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Inheritance and Alcohol as Factors Influencing Plasma Uric Acid Levels

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Variation in plasma uric acid levels in 206 pairs of male and female twins, aged from 18 to 34 years, was consistent with a simple model including only individual environmental and additive genetic effects and a heritability of $h^2 = 0.73$. Individual environmental variation was estimated to be approximately the same as variation of individuals measured on two occasions. Correlations of DZ pairs were also consistent with sex-linked genetic effects. In men there was a significant genetic correlation with weekly alcohol consumption and as much as 18% of the variation in uric acid levels could be accounted for by genetic variation in alcohol consumption.

Key words: Twins, Uric acid, Alcohol

INTRODUCTION

The inheritance of plasma uric acid concentration has been studied by a number of authors with mixed results (see Table 1). The subject is of interest for several reasons: the association of high uric acid levels with gout [19]; the influence of alcohol intake [16], probably mediated by effects on renal tubular anion transport [6]; the considerably higher uric acid levels in adult males than in adult females [13]; and the position of uric acid as the end product of purine metabolism in humans.

We have measured plasma uric acid in 206 pairs of male and female twins aged 18–34. A simple model including only effects of individual environment and additive genes accounts adequately for the observed variation. The degree of heritability (0.73) is similar to the repeatability of the measure. The pattern of DZ sib correlations is also compatible with sex-linked gene effects. In males we have detected a genetically determined correlation with alcohol intake.

TABLE 1. Previous Studies on the Inheritance of Plasma Uric Acid

Study	Numbers	Age	Conclusions
Jensen et al. 1965 [5]	67 pairs of twins, male and female	16–70	Significant heritability, h^2 about 0.36
Boyle et al. 1967 [1]	112 pairs of twins, male and female	12–70	Significant heritability in females but not males
Havlik et al. 1977 [4]	514 pairs of male twins	42–56	$h^2 = 0.52$
Rich et al. 1978 [13]	384 pairs of twins, 43 MZ half-sib families	all ages	h^2 about 0.7, evidence of sex-linkage
Park et al. 1980 [10]	37 pairs of twins, male and female, and their parents	11–12	Inconclusive
Rao et al. 1982 [12]	160 families		$h^2 = 0.25$, shared environment = 0.20

SUBJECTS AND METHODS

Pairs of monozygotic (MZ) and dizygotic (DZ) twins aged between 18 and 34 years (mean 23.1), were recruited from the Australian NH&MRC (National Health and Medical Research Council) Twin Registry for a study of alcohol metabolism and susceptibility to intoxication [7]. Both members of a twin pair attended on the same day, and the study extended over all seasons from April 1979 to May 1981. From these individuals, 87 (48 men and 39 women) attended on a second occasion and the results from these are used to assess medium-term repeatability of the measurements within an individual.

The twins arrived at about 9 a.m., having had a light, nonfatty breakfast at about 8 a.m., and blood and a nontimed urine sample were collected soon after arrival and before any alcohol was ingested. Venous blood (15 ml), taken into a tube containing heparin, was centrifuged within 2 hours of collection and analysed for uric acid by phosphotungstate reduction [14] on a Technicon SMAC (Tarrytown, NY).

The twins also answered a questionnaire including several questions on drinking habits, and the weekly alcohol consumption was calculated as the total number of glasses of beer, wine, or spirits reported to be consumed.

All twins were bloodtyped with the following antisera: anti-A, A_1, B, C, c, D, E, e, M, N, S, s, Fy^a, K, and Jk^a and were typed for the serum enzyme, alpha-1-antitrypsin (Pi). 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, coloring or other morphological features. In remaining cases of doubtful zygosity several more genetic markers were typed. It is possible, however, that there are a few pairs diagnosed as MZ who on still further typing would prove to be DZ.

Of the 206 twin pairs for whom measurements were available, there were 43 MZ female, 42 MZ male, 44 DZ female, 38 DZ male, and 39 DZ pairs of opposite sex (DZOS). There were no substantial differences in age distribution among the five zygosity groups.

The statistics to which models of variation are fitted are the between- and within-pair mean squares (WMS) from an analysis of variance of each separate group in n twin pairs:

Source	Degrees of freedom	Expected mean squares
Between pairs	$n - 1$	$S_w^2 + 2S_b^2$
Within pairs	n	S_w^2

A large difference in the means of males and females will inflate the WMS of DZ opposite sex (DZOS) pairs by an amount $n/2(\overline{M} - \overline{F})^2$ where there are n pairs, $\overline{M}$ is the male mean and $\overline{F}$ is the female mean. The DZOS WMS are thus corrected for this amount and the corresponding degree of freedom removed.

Models of variation to explain these mean squares can now be fitted using the method of iterative weighted least squares, described extensively elsewhere [2, 3].

A simple model for variation in MZ and DZ mean squares is shown in Table 2. E_1 is environmental variance within families and as such it is specific to the individual and will include error variance. E_2, on the other hand, includes sources of environmental variance shared by members of a family but differing between families. It will, thus, include the lasting effects of cultural and class differences and parental rearing practices. Here, it may include dietary habits that members of a twin pair share, but which differ between pairs. V_A is that part of the genetic variation due to the additive effects of genes in the absence of assortative mating. The appropriateness of different models is tested by the chi square criterion. A model is only elaborated if a simpler one fails or a significant improvement is made by adding a further parameter.

A sensible hierarchy of models is to first fit E_1 alone. Failure of this most simple model will indicate that there is significant between-families variation. A model incorporating E_1 and E_2 will test whether the between-families variation is entirely environmental in origin, while the E_1 V_A model will test whether it is entirely genetic. If both two-parameter models fail, then a model incorporating all three sources of variation must be considered.

There is no reason why the components of variation will be the same in both males and females, so models are first fitted to the sexes separately and then to the eight statistics together. At this stage, a heterogeneity chi square can be calculated by adding the two male and female chi squares for 4-k df and subtracting from the chi square (8-k df) for the

TABLE 2. 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

corresponding model fitted to all eight statistics. The heterogeneity chi square for k df will indicate whether the same parameters are appropriate for both sexes. If it is not significant, then the DZOS data may be added and the same model fitted to all ten statistics.

Because plasma uric acid concentration is partly determined by alcohol intake, at least in men [16], the effect of weekly alcohol consumption was also studied in this group. Two approaches were taken; first, the correlations between differences in log weekly alcohol consumption and differences in uric acid within a pair were calculated for each sex and zygosity group. The stronger the association between alcohol and uric acid, the greater this correlation will be, but while a correlation caused by an environmental source will be equally strong in MZ and DZ groups, a correlation with a genetic cause will be greater in the DZ group because there are no genetic differences within the MZ pairs. Second, by fitting environmental/genetic models to the mean products of uric acid and weekly consumption, we may estimate how much of the observed correlation between the two can be explained by genetical covariation and how much by E_1 covariation.

RESULTS

Variation Within Individuals

Eighty-seven individuals returned for a second visit at intervals ranging from 1 to 17 months (mean 4.5 months) after the first. Means and an analysis of variance between and within individuals are shown in Table 3. It will be seen that within-individual components of variance are equal for men and women but that the intraclass correlation is greater in men because of the larger between-individual component. When the two sexes are considered together the intraclass correlation is greater, because the sex difference in means increases the total variance.

Genotype × Environment Interaction and Scale

The correlation of individual MZ pair absolute differences (a measure of environmental effects) with their corresponding pair means (a measure of genetic effects) is now well established as a test for one class of systematic genotype × environment interactions [3]. Such interactions may confound any model for the additive action of genetic and environmental effects but can usually be removed by an appropriate transformation of the scale of measurement.

No significant sum-difference correlations were found for uric acid, and so no transformation was performed, but for weekly alcohol consumption significant correlations were found for both the male and female MZ twins. These could be removed by $\log_{10}$ transformation, so all calculations were done using the transformed values. This also removed the skewness in the frequency distribution of alcohol intake.

*TABLE 3. Means and Analysis of Variance for Twins Studied on Two Occasions**

	N	$\bar{x}$	S_W^2	S_B^2	R_i
Females	39	0.273	0.0008	0.0007	0.46[a]
Males	48	0.366	0.0008	0.0013	0.62[b]
All subjects	87	0.324	0.0008	0.0032	0.80[b]

*S_W^2, within-individual; S_B^2, between-individual components of variance; R_i, intraclass correlation = $S_B^2/(S_W^2 + S_B^2)$. Concentrations in μmol/liter.

[a] $.001 < P < .01$.

[b] $P < .001$.

Genetical Analysis

Although the mean plasma uric acid was higher for males than females, the standard deviations were the same (male 0.368 ± 0.053 μmol/liter, female 0.280 ±0.052 μmol/liter), and there was no significant difference in the means or variances between MZ and DZ twins of the same sex. Correlations with age were small (0.03 in females, 0.17 in males) so there was no need to correct between-pair mean squares for age. We therefore proceeded to estimate the relative importance of genetical and environmental factors on variation in plasma uric acid.

Mean squares, by sex and zygosity, are shown in Table 4. The results of fitting models of variation to the female and male data separately, the male and female data combined, and to these data sets plus the mean-corrected opposite-sex mean squares, are shown in Table 5. In both males and females the E_1 and E_1E_2 models are rejected and the E_1V_A model is accepted, with no significant improvement when all three parameters ($E_1E_2V_A$) are included. When the E_1V_A model is fitted jointly to the male and female data there is no significant heterogeneity of fit between the sexes ($\chi^2_6 = 4.86 - (\chi^2_2 = 1.98 + \chi^2_2 = 0.34) = \chi^2_2$ heterogeneity $= 2.54$). We may thus include the DZOS mean squares and fit the same model to all ten statistics. This provides a quite adequate account of the data ($\chi^2_8 = 7.13$) and the heritability ($h^2 = \hat{V}_A/[\hat{E}_1 + \hat{V}_A]$) is estimated to be 0.73 ± 0.04. Although any E_2 effects present are not large enough to require elaboration of the two-parameter model, there is some indication that they may account for up to 20% of variation in females but not in males.

Sex-Linkage Hypothesis

Without parental data the classical twin study provides only low power for the detection of sex-linked gene effects. However, if such effects are present the pattern of sib-sib correlations in DZ pairs is predicted to be in the order: female-female > male-male > female-male [8]. These correlations for plasma uric acid found were 0.43, 0.31, and 0.14, respectively, and although they are in the order consistent with sex-linked gene effects,

TABLE 4. Observed Mean Squares for Uric Acid Levels Used in Model Fitting

	df	Mean squares
MZ females		
Between	42	0.00567
Within	43	0.00062
MZ males		
Between	41	0.00468
Within	42	0.00090
DZ females		
Between	43	0.00331
Within	44	0.00131
DZ males		
Between	37	0.00445
Within	38	0.00203
DZ opposite-sex		
Between	38	0.00263
Within	38[a]	0.00197

[a]Corrected for difference in male and female means.

TABLE 5. Summary of Model-Fitting to Data for Uric Acid Showing Goodness-of-fit of the Competing Models and Estimates of $\hat{E}_1$, $\hat{E}_2$, and $\hat{V}_A$ Components of Variance

Data set	Model	$\hat{E}_1$	$\hat{E}_2$	$\hat{V}_A$	df	χ^2	h^2
Females	E_1	0.002703[c]	—	—	3	45.09[c]	
	E_1E_2	0.000968[c]	0.001756[c]	—	2	8.52[a]	
	E_1V_A	0.000586[c]	—	0.002028[c]	2	1.98	0.78 ± 0.05
	$E_1E_2V_A$	0.000603[c]	0.000497	0.001569[b]	1	1.47	0.59 ± 0.23
Males	E_1	0.002983[c]	—	—	3	23.33[c]	
	E_1E_2	0.001434[c]	0.001568[c]	—	2	6.25[a]	
	E_1V_A	0.000909[c]	—	0.002122[c]	2	0.34	0.70 ± 0.07
	$E_1E_2V_A$	0.000911[c]	0.000037	0.002086[a]	1	0.34	0.69 ± 0.30
Male & female pairs	E_1	0.002837[c]	—	—	7	67.13[c]	
	E_1E_2	0.001191[c]	0.001666[c]	—	6	18.82[b]	
	E_1V_A	0.000738[c]	—	0.002082[c]	6	4.86	0.74 ± 0.04
	$E_1E_2V_A$	0.000750[c]	0.000245	0.001846[c]	5	4.76	0.65 ± 0.19
Including DZ opposite-sex pairs	E_1	0.002736[c]	—	—	9	73.90[c]	
	E_1E_2	0.001336[c]	0.001414[c]	—	8	24.56[b]	
	E_1V_A	0.000752[c]	—	0.001983[c]	8	7.13	0.73 ± 0.04
	$E_1E_2V_A$	0.000744[c]	−0.000125	0.002104[c]	7	7.07	

[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$.

they are not significantly different from each other ($\chi^2_2 = 1.96$). We could fit models that explicitly include sex-linked effects to the mean squares, but these require several extra parameters [8] and the residual chi square for the autosomal genetic effects model is already so small that a significant improvement in chi square would not be gained. On the basis of these data we must remain agnostic about the role of sex-linked gene effects on uric acid levels.

Effect of Alcohol

The correlation between log weekly alcohol consumption and plasma uric acid was 0.34 ($p < 0.001$) in men but only 0.04 (NS) in women. The correlations between the within-pair differences in alcohol consumption and uric acid are shown in Table 6; the point to note is the significant correlation in male DZ pairs (0.38, $p < 0.01$) but not in the male MZ pairs (0.16, NS). Although these two correlations are not significantly different from each other, there is an indication that genetic differences in uric acid levels are associated with genetic differences in alcohol consumption.

To test this hypothesis more rigorously, mean products between uric acid levels and $\log_{10}$ weekly alcohol consumption (LCONW) were calculated for MZ and DZ male pairs of twins. These, together with the male mean squares for LCONW, are shown in Table 7, and the results of fitting models are shown in Table 8. Environmental models for variation in LCONW are strongly rejected, but the acceptable E_1V_A model indicates a high degree of genetic determination for alcohol consumption ($h^2 = 0.71$). Similarly, environmental models are rejected as an explanation of the cause of covariation between uric acid (UAC) and LCONW, but the E_1V_A model provides an acceptable fit to the data ($\chi^2_2 = 4.03$, $p = 0.13$), and suggests that up to 88% of the covariation may be genetic in origin.

TABLE 6. Correlation of Within-Pair Signed Differences in Plasma Uric Acid With Signed Differences in Log_{10} Weekly Alcohol Consumption

Group	N	r
MZ females	42	0.119
MZ males	42	0.158
DZ females	44	0.175
DZ males	38	0.377[a]
DZ opposite-sex	39	−0.050

[a]$P < 0.01$.

TABLE 7. Observed Mean Squares in Males for Log_{10} Weekly Alcohol Consumption (LCONW) and Mean Products of LCONW and Uric Acid (UAC)

	df	LCONW	LCONW/UAC
MZ males			
Between	41	0.384487	0.015987
Within	42	0.065515	0.001214
DZ males			
Between	37	0.297932	0.014782
Within	38	0.209281	0.008526

The expected genetic correlation between LCONW and UAC may now be calculated from the parameter estimates of Tables 8 and 5 as:

$$r_{V_A} = \frac{\hat{V}_{ALCONW/UAC}}{\sqrt{\hat{V}_{ALCONW} \cdot \hat{V}_{AUAC}}} = \frac{.0098}{\sqrt{.1760 \times .0021}} = 0.51.$$

Similarly, the expected environmental correlation $r_{E_1} = 0.16$ and the expected phenotypic correlation $r_{\hat{P}} = 0.40$, close to the observed phenotypic correlation of 0.34. We therefore expect 16% of the variation in UAC in males to be accounted for by variation in LCONW.

Given that the heritability of UAC in males is 0.70, we expect $0.70 \times 0.51^2 = 18\%$ of the total variance in UAC to be accounted for by genetic variation in alcohol consumption but only $0.3 \times 0.16^2 = 1\%$ to be accounted for by environmental variation in LCONW. The slight discrepancy between the sum of the genetical and environmental components (19%) and expected phenotypic variance in UAC due to LCONW (16%) is due to the negative covariance of E_1 and V_A estimates.

The fact that the E_1 correlation is low (0.16) probably indicates in part that the errors of reporting in the measure of alcohol consumption are reflected in the lack of correlation in uric acid levels. However, in so far as one could regard uric acid level as a "reliable" indicator of true alcohol consumption, 29 − 1 = 28% of variance in LCONW (nearly all the E_1 variance) could be regarded as "unreliable" and due to inaccuracies in reporting. Clearly this is too simple, but it does provide an hypothesis that could be tested independently and more powerfully if other biochemical and hematological correlates of alcohol consumption [16] were included.

DISCUSSION

Our estimate of the heritability of plasma uric acid concentration at 0.73 is rather higher than most previous studies. The restricted age range and comparative youth of our subjects may have reduced the importance of environmental factors compared to genetic ones.

We also found, from the subjects who attended twice, that the concentration of uric acid in the plasma of any single individual shows a much narrower range than do the population concentrations, as has been found by others previously [15,17]. Previous studies have compared the within-individual variance with the between-individual variance pooled over both sexes, but this seems inappropriate when there is a considerable sex

TABLE 8. Results of Fitting Models to LCONW Mean Squares and LCONW/UAC Mean Products Showing Goodness-of-Fit and Estimates of Components of Variance or Covariance

Data set	Model	$\hat{E}_1$	$\hat{E}_2$	$\hat{V}_A$	χ^2	df	h^2
LCONW	E_1	0.2373[a]	—	—	20.37[a]	3	
	E_1E_2	0.1338[a]	0.1048[a]	—	12.13[b]	2	
	E_1V_A	0.0719[a]	—	0.1760[a]	2.39	2	0.71 ± 0.07
LCONW/UAC	E_1	0.0100[a]	—	—	28.30[a]	3	
	E_1E_2	0.0047[a]	0.0054[a]	—	24.34[a]	2	
	E_1V_A	0.0013[a]	—	0.0098[a]	4.03	2	0.88 ± 0.03

[a] $P < 0.001$.
[b] $P < 0.01$.

difference in the means which inflates the intraclass correlation (Table 3). The within-individual variance is equal, within a small margin, to the estimate of the contribution of environmental (E_1) factors to the total variance. Analytical error is one of the contributors to this within-individual or environmental variance, but it does not seem to be the major one since we estimate it to account for only about a quarter of the E_1 variance (0.00017 μmol/liter^2 in 0.0008). Our data thus suggest that nearly all of the repeatable variance in uric acid levels is genetic in origin and that systematic environmental influences acting on the individual or on the twin pair have only minor effects. Since urate levels in both members of a twin pair were assayed in the same batch, between-batch analytical error would be estimated as E_2 so any such effect must be small.

The finding of Rich et al [13] that variation in plasma uric acid concentration is consistent with sex-linked inheritance is supported to some extent by the pattern of sibling correlations in our subjects, but ours is not a powerful test and the differences between the correlations do not reach significance.

Some explanation is needed for the considerable difference in means between men and women, and also for the fact that despite the genetic correlation with alcohol consumption, which is present in men but could not be demonstrated in women (probably because the range of alcohol intake was much less), the simple E_1V_A model is consistent with the data from both sexes. Because there is a greater mean and range of alcohol consumption in men we might expect them to have a greater variance in uric acid concentration but this was not found. The greater mean in uric acid level is present even in men and women who drink only small amounts [16]. The sex difference appears around the time of puberty, there being no difference in children [9], and has been ascribed to sex differences in renal urate clearance [18].

Usually, twin studies lead to an estimate of the proportion of the observed population variance due to additive genetic effects but can do little more; the nature of the genes involved cannot be inferred, although sometimes genetic markers associated with higher or lower values can be identified. In the present study, however, we can look beyond the simple statement of $h^2 = 0.73$ to a genetic effect of an apparently environmental factor, alcohol consumption, accounting for a part of the genetic variation in uric acid levels. Our data suggest, however, that variation in alcohol consumption itself has a large genetic component [see also 11] and that this heritable behaviour accounts for a considerable portion of the genetic variation in uric acid concentration in males.

The genetical covariation of uric acid levels and alcohol consumption provides an example of what may be a more general phenomenon of considerable importance. If, for example, the heritable nature of blood lipid abnormalities is partly due to a predisposition to choose an unsuitable diet, or the inheritance of hypertension is partly due to an inherited tendency towards exposure to conditions that lead to a rise in blood pressure, then the inherited risk might be changed by appropriate behavior modification. The practicality and consequences of modifying morbidity-related behavior in which variation is partly inherited needs further study.

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