly abnormal (Fig. 1).

The AC generally was of normal size for the brain weight in all mice, with the exception of one peculiar 129S1 / SvImJ mouse that had a minuscule AC area of only 0.01 mm^2. Several mice of the strains CAST/Ei, PERA/ Ei, and NZB/BINJ had AC index values in the range from 0.58 to 0.75, relatively small for the brain size but not markedly abnormal.

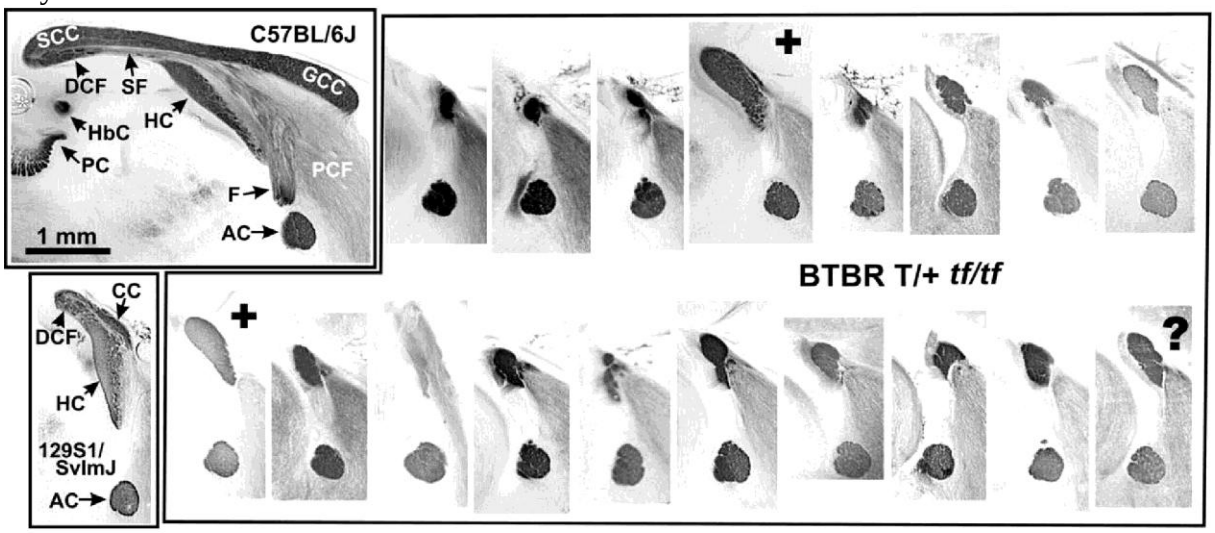

Fig. 2. Commissures at the mid-sagittal plane for 20 mice at the same magnification. Normal anatomy is shown for a C57BL/6J mouse. The asterisk (*) indicates an air bubble trapped against the thin glass slide when the video image of the half brain was taken. The brain of a 129S1/SvImJ mouse has a very small CC but normal HC. Among the 18 BTBR T/+ *tf*/*tf* mice, none has any CC fibers crossing between the hemispheres, and 15 clearly have abnormally small HC. Two have an HC of normal size (+) and one is on the borderline of normality (?). Abbreviations: AC, anterior commissure; CC, corpus callosum; DCF, dorsal commissure of the fornix; F, column of the fornix; GCC, genu of the CC; HC, hippocampal commissure; HbC, habenular commissure; PC, posterior commissure; PCF, precommissural fornix; SCC, splenium of the CC; SF, superior fornix.

The average CC index of abnormality was slightly but significantly (P=0.005) higher in Portland (0.95) than Edmonton (0.91). A similar pattern occurred for the HC index (Portland=0.98, Edmonton=0.95, P=0.002) and the AC index (Portland=1.03, Edmonton=0.98, P=0.00004). The very small site difference was overshadowed by the large strain differences and striking commissure deficits seen in BTBR T/ + *tf*/*tf* and 129S1 /SvImJ strains.

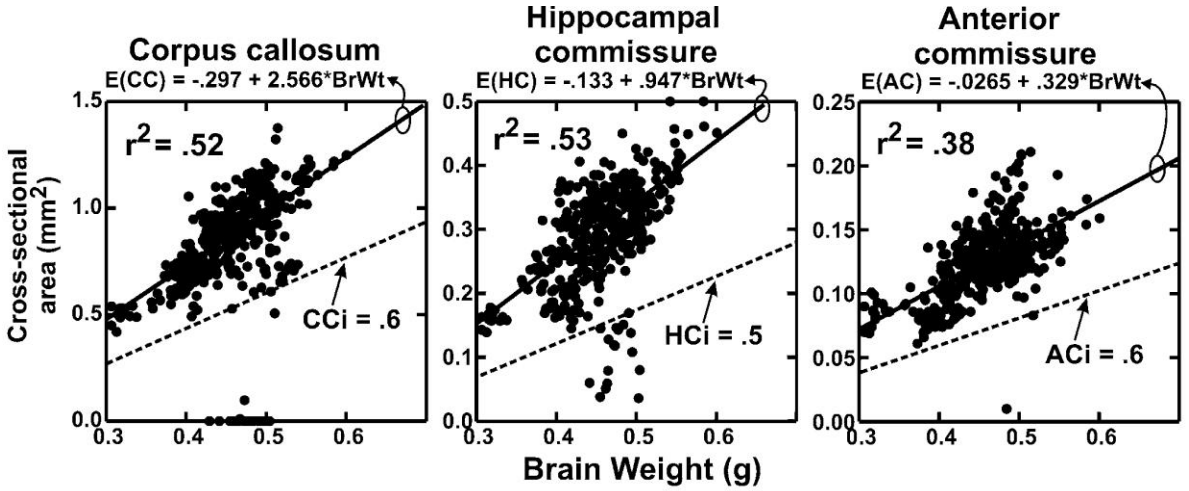

Fig. 3. Cross-sectional areas of three forebrain commissures at the mid-sagittal plane versus brain weight for all mice of 21 inbred strains. Solid lines show the linear regression of commissure size on brain weight (for normal mice only), and r^2 values indicate that the relations were generally very strong, such that half of the variance in CC and HC size was attributable to the linear relation with brain size. Regression equations were used to calculate the index of abnormality for the CC and HC shown in Fig. 1. Dashed lines indicate the criteria for abnormally small commissure in relation to brain weight, in terms of the index of abnormality for the CC (CCi), HC (HCi) and AC (ACi).

Outcomes of the crosses of BTBR T/+ *tf*/*tf* with three other inbred strains are shown in Fig. 4. As observed previously with other strains and crosses [8,22], the HC was abnormally small only when the CC was totally absent. The distribution of phenotypes for 9XCA×BTBR was almost the same as for BTBR itself; only three of

16 mice of this hybrid cross had an HC size in the normal range and one had a few CC axons crossing to the opposite hemisphere (CC index of abnormality = 0.07). When BTBR was crossed to the progenitors of the 9XCA strain, however, phenotypes were very similar to those of the 129P1 /ReJ and BALB/cWah1 strains [8,23].

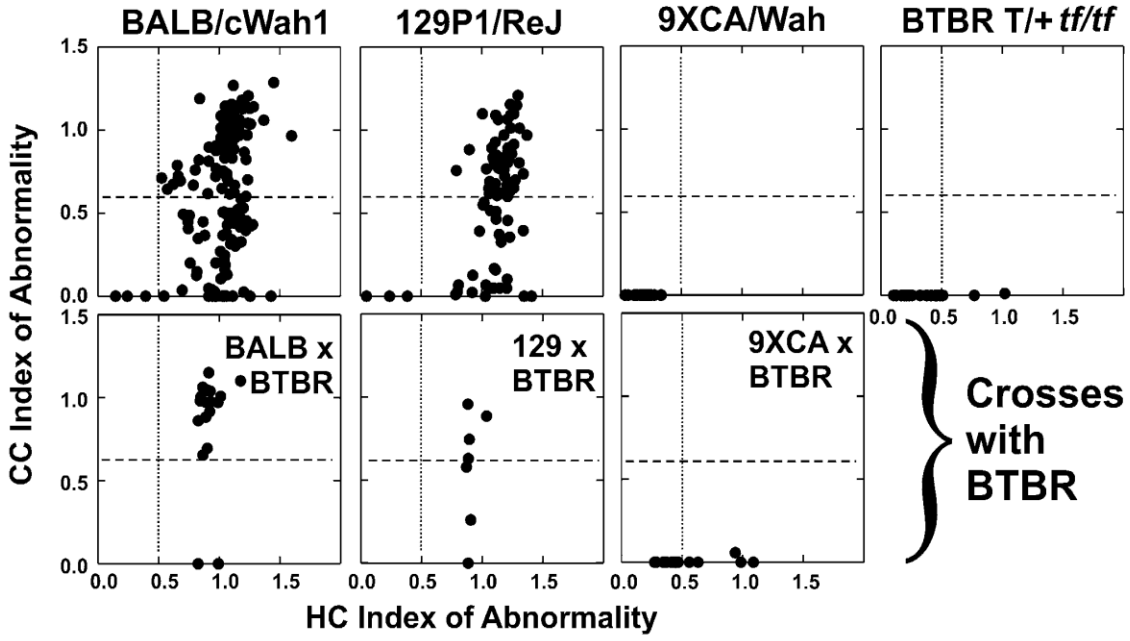

Fig. 4. Plots of the CC index of abnormality and HC index of abnormality for four inbred strains and three hybrid crosses with strain BTBR T/+ *tf*/*tf*. Data for the progenitor strains BALB/cWah1, 129P1/ReJ, and their recombinant inbred strain 9XCA/Wah are based on previous reports [8,9,23]. Mice with an index less than 0.6 (dashed line) are considered to have a CC that is abnormally small for the animal's brain size, whereas those with an HC index less than 0.5 (dotted line) are considered abnormal. Crossing BTBR T/+ *tf*/*tf* with either inbred progenitor strain resulted in mice with much less severe abnormalities than BTBR T/+ *tf*/*tf*, whereas crossing that strain with 9XCA/Wah resulted in hybrids with a defect almost as severe as BTBR T/+ *tf*/*tf*.

4. Discussion

Strain BTBR T/+ *tf*/*tf* has the most severe forebrain commissure defects of any strain from the Jackson Laboratory that has been examined in detail. Nevertheless, the strain breeds reasonably well [1], unlike the very difficult I/LnJ strain. It will therefore be useful for genetic, anatomical and behavioral research on the origin and role of the corpus callosum and hippocampal commissure. BTBR mice may prove especially valuable for investigating the role of the hippocampal commissure. The 9XCA/ Wah recombinant strain with severely reduced HC has an interesting deficit in paired-pulse facilitation of LTP in the hippocampal slice as well as slower extinction of con-textual conditioning [17]. If these deficits arise from the anatomical insufficiency of commissural inputs, then we would expect to observe similar deficits in BTBR.

Table 3
Proportion of microsatellite DNA alleles identical with the strain BTBR T/+ *tf*/*tf* allele

Strain	Identical alleles (%)
129S2/SvPas	57.8
129S6/SvEv	56.2
LP/J	54.7
129S1/SvImJ	52.3
129P3/J	49.4
129T2/SvEmsJ	49.0
C3H/HeSnJ	47.9
129X1/SvJ	46.4
CBA/CaJ	39.0

Source of allele data at 286 loci genotyped by the Center for Inherited Disease Research is http://www.cidr.jhmi.edu/mouse/mouse.html. Results are shown only for the top nine ranked strains.

Hereditary absence and surgical section of the CC impair performance on a challenging task involving high speed motor performance [16]. Nevertheless, strain BTBR T/ + *tf*/*tf* is among the best performers on the accelerating rotarod test of motor coordination [14,15]. Just as the effects of a targeted mutation that impair CC development depend on the genetic background [11], the behavioral consequences of an anatomical CC defect

may also depend on the genetic background. Research on this question will be aided by the availability of more than one strain with severe commissural defects.

The occurrence of the same anatomical defects in hybrids of BTBR and 9XCA as seen in the two parent strains indicates that they have very similar if not identical genetic defects relevant to commissure formation. Because the crosses of BTBR with either progenitor strain BALB/ cWah1 or 129P3/ReJ are much less severely afflicted than BTBR, the data support a model involving a difference between BALB/c and 129 progenitors at two major loci, where BALB/c has the recessive allele at one locus and 129 is recessive at the other locus [8,22]. According to this model, being homozygous recessive at just one of the loci produces mice showing incomplete penetrance for CC defects, whereas being homozygous recessive at both loci creates complete penetrance for a much more severe defect, total CC absence and reduced HC.

BTBR should be helpful in mapping the genes responsible for CC and HC defects as well as pinpointing the specific genes. A stock of mice from Dobrovolskaia-Zavadskaia [4] carrying the *T* gene was crossed with mice having the tufted (*tf*) mutation by Lyon to form the BTBR strain [10], and Dunn maintained the stock by crossing with strain 129 to preserve hardy backgrounds for his *t*-locus mutants (Flaherty, personal communication). Over 260 phenotypically neutral marker loci involving microsatellite DNA and widely distributed over all chromosomes have recently been genotyped in strain BTBR T/ + *tf*/*tf* and 53 other inbred strains by the Center for Inherited Disease Research (http://www.cidr.jhmi.edu/mouse/ mouse.html). Comparison of alleles possessed by these strains reveals that BTBR T/ + *tf*/*tf* is most similar to the various 129-derived strains (Table 3). Thus, there is good reason to believe that the allele of at least one of the major genes responsible for a severe deficit in both the 129P 1/ ReJ and BTBR T/+ *tf*/*tf* strains is identical by descent. Table 3 indicates a close relation of BTBR with LP/J, another strain initiated by Dunn in the same period when BTBR and 129 were created. Strain 101 came from the same source. The Mouse Brain Library (www.mbl.org) presents sections from 14 LP/J mice, none of which show CC defects. The 101 strain, maintained at the Institute for Human Genetics in Moscow, does not have the severe CC defects that characterize BTBR [7] (A. Revishin, personal communication).

Strain differences in brain sizes reported in this study are notably similar to those reported previously by Roderick and colleagues [13] and Williams [26], although some striking differences are apparent. For example, strain PL/J had an average brain weight of 0.506 g in the present study and 0.516 g in the Roderick study but 0.433 g in the Williams data (www.mbl.org), whereas the three studies found similar brain weights for C57BL/6J (0.495 g here, 0.489 for Roderick, and 0.482 for Williams). Previous data on brain size of eight strains from our laboratories [24] are very similar to the present data for the four strains included in both studies, whereas the former study with three laboratories found a significant main effect of laboratory but no significant interaction between strain and laboratory.

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