Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 5408–5412, June 1991
Genetics

Genetic dissection of susceptibility to audiogenic seizures in inbred mice

(epilepsy/genomic imprinting/recombinant inbred strains/A/J, C57BL/6J, and DBA/2J inbred mice)

PAUL E. NEUMANN*† AND ROBERT L. COLLINS‡

*Departments of Neurology, Children's Hospital and Harvard Medical School, Boston, MA 02115; and ‡The Jackson Laboratory, Bar Harbor, ME 04609

Communicated by Louis M. Kunkel, March 27, 1991 (received for review July 30, 1990)

ABSTRACT **Mice of some inbred strains, such as 21-day-old DBA/2J mice, have generalized convulsions when exposed to intense auditory stimulation. Analysis of susceptibility to audiogenic seizures in BXD recombinant inbred strains has demonstrated the influence of at least three loci. One locus, *Asp-1*, is located on chromosome 12 between *Ah* and *D12Nyu1*; another locus, *Asp-2*, is on chromosome 4, tightly linked to *b*. Here we report evidence that *Asp-2* is located within an 8-centimorgan segment distal to *b* and that *Asp-3* is linked to *Mtv-1* on chromosome 7. We also present evidence that these three loci account for most of the heritable variation in susceptibility to audiogenic seizures in crosses of DBA/2J and C57BL/6J mice and that susceptibility to audiogenic seizures is influenced by genomic imprinting. Thus, genomic imprinting may complicate linkage and mapping studies and should be considered in analyses of complex modes of inheritance.**

Convulsive seizures can be induced in experimental animals by intense auditory stimuli (1, 2). Susceptibility to audiogenic seizures (AS) varies widely between inbred strains of mice (2, 3). The genetic basis for the difference in susceptibility to AS between DBA and C57BL mice has been studied several times since the strain difference was discovered by Hall (1). The typical AS consists of wild running followed by a clonic seizure and then a tonic seizure that is usually fatal, unless the mouse is resuscitated (1, 2, 4). DBA/2J (D2) mice are susceptible from 14 to 42 days of age with peak sensitivity at 21 days (5), whereas C57BL/6J (B6) mice are resistant to intense auditory stimuli. Variation in AS susceptibility has been attributed to a single locus (6–8), two loci (9, 10), and multifactorial (or polygenic) modes of inheritance (11–14). The differing conclusions of these investigators can be attributed to many causes, including the use of different DBA and C57BL sublines, mice of different ages, and different experimental protocols (4, 15, 16).

Testing of the BXD series of recombinant inbred (RI) strains and F_1 hybrids from crosses between BXD RI strains and D2 revealed that at least three loci are involved in the genetic variation in AS susceptibility in crosses between D2 and B6 mice (14). Two of these loci have already been given chromosomal assignments. *Asp-1* (audiogenic seizure prone-1, formerly *Ias*) is tightly linked to the *Ah* locus on chromosome 12 (13, 14, 17), and *Asp-2* (formerly *asp*) is located on chromosome 4 (7, 8), tightly linked to *b* (brown) (14).

Here we report the mapping of *Asp-3* by a reevaluation of published data (8, 13, 14, 17–19) in the light of advances in our understanding of the mode of inheritance of susceptibility to AS in crosses of D2 and B6 mice. We also report the results of reciprocal backcrosses that confirm the conclusions of the genetic dissection.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

MATERIALS AND METHODS

The data from two multipoint crosses reported by Collins (8) were recompiled and reexamined in an attempt to place *Asp-2* on the linkage map (see Tables 1 and 2). In the first experiment, C57BL/6J-+ *Pt Gpd-1^a*/+ + *Gpd-1^a* and DBA/2J-*b* + *Gpd-1^b*/*b* + *Gpd-1^b* mice were crossed, and the pintail (*Pt*/+) progeny were backcrossed to the D2 parent. In the second breeding protocol, misty (C57BL/6J-+ *m*/+ *m*) and DBA/2J-*b* +/*b* + mice were crossed, and the F_1 progeny were intercrossed. Twenty-one-day-old progeny of the backcrosses and intercrosses were tested for susceptibility to AS as has been described (8). Apparent recombination frequencies with the marker loci were calculated for AS by treating the occurrence of AS as a mendelian recessive trait, although AS susceptibility has already been established as a multifactorial trait.

The previously published results of testing D2, B6, and 23 BXD RI strains (13, 17, 18) and the F_1 hybrids from crosses to D2 (14, 18, 19) for susceptibility to AS at 21 days of age are presented in Table 3. The response of each mouse was scored on the basis of the most severe phenomenon seen (i.e., no response = 0, wild running = 1, and clonic or tonic seizure = 2), and a mean seizure severity score (MSSS) was calculated for each population. These data were reconsidered after a linkage map position for *Asp-2* was derived from the multipoint crosses. Strain distribution patterns (SDPs) were constructed for potential loci influencing susceptibility to AS. These SDPs were compared to a table of published SDPs (20) to assist in mapping these *Asp* loci.

A/J females were crossed with DBA/1J and D2 males. F_1 hybrids of each sex were then backcrossed to A/J mice. Similarly, coisogenic albino (c^{2J}/c^{2J}) B6 mice were crossed with B6 mice, and F_1 hybrids of each cross were reciprocally backcrossed to albino B6 mice.

Twenty-one-day-old mice were placed individually into a clear plastic cylinder (30.5 cm in diameter, 30.0 cm in height) positioned with its floor centered 41.0 cm below an electric bell (10.5 cm in diameter). The bell and cylinder are enclosed within a sound-deadened box incorporating a window to permit observation. During initial testing (test 1), each mouse was exposed to bell ringing for 60 sec or until onset of convulsion, whichever came first. Sound level was 95 decibels with respect to a reference pressure of 0.0002 dyne/cm^2. Each mouse that did not convulse on initial testing was exposed 48 hr later (test 2) to bell ringing for 60 sec or until onset of convulsion.

RESULTS

The gene order *b–Pt–Gpd-1* and the recombination frequencies between these three loci determined from the results of

Abbreviations: AS, audiogenic seizures; RI, recombinant inbred; SDP, strain distribution pattern; B6, C57BL/6J; D2, DBA/2J; CAA, Ca^{2+}-ATPase activity.

†To whom reprint requests should be addressed.

Table 1. Seizures in 21-day-old backcross offspring of DBA/2J and C57BL/6J-*Pt*/+ inbred mice

Pt locus phenotype	AS, frequency		
	b locus phenotype		
	+	*b*	Total
+	8/11 (0.727)	131/175 (0.749)	139/186 (0.747)
Pt	118/193 (0.611)	8/12 (0.667)	126/205 (0.615)
Total	126/204 (0.618)	139/187 (0.743)	265/391 (0.678)

the pintail backcross (see Fig. 1) agree with the results of other investigators. Because susceptibility to AS is largely controlled by at least two other independent loci, the large "recombination frequencies" between AS susceptibility and *b*, *Pt*, and *Gpd-1* cannot be used directly, without further transformation. Assuming no recombination between *Asp-2* and *Pt*, because *Pt* has the lowest apparent recombination frequency with AS susceptibility (44.2 ± 2.5%), the apparent recombination frequency between AS susceptibility and *Gpd-1* is predictable. The relationship between *r*, the recombination frequency with *Asp-2*, and *R*, the apparent recombination frequency with AS susceptibility, is linear. Given the assumption of no recombination between *Pt* and *Asp-2*, *R* varies from 0.44 to 0.5 over the range of *r* (0–0.50). Therefore, when *r* is 0.25, the recombination frequency between *Pt* and *Gpd-1*, *R* is 0.47. This estimate agrees remarkably well with the apparent 47.3 ± 5.1% recombination between AS susceptibility and *Gpd-1*. Therefore, *Asp-2* appears tightly linked to *b* and *Pt*, although the gene order cannot be determined from these data.

The results of testing offspring of an intercross with brown and misty in repulsion (see Table 2) suggest that *Asp-2* is located between *b* and *m* because both marker loci have almost identical apparent recombination frequencies with AS susceptibility (41.2 ± 2.8% and 41.4 ± 3.4%, respectively). If *Asp-2* were located outside the interval between *b* and *m*, the respective apparent recombination frequencies with AS susceptibility would not be similar. Because the recombination frequency between *b* and *m* was 24.4 ± 3.8% in this sample, the recombination frequency between *Asp-2* and one of the markers would be >25%, and the apparent recombination frequency between AS susceptibility and this marker would probably be >45% were *Asp-2* not in the chromosomal segment bounded by *b* and *m*. Therefore, *Asp-2* is likely to reside in the segment (≈8 centimorgans in length) between *b* and *m*.

The hypothesis that at least three loci are involved in AS susceptibility in crosses between B6 and D2 mice is strongly supported by the fact that the RI strains can be divided into five distinct classes (see Table 3) (14). Traits influenced by segregation at three loci may have up to eight phenotypic classes in RI strain sets, so an effort was made to find more classes. BXD-5 has been placed in class 2, separate from class 1, because it differs from the strains in class 1 at the *Asp-2* locus (14). The separation between classes 6 and 7 is somewhat arbitrary. The postulated eighth class may be a null set. At each of the three loci, half of the classes will be homozygous for one parental allele, whereas the rest will be homozygous for the alternate allele. By using this principle, SDPs can be derived for each of the three postulated *Asp* loci.

Table 2. Seizures in 21-day-old F_2 offspring of DBA/2J × C57BL/6J-*m*/*m* inbred mice

m locus phenotype	AS frequency		
	b locus phenotype		
	+	*b*	Total
+	92/313 (0.294)	51/122 (0.418)	143/435 (0.329)
m	29/147 (0.197)	3/8 (0.375)	32/155 (0.206)
Total	121/460 (0.263)	54/130 (0.415)	175/590 (0.297)

Table 3. Distribution of DBA/2J, C57BL/6J, and BXD RI strains in seven phenotypic classes based on audiogenic responses of inbred mice and F_1 hybrids from crosses with DBA/2J mice

	Inbred strain		F_1 hybrids		Strain distribution patterns (SDP)		
	RFS, %	MSSS	RFS, %	MSSS	*Asp-1*	*Asp-2*	*Asp-3*
Class 1							
BXD-15	94	1.94	100	2.00	D	D	D
BXD-2	92	1.92	95	1.95	D	D	D
BXD-21	92	1.92	100	2.00	D	D	D
BXD-32	90	1.90			D	D	D
DBA/2J	91	1.88	91	1.88	D	D	D
BXD-9	93	1.85	100	2.00	D	D	D
Class 2							
BXD-5	68	1.64	79	1.57	D	B	D
Class 3							
BXD-27	29	1.29	82	1.82	D	D	B
BXD-24	22	1.09	94	1.89	D	D	B
BXD-28	22	1.00	67	1.58	D	D	B
BXD-19	35	0.73	55	1.41	D	D	B
Class 4							
BXD-23	40	1.16	0	0.45	D	B	B
BXD-11	21	1.04	0	0.59	D	B	B
BXD-8	23	0.57	11	0.76	D	B	B
Class 5							
BXD-25	0	0.36	80	1.80	B	D	D
BXD-14	8	0.33	76	1.76	B	D	D
BXD-12	0	0.30	83	1.83	B	D	D
BXD-13	0	0.10	74	1.61	B	D	D
Class 6							
BXD-29	0	0.09	27	0.92	B	D	B
BXD-30	0	0.00	16	0.63	B	D	B
Class 7							
BXD-16	0	0.21	0	0.79	B	B	B
BXD-1	0	0.20	0	0.36	B	B	B
BXD-6	0	0.14	5	0.47	B	B	B
BXD-18	0	0.07	0	0.11	B	B	B
C57BL/6J	2	0.07	3	0.30	B	B	B

The relative frequency of seizures (RFS) and mean seizure severity scores (MSSS) have been published elsewhere (13, 14, 17, 18). B and D are symbols of alleles inherited from C57BL/6J and DBA/2J mice, respectively.

Two SDPs for *Asp-1* were considered by Neumann and Seyfried (14). The first hypothesis holds that the RI strain data are most indicative of the genotype because allelic interactions are eliminated. Application of this hypothesis assigns the $Asp\text{-}1^b$ allele to RI strains resistant to AS (i.e., classes 5–7) and the $Asp\text{-}1^d$ allele to those that show moderate or high susceptibility (classes 1–4). The second hypothesis holds that the tests of F_1 hybrids may be more indicative of the *Asp-1* genotype because of a possible reduction in intergenic (nonallelic) interactions. This scheme would assign the $Asp\text{-}1^b$ allele to classes 4, 6, and 7 and the $Asp\text{-}1^d$ allele to classes 1–3, and 5. Surprisingly, both of these SDPs are consistent with a position for *Asp-1* between *Ah* and *D12Nyu1*, so that the placement of *Asp-1* between these loci on chromosome 12 is fairly certain (14).

Given the gene order *b*–*Asp*–2–*m*, an SDP for *Asp-2* can be derived from the data presented in Table 3 and the SDP for *Ifa* (21), which has also been mapped to this 8 centimorgan segment (22). Each class of RI strains was assigned a genotype at the *Asp-2* locus based on the most common genotype at the *Ifa* locus within the class. Therefore, classes 1, 3, 5, and 6 were assigned the $Asp\text{-}2^d$ allele, and classes 2, 4, and 7 were

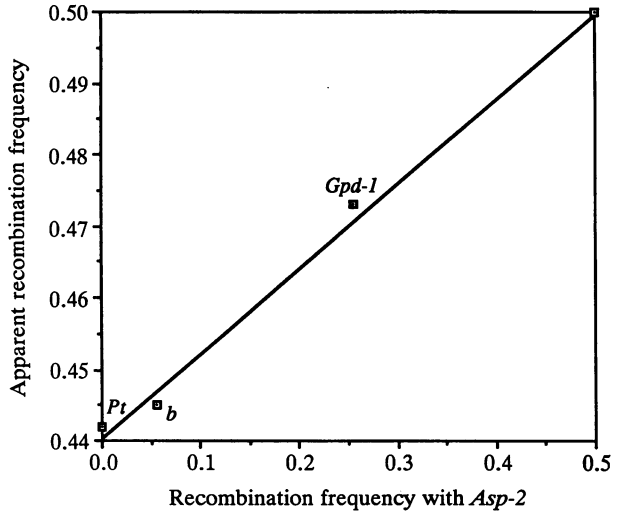

FIG. 1. Relationship between apparent recombination frequency with AS, treated as a recessive mendelian trait, and an estimate of the recombination frequency with a locus influencing susceptibility to AS in a backcross (see Table 1). For illustrative purposes, *Asp-2* was assumed to have no recombination with Pintail (*Pt*). The *Pt* locus is flanked by brown (*b*) and *Gpd-1*. The recombination frequencies between *b* and *Pt* and *Pt* and *Gpd-1* were 5.6 ± 1.2% and 25.5 ± 4.3%, respectively.

assigned the $Asp\text{-}2^b$ allele (see Table 3). This SDP for *Asp-2* makes the gene order *b–Ifa–Asp–2–m* most likely.

Attempts to combine the postulated SDPs for *Asp-1* and *Asp-2* show that the second SDP of *Asp-1* is incompatible with the hypothesis that three loci are responsible for most of the variation in AS susceptibility because three classes would have the $Asp\text{-}1^d$ and $Asp\text{-}2^d$ alleles. If the trait were controlled by three loci, there could be no more than two such classes. Therefore, for the sake of the three-loci model, we have provisionally accepted the first SDP for *Asp-1*. On the other hand, were the second SDP for *Asp-1* correct, AS susceptibility must be controlled by four or more loci. This provisional acceptance was subjected to a subsequent test; if an SDP for *Asp-3* generated using the first SDP for *Asp-1* failed to detect a possible linkage association, the provisional acceptance would have been abandoned.

An SDP for the postulated *Asp-3* locus was constructed by assigning the $Asp\text{-}3^d$ allele to the more AS-prone class in each pair of classes with identical genotypes at the *Asp-1* and *Asp-2* loci. On this basis, classes 1, 2, and 5 were assigned the $Asp\text{-}3^d$ allele, and classes 3, 4, and 6 were assigned the $Asp\text{-}3^b$ allele. Class 7 was assigned the $Asp\text{-}3^b$ allele because these strains were indistinguishable from the B6 parental strain. The proposed SDP for *Asp-3* is concordant with the SDP of *Mtv-1* (23) in 20/23 strains, and it is concordant with that "*B*" (24) in 19/22 strains. The proposed SDP for *Asp-3* is a plausible intermediate between those of these two linked loci, which are situated on chromosome 7 and are concordant in 16 of the 22 RI strains that have also been tested for AS susceptibility. According to a Bayesian statistical analysis (25), complete concordance between a test locus and a pair of linked markers in a set of 16 RI strains that show no recombination between the marker loci indicates linkage of the test locus to the two loci at the 99.4% confidence level. This confidence level assumes that the SDP for *Asp-3* is correct. Given that there are fewer than 200 published SDPs for the BXD RI strain set (20), the probability of randomly selecting an SDP completely concordant with an SDP consisting of 16 concordances between a pair of linked loci is ≈0.2%.

Confirmation of the linkage of *Asp-3* to chromosome 7 was sought in classical crosses. The most convenient linkage marker within 10 centimorgans of the proposed locus for *Asp-3* is *c*, albino. Although a coisogenic albino B6 inbred strain was available, backcrosses to this albino strain are unlikely to be informative about linkage because offspring of similar backcrosses do not differ significantly from B6 inbred mice in susceptibility to AS upon initial testing at 21 days of age or retesting 48 hr later (7). Therefore, further evidence of linkage of a locus influencing susceptibility to AS to chromosome 7 was searched for in backcrosses involving the mouse strains A/J, which is albino (*c*/*c*), D2, and DBA/1J. Unlike B6 mice, which can be "primed" by prior exposure to auditory stimulation (7, 26), A/J mice are resistant to both initial and "sensitization-dependent" AS (see Table 4) (2).

Table 4. Seizures in inbred mice and F_1 hybrids

Strain	*n*	AS, frequency		
		Test 1	Test 2	Cumulative
DBA/1J	31	0.161	0.923	0.935
DBA/2J	26	1		1
C57BL/6J	56	0	0.339	0.339
A/J	41	0.073	0	0.073
$AD1F_1$	117	0.205	0.892	0.940
$AD2F_1$	80	0.788	0.765	0.950

Data have been reported elsewhere (2).

When the heterozygous parent was female, no association between albinism and susceptibility to audiogenic seizures was evident (see Table 5). However, when the sire was the heterozygous parent, a genetic association was seen in crosses with both DBA sublines. When F_1 males were backcrossed to A/J females, albino offspring were less susceptible than pigmented littermates on initial testing in both crosses and on retesting in the cross involving DBA/1J mice.

Studies using albino B6 coisogenic inbred mice reveal no influence of the albino (c^{2J}) mutation itself on susceptibility to AS (see Table 6). No difference in susceptibility was found between offspring of the reciprocal crosses or between albino and pigmented offspring for either initial or sensitization-dependent AS. Thus, we believe the existence of a locus on chromosome 7 that influences susceptibility to AS has been confirmed, although the identity of *Asp-3* and the chromo-

Table 5. Seizures in offspring of reciprocal backcrosses of $AD1F_1$ and $AD2F_1$ mice to A/J inbred mice

Dam	Sire	Off-spring	*n*	AS, frequency		
				Test 1	Test 2	Cumulative
$AD1F_1$	A/J	*c*/*c*	128	0.195	0.436*	0.548*
		+/*c*	149	0.255	0.441	0.584
A/J	$AD1F_1$	*c*/*c*	100	0.130†	0.253‡	0.350§
		+/*c*	75	0.253†	0.500‡	0.627§
$AD2F_1$	A/J	*c*/*c*	143	0.441	0.375	0.650
		+/*c*	150	0.420	0.471	0.693
A/J	$AD2F_1$	*c*/*c*	110	0.245¶	0.434	0.573
		+/*c*	116	0.397¶	0.449‖	0.670‖

No significant association between coat color and seizure incidence was found in progeny of heterozygous dams in backcrosses of $AD1F_1$ and $AD2F_1$ mice to A/J, or in progeny of the reciprocal backcrosses of coisogenic B6 mice.

*Two mice that did exhibit seizure on initial testing died before the second test.

†The difference between seizure incidence in albino and brown offspring is significant by χ^2 test of independence, $\chi^2 = 4.36$ ($P < 0.05$).

‡$\chi^2 = 9.15$ ($P < 0.003$).

§$\chi^2 = 13.17$ ($P < 0.0005$).

¶$\chi^2 = 5.89$ ($P < 0.02$).

‖One mouse that did not exhibit seizure on initial testing died before the second test.

Table 6. Seizures in offspring of reciprocal backcrosses of coisogenic C57BL/6J mice

Dam	Sire	Offspring	n	AS, frequency, Test 2
c^{2J}/c^{2J}	$+/c^{2J}$	c^{2J}/c^{2J}	125	0.552
		$+/c^{2J}$	117	0.564
$+/c^{2J}$	c^{2J}/c^{2J}	c^{2J}/c^{2J}	144	0.542
		$+/c^{2J}$	140	0.543

some 7 *Asp* locus found in the cross between A/J and DBA inbred mice has not been rigorously established.

DISCUSSION

Three loci influencing susceptibility to AS in crosses of D2 and B6 inbred mice have been mapped. These loci account for most of the genetic variability in 21-day-old offspring of these crosses. No evidence exists at present for additional major genes influencing AS susceptibility in 21-day-old mice; however, testing offspring of crosses of D2 and B6 mice at other ages (13, 14) or testing offspring of other crosses (2, 3) is likely to uncover the effects of other major loci.

Palayoor and Seyfried (18) found a significant negative correlation between brainstem Ca^{2+}-ATPase activity (CAA) and mean seizure severity scores in the BXD RI strains. The covariation of these polygenic traits suggests a genetic association. *Asp-1* and *Asp-2* are both associated with differences in CAA in the BXD RI strains (14). With the SDPs given in Table 3, mean CAA in RI strains with the $Asp\text{-}1^b$ allele was 2.55 μmol of P_i liberated per hr per mg of protein; for $Asp\text{-}1^d$, this figure was 2.27; for $Asp\text{-}2^b$, 2.57; and for $Asp\text{-}2^d$, 2.28. *Asp-3* appears to have a similar association with CAA differences. RI strains with the $Asp\text{-}3^b$ allele have a mean CAA of 2.59, whereas those with the $Asp\text{-}3^d$ allele have a mean CAA of 2.14. Because the association between low CAA and AS susceptibility is probably not due to linkage, consideration of pleiotropy or a causal relationship is warranted. Evidence supporting a mechanism by which low CAA might increase AS susceptibility was recently reviewed (14).

A remarkable parental effect was noted in the reciprocal backcrosses to A/J. If one accepts the hypothesis that an *Asp* locus on chromosome 7 influences susceptibility to AS in crosses of DBA and A/J mice, this observation is consistent with only one explanation. Genomic imprinting appears to be masking the genetic association between chromosome 7 marker loci and AS susceptibility by negating most, or all, of the seizure resistance associated with the allele derived from A/J when it is inherited from female heterozygotes. Because the effect is associated with an autosomal locus, X chromosome- and Y chromosome-linkage, sex-limitation, mitochondrial and maternal inheritance, and other maternal effects do not account for this phenomenon. Genomic imprinting (27–31) could have been viewed theoretically as an additional source of complexity in linkage analysis and genetic mapping studies; however, to the best of our knowledge, the emphasis on the effect of imprinting on gene expression has obscured this insight. Hall (31) has suggested that genomic imprinting may be responsible for some of the variation seen in several human disorders, such as the higher risk of seizures in offspring of epileptic mothers than in offspring of fathers with epilepsy (32).

There is already reason to believe that genomic imprinting influences loci on chromosome 7; there is failure of complementation of unbalanced gametes (27, 33). Genomic imprinting of this region may have clinical relevance. Cloned DNA from the proximal region of human chromosome 15q has recently been mapped to mouse chromosome 7 (*D7Nic1*) (34, 35), within a few centimorgans of *Asp-3* (see Fig. 2). This region of chromosome 15q is associated with Angelman

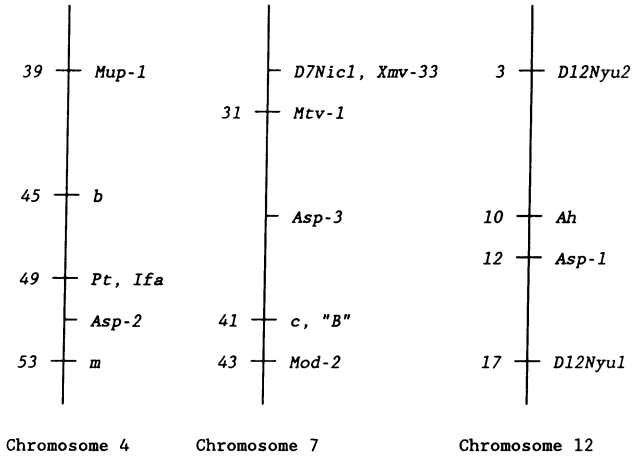

FIG. 2. Genetic map of segments of mouse chromosomes 4, 7, and 12, showing approximate map positions of *Asp-1*, *Asp-2*, and *Asp-3*. In each case, the centromere is toward the top, and numbers represent distances in centimorgans from the centromere taken from the linkage map of Davisson *et al.* (36). Map locations of *Xmv-33* and *D7Nic1* are based on their SDPs in RI strains (34, 37).

syndrome, which includes a severe seizure disorder, and Prader–Willi syndrome, which does not. Apparent differences in parental origins of microdeletions in the two syndromes (38) and detection of maternal uniparental disomy in some patients with Prader–Willi syndrome (39) suggest that the nature of the clinical syndrome may be determined by genomic imprinting.

We are grateful to Drs. D. W. Bailey, L. Kunkel, M. Lalande, J. Nadeau, R. D. Nicholls, T. N. Seyfried, B. A. Taylor, and L. Villa-Komaroff for critical readings of various drafts of this manuscript. This work was supported by the Howard Hughes Medical Institute and by grants from the Hays and Rosamond Clark Foundation and National Institutes of Health (GM 23618, EY 06631, P01-HD-18658, and P30-HD-18655). The Jackson Laboratory is fully accredited by the American Association for Accreditation of Laboratory Animal Care.

1. Hall, C. S. (1947) *J. Hered.* **38,** 2–6.
2. Collins, R. L. (1972) in *Experimental Models of Epilepsy: A Manual for the Laboratory Worker*, eds. Purpura, D. P., Penry, J. K., Tower, D. B., Woodbury, D. M. & Walter, R. D. (Raven, New York), pp. 347–372.
3. Fuller, J. L. & Sjursen, F. H., Jr. (1967) *J. Hered.* **58,** 135–140.
4. Seyfried, T. N., Glaser, G. H., Yu, R. K. & Palayoor, S. T. (1986) *Adv. Neurol.* **44,** 115–133.
5. Seyfried, T. N. (1982) in *Genetic Basis of the Epilepsies*, eds. Anderson, V. E., Hauser, W. A., Penry, J. K. & Sing, C. F. (Raven, New York), pp. 199–210.
6. Witt, G. & Hall, C. S. (1949) *J. Comp. Physiol. Psychol.* **42,** 58–63.
7. Collins, R. L. & Fuller, J. L. (1968) *Science* **162,** 1137–1139.
8. Collins, R. L. (1970) *Behav. Genet.* **1,** 99–109.
9. Ginsburg, B. E. & Miller, D. S. (1963) *Colloq. Int. C.N.R.S.* **112,** 217–225.
10. Ginsburg, B. E., Cowen, J. S., Maxson, S. C. & Sze, P. Y. (1967) *Excerpta Med. Int. Congr. Ser.* **175,** 695–701.
11. Fuller, J. L., Easler, C. & Smith, M. E. (1950) *Genetics* **35,** 622–632.
12. Schlesinger, K., Elston, R. C. & Boggan, W. (1966) *Genetics* **54,** 95–103.
13. Seyfried, T. N., Yu, R. K. & Glaser, G. H. (1980) *Genetics* **94,** 701–718.
14. Neumann, P. E. & Seyfried, T. N. (1990) *Behav. Genet.* **20,** 307–323.
15. Seyfried, T. N. (1982) in *The Mouse in Biomedical Research*, eds. Foster, H. L., Small, J. D. & Fox, J. C. (Academic, Orlando, FL), Vol. 4, pp. 97–124.
16. Henry, K. R. (1986) in *Perspectives in Behavior Genetics*, eds.,

Fuller, J. L. & Simmel, E. C. (Lawrence Erlbaum, Hillsdale, NJ), pp. 57–93.
17. Seyfried, T. N. & Glaser, G. H. (1981) *Genetics* **99,** 117–126.
18. Palayoor, S. T. & Seyfried, T. N. (1984) *J. Neurochem.* **42,** 1771–1774.
19. Seyfried, T. N. (1983) *Brain Res.* **271,** 325–329.
20. Taylor, B. A. (1989) in *Genetic Variants and Strains of the Laboratory Mouse*, eds. Lyon, M. F. & Searle, A. G. (Oxford Univ. Press, Oxford), 2nd Ed., pp. 773–796.
21. Nadeau, J. H., Berger, F. G., Kelley, K. A., Pitha, P. M., Sidman, C. L. & Worrall, N. (1986) *Genetics* **104,** 1239–1255.
22. De Maeyer, E. & Dandoy, F. (1987) *J. Hered.* **78,** 143–146.
23. Traina, V. L., Taylor, B. A. & Cohen, J. C. (1981) *J. Virol.* **40,** 735–744.
24. Racine, R. R. & Langley, C. H. (1980) *Biochem. Genet.* **18,** 185–197.
25. Neumann, P. E. (1990) *Genetics* **126,** 277–284.
26. Henry, K. R. (1967) *Science* **158,** 938–940.
27. Solter, D. (1988) *Annu. Rev. Genet.* **22,** 127–146.
28. Monk, M. (1988) *Genes Dev.* **2,** 921–925.
29. Monk, M. (1990) *Trends Genet.* **6,** 110–114.
30. Shire, J. G. M. (1989) *New Biologist* **1,** 115–120.
31. Hall, J. G. (1990) *Am. J. Hum. Genet.* **46,** 857–873.
32. Ottman, R., Annegers, J. F., Hauser, W. A. & Kurland, L. T. (1988) *Am. J. Hum. Genet.* **43,** 257–264.
33. Beechey, C. V. & Searle, A. G. (1987) *Mouse News Lett.* **77,** 126–127.
34. Nicholls, R. D. (1989) *Mouse News Lett.* **84,** 87–88.
35. Nicholls, R. D., Neumann, P. E. & Horsthemke, B. (1990) *Am. J. Hum. Genet.* **47,** A230 (abstr.).
36. Davisson, M. T., Roderick, T. H., Hillyard, A. L. & Doolittle, D. P. (1989) *Mouse News Lett.* **84,** 15–23.
37. Frankel, W. N., Stoye, J. P., Taylor, B. A. & Coffin, J. M. (1989) *J. Virol.* **63,** 1763–1774.
38. Knoll, J. H. M., Nicholls, R. D., Magenis, R. E., Graham, J. M., Jr., Lalande, M. & Latt, S. A. (1989) *Am. J. Med. Genet.* **32,** 285–290.
39. Nicholls, R. D., Knoll, J. H. M., Butler, M. G., Karam, S. & Lalande, M. (1989) *Nature (London)* **342,** 281–285.