10 Theory and Methods in Evolutionary Behavioral Genetics

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EVOLUTIONARY BEHAVIORAL GENETICS

It is a fascinating time to be a researcher interested in human evolution and genetics. Knowledge on molecular genetic variation is growing at a breathtaking pace, placing us in the midst of one of the remarkable revolutions of science—albeit one more akin to the empirically driven atomic revolution of the 20th century than to the theory-driven Darwinian one of the 19th century. In the last five years, researchers have collected data on up to several million of the most common DNA variants on tens of thousands of people. As a result, we know more about human genetics than that of any other animal—fruit fly and nematode worm notwithstanding. While some of this data was collected with the explicit aim to test evolutionary hypotheses, most of it awaits a unifying framework that only evolutionary theory can provide.

The principal goal of this chapter is to critically discuss how this new molecular genetic data, together with family and twin data traditionally used by behavioral geneticists, can be used to test evolutionary questions about the causes of human genetic variation. Our intended audience is the behavioral geneticist interested in evolution or evolutionary psychologist interested in genetics, and our treatment of these methods assumes a basic knowledge of population genetics and evolutionary theory and at least some familiarity with methods used in modern genetic analyses.

Before evaluating the methods that can be used to understand the evolution of human genetic variation, we briefly discuss the theoretical underpinnings of the new field we call *evolutionary behavioral genetics*. We argue that the central question in evolutionary behavioral genetics is: *What evolutionary forces account for the genetic variation observed in human traits?* For example, what evolutionary forces account for highly heritable disorders, such as schizophrenia? The fact that schizophrenia is heritable implies that alleles exist in the population that confer risk to the disorder. Why would such alleles exist and persist in the population in the first place? Similar questions could be asked regarding the heritability of any human trait, from extraversion to intelligence to athleticism to height.

Notice that the central question in evolutionary behavioral genetics is a much different one than typically asked by evolutionary psychologists. Whereas evolutionary psychology has typically been concerned with explaining the evolutionary forces that shaped human *universals* (adaptations), evolutionary behavioral genetics uses the theoretical lens of evolution to understand human *variation*, and in particular, human genetic variation. As discussed below, the main theoretical tool used by evolutionary psychologists to explain human universals, the theory of natural selection, is rarely the right tool to explain human genetic variation. This is for a very simple reason: while awesome in its ability to craft fine-tuned adaptations, natural selection tends to deplete rather than maintain genetic variation. Thus, investigating the central question in evolutionary behavioral genetics requires the use of a much more diverse, but equally fascinating, theoretical toolkit. These tools are largely drawn from the field of evolutionary genetics, although the way to apply these tools to modern human genetic data remains very much a work in progress.

PROXIMATE CAUSES OF GENETIC VARIATION

Almost every trait studied to date is heritable to some degree. *Heritability* is the ratio of genetic variation to total phenotypic variation, and therefore has a range of zero to one. Genetic variation is caused by differences in the DNA variants, or *alleles*, that people harbor at various locations across their chromosomes. *Alleles* can refer to any number of alternative sequences of base pairs that stretch hundreds or even thousands of base pairs in length. For example, 32% of the population may have the **T**ATGAC**C**AGCAAT**C** allele, 15% the **A**ATGAC**C**AGCAAT**G** allele, 6% the **T**ATGAC**A**AGCAAT**G** allele, etc… Although it is sometimes useful to think of alleles in this way, as being combinations of many base pairs in a row, it is often easier to think

of each varying base pair as its own allele. Such single nucleotide alleles are aptly named *single nucleotide polymorphisms* (SNPs). Note that the first, seventh, and fourteenth position of the above sequences are SNPs that vary between individuals. For example, 70% of the population may have a T (the major allele) and 30% an A (the minor allele) at the first SNP of the sequences. Due to the low likelihood of mutation at any single base pair (~10^{-8}), almost all SNPs have just two variants.

Over 95% of the 3.2 billion base pairs in the human genome are monomorphic: basically everyone in the population shares the same A, T, C, or G nucleotide at them. Such monomorphic base pairs contribute nothing to the genetic *variation* of any trait—even if critically important to creating universal adaptations. However, an estimated ten million (0.3%) base pairs harbor *common* alleles (by definition, SNPs with minor allele frequencies >1% in the population), and hundreds of millions of base pairs harbor rare alleles (SNPs with minor allele frequencies <1% in the population) (Kryukov, Pennacchio, & Sunyaev, 2007). SNPs are thought to serve as the principal substrate for the heritability of traits, although it has recently become apparent that structural variants, such as deletions and duplications, are much more common than previously thought (Feuk, Carson, & Scherer, 2006), and their role in the heritability of traits may also be significant.

Whereas *alleles* refer to variants in the population, *loci* (singular, *locus*), refer to locations along the genome where alleles may or may not exist. Loci that code for proteins are called *genes*. In colloquial usage, the term *gene* is often used where a geneticist would use the word *allele*, but technically the two terms have different meanings. A gene is a set of instructions for making a protein whereas an allele is one of two or more alternative variants of that set of instructions. While genes have traditionally been a central focus of evolutionists and geneticists, it has recently become apparent that an unknown but potentially large percentage of the genome is functional despite not coding for proteins (Birney et al., 2007). Thus, critiques of evolutionary psychology expressing doubt about how a small number of genes could possibly code for a large number of complex adaptations (Buller & Hardcastle, 2000), even if fundamentally misconceived (Hagen, 2005), should be updated to reflect the fact that a much larger p ercentage of the genome may be functional than previously thought.

ULTIMATE CAUSES OF GENETIC VARIATION

A proximate-level understanding of genetic variation does not shed light on the ultimate, or evolutionary, causes of genetic variation. Why does genetic variation exist in the first place? A moment's consideration will reveal why

this question is both fundamental and puzzling, especially when applied to genetic variation in traits related to Darwinian fitness. Consider an allele that affects a trait related to fitness. This allele must have a typical effect on the trait when averaged across all the bodies the allele finds itself in. If this typical effect increases fitness, it should "fixate" (reach 100% prevalence in the population) or by chance go extinct. On the other hand, if this typical effect decreases fitness, it should go extinct or (rarely) by chance reach fixation (Ohta, 1973; S. Wright, 1931). In no case should alleles that increase or decrease fitness on average exist for long at the non-zero frequencies required for them to contribute to genetic variation. Put another way, we should expect little genetic variation and low heritability in traits related to fitness (Fisher, 1930). Contrary to this expectation, the median heritability of fitness-related traits across many animal studies is quite far from zero—about 30% (Roff, 1997)—and several phenotypes thought in humans to lower fitness have heritabilities between 30–80% (Hughes & Burleson, 2000; Keller & Miller, 2006).

Forwarding testable and compelling theories for why heritability exists in fitness-related traits has been a central theme in evolutionary genetics. Given that most phenotypes of interest to psychiatrists and psychologists are probably related to fitness to varying degrees, explaining the genetic variation in fitness-related traits should take us some way toward generating testable hypotheses for the evolutionary existence of genetic variation in human psychological traits. In this section, we briefly discuss four evolutionary mechanisms that can explain the genetic variation in fitness-related traits, each of which leaves different, albeit messy, signatures in the genome. These mechanisms are in no way mutually exclusive: each may be important for different traits and all may simultaneously help to explain the genetic variation of a given trait.

Mutation-selection

Point mutations as well as deletions, duplications, translocations, and inversions are copying errors that occur during DNA replication. Those that arise in non-germline cells can result in diseases such as cancer but are of little interest evolutionarily because they are not transmitted to offspring. Mutations that occur during replication of sperm or egg cells, however, are central to the evolutionary process. Such mutation can be transferred to the fertilized ovum and eventually to every cell in the offspring's body, including the offspring's own germline cells and, potentially, any descendents of the offspring. This is what population geneticists mean when they say that mutations are 'introduced' into a population. It should be noted that the

term *mutation* refers to the original germline mutation as well as the copies of that mutation that exist in descendents. An observant reader may have noticed that, by this definition, *all* genetic polymorphisms would be mutations because every genetic polymorphism originally arises as a mutational event. For this reason, we follow the usual convention that the term *mutation* refers to alleles with minor allele frequencies up to 1% and use the term *polymorphism* to refer to alleles (e.g., SNPs) with minor allele frequencies greater than 1%.

Most new mutations arise in chromosomal locations that have no phenotypic effect (so-called 'junk DNA'), but those that do affect the phenotype almost always degrade its tightly coordinated performance, and such mutations are kept at low but calculable frequencies by natural selection (Falconer, 1989). For example, a mutation that decreases fitness by 1% will tend to exist in an average of 100 individuals and persist in a population for about 10 generations in multiple co-existing copies (García-Dorado, Caballero, & Crow, 2003). Thus, such deleterious mutations almost never reach a frequency of 1% where they would be termed polymorphisms. Mutation-selection models describe the equilibrium between new deleterious mutations being introduced into the population and their removal, often tens to hundreds of generations later, by selection.

The importance of mutation-selection in explaining trait variation has long been debated, but many evolutionary geneticists now consider it to be a primary factor in explaining the heritability of fitness-related traits (Charlesworth & Hughes, 1999; Houle, 1998). Although deleterious mutations are rare per locus, hundreds or even thousands of loci can influence complex traits, and so the *cumulative* number of mutations could be high enough to explain the heritability of complex traits. Indeed, it is likely that every human alive is affected by hundreds to thousands of rare (usually partially recessive) deleterious mutations that individually have minor effects on the phenotype (Fay, Wyckoff, & Wu, 2001). These deleterious mutations must cause maladaptive noise of some sort, but what does such variation look like? Mutations do not simply affect fitness directly—how could they?—rather, they decrease fitness by degrading the proper functioning of adaptations. Figure 10.1 presents the 'watershed' model of mutations (Cannon & Keller, 2006; Keller & Miller, 2006), showing how three classes of mutations (triangles) lead to abnormal genetic products, which in turn disrupt 'upstream' phenotypes (e.g., neuronal pruning in the dorsal medial amygdala), which in turn disrupt further downstream phenotypes (e.g., a fear conditioning adaptation). The ultimate downstream trait must be some fitness-related trait (e.g., survival to sexual maturation), which captures variation from many upstream traits and therefore represents a large 'target' for mutations.

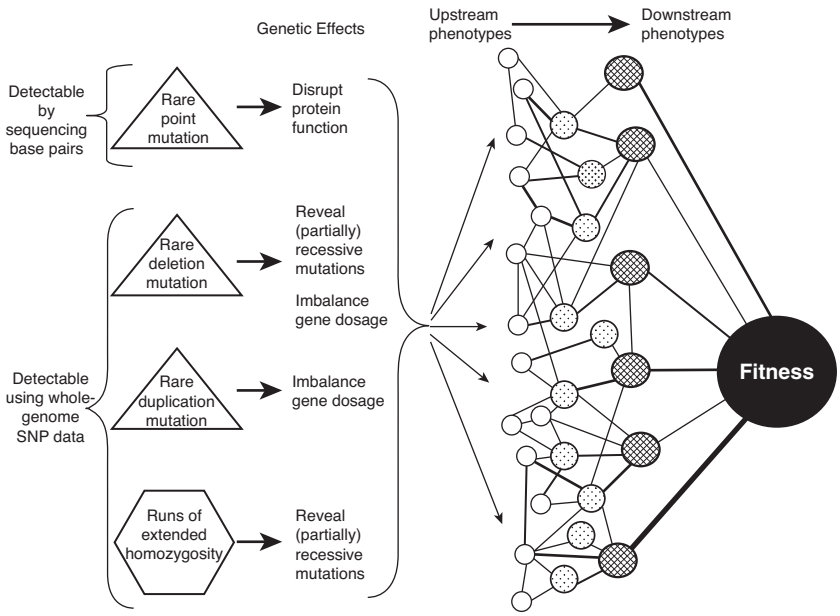

Figure 10.1. Deleterious effects of three types of mutations and extended homozygosity on genes, upstream phenotypes, and downstream phenotypes. Shading represents higher mutational 'target sizes.' Certain downstream phenotypes could be mental disorders.

Mutation-selection has been used to help explain why some disorders are both common and heritable despite being profoundly harmful to survival and reproduction (Gangestad & Yeo, 1997; Keller & Miller, 2006; Kryukov et al., 2007; McClellan, Susser, & King, 2007; Penke, Dennison, & Miller, 2007). Mutational models of disorders posit that mutations increase the risk for having adaptations that malfunction. By this view, common disorders are heterogeneous groups of dysfunctions in the thousands of upstream mechanisms affecting normal adaptive functioning. The final common pathways of various constellations of these upstream dysfunctions may increase risk for 'physical' disorders (e.g., chronic pain syndrome, fibromyalgia, irritable bowel syndrome, etc.), mental disorders (schizophrenia, bipolar disorder, attention-deficit hyperactivity disorder, autism, mental retardation, etc.) and other fitness-related traits (e.g., low intelligence, low attractiveness, poor athletic ability, etc.) that may appear to be singular diseases or dimensions, but that are highly heterogeneous etiologically.

Mutation-drift

The primacy of neutral evolution was most famously argued by Kimura (1983), but recent genetic evidence appears to confirm its truth—at least with respect to genetic sites rather than traits (Birney et al., 2007). The vast majority of base pairs across the genome either has no phenotypic effect whatsoever or contributes to variation in traits that have no effect on fitness. Over evolutionary time, the frequencies of alleles at such neutral sites are governed by "mutation-drift." This process is exactly the same as mutation-selection except that no allele is 'preferred' by natural selection, and therefore alleles 'drift' according to pure stochastic chance. The vast majority of new neutral mutations never gain an appreciable frequency in the population and eventually are lost. However, a small minority do become common and may, over a long period (depending on population size), "fixate," or reach 100% frequency in the population. Of course, at any snapshot of time, given the billions of opportunities, millions of such neutral alleles are at intermediate frequencies. For this reason, the vast majority of common SNPs and other structural variants are thought to be governed by mutation-drift, whereas rare alleles (i.e., mutations) are more likely to be deleterious (Kryukov et al., 2007).

Researchers and tax-payers have invested considerable capital attempting to relate common SNPs to common diseases. However, as noted above, common SNPs are probably common precisely because the vast majority of them have no functional effect and are thus unlikely to be associated with fitness-related phenotypes, including disease (A. F. Wright, Charlesworth, Rudan, Carothers, & Campbell, 2003). Such considerations argue against the long-term success of gene-hunting studies using SNP data (see section on whole-genome association studies). Nevertheless, some alleles affecting modern diseases may be common because they did not have a deleterious effect ancestrally. Some of the heritability for depression, for example, might be explained by alleles that were neutral in ancestral environments but that increase the risk of depression in modern environments. Social isolation is an important risk factor for depression, especially in women (Kendler, Myers, & Prescott, 2005). Humans evolved in small hunter-gatherer societies where social isolation would have been uncommon. Alleles that increase shyness and therefore the risk of social isolation, and hence depression, in modern environments may not have led to social isolation or depression in ancestral environments. Invisible to natural selection, such alleles might have drifted by chance to intermediate frequencies in ancestral environments and might help explain why susceptibility alleles for depression are so common today. This example demonstrates how the *mismatch hypothesis* (Gluckman &

Hanson, 2006) can also help explain the existence of genetic variation in traits seemingly related to fitness.

Directional (positive or negative) Selection

Against the backdrop of detrimental mutations that are constantly being purged by natural selection, new mutations occasionally arise that increase fitness. Via natural selection, these beneficial mutations can spread throughout a population, but once they fixate, they cause no genetic variation. For this reason, directional selection does not maintain genetic variation at equilibrium. Nevertheless, at any given time, many alleles are not at equilibrium but rather are rising (due to positive selection) or falling (due to negative selection) in frequency. This increase in beneficial alleles and decrease in formerly beneficial ones can cause a large amount of genetic variation in traits because such alleles are not necessarily rare (loci that house rare alleles tend to contribute less to variation than loci that house common alleles).

The ancestral-susceptibility model (Di Rienzo & Hudson, 2005) proposes that many current risk alleles are common because they were beneficial in ancestral human populations but are now being driven to extinction due to rapid changes in human environments. Indeed, molecular evidence suggests that human evolution has recently sped up, as rates of newly arisen SNPs replacing old ones (reflecting natural selection) are over 100 times higher in the last 10,000 years relative to the rates which characterized most of human evolution (Hawks, Wang, Cochran, Harpending, & Moyzis, 2007). In addition, several risk alleles for common diseases, such as Alzheimer's and hypertension, are ancestral (Di Rienzo & Hudson, 2005), and Lo et al. (2007) found that schizophrenia risk alleles in the GABA-A receptor 2 gene have been under recent negative selection. Thus, there is evidence that some of the genetic variation underlying common disorders is due to out-of-equilibrium alleles that are rising or lowering in frequency due to natural selection, although it remains unknown how general this explanation is for extant genetic variation.

Balancing Selection

Balancing selection occurs when two or more alternative alleles at a locus are actively maintained in a population by natural selection. This generally occurs when the fitness of an allele increases as it becomes rarer. Heterozygote advantage—where heterozygote individuals at some locus have higher fitness

than either homozygote—is a special case of this. For example, heterozygous individuals at the β-hemoglobin locus in equatorial Africa are protected against malaria, whereas homozygous individuals are either vulnerable to malaria or at risk of sickle-cell anemia (Allison, 1954). Each allele—and sickle-cell anemia—is maintained: if one allele becomes infrequent by chance, it more often finds itself paired with the opposite allele, increasing its fitness and frequency.

Antagonistic pleiotropy is another process that might lead to a balanced polymorphism. In this process, pleiotropic genes (which affect more than one trait) have a fitness-boosting effect on one trait but a fitness-lowering effect on another, which could potentially lead to the maintenance of two or more alleles at a locus and hence genetic variation within populations. For example, alleles that enhance reproductive fitness but reduce longevity, and vice-versa, have been found in fruit flies and nematode worms (for a review, see Leroi et al., 2005).

In principle, balancing selection can maintain genetic polymorphisms indefinitely. However, several theoretical and empirical studies in the last twenty years seem to suggest that balancing selection is evolutionarily transient, causing genetic variation for only short periods of time. With respect to antagonistic pleiotropy, either the positive effect or negative effect of an allele is generally stronger, leading to fixation or extinction of the highest fitness allele and no balanced polymorphisms (Curtisinger, Service, & Prout, 1994; Prout, 1999). For example, chance unequal crossovers during meiosis near loci governed by heterozygote advantage will result in both alleles residing on the same chromosomal arm. Such a 'heterozygote' allele will be strongly selected for and will therefore destroy the balancing selection. Essentially the genome tends to eventually re-arrange itself if fitness favors such an outcome, destroying this delicate balance created by the heterozygote advantage. Moreover, a recent whole-genome scan designed to detect signatures of ancient balancing selection found no loci governed by it aside from those few already known to exist (Bubb et al., 2006). Nevertheless, recent balancing selection (such as that responsible for sickle-cell anemia) may be more common, and may help explain genetic variation in fitness-related traits. Mealey (1995), for example, made a convincing case that antisocial personality disorder is a recently arisen psychological morph maintained in this way, and Tooby and Cosmides have theorized that the bulk of human behavioral genetic variation is a side effect of pathogen-driven balancing selection favoring biochemical diversity (Tooby, 1982; Tooby & Cosmides, 1990). All such balancing selection theories predict that alleles underlying traits maintained in this way will be common and therefore detectable using current approaches (section on whole-genome association studies). Thus, the

lack of success in gene hunting might indicate that balancing selection is a rare process in the human genome.

TESTING THE EVOLUTIONARY MECHANISMS ACCOUNTING FOR GENETIC VARIATION

In this section, we critically discuss several methods that evolutionary researchers might use to test hypotheses on which evolutionary mechanisms cause genetic variation in traits of interest. These methods include traditional behavioral genetic approaches (e.g., twin analyses) as well as approaches based on newer molecular data. We stress two things. First, our own ideas regarding how to test the evolutionary mechanisms above and the strengths/weaknesses of these methods remain a work in progress. Second, the conclusions that can be drawn from the methods we review fall short of the type of "strong inference" (Platt, 1964) that allows researchers to definitively exclude one or more alternative explanations. This is partly due to the non-experimental nature of human genetic data, and partly because each evolutionary mechanism discussed above (previous section) could *simultaneously* contribute to the genetic variation of a given trait. The true challenge in the years to come will be weighing findings appropriately in order to understand the degrees to which different mechanisms account for the genetic variation underlying different traits.

Genetic Correlations

Traditional behavioral genetic approaches use "genetically informative" relatives such as twins and adoptees to understand the roles of genetic and environmental factors in behavioral variation. Also exciting, and a major interest in behavioral genetics currently, is elucidating genetic correlations between traits (Kendler, Prescott, Myers, & Neale, 2003), which occur when the same genes affect two or more traits. Such shared genetic effects (called pleiotropy) induce trait correlations that are genetic in origin, and can be discerned by comparing, for example, the cross-trait identical twin correlation to the cross-trait fraternal twin correlation. A high ratio of identical to fraternal cross-trait correlations suggests that the correlation is partly or wholly genetic in origin.

Genetic correlations can provide clues about the evolutionary mechanisms responsible for traits' genetic variation. Mutation-selection predicts that traits related to fitness will demonstrate positive (low-fitness end with

low-fitness end) genetic correlations with each other. This is because mutation-selection keeps deleterious alleles at very low frequencies where they individually contribute little to a trait's genetic variation; only the cumulative effect of very many mutations—and thus very many genes—could maintain substantial genetic variation in a trait. If mutation-selection maintains substantial genetic variation in two fitness-related traits, simple probability dictates that the traits share many genes in common (Roff, 1997), and will therefore show a positive genetic correlation (high-fitness end of trait 1 with high-fitness end of trait 2).

Fitness-related traits whose genetic variation is explained by antagonistic pleiotropy, on the other hand, should show negative genetic correlations (high-fitness end of trait 1 with low-fitness end of trait 2). For example, alleles increasing fitness via increased creativity might also decrease fitness via increased risk for schizophrenia (Nettle & Clegg, 2006). Although theoretical treatments have cast doubt on the ability of antagonistic pleiotropy to maintain genetic variance indefinitely (see section on balancing selection), mutations with antagonistic effects on two fitness-related traits will tend to reach higher frequencies and persist for longer than unconditionally deleterious mutations. Thus, antagonistic pleiotropy may be an important contributor to variation in fitness-related traits, even if it does not maintain balanced polymorphisms indefinitely.

There is evidence in the animal literature supporting the idea that both mutation-selection and antagonistic pleiotropy play roles in genetic variation of fitness-related traits in nature. Fitness-related traits (e.g., survival to sexual maturity) do tend to show less positive genetic correlations than do other types of traits (e.g., morphological measurements), consistent with antagonistic pleiotropy, but most genetic correlations (~ 60%) between such traits are nevertheless positive, consistent with some degree of mutational variation (Roff, 1997). In humans, there is wide agreement that mental disorders typically show positive genetic correlations (reviewed in Keller, 2008), consistent with a mutational role. The mutation-selection model would similarly predict that intelligence, athleticism, physical health, facial and bodily attractiveness, and any other trait related to fitness/mate value will show positive genetic correlations; the antagonistic pleiotropy model predicts that they will show negative genetic correlations (Miller, 2000). With a few exceptions (Arden, Gottfredson, Miller, & Pierce, 2009), such studies have yet to be done. This appears set to change. In collaboration with the Genetic Epidemiology unit of the Queensland Institute for Medical Research, a consortium of evolutionary psychologists and behavioral geneticists is currently collecting evolutionarily relevant data in a large community twin sample in order to assess genetic correlations among several ostensibly fitness-related traits.

Relative Degree of Additive and Non-additive Genetic Variation

Non-additive genetic variation is caused by statistical interactions between alleles at either the same locus (dominance) or different loci (epistasis). If the combined effect of two or more alleles is different than what would be predicted from adding the effects of each one individually, then some degree of non-additive genetic variation will result. Traits most related to fitness have a higher ratio of non-additive to additive genetic variation (around 1) than traits under less intense selection (around .33) in non-human animals (Crnokrak & Roff, 1995). This is consistent with theoretical predictions, because selection depletes additive genetic variation faster than non-additive genetic variation (Fisher, 1930; Merilä & Sheldon, 1999). Psychoticism, neuroticism, extraversion, somatization, and panic/phobia show relatively high levels, and major depression shows modest levels, of non-additive genetic variation (reviewed in Coventry & Keller, 2005), which is consistent with the hypothesis that these traits have been subject to natural selection ancestrally.

Four important caveats should be kept in mind in using the level of non-additive genetic variance as a standard of evidence for inferring the intensity of selection:

1. There is high variation in estimates of the non-additive:additive ratios for fitness-related traits in nature, which typically fall between .25 and 7.5 (Crnokrak & Roff, 1995). Thus, a single estimate of this ratio in humans is not compelling evidence for inferring strength of selection.
2. Non-additive genetic variance can be seriously underestimated by twin and twin-plus-sibling designs (Keller & Coventry, 2005), and even those designs that include the necessary relative types (e.g., parents) to estimate it tend to estimate it imprecisely (Medland & Keller, 2009). Because of this, we have surprisingly little understanding of the true levels of non-additive genetic variation underlying phenotypes known to be highly heritable, such as IQ and most mental disorders.
3. As with any statistical interaction, non-additive genetic effects are sensitive to scale: a change in scale of a purely arbitrary and neutral character (such as skin conductance) can cause the appearance or disappearance of non-additivity (see Lykken, 2006). Such sensitivity to scale is problematic for most psychological traits, which tend to be measured on arbitrary scales.
4. The three caveats above highlight that the level of non-additive genetic variation provides weak evidence as to the strength of selection on traits. It provides even weaker information on which evolutionary mechanism maintains a trait's genetic variation. High levels of non-additive genetic variation can arise from either mutation-selection or certain types of balancing selection (e.g., heterozygote advantage), but other types of balancing selection

(e.g., frequency dependent selection) can lead to high levels of additive genetic variation (Merilä & Sheldon, 1999).

In conclusion, high levels of non-additive genetic variation provide weak evidence that a given trait has been under some type of natural selection, but most estimates that exist must be taken with a grain of salt, and even good estimates cannot elucidate what mechanism maintained the trait's genetic variation.

Inbreeding Depression

Inbreeding depression refers to a decline in the value of traits among offspring of genetic relatives. The first person to study the phenomenon scientifically was Darwin (1868, 1876), who, with characteristic insight, grew concerned that the poor health of his children might be due to his marriage to his first cousin, Emma Wedgwood (Bowlby, 1992). A century of subsequent research on domesticated and wild animals consistently corroborated what Darwin suspected: Inbreeding leads to lower values on fitness-related traits (Crnokrak & Roff, 1999). Because inbreeding depression is stronger among traits that have been under directional selection ancestrally, the degree to which a trait is affected by inbreeding can be used as a rough gauge for how strongly selection acted on the genes influencing that trait over evolutionary time (DeRose & Roff, 1999).

Inbreeding increases homozygosity (aa or AA rather than Aa), which may lower fitness by decreasing the probability of advantageous heterozygous alleles maintained by balancing selection or by exposing the full deleterious effects of partially recessive mutations (Figure 10.1) thought to be sprinkled throughout every genome (S. Wright, 1977). Some evidence supports the latter mutational mechanism (Charlesworth & Charlesworth, 1999; Crow, 1999). For example, if the mutational mechanism is correct, populations that have gone through many generations of inbreeding should have *higher* fitness once they outbreed because partially recessive mutations can be exposed and purged from the population during the inbreeding period. An increase in fitness following inbreeding has occurred in several experimental organisms (Barrett & Charlesworth, 1991; Strong, 1978; Templeton & Read, 1983), although for certain traits in *Drosophila* (and ostensibly in other species), balancing selection also appears to play some role in inbreeding depression (Charlesworth & Hughes, 1999).

Traditionally, inbreeding depression studies have used pedigree information. Such studies in humans have found evidence that inbreeding reduces IQ (Afzal, 1988; Morton, 1979) and general health (Rudan et al., 2006), and

increases the probability of learning disabilities (Rudan et al., 2002), osteoporosis (Rudan et al., 2004), schizophrenia (although see Saugstad & Ødegard, 1986), cancer, depression, gout, peptic ulcers, and epilepsy (Rudan et al., 2003). A more direct method of studying inbreeding depression uses whole-genome SNP data to quantify how homozygous individuals' genomes are (e.g., Lencz et al., 2007). Such measures of genomic inbreeding are quantified as the percent of each person's genome that exists in long stretches, or runs, of homozygosity. A given run of homozygosity probably reflects the pairing of two stretches of a chromosome that are "identical by descent," meaning that the two chromosomal stretches making up the run come from the same common ancestor at some point back in the family tree. Such "identical by descent" stretches guarantee that everything (or nearly so) in the run of homozygosity, including rare mutations that existed in that stretch of the common ancestor's chromosome, is also homozygous.

Genomic inbreeding measures are preferable to those based on pedigree information for three reasons. First, individuals who breed with known relatives are probably not representative of the general population, which introduces an alternative explanation to inbreeding findings based on pedigree information. Genomic measures of homozygosity, on the other hand, elucidate even distant and unintended inbreeding. Second, self-reported pedigree information can be inaccurate. Third, even when pedigree information is accurately reported, the true level of homozygosity in inbred offspring is unknown. For example, the percent of the genome in homozygous runs among progeny of first cousins averages 6.25%, but the 95% confidence interval around this is 1.4% to 11.0% (Carothers et al., 2006).

Few results exist as yet on how runs of homozygosity are associated with human traits. Lencz et al. (2007) found that schizophrenia cases have more runs of homozygosity in their genomes than controls, but their study only focused on locations were multiple runs were observed in the sample, limiting the study's generalizability. Our own lab is currently in the early stages of investigating the effect of runs of homozygosity on IQ and schizophrenia, and we hope to present results of these investigations in the near future.

Direct Assessments of Mutational Loads

There are several indirect methods for investigating whether mutations (and thus mutation-selection) contribute to trait variation. These include investigating the effects of brain trauma, ionizing radiation, parental inbreeding, and paternal age on phenotypes of interest (for a full explanation for why these methods provide evidence for a mutational model, see Keller &

Miller, 2006). However, one of the most exciting developments in genetics over the last few years has been the ability for researchers to *directly* assess certain types of mutations. At first blush, such direct assessment seems easy: just measure all the base pairs in a genome and note where rare or unique single base pair polymorphisms (point mutations) exist. An overall 'mutational load' could then be related to phenotypes of interest. For technical reasons, however, we are still 3–5 years away from being able to measure all 3.2 billion base pairs in large genome-wide scans, and those base pairs that are currently being measured focus on common SNPs rather than rare mutations. Thus, detection of single base pair mutations in large samples is not yet possible.

Nevertheless, current technology does allow measurement of rare deletion and duplication mutations. By combining *intensity data* (the strength of the signal for each allele at a SNP) across many SNPs in a row, researchers can infer whether a deletion (indicated by low intensity and apparent homozygosity across contiguous SNPs) or a duplication (indicated by high intensity and normal heterozygosity across contiguous SNPs) exists at a particular genetic location (see, e.g., Korn et al., 2008). Importantly, even though common SNPs are used to assay them, this technique allows detection of both common *and* rare (i.e., mutational) deletions and duplications. Using such a technology, it appears that deletion and duplication mutations are important contributors to variation in HDL cholesterol levels (Cohen et al., 2004), autism (Sebat et al., 2007), Parkinson's disease (Simon-Sanchez et al., 2008), mental retardation (reviewed in Lee & Lupski, 2006), Tourette's syndrome (Lawson-Yuen, Saldivar, Sommer, & Picker, 2008), and schizophrenia (Walsh et al., 2008). Evidence on the effects of rare deletions and duplications on bipolar disorder, obsessive-compulsive disorder, major depression, anxiety disorder, and other psychiatric and non-psychiatric conditions will probably be released within the next two years.

There are two important conclusions to take away from the studied effects of deletions and duplications on illness. First, deletion and duplication mutations play important roles in the etiology of these disorders, but it is difficult to put a quantitative estimate on *how big* of a role such mutations play. Presumably, once all classes of mutations can be accurately measured, investigators will be able to estimate the total contribution of mutations to trait heritability. Second, over the years, several evolutionary thinkers have postulated that disorders such as schizophrenia (Polimeni & Reiss, 2002) and autism (Gernsbacher, Dawson, & Mottron, 2006) might themselves be heritable, complex, adaptations maintained in the population by balancing selection. Finding that these same disorders are influenced by mutations *to any degree* rules against such hypotheses (Keller & Miller, 2006). This is because mutations disrupt complex adaptations; it is highly improbable that

deleterious mutations or other developmental insults would lead to full-fledged, complex adaptations by chance.

Whole-genome Association Studies

Alleles maintained by balancing selection should be relatively common (minor allele frequencies >1%) in the population at each locus (Barton & Keightley, 2002; Mani, Clarke, & Shelton, 1990). This prediction is true even if the balancing selection maintains one functional allele and any one of many potential loss-of-function alleles (Reich & Lander, 2001). Mutation-selection models, on the other hand, predict the opposite: One very common (most adaptive) allele at a given locus and many (hundreds or even thousands) extremely rare, lineage specific mutations in the population at that locus. As noted above (section on mutation-drift), the success of whole-genome association studies depends on common alleles being associated with traits of interest. For this reason, whole-genome association studies should be more successful for traits whose variation is maintained by balancing selection, directional selection, and mutation-drift than on traits whose variation is maintained by mutation-selection.

Whole-genome association studies have been successful at finding alleles that explain significant variation (e.g., cumulative >5%) for certain traits: lung cancer (Spinola et al., 2006), breast cancer (Easton et al., 2007), prostate cancer (Yeager et al., 2007), heart disease (Samani et al., 2007), macular degeneration (Li et al., 2006), nicotine dependence (Bierut et al., 2007), type 2 diabetes (Scott et al., 2007), and obesity (Herbert et al., 2006). These studies show that genome-wide association studies work as advertised when common alleles are responsible for some portion of genetic variation. However, despite great investment in treasure and effort, similar success has not occurred for many other disorders of interest, including any psychiatric disorder. In a paper that came out before the results of whole-genome association studies were known (Keller & Miller, 2006), we predicted that if the genetic variation underlying most mental disorders was largely mutational in nature, as we argued, then whole-genome association studies would have little success in finding mental disorder risk alleles of major effect. So far, this prediction has been born out in the data. Our interpretation of the pattern of whole-genome results to date is that they are being found for phenotypes that show large gene-by-environment interactions, such that common alleles that today are risk factors for nicotine dependence, obesity, diabetes, cancer, and heart disease were not risk factors for these diseases ancestrally, and did not decrease fitness in the environments in which humans evolved.

CONCLUSIONS

Evolutionary psychology has traditionally been concerned with understanding human universal adaptations. Behavioral variation was interesting to the degree that it was facultative (contingent on the situation) and elucidated universal adaptations, whereas genetic variation was deemed mostly as uninteresting side effects or as defenses against pathogens (Tooby & Cosmides, 1990). The field of behavioral genetics has traditionally focused on understanding the genetic and environmental contributions to trait variation, but has lacked a meta-theory that can suggest interesting new tests or that ties disjointed findings together in a cohesive way. Thus, to date, evolutionary psychology and behavioral genetics have largely talked past each other; what is chaff to one field has been wheat to the other (Mealey, 2001). But evolutionary psychology and behavioral genetics continue to ignore each other to their own detriment. We believe that much more dialogue and cross-fertilization between these fields is not only possible, but would mutually strengthen and benefit both fields. Evolutionary genetics is the bridge between evolutionary psychology and behavioral genetics that makes this "consilience" (Wilson, 1999) possible, and new data sources in molecular genetics offer many exciting ways to test questions of interest to researchers in this area. Evolution leaves fossils within DNA every bit as real and exciting—and sometimes confusing—as those buried in the soil. It is time for evolutionary psychology to take genes seriously, and for behavioral genetics to take evolution seriously.

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