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Integrating molecular mechanisms into quantitative genetics to understand consistent individual differences in behavior

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Abstract

It is now well appreciated that individual animals behave differently from one another and that individual differences in behaviors—personality differences—are maintained through time and across situations. Quantitative genetics has emerged as a conceptual basis for understanding the key ingredients of personality: (co)variation and plasticity. However, the results from quantitative genetic analyses are often divorced from underlying molecular or other proximate mechanisms. This disconnect has the potential to impede an integrated understanding of behavior and is a disconnect present throughout evolutionary ecology. Here we discuss some of the main conceptual connections between personality and quantitative genetics, the relationship of both with genomic tools, and areas that require integration. With its consideration of both trait variation and plasticity, the study of animal personality offers new opportunities to incorporate molecular mechanisms into both the trait partitioning and reaction norm frameworks provided by quantitative genetics.

Introduction

A thriving area of research in the study of animal behavior involves understanding consistent individual differences (‘animal personality’). There is growing appreciation that individual animals within natural populations behave differently from one another, and that they retain these behavioral differences through time and across situations. Consistent individual differences in behavior are interesting to animal behaviorists for at least three reasons. First, we want to know why individuals are different from one another; in other words, why is there variation? Second, we want to understand why behavioral traits are correlated in particular configurations (i.e. as components of behavioral syndromes). Why, for example, are boldness and aggressiveness correlated in some populations but not others?

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Conflicts of interest

None declared

Third, we want to know why individuals have a behavioral type that they maintain over time —what limits behavioral plasticity? The key features of personality—among individual (co)variation and within individual consistency—are what distinguishes the study of personality from simply the study of behavior.

Interest regarding animal personalities increasingly integrates research across levels of analysis and combines different methodological approaches. In particular there is growing interest in evolutionary processes that can generate consistent individual differences and widespread appreciation that understanding the proximate mechanisms underlying personality can shed light on its causation and evolution.

Quantitative genetics provides a framework for understanding personality

Quantitative genetics provides a strong conceptual basis for considering the key ingredients of personality: (co)variation and plasticity [1]. In particular, quantitative genetics provides a statistical framework for partitioning trait variation, covariation within and among individuals, and can estimate population and individual level behavioral plasticity [1]. For example, mixed effects statistical models can estimate reaction norms—phenotypic plasticity—using the phenotypic equation [2]:

$$y_{ij}=(\beta_0+ind_{0j})+(\beta_1+ind_{1j})x_{ij}+e_{0ij} \quad \text{(equation 1)}$$

where y_{ij} is the behavioral response of individual j at instance i [3]. The different parts of the equation correspond to population level average behavioral responses (β_0, assuming centering of predictor variables), the individual's deviation from this average (ind_{0j}, i.e. personality variation), and residual variation for that individual at that particular instance (e_{0ij}). Plasticity enters via x_{ij}, which is the environment experienced by that individual at that instance. If the population as a whole shows behavioral plasticity, this can be estimated (β_1) and individual level plasticity can also be estimated (ind_{1j}). Individual average behavior as it differs from the population mean (ind_{0j}) and individual plasticity as it differs from population level plasticity (ind_{1j}) might also be correlated such that *personality* and *plasticity* are correlated (for further details and assumptions see [3]). The emergence of quantitative genetics as an organizational basis for the field of personality research has allowed the rapid translation of statistical methods to the field and highlighted evolutionary questions of potential importance (e.g. [4]).

The problem: How to incorporate molecular mechanisms?

However, while quantitative genetics provides a conceptual basis for understanding consistent individual differences, the results from quantitative genetic analyses are often statistical abstractions, divorced from underlying molecular or other proximate mechanisms. Indeed, the prevailing approaches for studying the genetic basis of traits tend to focus on either the quantitative genetic or molecular side of the equation, and the two approaches require very different tools. Studies of quantitative genetics and molecular mechanisms are also often carried out in isolation of each other and their results are difficult to integrate. For example, one study might compute a genetic correlation between two behaviors [5], while another study in the same species finds correlated patterns of genome-wide expression

associated with these two behaviors [6,7]. Similarly, one study might estimate the slope of a behavioral reaction norm across environments, while another shows that gene expression changes across environments. Unfortunately the results from these approaches are not immediately comparable.

The gap between the statistical abstractions of quantitative genetics and the actual genetic or molecular mechanisms underlying them can be a problem because different mechanisms can produce the same outcome, and/or have different implications for evolution. For example, a relatively low estimate of heritability could reflect either low genetic variation or high non-genetic variation. Similarly, a genetic correlation between two behaviors could reflect either pleiotropy (when the same genes influence the two traits), physical linkage between loci or selection-induced linkage disequilibrium (when the traits are influenced by different, co-selected genes) [4,5,8]. Finally, phenotypic plasticity could reflect allelic sensitivity (different genes underlie the trait in different environments) or gene regulation (the same gene influences the trait in different environments, but the gene is regulated differently in the two environments [9]). Bridging this gap is an important priority for all of biology and emerging interest in personality offers an opportunity for combining molecular mechanisms and quantitative genetic approaches. Arguably, the advancement of personality research—with its concern for both variation among-individuals and for plasticity—necessitates this synthesis.

One strategy for bridging the divide between molecular mechanisms and traditional quantitative genetics is to identify the specific genetic variants that contribute to additive genetic variation and thus to phenotypic variation. Identification of such genetic variants can be achieved via quantitative trait loci (QTL) studies and genome-wide association studies (GWAS). While such approaches are currently limited to studying traits underlain by genes of large effect [10], finding such genes can be informative for understanding the proximate basis of traits, and can be used to address longstanding questions about the genetic basis of adaptation [11]. Identification of such genes also allows better understanding of the evolution of behavior and whether particular responses might be deeply conserved or novel. Finally, intensive public investment in GWAS was driven by concerns regarding human health, for which understanding how particular genes affect behavior can be highly relevant [12].

A number of recent papers have identified QTL associated with behavioral variation in natural populations, e.g. burrowing behavior in mice [13], schooling behavior in sticklebacks [14], aggressive behavior in *Drosophila* [15] and feeding behavior in *C. elegans* [16]. Importantly, such information from QTL studies can be integrated into the statistical framework provided by traditional quantitative genetics. For example, the proportion of phenotypic variation attributable to QTL variation can be framed in terms of heritability due to that QTL (but see [17]). Further, the phenotypic equation can be modified to include information about the influence of particular loci (e.g. QTL, expanding from [18]):

$$y_{ijm}=(\beta_0+ind_{0j}+G_{0m})+(\beta_1+ind_{1j})x_{ij}+e_{0ij} \quad \text{(equation 2)}$$

where the individual's phenotype is now also determined by a known loci (*m*, e.g. a particular QTL) which has an estimable average contribution to the phenotype (G_{0m}; as above this represents a deviation from the population level average, β_0). Within this framework, the contribution of variation at specific loci and epistatic interactions among them can thereby be estimated. Moreover, this framework can also be extended to include not only directly estimable genetic influences on behavior but also inferred genetic influences when pedigree information is known and relatedness included (i.e. application of the "animal model", [19]). However, it is likely to be challenging to apply this general framework to natural variation in behavioral traits with fitness consequences, because they are typically underlain by hundreds of genes of small effect and influenced by both genetic variation and the environment [20].

In principle, equation 2 can incorporate information about particular genes that might contribute to individual variation in plasticity, via the same manner by which individual plasticity was included:

$$y_{ijm}=(\beta_0+ind_{0j}+G_{0m})+(\beta_1+ind_{1j}+G_{1m})x_{ij}+e_{0ij} \quad \text{(equation 3)}$$

where the individual's known genotype (*m*) now has an estimable plastic effect on the behavior of the individual (G_{1m}) based on the environment currently experienced (x_{ij}). However it is likely to be challenging to empirically obtain these estimates.

An alternative to QTL and GWAS that comes closer to capturing molecular mechanisms associated with plasticity involves measuring genome-wide gene expression (e.g. [21–23]). The appeal of measuring genome-wide expression, as opposed to focusing on fixed genetic variation, is that it can reveal which genes in the genome are responsive to the environment, and therefore likely to be related to phenotypic plasticity. For example, recent genome-wide transcription studies have revealed that roughly ~10% of all of the genes in the genome are differentially expressed in response to a *mating opportunity* [24–29], *predation risk* [7,30,31], or a *territorial challenge* [6,32,33]. Recent evidence suggests that transcriptional responses can be the result of a conserved genomic response to social challenges [34]. Genome-wide gene expression studies have also detected differences in brain gene expression between behavioral types, e.g. scouts vs nonscout honey bees [35] and alternative mating types [29,36,37]. A few particularly exciting recent studies have both compared gene expression between behavioral types *and* changes in gene expression in response to the environment [29,38]. This strategy can inform our understanding of the evolution of plasticity by identifying potential targets of selection on plasticity [39]. However, studies measuring gene expression in regards to behavior largely occur in isolation of studies aimed at quantifying repeatability, heritability and genetic correlations – the traditional province of quantitative genetics (but see eQTL [40]). Unfortunately, how results from genome-wide gene expression studies translate to the conceptual framework of quantitative genetics remains to be resolved. This is not a trivial problem and there are several specific (e.g. Box 1) and general questions that must be addressed. It is, however, an essential problem as our theoretical understanding of evolution is in large part tied to quantitative genetic theory.

Box 1

Sample challenges for integrating molecular mechanisms into quantitative genetics, as applied to personality

- Can genome-wide gene expression data be used to link the **P** and **G** matrix?
- How to relate pleiotropy via a genetic correlation with patterns of gene expression?
- How to relate I × E or G × E reaction norms estimated within a quantitative genetic framework with gene expression measured in different environments?
- Is there a way to detect permanent environment, among-individual, within-individual and residual effects in gene expression data?
- Do differences in brain gene expression between behavioral types reflect additive genetic variation, among-individual variation or within-individual variation?

Conclusions: Personality requires integration

Understanding personality—consistent individual differences—requires consideration of both variation and plasticity. The study of personality has prompted questions about how processes that can generate variation can coexist alongside processes that allow within-individual plasticity, and indeed, how those processes are related to each other [41]. The study of personality therefore offers an opportunity for integration and improved understanding of both individual differences and behavioral plasticity. The study of personality also prompts a comprehensive synthesis of molecular mechanisms into both the variance partitioning and reaction norm frameworks provided by quantitative genetics. This integration of stability and plasticity alongside the integration of molecular mechanisms and quantitative genetics represents the next frontier for personality research and will similarly advance not only the study of animal behavior but evolutionary ecology as a whole.

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HIGHLIGHTS

- The study of animal personality is concerned with both variation and plasticity.
- Quantitative genetics provides a conceptual framework for personality.
- Recent studies have identified genes related to behavioral variation and plasticity.
- A challenge is to integrate molecular mechanisms into quantitative genetic theory.