Am. J. Hum. Genet. 42:160–166, 1988

Linkage of a Gene Regulating Dopamine-β-Hydroxylase Activity and the ABO Blood Group Locus

A. F. Wilson,* R. C. Elston,* R. M. Siervogel,† and L. D. Tran*

*Department of Biometry and Genetics, Louisiana State University Medical Center, New Orleans; and †Division of Human Biology, Department of Pediatrics, Wright State University School of Medicine

Summary

Previous studies have presented evidence suggesting that levels of dopamine-β-hydroxylase (DBH) activity are controlled by a gene linked to the ABO blood group locus. In this study, linkage analyses in four large families of whites and one family of blacks were performed on the untransformed and on the square root– and natural log–transformed DBH activity. In the families of white individuals, the results of both the sib-pair and lod-score linkage analyses strongly indicate that a gene regulating DBH activity is linked to the ABO blood group locus on chromosome 9q (i.e., lod score 5.88 at a recombination fraction of .0). However, the transformation used has a large effect on the maximum lod score and estimated recombination fraction. This putative gene does not appear to be polymorphic in the family of blacks.

Introduction

Dopamine-β-hydroxylase (DBH) is an enzyme that catalyzes the conversion of dopamine to norepinephrine (Kaufman and Friedman 1965). The biochemical characteristics, assay procedures, and regulation of DBH activity have been described in detail by Weinshilboum (1979). Elston et al. (1979), Goldin et al. (1982), and Asamoah et al. (1987) have reported different modes of inheritance at this locus on the basis of different assay procedures and different overall distributions of DBH activity. Nevertheless, each of these studies has presented evidence suggesting that levels of DBH activity in serum and plasma are controlled by a locus linked to the ABO blood group locus.

Elston et al. (1979) used the methods of Elston and Stewart (1971) to study one family in whom DBH activity was measured for 95 related individuals. Serum DBH activity was determined according to the spectrophotometric assay of Nagatsu and Udenfriend (1972). The data best fitted a mixture of two normal distributions under the natural log transformation of DBH activity, and analyses were performed on this scale. The hypothesis of a recessively inherited allele for low values of DBH activity fitted the data significantly better than did either dominant or environmental hypotheses, and the general Mendelian two-allele/one-locus hypothesis, which we shall call codominant inheritance, did not fit the data significantly better than did a recessive hypothesis. They applied these same methods to data from 22 families studied by Weinshilboum et al. (1975) and obtained nearly identical results. When a recessive model on the natural log scale was assumed, a linkage analysis of DBH activity in the 95-member family resulted in a lod score of 0.61 with the ABO blood group locus at a recombination fraction of .0.

Gershon and Goldin (1981) and Goldin et al. (1982) studied DBH activity measured for 411 individuals in 32 families. Plasma DBH activity was determined using the coupled radiochemical assay (Goldstein et al. 1971; Molinoff et al. 1971) modified according to the method of Gershon and Jonas (1975). The square-root transformation of DBH activity was used to minimize deviations from overall normality. The hypothesis that low values of DBH were either recessively or dominantly inherited was strongly rejected, as was an environmental hy-

Received March 26, 1987; revision received July 14, 1987.

Address for correspondence and reprints: Dr. Alexander F. Wilson, Department of Biometry and Genetics, Louisiana State University Medical Center, 1901 Perdido Street, New Orleans, LA 70112.

0002-9297/88/4201-0021$02.00

pothesis; codominant Mendelian transmission, however, was not rejected. When a codominant model on the square-root scale was assumed, a linkage analysis resulted in a maximum lod score of 1.82 with ABO at a recombination fraction of .10.

Asamoah et al. (1987) studied one family with DBH activity measured for 178 individuals. DBH activity was determined using the procedure of Nagatsu and Udenfriend (1972). Pedigree segregation analysis was performed on untransformed DBH activity and on the square-root and natural log transformations of DBH activity. The natural log transformation was found to maximize the log likelihood of the data after allowing for the Jacobian of the transformation (Wilson et al. 1984). In this family segregation analysis suggested evidence of a codominant gene for DBH activity, one that segregated with a gene frequency similar to that found by Goldin et al. (1982); and linkage analysis that assumed a codominant model on the natural log scale resulted in a lod score of 0.53 with ABO at a recombination fraction of .20.

Material and Methods

As part of a genetic study of hypertension, five families, designated as HGAR 6–10, were each ascertained through one middle-aged man with essential hypertension (i.e., high blood pressure of undefined origin). The five probands were ascertained from the original population screened in the National Heart, Lung and Blood Institute's Multiple Risk Factor Intervention Trial, although the probands were not enrolled in that study. These families have been described in detail in several previous studies (Siervogel et al. 1980, 1984; Wilson et al. 1984). Four of these families, HGAR 6 and 8–10, comprised 923 white individuals, with DBH activity determined for 499 individuals. HGAR 7, a family of 194 black individuals, had DBH activity determined for 54 individuals.

Blood samples were drawn in chilled tubes with no anticoagulant and then centrifuged and stored at −20 C. DBH activity was assayed using the spectrophotometric method of Nagatsu and Udenfriend (1972). Phenotypes were determined for the following 25 polymorphic marker loci: ABO, RH, KEL, MNS, P1, FY, JK, PGD, ADA, AK1, ACP1, PGM1, HBB, GPT, C3, HP, TF, GC, ORM, IGHG (GM), IGK (KM), BF, ESD, GLO1, and LE.

Multiple linear regression, with independence of the measures of DBH activity among individuals being assumed, was used to determine whether significant age, sex, or family effects were present in the data. Analysis of variance was used to test for significant differences in DBH activity among marker phenotypes for each marker system.

Robust sib-pair methods were used to screen the families for evidence of linkage or association (Haseman and Elston 1972; Elston 1984). The sib-pair marker data, together with parental marker data when available, were used to estimate the proportion of genes identical by descent for each sib-pair at each polymorphic marker locus. The squared sib-pair difference in DBH activity was then regressed on this estimated proportion of genes identical by descent at each locus, with all sib-pairs being assumed to be independent (Blackwelder and Elston 1985), to detect possible linkage between a major gene for the quantitative trait and the marker locus.

Pedigree analyses were performed separately within each family on the untransformed DBH activity and on the square-root and natural log transformations of DBH activity, to obtain estimates of the parameters required for lod-score linkage methods. In each case a mixture of three normal distributions was assumed, the means reflecting segregation of two alleles at an autosomal locus and the common variance being due to random environmental influences. In view of the very low correlations between DBH activity and systolic and diastolic blood pressures in these families ($r = -.02$ and $-.07$, respectively), all likelihoods were calculated under the assumption that the pedigrees were randomly sampled.

For the likelihood obtained under a transformation to be comparable to the likelihood of the untransformed data, it is necessary to allow for the Jacobian of the transformation (Box and Cox 1964, 1982). Let $L(x_1, x_2, \ldots, x_n)$ be the likelihood of the data points $x_1, x_2, \ldots, x_n$, the assumption being that they are distributed as mixtures of normal distributions. Then the corresponding likelihood L^*, on the assumption that the transformed values $y_i = f(x_i)$ are distributed as mixtures of normal distributions, is

$$L^*(x_1, \ldots, x_n) = L(y_1, \ldots, y_n) \cdot \prod_{i=1}^{n} \left| \frac{dy_i}{dx_i} \right| .$$

The appropriate log likelihood of the original data points $x_1, x_2, \ldots, x_n$, after undergoing the Box and Cox transformation $y_i = (x_i^p - 1)/p$, is thus

$$\ln L^*(x_1, \ldots, x_n) = \ln L(y_1, \ldots, y_n) + (p - 1) \cdot \sum_{i=1}^{n} \ln x_i ,$$

the second term allowing for the Jacobian of the transformation (Wilson et al. 1984).

To ensure that that final log likelihood was within the numerical range of the computer, it was necessary to analyze (1) scaled original data $y = k_1x$, (2) scaled square root–transformed data $y = (k_2x)^{1/2}$, and (3) scaled natural log–transformed data $y = \ln(k_3x)$. The appropriate log likelihoods of the original data points $x_1, x_2, \ldots, x_n$, under these scaled transformations, are then, respectively,

$$\ln L^*(x_1, \ldots, x_n) = \ln L(y_1, \ldots, y_n) + n \cdot \ln k_1 , \quad (1)$$

$$\ln L^*(x_1, \ldots, x_n) = \ln L(y_1, \ldots, y_n) - n \cdot \ln 2 + \frac{1}{2} n \cdot \ln k_2 - \frac{1}{2} \cdot \sum_{i=1}^{n} \ln x_i , \quad (2)$$

and

$$\ln L^*(x_1, \ldots, x_n) = \ln L(y_1, \ldots, y_n) - \sum_{i=1}^{n} \ln x_i . \quad (3)$$

Lod-score linkage analyses were performed, using the likelihood methods of Elston and Stewart (1971) as detailed by Ott (1974, 1985), between DBH and each of the marker loci for which linkage was indicated by the sib-pair analyses. $\log_{10}$ likelihoods for recombination fractions of .0, .1, .2, .3, and .4 were computed and expressed as lod scores relative to the $\log_{10}$ likelihood for a recombination fraction of .5 (i.e., no linkage).

Results

The mean, SD, skewness, and kurtosis of the distribution of untransformed, square root–transformed, and natural log–transformed DBH activity for all families combined are presented in table 1. Only the square-root transformation is neither significantly skewed nor significantly different from normal with respect to kurtosis. No significant age or sex effects were found when all families were considered as a single group or, allowing for multiple comparisons, when each of the five families was considered separately. However, a significant family difference ($P \leq .0001$) was found either when all families were combined or when only the four families of whites were considered.

When all families were combined and allowance was made for multiple comparisons, untransformed DBH activity was found to be marginally significant among marker phenotypes only at the GC locus (adjusted $P = .04$). When only the four families of white individuals were considered, low values of DBH activity were significantly associated with the "1" allele at the ADA locus (adjusted $P = .0025$). There were no significant differences in DBH activity among phenotypes in the family of blacks.

Table 1

Mean, SD, Skewness, and Kurtosis (Coefficient of Kurtosis − 3) of Untransformed and Square-Root– and Natural Log–transformed DBH Activity for All Families Combined ($N = 553$)

	Mean	SD	Skewness	Kurtosis
DBH	27.75	16.58	0.73**	0.43*
$\sqrt{\text{DBH}}$	5.00	1.66	−0.17	−0.10
ln DBH	3.07	0.87	−1.92**	5.95**

* $.01 < P \leq .05$.
** $P \leq .01$.

Sib-pair analyses were performed on the untransformed DBH activity and on the square-root and natural log transformations of DBH activity. When the P-values were adjusted for multiple comparisons and untransformed activity was analyzed for the four families of white individuals combined (567 sib pairs), significant regressions were found with the ABO ($P \leq .05$) and C3 ($P \leq .01$) loci. In view of the previous reports suggesting linkage to ABO, the unadjusted P-value for ABO ($P \leq .0008$) was also relevant. Similar results were found on regressing the squared sib-pair difference of the square root of DBH activity. When natural log–transformed DBH activities were used, however, a significant result was found for the AK1 locus (adjusted $P \leq .01$) but not for C3. Under the natural log transformation, the unadjusted significance level for ABO was marginal ($P \simeq .05$). No significant regression coefficients were found when the squared sib-pair differences were regressed on the proportion of genes identical by descent for any marker in the family of blacks (33 sib pairs).

The pedigree log likelihoods for DBH activity were calculated under the general Mendelian model, in which a two-allele autosomal locus is assumed to be segregating and giving rise to three separate genotypic means and a common variance. The use of the square-root transformation maximized the log likelihood of the original data in families HGAR 7–9 and was only marginally worse than either the untrans-

Table 2

Parameter Estimates of the Gene Frequency, Genotypic Means, and Common SD on the Indicated Scale

Family	P_A	μ_{AA}	$\mu_{AA'}$	$\mu_{A'A'}$	σ
		A. DBH			
HGAR 6	.831	15.06	32.28	28.40	6.91
HGAR 8	.671	16.64	37.58	61.03	9.57
HGAR 9	.939	24.33	54.77	52.84	13.46
HGAR 10	.804	18.70	36.74	79.14	10.59
		B. $\sqrt{\text{DBH}}$			
HGAR 6	.274	1.39	3.62	5.29	0.69
HGAR 8	.405	2.82	5.29	6.64	1.04
HGAR 9	.385	2.70	4.75	7.11	1.01
HGAR 10	.415	2.62	4.71	5.97	1.08
		C. ln DBH			
HGAR 6	.248	0.41	2.50	3.25	0.39
HGAR 8	.123	−0.55	2.41	3.58	0.43
HGAR 9	.413	1.89	3.32	3.77	0.49
HGAR 10	.115	−0.83	1.88	3.25	0.51

formed DBH activity in HGAR 6 or the natural log–transformed DBH activity in HGAR 10. On the square-root and natural logarithm scales Mendelian transmission under the general model was not rejected in any family, but on the untransformed scale it was rejected in two families. On all three scales dominant and recessive Mendelian models were rejected in at least two families.

Parameter estimates based on the general Mendelian model were assumed for lod-score analysis in the four white families and are presented in table 2. The estimate of the gene frequency on the square-root scale (the best transformation) for the family of blacks is .0, suggesting that the gene for DBH activity is not polymorphic in this family and linkage analysis was not performed. Lod scores for ABO in the four families of white individuals are presented in table 3. The maximum total lod score under the square-root transformation, when male and female recombination fractions are held equal, is 5.88 at a recombination fraction of .0. The maximum total lod scores (and recombination fractions) for the natural log transformation, the best transformation for each family, and the untransformed DBH activity are, respectively, 4.84 (.14), 3.11 (.12), and 1.80 (.17).

The ABO, AK1, and ORM loci are all located on chromosome 9q. Distally from the centromere, the order of the loci is thought to be ORM-AK1-ABO and the estimated recombination fractions are as follows: ORM-AK1 .30, AK1-ABO .18, and ORM-ABO .34 (Meera Khan and Smith 1984). In these data the estimated recombination fraction for ORM-ABO was .37, but the pedigrees were relatively uninformative for ORM-AK1 and AK1-ABO. Table 4 presents total lod scores both under the square-root transformation and under the best transformation for the family for the AK1 and ORM loci. Tight linkage between the DBH locus and AK1 is a possibility, but tight linkage with ORM is ruled out.

For the C3 locus under the untransformed and square root–transformed data and under the best transformation, the maximum total lod scores for each family are <.3. However, the maximum total lod score under the natural log transformation is 1.86 at a recombination fraction of .15.

Discussion

Sib-pair and lod-score linkage analyses of four families of white individuals strongly suggest that a locus involved in the regulation of DBH activity is linked to the ABO blood group locus. These findings are generally consistent regardless of the transformation used in the analysis. Maximum total lod scores under the square-root and natural log transformations and the best transformation for each family are all >3.0 and are higher than the maximum total lod score obtained for untransformed DBH activity (1.80). However, estimates of the recombination fraction are quite variable, ranging from .0 to .17.

The distribution of untransformed DBH activity in these families is highly skewed and leptokurtic, and the transformation used in pedigree analysis has a large effect on the estimate of the gene frequency. These estimates are fairly consistent within transformations, but the differences caused by the transformations are large. The overall mean and standard errors of the estimated gene frequencies for the families of whites are, respectively, .81 ± .11, .37 ± .07, and .22 ± .14 for untransformed DBH activity, square root–transformed DBH activity, and natural log–transformed DBH activity.

Under the square-root transformation the maximum total lod score for DBH activity and ABO, when male and female recombination fractions are held equal, is 5.88 at a recombination fraction of .0. This indicates odds in favor of linkage of 758,578:1. The maximum total lod scores (and recombination fractions) for the AK1 and ORM marker loci are

Table 3

Lod Scores for Families HGAR 6 and 8–10 between ABO and (*a*) Untransformed DBH Activity, (*b*) Square Root– and (c) Natural Log–transformed DBH Activity, and (*d*) Total Lod Scores under the Best Transformation

Family	Recombination Fraction				
	.0	.1	.2	.3	.4
			A. DBH		
HGAR 6[a]	0.414	0.408	0.317	0.185	0.057
HGAR 8[a]	−1.882	−0.030	0.240	0.174	0.041
HGAR 9[a]	2.298	2.004	1.521	0.932	0.309
HGAR 10[a]	−3.816	−0.766	−0.311	−0.137	−0.051
Total	−2.986	1.616	1.767	1.154	0.356
			B. $\sqrt{\text{DBH}}$		
HGAR 6	2.026	1.763	1.274	0.693	0.144
HGAR 8[a]	0.553	0.478	0.362	0.229	0.101
HGAR 9[a]	2.178	1.741	1.268	0.768	0.282
HGAR 10	1.127	1.375	1.157	0.753	0.280
Total	5.884	5.357	4.061	2.443	0.807
			C. ln DBH		
HGAR 6	1.203	1.082	0.765	0.389	0.071
HGAR 8	−9.976	0.573	0.517	0.271	0.092
HGAR 9	1.821	1.485	1.078	0.637	0.219
HGAR 10[a]	−1.787	0.422	0.453	0.270	0.069
Total	−8.739	3.562	2.813	1.567	0.451
		D. Total Lod Scores under the Best Transformation for Each Family			
	1.358	3.049	2.400	1.452	0.509

[a] Indicates the best transformation for each family.

0.528 (.0), and 0.41 (.27), respectively. These results suggest that the gene for DBH activity is tightly linked to the ABO locus, with very weak evidence of linkage to the AK1 locus. Linkage with ORM can be excluded at a recombination fraction of .0.

On the other hand, if the transformation that maximized the log likelihood of each family is used with the corresponding estimates of the gene frequency, genotypic means, and common variance, then the maximum lod scores (and recombination fractions) for DBH activity and the ABO and AK1 loci are, respectively, 3.11 (.12), and 0.81 (.0). Linkage with ORM is excluded at recombination fractions from .0 to .1. These results suggest that the gene involved in the regulation of DBH activity is linked to ABO at a recombination fraction of ~.12, with very weak evidence of a tight linkage to AK1. Although these recombination fractions are in closer agreement with the published recombination fractions for ABO and AK1 (.18) than are the recombination fractions estimated under the square-root transformation, the gene frequencies of the low-value allele for DBH activity, under the best transformation for each family, are quite variable (.81, .41, .39, and .12).

Obviously, care must be taken in combining, over families, lod scores of quantitative traits with different transformations, since these transformations can result in different "genotypic" classifications of individuals within a family. Depending on the transformation used, large differences can occur in lod scores within a family, particularly at low recombination fractions. These differences reflect the different probabilistic genotypic classifications of individuals involved in matings informative for crossing-over. Other factors involved include the large differences in estimates of the gene frequencies and the relatively high proportion of individuals with unknown phenotypes.

Table 4

Total Lod Scores for Families HGAR 6 and 8–10 between DBH Activity and the AK1 and ORM Marker Loci under (*a*) the Square-Root Transformation and (*b*) the Best Transformation for Each Family

Marker	Recombination Fraction				
	.0	.1	.2	.3	.4
A. Total Lod Scores under the Square-Root Transformation					
AK1	0.528	0.437	0.316	0.177	0.053
ORM	−4.953	−0.555	0.324	0.397	0.170
B. Total Lod Scores under the Best Transformation for Each Family					
AK1	0.807	0.636	0.439	0.235	0.070
ORM	−13.228	−2.138	−0.707	−0.187	−0.034

The assumed mode of inheritance and transformation of DBH activity are presented in table 5 for each of the three previous studies. Although it is perhaps undesirable to combine lod scores from studies differing so much in details of the estimated mode of inheritance, it is difficult to believe that the consistently positive lod scores are spurious. Furthermore, differences in the mode of inheritance are to be expected under scaling differences resulting from the use of different transformations. When the results from the previous studies are combined with the results from the present study (under the square-root transformation), the maximum total lod score for DBH activity and ABO is 8.37 at a recombination fraction of .0. Therefore, when the results of this linkage analysis are combined with the previous reports of Elston et al. (1979), Goldin et al. (1982), and Asamoah et al. (1987), there can be little doubt about the existence of a linkage relationship between DBH and the ABO blood group locus.

Finally, it is of interest to compare the power of the lod-score and sib-pair methods to detect the DBH-ABO linkage in these data. This can be done by converting the maximum lod score to a χ^2-statistic with 1 df, multiplying it by $2 \cdot \log_e 10$, and converting this to a (one-sided) *P*-value. This *P*-value is then comparable to the *P*-value for the sib-pair analysis before the latter is adjusted for multiple comparisons. For untransformed and square root– and natural log–transformed DBH activity, the lod-score *P*-values are, respectively, 2×10^{-3}, $<5 \times 10^{-7}$, and $<5 \times 10^{-6}$; and the sib-pair *P*-values are, respectively, 8×10^{-4}, 9×10^{-4}, and 5×10^{-2}. Thus, although the lod-score method is more powerful when what we assume to be an appropriate scale of measurement is used, the sib-pair method is less sensitive to the

Table 5

Reported Lod Scores between the ABO Blood Group Locus and DBH Activity from Three Previous Studies

Study	Hypothesis	Scale	Recombination Fraction				
			.0	.1	.2	.3	.4
Elston et al. 1979	Recessive	ln DBH	0.61	0.50	0.34	0.18	0.04
Goldin et al. 1982	Codominant	$\sqrt{\text{DBH}}$	1.71	1.50	1.03	0.48	0.10
Asamoah et al. 1987	Codominant	ln DBH	0.17	0.50	0.53	0.41	0.22
A. Total over Previous Studies, plus Scores under the Square-Root Transformation from the Present Study							
			8.37	7.86	5.96	3.51	1.17
B. Total over Previous Studies, plus Scores under the Best Transformation for Each Family from the Present Study							
			3.85	5.55	4.30	2.52	0.87

scale of measurement, reflecting its greater general robustness.

Acknowledgments

This study was supported in part by research grants HL28522 and HL23194 from the National Heart, Lung and Blood Institute and grants GM28356 and GM28157 from the National Institute of General Medical Sciences.

References

Asamoah, A., A. F. Wilson, R. C. Elston, E. Dalferes, Jr., and G. S. Berenson. 1987. Segregation and linkage analyses of dopamine-β-hydroxylase activity in a six-generation pedigree. Am. J. Med. Genet. 27:613–621.

Blackwelder, W. C., and R. C. Elston. 1985. A comparison of sib-pair linkage tests for disease susceptibility loci. Genet. Epidemiol. 2:85–97.

Box, G. E. P., and D. R. Cox. 1964. An analysis of transformations. J. R. Stat. Soc. [B] 26:211–252.

———. 1982. An analysis of transformations revisited, rebutted. J. Am. Stat. Assoc. 77:209–210.

Elston, R. C. 1984. Genetic Analysis Workshop II: Sib-pair screening tests for linkage. Genet. Epidemiol. 1:175–178.

Elston, R. C., K. K. Namboodiri, and C. G. Hames. 1979. Segregation and linkage analyses of dopamine-β-hydroxylase activity. Hum. Hered. 29:284–292.

Elston, R. C., and J. Stewart. 1971. A general model for the genetic analysis of pedigree data. Hum. Hered. 21:523–542.

Gershon, E. S., and L. R. Goldin. 1981. 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. Am. J. Hum. Genet. (Suppl.): 136A.

Gershon, E. S., and W. Jonas. 1975. A clinical and genetic study of erythrocyte soluble catechol-o-methyltransferase activity in primary affective disorder. Arch. Gen. Psychiatry 32:1351–1356.

Goldin, L. R., E. S. Gershon, C. R. Lake, D. L. Murphy, M. McGinniss, and R. S. Sparkes. 1982. Segregation and linkage studies of plasma dopamine-beta-hydroxylase (DBH), erythrocyte catechol-o-methyltransferase (COMT), platelet monoamine oxidase (MAO): possible linkage between the ABO locus and a gene controlling DBH activity. Am. J. Hum. Genet. 34:250–262.

Goldstein, M., L. S. Freedman, and M. Bonnary. 1971. An assay for dopamine-β-hydroxylase activity in tissues and serum. Experientia 27:632–633.

Haseman, J. K., and R. C. Elston. 1972. The investigation of linkage between a quantitative trait and a marker locus. Behav. Genet. 2:3–19.

Kaufman, S., and S. Friedman. 1965. Dopamine-beta-hydroxylase. Pharmacol. Rev. 17:71–100.

Meera Khan, P., and M. Smith. 1984. Report of the committee on the genetic constitution of chromosomes 7, 8 and 9. Human Gene Mapping 7(1984): Seventh International Workshop on Human Gene Mapping. Cytogenet. Cell Genet. 37:71–102.

Molinoff, P. B., R. Weinshilboum, and J. Axelrod. 1971. A sensitive enzymatic assay for dopamine-β-hydroxylase. J. Pharmacol. Exp. Ther. 178:425–431.

Nagatsu, T., and S. Udenfriend. 1972. Photometric assay of dopamine-β-hydroxylase activity in human blood. Clin. Chem. 18:980–983.

Ott, J. 1974. Estimation of the recombination fraction in human pedigrees: efficient computation of the likelihood for human linkage studies. Am. J. Hum. Genet. 26:588–597.

———. 1985. Analysis of human genetic linkage. Johns Hopkins University Press, Baltimore.

Siervogel, R. M., M. A. B. Frey, P. Kezdi, A. F. Roche, and E. Stanley. 1980. Blood pressure, electrolytes and body size: their relationship in young relatives of men with essential hypertension. Hypertension 2 (Suppl. 1): 83–92.

Siervogel, R. M., R. Weinshilboum, A. F. Wilson, and R. C. Elston. 1984. Major gene model for the inheritance of catechol-o-methyltransferase activity in five large families. Am. J. Med. Genet. 19:315–323.

Weinshilboum, R. M. 1979. Serum dopamine-β-hydroxylase. Pharmacol. Rev. 30:133–166.

Weinshilboum, R. M., H. G. Schrott, R. A. Raymond, W. H. Weidman, and L. R. Elveback. 1975. Inheritance of very low serum dopamine-β-hydroxylase activity. Am. J. Hum. Genet. 27:573–585.

Wilson, A. F., R. C. Elston, R. M. Siervogel, R. Weinshilboum, and L. J. Ward. 1984. Linkage relationships between a major gene for the inheritance of catechol-o-methyltransferase activity and 25 polymorphic marker systems. Am. J. Med. Genet. 19:525–532.