Istanbul Anthropological Review
İstanbul Antropoloji Dergisi

İSTANBUL UNIVERSITY PRESS

Istanbul Anthropological Review - İstanbul Antropoloji Dergisi, Issue/Sayı 1, 2021
DOI: 10.26650/IAR2021-1312 Research Article / *Araştırma Makalesi*

Random Developmental Variation of Human Phenotypic Traits, as Estimated by Fluctuating Asymmetry and Twin Studies

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Submitted/Başvuru: 25.08.2021
Revision Requested/Revizyon Talebi: 05.11.2021
Last Revision Received/Son Revizyon: 18.11.2021
Accepted/Kabul: 19.11.2021
Published Online/Online Yayın: 13.12.2021

Citation/Atıf: Graham, J. H. (2021). Random developmental variation of human phenotypic traits, as estimated by fluctuating asymmetry and twin studies. *Istanbul Anthropological Review - İstanbul Antropoloji Dergisi, 1*, 1–10. https://doi.org/10.26650/IAR2021-1312

ABSTRACT

Random developmental variation, or developmental noise, contributes to total phenotypic variation in the human species. Despite exhortations to examine it, especially with respect to human behavior and intelligence, there has been little research specifically devoted to doing so. Random developmental variation can be estimated in studies of fluctuating asymmetry and comparisons of monozygotic and dizygotic twins. Estimation of random developmental variation requires that both genotype and environment be held constant. In a small sample of bilaterally symmetrical traits (dermatoglyphic ridge counts, digit lengths, ear lengths and widths), I show how the random developmental component can be estimated. In these traits, the percentage of total phenotypic variation attributable to developmental noise ranges from 3 percent to more than 25 percent. Moreover, for dermatoglyphic ridge counts, fluctuating asymmetry and twin comparisons give essentially the same estimates.

Keywords: Bilateral symmetry, dermatoglyphics, fluctuating asymmetry, IQ, morphometric traits, phenotypic variation

Introduction

Random phenotypic variation, or developmental noise, is an often-unrecognized component of phenotypic variation in humans, as it is in all eukaryotes (Gärtner, 1990; Lajus, Graham, and Kozhara, 2003; Graham, 2020, 2021). Population geneticists, for example, focus on genetic and environmental sources of variation, either ignoring the random developmental sources or inappropriately pooling them with the environmental sources (Falconer and Mackay, 1996). But random (stochastic) developmental sources can account for a significant proportion of the variation in natural populations (Wright, 1920; Lajus, Graham, and Kozhara, 2003; Pinker, 2003). By not taking the random developmental component into account, one risks overestimating the true environmental component. For traits such as IQ, policy decisions may hinge on knowing the true environmental component. Moreover, random sources are easily estimated for many traits, especially bilaterally symmetrical ones.

Population geneticists have traditionally decomposed total phenotypic variation σ^2_{total} into three main components: (1) genetic σ^2_g, (2) environmental σ^2_e, and (3) the interaction of environmental and genetic sources of variation σ^2_{ge} (Falconer and Mackay, 1996). This can be represented as $\sigma^2_{total} = \sigma^2_g + \sigma^2_e + \sigma^2_{ge}$. These components of total phenotypic variation are generally estimated in twin and family studies. More recent approaches involving genome-wide association studies (GWAS) involving single nucleotide polymorphisms (SNPs) take a similar approach (Lee et al., 2018), but often result in significantly lower estimates of heritability (Shen and Feldman, 2020; Friedman, Banich, and Keller, 2021). Few of these studies attempt to estimate the contribution of random developmental variation. In contrast, Alexander Kozhara (1989, 1994) has proposed decomposing total phenotypic variation into factorial $\sigma^2_{factorial}$ and stochastic $\sigma^2_{stochastic}$ components. The factorial component is the variation among individuals and represents the combined genetic and true environmental components. The stochastic component is the within-genotype (or within individual) variation, representing random developmental variation (plus measurement error if that is not considered).

The stochastic component can be estimated from twin studies—monozygotic and dizygotic twins raised in a common environment (compared with monozygotic and dizygotic twins raised separately). In most twin studies, additive genetic effects, shared environmental effects, and unique (unshared) environmental effects can be estimated. The unique environmental component includes random developmental variation and minor environmental differences that the twins experience. This has been done, for example, for human IQ to estimate genetic, environmental, and residual sources of variation (Rao, Morton, Lalouel, and Lew, 1982). The residual component corresponds to the stochastic component of Kozhara's approach. For bilaterally symmetrical traits, the approach is simpler. If R_i is the trait value on the right side of individual i, and L_i is the trait value on the left side of the same individual, then $\frac{1}{2}$ Var$(R_i + L_i)$ is the total phenotypic variation σ^2_{total} and $\frac{1}{2}$ Var$(R_i - L_i)$ is the stochastic component $\sigma^2_{stochastic}$. The factorial component can be estimated as $\sigma^2_{factorial} = \frac{1}{2}$ Var$(R_i + L_i) - \frac{1}{2}$ Var$(R_i - L_i)$. If replicate measurements of R and L are made, then the contribution

of measurement error can be eliminated from the stochastic component by using a mixed-model ANOVA followed by the estimation of variance components for among individual variation σ_i^2, directional asymmetry σ_s^2, fluctuating asymmetry $\sigma_{s\,x\,i}^2$, and measurement error σ_m^2 (Leamy, 1984; Palmer and Strobeck, 1986; Graham, Raz, Hel-Or, and Nevo, 2010). The key assumption of both twin and asymmetry approaches is that both genotype and environment are held constant in monozygotic twins and right and left sides of the same individual.

Stephen Pinker (2003, 2004) has made a strong case for evaluating random developmental variation in humans. He argues that the personality differences among monozygotic twins cannot be explained by peer-group and other environmental differences. He throws a spotlight on a variety of random events inherent in development of the nervous system. This random developmental variation has been rarely quantified in humans. Studies that have examined random developmental variation in other species show how important it can be, on par with genetic and environmental components (Gärtner, 1990; Lajus, Graham, and Kozhara, 2003). Consequently, it makes sense to rephrase the sources of phenotypic variation not as nature and nurture, but as nature, nurture, and noise.

The Origins of Random Developmental Noise

Random processes involve chance, with negligible determinism (Tashman and Lamborn, 1979; Williams, 1997). Stochastic variation exists at all scales in the hierarchical organization of life: molecules, organelles, cells, tissues, organs, and organ systems. At the molecular level, the classic example of a stochastic process is Brownian motion, the thermal buffeting of small particles and macromolecules by much smaller water molecules moving at high velocity.

But random variation exists throughout the hierarchy of life. There is, for example, considerable within-cell variation among organelles, membrane-bound compartments in eukaryotic cells. These include mitochondria, chloroplasts, and leucoplasts. Mitochondria, in particular, are dynamic, growing and dividing continuously. The number of mitochondria per cell can vary widely. Most cells, for example, contain from 10 to several hundred mitochondria, although some types, such as liver cells, may have thousands (Wolfe, 1993). Even within a particular cell type and size, different cells contain different numbers of mitochondria (Tzagoloff, 2012; Robin and Wong, 1988). Finally, gene expression patterns often vary among neighboring cells of the same type (Elowitz, Levine, Siggia, and Swain, 2002; Raser and O'Shea, 2005). Much of this variation is random.

Cells of a particular tissue type, such as neutrophils, vary in size, shape, numbers of organelles, and numbers of metabolites and signaling molecules. Moreover, there is considerable variation among tissues within an organ. Some of this variation is due to differentiation, which is entirely deterministic, but some is also stochastic. When animals age, for example, muscle tissue begins degenerating unequally (Finch and Kirkwood, 2000). And there is also random variation among organs. This is especially noticeable when there is more than one organ per individual. Mammals, for example, have a pair of kidneys and a pair

of lungs. Annelids have excretory organs in every body segment. Flowering plants may have several flowers. Finally, organ systems vary as well. To see such variation, one must usually examine isogenic lines raised in a common environment. This is because most animals have only one organ system per individual.

Noise

Noise consists of unpredictable changes of any quantity varying in time. According to Schroeder (1990), there are at least five kinds of noise: white, pink, brown, black, and anti-persistent noise. Other authors may define these differently, but these colors of noise differ in their power spectra. Random events in a time series are white noise. The power spectrum of white noise is independent of frequency f; it has a power spectrum proportional to $1/f^0$. Brown noise has a power spectrum proportional to $1/f^2$. Pink noise ($1/f$) lies between white and brown noise, and black noise ($1/f^3$) lies beyond brown noise. White noise is said to be the least persistent (i.e., there is no memory); black noise is the most persistent. Beyond white noise in the opposite direction, however, is anti-persistent noise, which has a power spectrum proportional to $1/f^{-n}$; a fluctuation in one direction is likely to be followed by a fluctuation in the opposite direction. Pink, brown, and black noise are all commonly found in nature (Schroeder 1990).

Estimating the Stochastic Component of Human Phenotypic Variation

I will first demonstrate how to estimate the stochastic component of human phenotypic variation with a data set of dermatoglyphic counts published by Holt (1952). If we assume that measurement error is zero, or negligible, which is reasonable for meristic data if two or more repeated counts are in agreement, we can estimate the total phenotypic variance σ^2_{total} as ½ Var($R_i + L_i$), where $i = 1$ to n. Following Kozhara (1989, 1994), the stochastic component $\sigma^2_{stochastic}$ is ½ Var($R_i - L_i$). The factorial variance $\sigma^2_{factorial}$ is then the difference between the total phenotypic variance and the stochastic variance. The variances are multiplied by ½ to be consistent with the approach involving the mixed-model ANOVA of Leamy (1984). Holt (1952) studied 50 males and 50 females (parents from 50 families). In this instance, dermatoglyphic counts, the percentage contribution of random developmental noise is only 3.2% of the total phenotypic variation (Table 1). There is virtually no difference between the estimates for males and females.

Table 1. Stochastic and factorial components of total phenotypic variance from Holt's (1952) right and left dermatoglyphic counts (fingerprint ridges) of parents from 50 families (Holt's Table 1). Sample size for both males and females is $n = 50$.

Sex	Var($R + L$)	Var($R - L$)	σ^2_{total}	$\sigma^2_{factorial}$	$\sigma^2_{stochastic}$	Percent Factorial	Percent Stochastic
Males	3130.24	100.39	1565.12	1514.92	50.197	96.79	3.207
Females	2877.45	92.95	1438.72	1392.25	46.473	96.77	3.230

Holt (1952) also studied a small data set of monozygotic twins, some classified as psychotic or neurotic (n = 12 pairs) and others as normal (n = 6 pairs). The monozygotic twins offer an opportunity to distinguish stochastic and factorial components across monozygotic twins rather than across right and left sides. We take a parallel approach to what was done for right and left sides in Table 1. For each sibling (i = 1 to 2) in a pair, we have the total ridge count ($R_{ij} + L_{ij}$), where j = 1 to n, the pairs of twins. Total phenotypic variance σ^2_{total} is then ¼ Var($R_{1j} + L_{1j} + R_{2j} + L_{2j}$) and the stochastic variance $\sigma^2_{stochastic}$ is ¼ Var[($R_{1j} + L_{1j}$) – ($R_{2j} + L_{2j}$)] . As before, the factorial variance is $\sigma^2_{factorial} = \sigma^2_{total} - \sigma^2_{stochastic}$. I use ¼ of the variance because each pair of twins represent 4 measurements. Because the stochastic component of males and females was nearly identical in the previous analysis, they are pooled for this one. As can be seen in Table 2, the stochastic component across normal twins in very close to the estimate across sides. The estimate for psychotic or neurotic twins is only slightly lower. Thus, we can safely assume, as Danforth (1919) had done (see Graham, 2021), that the comparisons across monozygotic twins and those between right and left sides of the same individuals are measuring the same phenomenon, developmental noise.

Table 2. Stochastic and factorial components of total phenotypic variance from Holt's (1952) right and left dermatoglyphic counts (fingerprint ridges) of monozygotic twins [psychotic or neurotic, and normal (Holt's Table 3)]. Males and females are pooled within each group.

Category	Var (*R1* + *L1* + *R2* + *L2*)	Var ((*R1* + L1) – (R2 + *L2*))	σ^2_{total}	$\sigma^2_{factorial}$	$\sigma^2_{stochastic}$	Percent Factorial	Percent Stochastic
Psychotic or Neurotic	7786.08	133.48	1946.52	1913.15	33.369	98.290	1.714
Normal	5093.9	174.80	1273.47	1229.77	43.700	96.57	3.4317

The approach for bilaterally symmetrical traits that are continuous variables, with measurement error, is a little more complicated. It involves the estimation of variance components in a mixed-model ANOVA, first proposed by Leamy (1984) and then promoted by Palmer and Strobeck (1986). This ANOVA contains terms for sides (s), individuals (i), a sides x individuals interaction (s x i), and measurement error (m). Sides is a fixed effect, while individuals and measurement error are random. The sides x individuals interaction is a mixed effect. Most studies of fluctuating asymmetry test for a significant interaction effect because the interaction represents non-directional asymmetry (fluctuating asymmetry and antisymmetry). Graham, Raz, Hel-Or, and Nevo (2010), however, have argued that the only effect in the model worth testing is the sides effect (H_0: $\mu_r = \mu_l$). The other three effects are either random (i, m) or mixed (s x i). It makes no sense to test the null hypothesis that H_0: $\sigma^2_{s\ x\ i} = 0$. The researcher knows beforehand that random variation between sides is always present. Unless one is considering highly canalized meristic traits, it is impossible that every individual is perfectly symmetrical. The most important aspect of the mixed-model ANOVA is the estimation of the estimable variance components for i, s x i, and m. These should be reported in all studies of fluctuating asymmetry, but rarely are.

Table 3. Mixed-model ANOVA for the estimation of the estimable variance components in a study of fluctuating asymmetry. Table from Graham, Raz, Hel-Or, and Nevo (2010).

Source	df	MS	Expected Mean Squares	Interpretation
Sides	1	MS_S	$\sigma^2_m + R\,(\sigma^2_{s\,x\,I} + N\langle\sigma^2_s\rangle)$	Directional asymmetry
Individuals	$N-1$	MS_I	$\sigma^2_m + R\,(\sigma^2_{s\,x\,I} + 2\sigma^2_I)$	Size/Shape variation
Sides x Individuals	$N-1$	$MS_{S\,x\,I}$	$\sigma^2_m + R\,\sigma^2_{s\,x\,I}$	Fluctuating asymmetry and antisymmetry
Replicates (S x I)	$N(R-1)$	MS_{error}	σ^2_m	Measurement error

To demonstrate the mixed-model ANOVA, I use data from Ozener and Graham (2014). There were four bilateral variables, digit 2 length, digit 4 length, ear length, and ear width. These were measured on right and left sides, with replicate measurements made for all. Although the original data set contains equal numbers of inbred and outbred children, I pool them here because the goal is to demonstrate how this is done. The variance components analysis was done in R, with the VCA and lme4 packages.

The stochastic component of total phenotypic variance was less than 5% for the lengths of digits 2 and 4 (Table 4). In contrast, the stochastic component for ear width was 26%, and the stochastic component for ear length was 18.5%. These values are to be expected; digit length is undoubtedly under greater selection pressure than ear length and width. I should mention, however, that digit length ratios are sexually dimorphic (Zheng and Cohn, 2011) and are not the best traits for estimating the contribution of developmental noise if sex or gender are not taken into account.

Table 4. Variance components for human digit length, ear length and width, and measurement error. Data is from Ozener and Graham (2014).

Variable	σ^2_{total}	$\sigma^2_{factorial}$	$\sigma^2_{stochastic}$	σ^2_m	Percent Factorial	Percent Stochastic
Digit 2 Length	7.3433	6.9515	0.3187	0.000603	94.6633	4.3404
Digit 4 Length	7.6139	7.3410	0.2181	0.01810	96.4155	2.8639
Ear Length	11.6565	9.3838	2.1592	0.00077	80.5027	18.5241
Ear Width	6.9247	5.1141	1.8098	0.00078	73.8534	26.1354

Developmental Noise in Eukaryotes

Sewall Wright (1920) was probably the first scientist to fully appreciate the importance of random developmental variation. In a population of guinea pigs that had undergone brother-sister matings for 20 generations, he was amazed that "a guinea-pig with 20% of white in the coat may have a litter mate with as much as 90% of white" (Wright, 1920, p. 321). He employed path analysis to estimate the genetic, tangible environmental, and random developmental components of variance in the percentage of white in the coat. (This was one of the first uses of path analysis, a technique invented by Wright.) In an outbred control group, the genetic and tangible environmental components of total phenotypic variance were 42.1% and 0.31% respectfully. The stochastic component was 57.5%. The inbred group,

in contrast, had almost no genetic variation (2.7%) after 20 generations of inbreeding. The environmental component accounted for only 5.5% percent of the total variance, while the stochastic component accounted for a startling 91.8% percent. As one might expect, the inbred guinea pigs were less variable overall ($\sigma^2_{total} = 0.364$ compared to $\sigma^2_{total} = 0.643$ for the outbred ones). The missing variation was largely the genetic component.

Lajus, Graham, and Kozhara (2003) reviewed the literature on random developmental variation for several different species of eukaryotic plants and animals, including humans. For continuously distributed morphometric traits, the stochastic component accounted for 1 to 40% of the total phenotypic variation, while for meristic traits (counts), the range of variation was more like 50 to 70%. These figures, however, are over-estimates because most of these studies did not include estimates of measurement error. Moreover, traits studied for estimates of fluctuating asymmetry may be specifically chosen because they are more variable than other traits.

Developmental Noise in Human Populations

Very few studies involving humans include enough information to infer the stochastic component of phenotypic variation (Graham and Özener, 2016). Jolicouer (1963) studied symmetry of the humerus, femur, and tibia in humans and mink (*Martes americana*). Measurement error was not accounted for. The error component (developmental variation plus measurement error) was small (about 1% of the total variance) in both humans and mink. This might be expected for traits for which right-left symmetry is important.

IQ and Educational Attainment

The heritability of human intelligence, as measured by the Intelligence Quotient (IQ) has been controversial for more than a century. Most approaches partition phenotypic variation into just genetic and environmental components, rarely reporting the residual variation (Plomin and Loehlin, 1989). Recent papers have relied on genome-wide association studies (GWAS), identifying more than 100 single nucleotide polymorphisms (SNPs) that influence educational attainment (Lee et al., 2018; Bird, 2021), but these do not mention the residual variance either.

In contrast to most papers in the recent literature, Rao, Morton, Lalouel, and Lew (1982) report the residual variance in their estimates of various components of phenotypic variance in monozygotic twins raised together and apart. For one model, phenotypic homogamy, they estimated the additive genetic component at 31% of the total variance, and the cultural component at 42%. The covariance of these two components was 7.3%. The residual variance, which includes random developmental variation and measurement error, was estimated to be 19.3% of the total variance in IQ. Under other models, the residual variance ranged from 8.0% to 40.8% of the total variance. To the best of my knowledge, none of these studies have attempted to distinguish random developmental variation from measurement error.

Conclusion

Although there have been hundreds of studies of human fluctuating asymmetry in the literature, very few have presented the asymmetry variance of any trait as a proportion of the total phenotypic variation, after taking measurement error into account. Moreover, most studies fail to carry out replicate measurements. And as simple as this is to do, most studies that use the mixed-model ANOVA to estimate directional asymmetry and non-directional (fluctuating asymmetry and anti-symmetry) fail to estimate the variance components associated with these sources of variation. Those variance components (σ_I^2 and $\sigma_{S\times I}^2$) correspond to the factorial (genetic and environmental) and stochastic (developmental noise) components described by Kozhara (1994). Moreover, without singling out any papers, most studies carry out useless hypothesis tests of dubious value (Graham, Raz, Hel-Or, and Nevo, 2010), when the goal should be estimating the variance components. Until this is done as a routine part of reporting results, we will not have a handle on how much random developmental variation contributes to human phenotypic variation across a range of traits.

As simple as Kozhara's approach is in practice, it is restricted to bilaterally symmetrical traits. Traits that exhibit directional asymmetry or antisymmetry are best avoided, or treated separately. Most corrections for directional asymmetry, for example, over-estimate the contribution of fluctuating asymmetry to the observed directional asymmetry (Graham, Emlen, Freeman, Leamy, and Kieser, 1998). There are also instances in which transitions occur between fluctuating asymmetry and both directional asymmetry and anti-symmetry (Graham, Emlen, and Freeman, 1993, 2003).

For humans, twins raised in a common environment is the only complementary approach not restricted to symmetrical traits. Twin studies, however, have their own difficulties, mostly with the assumption of identical environments. Once twins are born, they are subject to different perturbations and accidents of development. Nevertheless, these two approaches are the only ways of holding both genotype and environment constant. If measurement error can be estimated and accounted for, any differences between right and left sides and between monozygotic twins can be attributed to developmental noise.

Informed Consent: Written consent was obtained from the participants.
Peer Review: Externally peer-reviewed.
Conflict of Interest: Author declared no conflict of interest.
Grant Support: The author declared that this study has received no financial support.

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