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Gene–Environment Correlation in Humans: Lessons from Psychology for Quantitative Genetics

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Abstract

Evolutionary biologists have long been aware that the effects of genes can reach beyond the boundary of the individual, that is, the phenotypic effects of genes can alter the environment. Yet, we rarely apply a quantitative genetics approach to understand the causes and consequences of genetic variation in the ways that individuals choose and manipulate their environments, particularly in wild populations. Here, I aim to stimulate research in this area by reviewing empirical examples of such processes from the psychology literature. Indeed, psychology researchers have been actively investigating genetic variation in the environments that individuals experience—a phenomenon termed "gene–environment correlation" (rGE)—since the 1970s. rGE emerges from genetic variation in individuals' behavior and personality traits, which in turn affects the environments that they experience. I highlight concepts and examples from this literature, emphasizing the relevance to quantitative geneticists working on wild, nonhuman organisms. I point out fruitful areas of crossover between these disciplines, including how quantitative geneticists can test ideas about rGE in wild populations.

Keywords: extragenetic inheritance, gene–environment correlation, gene–environment interplay, quantitative genetics

For decades, evolutionary ecologists have known that the phenotypic effects of genetic variants can reach beyond the individual to influence the environments that individuals experience. Recent topics of intense interest, such as indirect genetic effects (IGEs), multilevel selection, niche construction, and eco-evolutionary feedbacks are all predicated on this idea (Bailey 2012; Bailey et al. 2018). While important recent breakthroughs have begun to illuminate the evolutionary implications of such feedbacks between genes and the environment (reviewed in Dawkins 1982; Donohue 2005; Bailey 2012; Saltz and Nuzhdin 2014), we still know little about the quantitative-genetic and developmental dynamics that occur within individuals' lifetimes to produce these outcomes.

In parallel, psychologists have been studying the ways that genetic differences in exposure to important environments (such as parenting, recreational drugs, or traumatic life events) might drive individual risk of psychiatric disorders. Influential papers starting in the 1970s (Eaves et al. 1977; Plomin et al. 1977) outlined a phenomenon—gene–environment correlation (rGE)—in which different genotypes systematically experience different environments (Figure 1). In many ways, this body of literature is the inverse of evolutionary genetics literature in that the focus is on identifying the effects of rGE on the development of traits (e.g., psychiatric disorders) within the lifetime of individuals. Furthermore, the psychology literature includes an abundance of empirical data on genetic informative samples of human populations. Researchers studying "free-living" humans often face similar logistical challenges to quantitative geneticists studying wild populations; for example, psychologists cannot perform

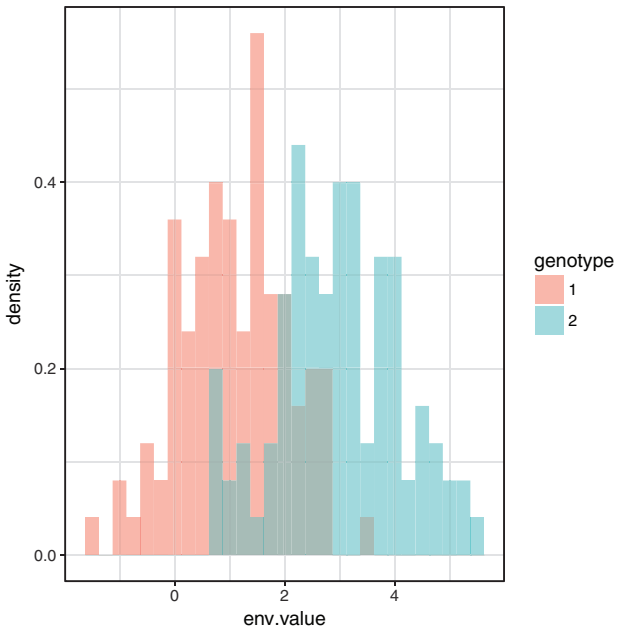

Figure 1. Hypothetical example of rGE for 2 genotypes (1 and 2). Each distribution is a histogram of 100 simulated individuals per genotype distributed across a continuously varying environment (*x* axis). Examples of such environments are temperature, time spent experiencing some environment, habitat quality, and so forth. The 2 genotypes differ in the environments that they typically experience, representing gene–environment correlation, rGE.

crosses nor (typically) experimentally manipulate individuals' environments.

Despite the shared motivation to understand the interplay between genes, traits, and environments, intellectual exchange between psychology and evolutionary biology has been limited (Bateson and Healy 2005; Uher 2011; Rowe and Healy 2014). Here, I aim to contribute to bridging this gap by reviewing concepts and examples from the psychology literature on rGE and articulating their relevance for quantitative geneticists working on nonhuman organisms.

Origins of rGE

The 20th century saw a rapid increase in genetic informative data sets on human behavior, such as pedigrees, adoption studies, and studies of twins reared together or apart. Analyses of these data sets revealed pervasive genetic effects on nearly everything that could be measured; but interpreting the meaning of the resulting heritability estimates provoked controversy (Layzer 1974; Plomin and Spinath 2004; Nisbett et al. 2012). Methods for estimating heritability in wild populations, namely parent–offspring regression, assume that offspring resemble their parents due to genetic inheritance. However, psychologists had long recognized that individuals in the same family not only had similar genotypes but also experienced similar environments—suggesting that trait values might aggregate in families for purely environmental reasons. Similarly, psychologists consider individuals to be active agents who, through their behaviors, personality, and other traits, often determine the environments they experience. This inability to separate genetic and environmental effects on traits seemed to invalidate attempts to estimate any heritable component of trait variation, particularly for controversial traits like intelligence quotient (IQ) and religiosity (Moran 1973; Layzer 1974; Plomin and Spinath 2004; Bradshaw and Ellison 2009; Nisbett et al. 2012). One paper characterized heritability as "numerology" (in the title! Layzer 1974). Without rearing humans in the lab, it was unclear how these limitations could be overcome.

This fierce debate spawned research into the causes and consequences of genetic variation in environmental exposures, a phenomenon termed gene– (or genotype–) environment correlation: rGE. Under rGE, different genotypes differ in traits by which individuals choose, manipulate, or inherit their environments. Thus, when rGE is present different genotypes are *expected* to systematically experience different environments as a consequence of these different traits. The concept of rGE thus formalized the intuition that genes and environments are linked and that environments as well as genes may "run in families."

"Gene"–environment correlation and "genotype"–environment correlation are used interchangeably in much of the rGE literature. This is usually reasonable because genotypic differences are assumed to be produced by functional-genetic differences, even if the relevant genes are not known. However, there are instances where distinguishing these terms may be valuable. Whereas "genotype"–environment correlation describes any (narrow- or broad-sense) heritability in environmental exposure, "gene"–environment correlation applies more narrowly to associations between specific genetic variants or quantitative trait locus and environment(s). For an example of a particular approach using *gene*–environment correlations, see the paragraph on Mendelian Randomization at the end of the paper.

Causes of rGE

In a seminal 1977 paper (Plomin et al. 1977), Plomin et al. outlined 3 general, nonexclusive types of mechanisms through which rGE can arise: passive rGE, active rGE, and evocative (originally called "reactive") rGE. Passive rGE describes the fact that parents contribute both genes and environments to their offspring. Genetic and environmental variation in parental traits influence the environments that offspring experience. When parental traits that influence offspring development vary among genotypes, these parental traits are therefore correlated with the offspring's genotype. Passive rGE thus corresponds to the quantitative genetics concepts of extragenetic inheritance and maternal/paternal effects, which emphasize that genetic variation in parental traits influence the *environmental* effects that shape offspring phenotype (Rossiter 1996; Slatkin 2009; Danchin and Wagner 2010; Danchin et al. 2011). These environmental effects are linked to the offspring's genotype because parents contribute both genes and environments to their offspring.

Active rGE refers to genetic variation in choice behaviors. In the psychology literature, relevant choices often include substance use and choice of friends (e.g., Harden et al. 2008). Quantitative geneticists and ecologists are accustomed to considering genetic variation in choice, including habitat choice, host choice, mate choice, foraging choices, and so forth (although the implications of such genetic variation in choice have not been fully explored (Saltz 2011; Saltz and Nuzhdin 2014); see below). In the animal behavior literature, this process is sometimes also referred to as "niche-picking" (Stamps 2016); in this context, niche picking only generates rGE when niche-picking traits vary among genotypes (Saltz and Nuzhdin 2014; Table 1).

Evocative rGE describes genetic variation in the responses that individuals elicit from conspecifics (including, but not limited to, their parents). For example, when paired with an unfamiliar playmate, preschoolers with a genetic predisposition toward aggressive social behaviors were also more likely to be aggressed against (DiLalla and John

Table 1. Comparisons between rGE concepts and evolutionary genetics concepts

rGE concept	Quantitative genetics concept	Similarities
Passive rGE	Parental effects (Badyaev and Uller 2009)	Passive rGE and parental effects are similar but not identical. Parental effects describe how parents alter their offspring's phenotype. Passive rGE emphasizes that these effects can vary among genotypes. Furthermore, passive rGE can exist without influencing offspring phenotype, that is, genotypes might differ in their parenting behavior (a heritable environment) but their parenting does not influence the offspring traits in a particular study.
Evocative rGE	IGEs (Wolf et al. 1998)	Evocative rGE is similar to the concept of IGEs in that different genotypes evoke different responses from interacting individuals. For evocative rGE to occur, however, the effect on the partner's phenotype must form an environment for the focal individual. For example, if 2 individuals interacted, and one's genotype influenced the other's phenotype years later, and the 2 individuals never met again, this would constitute an IGE but not rGE.
Evocative rGE	Niche construction (Odling-Smee et al. 1996)	Evocative rGE occurs when genotypes differ in niche-constructing traits.
Active rGE	Environment choice, niche picking (Stamps 2016)	Active rGE occurs when genotypes differ in niche-picking traits such as choice.
Active rGE	Nonrandom dispersal (Edelaar and Bolnick 2012)	Nonrandom dispersal can serve as a mechanism of rGE when particular genotypes disperse to particular environments. However, dispersal sometimes refers to movement among populations, whereas rGE refers to different environments experienced by individuals in the same population.
rGE	Extended phenotype (Dawkins 1982)	rGE and the extended phenotype are similar, but rGE emphasizes genetic differences in the environments individuals experience, whereas the extended phenotype concept just emphasizes that genes (per se) can have effects on the environment.
rGE effects on the development of other traits (scenario 1)	Environmental pleiotropy (Paaby and Rockman 2013)	Active and evocative rGE can produce environmental pleiotropy as described in scenario 1.

2014). Thus, evocative rGE corresponds approximately to the quantitative genetics concept of IGEs, in which genetic influenced traits of one interacting partner affect trait expression in another individual (Moore et al. 1997; Wolf et al. 1998; McGlothlin and Brodie 2009). The difference between evocative rGE and IGEs are subtle. IGEs describe *any* effect of a focal individual's genetic influenced traits on the traits of a social partner; however, such an effect would only constitute evocative rGE if this process occurred while the partners were interacting (or carried over to future interactions), so that the traits of the social partner provide an environment for the focal individual (Table 1). Similarly, processes by which individuals alter their environments—social, ecological, or abiotic—are referred to as "niche construction" in evolutionary ecology (Odling-Smee et al. 1996). As with niche picking, niche construction would only correspond to evocative rGE if the relevant niche-constructing traits varied among genotypes (Table 1).

Psychologists have, understandably, focused their study of rGE on interactions among conspecifics; but in quantitative genetics, this concept has been extended to heterospecifics as well, including in the wild. For example, different genotypes of eucalyptus trees attract strikingly different insect communities, a phenomenon that may be driven by genetic variation in plant defense compounds (Dungey et al. 2000).

The concepts of active and evocative rGE are particularly important because they suggest that the potentially confounding effects of rGE on quantitative genetics parameter estimates could not be overcome by studying adoptees and/or prenatal influences on behavior. Instead, nearly any type of environment was potentially subject to rGE, and thus rGE needed to be considered when interpreting heritability (Plomin et al. 1977).

Evidence for rGE

One of the most surprising but repeatable findings in human behavioral genetics is that environments are heritable (e.g., highlighted recently as one of the top 10 most replicated findings in behavior genetics; Plomin et al. 2016). Heritability of environmental measures can be computed the same way as phenotypic measures; that is, heritability of the environment quantifies the proportion of variation in environmental exposures that are attributable to additive genetic variation. This phenomenon represents rGE because if environments are to some extent heritable, then different genotypes experience different environments.

Do these patterns of environmental heritability arise from rGE? Or could they arise through some artifact and not represent rGE at all? Identifying the mechanisms that produce rGE in humans has only relatively recently become an active area of research (Rutter et al. 2006). Indirect evidence that rGE arises from genetic variation in the ways that individuals choose and manipulate their environments can be gleaned from differences in heritability across types of environments (Jaffee and Price 2012). Specifically, experiences that intuitively seem more "controllable" by individuals—such as getting a divorce or getting fired from a job—are more highly heritable than "less-controllable" experiences, like being hurt in an accident or being impacted by a natural disaster (Kendler and Baker 2007). Similarly, events that happen directly to a focal individual (e.g., getting fired) are more heritable than life events that happen to others in the focal individual's social network (e.g., a friend or family member getting fired; Bolinskey et al. 2004). These broad-scale summaries complement the large body of more-specific studies directly connecting genetic variation in specific behaviors to environments experienced (e.g., Kendler et al. 2003; Beaver et al. 2008; Harden et al. 2008; Distel et al. 2011). Together, these findings support the idea that rGE emerges from genetic variation in individuals' behavior and personality traits, which in turn affects the environments that they experience.

Some caution is needed when interpreting rGE findings, particularly the proposed mechanisms by which rGE may arise. For

example, humans' perception and recall of events can depend on personality, a problem termed "behavioral 'contamination' of the environmental measure" (Jaffee and Price 2007). This phenomenon leaves open questions about whether heritable personality traits cause different genotypes to have different experiences or whether personality mediates the ways that individuals perceive and/or remember a given environment. Under the latter hypothesis, multiple individuals may experience identical environments, as measured by an external observer, but some genotypes will experience those environments as stressful (for example) and other genotypes will not. Importantly, internalized perceptions of experiences can have important impacts on later behavior, suggesting that "perceived" rGE may be just as important to understanding trait variation as "externally measurable" rGE. In either case, considering the possibility of bias in self-reporting is important to identifying the causes of rGE. Similarly, rGE may arise not from individuals' own traits but from population-level processes such as discrimination. For example, due to economic inequality, ethnic minorities disproportionately live in environments with higher levels of toxicants (such as lead, smog, particulates, and dust mites), representing rGE (Williams and Sternthal 2010). Again, whether or not this distinction is important will depend on the details of the particular study. Finally, apparent rGE can arise due to selection, whereby specific genotypes are removed from environments to which they are maladapted. This explanation is relatively unlikely in psychology studies of humans but very important to carefully consider in studies of quantitative genetics in the wild. Here, I focus on nonselection explanations since most readers are likely already familiar with these.

Overall, then, while individual studies may provide incomplete explanations for observed patterns of apparent rGE, the bulk of the evidence strongly suggests that rGE exists and is likely common, at least in humans. One important implication of research in both psychology and quantitative genetics is that rGE is so pervasive that it can even occur under seemingly controlled conditions. A particularly important example is in studies of twins reared apart (i.e., twins adopted out to different families). These studies were initially viewed as "gold standard" genetics approach because individuals with the same genotype could be measured in independent environments (Bouchard et al. 1990; Martin et al. 1997; Zyphur et al. 2013). However, removing parenting effects only abrogates the opportunity for (postnatal) passive rGE while allowing evocative and active rGE. For example, children who inherit putative genetic risk factors for antisocial behaviors (based on family history) experience more harsh discipline from their parents, even from unrelated adoptive parents, relative to adoptees who are not at genetic risk (Jaffee and Price 2012). This example illustrates how evocative rGE can occur in (adoptive) parent–offspring interactions even when the potential for passive rGE is removed.

Indeed, cotwins raised in different families may actually experience quite similar environments because they evoke similar responses from their adoptive parents and because they choose similar friends and other environmental influences (and because adoptive families are, quite appropriately, not chosen at random; Bouchard et al. 1990). The pervasiveness of rGE even under "controlled" conditions is very relevant to quantitative genetics in the wild because the "twins reared apart" experimental design is identical to cross-fostering studies, reciprocal transplant experiments, and most other studies aimed at measuring phenotypic plasticity (Saltz et al. 2018). Indeed, rGE can be identified even under carefully controlled laboratory conditions (Saltz and Foley 2011; Foley et al. 2015; Kraft et al. 2016; Saltz 2017).

How Does rGE Produce Associations between Genotypes, Phenotypes, and Environments?

Once rGE has been caused (i.e., by passive, active, or evocative mechanisms), it may or may not influence trait variation and its genetic basis. Under rGE, genotypes, environments, and traits may all be correlated with one another. Because this pattern of correlations can result from several distinct underlying processes, rGE may obscure the causes of trait variation, particularly if the underlying rGE is not accounted for.

Here, I outline 3 nonexclusive scenarios by which trait variation may be influenced by rGE (Figure 2) and their implications for quantitative genetics, particularly heritability. These consequences can arise from active, passive, and/or evocative rGE. I focus on hypotheses most widely discussed in the psychology literature; thus, I ignore scenarios that include selection, which are already familiar to quantitative geneticists (e.g.. local adaptation: Kawecki and Ebert 2004).

Scenario 1: Environments Influence the Expression and/or Development of Some "Focal" Trait

Under rGE, different genotypes systematically experience different environments. Therefore, when rGE is present, different genotypes will experience different stimuli, cues, and experiences in the environment. These experiences in the environment, in turn, have the potential to influence trait development. Specifically, V_E describes the effect of environmental variation on trait variation. $V_E > 0$ whenever environmental variation contributes to trait variation, that is, when the trait is phenotypically plastic. Importantly, V_E does not describe variation in the environment itself, that is, V_E can be 0 even in a highly variable environment if the focal trait is aplastic.

In this scenario, rGE arises due to genetic variation in some niche-picking or niche-construction trait. Typical examples in psychology include personality traits such as sensation seeking (Roberti 2004) or negative affect (Avinun and Knafo 2014). As discussed above, the niche-picking/niche-constructing trait is often unknown and what is observed is simply that different genotypes experience different environments. Next, rGE-mediated exposure to a particular environment influences the development of some other phenotype, such as a psychiatric disorder (e.g., addiction; Roberti 2004). Thus, under rGE, V_E is not independent of genotype; rather, different genotypes experience different environmental effects on their traits (Figure 2, top). For example, genetic differences in personality predict whether adolescents will associate with "deviant" (rule-breaking) peers or not (Beaver et al. 2008). In this example, the mechanism is likely through active rGE because people seek out friends with particular characteristics (Harden et al. 2008; Fowler et al. 2011; Boardman et al. 2012). Friendships with deviant peers, in turn, increases risk of substance use disorders (i.e., problematic drinking and/or drug use; Kendler et al. 2012). Here, rGE arises due to genetic variation in personality, where some genotypes experience deviant peer groups and other genotypes do not. Then, rGE-mediated exposure to particular peer groups affect the development of substance use disorders.

In quantitative genetics, this scenario is also termed "environmental pleiotropy" (Paaby and Rockman 2013). The term pleiotropy applies because the genetic variants underlying the trait that generates rGE also influence expression of the focal trait, that is, the trait that is plastic with respect to the environment generated by rGE. In the example above, these traits would be personality traits and substance use disorders, respectively, and the relevant environment would be the peer group. The difference between "environmental" pleiotropy and other types of pleiotropy is that under environmental

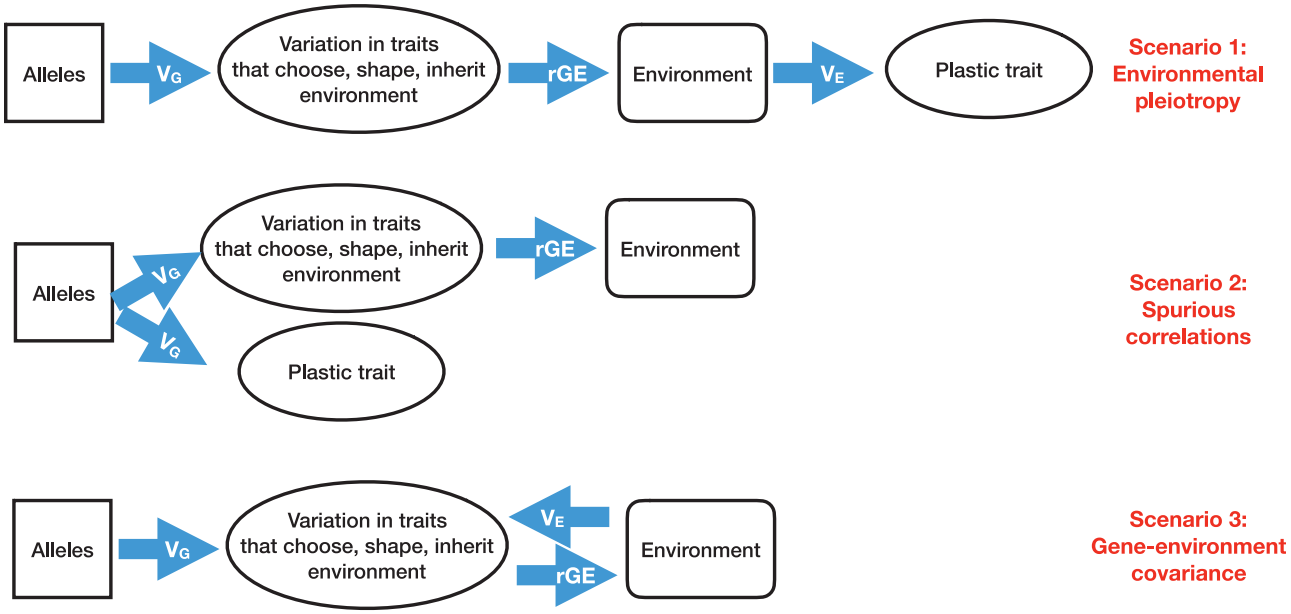

Figure 2. Three scenarios for how rGE can influence trait variation. Arrows indicate causal relationships. In scenario 1, genetic variation in some trait (in the focal individual or its parents) causes different genotypes to experience different environments—rGE. The environment that individuals experience also influences the expression or development of another, phenotypically plastic trait, resulting in environmental pleiotropy. In scenario 2, genetic variation in trait values again produces rGE, and this trait is genetic correlated with another trait. However, in this case, experience in the environment is not what causes the genetic correlation between these traits. This situation produces spurious (noncausal) correlations between environmental factors and traits. In scenario 3, genetic variation in a niche-picking or niche-constructing trait produces rGE, and the environment then further alters the expression of the trait, producing gene–environment covariance.

pleiotropy, the *mechanism* by which the genetic variants influence trait development is through the variants' effects on the environments that individuals experience. Environmental pleiotropy thus differs from other forms of pleiotropy, which emphasize the causal effects of alternate alleles within cells and tissues and typically ignore effects of the environment (Paaby and Rockman 2013; Saltz et al. 2017). An example of rGE and environmental pleiotropy in the quantitative genetics literature can be found in *Arabidopsis thaliana*. A gene, Delay of Germination 1 (*DOG1*), that controls germination is also associated with flowering time but only when rGE is allowed. Specifically, plants with different alleles at *DOG1* differ in the environmental conditions under which they germinate (Chiang et al. 2013), representing rGE. These different timings of germination influence the climate that plants experience during growth, which in turn impacts flowering time (Chiang et al. 2013). In the lab, where the environment is carefully controlled and, thus, rGE is prevented, *DOG1* only affects germination cueing, not flowering time.

Under this scenario, genetic differences in the focal trait will arise partly from rGE, that is, from the fact that different genotypes experienced different environments. In the *Arabidopsis* example described above, genetic variation in flowering time emerges from genetic variation in germination timing and the environmental effects of the subsequent climate experienced. Without this intervening active rGE, variation in *DOG1* does not produce genetic variation in flowering time.

This idea has profound implications for understanding how genes cause traits and disease. For example, the finding that environments are often heritable has given rise to some debate about whether the effects of rGE should be considered "genetic causes" or "environmental causes" (Rutter et al. 1997; Bradshaw and Ellison 2009; Falconer and Mackay 2009; Kong et al. 2018) with some researchers suggesting that under rGE, these categories may not be meaningfully distinct (Bradshaw and Ellison 2009). Another way of thinking about this same phenomenon is that rGE acts as a mechanism by which some genetic variants influence some traits (Falconer and Mackay 2009; Saltz and Nuzhdin 2014).

Scenario 2: Only Genotypes or Only Environments Cause Trait Variation, and the Other Associations are Spurious

Even for highly labile traits, the assumption that the environments shaped by rGE influence trait variation, that is, that $V_E > 0$, is by no means certain. It is entirely possible that different genotypes experience different environments but that these environments have no effect on trait expression (at least, for the focal trait in a particular study). In this case, rGE would be observed, but it would not contribute to trait variation. Instead, rGE would act as a "red herring" that would obscure causal associations between genetic variation, traits, and the environment (Figure 2, middle).

For example, individuals with a hereditary predisposition to schizophrenia are also more likely to use cannabis, which is considered a risk factor for psychosis (van Os and Marcelis 1998; Veling et al. 2008). One early interpretation of this discovery was that genetic variants cause schizophrenia by causing individuals to be exposed to this risk factor, that is, scenario 1 (van Os and Marcelis 1998). More recent analyses revealed a shared underlying genetic basis for both schizophrenia risk and cannabis use, which could be interpreted to mean that the link between cannabis and schizophrenia is due to pleiotropy rather than cannabis causally increasing risk of schizophrenia. This distinction is important. Under scenario 1—in which alleles that increase risk for cannabis use thereby also cause schizophrenia—public health interventions aimed at preventing cannabis use in susceptible teens would be warranted. If cannabis use

and schizophrenia are, instead, pleiotropic effects of genetic variants (scenario 2), rather than a causal chain of events, then this intervention would not be successful at reducing schizophrenia risk.

These possibilities are also mutually compatible, meaning that cannabis use can have multiple relationships with schizophrenia at the phenotypic and genetic levels (reviewed in Power et al. 2014). This ongoing debate about the meaning(s) of links between genotype, cannabis use, and schizophrenia illustrates how rGE can create complex and potentially spurious associations between trait values (e.g., disease state) and environmental variables.

Similarly, rGE can falsely imply that a trait is under genetic control when it is not. A spurious association between genotype and trait values can occur when environmental variables aggregate in families. In an extreme example, a disease called Kuru, which is endemic to Papua New Guinea, was initially thought to be a solely genetic disorder because it runs in families. Further investigation of the mechanisms of disease transmission actually revealed that Kuru is a prion-based disease. It spreads within families due to cannibalistic practices that take place as part of a funeral ritual (Furrow et al. 2011). An example from the quantitative genetics literature comes from great tits (*Parus major*), in which the heritability of egg-laying date is highest when daughters nest near their mothers (van der Jeugd and McCleery 2002). This finding suggests that parent–offspring covariance arises from similarities between mothers' and daughters' environments, not only from genetic inheritance from mothers to daughters. These examples illustrate how rGE can complicate efforts to identify the causes of trait variation even in seemingly straightforward cases, such as trait similarities between parents and offspring.

Overall, in scenario 2, exposure to an environment may have no effect on the focal trait, even though individuals with particular trait values occur in particular environments. Further, in scenario 2, phenotypes may run in families without being heritable in the traditional sense.

Scenario 3: Effects of Genes and Environments Covary

Scenarios 1 and 2 involve 2 traits: a niche-picking/niche-construction trait that produces rGE (in psychology, these are typically assumed to be personality traits) and a focal trait that is potentially influenced by rGE (typically a psychiatric diagnosis). In scenario 3, we consider the situation in which these are the same trait (Figure 2, bottom). In this case, genotypes that are predisposed to high (or low) values of a focal trait also experience environments expected to increase (or decrease) their focal trait value. A classic example is athletic achievement, in which children who are genetic predisposed to athleticism receive extra encouragement and coaching (Dickens and Flynn 2001). In this example, expression of the focal trait (athleticism) influences the environment that the individual experiences (coaching), and this environmental exposure feeds back to further influence expression of the focal trait (athleticism). A similar outcome can also be achieved through passive rGE, that is, in which both genotype and environment are provided by parents. For example, in cows, calves born to healthy mothers receive both genotypes that dispose them to health and abundant resources (milk) that further encourage health (Falconer and Mackay 2009). Here, the rGE arises not as any direct result of the offspring's genotype; such an effect is possible but would be evocative rGE. Instead, passive rGE arises because the offspring's genotype is correlated with its mother's genotype and also with the environment its mother provides.

In this scenario, different genotypes experience different environments, representing rGE. In addition, the effects of genotype on phenotype (V_G) and the effects of the environment on the same phenotype (V_E) are genetic correlated, a situation termed *gene–environment covariance* (Falconer and Mackay 2009). It is unfortunate that rGE and gene–environment covariance are very similar sounding because they are distinct (Saltz and Nuzhdin 2014); part of this confusion stems from the conflation of rGE and gene–environment covariance in early work on rGE, for example, (Plomin et al. 1977). Gene–environment covariance could be considered a "special case" of rGE because gene–environment covariance occurs when rGE is present *and* genotypes vary in the focal trait *and* the environment influenced by rGE influences focal trait expression. For more information on the distinction between these concepts, see Box 1.

The athleticism and milk examples above represent a positive gene–environment covariance, in which individuals with alleles that confer high values of the focal trait experience environments expected to further increase trait values and individuals with alleles that confer *low* values of the focal trait experience environments expected to further *decrease* trait values. In the cow example, healthy genotypes receive abundant resources and sickly genotypes receive few resources. Positive gene–environment covariance is thus expected to exacerbate differences among genotypes: under rGE and gene–environment covariance, the health differences between healthy and sickly cows will be greater than they would be if all cows received identical diets. In psychology, the focal trait is often a psychiatric or other disorder; here, positive gene–environment covariance represents a "double whammy," whereby individuals already at high genetic risk for a particular disorder are also more likely to experience environmental risk factors. For example, women at high genetic risk for depression are also more likely to experience trauma and abuse, which are environmental risk factors for depression (Kendler et al. 2005).

V_G and V_E may also be negatively correlated, representing negative gene–environment covariance. Negative gene–environment covariance results when environmental effects on trait expression counteract the effects of genotype. Not surprisingly, then, it is difficult to find examples of negative gene–environment covariance. This concept has had a controversial role in understanding the causes of variance in IQ and other measures of intelligence. IQ represents a "paradox" because it is both highly heritable, around 0.8 (as estimated through twin and family studies), and also highly plastic (as estimated through adoption and academic enrichment studies and changes over time; reviewed in Dickens and Flynn 2001; Gorey 2001; Sauce and Matzel 2018). How can additive genetic variance account for 80% of variance in IQ if environmental effects are also so potent? In addition, like many of the traits mentioned above, the heritability of IQ is lowest in young children and increases with age (Plomin and Spinath 2004). rGE and gene–environment covariance may contribute to reconciling these findings. In young children, effects of parenting are expected to be strongest, and children who struggle academically receive extra help. This situation may represent negative gene–environment covariation because genotypes with relatively low IQ disproportionately experience environments that raise IQ, thus flattening IQ differences among genotypes (Dickens and Flynn 2001; Sauce and Matzel 2018). As children get older, they have more control over their environments and *positive* gene–environment correlation takes over: academically gifted children enter enrichment programs, choose high-IQ peers, engage in intellectual leisure activities, while their less-gifted peers do not (Dickens and Flynn 2001; Nisbett et al. 2012). This process represents positive

Box 1: Distinguishing rGE and Gene–Environment Covariance

Defining rGE and Gene–Environment Covariance

rGE describes a correlation between the identity of a genotype and the identity of an environment—are some genotypes more common in particular environments than expected by chance? Here, "genotypes" and "environments" can be defined in a broad array of ways. Genotypes can be represented as clones, twins, siblings, and so forth; environments can be measured through exposure to specific cues (e.g., age of smoking initiation) or much more broadly (e.g., urban vs. rural).

Gene–environment *covariance* describes the covariance between V_G, which is the extent to which each genotype's trait values deviate from the population mean, and V_E, which is the extent to which the trait values of individuals who have experienced a particular environment deviate from the population mean. When genotypes predisposed to express high levels of the phenotype (or high risk for some disease) also experience environments that further *augment* expression of the phenotype, then gene–environment covariance is positive. When genotypes predisposed to express high levels of the phenotype also experience environments that *reduce* phenotypic expression (i.e., effects of genes and environments on the phenotype are opposite), then gene–environment covariance is negative. For more details and examples, see scenario 3 in main text.

Aren't Correlations and Covariances Interconvertible?

Since a correlation is just a normalized covariance, it would initially appear that rGE and gene–environment covariance should be basically interchangeable. However, they are not interchangeable because they represent relationships between different quantities. Gene–environment covariance describes the relationship between genotypic effects *on a phenotype* (e.g., breeding values) and environmental effects *on a phenotype* (i.e., phenotypic plasticity). In contrast, rGE describes a correlation between (some measure of) genotype *frequencies* and environment *frequencies* without any assumptions about the effects of genotypes or environments on any traits. Therefore, gene–environment covariance (i.e., covariance [phenotypic effect of G, phenotypic effect of E]) cannot be normalized to produce rGE (i.e., correlation [frequency (G), frequency(E)]). Another way of expressing this distinction is that rGE is a population-genetic parameter that describes a nonrandom association between genotypes and environments, while gene–environment covariance is a quantitative-genetic parameter that describes a covariance between environmental and genetic causes of phenotypic variation.

Unfortunately, the distinction between rGE and gene–environment covariance is not always made clear in the relevant literature (but see Saltz and Nuzhdin 2014; Saltz 2017). This muddling of terms may stem from confusion about how the terms differ in meaning or from the (inaccurate) assumption that rGE must always affect individuals' phenotypes in some way. Despite confusion about terms, the underlying conceptual distinction is made clear through the strong research emphasis on demonstrating causal links between environmental exposures and disease outcomes in the psychology and public health literatures, including on how to establish such links in the presence of rGE. For example, a recent paper, mentioned above, focused on understanding the relationships between specific alleles, cigarette smoking, and schizophrenia (Gage et al. 2017). Schizophrenia is highly heritable and schizophrenics smoke at much higher frequencies than nonschizophrenics, representing an example of rGE. This study found little support for a causal effect of smoking on schizophrenia development, suggesting that preventing smoking is unlikely to protect people from schizophrenia (Gage et al. 2017). For other examples of rGE that have no apparent effect on variation in the phenotype of interest, see scenario 2 in main text. Overall, distinguishing between rGE as a population-level pattern and the phenotypic consequences of that pattern (which could include gene–environment covariance) is critically important for the future of rGE research.

gene–environment covariance because genotypes with high IQ self-select into environments that further augment IQ, thus exacerbating differences between genotypes and increasing heritability. Although the diverse causes of variation in IQ are far from resolved, this controversy highlights the importance of considering rGE for understanding genetic variation in important traits across ontogeny.

rGE Affects Heritability

As noted above, rGE can contribute to genetic differences in trait development and, thus, to heritability. Under scenarios 1 and 3, and especially positive gene–environment covariance, rGE is expected to increase heritability, relative to the situation where rGE is absent. In contrast, under negative gene–environment covariance, rGE should reduce heritability because genetic and environmental influences on trait variation counteract one another (Begin et al. 2004).

If rGE influences heritability, typically by increasing it, then heritability should be higher in situations in which rGE is expressed and lower in situations in which rGE is restricted. Support for this idea in humans comes from analyses of variation in heritability across time and environments. For example, the heritability of alcohol use in adolescents is lower in social systems that enable adults to monitor adolescents (i.e., communities characterized by high religiosity or small communities; Kendler et al. 2012). This finding is consistent with the idea that more restrictive social systems prevent susceptible genotypes from expressing their preference to use alcohol. The inference is that if such restrictions were removed, the heritability of substance use would be higher; however, this prediction is currently impossible to test directly in humans, and population differences in trait heritability can occur without any contribution from rGE. Similarly, a wide variety of human traits become more heritable as people age; a meta-analysis of the heritability of human behaviors across ages revealed significant increases in heritability with age in the majority of the traits studied, including diverse measures of depression and anxiety, IQ, and "social attitudes" (Bergen et al. 2007). These patterns are consistent with the fact that as humans grow from babies to adults, they gain more and more opportunities to choose and otherwise alter their environments—and thus, for rGE—but again, age-related changes in trait heritability can also occur without any contribution from rGE. Finally, some investigators have

suggested that rGE may contribute to the "missing heritability" of complex traits (Plomin 2014). Whether the role of rGE in missing heritability is greater or lesser than the many other factors proposed to contribute to this phenomenon (Manolio et al. 2009; Zuk et al. 2012) remains to be seen.

In quantitative genetics, heritability comparisons have focused primarily on comparisons among classes of traits (e.g., morphological vs. life-history traits) and across environments that are evolutionarily novel (i.e., cryptic genetic variation McGuigan and Sgrò 2009) or more or less stressful (Robinson et al. 2009). Such comparisons often reveal that heritability of a trait can differ markedly across different environments (reviewed in Visscher et al. 2008). The rGE literature described above leads to the prediction that heritability variation across environments is associated with differences among environments in the opportunity for rGE; this prediction is testable (Bergen et al. 2007; Saltz and Nuzhdin 2014).

Moving Forward: rGE in Quantitative Genetics

The scenarios above should provide a "flavor" of the relevance of rGE to genotype–phenotype associations in the wild. These examples illustrate how rGE, if unaccounted for, can produce misleading results in quantitative genetics studies and represents an understudied mechanism by which different genotypes express different phenotypes. Importantly, these considerations apply equally to studies of quantitative genetics in the wild because all organisms (not just humans) have the potential to choose, inherit, and alter their environments (Odling-Smee et al. 1996).

Current Approaches in Quantitative Genetics Versus Psychiatric Genetics: Complementary or Talking Past Each Other?

As described under "evidence for rGE," psychologists have focused on establishing the heritability of environmental parameters as a first step to identifying rGE. This "environment first" approach contrasts with the approach typically taken in quantitative genetics, where individual *traits* are the focus of the analysis and the potential implications of genetic variation in such traits for generating rGE may not be fully explored (Donohue 2005; Snell-Rood 2012; Saltz and Nuzhdin 2014). For example, there is substantial evidence across numerous insects for genetic variation in host plant choice (Gripenberg et al. 2010) but few investigators have directly estimated the heritability of host plant occupancy. In other words, psychologists tend to test the heritability of environments themselves, while quantitative geneticists tend to test the heritability of putative niche-picking or niche-constructing traits.

These approaches provide complementary information but may not always be congruent, especially if the environments that individuals experience are determined by multiple traits. For example, in fruit flies (*Drosophila melanogaster*), the social group sizes that males experience are influenced by both their group-size preferences and by their aggressive behavior, both of which differ among natural genotypes (Saltz 2011; Saltz and Foley 2011; Foley et al. 2015). Therefore, the best approach for any particular study likely depends on the questions being asked. For example, in some cases, it may not matter *why* different genotypes experience different environments but only *that* they do. In this case, estimating the heritability of the relevant environments would be the most direct route to answering the question.

The opportunities for measuring rGE also differ fundamentally between humans and other organisms because humans can talk. Such direct communication between experimenter and subject allows investigators a detailed view of not only what environments people have experienced but also how they perceived and responded (cognitively) to such experiences. Such information about the internal experiences of nonhuman organisms (if such experiences even exist) is typically inaccessible (but see Iliadi 2009). However, there are also tradeoffs. Humans' perception and recall of events can depend on personality, a problem termed "behavioral 'contamination' of the environmental measure" (Jaffee and Price 2007, 2012). This phenomenon leaves open questions about whether heritable personality traits cause different genotypes to have different experiences or whether personality mediates the ways that individuals perceive and/or remember a given environment. In contrast, quantitative geneticists typically have greater ability to directly measure the environments that individuals experience rather than relying on retrospective recall. This is because nonhuman organisms have no expectations of privacy and can often be monitored during important experiences (e.g., mating).

Conceptual and Experimental Approaches in Psychology that Could be Directly Applied to Evolutionary Questions

As noted above, empirical methods for understanding rGE and its effects on trait variation will inevitably differ across species and studies. However, some strategies that have been helpful in psychiatric genetics are currently underutilized in studies of quantitative genetics in the wild. Below, I highlight a few of these approaches. Key papers providing more information on these methods are cited in the text and collected in Table 2.

A critical step in studying rGE in wild populations is to identify environments that are heritable. Quantitative geneticists can estimate the heritability of environments directly in nature using data that is already available. Many long-term data sets with pedigrees would be suitable for this purpose as long as at least one aspect of the environment for each individual is available. For example,

Table 2. Selected resources for conducting rGE research

Approach	Papers describing this approach	Example
Sequence-based approaches for estimating rGE and other quantitative genetics parameters	(Visscher et al. 2006; Plomin 2014; Krishna Kumar et al. 2016)	(Bailey and Hoskins 2014; Kong et al. 2018)
How to measure specific environments and understand their effects on traits	(Moffitt et al. 2006; Loehlin 2010; Boardman et al. 2013)	(Kendler et al. 2005)
Using structural equation modeling to understand rGE, G, E, and G×E	(Evans et al. 2002; Rijsdijk and Sham 2002)	(Kendler et al. 2005; Distel et al. 2011)
Using multiple regression to understand rGE, G, E, and G×E	(Purcell 2002; Zyphur et al. 2013)	(Harden et al. 2008)

Lea et al. found that "victimization"—that is, being aggressively attacked by conspecifics—is heritable in wild marmots (Lea et al. 2010). Other examples of environments could include characteristics of the individual's home location (e.g., nest site, den), parental care received, phenology, density or attributes of neighbors, and so forth. When more than one environmental attribute is recorded, multivariate quantitative approaches can be used to investigate genetic covariation in the environments experienced. In quantitative genetics, these statistical tools are commonly applied to traits (e.g., Blows 2007) but rarely to environments.

Such analyses would leverage existing data to provide new information about rGE and its variation across species, environments, populations, and so forth. For example, is rGE greater in populations with overlapping generations and, if so, for which environments? At minimum, identifying the *absence* of rGE in any particular data set would provide a firm foundation for eliminating rGE as a potential confound in further analyses. Such preliminary checks for rGE are routine in psychiatric genetics (Uher and McGuffin 2010; Dick et al. 2015).

One nontrivial concern in applying such approaches is that the relevant environment(s) for any particular trait (or other evolutionary question) may not be obvious. Environmental influences can exist in the present and/or in the past; they can be microscopic, such as a pathogen, or population-wide, such as social structure; they can be discrete (e.g., experienced or naïve) or continuous; and many other varieties. Clearly, there is no single "solution" to how to think about and measure environmental effects on trait development, but thoughtful discussions of this topic in relation to rGE and quantitative genetics can be found in Moffitt et al. (2006), Loehlin (2010), and Boardman et al. (2013).

Once rGE has been identified, it can be incorporated into our understanding of the causes of trait variation. This will be an exciting challenge, because genetic variation, environmental variation, genotype–environment interaction (G×E), and rGE might all contribute simultaneously to variation in a particular trait. rGE can hinder estimation of V_E and G×E because under rGE, the traits of most individuals of a particular genotype will be measured in the environment that they choose, create, and so forth (this is true by definition under rGE). This confound between genotype and environment can limit our ability to identify genetic and environmental effects on phenotypic variation because we do not know what phenotype the genotype would have expressed in alternate environments (e.g., nonpreferred environments; (Saltz 2017; Saltz et al. 2018)).

Luckily, with a large enough sample, or careful manipulation (e.g., cross-fostering), some individuals who have similar genotypes will end up in different environments. This occurs because rGE is only one of many factors that may determine which environment(s) that an individual experiences and because genetic differences in the traits (e.g., preferences, personality traits) that produce rGE are rarely completely predictable. In other words, under rGE, certain genotypes *tend to* experience particular environments, but some individuals will inevitably become exceptions to this pattern. Individuals who experience "unusual" environments for their genotype are especially valuable to researchers because they can provide information about what trait values a particular genotype would express if it experienced its nonpreferred environment (Saltz et al. 2018).

Given this framework, structural equation modeling and multiple regression can be used to simultaneously estimate the relative roles of genetic and environmental influences, and their interplay, on trait variation or disease risk. For example, analysis of longitudinal data can identify important early-life experiences, their effects on later trait expression, and the genetic contributions to each of these. Thus, investigators can trace the effects of early-life rGE to its developmental consequences. In the depression example mentioned above, Kendler et al. (2005) used structural equation modeling to determine that women at high genetic risk for depression are also more likely to experience trauma and abuse, which are environmental risk factors for depression. Furthermore, the first instance of abuse (tragically) facilitated future abusive experiences, exacerbating the rGE and its resultant effects on depression (Kendler et al. 2005). Papers describing the use of structural equation modeling in quantitative genetics include Evans et al. (2002) and Rijsdijk and Sham (2002).

Multiple regression analyses in psychology are based on the ACE model, which estimates *A*ddditive genetic variation, *C*ommon environmental effects (in twin studies, these are family-level variables expected to influence both twins equally, such as socioeconomic status), and individual-specific *E*nvironmental factors (including error). This canonical model can be elaborated to include rGE and G×E. For example, Harden et al. (2008) found that genetic factors predicted adolescents' likelihood of having close friends that were heavy alcohol and tobacco users. Such genetic differences in friend preferences represent rGE because different genotypes experience different peer groups. Furthermore, genotypes that chose substance-using friends were also more susceptible to the effects of peer pressure, representing a genotype-by-environment interaction (Harden et al. 2008). For a discussion of the uses of variance partitioning approaches in quantitative genetics, see Purcell (2002).

rGE in the "Post-Genomics" Era

The easy accessibility of full-genome sequences has revolutionized genetics, including rGE research. For example, investigators can now use sequencing-based metrics, rather than pedigree information, to estimate genetic similarity. This approach has several advantages, such as allowing incorporation of all individuals (i.e., even "unrelated" individuals) and providing more precise genetic similarity information than pedigrees (i.e., not all siblings are equally genetic similar to each other and to their parents). For a discussion of one such approach, Genome-wide complex trait analysis, in rGE research, see Plomin (2014).

Sequence information can also be used to measure the environment. For example, researchers recently used whole-genome sequence information from parent–offspring pairs to determine how alleles in parents influence offspring educational attainment, even if those alleles are not inherited by the offspring (Kong et al. 2018). This approach is similar to a genome-wide association study (GWAS) for IGEs (Bailey and Hoskins 2014). Furthermore, RNA-sequencing technology has been used to measure exposure to particular environments (Gaye et al. 2017)

A particular application of the genes-as-proxy-for-environments approach is called Mendelian Randomization (Davey Smith and Ebrahim 2003; Smith 2004; Lawlor et al. 2008). In this approach, researchers use known relationships between specific genetic variants and environmental exposures (e.g., from GWAS) to test hypotheses about causal relationships between environments and trait expression (often disease diagnoses). In this way, genetic variants associated with environmental exposures can serve as a "proxy" for the environment that was experienced, avoiding potential confounding factors such as biased recall. Furthermore, if there is a single large-effect variant for environmental exposure, it should segregate within families (the "Mendelian" part), avoiding additional confounds such as population stratification. For example, investigators have

used known associations between segregating variants and cigarette smoking to determine that phenotypic associations between cigarette smoking and mental illness (anxiety, depression, and schizophrenia) are more likely to reflect self-medication than a causal effect of smoking on mental illness (Gage et al. 2013, 2017)

Although potentially powerful, Mendelian randomization is subject to a wide variety of constraints, including that alleles underlying environmental exposures are known and of relatively large effect, and that these alleles do not have pleiotropic effects relevant to the disease (or other trait) of interest. For more information about this approach, see Davey Smith and Ebrahim 2003; Smith 2004; and Lawlor et al. 2008)

Conclusion: It Matters How Traits Are Caused

Evolutionary geneticists have long been interested in the mechanisms by which trait variation arises within and between populations and over generations. Yet, if different genotypes experience different environments, then the underlying conceptual framework for achieving this goal may need to be expanded. Indeed, there is increasing awareness that linkages between genotypes and environments might fundamentally alter the way(s) that genetic variation evolves, for example, through eco-evolutionary feedbacks. Yet, the potential for such feedbacks within the lifetimes of individuals has not been systematically considered, and diverse concepts linking genes and environments are siloed into different subfields (Bailey 2012;, Table 1).

Here, I suggest a quantitative genetics approach, borrowed from psychology, for understanding the relationships between genes, environments, and traits. This rich literature provides hypotheses and analysis tools for understanding rGE and its implications for trait variation. Examples and analyses from this literature indicate that measuring and accounting for rGE can help contextualize these results to identify the true underlying causes of trait variation.

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