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# Segregation and Linkage Studies of Plasma Dopamine-Beta-Hydroxylase (DBH), Erythrocyte Catechol-*O*-Methyltransferase (COMT), and Platelet Monoamine Oxidase (MAO): Possible Linkage between the *ABO* Locus and a Gene Controlling DBH Activity

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SUMMARY

Measurements of dopamine-beta-hydroxylase (DBH), catechol-*O*-methyltransferase (COMT), and monoamine oxidase (MAO) along with 27 polymorphic marker phenotypes were available for 162 patients with major affective disorders and 1,125 of their relatives. Levels of enzymes were previously found *not* to be associated with illness. Pedigree analysis methods for quantitative traits are used to test single-gene hypotheses for segregation of DBH in 32 families with 411 individuals, COMT in 30 families with 351 individuals, and MAO in 50 families with 309 individuals. The familial distribution of both DBH and COMT are consistent with two codominant alleles at the same locus that account for 56% and 59% of the total variance, respectively. MAO activity cannot be shown to be segregating as a single major gene, but a purely nongenetic hypothesis is also rejected. A possible linkage of a locus for DBH to the *ABO* locus is indicated by a maximum lod score of 1.82 at 0% and 10% recombination fractions for males and females, respectively. A lod score of 0.61 at 0% recombination for a similar analysis in a single large pedigree was reported by Elston et al., making the combined lod score for the two studies equal to 2.32 at 0% recombination.

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## INTRODUCTION

Three enzymes of catecholamine metabolism, dopamine-beta-hydroxylase (DBH), catechol-*O*-methyltransferase (COMT), and monoamine oxidase (MAO), can be measured in peripheral tissues and have been studied extensively because of: (1) their possible relationship to the development of psychiatric disorders, and (2) the evidence that genetic factors account for some of the variance in enzyme levels. Our study presents pedigree data compatible with two codominant alleles segregating at a single locus controlling activity of plasma DBH and with a similar mode of transmission for erythrocyte COMT, and it describes suggestive linkage of the plasma DBH locus to the *ABO* blood group locus.

DBH catalyzes the conversion of dopamine to norepinephrine. It is released into the plasma along with catecholamines from adrenergic nerve terminals. A detailed review by Weinshilboum of the biochemistry and genetics of DBH has recently been published [1]. In a population survey of DBH, Weinshilboum et al. [2] found a small subgroup of individuals (3%–4%) with very low DBH. First-degree relatives of individuals in the "low" group were studied. By dichotomizing the continuous DBH values into two types (low and not low), a single autosomal recessive gene was consistent with the segregation of "low" DBH in these families. Using a more powerful method of pedigree segregation analysis, Elston et al. [3] re-analyzed these data as a quantitative trait and showed that a single gene could account for 50% of the variation of DBH in the sample. In addition, transmission of DBH in a single large multigenerational pedigree of 95 individuals was consistent with a single major gene accounting for 75% of the variation.

COMT is a degradative enzyme of catecholamine metabolism found in both soluble and membrane-bound forms in erythrocytes. The distribution of COMT in a population survey by Weinshilboum and Raymond [4] appeared bimodal, with approximately 25% of the sample having "low" activity. When the distribution of COMT in siblings and parents of "low" individuals was studied (as with DBH), the trait of "low" COMT was found to be compatible with the segregation of a single autosomal recessive gene. In later studies by Scanlon et al. [5], subjects with "low" COMT were shown to have a more thermolabile enzyme than did individuals with "high" COMT. Spielman and Weinshilboum [6] have subsequently shown that the distribution of activity in siblings of "low" individuals is compatible with two alleles segregating at a single locus and three distinct genotypic distributions.

Monoamine oxidase (MAO) is a mitochondrial enzyme that degrades catecholamines and can be measured in a variety of tissues, including platelets. There are at least two types of MAO activity defined by substrate and inhibitor specificities. MAO type A preferentially degrades serotonin and norepinephrine while MAO type B preferentially degrades phenylethylamine and benzylamine. The drugs clorgyline and deprenyl selectively inhibit MAO type A and B, respectively [7]. Recent peptide mapping of MAO types A and B following proteolysis has revealed only one peak that shows a difference between types [8]. One explanation is that the two molecules represent separate loci, with one possibly arising through a gene duplication of the other. Another alternative is that one type is the result of

posttranslational modification of the other. In either case, structural genes coding for both types may reside on the same chromosome. Most tissues contain varying amounts of the two forms. Platelet MAO is homogeneously type B. Primate brains have also been shown to contain primarily type B. Fibroblast MAO is primarily type A, and its presence has recently been shown to be associated with the human X chromosome in mouse-human hybrid cells [9]. This is evidence that a structural locus on the X chromosome codes for MAO type A.

Twin studies of MAO have shown high heritability of enzyme activity [10, 11]. A study of platelet MAO in normal families by Pandey et al. [12] also demonstrated high heritability of enzyme activity, as measured by two different substrates. In these data, there was no evidence for dominance effects since parent-offspring correlations were similar to sibling-sibling correlations.

The relationship of DBH, COMT, and MAO activities to affective illness has been reviewed by us [13]. In brief, studies have shown no consistent alterations in DBH or COMT activity between affectively ill patients and normal individuals. Whether or not there is an alteration of MAO activity in affective illness is not yet resolved. Many studies have found lower MAO activity in bipolar patients than in controls, but several others have not confirmed this finding. In our study, we use pedigree segregation and linkage analyses to test hypotheses of single-gene transmission of enzyme levels in a sample of families ascertained through individuals with affective disorders.

## MATERIALS AND METHODS

### *Description of Sample*

Our sample consists of 162 (mainly Caucasian) patients having primary affective disorder, 1,125 of their relatives, and a group of normal controls. Black patients and relatives account for only about 2%–3% of the individuals included in these analyses. For DBH and COMT, we have found no differences in enzyme levels between affectively ill patients and either normal family members or normal controls [13]. These families can be considered a random sample with respect to DBH and COMT enzyme levels. For MAO, both ill patients and normal relatives have lower enzyme levels than do controls, but there are no differences between ill and well relatives. Whether this represents a real difference or some systematic problem with the assay is not known. Thus, our patients may or may not be a biased sample with respect to MAO. However, if genotypes at a single locus had different mean activity levels, segregation analysis should indicate a major locus, although the estimated gene frequency would not reflect the true population value.

As part of an earlier report on the relationship of these enzymes to affective disorders [13], the results of single-gene segregation analyses were briefly summarized. Here we present details of segregation and linkage analyses. For genetic analyses, a subset of families was selected according to the number of informative individuals. Families having 10 or more individuals were analyzed for segregation of DBH and COMT activities. Because of lack of data, families having five or more individuals were analyzed for segregation of MAO activity. The DBH sample consists of 32 families with 411 individuals, the COMT sample consists of 30 families with 351 individuals, and the MAO sample, of 50 families with 309 individuals.

Plasma DBH enzyme activity was measured using the procedure of Molinoff et al. [14], erythrocyte COMT according to Gershon and Jonas [15], and platelet MAO (using benzyl-

amine as substrate) according to Murphy et al. [16]. Data from some individuals were deleted because of drug effects. MAO values were deleted from individuals taking steroids, thyroid, tricyclics, or MAO inhibitors. COMT values were deleted from those taking steroids or thyroid. DBH values were deleted from individuals taking diuretics. Phenotypes for the following eight red cell antigen systems were determined: ABO, Rhesus (Rh), MNS, Kell (K), P, Duffy (Fy), Kidd (Jk), and Lewis (Le). ABH secretor status (Se) was determined indirectly, using the red cell Lewis phenotype results. Phenotypes were also determined using standard methods [17–19] for the following 17 red cell and serum systems: adenylate kinase (AK), adenosine deaminase (ADA), 6-phosphogluconate dehydrogenase (PGD), phosphoglucomutase 1 ($PGM_1$), phosphoglucomutase 2 ($PGM_2$), acid phosphatase (ACP), galactose-1-phosphate uridyl transferase (GALT), glutamic-pyruvic transaminase (GPT), esterase D (ESD), haptoglobin (Hp), transferrin (Tf), group specific component (Gc), $\alpha_1$-antitrypsin (Pi), pseudocholinesterase ($E_1$), third complement component (C3), amylase-2 ($AMY_2$), and glyoxalase 1 (GLO). $PGM_2$, Tf, Pi, $E_1$, $AMY_2$, and GLO were not segregating.

### *Statistical Analyses*

Preliminary analyses were performed on the *entire* sample of patients and relatives. The distributions of enzyme levels were first examined for significant deviations from normality. Transformations were chosen to minimize these deviations. After transformation, standard regression techniques were used to correct for age and sex differences where necessary. Maximum-likelihood methods [20] were then used to test for mixtures of two and three univariate components in the enzyme distributions.

The Elston-Stewart likelihood method [21] of pedigree segregation analysis was applied to the subsamples of families to estimate parameters and test hypotheses of single-gene transmission of enzyme traits.

The general pedigree model for a continuous trait controlled by a single, two-allele ($A$, $a$) locus assumes that there are three types of individuals denoted $AA$, $Aa$, and $aa$. After suitable transformation to meet normality assumptions, these types have mean enzyme levels $\mu_{AA}$, $\mu_{Aa}$, and $\mu_{aa}$ and common standard deviation $\sigma$. Persons marrying into the pedigree come from these distributions with probabilities $\psi_{AA}$, $\psi_{Aa}$, and $\psi_{aa}$, which are assumed to be in Hardy-Weinberg proportions. Persons of the three genotypes transmit allele $A$ to their offspring with probabilities $\tau_{AAA}$, $\tau_{AaA}$, and $\tau_{aaA}$, respectively, which under a simple Mendelian hypothesis are 1, ½, and 0. Under a nongenetic or "environmental" hypothesis that each individual's phenotype is independent of his parents' phenotypes, these transmission probabilities are equal. These hypotheses are each tested against the general alternative hypothesis of arbitrary transmission probabilities using the general likelihood ratio criterion (i.e., twice the difference in $\log_e$ likelihoods between the restricted and unrestricted hypotheses is distributed as a chi-square variable with degrees of freedom equal to the number of additional independent restrictions imposed on the unrestricted hypothesis). If one phenotype is dominant, then we can arbitrarily set $\mu_{AA} = \mu_{Aa}$. The program GENPED [22] was used to estimate parameters and compute the likelihood under the unrestricted model and under each hypothesis. The percent of variance due to major gene segregation was computed according to Elston et al. [23].

Initial studies by Weinshilboum et al. [2, 4] showed no indication of sex differences in the distribution of "low" COMT or "low" DBH in siblings of "low" individuals. Therefore, X-chromosome transmission is an unlikely mechanism for these traits. Since cell culture studies have shown that there may be a structural gene for MAO on the X chromosome, hypotheses of X-chromosome transmission were tested for MAO even though a variation in activity levels may not necessarily be related to a structural gene.

The computer program LIPED [24] was used to calculate lod scores for linkage between genes determining enzyme levels and marker loci.

## RESULTS

### *Preliminary Analyses*

Univariate statistics for the families used for segregation analysis are shown in table 1 in original scale and after square-root and $\log_e$ transformation. For all three enzymes, deviations from normality are minimized by taking a square-root transformation. COMT levels in females showed a significant age trend and were adjusted to age 35. Both COMT and MAO showed significant sex differences. Values of females were adjusted to have the same mean and variance as males. Age and sex adjustments were computed on the basis of the complete sample. DBH levels showed no age or sex variation.

After square-root transformations and age and sex adjustments, all distributions are unimodal (results not shown). Figures 1*A–C* show the cumulative distributions of enzyme levels in the subsamples of families. Although there is a small peak for "low" DBH activity in fig. 1*A*, this second component is not significant. If the variables are transformed to $\log_e$ units, DBH is significantly trimodal and both COMT and MAO are significantly bimodal. However, because of the large degree of skewness and kurtosis of the distributions in $\log_e$ units (table 1), all genetic analyses of variables were performed in square-root units.

### *Genetic Analyses*

Maximum-likelihood estimates from segregation analyses of DBH, COMT, and MAO are shown in tables 2–4 along with the *P*-value associated with each hypothesis. For DBH, the hypotheses that "low" values are either dominant or recessively inherited are strongly rejected ($\chi^2_4$ = 19.4 and 18.6, respectively). However, a hypothesis of codominant inheritance (i.e., with three distinct geno-

TABLE 1

UNIVARIATE STATISTICS OF DBH ACTIVITY (NMOL/ML PLASMA/HR), COMT ACTIVITY (NMOL/ML RBC/HR), AND MAO ACTIVITY (NMOL/$10^8$ PLATELETS/HR) AFTER AGE AND SEX ADJUSTMENT

| | Mean | SD | Skewness | Kurtosis |
|---|---|---|---|---|
| DBH (No. = 411): | | | | |
| Original units | 616.19 | 458.75 | 1.38* | 2.80* |
| Square-root units | 23.05 | 9.23 | 0.198 | 0.135 |
| Natural log units | 6.05 | 1.11 | −2.20* | 7.81* |
| COMT† (No. = 351): | | | | |
| Original units | 4.42 | 1.77 | 0.621* | 0.658‡ |
| Square-root units | 2.06 | 0.424 | −0.007 | 0.039 |
| Natural log units | 1.40 | 0.437 | −0.693* | 0.774‡ |
| MAO§ (No. = 309): | | | | |
| Original units | 8.61 | 3.73 | 0.662* | 0.945* |
| Square-root units | 2.86 | 0.656 | −0.188 | 0.652‡ |
| Natural log units | 2.04 | 0.536 | −1.91* | 9.13* |

* $P < .001$.

† COMT adjusted to age 35 in females (constant = 3.59, linear age coefficient = .011) and for sex (females: $\mu = 4.39$, $\sigma = 1.69$; males: $\mu = 3.98$, $\sigma = 1.67$).

‡ $P < .01$.

§ MAO adjusted for sex (females: $\mu = 10.15$, $\sigma = 4.62$; males: $\mu = 8.73$, $\sigma = 3.92$).

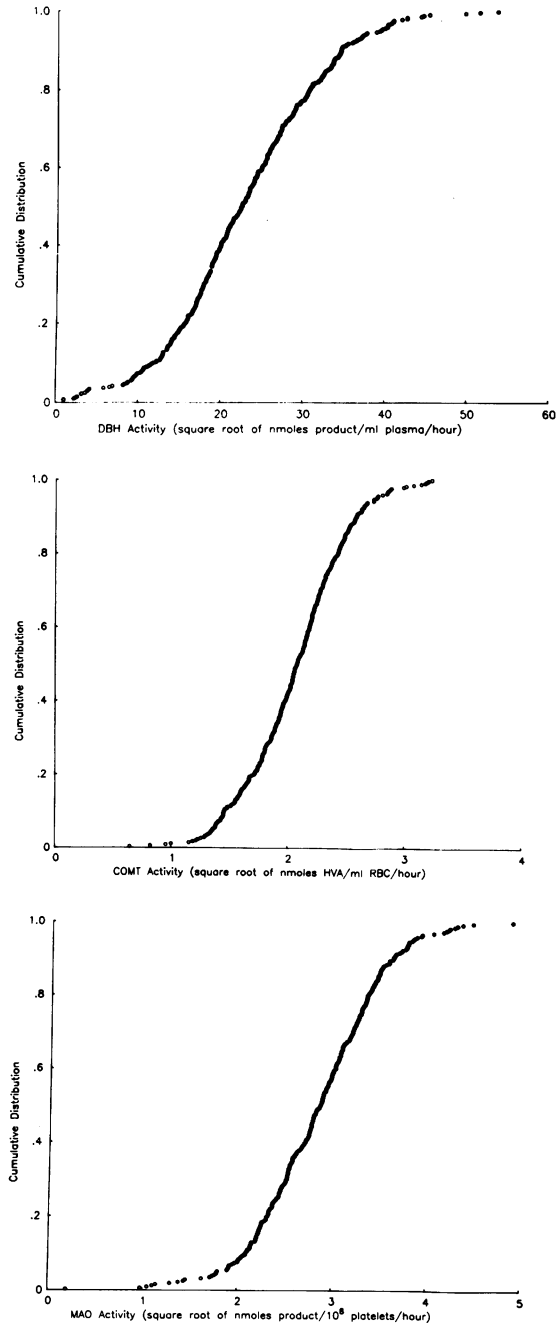


Fig. 1.—Cumulative distributions of age- and sex-adjusted variables: *A* (*top*), square root of DBH activity nmol/ml plasma/hr) in 411 individuals; *B* (*middle*), square root of COMT activity (nmol/ml RBC/hr) in 351 individuals; *C* (*bottom*), square root of MAO activity (nmol/$10^8$ platelets/hr) in 309 individuals.

TABLE 2

MAXIMUM-LIKELIHOOD ESTIMATES FROM SEGREGATION ANALYSIS OF PLASMA DBH (SQUARE ROOT OF NMOL PRODUCT/ML PLASMA/HR)

| | HYPOTHESIS | | | | |
|---|---|---|---|---|---|
| | MENDELIAN | | | | |
| PARAMETER | Recessive | Dominant | Codominant | ENVIRONMENTAL | UNRESTRICTED |
| Transmission probabilities: | | | | | |
| $\tau_{AAA}$ | 1 | 1 | 1 | .357 | 1 |
| $\tau_{AaA}$ | 1/2 | 1/2 | 1/2 | .357 | .453 |
| $\tau_{aaA}$ | 0 | 0 | 0 | .357 | 0 |
| Genotypic proportions: | | | | | |
| $\psi_{AA}$ | .175 | .687 | .259 | .280 | .211 |
| $\psi_{Aa}$ | .487 | .283 | .500 | .498 | .497 |
| $\psi_{aa}$ | .338 | .029 | .241 | .221 | .292 |
| Means: | | | | | |
| $\mu_{AA}$ | 18.488 | 18.138 | 14.010 | 18.284 | 13.851 |
| $\mu_{Aa}$ | 31.670 | 18.138 | 21.717 | 23.796 | 21.631 |
| $\mu_{aa}$ | 31.670 | 31.361 | 33.101 | 34.043 | 33.004 |
| Common SD, $\sigma$ | 6.789 | 6.903 | 6.113 | 7.797 | 6.096 |
| Difference in $\log_e$ likelihood | 9.365 | 9.701 | 0.166 | 44.942 | ... |
| *P*-Value for likelihood ratio test | $< .005$ | $< .005$ | .95 | $< .0005$ | ... |

typic distributions) is *not* rejected ($\chi^2_3 = .32$). A purely "environmental" hypothesis is also strongly rejected ($\chi^2_2 = 89.8$). The major gene under a codominant hypothesis has alleles with approximately equal frequencies ("low" allele frequency = .509) and accounts for 56% of the variance of the sample. However, there is considerable overlap among the three genotypic distributions (fig. 2).

The results for COMT (table 3) are essentially the same as for DBH with codominant inheritance being the only hypothesis not rejected ($\chi^2_3 = .08$). Again, the allele frequencies are approximately equal ("low" allele frequency = .507), and the major gene accounts for 59% of the sample variance. These results are illustrated in figure 3.

The results of segregation analysis of MAO levels are not clear. The environmental hypothesis is rejected ($\chi^2_2 = 13.5$), but all autosomal and X-chromosome hypotheses have similar likelihoods and are not rejected. However, an X-chromosome gene accounts for only 11% of the variance and an autosomal codominant gene accounts only for 25% of the variance, neither of which is an impressive proportion. Thus, the variation in MAO activity levels in this sample may be genetic but we cannot conclude that there is a single major gene involved.

Since distributions of DBH and COMT are compatible with autosomal codominant inheritance, linkage of 19 segregating marker loci to these putative genes was examined using the maximum-likelihood estimates of the genetic parameters (gene frequency, genotypic means, and variance) from segregation analyses. For COMT

TABLE 3

MAXIMUM-LIKELIHOOD ESTIMATES FROM SEGREGATION ANALYSIS OF RBC COMT (SQUARE ROOT OF NMOL HVA/ML RBC/HR)

| | HYPOTHESIS | | | | |
|---|---|---|---|---|---|
| | MENDELIAN | | | | |
| PARAMETER | Recessive | Dominant | Codominant | ENVIRONMENTAL | UNRESTRICTED |
| Transmission probabilities: | | | | | |
| $\tau_{AAA}$ | 1 | 1 | 1 | .477 | 1 |
| $\tau_{AaA}$ | 1/2 | 1/2 | 1/2 | .477 | .497 |
| $\tau_{aaA}$ | 0 | 0 | 0 | .477 | .014 |
| Genotypic proportions: | | | | | |
| $\psi_{AA}$ | .337 | .030 | .257 | .258 | .252 |
| $\psi_{Aa}$ | .487 | .287 | .500 | .500 | .500 |
| $\psi_{aa}$ | .176 | .683 | .243 | .242 | .248 |
| Means: | | | | | |
| $\mu_{AA}$ | 1.644 | 1.648 | 1.549 | 1.716 | 1.546 |
| $\mu_{Aa}$ | 2.247 | 1.648 | 2.075 | 2.074 | 2.073 |
| $\mu_{aa}$ | 2.247 | 2.215 | 2.517 | 2.281 | 2.518 |
| Common SD, $\sigma$ | 0.321 | 0.342 | 0.262 | 0.378 | 0.261 |
| Difference in $\log_e$ likelihood | 8.622 | 11.493 | 0.045 | 29.352 | ... |
| *P*-Value for likelihood ratio test | $< .005$ | $< .0005$ | .99 | $< .0005$ | ... |

(table 5), there are no lod scores above 1, the highest being 0.75 for the *Kell* locus. For DBH (table 6), the lod score at the *ABO* locus is 1.71 at $\theta = 0\%$. The maximum lod score is 1.82 at $\theta$ (males) $= 0\%$ and $\theta$ (females) $= 10\%$. This result itself is suggestive of linkage. Additionally, in the single large family of 95 individuals reported by Elston et al. [3], the lod score for DBH and ABO is 0.61 at $\theta = 0\%$. Combining their data with ours, the total lod score is *2.32* at $\theta = 0\%$, which makes linkage of DBH to the *ABO* locus very promising, although a score of 3 is the generally accepted criterion needed to "prove" linkage [25].

## DISCUSSION

Our data are consistent with the hypothesis that single major autosomal genes control DBH and COMT activity. Our DBH results agree essentially with those of Weinshilboum et al. [2] and Elston et al. [3]. Although they both attribute "low" DBH to a homozygous genotype and do not distinguish the heterozygote phenotype, their results actually suggest codominant inheritance. In the study by Elston, the codominant hypothesis (i.e., allowing for three genotypic distributions) fits the data better than the recessive hypothesis even though neither one is strictly rejected. This is true both in the single large pedigree and in the sample of 22 smaller families that were originally analyzed by Weinshilboum et al. [2]. To compare our DBH data more closely with the analyses of Elston et al. [3], segregation analysis was repeated after taking a $\log_e$ transformation of the data. As before, the codom-

TABLE 4

MAXIMUM-LIKELIHOOD ESTIMATES FROM SEGREGATION ANALYSIS OF PLATELET MAO (SQUARE ROOT OF NMOL/$10^8$ PLATELETS/HR)

| | HYPOTHESIS | | | | | |
|---|---|---|---|---|---|---|
| | MENDELIAN | | | | | |
| PARAMETER | Autosomal recessive | Autosomal dominant | Autosomal codominant | X-L codominant | ENVIRONMENTAL | UNRESTRICTED |
| Transmission probabilities: | | | | | | |
| $\tau_{AAA}$ | 1 | 1 | 1 | 1 | .159 | 1 |
| $\tau_{AaA}$ | 1/2 | 1/2 | 1/2 | 1/2 | .159 | 0 |
| $\tau_{aaA}$ | 0 | 0 | 0 | 0 | .159 | 0 |
| Genotypic proportions: | | | | | | |
| $\psi_{AA}$ | .963 | .469 | 540 | .576 | .047 | .851 |
| $\psi_{Aa}$ | .036 | .432 | .390 | .366 | .340 | .143 |
| $\psi_{aa}$ | .001 | .099 | .070 | .058 | .613 | .006 |
| Means: | | | | | | |
| $\mu_{AA}$ | 2.843 | 2.801 | 2.635 | 2.714 | 2.779 | 2.734 |
| $\mu_{Aa}$ | 3.901 | 2.801 | 3.072 | 3.039 | 2.779 | 3.170 |
| $\mu_{aa}$ | 3.901 | 3.645 | 3.766 | 3.506 | 2.931 | 4.076 |
| Common SD, $\sigma$ | 0.603 | 0.585 | 0.551 | 0.572 | 0.632 | 0.578 |
| Difference in $\log_e$ likelihood | 3.05 | 3.75 | 1.46 | 2.06 | 6.76 | ... |
| *P*-Value for likelihood ratio test | .19 | .11 | .41 | .25 | $< .005$ | ... |

inant hypothesis is not rejected and all other hypotheses (dominant, recessive, and environmental) are strongly rejected. However, the gene frequency of the "low" allele is lower (0.22 in $\log_e$ units vs. 0.51 in square-root units), and the corresponding genotypic means are also lower. The values of the genetic parameters are very close to those estimated by Elston et al. [3]. These results demonstrate some of the limitations of segregation analysis. The mode of transmission does not appear to depend on the transformation used, but there is uncertainty about the exact values of the genetic parameters. The distribution of enzyme activity can be divided into phenotypes in more than one way and still be consistent with single major gene inheritance. Lod scores for linkage of $\log_e$ DBH and *ABO* were also calculated. The maximum lod score is 1.23 at $\theta = 0\%$ as compared to 1.71 for DBH in square-root units. If linkage to *ABO* exists, we can conclude that, at least in our sample, the square-root transformation for DBH is "better" than the $\log_e$ transformation. However, if there is no linkage, then the opposite is true. It is also important to remember that the use of data transformations are sample specific and that there is not necessarily one correct transformation for all studies of the same trait.

In this study, results of segregation analyses of COMT activity are also compatible with those of both Spielman and Weinshilboum [6] about the likely mode of transmission.

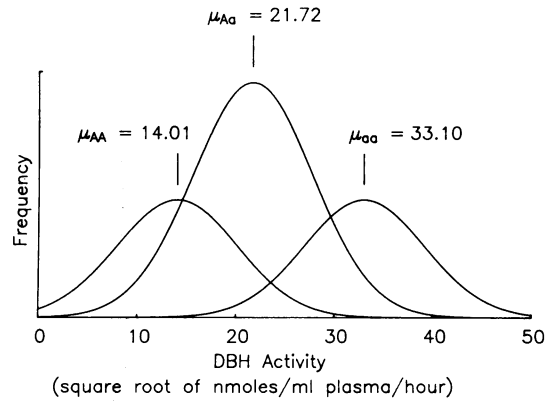


FIG. 2.—Genotypic distributions of DBH activity (square root of nmol/ml plasma/hr) under a codominant hypothesis; frequency of "low" allele = 0.51; variance due to major gene = 56%.

Because of the large amount of overlap among genotypes both for DBH and for COMT, we cannot eliminate the possibility of polygenic transmission in either case. However, the suggestion of linkage of DBH activity variation to *ABO* favors a single major gene affecting activity levels. In the case of MAO, nongenetic transmission is rejected and all single-gene hypotheses have similar likelihoods and are not rejected. Here, polygenic transmission may play a more important role in enzyme activity variation. Analyses of these data with a "mixed model" (major gene and polygene component) would allow single-gene and polygenic hypotheses to be tested under the same general model.

The existence of linkage between a major locus for DBH and the *ABO* locus is promising but needs to be confirmed with more data. The fact that a linkage can be detected in the presence of considerable overlap among genotypes is an important finding. *ABO* is located on chromosome 9 and is loosely linked to the *AK*

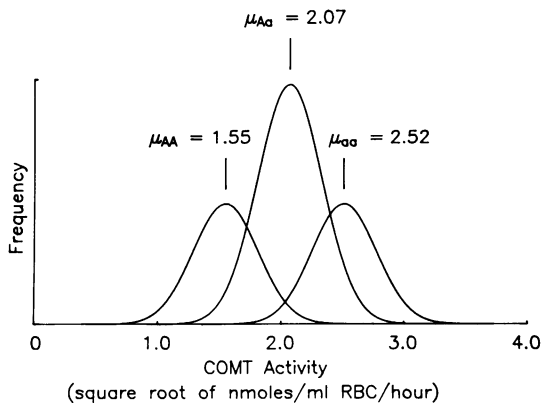


FIG. 3.—Genotypic distributions of COMT activity (square root of nmol/ml RBC/hr) under a codominant hypothesis; frequency of "low" allele = 0.51; variance due to major gene = 59%.

TABLE 5

LOD SCORES BETWEEN COMT AND 19 AUTOSOMAL MARKERS

| MARKER | NO. FAMILIES | RECOMBINATION FRACTION | | | | |
|---|---|---|---|---|---|---|
| | | 0 | .1 | .2 | .3 | .4 |
| ABO | 25 | −8.36 | −3.29 | −1.46 | −0.54 | −0.12 |
| Rh | 27 | −4.77 | −1.38 | −0.37 | −0.03 | 0.01 |
| MNS | 18 | −2.70 | −0.43 | 0.01 | 0.04 | 0.00 |
| P | 10 | −0.96 | −0.28 | −0.08 | −0.01 | 0.00 |
| K | 8 | 0.75 | 0.71 | 0.56 | 0.35 | 0.14 |
| Fy | 27 | −4.68 | −1.47 | −0.43 | −0.05 | 0.02 |
| Jk | 13 | −2.68 | −1.36 | −0.67 | −0.26 | −0.05 |
| Le | 5 | −0.53 | −0.22 | −0.07 | −0.01 | 0.00 |
| Se | 20 | 0.43 | 0.61 | 0.54 | 0.34 | 0.12 |
| AK | 10 | −0.34 | −0.18 | −0.09 | −0.03 | −0.01 |
| ADA | 9 | −0.54 | −0.30 | −0.17 | −0.11 | −0.06 |
| $PGM_1$ | 20 | −0.34 | 0.25 | 0.31 | 0.21 | 0.07 |
| ACP | 20 | −3.09 | −0.82 | −0.18 | 0.02 | 0.04 |
| GALT | 8 | 0.16 | 0.16 | 0.09 | 0.04 | 0.01 |
| GPT | 24 | −6.44 | −1.87 | −0.67 | −0.18 | −0.01 |
| ESD | 14 | −2.14 | −0.53 | −0.13 | −0.00 | 0.02 |
| Gc | 19 | −3.28 | −0.53 | −0.16 | −0.04 | 0.00 |
| Hp | 27 | −3.47 | −1.27 | −0.41 | −0.08 | −0.01 |
| PGD | 2 | −0.13 | −0.07 | −0.03 | −0.01 | 0.00 |

locus [26]. The average recombination fraction between *ABO* and *AK* is 16% ($\theta$ = 8% in males and 26% in females). Both in our data and in the study of Elston et al. [3], lod scores between DBH and *AK* are slightly negative so that existence of linkage cannot be determined. This is not necessarily inconsistent with linkage of

TABLE 6

LOD SCORES BETWEEN DBH AND 19 AUTOSOMAL MARKERS

| MARKER | NO. FAMILIES | RECOMBINATION FRACTION | | | | |
|---|---|---|---|---|---|---|
| | | 0 | .1 | .2 | .3 | .4 |
| ABO | 24 | 1.71 | 1.50 | 1.03 | 0.48 | 0.10 |
| Rh | 26 | −0.36 | 0.26 | 0.39 | 0.29 | 0.10 |
| MNS | 24 | −3.72 | −1.88 | −0.86 | −0.33 | −0.07 |
| P | 9 | −1.05 | −0.51 | −0.24 | −0.09 | −0.02 |
| K | 10 | −1.45 | −0.65 | −0.32 | −0.14 | −0.03 |
| Fy | 26 | −1.48 | −0.62 | −0.18 | −0.00 | 0.04 |
| Jk | 11 | −0.11 | 0.05 | 0.10 | 0.08 | 0.04 |
| Le | 5 | −0.30 | −0.16 | −0.08 | −0.03 | −0.01 |
| Se | 17 | −0.45 | −0.12 | 0.00 | 0.02 | 0.01 |
| AK | 8 | −0.97 | −0.54 | −0.28 | −0.11 | −0.03 |
| ADA | 9 | −1.37 | −0.61 | −0.28 | −0.10 | −0.02 |
| $PGM_1$ | 20 | −1.00 | −0.56 | −0.28 | −0.12 | −0.03 |
| ACP | 20 | −1.97 | −0.93 | −0.43 | −0.18 | −0.06 |
| GALT | 10 | 0.22 | 0.20 | 0.13 | 0.07 | 0.02 |
| GPT | 21 | −1.78 | −0.79 | −0.31 | −0.10 | −0.02 |
| ESD | 11 | 0.22 | 0.35 | 0.31 | 0.19 | 0.07 |
| Gc | 20 | −2.16 | −1.04 | −0.51 | −0.21 | −0.06 |
| Hp | 26 | −2.00 | −0.70 | −0.22 | −0.04 | 0.00 |
| PGD | 3 | −0.04 | −0.03 | −0.01 | −0.005 | −0.001 |

DBH and *ABO* considering the distance between *ABO* and *AK*. (In our own data, the maximum lod score for *ABO* and *AK* in nine families is only 0.37 at $\theta = 20\%$.)

Genetic variants of DBH have been described such as a thermolabile variant [27] and an immunoreactive variant [28]. These variants are independent of enzyme activity but it would be interesting to study the linkage relationships of these DBH genes to marker loci.

This study further confirms that single-locus control of a quantitative trait can be implied by pedigree segregation analysis and then corroborated from biochemical evidence or chromosomal linkage. This is true for COMT, where thermolability was shown to be associated with the "low" activity allele [5], for hypercholesterolemia, where a major gene [29] was shown to be linked to the *C3* locus [30], and for hemochromatosis possibly linked to *HLA* [31]. Here we have shown that even though significant admixture cannot be detected in the distribution of DBH activity, a major gene is detectable from segregation analysis and is further supported by demonstration of possible linkage to the *ABO* locus.

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