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Genetic and Environmental Influences on the Size and Number of Cells in the Blood

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The heritabilities of human blood cell characteristics were estimated in a study of 206 pairs of young adult twins, male and female. White cell numbers, indices related to circulating red cell mass (haemoglobin, red cell count, and haematocrit), and platelet numbers and size all appeared to be accounted for by genetic and nonshared environmental influences only. Mean cell volume (of the erythrocytes) appeared to be influenced by environmental factors shared by siblings as well as the other two sources of variation.

Correlation between red cell count and haemoglobin is modulated by both genetic and environmental factors, but the negative correlation between red cell numbers and size is due mainly to genetic factors independent of those influencing haemoglobin. A significant negative correlation also exists between platelet numbers and size.

In males, alcohol consumption increased mean cell volume, and genetic factors influencing alcohol consumption are partly responsible for the correlation between them.

Key words: white blood cells, red blood cells, platelets, mean cell volume, alcohol, twins

INTRODUCTION

The cells of the blood comprise an important, accessible, and widely studied organ system. The cell numbers and size, and in the case of red cells, the concentration of the functional protein haemoglobin, are known to vary between people, and there are strong interrelations between these variables so that study of the factors influencing each must also take account of the others. Although the pathological

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causes of differences between people, both inborn and acquired, have been extensively studied, there is little information on the genetic and environmental causes of variation between normal people.

The degree to which people show individual levels, constant over time, has previously been studied for WBC haemoglobin and haematocrit [Statland et al, 1977] and platelet numbers [Meade and North, 1977]. There is little information on the genetics of these quantitative variables, although one study [Lindemann et al, 1977] on 256 middle-aged male twins found evidence for heritability of RBC and mean cell volume (MCV). The influences on the inverse correlation between RBC and MCV have not been analysed within the human population, but a study of red cell size and numbers across a number of animal species has been published [Norton and Rand, 1980].

We have studied the commonly determined haematological variables, white cell count (WBC), red cell count (RBC), haemoglobin, and MCV, together with the derived variables haematocrit, mean cellular haemoglobin (MCH), and mean cellular haemoglobin concentration (MCHC) in 206 pairs of young adult male and female pairs of twins. Results for platelet count (PLT) and mean platelet volume (MPV) were also available in 92 of these twin pairs. This paper reports on the repeatability of these measures within individuals, the general genetic and environmental determinants of their individuality, the specific association of some with alcohol intake, and the genetic and environmental influences on the underlying factors that affect two or more of these variables.

SUBJECTS AND METHODS

Two hundred six pairs of monozygotic (MZ) and dizygotic (DZ) twins aged between 18 and 34 years (mean 23.1) were recruited from the Australian NH&MRC Twin Registry for a study of alcohol metabolism and susceptibility to intoxication [Martin et al, 1984]. All were of European extraction and lived in the Sydney area. Both members of a pair attended on the same day. Of these twins 87 individuals (48 men, 39 women) attended on a second occasion from 1 to 17 months later (mean 4.5 months), and the results from these visits are used to assess medium-term repeatability of the measurements within an individual.

Blood was taken at about 10 AM (before the subjects took any alcohol) into an EDTA tube. WBC, RBC, haemoglobin, and MCV measurements were made using a Coulter Model S or S Plus counter; from these the instrument also calculated haematocrit, mean cell haemoglobin, and mean cell haemoglobin concentration.

Platelet measurements were also made using the Coulter S Plus on 92 pairs, of whom 20 men and 11 women had estimations made on two occasions.

All twins were typed with 15 blood group antisera and for α_1-antitrypsin [Whitfield and Martin, 1983a]. Twins were diagnosed as DZ on the basis of a difference in sex, at least one marker locus, or in a few cases large differences in height, colouring, or other morphological features; in remaining cases of doubtful zygosity several more genetic markers were typed. It is possible that there were a few pairs assigned to the MZ group who on further typing would prove to be DZ, but previous examination of this panel of tests has shown that the probability of dizygosity given concordance is less than 3% [Martin and Martin, 1975].

Of the 206 twin pairs for whom measurements were available, there were 43 MZ female, 44 DZ female, 42 MZ male, 38 DZ male, and 39 DZ pairs of opposite sex (DZOS). There were no substantial differences in age distribution between the five zygosity groups, and no significant differences in means or variance of these haematological variables between MZ and DZ pairs of the same sex.

A small number of results were clearly outside the accepted reference range, and because this study was concerned with the normal population rather than with the effects of pathology they were excluded from further consideration. The range of acceptable values and the number of subjects with acceptable results for each are shown in Table II.

The presence of significant differences between individuals over time was tested by calculating the within-person and between-person components of variance on the 87 people who attended on two occasions. The ratio of between-person to total variance is an intraclass correlation and is a measure of the degree of repeatable difference between people, variously known as individuality, repeatability, or test-retest reliability.

The within-pairs and between-pairs mean squares for each of the five twin groups were calculated from a nested analysis of variance and a series of models of genetic and environmental contributions to total population variance was fitted to these using an iterative, weighted least squares procedure [Eaves et al, 1978]. The model of variation in MZ and DZ mean squares is shown in Table I. Possible sources of variance included in the models are: V_A, additive genetic variance; E_2, variance due to environmental effects such as dietary habits shared by both members of a pair regardless of zygosity but differing between pairs; and E_1, variance due to environmental effects unique to each individual. The simplest model, that only E_1 effects contribute, is tested first and if it is rejected then more complex models, E_1E_2 and E_1V_A, are fitted to the mean squares to test whether or not the between pairs variance can be adequately explained by either family environment effects or additive genetic variance. The fit of alternative models is assessed by the χ^2 criterion.

TABLE I. Model for Twin Mean Squares

Mean squares	E_1	E_2	V_A
MZ females			
Between	1	2	2
Within	1	0	0
MZ males			
Between	1	2	2
Within	1	0	0
DZ females			
Between	1	2	3/2
Within	1	0	1/2
DZ males			
Between	1	2	3/2
Within	1	0	1/2
DZ opposite sex			
Between	1	2	3/2
Within	1	0	1/2

If one of these two-parameter models (E_1 and E_2, or E_1 and V_A), is rejected and the other is not, the latter is accepted; otherwise a model with contributions from all three sources of variance, E_1, E_2, and V_A, is required. This procedure leads to a preferred model, estimates of the variance attributable to each source, and a test of the significance of each.

RESULTS

Frequency Distributions

Inspection of the frequency distributions led to the exclusion of a small number of results that appeared to be abnormal outliers. The ranges regarded as acceptable, and the number of subjects, are shown in Table II; 12 (2.9%) of the possible results were excluded or missing for white cell count and seven (1.7%) or less for other measurements.

The means and standard deviations for men and women separately are shown in Table II. The means were significantly different between the sexes for all except MCHC and MPV, but the variances were not significantly different. The skewness and kurtosis of the distributions were also assessed, but only WBC showed significant values consistent across the sexes (skewness 1.74 and 1.16, and kurtosis 7.77 and 3.02, for men and women, respectively).

Repeatabilities

Repeatabilities of these haematological characteristics in these subjects are shown in Table III, which gives the intraclass correlations for men and for women. All are significant except for MCHC, which showed much lower repeatability than the variables from which it was derived.

Genetic and Environmental Sources of Variation

The data from the twin pairs showed no systematic genotype × environment interaction [Clark et al, 1980]. This was assessed by checking for significant correlation between MZ pair absolute differences (which can only be environmental in

TABLE II. Means and Standard Deviations (S.D.) for Men and Women Separately[a]

			Men			Women		
Variable	Units	Inclusion limits	N	Mean	S.D.	N	Mean	S.D.
White cell count (WBC)	Cells/1 × 10^{-9}	0–15	191	6.11	1.56	209	6.68	1.66
Red cell count (RBC)	Cells/1 × 10^{-12}	3.9–6.3	196	5.35	0.35	212	4.72	0.32
Haemoglobin (HB)	gm/100 ml	12.0–20.0	199	16.0	0.9	212	14.3	0.8
Haematocrit (HCT)		0.35–0.60	198	0.47	0.03	212	0.42	0.03
Mean cell volume (MCV)	fl	78–100	195	87.9	3.8	210	89.0	4.0
Mean cell haemoglobin (MCH)	pg	26–34	196	30.0	1.2	210	30.4	1.2
Mean cell haemoglobin concentration (MCHC)	gm/100 ml	0–40	198	34.2	1.1	213	34.1	1.1
Platelet count (PLT)	Cells/1 × 10^{-9}	All	86	253	67	98	275	71
Mean platelet volume (MPV)	fl	0–13	86	9.54	0.94	96	9.66	1.05

[a]The variance for men and women did not differ significantly, but the means differ significantly ($P < 0.01$) for all variables except MCHC and MPV.

TABLE III. Repeatability, Expressed as Intraclass Correlation Coefficients, for Subjects Who Attended on More Than One Occasion

Variable	Men (N = 44–48)	Women (N = 38–39)
White cell count	0.41**	0.36*
Red cell count	0.64***	0.62***
Haemoglobin	0.70***	0.70***
Haematocrit	0.50***	0.45**
Mean cell volume	0.81***	0.60***
Mean cell haemoglobin	0.82***	0.72***
Mean cell haemoglobin concentration	0	0.14
Platelet count[a]	0.71***	0.65*
Mean platelet volume[a]	0.86***	0.68*

[a]For platelet count and mean platelet volume there were 20 male and 11 female repeat subjects.
*P < 0.05.
**P < 0.01.
***P < 0.001.

origin) and their corresponding pair means (a measure of genetic effects). Such interactions can confound any model for the additive action of genetic and environmental effects but can usually be removed by an appropriate transformation. In this case there were no such significant correlations and thus no requirement for transformation.

There were no significant differences in the variances of monozygotic and dizygotic twins of the same sex. The mean squares within and between pairs, by sex and zygosity, are shown in Table IV, and Table V gives the outcome of the model fitting using these mean squares, giving the test of goodness-of-fit for the various models. Table VI shows the estimates of variance attributable to each source in the chosen models and the heritabilities. In each case the simplest hypothesis, that only individual environmental (E_1) influences exist, is decisively rejected, and so we proceed to test for the existence of shared environmental factors (E_2), additive genetic variance (V_A), or both.

For WBC the E_1E_2 hypothesis is rejected ($P < 0.05$) and the E_1V_A hypothesis is accepted; similarly for RBC, haemoglobin, and haematocrit. For MCV also the E_1V_A model is just acceptable ($P = 0.109$), but because of this rather poor fit and because the model containing all three sources of variation has a considerably higher probability ($P = 0.652$) we choose $E_1E_2V_A$ model. For MCH it was necessary to specify different variance estimates for men and women to achieve a satisfactory fit, although the E_1V_A model with common estimates for men and women cannot be entirely ruled out. For MCHC all three sources of variation again appear to contribute. For both platelet count and MPV the E_1E_2 model was rejected despite the smaller numbers of subjects, and the E_1V_A models were accepted.

Correlations and Covariance

Correlations between the red cell variables are shown in Table VII and for the platelets in Table VIII. The twins also answered questions on their usual drinking

TABLE IV. Within- and Between-Pair Mean Squares, With Their Associated Degrees of Freedom for the Five Zygosity Groups

	MZM[a]		MZF		DZM		DZF		DZOS	
Variable	Within	Between	Within	Between	Within	Between	Within	Between	Within	Between
WBC	0.848 (41)	4.184 (40)	1.170 (44)	3.595 (43)	1.634 (35)	2.590 (34)	1.973 (41)	3.531 (40)	2.564 (36)	3.646 (36)
RBC	0.261 (41)	0.2538 (40)	0.0295 (43)	0.1738 (42)	0.0601 (38)	0.1435 (37)	0.0756 (44)	0.1356 (43)	0.0862 (37)	0.1400 (37)
HB	0.292 (42)	1.682 (41)	0.299 (43)	0.926 (42)	0.425 (38)	0.897 (37)	0.501 (44)	0.814 (43)	0.541 (38)	0.781 (38)
HCT[b]	0.260 (42)	0.1609 (41)	0.253 (43)	0.0831 (42)	0.0399 (38)	0.1073 (37)	0.0504 (44)	0.1035 (43)	0.0511 (37)	0.0806 (37)
MCV	1.57 (40)	31.82 (39)	2.67 (42)	31.62 (41)	5.68 (38)	24.45 (37)	4.77 (44)	25.89 (43)	6.62 (38)	20.08 (38)
MCH	0.139 (41)	3.573 (40)	0.275 (42)	1.981 (41)	0.665 (38)	1.512 (37)	0.602 (44)	2.446 (43)	0.926 (37)	2.209 (37)
MCHC	0.149 (42)	2.560 (41)	0.092 (44)	2.482 (43)	0.154 (38)	2.020 (37)	0.202 (44)	2.021 (43)	0.264 (37)	2.286 (37)
PLT	389 (20)	8,772 (19)	919 (20)	10,532 (19)	4,207 (13)	4,183 (12)	1,622 (20)	8,279 (19)	1,901 (17)	6,840 (17)
MPV	0.111 (20)	1.888 (19)	0.129 (19)	1.263 (18)	0.253 (13)	1.601 (12)	0.316 (20)	1.886 (19)	0.786 (17)	1.495 (17)

[a]MZM denotes male MZ, MZF female MZ, DZM male DZ, DZF female DZ, and DZOS opposite sex DZ pairs.
[b]For haematocrit all the mean squares have been multiplied $\times 100$ for ease of tabulation.

TABLE V. Goodness-of-Fit of Alternative Models of Genetic and Environmental Sources of Variation (for explanation of abbreviations see text)

Variable	Model	χ^2	df[a]	p
WBC	E_1	36.64	9	0.000
	E_1E_2	15.56	8	0.049
	E_1V_A	5.62	8	0.690
RBC	E_1	73.54	9	0.000
	E_1E_2	26.38	8	0.001
	E_1V_A	4.17	8	0.842
HB	E_1	62.19	9	0.000
	E_1E_2	17.31	8	0.027
	E_1V_A	6.86	8	0.552
HCT	E_1	64.62	9	0.000
	E_1E_2	16.29	8	0.038
	E_1V_A	5.95	8	0.653
MCV	E_1	117.32	9	0.000
	E_1E_2	22.19	8	0.005
	E_1V_A	13.09	8	0.109
	$E_1E_2V_A$	5.07	7	0.652
MCH	E_1	110.60	9	0.000
	E_1E_2	38.29	8	0.000
	E_1V_A	13.43	8	0.098
	$E_1V_AE_{2F}$	5.27	4	0.260
MCHC	E_1	156.85	9	0.000
	E_1E_2	12.63	8	0.125
	E_1V_A	40.38	8	0.000
	$E_1E_2V_A$	5.77	7	0.567
PLT	E_1	50.62	9	0.000
	E_1E_2	27.10	8	0.001
	E_1V_A	9.85	8	0.276
MPV	E_1	47.35	9	0.000
	E_1E_2	28.49	8	0.000
	E_1V_A	7.83	8	0.450

[a]The degrees of freedom, df = n − K, where models comprising K statistics are fitted to data sets including n mean squares.

TABLE VI. Estimates of the Variance Due to the Genetic and Environmental Sources of Variation in the Chosen Models (for explanation of abbreviations see text)

	Estimated components of variance			
Variable	E_1	E_2	V_A	Heritability
WBC	1.09	—	1.52	0.58 ± 0.06
RBC	0.028	—	0.084	0.75 ± 0.04
HB	0.29	—	0.42	0.59 ± 0.06
HCT	0.00025	—	0.00047	0.65 ± 0.05
MCV	2.12	6.10	7.21	0.47 ± 0.11
MCH				
Male	0.14	—	1.31	0.91 ± 0.02
Female	0.28	0.50	0.61	0.44 ± 0.20
MCHC	0.12	0.93	0.18	0.14 ± 0.05
PLT	640	—	40.94	0.86 ± 0.03
MPV	0.12	—	0.84	0.88 ± 0.03

habits, from which weekly alcohol consumption was calculated. The logarithm of this measure (logALC) is also correlated with the haematological variables in Table VII.

We shall confine our full analysis to the independently measured red cell variables, RBC, haemoglobin, and MCV, and their relationships with logALC. Correlations are much the same in males and females except for those with alcohol consumption, which is only slightly correlated with MCV in females but more substantially so in males. The most elegant way to address the question of the environmental and genetic factors underlying these correlations is through the genetic analysis of covariance structure [Martin and Eaves, 1977], which simultaneously tests hypotheses concerning both the sources and structure of covariation.

We shall consider the causes of covariation only in males, first the sources of covariation. From our univariate model fitting (Table VI), we see that variance in RBC and haemoglobin is due only to individual environmental influences (E_1) and additive genetic variance (V_A), whereas for MCV shared environmental influences (E_2) are also important. Analysis of logALC in males demonstrates that, in this sample, genetic factors account for most variation in weekly alcohol consumption and that no variation due to shared environment can be detected. (In a much larger sample of twins, up to 20% of male variance in alcohol consumption could be shown to be due to E_2 [Jardine and Martin, 1984].) In the present sample we shall consider that covariance can be due either to E_1 or V_A but not to E_2, which accounts only for variation specific to MCV.

We observe that RBC is highly correlated with haemoglobin and to a lesser extent and negatively with MCV. Haemoglobin and MCV are uncorrelated. We thus postulate two factors: Factor I loads on RBC and haemoglobin and factor II loads on RBC and MCV. We also postulate a third factor to account for covariation between MCV and alcohol consumption. Our model specifies that these three factors are independent. Although there may be variation specific to each variable that cannot be accounted for by any of the factors, numerical constraints allow us to estimate specific variance components for only one variable, logALC. We specify the same factor structure for the E_1 and V_A sources of covariance and the results of fitting this model are shown in Table IX. The table gives, for each character, percentages of variance due to the factor and specific sources described above. Thus for RBC we see that 19% of variance is due to E_1 influences, which also affect haemoglobin (factor I), 4% to E_1 influences, which also act on MCV. Genetic variance accounts for 77% of

TABLE VII. Correlations Between the Three Independently Measured Red Cell Variables and Alcohol Consumption

		Men (N = 194)			
		RBC	HB	MCV	logALC
	RBC	—	0.78***	− 0.44***	− 0.01
	HB	0.77***	—	− 0.02	0.10
Women	MCV	− 0.45***	− 0.02	—	0.30***
(N = 209)	logALC	− 0.19**	− 0.11	− 0.11	—

**P < 0.01.
***P < 0.001.

the total (compare the RBC heritability of 0.75 in Table V), and this is divided into 46% in common with haemoglobin and an independent 31% in common with MCV.

The most important conclusion from Table IX is that, whereas the correlation between RBC and haemoglobin is modulated by both genetic and environmental factors, so that the environmental and genetic correlations (Table X) are both high (0.92 and 0.77, respectively), the inverse correlation between RBC and MCV is modulated almost entirely by genetic factors. This can be seen by contrasting the percentages of variance accounted for in these two variables by the environmental factor II (4% and 3%) with those due to the genetical factor II (31% and 50%). To emphasize the point, note the difference between the environmental and genetic correlations of red cell numbers and volume (0.20 and 0.62, respectively).

Most of the variance in alcohol consumption is specific to logALC, but we can see that both genetic and environmental causes of variation in alcohol consumption are responsible for the covariation with MCV. We have the perhaps surprising result that genes contributing to variation in a behavioural character (alcohol consumption) may also contribute some of the genetic variance in a haematological parameter. We have found similar results with other variables affected by alcohol intake, plasma uric acid [Whitfield and Martin, 1983b] and some liver-derived enzymes [Whitfield and Martin, 1985].

For the platelets, as for the red cells, there was a significant inverse relationship between cell size and cell numbers both in men and in women. This association was not explored further through the analysis of covariance structure because of the smaller number of subjects for whom these data was available.

TABLE VIII. Correlations Between the Two Independently Measured Platelet Variables

		Men (N = 86)	
		PLT	MPV
Women (N = 98)	PLT	—	− 0.58***
	MPV	− 0.50***	—

***P < 0.001.

TABLE IX. Percentage Contributions to Variance and Covariance of RBC, HB, MCV, and logALC of Genetic and Environmental Factors (see text for explanation)

	E_1				V_A				E_2
	I	II	III	Specific	I	II	III	Specific	Specific
RBC	19	4	—	—	46	31	—	—	—
HB	35	—	—	—	65	—	—	—	—
MCV	—	3	7	—	—	50	2	—	38
logALC	—	—	4	22	—	—	14	60	—

TABLE X. Genetic and Environmental Correlations of Red Cell Variables and Alcohol Consumption

		Environmental			
		RBC	HB	MCV	logALC
	RBC		0.92	0.20	—
	HB	0.77		—	—
Genetic	MCV	0.62	—		0.32
	logALC	—	—	0.09	

DISCUSSION

Several of the variables were strongly correlated with each other, and it is not surprising that the results of the genetic and environmental model fitting were similar. Red blood cell count, haemoglobin concentration, and haematocrit are all measures that are strongly interdependent, and similarly mean cell volume and mean cellular haemoglobin would be expected to show similar results. Moreover, the Coulter counter makes only four measurements (WBC, RBC, haemoglobin, and MCV); the other three variables (haematocrit, MCH, and MCHC) are derived from them. The number of variables to be considered therefore decreases.

The white blood cell count was found to be significantly influenced by genetic factors, with no evidence for shared environmental effects such as minor infections common to both members of a twin pair. The heritability, at just over 50%, was slightly greater than the repeatability, so that all the long-term differences between individuals seem to be due to genetic differences. Previous studies of the repeatability of WBC in healthy people have also shown that each person has a characteristic range of values that is much less than the population range, and the data given in one of these studies [Statland et al, 1977] allows calculation of the intraclass correlation. This was 0.81, which is higher than our value, but that study was over a shorter term (4 weeks) and there might well be more variation over a few months than a few weeks.

These findings relate only to healthy subjects, and a few subjects with high white cell counts were excluded. The degree to which increases in white cell count in response to stimuli such as infection are genetically determined is unknown, but it would be interesting to study the environmental and genetic components of this response.

For white cell numbers, and indeed for all the variables, it might be claimed that MZ twin pairs share a more similar environment than DZ pairs. This would lead to an overestimate of the heritability. This criticism, among others, has been analysed by a number of authors and generally discounted. A discussion of twin studies of schizophrenia [Kendler, 1983] covers this point.

The three variables related to circulating red cell mass (RBC, haemoglobin, and haematocrit) were also determined by genetic and nonshared environmental factors only. The heritability varied between 59% and 75% and tended to be slightly higher than the repeatability, again indicating genetic control of variation between people in their long-term means. The repeatability of RBC was less than that found in the 4-week study previously cited [Statland et al, 1977], again allowing the possibility of environmental influences on shorter-term individuality. The heritability is in agree-

ment with previously reported results [Lindemann et al, 1977] that showed a significant estimate of genetic variance for red cell count. However, haematocrit did not show significant heritability in that study, possibly because of smaller numbers of subjects. In view of the strong correlation between haemoglobin, RBC, and haematocrit (Table VII) genetic effects might be expected to act on all three measurements, as we have found.

The conclusion that individual values are strongly influenced by genetic factors suggests that whether or not an individual's test results are abnormal should be judged relative to that person's own previous results rather than the "normal range" in the population. In clinical practice this is usually not possible, because the patients' normal values are unknown. There are some practical consequences for experimental studies; the cotwin control method is especially powerful when effects on highly heritable characteristics are being investigated.

Red cell size, unlike the other variables, showed shared environmental effects, especially when judged by MCV. MCH showed different results for men and for women. Both E_2 and V_A estimates were significant for MCV, and models containing only two sources of variation had a considerably lower probability.

Part of the variation in MCV can be ascribed to differences in alcohol consumption [Chalmers et al, 1979] as discussed above, and part to a genetic factor that exerts a simultaneous and opposite effect on red cell size and numbers. That is, the degree to which the circulating red cell mass is split up into cells shows genetic variation within humans, just as it does between different species [Norton and Rand, 1980], with some people inheriting a tendency towards fewer but larger cells and others inheriting a greater subdivision of the erythron. Each extreme might have advantages in different situations, with relevant considerations including viscosity, speed of gas exchange, and economy of membrane protein synthesis.

The platelet numbers and the MPV both showed significant repeatability in both sexes, despite the very small numbers. One previous report [Meade and North, 1977] also showed some individuality in the platelet count, with half the total variance due to variation within people and half to differences between them. We have found both these platelet variables to be influenced strongly by genetic factors, and there is also the reciprocal relationship between cell size and numbers seen for the red blood cells. We have not determined whether or not this relationship is also genetically determined, but if it is then the genetic influences must be different because the RBC/PLT and MCV/MPV correlations are small and nonsignificant.

The general conclusion from this study is that for each of the three types of blood cell—red cells, white cells, and platelets—the numbers of circulating cells differ among individuals and that the differences are due to the additive effects of a number of genes, each of small effect. In addition, the degree to which the circulating cell mass is divided into a larger number of small cells or a smaller number of larger cells differs among people and, for at least the red cells, the variation in this is largely genetically determined.

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