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Models for the longitudinal genetic analysis of same-age twins: application to HDL cholesterol

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Models are presented for the analysis of longitudinal data from same-age twins which permit the exploration of a remarkably diverse array of alternative explanations for continuity and change during development. Data of this type permit the detection of new sources of genetic or environmental covariation during development that are not expressed at earlier ages and, because they include the effects of age-specific genes, the resulting heritability estimates are more reliable than those obtained from relatives who differ in age. The proposed models were applied to measurements of HDL cholesterol obtained on 81 pairs of monozygotic (MZ) twins and 69 dizygotic (DZ) pairs at 11, 12.5 and 14 years of age. All three MZ co-twin correlations were substantially higher than the self correlations across occasions, suggesting that new sources of genetic or environmental covariation must be expressed during early adolescence. This interpretation was confirmed by analysis of the full covariance matrices which showed that only models which assumed the expression of new or age-specific genes could explain the observed pattern of covariation. Because they include the effects of age-specific genes, the resulting heritabilities (0.80–0.83) were substantially higher than many previous estimates.

Keywords: twins, HDL, cholesterol, multivariate, development

Introduction

Any quantitative genetic analysis of developmental changes in gene expression must allow for the possibility that new genes or environmental effects may be expressed at different ages, thus altering the total individual or phenotypic variance. In 1983, in a study of genetic, maternal and parity effects on birth weight in the offspring of MZ twins, we showed how path analysis could readily be extended to accommodate sequential changes in the phenotypic variance and raised the possibility that a similar approach might be applied to the analysis of longitudinal data.[1] This idea was greatly extended by Eaves et al[2] and by Hewitt et al[3] who formulated a variety of alternative explanations for continuity and change during development. They showed how the resulting models could be distinguished by an analysis of the covariance matrices of related individuals across multiple occasions of measurement, and explored the feasibility of such studies by power analyses using simulated data. This article describes two alternative models for developmental change in gene expression which are then applied to longitudinal observations on the serum concentrations of HDL cholesterol in monozygotic and dizygotic twins during adolescence.

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Research design

If all the pairwise combinations of individuals with themselves and their co-twins are considered across n occasions of measurement, a total of n(2n + 1) distinct variances and covariances can be estimated from data on each group of twins. In order to perform a simultaneous genetic analysis of the resulting covariance matrices for MZ and DZ twins, we can postulate the causal model depicted by the path diagram shown in Figure 1, where n = 3 indicating that the phenotypes of twin A and B have each been observed on three occasions, $P_{.1}$, $P_{.2}$ and $P_{.3}$. It is assumed that on the first occasion of observation genetic ($G_{.1}$), as well as common and random environmental factors ($C_{.1}$ and $E_{.1}$) influence the phenotype. The genes and common environmental

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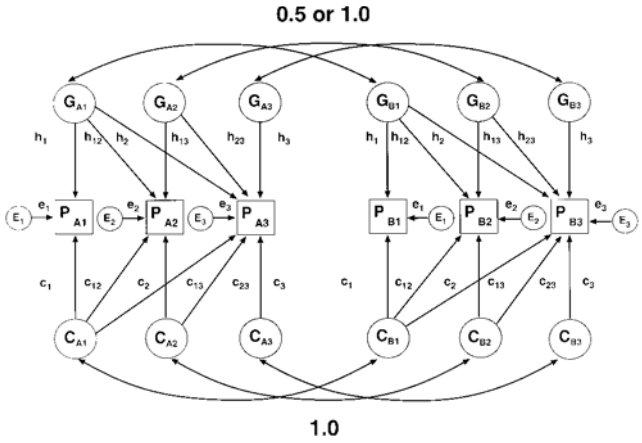

Figure 1 Path diagram showing effects of new and previously expressed genes (G) and common environmental effects (C) as well as random environmental effects (E) on the phenotypes of twins (P) measured at three ages.

effects that are active initially may also have persistent effects on the subsequent occasions of measurement as indicated by the arrows from $G_{.1}$ and $C_{.1}$ to $P_{.2}$ and $P_{.3}$. In a similar manner (not shown in the diagram), the random environmental effects could also have persistent effects on an individual which were not correlated between the members of a twin pair. However, the model also admits the possibility that new genes ($G_{.2}$ and $G_{.3}$) or environmental circumstances ($C_{.2}$, $C_{.3}$ and $E_{.2}$, $E_{.3}$) may influence the phenotypes measured at later ages which were not expressed at the first occasion.

The intensity of the unobserved or latent genetic and environmental causes are measured by the path coefficients $h_{.i}$, $c_{.i}$, $e_{.i}$. The correlations between the relevant genotypes for MZ and DZ twins are fixed at 1.0 and 0.5 while the common environmental correlation is fixed at 1.0 for both MZ and DZ twins. Since the phenotypes at later ages have a greater number of possible 'causes', there is no reason to expect the phenotypic variances at different ages to be the same. In principle, dominance can also be included in the model. The pattern would be identical to those shown for additive genetic and common environmental effects except that the appropriate correlations for MZ and DZ twins would be 1.0 and 0.25 respectively. Finally, alternative formulations of the latent genetic and environmental effects are possible. For example, it would be possible to postulate that one set of genes influences HDL cholesterol measurements throughout life, and that its effects are supplemented by age-specific genes (Figure 2). A formal distinction between this model and the full 'triangular decomposition' model shown in Figure 1 is only possible when four or more occasions of measurement are available for analysis.

Using the path diagram and the tracing rules of path analysis,[4] it would readily be possible to obtain the expected values for all 42 of the observed variances and covariances in terms of the unknown path coefficients we wish to estimate. However, the LISREL 7 computer program[5] permits specification of the unknown parameters in an intuitive graphical format as matrix elements in a likelihood equation along with the known correlations and fixed constraints. The program then obtains maximum likelihood estimates of the unknown parameters along with statistical tests of the goodness of fit of each postulated model. Examples of the use of the LISREL VII program for univariate, multivariate and longitudinal genetic analyses have been presented in detail.[6,7]

Materials and methods

Subject population

Eighty-one pairs of MZ twins and 69 DZ pairs were ascertained from the population-based Virginia Twin Registry and school systems within the central Virginia area. The twins were the members of the first two of six cohorts of same-age twins who are currently being followed longitudinally as part of an ongoing genetic study of cardiovascular risk factors during adolescence. All the twins included in the present analysis have been seen on three occasions, as close as possible to attaining the ages of 11, 12.5 and 14 years respectively. Details about the research protocol, methods of determining zygosity and demographic characteristics of the study population have been published elsewhere.[8]

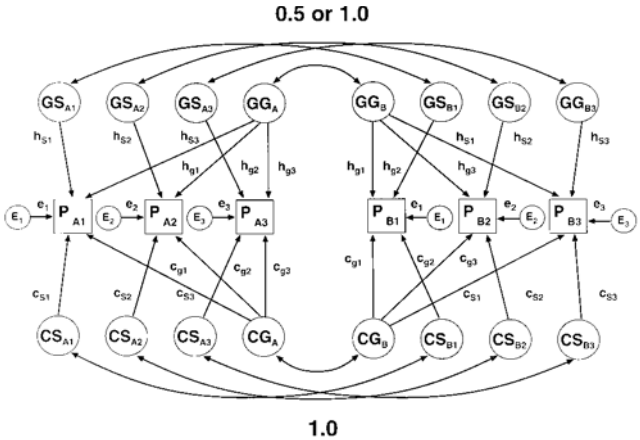

Figure 2 Path diagram showing the effects of general (CG) and specific (GS) genetic effects, general (CG) and specific (CS) common environmental effects, and random environmental (E) effects on the phenotypes of twins (P) measured at three ages.

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Laboratory methods

Seven ml of whole blood were collected from each twin 2–4 hours after a light breakfast using EDTA as an anticoagulant. The plasma was stored at 4°C until shipment by air to the laboratory of Dr Jere Segrest in Birmingham, Alabama, where plasma HDL cholesterol concentrations were measured by vertical spin ultracentrifugation.[9] In a series of 853 control samples, the serum HDL cholesterol concentration was 36.2 ± 1.6 mg per dl. A correlation of 0.95 was found when split samples from 221 subjects were assessed for total cholesterol by the Birmingham Lipid Laboratory and the Northwest Lipid Research Center.

Results

Our sample included 140 males, 160 females, 238 whites and 62 non-whites (Table 1). The mean values for HDL cholesterol agreed closely with previously reported data for children of the same age, race and sex.[10–13]

Table 1 Variation in serum HDL cholesterol levels (mg/dl) by age, race and sex

		age in years					
		11		12.5		14	
class	number	mean	s.d.	mean	s.d.	mean	s.d.
White							
Male	114	48.3	10.2	47.3	8.6	41.0	7.8
Female	124	46.0	7.1	45.1	8.3	42.0	8.4
Non-White[a]							
Male	26	49.2	11.8	47.8	12.6	45.3	9.6
Female	36	53.9	10.7	54.7	9.6	49.5	10.0

[a]Includes 58 black children, 2 orientals and 2 children of mixed ancestry.

In Table 2 and Table 3, the variances of the first and second members of the MZ and DZ twin pairs across the three occasions of measurement are given along the main diagonal with the observed correlations in the off diagonal cells to facilitate comparisons. Self correlations are indicated by italics while the occasion specific co-twin correlations are shown in bold face. The self correlations of the MZ and DZ twins across occasions were remarkably consistent, ranging from 0.45–0.65 and were no higher in the MZ (0.55) than the DZ (0.57) twins. The occasion-specific MZ twin correlations of 0.81–0.82 were also remarkably similar at all three ages while the DZ correlations ranged from 0.21–0.30. The fact that the occasion-specific MZ twin–twin correlations were found to be substantially higher than the self correlations at different ages strongly suggests that new sources of genetic or environmental covariation must be expressed at the two later ages.

Table 2 Observed variances and correlations for HDL cholesterol in 81 pairs of MZ twins studied on three occasions during adolescence

		twin A			twin B		
twin	age	11 yr	12.5 yr	14 yr	11 yr	12.5 yr	14 yr
	11 yr	98					
A	12.5 yr	0.47	88		—symmetric—		
	14 yr	0.51	0.59	79			
	11 yr	0.82	0.56	0.57	110		
B	12.5 yr	0.51	0.82	0.57	0.56	90	
	14 yr	0.56	0.60	0.81	0.59	0.60	96

Bold: indicates occasional-specific co-twin correlations; Italic: indicates self correlations.

Table 3 Observed variances and correlations for HDL cholesterol in 69 pairs of DZ twins studied on three occasions during adolescence

		twin A			twin B		
twin	age	11 yr	12.5 yr	14 yr	11 yr	12.5 yr	14 yr
	11 yr	94					
A	12.5 yr	0.58	107		—symmetric—		
	14 yr	0.60	0.65	83			
	11 yr	0.23	0.15	0.16	64		
B	12.5 yr	0.03	0.30	0.13	0.61	74	
	14 yr	0.08	0.10	0.21	0.45	0.58	55

Bold: indicates occasional-specific co-twin correlations; Italic: indicates self correlations.

To verify this interpretation, a variety of alternative explanations for the data were explored. As shown in Table 4, the full 'triangular decomposition' model in which a total of 18 separate parameters are estimated for the genetic, random and common environmental effects, provides an adequate explanation for the data. However, as shown by model 1, the data provide no hint that the magnitude of the random environmental effects differ between occasions or have any lasting influence on the phenotype, such that the reduced model, which is the one depicted in Figure 1, provides an even better and more parsimonious explanation for the data. In models 2–4, the consequences of omitting the genetic and common environmental effects are explored. When both of these sources of covariation are omitted (model 2), the remaining random environmental effects provide an inadequate explanation for the observed pattern of covariation. Similarly, the removal of genetic effects from the general model can be rejected (model 3). However, when the common environmental parameters were omitted (model 4), there was a non-significant increase in the chi square (χ^2 = 4.7, 6 df, P > 0.5) with a further improvement in the overall fit, thus providing no

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statistical justification for the inclusion of the common environmental parameters in the explanatory model. However, as shown by model 7, the hypothesis that no new genes are expressed during the second and third occasions of observation was clearly unacceptable ($P \simeq 0.0$).

Models 8–10 show an alternative formulation of the genetic effects (Figure 2) in which it is assumed that the phenotype on each occasion of measurement is influenced by a set of 'occasion specific' genes, and another 'general' set of genes which remain active throughout development. The full model also includes six genetic parameters and yields χ^2 and P values which are identical to those of model 4. However, the two constrained models (9 and 10) do provide more parsimonious explanations for the data that are not associated with significant increase in the goodness of fit χ^2 ($\chi^2 = 1.5$, 2df, $P > 0.25$; $\chi^2 = 4.0$, 2df, $P > 0.1$). The former has the highest probability of any model tested, but the latter is somewhat more parsimonious postulating that there is one set of genes (general factor) which has a constant effect throughout development along with three different sets of genes whose specific effects at each age are comparable. This solution is remarkable in that it utilizes only three parameters to provide an adequate prediction of the entire set of 42 observed variances and covariances. The model asserts that there are no differences in the 12 total variances, that the 3 MZ and 3 DZ twin covariances remain constant with age, that the 12 self covariances across time are all constant and that the 12 co-twin covariances across the intervals of measurement differ only between zygosities.

In Table 5, the parameter estimates associated with four selected models are given and in Table 6, estimates are provided of the components of heritability that are attributable to newly expressed and previously expressed genes under three competing models. All three models predict comparable total heritabilities with virtually no age-related change. In the absence of previous observations, it is not possible to be certain in the 11-year-old twins what proportion of the genetic effects can be attributed to genes that were expressed at an earlier age. However, at the two later ages, the three models suggest that 24–48% of the heritable variation results from the expression of new genes that do not contribute to the initial phenotypic variation at age 11.

Table 4 Longitudinal genetic analysis of HDL cholesterol

model no.	parameters estimated E	G	C	χ^2	df	P
Full	e_1, e_2, e_3 e_{12}, e_{13}, e_{23}	h_1, h_2, h_3 h_{12}, h_{13}, h_{23}	c_1, c_2, c_3 c_{12}, c_{13}, c_{23}	27.07	24	0.379
1	$e_1=e_2=e_3$	h_1, h_2, h_3 h_{12}, h_{13}, h_{23}	c_1, c_2, c_3 c_{12}, c_{13}, c_{23}	28.66	29	0.483
2	$e_1=e_2=e_3$			537.5	41	0.000
3	$e_1=e_2=e_3$		c_1, c_2, c_3 c_{12}, c_{13}, c_{23}	203.2	33	0.000
4	$e_1=e_2=e_3$	h_1, h_2, h_3 h_{12}, h_{13}, h_{23}		33.3	35	0.55
5	$e_1=e_2=e_3$	h_1, h_2, h_3 h_{12}, h_{13}, h_{23}		34.1	36	0.56
6	$e_1=e_2=e_3$	h_1, h_2, h_3 h_{12}, h_{13}, h_{23}		44.8	37	0.18
7	$e_1=e_2=e_3$	h_{11}, h_{12}, h_{13}		139.2	38	0.000
8	$e_1=e_2=e_3$	h_{c1}, h_{c2}, h_{c3} h_{s1}, h_{s2}, h_{s3}		33.3	35	0.55
9	$e_1=e_2=e_3$	$h_{c1}=h_{c2}=h_{c3}$ h_{s1}, h_{s2}, h_{s3}		34.4	37	0.59
10	$e_1=e_2=e_3$	$h_{c1}=h_{c2}=h_{c3}$ $h_{s1}=h_{s2}=h_{s3}$		38.4	39	0.50

Table 5 Parameter estimates for selected models

parameters	model number 4	5	8	9	10
$e_1=e_2=e_3$	4.02	4.02	4.02	4.02	4.02
h_1	8.85	8.84	–	–	–
h_2	6.40	6.43	–	–	–
h_3	4.90	4.88	–	–	–
h_{12}	6.13	5.83	–	–	–
h_{13}	5.60	5.83	–	–	–
h_{23}	3.12	3.10	–	–	–
h_{1s}	–	–	5.36	5.28	4.60
h_{2s}	–	–	4.37	4.66	4.60
h_{3s}	–	–	3.93	3.74	4.60
h_{1c}	–	–	7.04	7.25	7.26
h_{2c}	–	–	7.70	7.25	7.26
h_{3c}	–	–	7.04	7.25	7.26
χ^2	33.29	34.11	33.29	34.37	38.38
df	35	36	35	37	39
P	0.551	0.559	0.551	0.593	0.498

Table 6 Source of heritable variation in HDL cholesterol at different ages

genes contributing to heritability	model 4			model 8			model 10		
	11 yr	12.5 yr	14 yr	11 yr	12.5 yr	14 yr	11 yr	12.5 yr	14 yr
previously expressed	–	43	51	–	63	61	–	59	59
newly expressed	–	40	29	–	20	19	–	23	23
total heritability	83	83	80	83	83	80	82	82	82

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Discussion

Many previous twin and family studies have shown that genetic factors make an important contribution to variation in HDL cholesterol. Studies of nuclear families have generally yielded sibling correlations for HDL cholesterol that range from 0.12 to 0.38.[14–18], with heritability estimates of 0.28 to 0.59.[18–21] In contrast, large twin studies have documented DZ correlations of 0.34 to 0.39 and MZ correlations of 0.68 to 0.75 even among adult pairs of variable age.[22–25] In a study involving both twin and nuclear family data, Hunt et al[25] obtained a higher heritability estimate (0.51) for HDL cholesterol from the twin correlations (MZ: 0.75; DZ: 0.39) than from the nuclear family data (0.45) and observed even greater differences in the estimated heritability for other variables such as total cholesterol, blood pressure and body mass index. Similarly, in an application of the twin family design[26] to the analysis of HDL cholesterol, McGue et al[24] found correlations of 0.72 and 0.38 in adult MZ and DZ twins in comparison with a sib correlation of 0.28.

The rather consistent observation that heritability estimates derived from twin studies, along with MZ twin correlations themselves, frequently exceed estimates obtained from nuclear families has often been attributed to the presence of unique environmental similarities between twins, especially monozygotic pairs. However, attempts actually to identify relevant environmental similarities for specific traits have generally failed,[27] and to the extent that the very real prenatal differences (28–32) between twin and single pregnancies may have a lasting influence on the phenotype, one would expect factors such as superfetation, superfecundation, the twin transfusion syndrome, intra-uterine competition, somatic mutation, or Lyonization, to decrease rather than increase the observed correlations of both MZ and DZ twins. Our observation that the self correlations of MZ twins are no higher than those of DZ twins provides further reason to doubt that unique twin environmental similarities are a satisfactory explanation for the high correlations of MZ twins. If such effects do exist, it is difficult to imagine how they could contribute only to the co-twin correlations of MZ twins and not to their self correlations across occasions.

Our results suggest another reason why twin studies might be expected to yield higher heritability estimates than nuclear family data. As noted by Eaves,[33] sib and parent offspring correlations can, at best, only reflect the covariation attributable to those genes which continue to be expressed at different ages. In contrast, since the members of a twin pair are the same age, all the genes whose age-related effects contribute to their phenotypic variation (denominator of correlation coefficient) can also contribute to their covariation (numerator of correlation). Observations on cohorts of same-age twins thus provide point estimates of total heritability which include age-specific genetic effects that cannot be recovered from nuclear family data even when age regressions are included in the analysis. Our heritability estimates of 0.80–0.83 for HDL cholesterol at ages 11, 12.5 and 14 years are among the highest to have been reported to date. Far from being biased by unidentified twin environmental effects, we believe that data on same-age twins provide a more reliable estimate of the total heritability because they include the effects of age-specific genes, and strongly suggest that genetic differences are the major cause for biologic variation in HDL cholesterol during adolescence.

The analysis of complex traits that are not fully expressed at birth is an important contemporary challenge for human genetics. As we have shown, when longitudinal observations are available on same-age twins, they can readily be used to explore the causes for phenotypic continuity and change, and to confirm the existence of differential gene expression during development. These studies could readily be extended to attempt to identify the specific loci that are involved in developmental changes in gene expression or to search for possible sex differences in gene expression by the inclusion of data on unlike sexed DZ twins. Our study was specifically designed with these goals in mind and should permit us to address these issues when the full data set is available for analysis.

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