Heritability of Systolic Blood Pressure
Analysis of Variance in MZ Twin Parents and Their Children

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Systolic blood pressure, standardized for age and sex, was measured in 76 MZ twin pairs and their 341 children. Maximum likelihood estimation of genetical and environmental parameters from the independent parental and offspring ANOVAs indicated a complete absence of both maternal and shared environmental effects, together with a heritability of 63%. These results are shown to be reasonably consistent with those from previous studies.

Key words: Systolic blood pressure, Maximum likelihood genetic analysis, Twin model

INTRODUCTION

Estimation of genetic and environmental sources of human variation is the raison d'être of traditional twin studies. Partioned variances of monozygotic (MZ) and dizygotic (DZ) twins are compared, and estimates of genetic variance are derived. This approach, simple, yet sound, has formed the cornerstone of quantitative human genetics.

In the past decade, however, advances have been made both in methodological designs employing twin subjects and in analytic methods for estimating sources of variation. The purpose of this report is to illustrate a maximum likelihood procedure [5] for estimating genetic and environmental parameters. The application is to standardized systolic blood pressures measured in MZ twin parents and their children [13].

Familial aggregation of blood pressure is well established, and recent evidence documents sibling resemblance early in life [16]. Twin studies have revealed significant genetic variance in blood pressure levels at different ages [2, 6, 9]. Uncertainty remains, however, over the nature and magnitude of maternal effects and the influences of common family

environments. To evaluate the contribution of such effects to familial aggregation of blood pressure, we have estimated sources of variation in systolic pressures in MZ twin parents and their children. The multiple relationships that exist within the families of identical twin parents permit a direct test of maternal effects and an appraisal of several sources of common environmental influence.

METHOD

Study Population

The subjects in this study were 76 MZ twin pairs and 341 of their offspring divided into 28 paternal and 48 maternal kinships according to the gender of their twin parent. Ascertainment of the families and the methods of measurement of blood pressure are described in an earlier report [13].

Analyses of Variance

For each of the two kinds of kinships, an analysis of variance of offspring blood pressure was carried out to estimate variation arising from the three levels of hierarchy illustrated in the Figure. These three levels derive from the full sibships nested within the structure of the kinships of MZ twin parents.

The three levels of hierarchy give rise to the three mean squares for maternal and paternal kinships shown in the ANOVA in Table 1. The highest level in the analysis reflects variation between the means of the 28 paternal and 48 maternal kinships; these sources, therefore, have 27 and 47 df, respectively. The intermediate level in the hierarchy reflects the pooled variation between the means of pairs of sibships nested within each of the kinships. Members of each sibship are related to members of the other as half-siblings, since in each kinship either the mothers or fathers are genetically identical MZ twins. The lowest level in the hierarchy simply reflects pooled variation among individuals within the sibships.
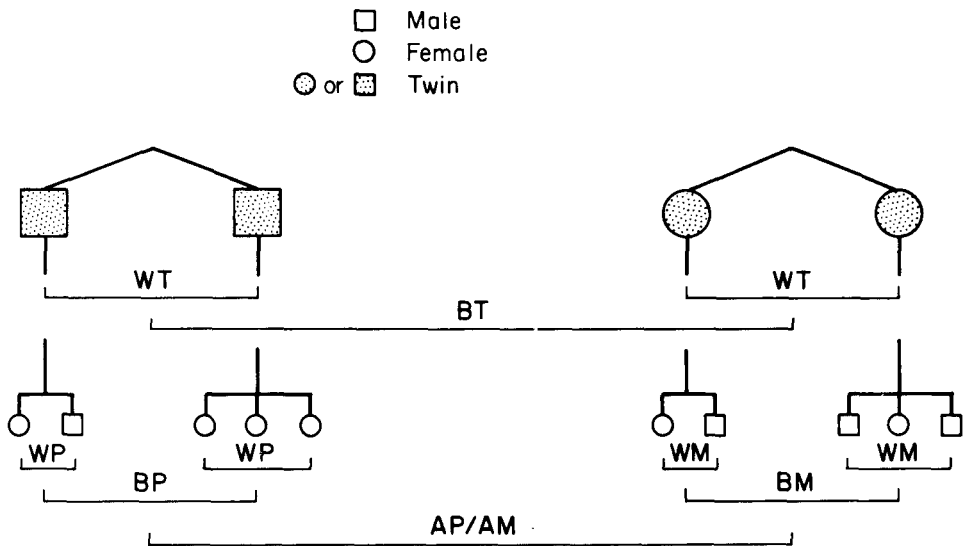

Figure. Analyses of variance in MZ twin parents and their offspring. Variation observed in the twin parents is partitioned into two components arising within (WT) and between (BT) twin pairs. A hierarchical analysis of offspring data partitions variance into that among unrelated paternal (AP) and maternal (AM) kinships, that between paternal and maternal half-sibships (BP and BM), and that within sibships in paternal (WP) and maternal (WM) kinships.

TABLE 1. Analyses of Variance of Standardized Systolic Blood Pressure in MZ Twin Parents and Their Children

Source	df	MS	EMS
Paternal families			
Among kinships	27	1.51	$\sigma^2_{WP} + 2.38\sigma^2_{BP} + 4.40\sigma^2_{AP}$
Between sibships within kinships	28	0.63	$\sigma^2_{WP} + 2.04\sigma^2_{BP}$
Within sibships	68	0.61	σ^2_{WP}
Maternal families			
Among kinships	47	1.75	$\sigma^2_{WM} + 2.40\sigma^2_{BM} + 4.51\sigma^2_{AM}$
Between sibships within kinships	48	0.74	$\sigma^2_{WM} + 2.12\sigma^2_{BM}$
Within kinships	121	0.82	σ^2_{WM}
Twin pairs			
Between pairs	75	1.49	$\sigma^2_{WT} + 2\sigma^2_{BT}$
Within pairs	76	0.30	σ^2_{WT}

In addition to these two hierarchical analyses of variance, an ANOVA of the blood pressures of the twin parents in the 76 kinships yields two more independent between- and within-pair mean squares listed in Table 1. These mean squares reflect pair similarities and differences and can be used to calculate the intraclass correlation, should that be required. Including only the ANOVA of the twin parents, but ignoring parent-offspring resemblance and other relationships their presence allows, we are treating the parental data as deriving from an independent sample of twins. This procedure, which is statistically perfectly legitimate, also allows us to simplify the model in a convenient manner. Inclusion of the additional relationships over and above those expressed in the three ANOVAs leads to the proliferation of environmental parameters of doubtful status, with little or no additional information concerning the parameters in our present model.

In all, there are eight mean squares and eight corresponding components of variance in the three ANOVAs summarized in Table 1. In the two hierarchical analyses, these components are designated by subscripts AP, BP; WP, representing the three levels in the paternal kinships, and by AM, BM, WM, representing the corresponding levels in the maternal kinships. Finally, there are the two components subscripted BT and WT in the mean squares deriving from the twin parents.

The coefficients of these components in the expected mean squares reflect the distribution of the numbers of individuals in the families. In the hierarchical analyses, the number of sibships nested within each half-sibship is fixed at two, whereas the number of offspring within each sibship varies, and that variation is reflected in the fractional nature of the coefficients. The coefficients were computed from the observed distribution of family size [15]. In the analysis of twin pairs, family size is, of course, fixed at two, and that regularity is reflected in the coefficient of two listed in Table 1.

The components of variance reflect the sources of variation in the raw data. In turn, these components are expected to reflect the genetical and environmental sources of variation shown in Table 2.

Model

So far as the genetical component is concerned, we have assumed the simplest of all possible models; namely, that involving only additive genetic variation, V_A. Further, the coefficients of ¼, ½, and 1, used to characterize the contribution of V_A to the components, embody the assumption that mating with respect to blood pressure is at random. This assumption is probably met imperfectly [14], but it may suffice to a first degree of

TABLE 2. Component Expectations Derived From Model Incorporating Additive Genetic Effects and All Sources of Environmental Influence

Component	Expected value
σ^2_{AP}	$\frac{1}{4}V_A + V_{EH}$
σ^2_{BP}	$\frac{1}{4}V_A + V_M + V_{ES}$
σ^2_{WP}	$\frac{1}{2}V_A + V_{EW}$
σ^2_{AM}	$\frac{1}{4}V_A + V_M + V_{EH}$
σ^2_{BM}	$\frac{1}{4}V_A + V_{ES}$
σ^2_{WM}	$\frac{1}{2}V_A + V_{EW}$
σ^2_{BT}	$V_A + V_M + V_{EH} + V_{ES}$
σ^2_{WT}	V_{EW}

approximation. One of the merits of the estimation procedure we will be using is that this assumption, along with others, is tested during the model-fitting procedure.

A unique feature of the MZ half-sib design is that it allows us to differentiate between at least three additional sources of familial resemblance reflected in the components V_{EH}, V_{ES}, V_M. The first two components are purely environmental in origin and represent a partition of the biometrical genetical component, E_2, as defined by Jinks and Fulker [8], or of c^2 as defined by Rao et al [12] in their path analytic model. V_{ES} reflects differences in nuclear family environment, but within the kinships — that is, environmental differences between half-sib families in this design. V_{EH}, however, reflects environmental differences between unrelated kinships. Clearly, the two components together should reflect the full range of environmental differences between families in the general population. Of most interest in this design, however, is the third component, V_M, representing the effect of maternal environment. This source of variation creates similarity between half-siblings within those kinships where the MZ parents are females. In such cases, the half-sib families not only share the genotypic contribution from the mother, but any contribution that mother's genotype makes to the pre- and postnatal environment as well. Where the MZ twin parents are male, these maternal effects will originate from two unrelated female spouses and consequently contribute to the dissimilarity of paternal half-sibs. These differing effects of V_M can be seen in the expectations listed in Table 2. Lastly, we have V_{EW}, the specific or within-family environmental effect designated E_1 in the biometrical formulation.

The model we have adopted is essentially that of Nance and Corey [11], although we have omitted data from spouses and made a minor correction in the expectations of the environmental components for twin parents. More important, however, we have employed a maximum likelihood (ML) estimation procedure to estimate the genetic and environmental components of the model. The ML procedure is not only statistically optimal for estimating components of variance from ANOVA, but also it is simple to employ.

Maximum Likelihood Estimation

In order to employ an ML estimation procedure, we need to know the distribution of our data. Since the raw data were age-banded and normalized separately by sex, the assumption

of normality is clearly appropriate. In this case, the eight independent mean squares (MS) calculated from the data and to which we fit our model via the eight corresponding expected mean squares (EMS) will follow a sampling distribution related to χ^2. The probability density function for each MS, f(MS), has the form: $f(MS) \propto EMS_8^{-\frac{1}{2}N} e^{\frac{1}{2}N \cdot MS/EMS}$, where N is df. The joint likelihood, L, of the eight MS is therefore $L = \prod_{i=1}^{8} f(MS_i)$.

If the L, given the expected form of the mean square on our model, is designated L_1, and the perfect fit case, where the EMS_i equal the MS_i is L_0, then it follows from ML theory that the log likelihood ratio expression $2 (\log_e L_0 - \log_e L_1) = \chi^2$. Substituting the expression for f(MS) into the log likelihood ratio expression gives

$$\chi^2 = \sum_{i=1}^{8} N_i [\log_e(EMS_i/MS_i) + (MS_i/EMS_i) - 1] .$$

Finding values of our parameters that minimize this χ^2 will produce the ML estimates we require.

The algorithm for producing these estimates is very straightforward, given we have a computer routine for minimizing a function such as the χ^2 above. Such routines are readily available through most university computer centers, since they are extensively used by mathematicians and engineers.

The routine we have used was developed by the Computer Center of the European Organization for Nuclear Research (CERN), and requires only a single FORTRAN subroutine of some 50 cards length to be written in order to execute the required minimization. The minimization routine is iterative and starts with rough trial values of the six parameters shown in Table 3. These estimates are substituted into the eight EMS according to the formulae in Table 1. Then, the eight EMS_i, MS_i, and df_i are substituted into the likelihood ratio χ^2 expression given above. At this point, the minimization routine takes over automatically and adjusts the estimates of the six parameters until χ^2 is as small as possible.

The value of χ^2 permits a test of the adequacy of the model, and the routine provides numerical estimates of the standard errors of the parameter estimates. In addition, simple constraints may be imposed on the estimates to keep them within reasonable bounds. In the present analysis, for example, we required the components of variance to remain positive, clearly a necessary condition for parameters that define the average of squared effects. Where the data cannot reasonably bear such constraints, a model failure should be indicated by the χ^2.

RESULTS AND DISCUSSION

The outcome of the estimation procedure is shown in Table 3. During the minimization, the non-negative constraints on the shared environment parameters were made operative, so that, in effect, they were set to zero. The nonsignificant χ^2_6 (= 8.29, P > 0.2) indicates that this condition did no great violence to the data and resulted in just two significant parameters: V_A, the additive genetic variance, and V_{EW}, the specific within-family environmental variance.

Our failure to find shared environmental effects appears to be consistent with other studies of blood pressure. In a recent study of systolic pressure in the large NAS-NRC registry of veteran twins, Feinleib et al [4] report MZ and DZ correlations of 0.55 and 0.25, respectively. On the model we have adopted here, $V_{EH} + V_{ES} = 2 (0.25) - 0.55 = -0.05$, a small and nonsignificant negative component, for which a constrained estimation

TABLE 3. Maximum Likelihood Estimates of Genetic and Environmental Parameters

V_A	$= 0.59 \pm 0.09$
V_M	$= 0.0$
V_{EH}	$= 0.0$
V_{ES}	$= 0.0$
V_{EW}	$= 0.34 \pm 0.05$
χ^2_6	$= 8.29 \, ; \, P > 0.20$
h^2	$= 0.63 \pm 0.10$

Note: Since only additive genetic variance was assumed in the simple model tested here, the parameter for dominance, V_D, was set to zero.

procedure will yield the zero components obtained in the present study. Investigations of adopted and step-children, which permit direct tests of common environmental influences, also indicate negligible effects from shared environments [1, 3, 7].

By contrast, V_A is highly significant, being more than five times its standard error; the result indicates a substantial heritability (h^2):

$$h^2 = \frac{V_A}{V_A + V_{EW}} = \frac{0.59}{0.59 + 0.34} = 0.63 \text{ or } 63\%$$

Again, this is a finding consistent with earlier reports. Longitudinal studies of representative samples in South Wales [10] report single parent-offspring regressions for age-standardized systolic pressures that yield heritability estimates of 0.51 for male probands and 0.56 for female probands. Based on regression of offspring on single parent, a heritability estimate of 0.52 was reported for the present data [13]. Finally, the NHLBI study [4] of 514 middle-aged veteran twins yielded an h^2 estimate of 0.60, while an analysis of basal systolic pressures in 155 pairs of adolescent twins [9] obtained correlations of 0.85 and 0.50, implying an h^2 of 0.70. The present study is thus consistent with previous ones in indicating substantial additive variation for systolic blood pressure and a negligible effect of shared or common environment.

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