Heritability of the Second to Fourth Digit Ratio (2d:4d): A Twin Study

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The second to fourth finger length ratio (2d:4d) has been the subject of much recent work and is thought to be related to diverse gender and hormone-related traits including sports ability, disease susceptibility, attractiveness and sexuality. It is established *in utero* and remains constant in adulthood. Familial clustering has been thought to contribute to the development of 2d:4d from early studies but no twin studies exploring heritability have been reported to date. In this study, a sample of 456 female twin pairs (148 monozygotic [MZ], 308 dizygotic [DZ]) aged 18 to 79 years was used to estimate the heritability of 2d:4d for the right and left hands. Finger lengths were derived from hand x-rays. Variance components analysis was used to estimate and contrast genetic and environmental effects on this phenotype. The mean 2d:4d was 0.92 (SD = 0.001) for both hands. The MZ intraclass correlation was higher than in DZ (.66 vs. .35 for right 2d:4d, and .71 vs. .37 for left 2d:4d). The best fit model included additive polygenic and unique environmental effects ('AE' model), with no significant common environmental effects detected. Heritability was estimated to be approximately 66% for 2d:4d (95% confidence interval 0.5–0.78). These results suggest a substantial genetic contribution to the determination of this hormonally related skeletal ratio in women, which could be more influential than the effects of common prenatal environmental factors. However the current study design does not preclude the possibility of confounding between heritability estimates and unobserved prenatal effects.

The ratio of the length of the index finger to the ring finger (2d:4d) has been the subject of much recent research although the sexually dimorphic nature of this ratio has been reported for over 50 years (Phelps, 1952).

There is speculative evidence that this ratio may be established during early fetal life (Phelps et al., 1975) and there is evidence that associates the prenatal sex hormone environment with 2d:4d (Lutchmaya et al., 2003). It also appears that the ratio is stable during life (Manning, 2002) excepting external factors, that is, arthropathies and traumatic amputation. Most studies have shown that males tend to have a lower 2d:4d ratio than females.

Diverse phenotypes (including sperm counts, reproductive success, sexual orientation, autism, age at development of breast cancer, age at development of myocardial infarction, sports ability, musical ability, resistance to toxoplasma infection, and aspects of cognitive ability and personality) have all been associated with 2d:4d although results have often been conflicting and based on small sample sizes (Putz et al., 2004).

To date, no-one has performed a twin study of 2d:4d. Studies of monozygotic (MZ) and dizygotic twins (DZ) allow important insight into the relative contributions of genetic and environmental factors of a phenotype. It is assumed that both types of twins share their common family environment to the same extent so any greater similarity between MZ compared to DZ pairs reflects genetic influences (Kyvik, 2000). The aim of this study was to examine the genetic influences on x-ray determined digit ratios using a classic twin study design.

Materials and Methods

Subjects

The study subjects comprised female twin pairs recruited from the St Thomas' Adult Twin Registry (Spector & MacGregor, 2002). Only females were included as no males had hand x-rays performed. Recruitment of these subjects has been described elsewhere (Spector et al., 1996) and subjects were unaware of any particular hypotheses being tested. Zygosity was determined by questionnaire and genotyping. The St Thomas' Ethics Committee approved the study, and informed consent was obtained from all subjects.

X-Rays

X-rays of both hands were taken from the dorsal surface at 55 KVp, 5 mA at a collimator distance of 100 cm. Using digital vernier callipers measuring to 0.01 mm, the lengths of the second and fourth fingers

Simon N. Paul, Bernet S. Kato, Lynn F. Cherkas, Toby Andrew, and Tim D. Spector

of each hand (in keeping with previous studies) were measured from the proximal end of the proximal phalanx to the distal tip of the distal phalanx. X-rays were excluded in the presence of total or partial amputation of the second or fourth digit, evidence of arthropathy, or indistinct/unreadable images.

A single reader conducted all the measurements. Finger lengths from hand x-rays of 31 twin pairs were read twice on a standard horizontal light box with an interval of a week to test reproducibility. Repeatability of finger lengths was calculated as an intraclass correlation coefficient and was very high (.99) for all lengths. Repeated measures ANOVA was used to calculate the ratio between groups mean squares and error mean squares (F value). The between individual variance was far greater than the measurement error for all lengths (right second finger length $F = 406$, $p = .039$, right fourth finger length $F = 2315$, $p = .0052$, left second finger length $F = 676$, $p = .0305$, left fourth finger length $F = 451$, $p = .037$). From these findings, we established that our measurements were highly repeatable and reflected real differences between subjects.

Genetic Modeling and Statistical Analysis

A higher MZ than DZ intraclass correlation (r) provides an initial impression of the magnitude of genetic influence. One-way ANOVA models for the 2d:4d of both hands were used to estimate the degree of intraclass correlation.

Quantitative genetic model fitting based on comparison of covariance (or correlations) of the phenotype in MZ and DZ pairs allows a more extensive separation of the observed phenotypic variance into additive polygenic (A) and dominant (D) genetic, and common (C) and unique (E) environmental components, assuming that the variation of the 2d:4d follows a normal distribution (Neale & Cardon, 1992; Sneider et al., 1997), the variance components are independent of one another (e.g., there are no gene–environment interactions) and that the phenotypic correlation between siblings are not confounded by zygosity (Hopper, 1992). Univariate analysis was performed to estimate variance components using DeFries and Fulker (DF) linear regression (DeFries & Fulker, 1985). DF analysis was performed by regressing the twin quantitative trait upon the co-twin phenotype (using double-entered data for unselected twins) as follows:

$$T = \beta_0 + \beta_1 P + \beta_2 R + \beta_3 PR + \beta_4 D + \varepsilon$$

where T is the twin quantitative trait, P is the proband or co-twin quantitative trait, R is the coefficient of relationship (coded 1 for MZ twins and .5 for DZ twins), D represents dominance (coded 1 for MZ twins and .25 for DZ twins), and ε represents the Gaussian distributed random error term from the ordinary least squares regression. PR and PD are interaction terms, calculated by taking the product of P with R and D, respectively. In this parameterization, the regression coefficient β_2 is the estimated propor-

tion of variance due to shared environmental factors (C), β_3 is the estimated additive genetic variance component (A), and β_4 is the dominant genetic variance (D). Because of collinearity, only one of the two terms, PR or PD, can be included in a single regression analysis in conjunction with P. Model standard errors were corrected by a factor of $\sqrt{2}$ to account for the double-entered data. An implementation of this method programmed for the statistical software package Stata release 8 (StataCorp, 2003) is available upon request from the authors.

The significance of the additive genetic and common environmental factors were calculated by comparing the deterioration in model fit between the full and submodels.

Results

All data was derived from female subjects. Two hundred and twenty-three individual sets of hand x-rays (148 MZ, 75 DZ) were excluded for various reasons and the mean age of the subjects at time these x-ray were performed was 54.4 years ($SD = 12.2$). The reasons for exclusion were as follows: co-existent arthropathy in 118 (15 rheumatoid arthritis, 103 osteoarthritis [OA]), singleton data only 56, poor image quality 40, unknown zygosity 6, and digit amputation 3. Since the mean age of studied and excluded subjects was similar (54.4, $SD = 12.2$, and 54.4, $SD = 8.46$, respectively), we feel that the study group was representative of the sample as a whole and that in order to draw valid conclusions, it was necessary to exclude arthritic digits as, due to deformity these may give a false estimate of 2d:4d.

Complete data was available on 148 MZ and 308 DZ pairs. 2d:4d for both hands in MZ and DZ pairs was normally distributed and Table 1 illustrates their demographic data.

No significant differences were found between zygosity groups for mean age or mean right 2d:4d but mean left 2d:4d was slightly larger in DZ subjects (difference = 0.02, $p = .03$). Mean 2d:4d for right and left hands did not differ significantly within zygosity groups.

For right 2d:4d, the intraclass correlations were .66 ($SD = 0.03$) and .35 ($SD = 0.04$) for MZ and DZ twins respectively. For left 2d:4d, corresponding values were .71 ($SD = 0.03$) and .37 ($SD = 0.04$; see Figure 1). Model fitting to these results indicated a significant genetic influence.

Table 1

Basic Demography of MZ and DZ Pairs

	MZ	DZ
Number of pairs	148	308
Mean age in years (*SD*)	56.8 (7.58)	52.5 (8.47)
Mean right 2d:4d (*SD*)	0.923 (0.001)	0.924 (0.0007)
Mean left 2d:4d (*SD*)	0.925 (0.001)	0.927 (0.0008)

Scatterplot for Right 2d:4d in MZ twins

Scatterplot for Left 2d:4d in MZ twins

Scatterplot for Right 2d:4d in DZ twins

Scatterplot for Left 2d:4d in DZ twins

Intraclass correlation .6563 (*SD* = 0.0387)

Intraclass correlation .7134 (*SD* = 0.0328)

Intraclass correlation .3467 (*SD* = 0.0470)
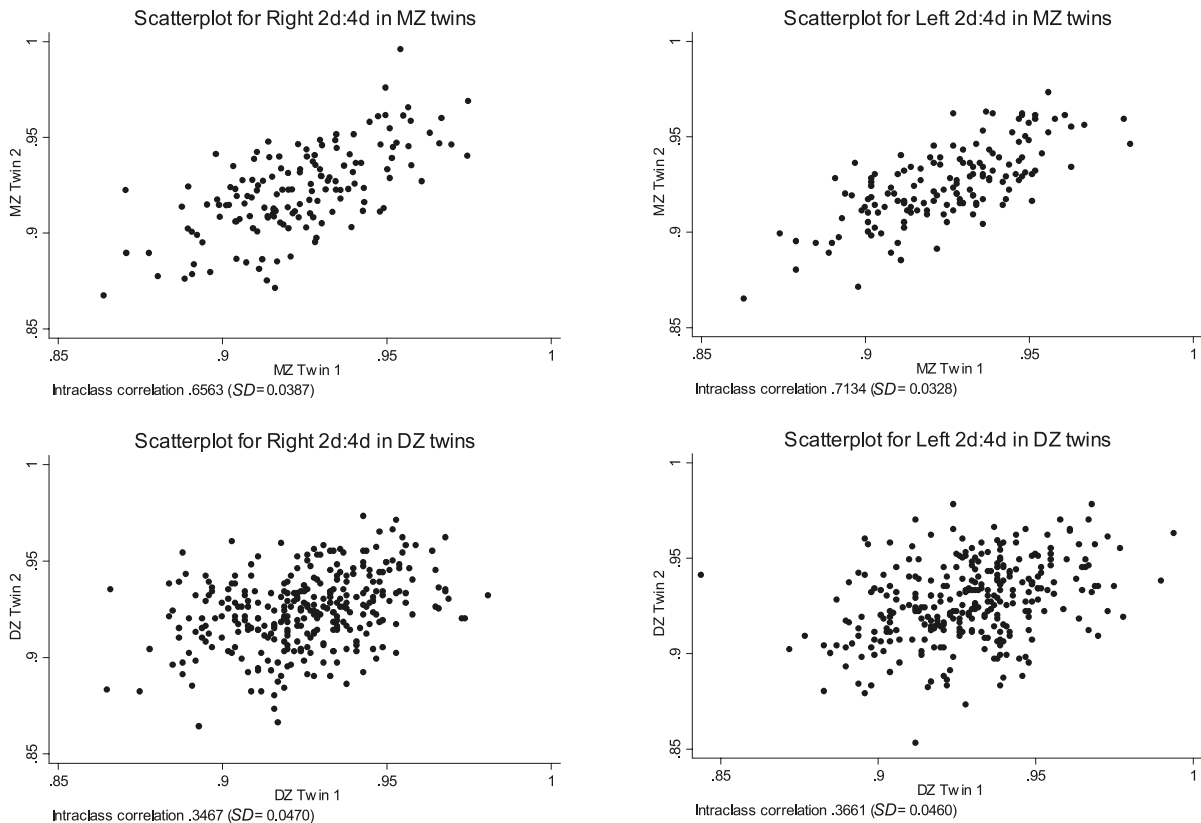
Intraclass correlation .3661 (*SD* = 0.0460)

Figure 1
Scatter plots for MZ and DZ pairs.

Table 2 shows heritability estimates calculated using the DF regression analysis and illustrates that for both right and left 2d:4d, the contribution of the shared environment of the twins (C) could be dropped without significant worsening of fit and this model of additive genetic factors (A) and the unique twin environment (E) best explained the variance in 2d:4d in this population. Heritability for right 2d:4d using this model was estimated to be .66 (95% confidence interval 0.55–0.78), and heritability for left 2d:4d was estimated to be 0.71 (95% confidence interval 0.60–0.83). Similar results were obtained using structural equation modeling implemented using Mx software (Neale, 2004).

Discussion

This is the first study to demonstrate a clear genetic influence on precisely measured 2d:4d in females. Published data related to the genetic influence over this interesting phenotype is scarce. Ramesh and Murty (1977) examined the relative lengths of the index and ring fingers of the parents and children of 190 families sampled from a mainly agricultural community living in India by visual comparison of the outstretched hand aligned on graph paper. Heritabilities of between 40% and 68% were estimated from parent–offspring regression and 33 and 66% from full sibling intraclass correlation data. Using this design the authors could not

separate shared environmental and genetic factors and also failed to find evidence of influence by sex-linked additive genes nor interestingly the 2d:4d sex difference that most other studies have found.

Table 2

Genetic Modeling Analysis for 2d:4d With Standardized Estimates

Trait	Model	A (95% CI)	C/D (95% CI)	Model fit statistic Adjusted R^2
Right 2d:4d	ACE	0.61 (0.28–0.95)	0.03 (–0.2–0.28)	.2139
	CE	—	0.46 (0.38–0.54)	.1992
	AE	**0.66 (0.55–0.78)**	**—**	**.2139**
	ADE	0.73 (0.3–1.16)	–0.07 (–0.56–0.41)	.2139
Left 2d:4d	ACE	0.70 (0.35–1.05)	0.01 (–0.23–0.25)	.2422
	CE	—	0.47 (0.39–0.55)	.2192
	AE	**0.71 (0.60–0.83)**	**—**	**.2429**
	ADE	0.73 (0.32–1.15)	–0.02 (–0.5–0.46)	.2422

Note: A = additive genetic, D = dominant genetic, C = common environment, E = unique environment. The best fitting models are in bold. The standardized estimates obtained from DF regression with the point estimates are not constrained to lie between 0 and 1. However, point estimates outside these intervals are clearly not biologically interpretable and such estimates are an additional indication of poor model fit. The variance component E is conflated with the random error term ε in the ordinary least squares regression and therefore the confidence intervals for E cannot be explicitly estimated using DF methods. However, the point estimate for E can be estimated by subtracting the other estimated variance components from 1.

Simon N. Paul, Bernet S. Kato, Lynn F. Cherkas, Toby Andrew, and Tim D. Spector

In our study, genetic modeling has suggested that at least 66% of the variance in 2d:4d is due to genetic factors. Twin studies, unlike family studies, have the advantage of being able to discriminate between genetic and shared environmental factors, and have the added advantage of matching for age and unknown cohort effects. We have demonstrated moderate to high levels of heritability of this interesting skeletal ratio.

Most work on 2d:4d has involved measuring finger lengths from hand photocopies which reduces collection time, and provides a permanent record; this form of measurement may yield lower ratios than direct finger measurements (Manning et al., 2005) although correlation is reportedly high for both these methods (Robinson & Manning, 2000). Manning et al. (2000) confirmed that the measurement of 2d:4d from hand photocopies and x-rays are significantly correlated although mean x-ray-derived 2d:4d showed less sexual dimorphism and ratios were lower than those derived from photocopies and the authors suggested this may be because photocopy measurement includes measuring soft tissue as well as bone lengths.

Genes underlying this skeletal ratio may be important for growth and hormone production. Much recent work has focused on the intrauterine sex hormone environment and loci that determine hormone expression may be a good place to start. In humans, Homeobox genes appear to control both digit and testicular/ovarian development (Manning, 2002) and this along with the fact that particular *Hox* mutations produce abnormalities of digits and genitals has led some researchers to link the intrauterine sex hormone environment and skeletal development together.

The effect of common environmental factors, C (be it *in utero*, antenatal life, childhood, etc.), is probably not large. Although twin models may underestimate values of C (Hopper, in Spector et al., 2000), this contribution is relatively small compared to that from additive genetic factors. The intrauterine environment can be very different even for MZs, and differential placental blood supply or hormone exposure are two of many possible sources of environment induced variance in 2d:4d. Recently much work has focused on the influences of prenatal androgen in determining 2d:4d. Van Anders et al. (2005) have suggested that hormone transfer between opposite-sex twins may influence the determination of 2d:4d for the left hand. In their study, photocopy determined 2d:4d from nine opposite-sex twin pairs was compared with that from 19 single-sex pairs. The mean age of subjects was 10.2 years. The authors found that left (but not right) 2d:4d was significantly lower in females of opposite-sex pairs and suggested that high prenatal androgens in opposite-sex males may exert a masculinizing effect on their female co-twin at a time when 2d:4d is developing.

Selection bias is unlikely to be a problem in our study as x-rays were performed for other reasons. Also, the study population has been found to be similar to a population-based singleton sample for a number of common medical conditions and lifestyle characteristics (Andrew et al., 2001). The results of this study may be applicable to males although mean ratios are likely to differ.

In conclusion, using a precise phenotype and classical twin study design we have clearly demonstrated the heritability of 2d:4d. The results suggest a strong genetic component to the development of the ratio and further work should focus on genes and diseases that may be influenced by 2d:4d as well as likely gene-environment interactions.

Acknowledgments

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