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A Genetic Analysis of Taste Threshold for Phenylthiocarbamide

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Taste threshold for phenylthiocarbamide (PTC) was measured in 393 offspring from the families of 85 monozygotic (MZ) twin pairs. PTC scores were bimodally distributed with modes at one and eight and the antimode at five. Because of the non-normality of the distribution, a jackknife procedure was used to obtain 95% confidence intervals for the estimates of genetic, maternal, and environmental parameters. Analyses which assumed no epistasis and which included additive genetic effects revealed that 37.9% of the observed variation in PTC threshold was due to additive genetic effects, 16.6% was due to dominance effects, 14.2% was due to maternal effects, 13.7% was due to a common sibship environment, and 17.6% was due to random environmental effects, yielding a broad sense heritability of 0.55 for the threshold ability to taste PTC. Analyses which did not include additive genetic effects revealed 26.6% of the observed variance was due to dominance effects, 23.6% to maternal effects, and 49.8% to environmental effects at the 0.67 confidence levels, but that environmental factors accounted for 72.4% and dominance effects for 23.6% of the observed variation at the 95% level.

Key words: Phenylthiocarbamide (PTC), Twin model, Jackknife procedure, Polygenic trait

INTRODUCTION

Variation in the ability to taste phenylthiocarbamide (PTC) was first detected in a random sample of volunteers from Delaware by A. L. Fox [4]. Extensive research has been conducted since that time concerning the mode of inheritance of taste sensitivity to PTC, and there has been increasing evidence that PTC taste sensitivity is controlled by a major gene. Multiple analyses [2, 3, 7, 12, 13] have led to the conclusion that the ability to taste PTC is inherited as an autosomal dominant. However, in many of the earlier studies the ability to taste PTC was treated as a dichotomy, thus permitting only monogenic patterns of inheritance to be investigated.

In 1949, Harris and Kalmus [5] devised a method to determine PTC taste threshold by administering serial dilutions of the chemical. This technique permitted a quantification of PTC sensitivity that has demonstrated the existence of wide variability within taster and

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non-taster categories. Results of quantitative analyses to explore the etiology of the trait under a polygenic hypothesis have been difficult to interpret, however, due to the extreme bimodality of the distribution of PTC taste threshold scores and the lack of a well-defined boundary clearly separating "taster" from "non-taster." While results of quantitative studies have not provided strong evidence supporting a polygenic etiology for PTC taste sensitivity, the monogenic explanation, given the wide variation in taste threshold, can be valid only if the high degree of variation observed within the taster and non-taster categories results from environmental or other nongenetic sources. To date, environmental effects have not been demonstrated as important factors in determining an individual's ability to taste PTC.

The present study was conducted to test several hypotheses concerning the overall variation in PTC taste threshold, including differences between and around the two modes. The methodology employed [10] permits the detection of variation due to additive, dominance, maternal, and environmental sources through the study of the offspring of monozygotic twins. This analysis provides an opportunity to validate the previous finding of dominance based on qualitative genetic studies through the use of an approach that can detect variance due to dominance effects for a quantitative trait.

MATERIALS AND METHODS

Three hundred ninety-three offspring from 32 male and 53 female monozygotic twin kinships seen at the Medical College of Virginia and Indiana University were tested with serial dilutions of phenylthiocarbamide (PTC) to determine their taster status. The subjects ranged in age from one to 45 years, with a median age of 13 years. A modification of the methodology of Harris and Kalmus [5] was employed in preparing the solutions. All PTC solutions were made up in twofold dilutions with tap water at room temperature. The strongest solution used (approximately 0.26% PTC) was mixed overnight and then filtered the next morning to remove any undissolved chemical. The solution (number 1) was then serially diluted to give 13 solutions with different concentrations of PTC. The concentration of each solution in the sequence was half that of the one above it, such that the scale of concentrations was logarithmic. The serial dilutions were placed in plastic squirt bottles and administered directly onto the tongue. Each subject was given a few cc of plain tap water before starting with the weakest concentrations of PTC and working up to the most dilute solution, or threshold, at which a distinct taste, usually described as bitter, could be perceived. After the subject responded to a solution, the PTC-tester administered a solution two dilutions weaker and then proceeded with the test as before to determine whether the same dilution would elicit a response. If the subject responded again at the same number dilution, that dilution was thought to represent the concentration of PTC corresponding to the individual's threshold value. In cases where the individual did not respond again to the dilution eliciting the initial response, the PTC-tester would proceed with the test until a definite taste was determined or, as may be the case with a non-taster, no taste was perceived. To rule out the psychological influence of expectation, those about to be tested were not present when the test was given to others. Also, it was a practice not to inform the subject what taste sensation to expect in the event that an error would be made in identification of the threshold value due to anticipation of a bitter taste.

STATISTICAL METHODS

In a preliminary analysis, the sample was subdivided into age groups of six-year intervals, and a χ^2 contingency test was performed in order to detect any association between age and PTC sensitivity. The sample was then divided into two dichotomous subsamples by sex, and a t-test on the group means was conducted to detect sex differences for PTC threshold.

Separate nested analyses of variance were performed on the PTC scores of the offspring contained in the male and female monozygotic twin kinships according to the following linear model: $y_{ijk} = \mu + \text{kinship}_i + \text{sibship}_j(\text{kinship}_i) + E_{ij}$. This procedure permitted the calculation of point estimates of variance components resulting from differences among kinships (σ^2_a), differences between sibships within kinships (σ^2_b), and differences within sibships (σ^2_w).

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Five variance components were obtained from the nested analyses of variance and set equal to their genetic and environmental expectations under a model postulating effects due to additive genetic, dominance, maternal, sibship environmental, and individual environmental factors. Epistatic effects were assumed to be zero. Since the resulting series of equations were linearly dependent (Table 1), a solution was obtained using a generalized inverse procedure (Matrix Procedure of the Statistical Analysis System of the SAS Institute).

The bimodality of the distribution of PTC scores precluded the use of statistical procedures requiring the assumption of normality. Therefore, 95% confidence intervals for the parameter estimates were computed using a jackknife procedure [1]. Table 2 gives the specific formulas used for obtaining these confidence interval estimates. The jackknife procedure involves reanalyzing the data set 85 times, each time deleting one kinship. Eighty-five estimates were obtained for the component of variance due to each genetic and environmental parameter. The 85 estimates of V_A can then be treated as independent and identically distributed random variables following a t distribution with 84 degrees of freedom. The jackknife procedure is known to yield broad confidence bands, but under the condition of non-normality, it provides a reliable method for determining the variability in estimates of genetic and environmental parameters.

RESULTS

Threshold values in our sample of 393 individuals ranged from zero (non-taster) to 12, with a mean of 6.35 ± 2.88. Data were tested for departures from normality and found to be bimodally distributed with a mode at one, a second mode at eight, and the antimode at five (Figure). One hundred thirteen persons, or 28.8% of the population, were classified as non-tasters by their inability to taste solutions of PTC equal to or greater than solution number 6. The mean threshold value for tasters was 8.04 ± 0.97, which was significantly different (P = 0.0001) from the mean threshold value for non-tasters, 2.19 ± 1.46.

The mean age for tasters, 13.9 years, did not differ significantly (P = 0.89) from the

TABLE 1. Genetic Expectation Equations

Variance component	Genetic parameters				
	V_A	V_D	V_M	V_{ES}	V_{EW}
σa_{δ}^2	0.25	0	0	0	0
σb_{δ}^2	0.25	0.25	1	1	0
σ_W^2	0.50	0.75	0	0	1
σb_{φ}^2	0.25	0.25	0	1	0
σa_{φ}^2	0.25	0	1	0	0

TABLE 2. Jackknife Procedure for Confidence Interval Estimate of Parameter Θ

$\hat{\Theta}$ = original estimate of the parameter

$\hat{\Theta}(i)$ = estimate of the parameter with the ith kinship removed from the analysis

$$J_i(\hat{\Theta}) = 85\hat{\Theta} - 84\hat{\Theta}(i)$$

$$J(\hat{\Theta}) = 85\hat{\Theta} - (84/85) \sum_{i=1}^{85} \hat{\Theta}(i)$$

95% confidence limits for parameter Θ

$$J(\hat{\Theta}) \pm t_{84,.975} \frac{\sqrt{\sum_{i=1}^{85} [J_i(\hat{\Theta}) - J(\hat{\Theta})]^2}}{\sqrt{85(84)}}$$

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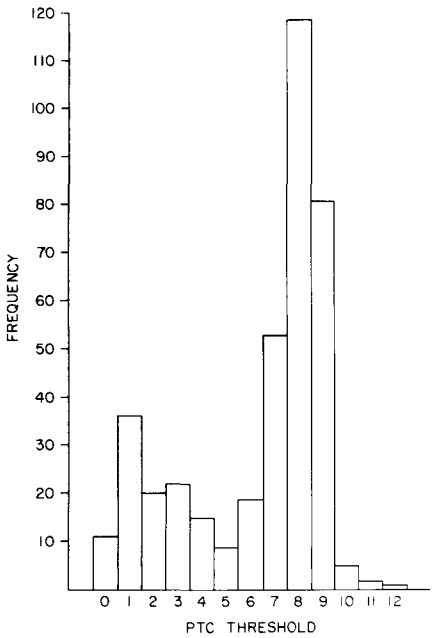

Figure. Distribution of PTC taste threshold in study population.

mean age for non-tasters, 13.8 years. The age ranged from one to 40 years in the tasters and four to 45 years in the non-tasters. To detect age effects on the threshold value, a contingency table was constructed and a χ^2 test of association performed. No significant age effect on PTC threshold was detected for this population (Table 3). Furthermore, no significant differences due to sex were found in mean PTC values, with males having a mean value of 6.42 ± 2.87 and females, 6.28 ± 2.91.

Mean squares from the nested analyses of variance and the corresponding variance component estimates are presented in Table 4. Since no significant heterogeneity in the within-sibship mean squares was found in the analyses on the offspring of the male and female twins, these estimates were pooled to obtain a more precise estimate of the within-sibship variance component (σ^2_w). Maternal effects can be detected by contrasting the results of nested analysis of variance for the offspring of male versus female twins where a maternal effect would be suggested by large between-full-sibships-within-male-half-sibships and among-female-half-sibship components in conjunction with small among-male-half-sibships and between-full-sibships-within-female-half-sibship components.

A model containing additive, dominance, maternal, and environmental parameters was postulated for PTC threshold. Dominance effects were included in order to validate previous findings of dominance suggested from qualitative studies [2, 3, 12, 13]. Environmental effects were included because, in the presence of a dominant major gene, such effects could explain the pattern of variability in the trait. Maternal effects were included because they were suggested by the pattern of variance components shown in Table 4.

Solutions for the genetic and environmental parameters were obtained through a least-squares procedure, and their point estimates are given in Table 5. Estimates indicate that, if the postulated model is an appropriate one, approximately half of the variation in PTC may be attributed to additive and dominance genetic effects, while the remainder results from maternal, sibship environmental, and individual environmental factors.

TABLE 3. Test for Age Effects on PTC Taste Threshold

	PTC Threshold				
Age (years)	0–3	4–7	8	9–12	Total
0–6	13	24	19	12	68
7–10	20	18	19	21	78
11–13	18	18	21	19	76
14–16	16	5	22	13	56
17–20	12	13	17	6	48
⩾21	10	18	21	18	67
Total	89	96	119	89	393

$\chi^2_{15} = 20.07$; p value = 0.17.

TABLE 4. Summary of Results From Nested Analyses of Variance

Source	df	Mean squares	Variance component
Male half-sibships	31	15.16	$\sigma^2_a = 0.79$
Full sibships/male half-sibships	32	10.10	$\sigma^2_b = 3.44$
Within full sibs	223	4.06	$\sigma^2_w = 4.06$
Full sibships/female half-sibships	53	9.70	$\sigma^2_b = 2.25$
Female half-sibships	52	19.19	$\sigma^2_a = 1.95$

TABLE 5. Estimates of Genetic, Environmental, and Maternal Effects

Parameter	Estimate	Percent of variance
V_A	3.14	37.9
V_D	1.38	16.64
V_M	1.17	14.17
V_{ES}	1.13	13.66
V_{EM}	1.46	17.63

$h^2_b = 0.55$.

Results from the jackknife procedure revealed wide variability in the estimates for the postulated model. All confidence bands were large and included zero for each parameter.

A jackknife procedure performed on the original variance components revealed that the confidence interval for the among-component for males also includes zero. Since its genetic expectation is additive variance only, it was decided to exclude additive genetic effects from the model.

Estimates and confidence intervals for the model containing dominance, maternal, sibship environmental, and individual environmental effects are given in Table 6. Intervals are narrow, and all parameters in the model have been detected at the 2/3 (or 67%) level of confidence. Only dominance and individual environmental effects can be detected at the 95% level of confidence, however.

Under this postulated model, the heritability of PTC taste threshold is 0.27, with 73% of the variance due to environmental effects. To investigate further a possible environmental influence on PTC threshold, differences in PTC threshold values between 90 monozygotic twins were determined, and 47% of the pairs were found to be discordant, five pairs differing by three scores or greater.

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TABLE 6. Estimates of Genetic, Environmental, and Maternal Effects

Parameter	Estimate	Percent of variance	2/3 Confidence interval estimate	95% Confidence interval estimate
V_D	1.88	26.6	(1.45, 2.31)	(1.06, 2.70)
V_M	1.66	23.6	(0.68, 2.65)	(−0.22, 3.54)
V_{ES}	1.51	21.4	(0.60, 2.43)	(−0.23, 3.26)
V_{EW}	2.00	28.4	(1.40, 2.60)	(0.85, 3.15)

$h_b^2 = 0.27$.

DISCUSSION

The present study of PTC threshold in the offspring of identical twins is unique in that the method of analysis used permits the estimation of the contribution of additive and dominance effects, maternal effects, and sibship and individual environmental effects to the observed variance [10]. The finding of a heritability for PTC threshold of 0.27 suggests that the major portion of the variance is due to environmental effects. Whether the extremely low heritability for PTC threshold estimated in this study results from too small a sample size and the associated inability to obtain estimates of additive variance significantly greater than zero or is a true representation of the nature of the factors determining this trait cannot be determined. The analysis of this particular study population examined only had the power to detect significant dominance and environmental effects. The environmental effects detected may be prenatal as well as postnatal, as positive maternal effects were noted. Furthermore, differences in PTC threshold values in MZ twins, who are necessarily concordant for genotype, may reflect an environmental influence. It appears, therefore, that the ability to taste PTC is controlled by a major gene that exhibits dominance, while PTC taste threshold is influenced by environmental factors.

Several investigators have reported results of PTC taste sensitivity from various racial groups. The first application of the PTC test to racial study was the work of Levine and Anderson [6], testing 183 pure North American Indians at the Haskell Institute, Lawrence, Kansas. Our study of white Americans from Indiana and Virginia revealed that 28.8% of the total population was unable to taste solutions of PTC equal to or greater than solution number 6. This finding is very similar to those of Snyder [11] and Parr [11], who tested white Americans from Ohio State University (29.8% non-tasters) and Washington, DC (30.9% non-tasters), respectively.

Parr [11] reported that taste acuity for PTC had no close relationship to taste acuity for other bitter compounds such as picric acid and quinine sulphate, nor did it appear to be affected by such factors as age, sex, state of health, time of day, recency of taking food, salivary pH, gum chewing, use of tobacco, mouth rinses, false teeth, or other factors that might be present to affect taste perception. Our study is in agreement with that of Parr, as no significant age effect on PTC threshold was detected. However, the range of our sample is not large enough to allow definitive verification of this finding.

Studies of Harris and Kalmus [5], Mohr [9], and others have indicated that taste sensitivity to PTC decreases with age. The Harris and Kalmus report consisted of 441 British males ranging from ten to 91 years of age. They found the modes of the taster and non-taster groups, as well as the antimode dividing the two groups, to be shifted in the direction of more concentrated solutions with increasing age. They proposed that in the classification of an individual's taster status, reference must be made to the threshold

distribution of his age group. A possible explanation for this decreased sensitivity to PTC with increasing age is the finding of Mochizuki [8] of a decreased number of taste buds in the aging foliate papillae.

The evidence for maternal influences on PTC threshold provided by our analyses are of particular interest. Maternal effects can arise from prenatal or intrauterine influences on fetal development, cultural effects related to infant care and child-rearing practices, or heritable cytoplasmic differences. That cytoplasmic inheritance also occurs in man has been recently demonstrated by analysis of the familial pattern of transmission of polymorphic differences in endonuclease excision sites in mitochondrial DNA [14]. What the mechanism for the apparent maternal effect on PTC may be remains to be determined.

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