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Quantitative Genetic Analysis of Longitudinal Trends in Height: Preliminary Results from the Louisville Twin Study

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Abstract. A preliminary series of quantitative genetic models was applied to a subset of longitudinal height data, spanning birth to maturity, gathered from twin families in the Louisville Twin Study. Descriptive Cholesky factor parameterization was found to give more satisfactory results than did a system of constraints based on a model of developmental transmission of a time-constant and time-specific factors. The results from application of two autosomal sex-limitation models are contrasted with those from a model specifying both autosomal and sex-chromosomal patterns of inheritance. The latter model was more conducive to parameter reduction. Although these models do not constitute conclusive tests of autosomal sex-limitation versus sex-linkage, the more parsimonious model is consistent with previous research suggesting a stature locus on the long arm of the Y chromosome. Heritability of height is estimated at about 90% or greater from 6 years of age on. Substantial and fairly constant longitudinal genetic correlations are found from 3 years of age on. Shared environmental effects unrelated to parental height were seen for birth length, corrected for gestational age, to height at 3 years of age, but these are not satisfactorily differentiated from possible twin effects in the present sample. The genetic consequences of assortative mating are emphasized since failure to take assortment into account can lead to overestimation of shared environmental effects and under-estimation of genetic effects. The results indicate that about 20% of within-gender variability for mature height can be attributed to the genetic consequences of assortment, even though the phenotypic marital correlation of 0.22 is quite modest. The importance of testing the assumption of multivariate normality underlying the application of the method of maximum-likelihood is also highlighted.

Key words: Height, Longitudinal analysis, Assortative mating, Genetic covariance, Twin families

INTRODUCTION

Human stature is often referenced as the premier example of a polygenic trait. It is normally distributed, highly heritable, and is exempt from the measurement and scaling ambiguities that often complicate the genetics of behavior. Height has been called the "benchmark" trait; it is used for comparisons with the results from quantitative genetic analyses of other polyfactorial variables, particularly behavioral ones. Although there is no *a priori* reason that patterns of behavioral development should mirror those of physical growth [36,38], the qualities that make height the benchmark polygenic trait also make it a natural candidate for early explorations in quantitative developmental genetics.

The purpose of this report is to present the results from a preliminary series of quantitative genetic analyses of longitudinal height data gathered from participants in the Louisville Twin Study. Specifically, we test for the presence of between-family environmental effects related to parental stature and examine the effects of assortative mating on latent covariance structures. Furthermore, in the absence of strong developmental genetic theory of individual differences in human growth, the application of longitudinal factor models [29] helps to bring into focus the overall patterns of constancy and change among latent genetic sources of variance.

METHODS

Sample and Measures

The twin families in this investigation were recruited as part of an ongoing longitudinal twin-family study of human development, now in its fourth decade. The overall project and sample have been described in detail elsewhere [37,39].

Data on birth length and gestational age (based on last menses date) were obtained from hospital and birth records. Incomplete reports or those that showed marked discrepancy with clinical assessments were excluded. In addition to birth length, measures of height at ages 3, 6, 9, 12, 15, and 18 years were selected for study. All heights other than birth length were measured (to the nearest millimeter) during scheduled visits to the research center of the Louisville Twin Study. Height measured at age 18 years or later was assumed to be the equivalent of height at age 18 and of mature height. Except for mature height, only those measures of height made within two weeks of the birthday for the selected ages were included in the present analyses. A few measurements were excluded from the analyses because of severe childhood maladies presumed to have a marked effect on growth. These maladies were cerebral palsy, failure to thrive, maternal substance abuse during pregnancy, severe congenital anomaly, and bone disease.

The data were further screened to strengthen the meaningfulness of tests for cultural effects. For example, the magnitude of between-family environmental effects associated with parental phenotype might be reduced if a sample included children not living with both parents. Should such cultural effects not then be

detected, the failure might be due only to the uninformative nature of the sample. Therefore, each family's history was reviewed for parental absence, death, divorce and/or separation, conditions which are found in about 25% of the sample. Offspring data were excluded beginning at any point in time prior to maturity when children were no longer living in intact families with both biological parents. In the present analyses, several large families were also excluded in the interest of resource conservation since the analyses required substantial amounts of computer time. These were: families having more than one multiple birth, families in which the parents of twins were siblings of other parents in the study, and families in which the parents were participants in the study when they were children.

Sample sizes, means and standard deviations for gestational age in months and height in centimeters are given in Table 1 for twins, singleton siblings and parents.

Modeling Gender Effects

The summary statistics in Table 1 reflect increasing gender differences in height variance during development, especially at adolescence. While it is possible that these differences are due to gender-specific environmental effects, previous research suggests that they are associated with genetic effects [15,26]. The important growth-associated factors that have been mapped thus far involve only autosomes [4,27,34], and it is usually thought that gender differences in the development of stature reflect some form of sex-limitation of autosomal effects. However, investigations in several areas indicate that the Y chromosome may have one or more loci influencing stature independently [1,2,3,33,41]. One line of research points to a locus for stature on the long arm of the Y chromosome [1], whereas the recently cloned testis-determining gene [28] is located on the short arm. The involvement of the X chromosome has been postulated as well [17]. Therefore, in addition to testing two models of sex-limitation of autosomal effects, expectations were formulated for simple hypotheses of additive genetic effects consistent with the classical principles of autosomal, X and Y chromosome patterns of inheritance. It is now known, however, that the X and Y chromosomes contain homologous regions and engage in meiotic pairing and pseudoautosomal X-Y exchange [6,7,9,30,31]. Should the cross-over regions be related to phenotypic variability, the mode of inheritance of their effects would tend to resemble autsosomal patterns of genetic segregation rather than the classical sex-chromosomal patterns.

For X inheritance, a model assuming no dominance and no sex-limitation of X effects was formulated, following Haley [19]. For Y inheritance, the following model was specified: complete genetic transmission from father to son, no genetic segregation, and covariance among first degree male relatives equal to the male variance. Table 2 gives the modeling weights for genetic transmission and segregation as well as expected variances and covariances among various classes of relatives that were used in deriving expectations.

Two autosomal sex-limitation models [11,14] were used to derive alternative expectations. One of these models is formed around the hypothesis that the same

Table 1 - Descriptive statistics

		N	$\overline{X}$	s
Gestational age (mo)				
Females:	Twins	230	8.68	0.63
	Siblings	26	9.14	0.46
Males:	Twins	213	8.77	0.60
	Siblings	23	9.10	0.40
Birth length (cm)				
Females:	Twins	422	47.37	3.11
	Siblings	163	50.70	2.79
Males:	Twins	373	48.01	3.33
	Siblings	155	51.98	3.01
Height age 3 (cm)				
Females:	Twins	409	92.67	3.42
	Siblings	31	92.80	3.32
Males:	Twins	387	93.68	3.77
	Siblings	28	96.21	3.30
Height age 6 (cm)				
Females:	Twins	330	114.03	4.35
	Siblings	22	113.35	5.13
Males:	Twins	290	115.12	4.85
	Siblings	22	118.32	4.80
Height age 9 (cm)				
Females:	Twins	249	132.07	5.68
	Siblings	23	131.13	6.54
Males:	Twins	202	132.86	5.88
	Siblings	18	138.07	4.47
Height age 12 (cm)				
Females:	Twins	23	149.38	10.33
	Siblings	0		
Males:	Twins	23	151.60	8.13
	Siblings	0		
Height age 15 (cm)				
Females:	Twins	91	162.49	5.99
	Siblings	11	162.94	6.08
Males:	Twins	86	168.88	8.84
	Siblings	9	173.79	7.59
Mature height (cm)				
Females:	Twins	54	164.19	6.55
	Siblings	2	164.85	0.21
	Mothers	438	163.52	6.15
Males:	Twins	47	177.26	7.86
	Siblings	0		
	Fathers	139	177.64	7.22

genes influence height in both sexes, but the magnitude of the expression of the genetic factors varies between the sexes. In the second sex-limitation model, genetic effects common to males and females are specified along with gender-specific factors.

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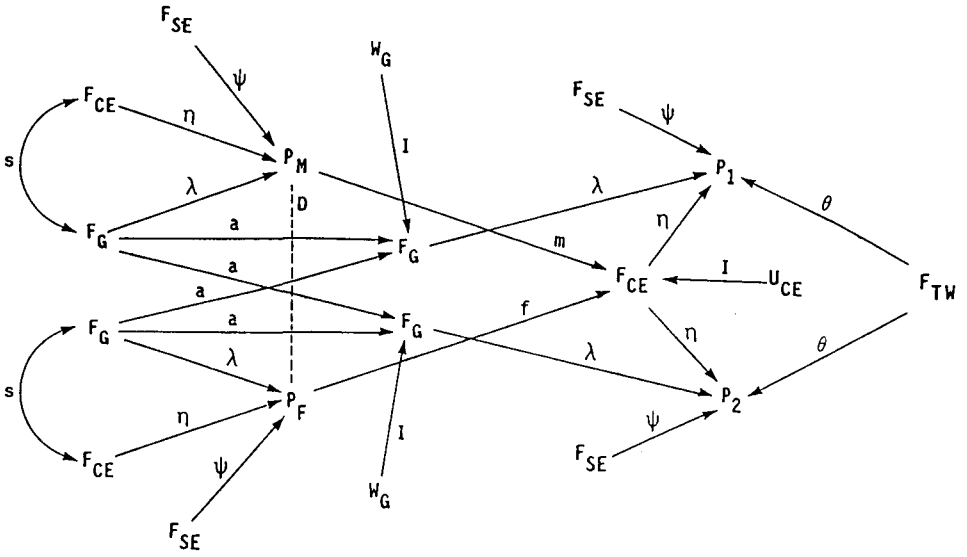

Fig. 1. General twin-family structural model.

Twin-Family Model

The general structure fitted to twin-family data is diagrammed in Fig. 1 for the case of parents ($\mathbf{P_M}$ and $\mathbf{P_F}$) and two offspring ($\mathbf{P}_1$ and $\mathbf{P}_2$). The model is essentially the same as that formulated for application to adoption data [29] with a few modifications. Latent factor vectors ($\mathbf{F}$) are hypothesized for additive genetic ($\mathbf{G}$), shared family environmental ($\mathbf{CE}$), nonshared environmental ($\mathbf{SE}$) and special twin ($\mathbf{TW}$) effects. The vectors of phenotypes ($\mathbf{P}$) load on these latent factors via factor patterns $\boldsymbol{\lambda}$, $\boldsymbol{\eta}$, $\boldsymbol{\psi}$, and $\boldsymbol{\theta}$, respectively. Cultural transmission effects from adult phenotypes of mothers and fathers ($\mathbf{P_M}$ and $\mathbf{P_F}$) to environments shared by offspring ($\mathbf{F_{CE}}$) are modeled via matrices $\mathbf{m}$ and $\mathbf{f}$, respectively. Genetic transmission from parents to offspring is specified in regression matrix $\mathbf{a}$. It contains fixed weights on the diagonal, such as those given in Table 2, and these may vary according to gender of parent and of offspring. Passive genotype-shared environment covariance ($\mathbf{G}$-$\mathbf{C}E$ covariance) is modeled in the derived matrix $\mathbf{s}$, which is a function of combined genetic and cultural transmission. The variable and parameter matrices shown in the diagram and used in the analyses are listed in the Appendices along with model expectations for familial resemblance.

The genetic factor vector ($\mathbf{F_G}$) can include both sex-associated and autosomal factors. The values of the genetic variances under random mating are obtained as free parameter estimates. Then the post-assortment equilibirium variances of the genetic factors and their assortment-induced covariances are derived at each func-

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tion evaluation during the model-fitting computer runs by means of an iterative sequence [29] related to Banach's contraction-mapping theorem and successive approximation [5,22]. This procedure obviates the need for non-linearly constrained optimization. It requires that expected covariance matrices be rescaled by a constant fraction prior to the iterative sequence if values would otherwise be expected to exceed unity during this derivation process. Of course, the matrices must then be scaled back to the previous metric prior to function evaluation. For polygenic traits such as height, the genetic segregation variances in $\mathbf{W_G}$ can be treated as essentially unaffected by assortative mating [10,40].

Table 2 - Modelling weights for sex-chromosomal and autosomal effects under random mating

	Genetic effects		
	X	Y	Autosomal
A. Variances			
Females			
Between families	3/4	0	1/2
Segregation	1/4	0	1/2
Total	1	0	1
Males			
Between families	1	1	1/2
Segregation	1	0	1/2
Total	2	1	1
B. Genetic transmission regression weights			
MO-DAU	1/2	0	1/2
MO-SON	1	0	1/2
FA-DAU	1/2	0	1/2
FA-SON	0	1	1/2
C. Covariances			
MO-DAU	1/2	0	1/2
MO-SON	1	0	1/2
FA-DAU	1	0	1/2
FA-SON	0	1	1/2
MZf	1	0	1
MZm	2	1	1
SIBf/DZf	3/4	0	1/2
SIBm/DZm	1	1	1/2
SIBfm/DZfm	1/2	0	1/2

Likewise, the variances of shared family environmental factors ($\mathbf{F_{CE}}$) are derived as functions of the freely estimated variances of factors unrelated to parental phenotype ($\mathbf{U_{CE}}$) and of additional derived variance and covariance arising from cultural transmission and assortative mating. In the present application, it is not expected that parental height itself has a direct effect, but the attempt is made

to detect between-family environmental effects that are associated with parental height. Should such effects be found, further research would seek to uncover the mediating variables.

The model also includes exogenous environmental factors for effects unique to the individual ($\mathbf{F_{SE}}$), including measurement error, and exogenous twin effects ($\mathbf{F_{TW}}$). Both types of effects are assumed to be unrelated to genotype, environmental effects shared by all siblings, and parental phenotype.

Assortative mating is modeled via the sparse delta matrix **D** [35], that has a single element representing direct matching on the basis of adult phenotype. In the univariate case, the standardized value of the delta path is equivalent to the expected marital correlation.

The construction of the latent factor patterns $\boldsymbol{\lambda}$, $\boldsymbol{\eta}$, $\boldsymbol{\psi}$, and $\boldsymbol{\theta}$ can be varied within the framework of the general twin-family model described above. For multivariate analyses or preliminary explorations of longitudinal data, a Cholesky factor decomposition [16] can be employed. In the developmental case, the Cholesky structure can be constrained to reflect the orderly accumulation and/or decay of variance effects over time [29], following developmental models originated by Eaves and colleagues [12,13].

In the present application, the loading at the top of each factor pattern column, corresponding to the first detected appearance of the effects of the factor, was fixed at unity in order to estimate directly the latent variance innovations. Subsequent loadings down the column were obtained as free parameter estimates or functions of develomentally specified free parameters representing developmental transmission of variance effects.

Latent variance innovations at age 12 were equated with those at age 15 since the sample at age 12 is presently still fairly small. Thus, variance innovations during adolescence are averaged across a fairly large age range, and the model-fitting results reported here should not be expected to reflect in fine detail the adolescent patterns of height variability, particularly variance effects related to variable age at onset of puberty. Several subdiagonal parameters in the latent factor pattern matrices were also equated where sample sizes for cross-age or cross-twin-cross-age comparisons were deemed too small to be of independent use. Phenotypic means were fixed at observed values in order to conserve computer time. Separate twin and sibling means were used for gestational age, birth length and heights at ages 3, 6 and 9. Phenotypic assortative mating was estimated as a free parameter.

Pedigree Analysis for Multivariate-Normal Data

The inevitable picture presented by a longitudinal data set is one of missing data. Such data are modeled by means of the application of maximum-likelihood pedigree analysis. Although it requires substantial computer resources, the pedigree method has the significant advantage of utilizing all available information in a data set, whereas fitting models to observed covariance structures requires complete cases.

For height or other normally distributed traits, the strong assumption of multivariate normality permits the use of maximum-likelihood theory. A log-likelihood is calculated for each family's vector of data, and these are summed across families. For large samples, twice the difference between two log-likelihood sums is distributed asymptotically as chi-squared, permitting the use of the log-likelihood ratio statistic in comparing models for relative goodness-of-fit. Following Hopper and Matthews [21], the normality of the model-fitting errors is also tested as an additional means of evaluating a model. The Anderson-Darling statistic (A^2) calculated from the modeling residuals is evaluated by means of a table of probabilities given by Stephens [32]. Significantly large values of A^2 indicate violation of the assumption of normality.

Maximization of the sample log-likelihood sum is achieved by minimization of its negative value. Parameter estimation and function minimization were carried out on a Cyber 205 at the John von Neumann National Supercomputer Center, Princeton, NJ, using the MINUIT optimization package [8] together with user supplied routines.

Standardization formulas are given here for unstandardized matrices $\boldsymbol{\lambda}$, $\mathbf{D}$, $\mathbf{m}$, and $\mathbf{s}$. Standardization procedures for $\boldsymbol{\lambda}$ apply to $\boldsymbol{\eta}$, $\boldsymbol{\psi}$, and $\boldsymbol{\theta}$; those for $\mathbf{m}$ apply to $\mathbf{f}$. Let $\mathbf{S}$ denote a diagonal matrix of expected phenotypic standard deviations, and let subscript $\mathbf{s}$ indicate that the subscripted matrix is standardized. Furthermore, let $\mathbf{G}$ and $\mathbf{C_E}$ denote diagonal matrices of the square roots of the variances in $\mathbf{C_{FG}}$ and $\mathbf{C_{FCE}}$, respectively:

$$\boldsymbol{\lambda}_s = \mathbf{S}^{-1}\boldsymbol{\lambda}\mathbf{G}\,,$$

$$\mathbf{D}_s = \mathbf{S}\,\mathbf{D}\,\mathbf{S}\,,$$

$$\mathbf{m}_s = \mathbf{C}^{-1}\mathbf{m}\,\mathbf{S}\,, \qquad \text{and}$$

$$\mathbf{s}_s = \mathbf{G}^{-1}\mathbf{s}\,\mathbf{C}_{\mathbf{E}}^{-1}\,.$$

RESULTS

Initially, a developmental model involving both a time-constant and time-specific latent factors was applied [12,13,29]. The notable outcomes of this approach were: 1) prohibitive skewness in the residuals from model-fitting, 2) unusually high estimates for the cultural transmission parameters, and 3) estimates of developmental transmission exceeding 1.0 and in some cases 2.0. Two steps were taken to remedy the lack of normality.

First, gestational age was omitted from the directly-fitted data set and was used instead as a main effect on birth length. Although birth weight has been shown to be substantially reduced by the twinning condition itself, over and above the effects of gestational age [18], birth length appears to be less affected by twinning [23]. For the present sample, separate regressions of birth length on gestational age

Table 3 - Regression functions for the effect of gestational age on birth length

		N	Constant	Slope
Females	Twins	221	18.69	3.23
	Siblings	19	17.83	3.50
	All	240	17.37	3.40
Males	Twins	198	19.74	3.21
	Siblings	19	28.95	2.55
	All	217	17.87	3.46
All children		457	17.08	3.48

Table 4 - Model A standardized genetic factor patterns and unstandardized genetic variance innovations

AGE	FA0	FA3	FA6	FA9	FA12	FA15	FA18
0	61 (72)						
3	16 (17)	85 (90)					
6	27 (28)	82 (86)	23 (23)				
9	20 (21)	77 (81)	30 (31)	23 (24)			
12	19 (19)	52 (52)	60 (60)	30 (30)	21 (21)		
15	11 (14)	54 (67)	15 (19)	23 (29)	24 (30)	19 (24)	
18	13 (14)	64 (73)	12 (14)	18 (20)	31 (35)	27 (31)	0 (0)
INNOV	314	765	117	179	234	234	0
AGE	FX0	FX3	FX6	FX9	FX12	FX15	FX18
0	39 (33)						
3	12 (9)	31 (23)					
6	0 (0)	26 (19)	0 (0)				
9	1 (1)	23 (17)	0 (0)	0 (0)			
12	1 (0)	19 (13)	0 (0)	0 (0)	0 (0)		
15	1 (1)	33 (29)	0 (0)	0 (0)	0 (0)	0 (0)	
18	1 (1)	7 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
INNOV	134 (67)	115 (57)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AGE	FY0	FY3	FY6	FY9	FY12	FY15	FY18
0	46						
3	17	17					
6	0	21	0				
9	3	23	0	0			
12	0	6	0	0	0		
15	5	54	0	0	0	0	
18	5	0	0	0	0	0	39
INNOV	180	35	0	0	0	0	772

Note: FA, Autosomal factors; FX, X factors; FY, Y factors; INNOV, Genetic variance innovation. Loadings and innovations are shown ×100, female values in parentheses.

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for twins and singleton siblings by gender tended to yield similar regression weights and constants, as shown in Table 3. Definitive tests of twin-singleton regression differences by sex were precluded, however, by the very small number of gestational age measures available for singletons. Thus, a single regression function was used across groups to obtain birth length corrected for gestational age. Although birth length and gestational age both showed marked skewness, the birth length residuals, corrected for gestational age, were normal. The models were fitted to these residuals together with all other height measurements. This procedure greatly reduced the skewness in the model-fitting errors but still did not result in an acceptable degree of normality.

Second, specification of a developmental transmission model was abandoned in favor of more descriptive Cholesky factor structures for genetic effects. This further modification resulted in an acceptable level of normality of error which held for all remaining analyses. The developmental specification of time-specific environmental factors was retained, with developmental transmission of environmental effects varying across the three-year age intervals.

In the first model of this series, no shared environmental or cultural transmission effects were specified. Cholesky factor patterns were estimated for autosomal, X, and Y inheritance factors using the regression and variance weights shown in Table 2. The model with 80 free parameters, not counting fixed mean effects, yielded a log-likelihood of -4885.475 and A^2 of 2.048 ($P > 0.05$). The overall organization of the genetic factor pattern estimates was rather striking. The estimates are given in Table 4 in standardized metric along with the unstandardized variance innovation estimates. There was a noticeable similarity in the configurations of the X and Y standardized factor patterns. The X variance innovations were smaller, however, and there was a very large variance innovation estimate of Y effects appearing between ages 15 and 18. Except for this large innovation, the results strongly suggested the absence of sex-associated innovations after age 3. Where not tending to very small values, the subdiagonal loadings generally showed a pronounced *increasing* trend, and they exceeded unstandardized values of 1.0 in most instances. The largest loading estimates appeared in the rows representing adolescence. Two major exceptions to this dichotomous pattern were seen. First, the autosomal factor loadings on the birth variance innovation suggested a nondecaying persistence of effects. Second, the sex-associated birth factor loadings indicated rapid decay of effects after age 3. As would be expected, the likelihood was virtually unchanged by the deletion of the following: parameters representing X and Y innovations beyond age 3 (except the Y innovation at 18); loadings on the X and Y birth factors after age 3; and the autosomal variance innovation at age 18 ($\chi^2_{28} = 0.158$, $P > 0.99$). The extremity of this probability reflects both the *a posteriori* nature of the selection of the reduced structure and the tendency of X parameters to be highly correlated with autosomal parameters.

The next model added shared environmental effects. The specification included time-specific variance innovations for shared environmental effects with developmental transmission varying across age intervals. Between-family environmental effects associated with parental height were modeled as well. For offspring ages 0

through 18 at three year intervals, standardized estimates of the elements of **m** were 0.15, 0.02, 0.00, 0.01, 0.00, 0.00 and 0.00, respectively. The corresponding standardized estimates of **f** were 0.00, 0.00, 0.94, 0.97, 0.00, 0.00 and 0.00. Although two of these estimates appear large numerically, they have been standardized against extremely small shared environmental variance estimates. These are reflected in the derived c^2 (ratio of shared environmental variance to phenotypic variance) values of 0.19, 0.125, 0.0002, 0.0014, 0.0000, 0.0000 and 0.0095 for females, and 0.134, 0.113, 0.0002, 0.0013, 0.0000, 0.0000 and 0.007 for males. The increase in the likelihood for the addition of this large complement of between-family environmental effects was not significant ($\chi^2_{21} = 25.864$, $P > 0.20$). However, the addition of a smaller set of these parameters did increase the likelihood significantly; these were shared environmental variance innovations at birth and age 3, a single developmental transmission parameter for shared environment between birth and age 3, and the largest variance effect arising from **m** and **f**, which was the maternal environmental effect on birth length ($\chi^2_4 = 16.95$, $P < 0.01$). A separate test of this largest value in **m** proved not to be significant ($\chi^2_1 = 1.646$, $P > 0.20$). This left a reduced model (Model A) with 55 free parameters.

Table 5 - Sex-limitation Model I standardized genetic factor patterns and unstandardized genetic variance innovations

AGE	FA0	FA3	FA6	FA9	FA12	FA15	FA18
0	60 (53)						
3	11 (12)	89 (88)					
6	31 (28)	91 (89)	9 (20)				
9	25 (20)	86 (82)	23 (33)	19 (22)			
12	45 (19)	58 (50)	35 (63)	26 (33)	26 (22)		
15	9 (14)	76 (69)	52 (19)	0 (28)	0 (36)	23 (29)	
18	10 (15)	78 (67)	0 (17)	48 (12)	0 (40)	0 (37)	20 (19)
INNOV	283 (197)	922 (768)	17 (86)	121 (158)	348 (324)	348 (324)	200 (137)

Note: FA, Autosomal factor with magnitude of expression varying between males and females; INNOV, Genetic variance innovation. Loadings and innovations are shown x100, female values in parentheses.

Next, the first of two alternative autosomal sex-limitation models was fitted. In Sex-limitation Model I, Cholesky loadings for genetic effects were parameterized to reflect gender-common autosomal latent factors but with magnitude of expression of these effects varying between males and females. This model, with 63 free parameters, did not compare favorably with Model A ($\chi^2_8 = 11.654$, $P > 0.20$). Perhaps more importantly, the genetic factor pattern and variance innovation estimates from Sex-limitation Model I, listed in Table 5, are less well-organized than those found previously, and no simple method of parameter reduction is suggested by the overall configuration.

In the Sex-limitation Model II, Cholesky matrices were formed for both gender-common and gender-specific autosomal factors. The magnitudes of gender-common effects were equated across males and females. This model, with 71 free parameters,

Table 6 - Sex-limitation Model II standardized genetic factor patterns and unstandardized genetic variance innovations

AGE	FC0	FC3	FC6	FC9	FC12	FC15	FC18
0	35 (40)						
3	23 (24)	80 (83)					
6	28 (28)	86 (87)	2 (2)				
9	18 (18)	82 (82)	2 (2)	19 (19)			
12	13 (16)	61 (74)	2 (2)	23 (28)	0 (0)		
15	14 (16)	63 (74)	2 (2)	24 (28)	0 (0)	0 (0)	
18	15 (17)	69 (76)	2 (2)	26 (29)	0 (0)	0 (0)	0 (0)
INNOV	105 (105)	710 (710)	1 (1)	112 (112)	0 (0)	0 (0)	0 (0)

AGE	FF0	FF3	FF6	FF9	FF12	FF15	FF18
0	(35)						
3	(1)	(13)					
6	(18)	(21)	(5)				
9	(25)	(25)	(9)	(14)			
12	(2)	(8)	(8)	(21)	(24)		
15	(2)	(8)	(8)	(21)	(30)	(24)	
18	(2)	(0)	(5)	(0)	(30)	(30)	(7)
INNOV	(127)	(30)	(9)	(103)	(360)	(360)	(31)

AGE	FM0	FM3	FM6	FM9	FM12	FM15	FM18
0	57						
3	24	18					
6	9	28	11				
9	9	28	19	11			
12	18	47	0	26	28		
15	19	49	0	27	0	29	
18	20	0	53	0	0	0	3
INNOV	423	66	37	56	736	736	6

Note: FC, Gender-common factors; FF, Female-specific factors; FM, Male-specific factors; INNOV, Genetic variance innovation. Loadings and innovations are shown x100, female values in parentheses.

also fared poorly against Model A ($\chi^2_{16} = 5.914$, $P > 0.95$). The standardized genetic factor pattern estimates and unstandardized genetic variance innovation estimates from Sex-limitation Model II are given in Table 6. Although the loadings are interesting in relation to those in Tables 4 and 5, no clear method of general model reduction is suggested by the pattern of the innovations and loadings. Of the two autosomal models, Sex-limitation Model I (sex-limited expression of gender-common autosomal effects) was preferable ($\chi^2_8 = 5.74$, $P > 0.60$).

Returning to Model A, the remaining X effects were successfully dropped altogether (Model B, $\chi^2_7 = 7.644$, $P > 0.30$). Finally, the deletion of the 9 remaining Y parameters was attempted. In order to allow gender differences in variance, 6 parameters were added to permit gender specificity in the nonshared environmental variance innovations. Gender-invariant parameterization of developmental transmission of nonshared environmental effects was retained. The autosomal variance

innovation at age 18, previously set to zero, was also freed. This model failed relative to Model B ($\chi^2_2 = 52.91$, $P < 0.001$). The failure holds even if the 7 added parameters are not considered in calculating degrees of freedom.

Table 7 - Model B percentages of variance due to latent genetic and environmental effects.

		Age						
		0	3	6	9	12	15	18
h^2	females	38	81	94	92	89	92	94
	males	54	82	94	93	89	95	95
c^2	females	25	11					
	males	18	10					
e^2	females	37	8	6	8	11	8	6
	males	27	7	6	7	11	5	5
t^2	females	0	2					
	males	0	2					

Note: Proportions: h^2, additive genetic; c^2 shared environmental; e^2, nonshared environmental; t^2, special twin effects as a proportion of singleton variance.

Table 8 - Model B age-to-age genetic correlations x100 for males (above the diagonal) and females (below the diagonal)

	Age						
Age	0	3	6	9	12	15	18
0		32	25	20	18	13	15
3	29		96	91	66	77	73
6	36	97		97	80	80	74
9	30	92	96		88	85	76
12	26	67	81	90		70	69
15	22	84	84	89	82		71
18	23	83	83	86	75	96	

Table 7 lists Model B estimates of percentages of variance attributable to additive genetic, shared and nonshared environmental and special twin effects for corrected birth length and stature at three-year intervals from ages 3 through 18. Estimates of age-to-age genetic correlations are given in Table 8. The estimated longitudinal genetic variance/covariance matrices are diagrammed in Figs. 2 and 3 for males and females, respectively. The surfaces in these diagrams have been interpolated in order to approximate the effects for yearly intervals. The estimated phenotypic variance/covariance matrices (not shown) are quite similar to the genetic ones.

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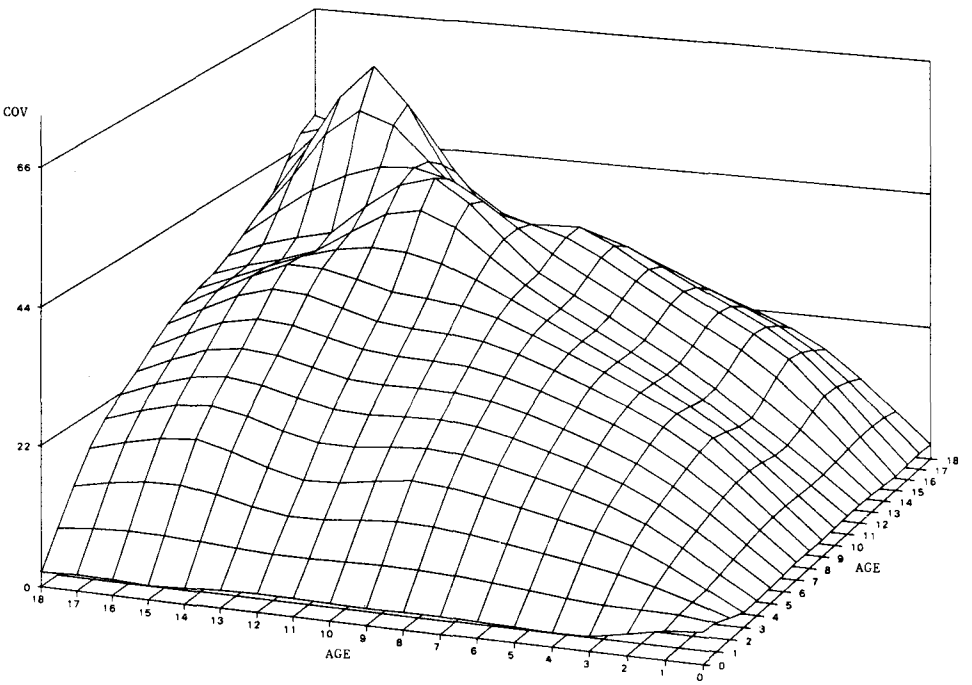

Fig. 2. Age-to-age genetic covariance matrix for males.

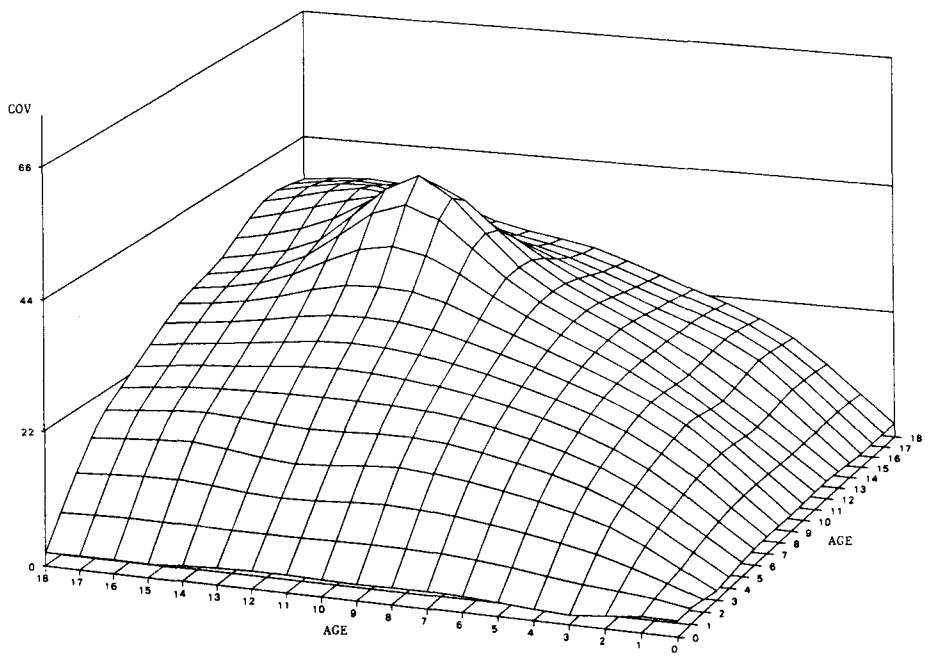

Fig. 3. Age-to-age genetic covariance matrix for females.

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Table 9 - Model B percentages of genetic (lower triangle) and phenotypic (upper triangle) variance and age-to-age covariance attributable to the effects of assortative mating

Age	Age 0	3	6	9	12	15	18	Age
Females								
	0	8	9	11	11	17	17	0
		11	13	14	16	17	18	3
0	1		12	13	14	17	18	6
3	13	13		13	12	17	18	9
6	10	14	13		10	15	18	12
9	13	15	14	14		16	18	15
12	13	18	15	14	11		18	18
15	19	18	18	18	17	18		
18	19	19	19	19	19	19	19	
Males								
	0	6	9	11	11	17	21	0
		10	12	13	16	15	22	3
0	1		12	13	13	14	22	6
3	8	12		12	12	14	22	9
6	10	13	13		10	14	21	12
9	13	14	13	13		11	22	15
12	13	17	15	13	11		21	18
15	19	15	15	15	16	12		
18	23	23	23	23	23	23	22	

The genetic effects of assortative mating are reflected in the estimates given in Table 9, in which the equilibrium values of assortment-induced genetic variance and age-to-age covariance are listed as percentages of total genetic and phenotypic variance and covariance. The standardized assortment delta path estimate of 0.22 was very near the 0.23 observed marital correlation.

DISCUSSION

A very important outcome of these exploratory analyses was the inability of the initial developmental models to capture the increasing variance/covariance trends in the data. This was reflected in the marked tendency of developmental transmission parameters to exceed 1.0, particularly at adolescence, and it contributed to a lack of normality in modeling errors. Future research could focus on parameterizations specifically designed to capture variance effects arising from variable age at onset of puberty [24]. The nondecaying pattern of loadings in Table 4 suggests that at least for prepubertal height there is marked developmental persistence of genetic variance effects. The results of all models point to a large genetic innovation between birth and age 3, the effects of which continue all through the growth period and into maturity.

The quantitative specifications used in the present study do not constitute conclusive tests for sex-linkage as opposed to sex-limited autosomal expression [25]. The *a posteriori* nature of the reduction of Model A should also engender caution. However, we are not obliged to consider only sex-limited models of autosomal inheritance when exploring longitudinal trends in twin-family research. The inheritance models used in the present analyses are three among many that could be applied towards the goal of capturing, as reliably and parsimoniously as possible, the developmental patterns of individual differences found in males and females.

While far from conclusive, the results here are consistent with existing research findings suggesting one or more Y loci influencing stature. The results suggest that Y-like effects are initiated during prenatal, infant and adolescent stages of development. They also hint at the possibility of smaller but similarly patterned X effects initiated during early growth.

It should be noted that the Y chromosome modeling weights listed in Table 2 are almost completely identical to those that would be employed in specifying between-family environmental effects specific to males. Differences between Y chromosomal and male-specific shared environmental modeling outcomes could arise for father-son resemblance depending on the magnitude and nature of environmental transmission and adult/parental variance estimates. However, the existence of detectable between-family male-specific environmental effects seems unlikely in light of the paucity of between-family environmental effects found generally. Where shared family environmental effects have been suggested, they have tended to shrink, if not evaporate entirely, when the genetic consequences of assortative mating have been taken into account (see, for example, [14]). The genetic effects of assortment shown in Table 9, for a trait showing only modest assortment but high heritability, are far from trivial.

The results indicated no shared environmental effects associated with parental height. The failure to detect this type of between-family environmental effect was strengthened by the fact that the data were carefully screened to exclude measurements gathered from children beyond any time point, prior to maturity, when they were not living in intact homes with both biological parents. Shared environmental effects unrelated to parental stature were indicated only for birth length (corrected for gestational age) up through age 3. Failure to take into account the genetic consequences of assortative mating can result in spurious findings of between-family environmental effects as well as under-estimatation of genetic effects.

The twin effects estimates were trivial; this may reflect the inadequate singleton sample sizes in the present analyses.

The results also demonstrate the need for and value of testing statistical assumptions when possible. Although the initial lack of normality in the modeling errors was largely corrected by fitting to birth length residuals rather than directly to gestational age and uncorrected birth length, the non-normality also provided a clue to the insufficiency of the initial models that were fitted. The use of maximum-likelihood pedigree analysis for continuous traits should always be accompanied, as emphasized by Hopper [20], by tests of the normality assumption. This is especially important since pedigree analysis does not yield a likelihood ratio statistic

that can be used to evaluate the goodness-of-fit of the initial model that is tried. In addition, the examination of pedigree residuals should be considered even in applications to summary statistics such as covariance matrices, especially when liberally parameterized models do not fit the data.

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Appendix I

Variable and Parameter Matrices

Symbol	Type	Description
Observed variables		
$\mathbf{P}$	Vector	Phenotypes
Latent variables		
$\mathbf{F_G}$	Vector	Gentic factors
$\mathbf{F_{CE}}$	Vector	Shared environmental factors
$\mathbf{F_{SE}}$	Vector	Nonshared environmental factors
$\mathbf{F_{TW}}$	Vector	Twin factors
Estimated parameters		
$\boldsymbol{\lambda}_m$	Matrix	Male genetic factor pattern
$\boldsymbol{\lambda}_f$	Matrix	Female genetic factor pattern
$\boldsymbol{\eta}$	Matrix	Shared environmental factor pattern
$\boldsymbol{\psi}$	Matrix	Nonshared environmental factor pattern
$\boldsymbol{\theta}$	Matrix	Twin effects factor pattern
$\mathbf{m}$	Matrix	Maternal cultural transmission
$\mathbf{f}$	Matrix	Paternal cultural transmission
$\mathbf{D}$	Matrix	Assortative mating delta paths
$\mathbf{V_{Gf}}$	Diagonal matrix	Random-mating genetic factor variances for females
$\mathbf{V_{Gm}}$	Diagonal matrix	Random-mating genetic factor variances for males
$\mathbf{U_{CE}}$	Diagonal matrix	Shared environmental factor variances unrelated to parental phenotype
$\mathbf{V_{SE}}$	Diagonal matrix	Nonshared environmental factor variances
$\mathbf{V_{TW}}$	Diagonal matrix	Twin effects factor variances
$\boldsymbol{\mu}$	Vector	Phenotypic means

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Appendix II

Summary, Derived and Fixed Parameter Matrices

Matrix	Description	Derivation formula
$\mathbf{T_m}$	Male G, P covariance	$\mathbf{C_{FGm}\lambda'_m + s_m\eta'}$
$\mathbf{T_f}$	Female G, P covariance	$\mathbf{C_{FGf}\lambda'_f + s_f\eta'}$
$\mathbf{M}$	Wife, husband covariance	$\mathbf{C_{Pf}DC_{Pm}}$
$\mathbf{a_{ms}}$	Mother, son genetic transmission	See text and Table 2
$\mathbf{a_{md}}$	Mother, daughter genetic transmission	See text and Table 2
$\mathbf{a_{fs}}$	Father, son genetic transmission	See text and Table 2
$\mathbf{a_{fd}}$	Father, daughter genetic transmission	See text and Table 2
$\mathbf{g_m}$	Segregation proportion of random-mating genetic variance, males	See text and Table 2
$\mathbf{g_f}$	Segregation proportion of random-mating genetic variance, females	See text and Table 2
$\mathbf{W_{Gm}}$	Male genetic segregation variance	$\mathbf{V_{Gm}g_m}$
$\mathbf{W_{Gf}}$	Female genetic segregation variance	$\mathbf{V_{Gf}g_f}$
$\mathbf{C_{FGm}}$	Male genetic factor covariance	$\mathbf{a_{ms}C_{FGf}a'_{ms} + a_{fs}C_{FGm}a'_{fs}}$ $\mathbf{+a_{ms}T_fDT'_ma'_{fs} + a_{fs}T_mD'T'_fa'_{ms}}$ $\mathbf{+W_{Gm}}$
$\mathbf{C_{FGf}}$	Female genetic factor covariance	$\mathbf{a_{md}C_{FGf}a'_{md} + a_{fd}C_{FGm}a'_{fd}}$ $\mathbf{+a_{md}T_fDT'_ma'_{fd} + a_{fd}T_mD'T'_fa'_{md}}$ $\mathbf{+W_{Gf}}$
$\mathbf{C_{FCE}}$	Shared environment factor covariance	$\mathbf{mC_{Pf}m' + fC_{Pm}f' + mMf'}$ $\mathbf{+fM'm' + U_{CE}}$
$\mathbf{C_{FSE}}$	Nonshared environment factor covariance	$\mathbf{V_{SE}}$
$\mathbf{C_{FTW}}$	Twin effects factor covariance	$\mathbf{V_{TW}}$
$\mathbf{s_m}$	Male G-CE covariance	$\mathbf{a_{ms}T_fm' + a_{fs}T_mf'}$ $\mathbf{+a_{ms}T_fDC_{Pm}f' + a_{fs}T_mD'C_{Pf}m'}$
$\mathbf{s_f}$	Female G-CE covariance	$\mathbf{a_{md}T_fm' + a_{fd}T_mf'}$ $\mathbf{+a_{md}T_fDC_{Pm}f' + a_{fd}T_mD'C_{Pf}m'}$
$\mathbf{C_{Pm}}$	Male age-to-age phenotypic covariance (non-twin)	$\mathbf{\lambda_mC_{FGm}\lambda'_m + \eta C_{FCE}\eta'}$ $\mathbf{+\psi C_{FSE}\psi' + \lambda_ms_m\eta' + \eta s'_m\lambda'_m}$
$\mathbf{C_{Pf}}$	Female age-to-age phenotypic covariance (non-twin)	$\mathbf{\lambda_fC_{FGf}\lambda'_f + \eta C_{FCE}\eta'}$ $\mathbf{+\psi C_{FSE}\psi' + \lambda_fs_f\eta' + \eta s'_f\lambda'_f}$

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Appendix III

Expectations for Covariances among Family Members

Covariance	Expectation
Mother, father	$\mathbf{M}$
Mother, son	$\mathbf{T}_f'\mathbf{a}_{ms}'\boldsymbol{\lambda}_m' + \mathbf{C}_{Pf}\mathbf{D}\mathbf{T}_m'\mathbf{a}_{fs}'\boldsymbol{\lambda}_m' + (\mathbf{C}_{Pf}\mathbf{m}' + \mathbf{M}\mathbf{f}')\boldsymbol{\eta}'$
Mother, daughter	$\mathbf{T}_f'\mathbf{a}_{md}'\boldsymbol{\lambda}_f' + \mathbf{C}_{Pf}\mathbf{D}\mathbf{T}_m'\mathbf{a}_{fd}'\boldsymbol{\lambda}_m' + (\mathbf{C}_{Pf}\mathbf{m}' + \mathbf{M}\mathbf{f}')\boldsymbol{\eta}'$
Father, son	$\mathbf{T}_m'\mathbf{a}_{fs}'\boldsymbol{\lambda}_m' + \mathbf{C}_{Pm}\mathbf{D}'\mathbf{T}_f'\mathbf{a}_{ms}'\boldsymbol{\lambda}_m' + (\mathbf{C}_{Pm}\mathbf{f}' + \mathbf{M}'\mathbf{m}')\boldsymbol{\eta}'$
Father, daughter	$\mathbf{T}_m'\mathbf{a}_{fd}'\boldsymbol{\lambda}_f' + \mathbf{C}_{Pm}\mathbf{D}'\mathbf{T}_f'\mathbf{a}_{md}'\boldsymbol{\lambda}_f' + (\mathbf{C}_{Pm}\mathbf{f}' + \mathbf{M}'\mathbf{m}')\boldsymbol{\eta}'$
MZ males	$\boldsymbol{\lambda}_m\mathbf{C}_{FGm}\boldsymbol{\lambda}_m' + \boldsymbol{\eta}\mathbf{C}_{FCE}\boldsymbol{\eta}' + \boldsymbol{\lambda}_m\mathbf{s}_m\boldsymbol{\eta}' + \boldsymbol{\eta}\mathbf{s}_m'\boldsymbol{\lambda}_m' + \boldsymbol{\theta}\mathbf{C}_{FT}\boldsymbol{\theta}'$
MZ females	$\boldsymbol{\lambda}_m\mathbf{C}_{FGf}\boldsymbol{\lambda}_f' + \boldsymbol{\eta}\mathbf{C}_{FCE}\boldsymbol{\eta}' + \boldsymbol{\lambda}_f\mathbf{s}_f\boldsymbol{\eta}' + \boldsymbol{\eta}\mathbf{s}_f'\boldsymbol{\lambda}_f' + \boldsymbol{\theta}\mathbf{C}_{FT}\boldsymbol{\theta}'$
DZ males	$\boldsymbol{\lambda}_m\mathbf{a}_{ms}(\mathbf{C}_{FGf}\mathbf{a}_{ms}' + \mathbf{T}_f\mathbf{D}\mathbf{T}_m'\mathbf{a}_{fs}')\boldsymbol{\lambda}_m'$ $+\boldsymbol{\lambda}_m\mathbf{a}_{fs}(\mathbf{C}_{FGm}\mathbf{a}_{fs}' + \mathbf{T}_m\mathbf{D}'\mathbf{T}_f'\mathbf{a}_{ms}')\boldsymbol{\lambda}_m'$ $+\boldsymbol{\eta}\mathbf{C}_{FCE}\boldsymbol{\eta}' + \boldsymbol{\lambda}_m\mathbf{s}_m\boldsymbol{\eta}' + \boldsymbol{\eta}\mathbf{s}_m'\boldsymbol{\lambda}_m' + \boldsymbol{\theta}\mathbf{C}_{FT}\boldsymbol{\theta}'$
DZ females	$\boldsymbol{\lambda}_f\mathbf{a}_{md}(\mathbf{C}_{FGf}\mathbf{a}_{md}' + \mathbf{T}_f\mathbf{D}\mathbf{T}_m'\mathbf{a}_{fd}')\boldsymbol{\lambda}_f'$ $+\boldsymbol{\lambda}_f\mathbf{a}_{fd}(\mathbf{C}_{FGm}\mathbf{a}_{fd}' + \mathbf{T}_m\mathbf{D}'\mathbf{T}_f'\mathbf{a}_{md}')\boldsymbol{\lambda}_f'$ $+\boldsymbol{\eta}\mathbf{C}_{FCE}\boldsymbol{\eta}' + \boldsymbol{\lambda}_f\mathbf{s}_f\boldsymbol{\eta}' + \boldsymbol{\eta}\mathbf{s}_f'\boldsymbol{\lambda}_f' + \boldsymbol{\theta}\mathbf{C}_{FT}\boldsymbol{\theta}'$
DZ female, male	$\boldsymbol{\lambda}_f\mathbf{a}_{md}(\mathbf{C}_{FGf}\mathbf{a}_{ms}' + \mathbf{T}_f\mathbf{D}\mathbf{T}_m'\mathbf{a}_{fs}')\boldsymbol{\lambda}_m'$ $+\boldsymbol{\lambda}_f\mathbf{a}_{fd}(\mathbf{C}_{FGm}\mathbf{a}_{fs}' + \mathbf{T}_m\mathbf{D}'\mathbf{T}_f'\mathbf{a}_{ms}')\boldsymbol{\lambda}_m'$ $+\boldsymbol{\eta}\mathbf{C}_{FCE}\boldsymbol{\eta}' + \boldsymbol{\lambda}_f\mathbf{s}_f\boldsymbol{\eta}' + \boldsymbol{\eta}\mathbf{s}_m'\boldsymbol{\lambda}_m' + \boldsymbol{\theta}\mathbf{C}_{FT}\boldsymbol{\theta}'$

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