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Inheritance of Low Erythrocyte Catechol-*O*-Methyltransferase Activity in Man

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INTRODUCTION

Catechol-*O*-methyltransferase (EC.2.1.1.6, COMT) is one of the two enzymes that catalyze the metabolism of the catecholamines: norepinephrine, epinephrine, and dopamine [1]. COMT activity is found in many tissues including the red blood cell (RBC) [1, 2]. In experimental animals RBC COMT is biochemically and immunochemically similar to the enzyme in other tissues [2–4]. The recent observation that both partially purified rat liver COMT and human RBC COMT are inhibited by calcium has made it possible to develop a new and more accurate procedure for the measurement of erythrocyte COMT activity [5, 6]. When this procedure was used to determine RBC COMT activity in human blood samples, a highly significant correlation of the enzyme activity in blood from siblings was found, and the distribution of values of human erythrocyte COMT activity was bimodal [7]. Because of the possibility that heredity plays a role in the determination of human RBC COMT activity, we studied the COMT activity in blood samples from a large, randomly selected population of adolescents and adults and from first-degree relatives of individuals with low erythrocyte COMT activity.

METHODS

Catechol-O-Methyltransferase Assay Procedure

COMT activity was measured by the method of Raymond and Weinshilboum as previously described [6]. The procedure is based on the conversion of 3,4-dihydroxybenzoic acid to 4-hydroxy-3-methoxybenzoic acid by COMT in the presence of ^{14}C-S-adenosyl-1-methionine, a methyl donor, and of magnesium ion, an activator of COMT. 3,4-Dihydroxybenzoic acid yields the same relative COMT activity in lysates of human erythrocytes as does a "natural" substrate such as norepinephrine, but it offers several technical advantages over norepinephrine as a substrate [6]. After 45 min of incubation at 37°C, the reaction is terminated by the addition of HCl, and organic solvent extraction is carried out. An aliquot of the organic solvent is removed after centrifugation, and its radioactivity is measured in a liquid scintillation counter. All blood lysates are exposed to the solid chelating resin, Chelex-100, to remove calcium [6]. Blank samples consist of lysate to which no substrate is added. Heat inactivated samples are not

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appropriate blanks because of an enzymatic activity in erythrocytes that results in the formation of radioactively-labeled methanol in the presence of ^{14}C-S-adenosyl-l-methionine [2]. Hematocrit values of all blood samples are obtained, and the enzyme activity is expressed as nmol of 4-hydroxy-3-methoxybenzoic acid formed per ml of packed red blood cells per hour. The individual who carried out the assay procedure for this study was unaware of the identities of the subjects.

Population Sample

Blood was obtained by venipuncture from 373 subjects (372 whites and one black) age 16–18 at school in the morning after an overnight fast. Both the parents and the adolescent subjects gave written consent before blood samples were obtained. Blood samples were also obtained from 262 white, unrelated adult blood donors at the Mayo Clinic, Rochester, Minnesota. None of these subjects were taking medication at the time that the blood samples were withdrawn.

Selection of Families for Genetic Analysis

The first 62 consecutive families in which at least one child with low RBC COMT activity (< 8 U) had been identified were asked to participate in the family study; fourteen families refused to participate. Family histories were obtained from participating families by genetic case workers, and pedigrees were constructed. Four families (nos. 11936, 26544, 28840, and 41082, see Appendix) had more than one child with "low" COMT activity discovered during the screening study at school. The proband for each family was the oldest sibling in the family with an erythrocyte COMT activity of less than 8 U who was discovered in the screening studies. Blood was obtained from 201 of 221 living first-degree relatives of probands (91%) in the 48 families that took part in the study. Written informed consent was obtained from all participants.*

RESULTS

Population Studies

The frequency distribution of erythrocyte COMT activity values in 577 blood samples from adult blood donors and high school students is shown in figure 1. Since blood from siblings is often obtained during school sampling, the COMT activity of one randomly chosen sibling was included with these data. Therefore, the figure shows the results from 315 subjects aged 16–18 and 262 adult blood donors. We have reported previously that the distribution of RBC COMT activity in blood from randomly selected populations aged 13–15 and 16–18 is nonunimodal with a nadir at approximately 8 U of enzyme activity [7]. For this study, data from the adult blood donor population was pooled with data from high school age subjects (16–18) to enlarge the sample. The distribution in figure 1 also appears to be nonunimodal with a nadir at approximately 8 U of activity. This nadir is present in the data for the entire group as well as in the separate distributions for male and female subjects. Although the distribution may be multimodal rather than bimodal, the only subgroups which are possible to distinguish are those made up of subjects whose activities are greater than and less than 8 U.

We have previously demonstrated by the addition of purified rat liver COMT to blood samples with low and high enzyme activity that the distribution shown in figure 1

* All data were recorded on computer punch cards and stored on magnetic tape for further analysis on a Control Data 3500 computer.

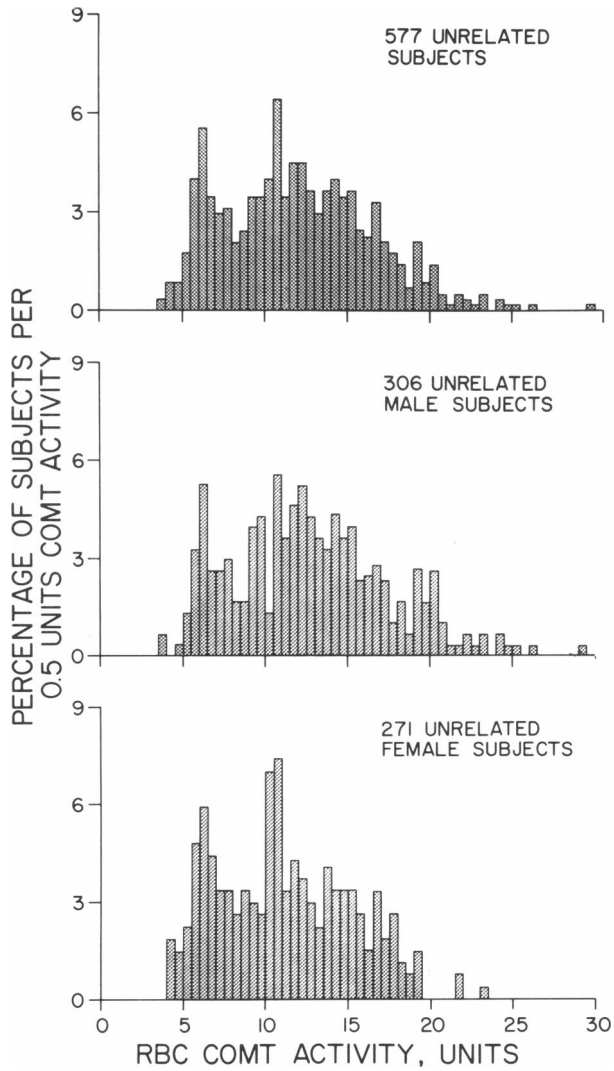

FIG. 1.—Frequency distributions of RBC COMT activity in successive 0.5 U increments. Population includes 262 unrelated adult blood donors and 315 unrelated high school students age 16–18. Separate distributions for male and female subjects are also shown.

is not due to the presence of different levels of either endogenous inhibitors or activators of the enzyme [7]. The mean RBC COMT activity in blood samples from the population depicted in figure 1 is 11.98 ± 4.48 (mean ± standard deviation) with an average value for male subjects of 12.74 ± 4.71 and for female subjects of 11.2 ± 4.06. Of the total population, 22.9% had RBC COMT activity of less than 8 U. Because of the apparent bimodal distribution of human RBC COMT activity and because of the significant sibling-sibling correlation of this enzyme activity [7], detailed studies of the enzyme activity in blood obtained from family members of

individuals with "low" RBC COMT activity (< 8 U) were performed. The decision to use 8 U as the point of separation between subjects with "low" and "high" enzyme activity was made before family studies were performed.

Family Studies

The RBC COMT activity, age, and sex of each member of the 48 families studied are listed in the Appendix. Henceforth, a subject with RBC COMT activity of less than 8 U will be referred to as having "low activity." Misclassification of some subjects in both directions was anticipated because of overlap of the distributions for the postulated low and high activity subgroups. Both parents had erythrocyte COMT activity of 8 U or greater in 16 families (33.3%); only one parent had low activity in 27 families (56.3%), and both parents had low activity in five families (10.4%). Among the 91 low activity offspring in these 48 families, there were 47 females and 44 males. If low RBC COMT activity is inherited by a single gene of large effect, the approximately equal representation of low activity males and females makes sex-linked inheritance extremely unlikely. The relatively large number of families (one-third) in which a lack of vertical transmission is present makes dominant inheritance less likely, and although low activity parents occur frequently in the families studied, the mating frequencies found are not incompatible with autosomal recessive inheritance (see below).

Segregation analysis. The possibility of autosomal recessive inheritance of low RBC COMT activity was tested by several different methods of segregation analysis. The "direct a priori" method, a method that assumes complete ascertainment [8], gave segregation parameters of 0.287 for matings of two high activity parents and 0.554 for matings with one low activity parent. When a method was used that is based on the assumption of very incomplete ascertainment or "single ascertainment" [8], values of 0.231 ± 0.067 (± SE) and 0.464 ± 0.067 for the mating types described above were calculated. As expected, the estimates based on the assumption of complete ascertainment are slightly higher than the expected values of 0.25 and 0.50, respectively, and those calculated on the basis of the assumption of single ascertainment are slightly lower than the expected values [8]. When the "Weinberg proband method," a method of segregation analysis that does not assume complete ascertainment [9], was used, a corrected value, $\hat{P}$, of 0.249 ± 0.069 (SE) for matings of two high activity parents was calculated. These results are compatible with the autosomal recessive inheritance of an allele for low RBC COMT.

RBC COMT activity in heterozygotes. If the inheritance of low erythrocyte COMT is by an autosomal recessive mechanism, then the high activity parents in the study are heterozygotes for the recessive allele. The mean and standard deviation of RBC COMT activity in blood from the 59 high activity parents of low activity children were 13.25 ± 2.96, and those of the adult subjects in the blood donor population who had COMT activity in blood from the 59 high activity parents of low activity children were 13.25 significantly different ($P > .10$). Individuals in the blood donor population with low COMT activity were excluded from consideration to make the "control" group comparable to the group of parents of probands. One reason why it might be difficult to demonstrate a "dose effect" for the allele for low RBC COMT even if such a dose

effect exists is the high gene frequency of the allele for low COMT. If approximately 23% of a randomly selected population is homozygous for the allele, and if the possibility of consanguinity is neglected, the gene frequency of the allele for low COMT (C_L) is approximately .48 ($\sqrt{.23}$). A population breeding randomly with regard to this allele would be expected to consist of 23% homozygotes for C_L and 50% heterozygotes (2 × .48 × .52). Therefore, if homozygotes for C_L are excluded, 65% (.50/.77) of a randomly selected population would be heterozygotes, and it might be difficult to demonstrate differences in the RBC COMT activity in such a "control" group as compared with a population composed of obligate heterozygotes.

Figure 2 shows the frequency distribution histogram for the 103 siblings of the probands included in this study. It is significant that this distribution also shows a nadir at about 8 U of enzyme activity. The siblings of probands of matings of low with high activity parents are another group of obligate heterozygotes for the allele for low RBC COMT activity. The COMT activity in blood samples from the 30 high activity siblings of probands from matings of low with high activity parents was 12.45 ± 2.26 (mean ± standard deviation). The average COMT activity for the 26 low activity siblings of probands from these matings was 6.5 ± 0.97 (mean ± standard deviation). The RBC COMT activity in blood from 234 randomly selected subjects ages 16–18 with enzyme activity greater than 8 U was 13.32 ± 3.39. This value was not significantly different from values of COMT activity in blood of high activity siblings of probands from matings of low with high activity parents ($.10 > P > .05$). Overall, the percentages of low activity siblings of probands in families in which neither parent was low, in which one parent was low, and in which both parents were low were 21%, 47%, and 100%, respectively.

Mating frequencies. The majority of matings in the families studied were of low with high activity individuals. This finding is compatible with the recessive hypothesis.

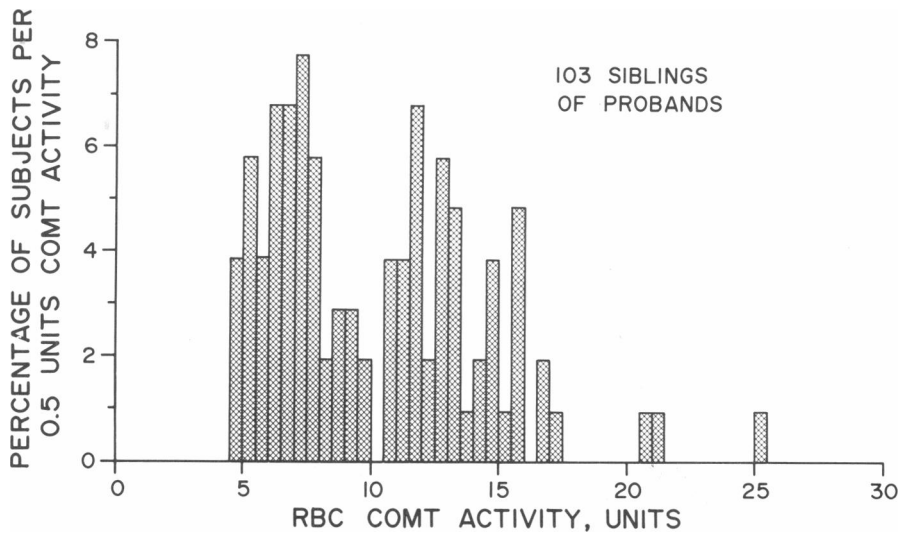

FIG. 2.—Frequency distribution of RBC COMT activity in blood from 103 siblings of probands.

If low RBC COMT activity in man is inherited in an autosomal recessive fashion and if approximate values for the gene frequency of the allele involved (C_L) are calculated, then crude estimates of the expected frequencies of matings that might result in low activity individuals can be made. Since the actual frequencies will be biased by the method of ascertainment, this bias must also be taken into account. For example, for families with three children it would be expected that the percentages of matings of two low activity individuals, one low activity with a high activity individual, and two high activity parents would be 13.1%, 54.1%, and 32.8%, respectively. For families with four children the values would be 11.9%, 52.7%, and 35.4%. The actual percentages found in this study were 10.4%, 56.3%, and 33.3%, respectively. The relative frequency of vertical transmission in the pedigrees of the families included in this study is compatible with recessive inheritance.

DISCUSSION

Catechol-*O*-methyltransferase is one of the major enzymes involved in the metabolic inactivation of catecholamines [1]. Other investigators have measured the activity of COMT in blood samples from subjects with various neurologic and psychiatric diseases [10, 11]. To interpret the results of these studies correctly, it is essential to take the important role of familial factors in the determination of human RBC COMT activity into account. A significant sibling-sibling correlation of erythrocyte COMT value [7, 12] and the presence of an apparently bimodal distribution of RBC COMT activity in human blood have raised the possibility that heritability plays an important role in the determination of this enzyme activity [7]. Evidence from family studies presented here is compatible with the existence of an allele for low RBC COMT activity (C_L) inherited in an autosomal recessive fashion. Although polygenic inheritance of low erythrocyte COMT cannot be excluded, the evidence supports monogenic inheritance by an autosomal recessive mechanism. The results of segregation analysis are compatible with recessive inheritance. The frequency distribution of RBC enzyme activity among siblings of low activity children suggest at least two populations of values with one mode for low (< 8 U) and one for subjects with enzyme values similar to those of high activity individuals. Finally, the frequency of various types of matings discovered in the course of the family studies reported here are compatible with the recessive hypothesis. It is not surprising that earlier studies of COMT activity in human erythrocytes did not report a bimodal distribution [10, 12], since these studies were carried out before it was known that COMT is inhibited by calcium [5]. Therefore, no effort was made to remove calcium from the reaction system in these earlier studies; so the enzyme activities measured were all inhibited to a greater or lesser degree. The development of a new and more accurate assay procedure in which one step involves the removal of calcium made our studies possible [6]. The results described here apply only to soluble COMT and not to the small amount of COMT activity that is membrane bound [4].

Partially because of the relatively high gene frequency of the allele for low RBC COMT, it is difficult to ascertain whether a dose effect for this allele exists. This possibility cannot be excluded, but our data do not give any clear evidence for such a dose effect. In addition, the model described here does not exclude the possibility that

other familial factors, due either to genetic or environmental influences might also affect RBC COMT activity.

It might be anticipated that erythrocyte COMT activity would reflect the activity of this important enzyme in other tissues such as the liver, heart, and brain. In experimental animals red blood cell COMT activity has been shown to be biochemically similar to the enzyme in other tissues [2, 3], and in inbred strains of rats with markedly different hepatic COMT activity, erythrocyte COMT activity reflects the enzyme activity present in the liver (Weinshilboum, unpublished observation). Caution must be exercised, however, in the extrapolation of these findings to the situation in man.

The results of this study raise the possibility of significant genetically determined individual differences in enzymatic *O*-methylation of catecholamines in man. Heredity plays an important role in the determination of the activity of the other major catecholamine degradative enzyme, monoamine oxidase, in human platelets [13, 14]. The serum activity of dopamine-β-hydroxylase, a catecholamine biosynthetic enzyme, is largely controlled by inheritance [15]. Increased understanding of genetic differences in the biosynthesis and degradation of catecholamines in man may eventually make it possible to better characterize the status and function of the sympathetic nervous system in individual human subjects.

SUMMARY

Catechol-*O*-methyltransferase activity was measured in blood obtained from 373 randomly selected subjects aged 16–18, 262 consecutive adult blood donors, and 201 first-degree relatives of subjects with RBC COMT activity of less than 8 U. The distribution of RBC COMT activity in a randomly selected population was apparently bimodal with a nadir at approximately 8 U. Of a randomly selected population, 23% had low RBC COMT activity (< 8 U). Because of previous reports of a significant sibling-sibling correlation of RBC COMT activity and because of the presence of a subgroup of subjects with low enzyme activity, RBC COMT activity was measured in blood from first-degree relatives of probands with low erythrocyte enzyme activity in 48 families. The results of segregation analyses of the data were compatible with autosomal recessive inheritance of an allele for low RBC COMT activity. RBC COMT in blood samples from siblings of probands in these families also showed an apparent bimodal distribution.

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APPENDIX

ERYTHROCYTE CATECHOL-*O*-METHYLTRANSFERASE

Family No.	Sex	Age	Value	Family No.	Sex	Age	Value
938:							
I-1	M	44	6.6	II-1	F	21	5.3
I-2	F	42	8.9	II-2	M	18	5.9*
II-1	M	18	11.0				
II-2	F	17	5.9*	1920:			
II-3	M	15	7.2	I-1	M	46	13.7
II-4	M	13	10.7	I-2	F	43	12.7
II-5	M	5	13.2	II-1	F	22	11.8
				II-2	M	...	NA†
960:				II-3	M	19	14.0*
I-1	M	42	13.9	II-4	F	16	5.9*
I-2	F	51	7.0				
II-1	M	...	NA†	3398:			
II-2	M	18	7.2	I-1	M	46	4.8
II-3	M	17	5.5*	I-2	F	46	8.4
II-4	F	15	5.2	II-1	F	...	NA†
II-5	M	13	15.1	II-2	F	...	NA†
II-6	F	10	6.0	II-3	F	19	6.2*
				II-4	M	15	10.7
1376:							
I-1	M	49	6.4	4016:			
I-2	F	44	6.4	I-1	M	50	13.7

Family No.	Sex	Age	Value
I-2	F	49	9.7
II-1	M	...	NA†
II-2	F	20	8.5
II-3	M	18	6.9*
II-4	M	15	8.7
II-5	M	12	11.1
5683:			
I-1	M	44	5.0
I-2	F	46	6.6
II-1	M	17	4.5*
II-2	F	13	5.2
II-3	M	11	5.9
II-4	M	5	6.6
6760:			
I-1	M	38	7.9
I-2	F	38	15.4
II-1	F	18	12.7*
II-2	F	16	5.6*
II-3	F	15	12.5
II-4	F	14	8.7
II-5	M	9	14.5
II-6	M	8	6.4
7486:			
I-1	M	43	4.9
I-2	F	45	12.1
II-1	F	17	6.9*
II-2	F	15	6.1
II-3	F	...	NA†
8590:			
I-1	M	44	14.8
I-2	F	43	5.8
II-1	M	17	13.1*
II-2	F	16	7.0*
II-3	F	14	12.9
II-4	F	10	15.6
II-5	M	9	16.6
II-6	M	6	7.7
9173:			
I-1	M	42	7.0
I-2	F	42	10.1
II-1	F	21	11.1
II-2	M	19	5.7*
II-3	F	11	5.5
11056:			
I-1	M	40	15.7
I-2	F	40	7.8
II-1	F	...	NA†
II-2	F	...	NA†
II-3	M	17	6.4*
11287:			
I-1	M	42	15.5
I-2	F	43	6.3
II-1	M	18	6.0*
11936:			
I-1	M	43	16.9
I-2	F	42	6.7
II-1	F	23	13.4
II-2	M	19	7.0*
II-3	M	17	6.0*
II-4	M	15	14.6
II-5	F	11	7.7
15409:			
I-1	M	49	23.4
I-2	F	47	3.9
II-1	M	19	9.2*
II-2	F	17	6.0*
16698:			
I-1	M	45	14.3
I-2	F	42	8.3
II-1	M	...	NA†
II-2	F	17	5.1*
II-3	F	15	7.4
17410:			
I-1	M	39	16.3
I-2	F	36	6.8
II-1	F	16	6.2*
II-2	F	15	6.7
II-3	M	14	14.1
II-4	M	9	7.5
17880:			
I-1	M	56	5.5
I-2	F	50	5.9
II-1	F	18	4.2*
19066:			
I-1	M	53	13.4
I-2	F	47	7.5
II-1	F	20	6.9
II-2	F	18	5.9*
II-3	F	10	13.9
19504:			
I-1	M	54	13.7
I-2	F	50	13.1
II-1	F	23	15.6
II-2	F	18	4.3*
19624:			
I-1	M	58	11.0
I-2	F	52	13.0
II-1	M	...	NA†
II-2	F	...	NA†
II-3	F	17	6.8*
19963:			
I-1	M	50	7.9
I-2	F	48	13.5
II-1	M	24	7.0
II-2	M	22	14.6
II-3	M	19	6.3*
21186:			
I-1	M	56	15.0
I-2	F	56	16.9

Family No.	Sex	Age	Value
II-1	M	...	NA†
II-2	F	18	5.4*
23694:			
I-1	M	46	9.7
I-2	F	46	5.0
II-1	M	22	8.2
II-2	F	20	7.2
II-3	F	17	4.9*
23709:			
I-1	M	39	14.9
I-2	F	39	7.5
II-1	F	16	5.8*
II-2	M	14	9.1
25181:			
I-1	M	46	9.2
I-2	F	44	13.8
II-1	M	19	8.3
II-2	F	18	6.1*
II-3	M	16	15.7
26544:			
I-1	M	43	8.6
I-2	F	41	6.5
II-1	M	...	NA†
II-2	F	18	6.3*
II-3	M	16	5.5*
II-4	M	14	7.6
27872:			
I-1	M	50	11.5
I-2	F	43	13.5
II-1	F	19	9.4*
II-2	M	17	6.2*
II-3	M	15	11.6
28144:			
I-1	M	50	2.3
I-2	F	47	8.8
II-1	F	21	6.3
II-2	M	18	5.9*
30104:			
I-1	M	46	16.6
I-2	F	40	12.1
II-1	M	21	19.0
II-2	F	19	19.3
II-3	M	18	6.8*
II-4	M	12	21.4
II-5	M	6	13.0
II-6	F	6	20.8
30812:			
I-1	M	52	11.0
I-2	F	51	12.7
II-1	M	...	NA†
II-2	M	18	6.1*
II-3	F	17	11.7
34543:			
I-1	M	57	8.5
I-2	F	53	5.9
II-1	M	23	7.4
II-2	F	...	NA†
II-3	M	19	6.9*
II-4	F	16	NA†
II-5	M	11	4.9
34549:			
I-1	M	42	16.0
I-2	F	41	14.3
II-1	F	18	4.0*
II-2	F	17	9.9*
II-3	M	13	25.1
II-4	F	11	7.5
II-5	F	7	17.0
II-6	M	5	18.7
37810:			
I-1	M	46	13.8
I-2	F	40	11.5
II-1	F	23	11.7
II-2	F	21	9.8
II-3	F	19	6.9
II-4	F	18	6.7*
II-5	F	16	11.8*
II-6	M	15	12.2
II-7	M	14	15.7
38840:			
I-1	M	50	13.1
I-2	F	45	14.6
II-1	M	...	NA†
II-2	F	...	NA†
II-3	M	20	2.6*
II-4	M	17	6.6*
II-5	F	12	6.9
II-6	M	7	14.8
II-7	M	2	15.9
39279:			
I-1	M	44	12.8
I-2	F	36	4.9
II-1	F	17	5.9*
II-2	M	16	11.5*
II-3	F	13	5.2
II-4	M	11	12.8
II-5	M	8	12.8
II-6	F	7	4.7
39968:			
I-1	M	48	16.2
I-2	F	45	13.8
II-1	F	17	6.6*
41020:			
I-1	M	50	9.5
I-2	F	47	4.7
II-1	F	...	NA†
II-2	M	...	NA†
II-3	M	18	3.5*
II-4	M	6	5.2
41056:			

Family No.	Sex	Age	Value
I-1	M	45	13.9
I-2	F	35	8.9
II-1	F	16	6.1*
II-2	F	15	5.5
II-3	F	12	12.8
II-4	M	8	4.6
II-5	M	5	13.4
41082:			
I-1	M	42	10.2
I-2	F	41	6.9
II-1	M	18	7.5*
II-2	F	18	7.2*
43375:			
I-1	M	46	13.0
I-2	F	44	12.5
II-1	M	17	5.5*
II-2	M	15	4.6
II-3	F	12	12.0
II-4	M	6	5.3
43510:			
I-1	M	44	14.5
I-2	F	44	6.5
II-1	M	20	6.9
II-2	M	18	6.3*
II-3	M	16	11.0*
II-4	F	15	11.8
43549:			
I-1	M	56	17.6
I-2	F	50	7.6
II-1	M	17	5.6*
45344:			
I-1	M	47	18.7
I-2	F	43	7.9
II-1	F	23	10.7
II-2	F	21	7.8
II-3	F	18	5.3*
II-4	F	15	16.9
45693:			
I-1	M	50	16.1
I-2	F	42	4.7
II-1	F	21	NA†
II-2	M	19	6.0*
II-3	F	17	10.6*
45708:			
I-1	M	39	7.1
I-2	F	39	7.8
II-1	M	19	6.4
II-2	M	18	6.3*
II-3	M	16	7.4
II-4	F	10	6.3
45784:			
I-1	M	48	7.0
I-2	F	48	6.8
II-1	F	19	6.2*
II-2	F	13	7.7
47157:			
I-1	M	52	16.2
I-2	F	52	4.9
II-1	M	...	NA†
II-2	F	19	6.0*

* RBC COMT measured in initial school screening study.
† Sample not obtained.