Genetic Study of Beta-Aminoisobutyric Acid Excretion by Japanese

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The concentration of β-aminoisobutyric acid (BAIB) in human urine is generally accepted to be strongly influenced by genetic factors, as was first proposed by Harris (1953). The results of family studies have been in general agreement with the hypothesis that the homozygote for a recessive allele is a high excretor and both the homozygote and heterozygote for a dominant allele are low excretors, but the hypothesis has not gained sufficient experimental support in previous investigations, due to the small number of observations, inadequate evidence for the bimodal distribution of BAIB concentration, and inappropriate methods of determination of BAIB (reviewed by Sutton, 1960).

The families have been mostly sampled from Caucasoid populations, where the frequency of high excretors is lower than 10%, in contrast with 40% in Oriental populations. Thus the frequency of matings of high × high excretors is less than 1% of all Caucasian matings. The present study was undertaken in a large Japanese population to attempt further determination of the mode of heredity of BAIB excretion.

MATERIAL AND METHODS

The 214 families were collected at random from three areas of Osaka and a town near Okayama City. In most cases, one morning urine specimen was collected from each subject. Urine was also collected from psychotic patients without other medical problems in mental hospitals in Osaka, Okayama, Fukuoka, Tottori, and Niigata and from residents of Morioka. These groups, totaling 1,373 physically normal subjects, were considered to represent the general population.

Approximately 10 ml of urine was collected from each subject and stored in a polyethylene bottle containing 2 ml of isopropanol at $-20°$ C until analysis.

Determination of BAIB

Creatinine concentration in urine was determined by the alkaline picrate method. An amount of urine containing 1 mg of creatinine was passed through a 0.9 × 3 cm column of Amberlite IR-120, H^+ form; the resin was washed with 10 ml of water; and BAIB was eluted with 6 ml of 2 M pyridine. The eluate was dried in a vacuum desiccator over sulfuric acid, the residue was dissolved in 0.1 ml of water, and the

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10 μl aliquot was subjected to paper electrophoresis. The filter paper was 30 cm in width and 50 cm in length. Eight samples could be run simultaneously on a sheet of paper along with 10 μg of BAIB as standard. The electrophoresis was carried out at a voltage gradient of 3,000 v per 40 cm for 30 min with a buffer consisting of pyridine, acetic acid, and water (1:10:189).

The paper was dried, immersed in a mixture of 0.2% ninhydrin in acetone and acetic acid (8:2), and heated at 100° C for 10 min. The colored band corresponding to BAIB was eluted with 4 ml of 50% ethanol, and the optical density of the solution was measured at 570 mμ. The area of the band contained no ninhydrin-positive substance other than BAIB. This was confirmed by paper chromatography of the eluate in several solvent systems. Duplicate determinations of BAIB in 10 different urine

TABLE 1

DAILY VARIATION OF THE CONCENTRATION OF BAIB

SUBJECTS	DAYS OF URINE COLLECTION						
	1	2	3	4	5	6	7
1.......	108	125	111	122	136	92	122
2.......	....	185	108	135	143	118	110
3.......	118	120	103	154	67	87	105
4.......	158	205	161	150	150	253	234
5.......	43	20	32	27	20	30	32
6.......	14	8	3	3	3	6	3
7.......	....	20	13	20	20	10	13
8.......	6	4	11	11	11	8	8
9.......	8	13	13	13	4	17	13

NOTE.—Urine was collected at an unspecified time from each subject for a week. Subjects 1–8 are psychotic patients, and 9 is a normal subject. The number in the table represents the ratio of the amount of BAIB (μg) to that of creatinine (mg).

specimens showed that errors of the measurements with the above procedure were within 5% when the ratio of BAIB to creatinine was between 5 and 200 μg/mg. Authentic BAIB added to the urine was quantitatively recovered.

RESULTS

Daily Fluctuation of BAIB Excretion

Urine specimens were collected from nine individuals for a week. Time of day of urine was not specified. The ratios of the amount of BAIB to creatinine are shown in Table 1, which indicates that the ratio is relatively constant for an individual and that time of the urine collection is not critical for the later experiments.

Genetic and Environmental Influences in BAIB Excretion

The concentrations of BAIB in urine specimens of 13 pairs of monozygotic twins were similar within each pair, as shown in Figure 1. Influence of diet was negligible, as indicated by the absence of significant correlation between husband and wife pairs (Fig. 2). These two facts suggest that the concentration of BAIB is determined predominantly by genetic factors.

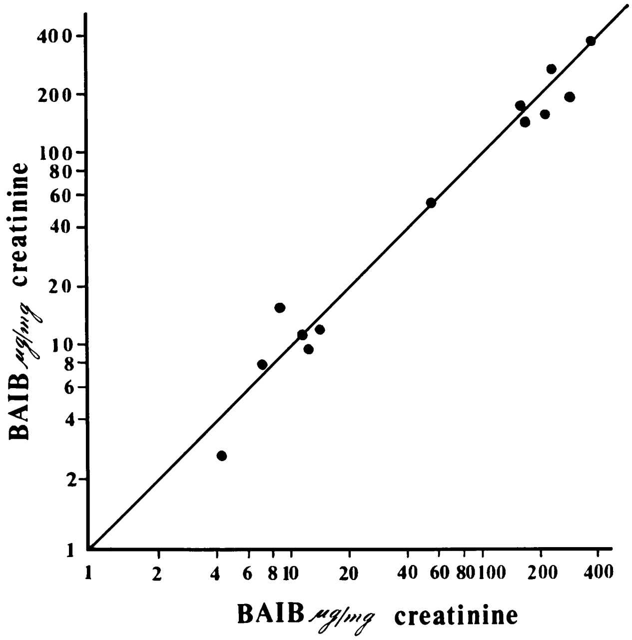

FIG. 1.—Correlation of the urinary concentration of BAIB within pairs of monozygotic twins

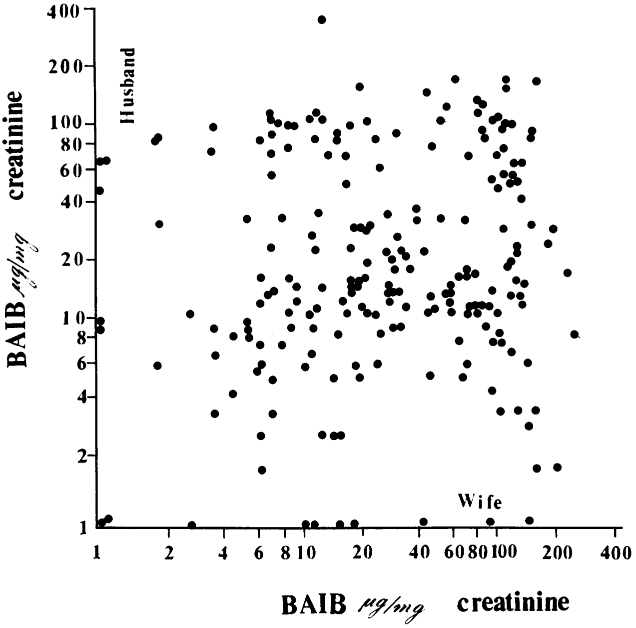

FIG. 2.—Correlation of the urinary concentration of BAIB between husband and wife pairs

Bimodality of the Distribution of the Concentration of BAIB and Differences by Sex and Age

Figure 3 represents the distribution of the concentration of BAIB of Japanese males and females. The family sample is not included. Bimodality was evident in both sexes, although the two modes overlap each other. As will be demonstrated below, the lower mode consists of both the homozygous and heterozygous low excretors, and the concentrations of BAIB in the urine of the heterozygotes are higher than those of the homozygous low excretors. This may explain that curves of both the high and low

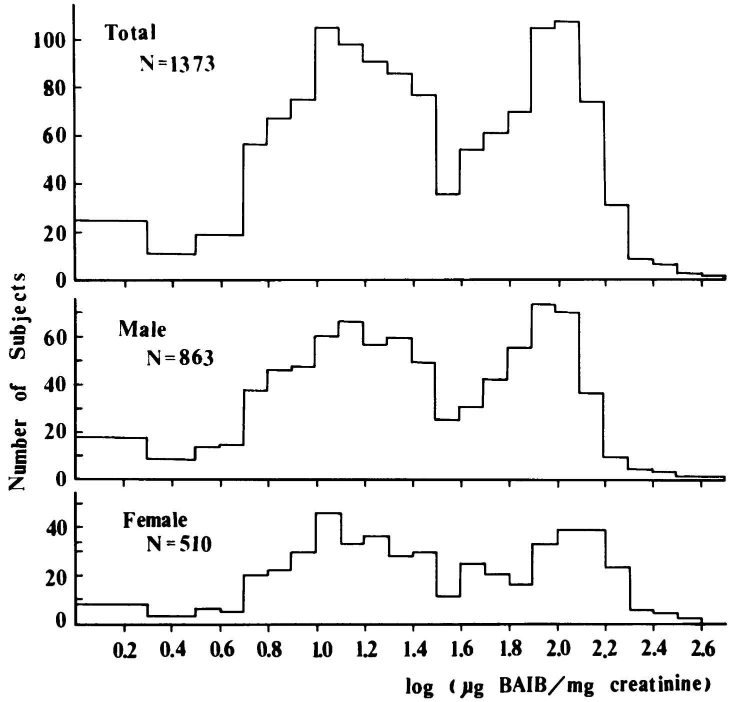

FIG. 3.—Distribution of the urinary concentration of BAIB in a Japanese population

modes skew toward the antimode. Accurate determination of the dividing line between the high and low excretors, therefore, was difficult. Assuming a symmetrical curve in the higher mode, the dividing line was tentatively set at 1.7 (= log 50.1) for both sexes. This value seems reasonable from the distribution of the concentration of BAIB in the family sample shown in Figure 6.

The concentration of BAIB is slightly higher in females than in males as seen in Figure 3. This higher value is expected when an amount of a given substance is expressed on a creatinine basis, since the excretion of creatinine is less in females than in males. Calculation of the frequency of the high excretors with a common dividing line for both sexes causes a higher frequency for females (0.374) than for males (0.341). For analysis of the family material, a mean value (0.358) of the two frequencies was taken as the frequency of high excretors in the Japanese population.

The amount of BAIB per unit amount of creatinine has been reported higher in young children (Calchi-Novati *et al.*, 1954; Gartler, 1956). This was the case for both sexes in our investigation, as illustrated in Figures 4 and 5. The average amount of BAIB was higher in the subjects under 10 years of age. The frequency distribution of this age group is given in Figure 6. Although the curve is not smooth, the antimode of this distribution is apparently at 1.9 (= log 79.4). This was taken tentatively as a dividing line between the high and low excretors of the children's group. Validity of this classification was confirmed by genetic analysis, as will be described later. It should be more reasonable to assume a gradual drop of the antimode from birth to

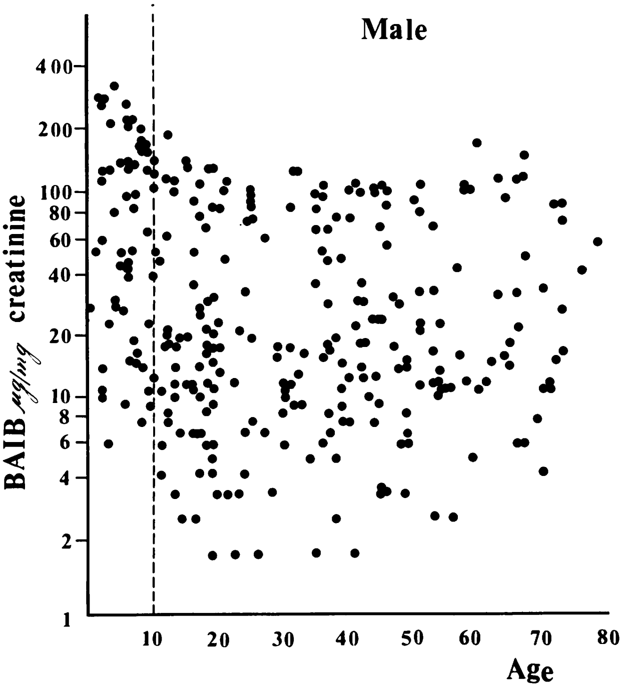

FIG. 4.—Relationship between the urinary concentration of BAIB and age (male)

10 years of age rather than to assume a sudden drop at 10 years of age, but the sample size is too small to determine the dividing line specified for each age.

Family Study

Family data are given in the Appendix. The hypothesis was tested that the high excretion of BAIB is inherited as an autosomal recessive trait. The high excretor will be expressed by *tt* and low excretor by $T/-$, the latter including both *Tt* and *TT*. Of 214 families, the numbers of matings of $T/- \times T/-$, $T/- \times tt$, and $tt \times tt$ were 100, 86, and 28, respectively, which do not deviate significantly from the expected numbers of the three types of matings, calculated from the frequency of high excretors (0.358) in the general population on the assumption of random mating: 88.2, 98.4, and 27.4, respectively. If the hypothesis is correct, the mating of high × high excre-

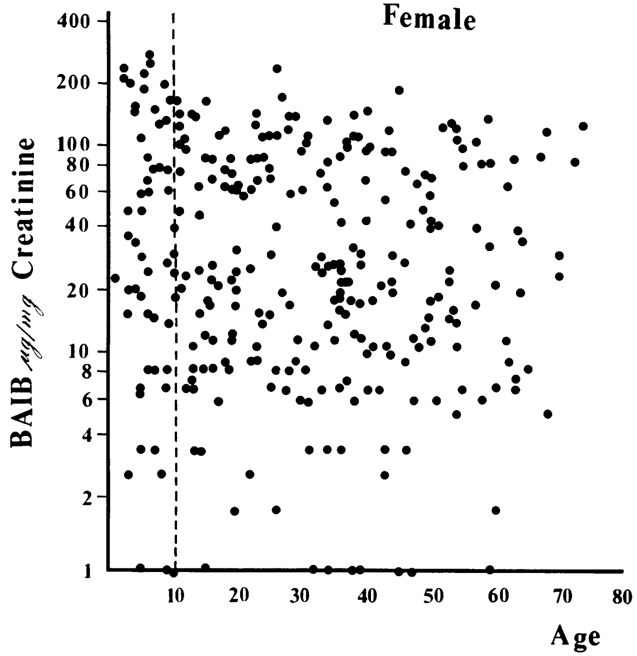

FIG. 5.—Relationship between the urinary concentration of BAIB and age (female)

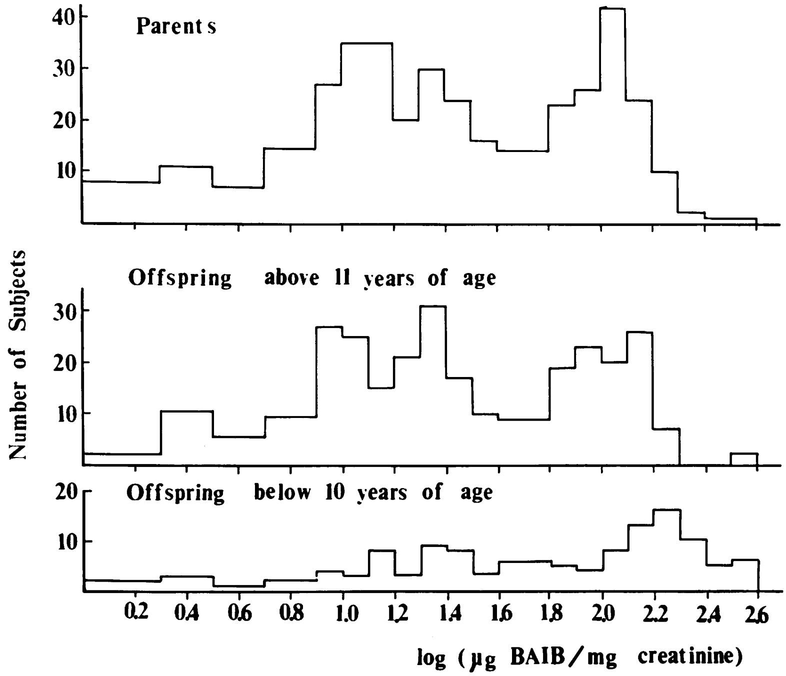

FIG. 6.—Distribution of BAIB levels in young children compared with their parents and older siblings.

tors should result only in high excretor offspring from these matings; 59 were high excretors and one was a low excretor. This can be taken as essentially in agreement with the hypothesis, considering the misclassification of high and low excretors due to incomplete separation of the two modes.

The hypothesis of autosomal recessive inheritance was tested further by Fisher's method (1939), as in Table 2. Taking 0.598 as the gene frequency of a recessive allele calculated from the data obtained from the general population, the agreement of the data with a monofactorial hypothesis was excellent in the types of matings $T/- \times T/-$ and $tt \times tt$. Further analysis of data from $T/- \times T/-$ and $T/- \times tt$ matings was carried out according to the a priori method. Agreement of the data with the hypothesis was complete, as shown in Table 3. These analyses supported the hypothesis.

TABLE 2

TEST OF RECESSIVE HYPOTHESIS*

Mating	Class of Family	No. of Families		χ^2	Degrees of Freedom
		Observed	Expected		
$T/-\times T/-$	All children $T/-$	73	74.4	0.10	1
	At least one child tt	27	25.6		
$T/-\times tt$....	All children $T/-$	26	40.1	9.29	1
	At least one child tt	60	45.9		
$tt\times tt$.......	All children $T/-$	1	0.0	....	....
	At least one child tt	27	28.0		

* Test of hypothesis that the high excretion of BAIB is inherited as an autosomal recessive trait according to Fisher (1939), on the basis of a gene frequency of the recessive allele of 0.598 estimated from the general population.

Deviation of the data in the mating $T/- \times tt$ from the hypothesis is significant, as seen in Table 2. If this type of mating was classified into the mating of $T/-$ father $\times$ tt mother and that of tt father $\times$ $T/-$ mother, the latter type of mating produced the expected number of high excretor offspring, while the deviation in the former type of mating was significant, as shown in Table 4. The same conclusion was drawn from the analysis of data in the Appendix, as shown in Table 5. In this table, male and female children produced from the two types of matings between tt and $T/-$ are classified, and the deviation in the female offspring from the mating of $T/-$ father $\times$ tt mother is apparent, but not in male offspring. Another fact noted in this table is the reduction in the number of the low excretors in the female offspring produced from the mating of $T/-$ father $\times$ tt mother in comparison to that in the male offspring from the same type of mating. Whether or not the reduction of the female low excretor offspring is the result of a type of incompatibility could not be determined from further analysis of our family sample. A large sample may be required to solve this problem.

Concentration of BAIB in Heterozygotes

As has been demonstrated, the low excretor is either heterozygous or homozygous for a dominant allele, if the population is classified into high and low excretors according to a bimodal distribution of the concentration of BAIB. There remains, however, a possibility that the heterozygote ($T/-$) excretes a higher concentration of BAIB than the homozygous low excretor (T/T). Low excretors produced from the matings of high (tt) × low ($T/-$) excretors, the low excretor parents ($T/-$) having

TABLE 3

DISTRIBUTION OF HIGH EXCRETORS OF BAIB IN OFFSPRING WHERE AT LEAST ONE OFFSPRING IS A HIGH EXCRETOR (A PRIORI METHOD)

Family Size	No. of Families	No. of High Excretors Observed	No. of High Excretors Expected	Variance
Low×Low Excretor Matings				
2	17	22	19.5	2.1
3	5	5	6.5	1.3
4	2	3	2.3	0.8
5	1	1	1.6	0.6
Total	25	31	29.9	4.8
High×Low Excretor Matings				
2	26	34	34.7	5.8
3	11	19	18.9	5.4
4	6	14	12.8	4.7
Total	43	67	66.4	15.9

TABLE 4

TEST OF RECESSIVE HYPOTHESIS*

Mating Father×Mother	Class of Family	No. of Families: Observed	No. of Families: Expected	χ^2	Degrees of Freedom
$tt \times T/-$	All children $T/-$	13	15.8	0.93	1
	At least one child tt	21	18.2		
$T/- \times tt$	All children $T/-$	13	24.3	9.86	1
	At least one child tt	39	27.7		

* Test of hypothesis that high excretion of BAIB is inherited as an autosomal recessive trait according to Fisher (1939) in the matings of high excretor father × low excretor mother and low excretor father × high excretor mother.

at least one high excretor offspring (*tt*), were sampled as heterozygotes from the family sample described in the Appendix. The concentrations of BAIB of 180 heterozygotes above 10 years of age were significantly higher ($P < 0.001$) than those of the remaining group, which consisted of 319 both heterozygous and homozygous low excretors, as shown in Figure 7. In this group, 193 of 319 low excretors were calculated to be heterozygotes on the basis of gene frequency of the recessive allele being 0.598. Mean concentration of BAIB of the heterozygotes is 18.9 μg/mg of creatinine and that of the mixed group of homozygous and remaining heterozygous low excretors is 13.0. Calculation of theoretical concentration of BAIB for the homozygous low excretors yields 4.04 μg/mg creatinine.

TABLE 5

TEST FOR AUTOSOMAL RECESSIVE INHERITANCE IN TWO TYPES OF MATINGS BETWEEN HIGH AND LOW EXCRETORS

Mating Father × Mother	Class of Offspring		No. of High Excretor Offspring	
			Observed	Expected
$tt \times T/-$	Male	$T/-$	26	23.7
		tt	12	14.3
	Female	$T/-$	17	20.0
		tt	15	12.0
$T/- \times tt$	Male	$T/-$	35	40.6
		tt	30	24.4
	Female	$T/-$	15	26.9
		tt	28	16.1

NOTE.—Because some of the offspring are related, it is not possible to make a formal test of significance.

Since the concentrations of BAIB are higher in heterozygous carriers than in homozygous low excretors, it is expected that the matings between low excretor parents whose concentration of BAIB is high within the mode of the low excretors produce a greater proportion of high excretor offspring than those whose concentration of urinary BAIB is low in the same mode, since the former group more likely involves matings between heterozygotes, and the latter more likely involves matings between homozygotes. This was the case, as is shown in Table 6. When a similar test was performed for the matings between high and low excretors, the same conclusion was drawn as is shown in this table.

DISCUSSION

Harris (1953) first reported that the high excretion of BAIB is determined by homozygosity for a recessive allele, but his method of determination of BAIB depended on the visual comparison of the intensity of the BAIB spot with that of alanine on a paper chromatogram. This method is arbitrary in assigning bimodality to a

Caucasoid population where bimodality of the distribution of the concentration of BAIB had not been detected. Experiments by Calchi-Novati *et al.* (1954) were based on the method used by Harris, with a similar result. Gartler (1956) obtained 60 families in New York, but he also encountered difficulty in dividing high from low excretors, since his sample did not show a bimodal distribution and the frequency of high excretion was low, with no example of matings of high × high excretors in his family sample. Gartler *et al.* (1957) later collected a sample of 32 families from the

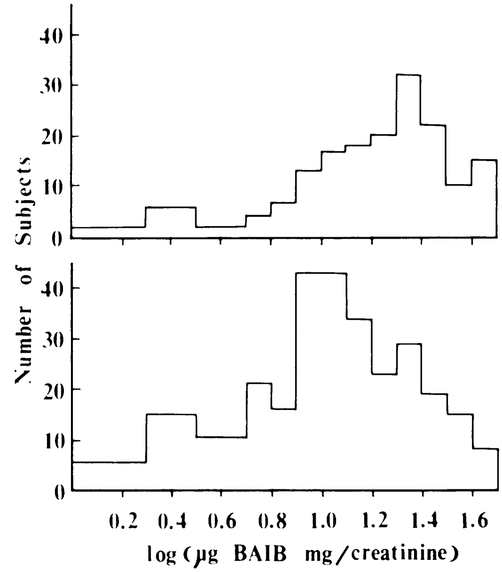

FIG. 7.—The upper figure represents distribution of the concentration of BAIB in urine of heterozygous low excretors obtained from family material. These were identified as low excretor offspring from matings of high × low excretor parents, the low excretor parent having at least one high excretor offspring. The lower figure represents distribution of the concentration of BAIB in urine of low excretors who could not be classified either as heterozygous or homozygous low excretors in the same family material. In both figures, subjects under 10 years of age are omitted.

TABLE 6

NUMBER OF HIGH EXCRETOR OFFSPRING PRODUCED FROM LOW × LOW EXCRETORS AND LOW × HIGH EXCRETORS*

CLASS OF MATINGS	CONCENTRATION OF BAIB IN PARENTS	NO. OF OFFSPRING	
		High Excretors	Low Excretors
$T/- \times T/-$	Below 14×below 14	5	71
	Below 14×above 15	8	81
	Above 15×above 15	21	40
$T/- \times tt$	Below 14×high	47	64
	Above 15×high	38	29

* Low excretors were divided into two classes by the BAIB concentration of 14.5 on the assumption of the concentration of heterozygotes being higher than homozygous low excretors.

Black Carib population, which showed a bimodal distribution with considerable overlap between the two modes and a reasonable concordance with monogenic autosomal inheritance. They expressed the amount of BAIB on the basis of the glycine, but the amount of glycine varies widely from person to person, and experience in our laboratory showed that the concentration of glycine is also under considerable genetic influence independent from the genetic control of BAIB. A study by Grouchy and Sutton (1957) was carried out with 17 Chinese and Japanese families. They could not demonstrate a bimodal distribution, probably due to the small sample size, and did not come to a conclusion on heredity.

The difficulties in the above studies were mostly overcome in the present study by collecting a larger family sample from a population where the two phenotypes are sufficiently numerous and by improving the method of determination of BAIB to obtain more accurate values. This study provided confirmative evidence that the high excretion of BAIB is determined by homozygosity for a recessive allele.

Bimodality of the distribution of BAIB concentration in urine was shown, with a considerable overlap. One of the reasons for poor resolution of the two modes is that the heterozygotes excrete a higher concentration of BAIB than the homozygous low excretors. Although the distribution curves of BAIB concentration of homozygous (T/T) and heterozygous (T/t) low excretors were not separable, the concentration of the former group is clearly higher than that of the latter group. This was confirmed by sampling heterozygous carriers from the family material and by comparing frequency of high excretors produced from the matings between low excretors whose concentrations of BAIB were classified into higher and lower concentrations. The concentration of BAIB in the urine of Oriental low excretors may be higher than that of the Caucasoid low excretors, since frequency of heterozygotes in the low excretor group is higher in the former population than in the latter population.

A factor which makes the concentration of urinary BAIB on a creatinine basis generally higher in young children is probably a lower concentration of creatinine per body weight in the lower-age group. In a few previous studies, children under five years of age have been omitted from family samples for analysis, but this group was incorporated into the present investigation by lifting the dividing line to 79.4 μg/mg creatinine between high and low excretors. In order to examine the validity of this procedure, only children under 10 years of age were used to test for autosomal recessive inheritance, as shown in Table 7. Agreement of the data with the genetic hypothesis was good, with the exception of female children produced from the mating of $T/-$ fathers $\times$ tt mothers. This was also the case in the analysis of the whole family sample. Again, if the children younger than 10 years of age were excluded from from the family data, the conclusion obtained was unchanged.

Loss of low excretor daughters (T/t) produced from low excretor fathers ($T/-$) $\times$ high excretor mothers (tt) observed in our family material may be of importance when polymorphism of BAIB excretion is considered. This loss causes an increase in the frequency of t if it is above 0.5, as in the Japanese population, and a decrease if the frequency of t is below 0.5, as in Caucasoid populations. Therefore, the polymorphism of BAIB excretion may be transient in both populations.

Mechanism of the loss of T/t daughters is unknown. If an antibody is formed in tt mothers, who do not carry D(−)-BAIB : pyruvate aminotransferase, on stimulation by a T/t fetus, and if the antibody affects the second T/t child, loss of daughters should not occur in the first child. This was not the case in our family material. Age intervals between siblings also were not significantly different in the above class of matings.

The mechanism of expression of the genotypes is of importance from a geneticobiochemical point of view. It was established that high excretors lack the ability to break down D(−)-BAIB in the body (Armstrong *et al.*, 1963; Gartler, 1959), but the enzyme which participates in the metabolism of D(−)-BAIB has not been identified. BAIB:α-ketoglutarate aminotransferase was once believed to be an enzyme responsible for BAIB metabolism (Kupiecki and Coon, 1957), but we demonstrated that this enzyme catalyzes the transamination of L(+)-BAIB but not D(−)-BAIB

TABLE 7

ANALYSIS OF OFFSPRING UNDER 10 YEARS OF AGE WITH A DIVIDING LINE OF 79.4 μg BAIB PER mg CREATININE BETWEEN HIGH AND LOW EXCRETORS

Mating Father×Mother	Class of Offspring	No. of Children		χ^2	Degrees of Freedom
		Observed	Expected		
$T/-\times T/-$	$T/-$	48	53.3	3.75	1
	tt	14	8.7		
$tt\times T/-$	$T/-$	13	15.0	0.71	1
	tt	11	9.0		
$T/-\times tt$	$T/-$	12	19.4	7.54	1
	tt	19	11.6		
$tt\times tt$	$T/-$	0	0	...	...
	tt	20	20.0		

and that the activity of the enzyme is not different in the kidney of high excretors compared with low excretors (Kakimoto *et al.*, 1968). In our recent study (Kakimoto *et al.*, 1969), a different enzyme, D(−)-BAIB: pyruvate aminotransferase, was found in mammalian liver. The enzyme activity was detected in human liver specimens obtained at autopsy when the urine of the subjects contained a low concentration of BAIB in bladder urine, while there was little or no enzyme activity in the liver of subjects who carried a high concentration of BAIB. Since a high concentration of BAIB in urine specimens obtained at autopsy may reflect either genetic or pathological high excretion, some of the subjects with a high concentration of BAIB might be properly classified as genetic low excretors. Considering the possibilities of misclassification, the most probable conclusion of our biochemical study is that a dominant allele (T) controls the formation of liver D(−)-BAIB: pyruvate aminotransferase. High excretors (tt) lack the ability to metabolize BAIB formed in the body and consequently excrete BAIB in a larger amount. A gene dose effect exists for the dominant allele, since the concentration of BAIB in urine is higher in heterozygotes (Tt) than in homozygotes (TT) for the dominant allele.

SUMMARY

Bimodal distribution of the concentration of BAIB was demonstrated with urine samples from 1,373 unrelated Japanese subjects. Frequency of high excretors was 35.8%. A sample of 214 families, including 462 offspring, was obtained separately from the same population, and results of the analysis of the data were consistent with a hypothesis of autosomal recessive inheritance, high excretors being homozygous for the recessive allele. Female offspring produced from the matings of low excretor fathers with high excretor mothers were, however, significantly fewer than male offspring from these matings and were fewer than calculated on the basis of random mating. The possibility of selection through mother-child incompatibility is suggested. Heterozygous carriers of the dominant allele excrete a higher concentration of BAIB than do homozygous low excretors.

ACKNOWLEDGMENTS

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APPENDIX

Amount of BAIB (µg per mg Creatinine) in the Urine of Families

Family	Parents		Offspring				
	Father	Mother	1st	2d	3d	4th	5th
1	141	_85_	_51_	_94_	_56_		
2	66	_133_	_85_	180			
3	117	_106_	_135_				
4	51	_135_	118	135*			
5	66	_140_	58	_74_	98	57	
6	58	_115_	_92_	_112_	151	117*	
7	92	_157_	135*	_166*_			
8	137	_58_	194*	373*			
9	163	_118_	153*				
10	72	_105_	78	_98_			
11	136	_102_	_235*_	324*			
12	78	_112_	128	117*	_140*_	239*	
13	53	_134_	95	_162_	_63_	_65_	
14	112	_102_	100	_65_			
15	182	_117_	114				
16	129	_91_	_143_	180*			
17	100	_151_	112				
18	97	_89_	_122_	_97_			
19	105	_120_	_160_	_182*_	_168*_		
20	93	_93_	71				
21	71	_76_	_76_	_83_			
22	102	_114_	107	54			
23	54	_100_	152*	296*			
24	107	_118_	_83_				
25	122	_85_	93				
26	58	_128_	35				
27	180	_64_	_53_	_106_	_174_	_174*_	
28	178	_170_	_340*_	_230*_			
29	111	_43_	_66_	14	37		
30	83	_45_	57				
31	154	_44_	49*				
32	95	_15_	9				
33	87	_15_	13*	_119*_			
34	78	_3_	7	3			
35	89	_12_	_196*_	56*			
36	59	_7_	7	16	30		
37	170	_20_	45*	_85*_			
38	111	_22_	_19_	_158_	186*		
39	93	_24_	_34_	_15_	_49_	_123_	
40	80	_0_	8				
41	63	_26_	_19_	26	16		
42	96	_7_	139	181	_149_	106	
43	103	_3_	8	_28_	_7_		
44	121	_7_	_46_				
45	89	_6_	57*	_182*_			
46	69	_0_	15*	56*			
47	109	_9_	_70_	9			
48	94	_2_	_75_	_26_	73		
49	107	_19_	153*				
50	117	_7_	4*	69*	_9*_		
51	106	_9_	_0*_				
52	96	_31_	134				
53	116	_11_	_3_	_156_			
54	71	_14_	_27_	50			
55	126	_12_	136				
56	69	_0_	_67*_	156*			
57	110	_8_	7	9	141*		

An italicized number represents a female, and a number marked with an asterisk represents a subject under 10 years of age. Families 1–28, 29–114, and 115–214 are the types of mating high × high, high × low, and low × low excretors, respectively.

Family	Parents		Offspring				
	Father	Mother	1st	2d	3d	4th	5th
58	116	*13*	*12*	*52*			
59	51	*17*	*20**	139*			
60	74	*13*	*151*	*16*			
61	376	*13*	*266**	*115**			
62	76	*8*	7				
63	43	*142*	83				
64	3	*133*	*126*	*143*	*66*	*20*	
65	7	*126*	*252*				
66	11	*73*	*13*				
67	2	*165*	14	22			
68	2	*213*	303*				
69	31	*155*	29*				
70	8	*103*	*23*	20			
71	17	*71*	145	*149*	611		
72	15	*60*	9*	338*			
73	11	*60*	17	123			
74	12	*82*	63*				
75	3	*106*	10	147			
76	0	*150*	23	*43*			
77	14	*136*	136	*133*	*85*	34	
78	5	*69*	213*	*192**	*196**		
79	12	*144*	*191*	94	26		
80	34	*53*	127	*131*			
81	17	*66*	28*	*225**			
82	23	*137*	12	111	83		
83	15	*99*	*85*	*102*			
84	11	*103*	14	21			
85	12	*94*	20	*20*	*146*		
86	3	*162*	3	*139*	*147**		
87	6	*152*	1*	*308**			
88	18	*81*	*65**	*168**			
89	12	*79*	24	12	20	20	
90	4	*98*	94				
91	49	*110*	243*				
92	13	*58*	54*	*9**			
93	11	*83*	*12*	19	*12*	12	
94	19	*72*	157				
95	20	*123*	119	19	134*		
96	14	*126*	*245**	*231**			
97	8	*66*	47*				
98	8	*109*	12	124	*13**		
99	9	*106*	*3*	*2*	*94*	*6*	
100	6	*71*	69				
101	20	*126*	248*				
102	29	*211*	31	*71*			
103	9	*92*	*274**	328*			
104	34	*71*	*24*	28	66		
105	25	*130*	22	153	46	103*	
106	15	*60*	83	100			
107	12	*77*	*122*				
108	18	*154*	*174**				
109	9	*263*	11*				
110	0	*94*	78	94			
111	26	*194*	5	26			
112	30	*114*	141*	*54**			
113	16	*130*	*218**				
114	15	*145*	128				
115	38	*47*	83	*94*			
116	35	*4*	19	2	*19*	5	
117	37	*28*	*89**	*99**			
118	37	*12*	*75**	31*			

Family	Parents		Offspring				
	Father	Mother	1st	2d	3d	4th	5th
119	35	_7_	_33_	_15*_	20*	_26*_	...
120	12	_35_	17*	41*	_37*_	...	...
121	4	_46_	_26*_	7*	15*	...	...
122	0	_43_	_98_	17	11	...	...
123	23	_44_	20	_144_	18	...	...
124	11	_46_	32	_14_	...	...	...
125	14	_47_	_69_	_28_	11	_32*_	...
126	22	_35_	18	18	_263_	_16_	_16_
127	20	_37_	20	...	...	...	...
128	4	_6_	_9_	37	_6_	...	...
129	20	_22_	75	_7_	...	...	...
130	0	_11_	_15_	_18_	0	_23_	_13_
131	17	_21_	21	_4_	_21_	14	50
132	9	_32_	7	...	...	...	...
133	9	_31_	20	37	...	...	...
134	5	_2_	14*	...	...	...	...
135	14	_6_	30	...	...	...	...
136	15	_13_	_15*_	10*	...	...	...
137	9	_5_	12	_9_	...	...	...
138	4	_4_	4	_8_	...	...	...
139	11	_3_	_85*_	_6*_	...	...	...
140	13	_9_	_16*_	5*	_24*_	...	...
141	9	_5_	_5_	_18_	_8_	_3_	...
142	9	_3_	0*	3*	...	...	...
143	0	_0_	_216*_	_0*_	3*	...	...
144	17	_9_	3	...	...	...	...
145	3	_14_	11*	107*	...	...	...
146	.0	_10_	_21_	_6*_	...	...	...
147	15	_28_	20*	_29*_	...	...	...
148	5	_15_	12	3	2	...	...
149	8	_20_	_6_	_6_	...	...	...
150	23	_27_	_184_	9*	...	...	...
151	9	_0_	4	0	_0*_	...	...
152	11	_22_	9	...	...	...	...
153	9	_9_	_264_	300*	...	...	...
154	12	_12_	3	15	...	...	...
155	6	_25_	_28_	_47_	_4_	_10_	...
156	20	_28_	170*	49*	...	...	...
157	0	_0_	_21_	_49_	3	...	...
158	9	_15_	_11_	9	13	_20_	...
159	0	_3_	_5_	_24_	...	...	...
160	9	_4_	12	...	...	...	...
161	15	_30_	_49_	_15_	_7_	...	...
162	13	_6_	24	...	...	...	...
163	24	_33_	33	_71_	...	...	...
164	15	_18_	_10_	_9_	...	...	...
165	3	_13_	_28_	...	...	...	...
166	6	_6_	12	...	...	...	...
167	3	_6_	8	5	...	...	...
168	13	_28_	3	20	_3*_	...	...
169	16	_26_	16	78	95	_9_	...
170	13	_16_	_39*_	...	...	...	...
171	11	_9_	24*	...	...	...	...
172	16	_20_	145*	127*	...	...	...
173	31	_23_	_106_	42*	_31*_	...	...
174	15	_18_	_9_	...	...	...	...
175	31	_23_	_9_	15	...	...	...
176	7	_3_	_7*_	_16*_	...	...	...
177	10	_5_	_3_	...	...	...	...
178	12	_21_	8	...	...	...	...
179	7	_6_	_11_	0*	...	...	...

APPENDIX—_Continued_

Family	Parents		Offspring				
	Father	Mother	1st	2d	3d	4th	5th
180	15	_32_	_26_	26*			
181	32	_12_	_9_				
182	11	_11_	_3_				
183	31	_21_	_161_	198*			
184	8	_8_	21	14	8		
185	49	_0_	_35_	31	_20_	_31_	18
186	12	_49_	_9_	_122_			
187	11	_25_	8				
188	27	_11_	_11_	11			
189	31	_19_	_16_	173*			
190	9	_26_	223*	_20*_			
191	11	_17_	10	3			
192	25	_18_	_22_	205			
193	21	_29_	2	5	_25_		
194	10	_0_	7	24*			
195	3	_15_	9	6	_9_		
196	25	_7_	_9_	12			
197	7	_11_	7	_18_			
198	15	_28_	_15*_	_67*_			
199	15	_9_	_3_	_13_			
200	6	_20_	22				
201	0	_15_	_96_	0	9		
202	32	_2_	_12_	_11_	_18_	2	4
203	9	_11_	_3*_	3*			
204	0	_18_	_21*_	_21*_			
205	6	_6_	2				
206	2	_6_	9				
207	3	_7_	_6_	7	_8_		
208	17	_6_	_0_	0	0		
209	3	_3_	6	_3_	6	_3*_	
210	5	_20_	_111*_	_110*_			
211	27	_31_	116				
212	6	_10_	12				
213	14	_7_	30				
214	33	_41_	106	21			

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