EVIDENCE FOR SINGLE LOCUS CONTROL ON CHROMOSOME 7*

Genetic Regulation of Coumarin Hydroxylase Activity in Mice

matings between ARD2F1/J and AKR/J mice indicates and the albino locus (c) in the progeny of backcross combination percentage of 21 ± 6% between the Coh locus indicating high and low activity alleles, respectively. A recombinant pretreated ARR/J, DBA/PJ, and AKD2F1/J mice indicate that coumarin hydroxylase activity is inherited additively as a single autosomal trait. The proposed locus symbol is Coh with superscripts h and l designating high and low activity alleles, respectively. A recombination percentage of 21 ± 6% between the Coh locus and the albino locus (c) in the progeny of backcross matings between AKD2F1/J and AKR/J mice indicates linkage of the two loci on mouse chromosome 7. The distribution pattern of alleles at the glucose phosphate isomerase (Gpi-1), Coh, and hemoglobin β chain (Hbb) loci in 24 recombinant inbred strains derived from matings of C57BL/6J with DBA/2J mice establish that Coh is closely linked to Gpi-1. A similar analysis of the alleles at the Gpi-1, Coh, and c loci in nine recombinant inbred strains derived from C57BL/J and SWR/J mice reveal concordant inheritance of Coh and Gpi-1 in these strains. Three-point test crosses involving the Coh, Gpi-1, and pink-eyed dilution (p) loci indicate that the Coh locus is on the centromeric side of Gpi-1 with the gene order Coh-Gpi-1-p.

Coumarin, like many lipophilic compounds such as steroids, fatty acids, pesticides, drugs, and polycyclic hydrocarbons, is oxidatively metabolized in the liver by a microsomal cytochrome P-450-dependent mixed function oxidase system (1-3). We have previously shown that the basal and phenobarbital-induced activities of hepatic coumarin hydroxylase are severalfold higher in the DBA/2J inbred strain of mouse compared to the C57BL/6J, C3H/HeJ, and AKR/J mouse strains (4). An intermediate coumarin hydroxylase activity in the offspring of matings between DBA/2J and the other three low activity strains indicated an additive mode of inheritance in these crosses. Biochemical characterization of coumarin hydroxylase in liver microsomes of DBA/2J, AKR/J, and AKD2F1/J mice suggested that a different form of cytochrome P-450 metabolizes coumarin in the two parental strains (5). The studies described in this communication were undertaken to analyze the genetic basis of strain differences in coumarin hydroxylase activity in the mouse.

EXPERIMENTAL PROCEDURES

Materials—Coumarin and 7-hydroxycoumarin were obtained from Aldrich Chemical Co., Milwaukee, WI, sodium phenobarbital from Merck and Co., Rahway, NJ, and metyrapone from Ciba Pharmaceutical Co., Summit, NJ. All other reagents were purchased from Sigma Chemical Co., St. Louis, MO.

Animals—Mouse strains were obtained from the production and research stocks of The Jackson Laboratory, Bar Harbor, ME. The recombinant inbred (RI) strains of mice designated BXD and SWXL were derived by inbreeding the F1 generation of crosses C57BL/6J × DBA/2J and SWR/J × C57L/J, respectively (6). Mice whose livers were assayed for coumarin hydroxylase activity were fed Purina Lab Chow ad libitum for 2 weeks prior to use. For induction of coumarin hydroxylase activity, sodium phenobarbital was administered in the drinking water (0.5 mg/ml) for 8 days prior to killing. Both sexes of offspring from backcross and intercross matings were assayed for coumarin hydroxylase activity. Although no sex difference in enzyme activity was observed, male mice were used in all other studies. All mice were 7 to 10 weeks of age at the time of experimentation.

Preparation of Liver Homogenates and Microsomes—Mice were killed by decapitation, and their livers were immediately removed, weighed, and homogenized in 4 volumes of ice cold 0.05 M Tris-HCl containing 1.15% KC1 and 10 mM EDTA (final pH 7.6) using a glass Teflon Potter-Elvehjem homogenizer. Microsomes were prepared from the 20% homogenates as previously described (7).

Assay of Coumarin Hydroxylase Activity—Whole liver homogenates were diluted 10-fold in 0.05 M Tris-HCl containing 0.25 M sucrose and 0.003 M MgCl2 (final pH 7.6) for the determination of coumarin hydroxylase activity. Generally, 2 mg of tissue, wet weight, was used in the assay which was conducted exactly as previously described (4, 5). Activity units are expressed as picomoles of 7-hydroxycoumarin formed per min at 37°C per mg of tissue, wet weight. When microsomes were used as the source of coumarin hydroxylase, activity units are expressed as nanomoles of 7-hydroxycoumarin formed per min at 37°C per mg of microsomal protein. Protein was determined by the method of Lowry et al. (8).

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sustainable to skin ulceration and the noninducible genotype (Ah'/Ah'') is resistant.

**RESULTS**

**Strain Survey of Coumarin Hydroxylase Activity**—Basal and phenobarbital-induced coumarin hydroxylase activities in liver homogenates from 16 inbred strains of mice are summarized in Table I. Five strains (C57BR/cdJ, C57L/J, DBA/1J, DBA/2J, and 129/J) have average basal and induced activities greater than 30 and 240 units, respectively, and are classified as having high coumarin hydroxylase activity. In contrast, the average control activity in the remaining 11 strains, classified as having low activity, is below 25 units; phenobarbital pretreatment, with the exception of CBA/CaJ, does not induce activity above 92 units. Since the absolute and relative differences between high and low activity strains is greater after phenobarbital pretreatment, further studies were performed with the induced enzyme.

**Aniline and Metyrapone Inhibition of Coumarin Hydroxylase**—Coumarin hydroxylase assayed in hepatic microsomes from either untreated or phenobarbital-pretreated DBA/2J and AKR/J mice can be selectively inhibited by aniline and metyrapone, respectively (5). Similar inhibition studies with several strains of mice with high and low coumarin hydroxylase activity were undertaken to determine whether the selective inhibition was a general phenomenon that could distinguish high and low classes of enzyme activity. The results (Table II) indicate that at an equal concentration of aniline, the mean inhibition of coumarin hydroxylase from five high activity strains is 40%, while only 20% inhibition is observed in three low activity strains. Conversely, metyrapone inhibits the coumarin hydroxylase of low activity strains an average of 47%, while enzyme from the high activity group is inhibited an average of 43%. Using a t test for unpaired data, the intergroup differences in both aniline and metyrapone inhibition were highly significant (p < 0.005).

**Inheritance of Coumarin Hydroxylase Activity in DBA/2J and AKR/J Mice**—Fig. 1 summarizes the coumarin hydroxylase activity of liver homogenates from DBA/2J and AKR/J mice as well as their hybrid offspring produced by mating the parental strains. Enzyme activity was determined as described under “Experimental Procedures.”

**TABLE I**

| Mouse strain | Coumarin hydroxylase activity |
|--------------|-------------------------------|
|              | Control | Phenobarbital-prepared |
| A/HeJ        | 11:11   | 38:42 |
| A/J          | 10:12   | 33:36 |
| AKR/J        | 13:18   | 37:39 |
| B10.BR/BnJ   | 20:27   | 64:72 |
| CBA/CaJ      | 18:19   | 136:156 |
| C3H/HeJ      | 15:19   | 45:45 |
| C57L/6J      | 13:14   | 50:57 |
| C57L/J       | 31:37   | 420:492 |
| C57BR/cdJ    | 48:48   | 438:492 |
| DBA/1J       | 36:37   | 263:271 |
| DBA/2J       | 36:42   | 221:271 |
| PL/J         | 21:25   | 55:55 |
| HF/J         | 16:17   | 84:92 |
| SJL/J        | 13:15   | 62:62 |
| SWR/J        | 18:34   | 80:91 |
| 129/J        | 52:59   | 309:440 |

**TABLE II**

| Mouse strain | Percentage of inhibition of coumarin hydroxylase activityb |
|--------------|-------------------------------------------------------------|
|              | Aniline (0.6 mm) | Metyrapone (0.025 mm) |
| High activity strains |                     |                     |
| DBA/2J       | 41 ± 0.9         | 42 ± 0.2            |
| DBA/1J       | 39 ± 0.2         | 41 ± 0.5            |
| C57BR/cdJ    | 39 ± 0.8         | 46 ± 0.9            |
| C57L/J       | 43 ± 0.7         | 42 ± 0.7            |
| 129/J        | 40 ± 1.1         | 42 ± 0.9            |
| Low activity strains |                   |                     |
| AKR/J        | 23 ± 0.4         | 67 ± 0.8            |
| C57BL/6J     | 22 ± 0.3         | 63 ± 0.3            |
| SWR/J        | 14 ± 0.3         | 72 ± 1.3            |

a Enzyme activity is expressed as (1 - V/V0) x 100 where V is the activity observed in the presence of the inhibitor and V0 is the activity in the absence of inhibitor. Values represent the mean ± standard error of three replicate incubations. Hepatic microsomes from phenobarbital-induced animals were used. Assays were performed as described under “Experimental Procedures” except that the inhibitors, at the final concentrations indicated, were preincubated with the microsomes (0.15 mg of protein) for 5 min at 30°C prior to the addition of the substrate, cofactors, and the 5-min incubation at 37°C.

b Units (nanomoles/min/mg of microsomal protein ± standard error) of uninhibited enzyme activity in DBA/2J, DBA/1J, C57BR/cdJ, C57L/J, and 129/J strains were 3.9 ± 0.01, 5.2 ± 0.08, 8.8 ± 0.12, 7.4 ± 0.06, and 8.5 ± 0.08, respectively.

Fig. 1. Coumarin hydroxylase activity in whole liver homogenates of phenobarbital-pretreated DBA/2J and AKR/J mice and of phenobarbital-pretreated offspring from genetic crosses of these mice. Enzyme activity was determined as described under “Experimental Procedures.”

The Genetics of Coumarin Hydroxylation in Mice

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AKD2F1/J hybrid mice to AKR/J mice produced an equal number of offspring with low and intermediate hydroxylase activity. The backcross of the AKD2F1/J hybrid to the DBA/2J parental strain produced offspring with two classes of coumarin hydroxylase activity (intermediate and high) in a ratio of approximately 1:1. The mean activity of the AKD2F1/J hybrid is clearly intermediate, but nearer the activity of the AKR/J parental strain. The means of the high activity segregants in the F2 generation and in the backcross to DBA/BJ are not as great as DBA/2J itself, suggesting that the DBA/2J strain may possess a combination of minor modifying genes that enhance coumarin hydroxylase activity. However, the distributions of phenotypes in the F2 and backcross generations are entirely consistent with single major gene inheritance of coumarin hydroxylase activity with intermediate levels in heterozygotes.

**Linkage of the Locus Controlling Coumarin Hydroxylase Activity—**Examination of the offspring of the backcross AKD2F1/J to AKR/J revealed, as expected, the equal numbers of mice with intermediate (F1) and low (AKR) hydroxylase activity and with pigmented (+/c) and albino (c/c) coats (Table III). Although the preponderance of low activity strains is unusual, the genetic loci which control the electrophoretic variations of glucose phosphate isomerase (Gpi-1) and the hemoglobin \(B\) chain (Hbb) are separated by a distance of 33 centimorgans (CM) and are located on the centromeric and noncentromeric side, respectively, of the albino locus on chromosome 7 (10). The alleles for Gpi-1 and the c locus (6 mice) or intermediate activity and an albino coat (five mice). This nonrandom assortment of the two traits indicates that the locus controlling coumarin hydroxylase activity is on the same chromosome as the albino locus \((c)\), with an estimated map distance of 21 ± 6 centimorgan (cM). The albino locus is located on chromosome 7 (Linkage Group I) of the mouse (14). Coh is proposed as the locus symbol for coumarin hydroxylase, with superscripts \(h\) and \(l\) designating the high and low activity alleles, respectively.

**Inheritance of Coumarin Hydroxylase Activity in DBA/2J and C57BL/6J Mice—**Table IV summarizes coumarin hydroxylase activity in whole liver homogenates of phenobarbital-pretreated mice. Number in parentheses is the total number of mice of each strain assayed.

### Table IV

| Mouse strain | Coumarin hydroxylase activity<sup>a</sup> | Coh<sup>b</sup> | Gpi-1 | Hbb<sup>b</sup> | Ah<sup>b</sup> |
|--------------|------------------------------------------|--------------|-------|----------------|---------|
| DBA/2J       | 249 ± 12 (27)                            | D            | D     | D             | D       |
| C57BL/6J     | 52 ± 3 (27)                              | B            | B     | B             | B       |
| B62D2F1/J    | 141 ± 8 (22)                             | B            | B     | B             | B       |
| BXD-1        | 60 ± 5 (3)                               | B            | B     | B             | B       |
| BXD-2        | 216 ± 22 (7)                             | D            | D     | × B           | B       |
| BXD-5        | 53 ± 4 (7)                               | B            | B     | × D           | B       |
| BXD-10       | 1/4 ± 1 (6)                              | D            | D     | × B           | B       |
| BXD-8        | 58 ± 4 (3)                               | B            | B     | B             | B       |
| BXD-9        | 69 ± 7 (6)                               | B            | B     | × D           | B       |
| BXD-11       | 77 ± 7 (6)                               | B            | B     | B             | B       |
| BXD-12       | 309 ± 32 (5)                             | D            | D     | D             | B       |
| BXD-13       | 79 ± 1 (3)                               | D            | D     | × B           | D       |
| BXD-14       | 359 ± 80 (5)                             | D            | D     | × B           | B       |
| BXD-15       | 63 ± 5 (5)                               | B            | D     | × D           | D       |
| BXD-16       | 35 ± 2 (3)                               | B            | B     | B             | B       |
| BXD-18       | 50 ± 10 (7)                              | B            | D     | × B           | D       |
| BXD-19       | 48 ± 5 (8)                               | B            | B     | D             | B       |
| BXD-20       | 90 ± 15 (4)                              | B            | B     | D             | B       |
| BXD-21       | 64 ± 7 (4)                               | B            | B     | D             | B       |
| BXD-22       | 68 ± 2 (5)                               | B            | B     | B             | B       |
| BXD-23       | 47 ± 1 (4)                               | B            | B     | D             | B       |
| BXD-24       | 32 ± 3 (3)                               | B            | D     | × D           | B       |
| BXD-25       | 64 ± 10 (4)                              | B            | B     | × D           | B       |
| BXD-26       | 39 ± 14 (3)                              | R            | × D   | R             | D       |
| BXD-27       | 67 ± 6 (3)                               | B            | D     | D             | B       |
| BXD-28       | 32 ± 5 (3)                               | B            | D     | D             | B       |
| BXD-29       | 50 ± 8 (8)                               | R            | × D   | × R           | R       |

<sup>a</sup> Values represent units of enzyme activity ± standard error of the mean as determined in whole liver homogenates of phenobarbital-pretreated mice. Numbers in parentheses is the total number of mice of each strain assayed.

<sup>b</sup> These regions where crossovers have resulted in recombination of the parental alleles in the different BXD lines are denoted by a ×.

**Progeny of AKR × AKD2F1, classified for alleles at c and Coh—**Recombination percentage, 11/52 = 21 ± 5.8%. Data are from Fig. 1.

| Phenotype | Pigmented | Albino | Pigmented | Albino |
|-----------|-----------|--------|-----------|--------|
| Genotype  | + Coh<sup>a</sup> | c Coh<sup>c</sup> | + Coh<sup>a</sup> | c Coh<sup>c</sup> |
|           | c Coh<sup>b</sup> | c Coh<sup>c</sup> | c Coh<sup>b</sup> | c Coh<sup>c</sup> |
| Number observed | 21         | 20      | 6         | 5      |
centromeric or noncentromeric side of Gpi-1.

Three-point Crosses to Establish Gene Order—The pink-eye dilution locus (p) is located approximately 13 to 14 cM distal to Gpi-1 (16, 17). Two crosses were carried out to establish the location of Coh relative to Gpi-1 and p. The first cross consisted of successive backcrosses of C57L/J to C57BL/6J to establish the unstable allele of p that arose in C57BL/6J (18). The cross can be represented as (C57L/J × C57BL/6J-p"m"), × C57BL/6J-p"m"/p"m", where n represents the number of crosses of the heterozygous female parent to the C57BL/6J-p"m" stock. In each generation, one or more females bearing the normal allele of p and the Gpi-1" allele of C57L/J were selected to continue the incipient congenic line. Siblings were tested for their Gpi-1 allele and coumarin hydroxylase activity in order to accumulate three-point linkage data and to assure that the C57L/J allele from C57L/J had not been lost by crossing over in the previous generation. A total of 69 progeny were tested and the results are summarized in Table VI. There were 15 recombinants between Gpi-1 and p and 4 recombinants between Coh and Gpi-1. No double crossovers were observed and again the gene order Coh-Gpi-1-p is indicated. Utilizing the data from both experiments, the estimate of the recombination frequency between Coh and Gpi-1 is 5.8 ± 2.5%. The estimated recombination frequency between Coh and p is 19.5 ± 4.3% which is in agreement with previous estimates (16, 17).

**Table V**

| Mouse strain | Coumarin hydroxylase activity | Locus genotype |
|--------------|-------------------------------|---------------|
| C57L/J       | 379 ± 62 (3)                 | L             |
| SWR/J        | 50 ± 3 (3)                   | S             |
| (C57L x SWR)F1 | 185 ± 10 (4)               | S             |
| SWXL-2A      | 51 ± 11 (3)                  | S             |
| SWXL-3A      | 313 ± 47 (3)                 | L             |
| SWXL-6A      | 188 ± 17 (3)                 | L             |
| SWXL-7A      | 317 ± 29 (3)                 | L             |
| SWXL-12A     | 41 ± 4 (3)                   | L             |
| SWXL-14A     | 270 ± 37 (3)                 | L             |
| SWXL-15A     | 53 ± 2 (4)                   | S             |
| SWXL-16A     | 52 ± 2 (4)                   | S             |
| SWXL 17A     | 327 ± 2 (3)                  | L             |

a *See legend to Table IV.

b "S" and "L" are used as generic symbols for alleles inherited from the SWR/J and C57L/J strains, respectively. The SWR/J genotype is Coh" Gpi-1" c Ah/"Coh" Gpi-1" c Ah/". The C57L/J genotype is Coh" Gpi-1" + Ah/"Coh" Gpi-1" + Ah/". Regions where crossovers have resulted in recombination of the parental alleles in the different SWXL lines are denoted by a x.

SWXL-2 and SWXL-6 are now extinct.

**Table VI**

| Genotype | Number observed |
|----------|----------------|
| Coh" Gpi-1" p"m" | 24 |
| Coh" Gpi-1" p"m" | 20 |
| Coh" Gpi-1" + | 10 |
| Coh" Gpi-1" + | 5 |
| Coh" Gpi-1" p"m" | 2 |
| Coh" Gpi-1" p"m" | 2 |

* Alleles contributed by the heterozygous parent. See text.
In the BXD recombinant inbred strains (Table IV), there is an excess of lines fixed for the Coh allele. Were it not for the fact that close linkage is observed between Coh and Gpi-1, one might question whether a single locus model adequately accounts for the data. However, since Gpi-1 is certainly controlled by a single locus (9), there is no inconsistency in ascribing single locus control to coumarin hydroxylase activity. The predominance of the Coh and Gpi-1 alleles in the BXD strains may be attributable to a closely linked gene in the DBA/2J strain that is detrimental to survival or reproduction (or both).

In addition to the data just described, results of studies with two additional lines of mice support our assignment of the Coh locus proximal to the Gpi-1 locus on chromosome 7. As shown in Tables I and II, the 129/J strain has high coumarin hydroxylase activity, while the C57BL/6J strain has low activity. The PRO/Re mouse strain was derived from the cross of C57BL/6J with 129/J (22) with selection for the 129/J allele in the albino (c) and pinkeye dilution (p) loci. The strain carries predominantly C57BL/6J alleles at loci unlinked to p and c, but is homozygous for the 129/J alleles at both the Hbb and Gpi-1 loci. Presumably, the PRO/Re strain inherited most, if not all, of the segment of chromosome 7 from somewhere proximal to Gpi-1 to somewhere distal to Hbb from its 129/J progenitor. When the PRO/Re strain was tested for coumarin hydroxylase activity it was found to have low activity like its C57BL/6J progenitor strain. This finding suggests that Coh is proximal to Gpi-1 since assignment of the locus to the distal side of Gpi-1 would require a double crossover. The B10.D2(21M) congenic strain was developed through insertion of the histocompatibility locus 4 allele (H-4") and the closely linked pinkeye dilution mutation (p) from the 129/J strain into the C57BL/10Sn genetic background by successive crossing and intercrossing (23). The linked segment of chromosome 7 from 129/J is bounded by Gpi-1 and c (24). The B10.D2(21M) was tested for coumarin hydroxylase activity and found to be Coh like the inbred partner, again suggesting the gene order Coh-Gpi-1-p.

A congenic strain has been started in which the Coh allele of the C57BL/6J strain is being transferred to the genetic background of the C57BL/6J strain. When sufficient backcross generations have been attained and the Coh allele has been made homozygous by intercrossing, the resultant congenic strain should provide the best opportunity to further define the physiologic effects of allelic differences at the Coh locus.

By binding the substrate as well as molecular oxygen, cytochrome P-450 determines the substrate specificity of the microsomal mixed function oxidase system. Recent studies have shown that this hemeprotein exists in multiple forms each of which may exhibit characteristic catalytic, physical, or immunologic properties (Ref. 25 and references in Ref. 5). Biochemical studies (5) utilizing DBA/2J, AKR/J, and AKD2F1/J mice have suggested that the form(s) of cytochrome P-450 responsible for the 7-hydroxylation of coumarin differ in the strains of mice with high and low coumarin hydroxylase activity. Clearly, a congenic line and the inbred partner provide an ideal model with which to extend those studies and better define the regulation of the cytochrome P-450-dependent mixed function oxidase systems.

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