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Blood Uric Acid Level and IQ: A Study in Twin Families

E. Inouye[1,2], K.S. Park[3], A. Asaka[4]

[1] Institute of Brain Research, University of Tokyo School of Medicine; and [2] Institute for Developmental Research, Kasugai, Aichi, Japan; [3] Sungshin Women's University, Seoul, Korea, [4] Department of Mental Health, University of Tokyo School of Medicine

Abstract. Applying newly devised model, heritability (V_A/V_P) of plasma uric acid level, corrected for age and sex and standardized, was estimated at 0.8 in families consisting of twin parents, spouses and children. Correlation between spouses due to common genotype (ρ) was approximately 0.1, and variance due to common familial environment (V_{EC}/V_P) was -0.3. Analysis of families of selected twin children and their parents resulted in two estimates of heritability: approximately 0.7 and 0.3, ρ being 0.34 and 0.04, and V_{EC}/V_P being 0.04 and 0.34, respectively. Regression of IQ (y) on corrected and standardized plasma uric acid level (x) in the twin children was $y = 5.56x + 123$, correlation being 0.334 ($p < 0.025$). The result indicates a genetic basis of blood uric acid level, which may have resulted from polymorphisms in purine metabolism pathway, end product of which is uric acid in man. The significant correlation between plasma uric acid level and IQ suggests a contribution of partly common gene loci to the two quantitative traits.

Key words: Uric acid, Twin family, Heritability, Assortative mating, Common familial environment, IQ

INTRODUCTION

The present study is a part of an attempt to elucidate the genetic basis of human behaviour. It deals with the heritability of the blood concentration of uric acid and with the correlation of the latter with IQ. The study was conducted several years ago [8,15] and the data were reanalysed recently.

Uric acid is the end product of purine metabolism in man. Lower mammals have an enzyme uricase which degrades uric acid to more water-soluble allantoin, but man and higher apes lack the enzyme, and uric acid is excreted in urine. The commonest disorder of purine metabolism is gout, characterized by an excess production of uric acid and deposition of its sodium salt in various parts of the body.

Since the last century, it has been noted that gout patients are found often in higher social class. In 1955, Orowan [14] postulated that in the evolutional process of mammals, gene mutation leading to a loss of the enzyme uricase was a crucial step on the way to the emergence of human ancestor. His notion was that the loss of the enzyme had resulted in higher concentration of uric acid in the body, and may have played a decisive part in the development of intelligence, on the assumption that uric acid has a stimulating effect on the brain like other purines such as theobromine and caffeine.

Having been prompted by Orowan's hypothesis, several studies were conducted on the correlation of blood uric acid level and human behaviour in the late 1950s and 1960s. Stetten and Hearon [17] reported a positive and significant correlation ($r = 0.07$) between serum uric acid level and the score of an intelligence test. Other studies [4,12,3,11,1] reported that serum or plasma uric acid level was higher in executives or Ph.D. than craftsmen or general population, in highschool students who engaged in extracurricular activities more often than those who did less so, in students with a higher educational level than those with a lower level, and in those with higher score or degree of drive, activity, leadership or achievements than those with a lower score.

However, one may ask whether the level of blood uric acid is endogenous and therefore a primary event, whereby the level of activity, achievements, intelligence, etc, is secondarily determined. Or vice versa, one may suspect that an intake of meals rich in protein and purines by active, leading or intelligent people, is a major cause of the high level of blood uric acid, because it is known that the latter is influenced by such exogenous factor as intake of protein, purines and alcohol.

In order to answer the question, we need to look for genetic basis of each of the two quantitative characters. As to behaviour, substantial evidence has been accumulated regarding the genetic basis of IQ. Among the genetic studies of blood uric acid level in the general population, early studies [10,13,2] neglected sex and/or age differences. If corrected for sex and age, heritability of serum uric acid level was about 0.3 in one study [6], and it was as high as 0.8 in a recent study, if estimated solely on correlation of MZ twins [16].

Most of the previous studies took little account of common familial environment like other heritability studies on human quantitative characters. Common familial environment may increase similarity of family members and thus mimic the biological heritability. Actually a recent study [7] using path analysis method suggested the presence of cultural transmission of plasma uric acid level, but heritability was still about 0.25.

MATERIALS AND METHODS

Fig. 1 shows the plasma uric acid level according to sex and age in a population consisting of twin children and their parents. Twins are six-graders at primary schools, and applied for admittance to the Junior Highschool of the University of Tokyo School of Education. They were selected by an achievement test, and are above a certain level to the test results. Informed consent was given by the subjects and school administration. Heparinized blood was taken in the morning, and uric acid was measured by colorimetric method on the same day (0.2 ml of plasma was incubated at 37° C for 60 minutes, and measured at 410 nm using Boehringer-Mannheim uric acid uricase color test and 6 mg/dl standard solution or uric acid). The same procedure was followed throughout the study.

In this population, uric acid level increases with age in females. For simplicity, we assume a linear regression of uric acid level on age, separately for males and females. Regression lines and equation are shown in Fig. 1. Next, we corrected each measurement to a fixed age using the regression equation

separately for males and females, and finally the corrected values were standardized by z-transformation ($z = (\bar{x} - \bar{x})/\sigma$, x is mean, σ is SD), again separately for males and females, so that plasma uric acid level is distributed with mean zero and SD 1 in each population. By doing so, we can pool data of different populations, if artefacts are discarded, and can derive regression and correlation equally from same- and different-sexed pairs.

Fig. 2 shows a distribution of the corrected and standardized plasma uric acid level in a pooled population consisting of twin children and their parents examined in two consecutive years. Histograms represent actual numbers of subjects, which is in good agreement with the theoretical curve of normal distribution. The slight positive skewness is not significant.

The present study consists of two parts. In the first part (left half of Fig. 3) we examined adult twins, their spouses and children invited to thorough health care. Here, we can derive four equations: husband-wife correlation ($r_{H \cdot W}$), parent-offspring regression ($b_{p \cdot O}$), mid-parent-offspring regression ($b_{\bar{p} \cdot O}$), and correlation between offspring of MZ twins (genetic half-sibs, r_{HS}). Other equations were discarded because of a small sample size. Actual number of pairs and regression or correlation after correction and standardization are seen in Fig. 3.

In the second part of the study (right half of Fig. 3) we examined families consisting of selected twin children and their parents mentioned above. After correction and standardization, we obtained four equations with an ample sample size: correlation of MZ twins reared together (r_{MZt}), husband-wife correlation, parent-offspring regression, and mid-parent-offspring regression. Here, husband-wife correlation is not negligible, and we introduced a parameter of assortative mating in the model.

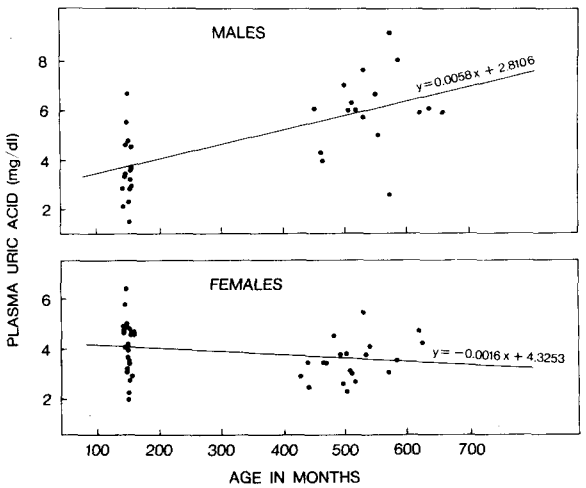


Fig. 1

Fig. 1 - Effect of sex and age on plasma uric acid level. Straight lines are regression lines; y is plasma uric acid level (mg/dl), and x is age in months. Subjects are twins and their parents.

Fig. 2 - Distribution of corrected and standardized plasma uric acid level in selected twin children and parents.

Fig. 3 - Data. See text for symbols.

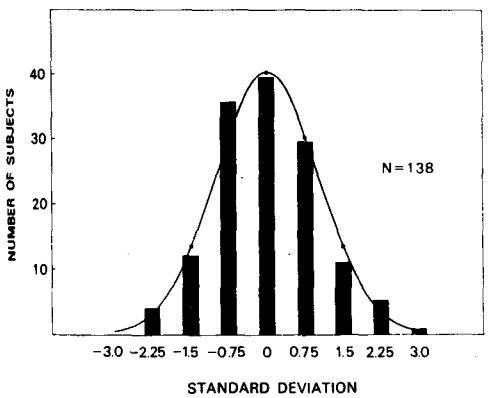
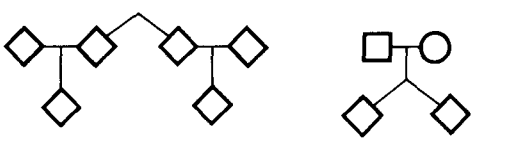


Fig. 2



r_{Mzt}	—		0.8429	N=31
$r_{H \cdot W}$	−0.2390	N=12	0.3771	N=31
$b_{P \cdot O}$	0.1269	N=60	0.5100	N=130
$b_{\bar{P} \cdot O}$	0.3051	N=26	0.7516	N=62
r_{HS}	0.2700	N=18	—	

Fig. 3

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The model used for the analysis is shown in the Table. It was published elsewhere [9], and it owes greatly to the original work of Fisher [5]. In addition to the parameter of assortative mating, the model incorporates a parameter of the effect of common familial environment.

In this model, there are five parameters to be estimated: additive variance (V_A), dominance variance (V_D), variance due to common familial environment (V_{EC}), variance due to common environment arising from maternal genotype (V_{EM}), and correlation between spouses due to common genotype (ρ). On the other hand, there are only four equation in each part of the study. But there was no difference between correlations of genetic half-sibs born to male (r_{mHS}) and female (r_{fHS}) MZ twin parents ($p = 0.37$), and therefore V_{EM} can be discarded. Still, there are four unknown parameters and four equations, so we reduced the number of parameters using the equation of husband-wife correlation and fixed the sum of ρ and V_{EC} so that the data can be subjected to the estimate of parameters.

RESULTS

Fig. 4 shows the result in the first part of the study. Three lines of half-sib correlation (r_{HS}), mid-parent-offspring regression ($b_{\bar{P}\cdot O}$), and parent-offspring regression ($b_{P\cdot O}$) converge at the point of heritability (V_A/V_P) about 0.8. Corresponding V_{EC} is about -0.3 and ρ is about 0.1.

The result indicates a high heritability of plasma uric acid level. In order to confirm the result, we conducted the second part of the study (Fig. 5). Here we obtained two sets of estimates from crossings of two lines: one with heritability about 0.7, and the other about 0.3. Corresponding estimates of other parameters are shown in Fig. 5 (V_{EW} is remainder of environmental variance).

Sample size of this study is still small, and we do not know which estimate is correct. Tentative conclusion is that heritability of plasma uric acid is not less than 0.3, which indicates a genetic control of the quantitative character.

Some twin children in the second part of the study were admitted to the Junior Highschool, and were given intelligence test (Shin Tanaka B2 Test). Fig. 6 shows the regression of IQ on corrected and standardized plasma uric acid level. It is seen that, as the level of plasma uric acid increases, IQ increases. The correlation is about 0.3, which is significant in this population of selected twin children with a high average of IQ, about 120.

Table. The Model.

Living Together	
MZ Twins	$r_{MZt} = (V_A + V_D + V_{EC} + V_{EM})/V_P$
Husband-wife (Inouye 1979)	$r_{H\cdot W} = \rho + V_{EC}/V_P$
Parent-offspring (Fisher 1918)	$b_{P\cdot O} = \frac{1}{2}(1+\rho)V_A/V_P + V_{EC}/V_P$
Mid-parent-offspring (Inouye 1979)	$b_{\bar{P}\cdot O} = (V_A + 2V_{EC})/(V_P + V_{EC})$
Living Apart	
Offspring of Male MZ Twins (Inouye 1979)	$r_{mHS} = (\frac{1}{4} + \frac{3}{4}\rho)V_A/V_P$
Offspring of Female MZ Twins (Inouye 1979)	$r_{fHS} = (\frac{1}{4} + \frac{3}{4}\rho)V_A/V_P + V_{EM}/V_P$

Symbols r : intraclass correlation b : regression

ρ : intraclass correlation of spouses due to assortative mating based on common genotype

Variances V_P : phenotypic (total) V_A : additive

V_D : dominance V_{EC} : common familial environment

V_{EM} : common environment due to maternal genotype

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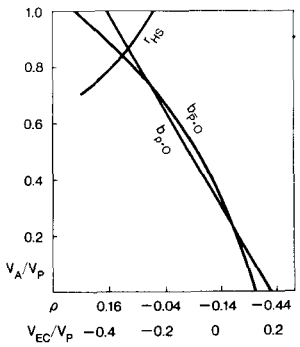

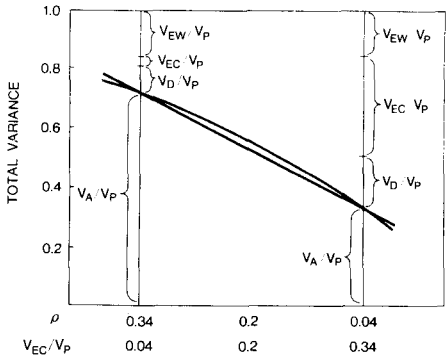

Figs. 4 - 5 - Estimate of heritability (V_A/Vp) and other parameters in standardized plasma uric acid level. First and second part of the study.

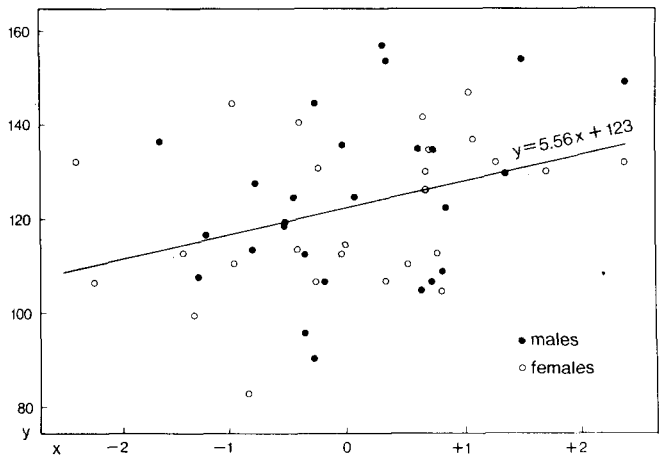

Fig. 6 - Regression of IQ (y) on standardized uric acid level (x) in selected twin children.
$r = 0.3343$, $P < 0.025$.

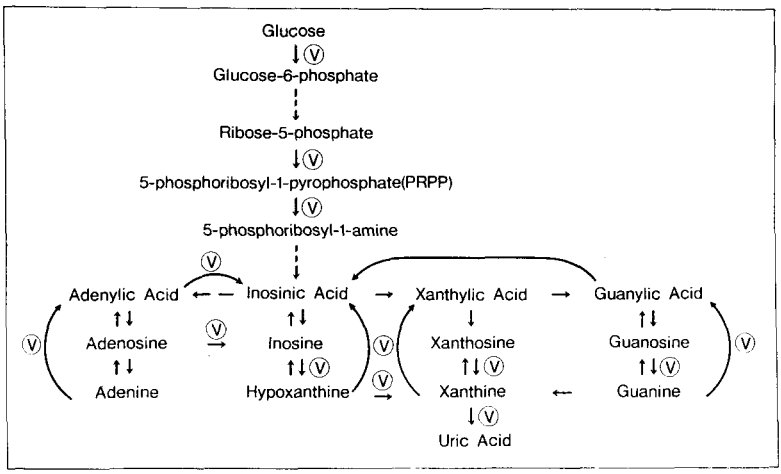

Fig. 7 - Purine metabolism pathway.

Ⓥ : Reported/suggested enzyme defect/polymorphism

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DISCUSSION AND CONCLUSIONS

The above finding indicates that additive effect of polygenes plays a part in the variation of plasma uric acid level in the population. A similar conclusion can be drawn for IQ on the basis of accumulated evidence. In addition, the two variables are significantly correlated, suggesting that the two quantitative characters share common gene loci.

The finding may ultimately lead to identification of specific genes responsible for normal quantitative behavioural traits in man. Fig. 7 shows a part of the purine metabolism pathway, the end product of which is uric acid in man. At various steps of metabolism marked by "v" in Fig. 7, variant enzymes have been reported. It would be worth to look for polymorphism at each step of purine metabolism and an association of polymorphism with IQ variation.

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Correspondence: Eiji Inouye, M.D., Director, Institute for Developmental Research, Kamiyacho, Kasugai, Aichi 480-03, Japan.