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Are Genetically Informed Designs Genetically Informative? Comment on McGue, Elkins, Walden, and Iacono (2005) and Quantitative Behavioral Genetics

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M. McGue, I. Elkins, B. Walden, and W. G. Iacono (2005) presented the findings from a twin study examining the relative contributions of genetic and environmental factors to the developmental trajectories of parent–adolescent relationships. From a behavioral genetics perspective, this study is well conceptualized, is well implemented, and raises some interesting developmental questions. Yet, the classic twin methodology and heritability estimates obfuscate the dynamic gene–ecology transactions that underlie these social developmental trajectories. There is a growing divide between the findings of quantitative behavioral genetics, with its foundational estimate of a statistical genetic influence, and developmental molecular genetics. This comment provides a brief overview of this divide and its implications for the findings of McGue et al. as well as quantitative behavioral genetics more broadly.

Keywords: behavioral genetics critique, developmental genetics, twin designs

A central focus of contemporary developmental theory is the elucidation of the manner in which key person–context reorganizations influence developmental trajectories across the life span (e.g., Baltes & Smith, 2004). Such periods of reorganization are characterized by substantial quantitative and qualitative changes cascading through an integrated system of biological, psychological, and ecological domains (see García Coll, Bearer, & Lerner, 2004). There is little doubt that the transition from childhood to adolescence is one such critical period of reorganization (see Lerner et al., 1996). As McGue, Elkins, Walden, and Iacono (2005) cogently argued, despite the potential impact of changes in the quality of the parent–adolescent relationship on the adolescent life course, there is a paucity of longitudinal research examining this important question. In extending this area of inquiry, McGue et al. reached three primary conclusions:

1. It is important to recognize the multifaceted nature of developmental change by explicitly considering mean-level continuity, rank-order stability, and continuity of scale variance simultaneously (see Bornstein & Suess, 2000; Nesselroade & Ghisletta, 2000). Indeed, it is the latter index of developmental change that might be of most use in understanding and promoting successful transitions through adolescence to early adulthood. Though the effect McGue et al. (2005) found is moderate, it does suggest a divergence of adolescent perceived relationship quality with their parents, and in the majority of cases it is the increase in negative perceptions that leads to increased scale variance. McGue et al. raised the pressing question of what, then, accounts for this increased variability?

2. In explaining the moderate level of instability in perceived relationship quality, McGue et al. (2005) first turned to gender. Given the literature on gender differences in early adolescent experiences, this seems a reasonable source of variance. Consistent with previous literature, this study revealed modest gender differences in perceived relationship quality.

3. Finally, McGue et al. (2005) concluded that a key source of increasing variability in adolescent perceptions of their relationships with their parents is genotypic variation. The authors interpreted this finding as being the result of an evocative genotype–environment correlation process (Scarr & McCartney, 1983) in which, presumably, genotypic variation leads to endophenotypic variation (e.g., personality characteristics, cognitive processing of social cues) in the adolescent, and as the adolescent ages these endophenotypic traits play a more pronounced role in defining the parent–child relationship. In reaching this conclusion, McGue et al. used leading biometric modeling techniques and a respectable rigor within the framework of quantitative behavioral genetics (Plomin, DeFries, McClearn, & Rutter, 1997).

It is in regard to this last point that I am most critical of their article. From within a quantitative behavioral genetic framework, McGue et al. (2005) have done a commendable job. Indeed, their study employs a rigorous quantitative behavior genetic methodology. What is at issue is that these putatively genetically informed methods are not genetically informative. My critique is not a traditional gene versus environment argument couched in the ever-familiar nature–nurture debate. As a discipline, developmental psychology has reached near-unanimous consensus that it is the interaction of genes and experiences that shapes behavioral development. Genes are certainly a critical component of the dynamic biopsychosocial system in which ontogeny takes place. Rather, what is at issue is the fundamental nature of how genes contribute to behavior and interact with experiences. To be more specific, McGue et al. concluded that the increase in variation in adolescents' perceptions of the quality of their relationships with their parents was due largely to genetic factors, and yet these putative

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genetic factors have little to do with what most of us think of as genes.

Criticisms of quantitative behavioral genetics in general and twin methodology in particular are certainly not new and, indeed, are many (e.g., Lerner, 2004). Some of the more prominent criticisms include the following:

1. The subtle distinctions between the statistical notion of heritability and the genetic process of inheritance are left out of behavioral geneticists' discussions of their methodology, thus implying a genetic mechanism of influence when this is in fact not the case (e.g., Ehrlich, 2000; Feldman, Otto, & Christiansen, 2000; Lerner & von Eye, 1992).

2. The assumption of a linear additive genetic contribution is difficult to support given the growing recognition of genetic interdependencies (e.g., Hood, Heath, Phelps & Lin, 2004). Population biologists are now using nonadditive statistical models based on Waddington's (1947) notion of *genetic epistasis*—the notion that the contribution of a particular gene is dependent on the functioning of one or more other genes as well as environmental factors (see Wolf, Brodie, & Wade, 2000).

3. These models do not measure environmental factors but rather assume environmental sources of variance as part of the residual term in the regression model (Schönemann, 1997).

4. Foundational assumptions, such as the equality of environmental influence across MZ and DZ twins, are untenable and thus lead to overestimates of heritability coefficients (e.g., Pam, Kemker, Ross, & Golden, 1996).

Although these are valid and serious criticisms of quantitative behavioral genetics, I do not reiterate them in full here. Instead, I focus on what I think is the most misleading aspect of quantitative genetic analyses and twin designs.

The foundation of quantitative behavioral genetics rests on the neopreformationist assumption that the structural sequencing of nucleotides in the genome encodes an algorithmic program that guides development. This field acknowledges environmental influences, but only in a limited way. From a quantitative behavioral genetics perspective, the environment is quite literally error variance around the genotypic "true-score" phenotypic proscription. However, this theoretical view of the genome and its relationship to behavior is inconsistent with the empirical findings of experimental embryology, developmental molecular genetics, and developmental psychobiology. Indeed, the disconnect between the statistical concept of genetic effects and genetic functioning is so great that there is little relationship between the two domains of inquiry. That is to say, McGue et al.'s (2005) claim that increases in perceived adolescent–parent relationship quality are primarily due to genetic sources of variance only has meaning in the context of the statistical assumptions of behavior genetic models and does not refer to genetic effects in the sense of DNA.

It does seem odd that twin-design behavioral genetic studies, which are often referred to by their proponents as genetically informed designs, do not actually measure genetic variability. Being a developmentalist, I find it useful to put this into a historical perspective. The basic conceptual structure of quantitative behavioral genetics has its roots in population genetics, which is a much older area of study than molecular genetics. Population genetics has its origins in the work of Mendel and in Fisher's (1918) derivation of the statistical models accounting for Mendelian heritability ratios. This work substantially preceded chromosomal theory and the discovery of DNA and its transcriptional properties. It was the genetic heritability theory developed in conjunction with Fisher's statistical models that led Schrödinger (1948) to suggest, and later Watson and Crick (1953) to identify, an intrachromosomal molecule with transcriptional properties. The result of this historical development of behavioral genetics is that it has allowed the field to indirectly estimate genetic variability in a theoretically self-referential manner without the need to assess empirically the construct validity of the variance component estimates. In other words, quantitative behavioral genetics, while internally consistent, has become completely insular to empirical genetics.

As a result, quantitative behavioral genetic studies explicitly measure neither sources of environmental variance (shared or unique) nor genetic variance. Indeed, it is only the dependent variable that is actually explicitly measured. It is true that the zygosity of each twin pair is measured as an indirect measure of the sequential structure of DNA, but this is not the same as genetic variance. The use of zygosity as a surrogate index of genetic variance is only valid if one adopts a preformationist concept of a genotype. It is assumed that there is a limited phenotypic range about the prescribed genotypic potential through which environmental factors can influence the ultimate phenotypic outcomes.

This preformationist conceptualization is inherent in the fundamental equations of quantitative behavior genetics. It is explicitly assumed that phenotypic variance is an additive function of genetic, common environmental, and unique environmental factors. Algebraically this is represented as

$$\mathrm{P} = h^2 + c^2 + e^2,$$

where P is the observed variance in some phenotypic trait, h^2 is the proportion of variance due to genetic factors, c^2 is the proportion of variance due to common environmental influences, and e^2 is the proportion of variance due to unique environmental experiences. Given that the DNA sequences in monozygotic twins are identical, it is assumed that monozygotic twins should have identical genotypes and thus, absent environmental influences, identical phenotypes. Because the genomes of dizygotic twins have on average only half of their DNA sequences in common, sans environmental influences they should, on average, share about 50% of their phenotype. According to this preformationist logic, then, the proportion of genetic influence can be inferred from the discrepancy between monozygotic (mz) and dizygotic (dz) twin pairs' phenotypic correlations:

$$h^2 = 2(r_{\mathrm{mz}} - r_{\mathrm{dz}}).$$

Environmental influences common to both twins in a twin pair, such as having the same parents, are then estimated as the difference between the monozygotic correlation and the proportion of that correlation that is due to putative genetic factors:

$$c^2 = r_{\mathrm{mz}} - h^2.$$

Finally, environmental factors that are unique to each member of a twin pair are simply the residual term:

$$e^2 = 1 - h^2 - c^2.$$

It is clear from this set of equations that genetic variability is inferred from the relative degree of phenotypic similarity in

monozygotic and dizygotic twins. This is not the same thing as observed genetic variability. Moss (2002) made this important distinction, referring to genetic variance inferred from phenotypic similarity as P-genes and to observed genetic variance as D-genes. The critical point is that P-genes are not informative about DNA and that D-genes are largely not informative with respect to phenotypes (see Moss, 2002, p. 224). In fact, basic cellular biology texts make this point: "The relationship between genotype and phenotype is very obscure. . . . structural similarity between proteins does not necessarily imply [DNA] sequence similarity" (Gerhart & Kirschner, 1997, p. 23).

As such, when McGue et al. (2005) stated that genetic factors account for the majority of increased variance in perceived adolescent–parent relationship quality, they did not really mean genetic factors; what they really meant is that the discrepancy between the monozygotic correlations and the dizygotic correlations had increased. This is an interesting finding and could potentially lead to important insights about developmental processes, but the limited attribution of this finding to statistical genetic effects restricts further analysis. If structural sequences in the genome were isomorphic to genetic function and, more important, to protein function, then the inferred genetic variability assumed by behavioral genetic models might be more instrumental. However, genes, rather than being static structural entities, are dynamic processes. Not only is their nucleotide structure important but so also are their linear spatial location in the genome, their spatial location in the intranuclear environment, their individual temporal patterns of expression, and the patterns of expression and inhibition across the entire genome. Moreover, gene expression is far from a straightforward process. It is highly dependent on complex genetic regulatory networks (Hood, Heath, Phelps & Lin, 2004) as well as extracellular factors. Gottlieb (2000) identified no less than 16 empirical studies demonstrating behavioral or environmental factors affecting gene or protein expression. Moreover, a single gene is capable of synthesizing more than a single protein, which has severe consequences for the relation of genes to phenotypic outcomes when compared with the assumption that there is a one-to-one relationship between genes and proteins. Thus, knowledge of the gene sequence itself, without the developmental conditions differentiating when a given protein might be synthesized, provides little information about how gene sequences relate to proteins let alone complex behaviors such as perceptions of adolescent–parent relationship quality.

Given this more dynamic, integrative systems understanding of gene expression (see Bearer, 2004), the conceptualization of the structural genotype as a set of special instructions guiding development is in direct conflict with empirical findings. Structural sequences of DNA have no independent developmental information. It is only in the context of developmental transactions of gene–gene and gene–environment (broadly defined) regulatory networks that the genome takes on any developmental salience. This completely undermines the utility of inferring genotypic variation from the relative phenotypic correlations of monozygotic and dizygotic twins. When McGue et al. (2005) referred to proportions of variance due to genetic factors, they were really reporting variance due to both genotypic and *epigenotypic* variance. The latter term was coined by Waddington to describe the "organizers and organizing relations to which a piece of tissue will be subject during development"(cited by Van Speybroeck, 2002, p. 69).

What, then, are the implications of quantitative behavioral genetic findings? If proportions of genetic variance are not tied in some meaningful way to actual genetic variability, then what can be inferred from this statistical estimate? One argument is that quantitative behavioral genetics can be used to identify candidate behaviors for molecular genetic study. Presumably in this particular case, the relatively strong "genetic" influences on the increasing variability in perceived parent–adolescent relationship quality would suggest that it might be fruitful to undertake molecular genetic studies to identify candidate genes underlying this phenotypic trait. Yet, because of the indeterminate relationship between the hypothetical statistical genes of quantitative behavioral genetics and actual genetic variability, this rationale does not work. Indeed, in quantitative trait loci and single nucleotide polymorphism studies of some of the strongest behavioral candidates on the basis of heritability estimates, such as schizophrenia and major depression, one finds that actual genetic variability is not significantly associated with behavioral variability, with effect sizes of less than 1% of covariance (Plomin & McGuffin, 2003). Another purported benefit of quantitative behavioral genetic findings is in the use of behavioral genetic models to identify genetic predispositions or risks for developing various disorders. However, because there is such a disparate relationship between genetic mechanisms and observed phenotypes, this use of behavior genetic findings also must be undertaken with caution. Gluckman and Hanson (2004), in a recent review of data regarding adult chronic disorders such as hypertension and diabetes mellitus, which are generally thought to be reflective of genetic predispositions, found that these disorders are more highly related to prenatal environmental experiences than to statistically estimated genetic susceptibility. So the empirical literature seems to suggest, much as developmental biologists, experimental embryologists, and developmental psychobiologists have suspected (see Michel & Moore, 1995), that the presence of a high heritability estimate provides little information about the relationship between actual genes and behavior.

As I said at the beginning of this comment, this is not an argument that is either pro-gene or anti-gene, pro-environment or anti-environment. Rather, my criticism of quantitative behavioral genetic approaches such as that used by McGue et al. (2005) is that they are not grounded in empirical genetics and give a misleading impression about the potential relationships between genetic functioning and the development of complex behaviors. Though the methodology and analytic approaches are not simple, I firmly believe that the future of gene–behavior research lies in shifting toward a more probabilistic epigenetic orientation. We now have the measurement capacity to observe rather than infer genetic variability both structurally and in terms of gene expression. Future genetic research should emphasize the transactional role between gene expression and developmental regulation across genetic and supragenetic levels of gene expression. For instance, one approach to gene–environment transactions would be to examine the manner in which concentrated conditions of poverty affect intrauterine environments and pre- and postnatal nutrition and, further, how these factors might influence the expression of key neurotransmitter receptors in the limbic system. The gene-expression/neural-function relationship, then, might be associated with increased probabilities of internalizing disorders, which in

turn place strains on parent–child relationships. This system would also include feedback loops in which the breakdown of the parent–child relationship results in poorer child behavioral and emotional regulation. This breakdown then would influence multiple socio-emotional developmental outcomes, increasing the likelihood of remaining in an environment with high levels of concentrated poverty. This set of hypotheses, although certainly beyond the scope of a single study, provides a broad framework for organizing developmental data from multiple and integrated levels of analysis and represents a set of gene–environment–behavior hypotheses that would be substantively meaningful and consistent with the transactional dynamic manner in which genes and environments are fused over the course of ontogeny.

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