The Nature of Genetic Influences on Behavior: Lessons From "Simpler" Organisms

Kenneth S. Kendler, M.D.

Ralph J. Greenspan, Ph.D.

Substantial advances have been made in recent years in the understanding of the genetic basis of behavior in "simpler" organisms, especially the mouse and the fruit fly *Drosophila*. The authors examine the degree of similarity between the genetic underpinnings of psychiatric illness and genetic influences on behavior in such simpler organisms. Six topics are reviewed: 1) the extent of natural genetic variation, 2) the multigenic nature of natural variation, 3) the impact of individual genes on multiple traits, 4) gene-environment interactions, 5) genetic effects on the environment, and 6) gene-by-sex interactions. The results suggest that the pattern of results emerging in psychiatric genetics is generally consistent with the findings of behavioral genetics in simpler organisms. Across the animal kingdom, individual differences in behavior are nearly always influenced by genetic factors which, in turn, result from a substantial number of individual genes, each with a small effect. Nearly all genes that affect behavior influence multiple phenotypes. The impact of individual genes can be substantially modified by other genes and/or by environmental experiences. Many animals alter their environment, and the nature of that alteration is influenced by genes. For some behaviors, the pathway from genes to behavior differs meaningfully in males and females. With respect to the broad patterns of genetic influences on behavior, *Homo sapiens* appears to be typical of other animal species.

(Am J Psychiatry 2006; 163:1683–1694)

In his work on "The Descent of Man," Darwin (1) strove to demonstrate the degree of continuity that existed between humans and other animals from which he sought to argue that "man is the modified descendent of some preexisting form." Of the seven chapters of his book, three were devoted to the similarities of the psychological and behavioral traits of humans and "simpler" organisms.

This essay also seeks to examine the degree of continuity between humans and nonhuman animals with respect to psychological or behavioral traits. Our focus, however, differs from that of Darwin. Building on recent advances in both psychiatric and animal behavior genetics, our aim is to examine the degree of similarity in the genetic underpinnings of psychiatric illness and genetic influences on behavior in other, simpler organisms.

In short, we attempt to answer the following question: How similar, in broad outline, are the findings emerging in psychiatric genetics and the genetics of behavior in simpler organisms?

Discontinuities certainly exist between the human mental and behavioral dysfunctions that constitute psychiatric illness and the well-studied behaviors of simpler organisms. Nonetheless, as suggested by Darwin, there is potentially sufficient cross-species commonality of mechanisms that a comparison of findings will be useful. Our review will focus on, but is not limited to, behavior genetic studies of the mouse and the fruit fly *Drosophila*, since these two species have been the most intensively studied.

Traditionally, two distinct approaches have been taken with regard to behavior genetics in simpler organisms: the measurement and manipulation of naturally occurring variation in laboratory or wild strains, and the isolation and study of newly induced mutations. The former assesses the extent of the typically mild mutational variation that survives in nature and exerts effects on behavior. Such studies are analogous to our investigations of psychiatric disorders in human populations. The latter—which has no parallel in human research—identifies genes and mechanisms subserving particular behaviors by producing more drastic genetic lesions than would typically survive the rigors of selection in natural populations. Both methods can clarify how genetic variation contributes to behavior. However, a synthesis between the two, made possible by recent advances in molecular biology, holds the most promise for a deeper understanding of the relationship between genes and behavior.

For this essay, we identified six areas of research in psychiatric genetics where the broad pattern of results is beginning to be clear. After outlining briefly these findings, we then review what has been learned about this question in genetic studies of behavior in simpler organisms. Each of these "mini-reviews" is meant to be illustrative and not

This article is featured in this month's AJP Audio.

exhaustive (we do not, for example, attempt to review the genetics of mental retardation or dementia). We then examine two important areas where the findings in psychiatric genetics are too scant to permit any broad conclusions. In each of these, clear findings are emerging in behavioral genetic studies of simpler organisms that might foreshadow results that will be found in psychiatric disorders.

Extent of Natural Genetic Variation

Psychiatric Disorders in Humans

Genetic risk factors have been found for every psychiatric condition that has been seriously studied (2, 3). For most disorders, evidence for genetic risk factors has been replicated using the same research design (most commonly twin studies) and for some disorders replicated across twin and adoption designs. Significant genetic influences have also been found for more "normative" human traits such as personality (4) that are also important risk factors for psychiatric illness (5). Heritability—the proportion of individual differences in liability to illness that results from genetic differences between individuals in a particular population—appears to vary meaningfully between psychiatric disorders, with relatively consistent results across studies: from 20% to 30% for most anxiety disorders (6), 30%–40% for major depression (7), 50%–60% for alcoholism (8, 9), and 80% or higher for schizophrenia, bipolar illness, and autism (10–12).

Behavior in Simpler Organisms

Considerable genetic variation influencing behavior appears to exist for nearly all traits, in all populations, in all species. Heritability can be estimated in several different ways in animal populations. Like twin or adoption studies in humans, these studies do not provide information about the action of specific genes at a biological level but rather estimate statistically the aggregate effects of all genes distributed across the genome within the specific population under study.

Mousseau and Roff reviewed heritability estimates for a variety of traits derived largely from parent-offspring correlations, first from *Drosophila* (13) and then from 75 other invertebrate and vertebrate species (14). Of these traits, 38 from *Drosophila* and 105 from the other organisms were behavioral. Considerable variation in the heritability of individual traits was found with the 25th, 50th, and 75th percentiles estimated to be 12%, 25%, and 43%, respectively. In a more recent review of 57 studies of animal behavior, Meffert et al. report the mean heritability to be equal to 38% (14a).

Another approach to assessing genetic variation in simpler organisms draws on the ancient strategy of selective breeding. Artificial selection experiments have been conducted by farmers and animal breeders for millennia, and virtually any trait seems to respond. Selection studies depend on the preexistence of genetic variation in the population undergoing selection, thereby providing an assay for the level of existing natural variation.

How extensive is natural genetic variation so assessed? The question has been concisely answered by the population geneticist Lewontin (15): "There appears to be no character—morphogenetic, behavioral, physiological, or cytological—that cannot be selected in *Drosophila*." He cited the fruit fly simply because more selection experiments had been conducted on it than any other animal, but the conclusion applies equally well to the mouse and other species. Traits responding to selection include phototaxis (movement toward light), geotaxis (movement in response to gravity), circadian rhythms, courtship behavior (a stereotypical, innate behavior in the fruit fly), and learning ability (reviewed by Greenspan [16]). Selection studies in rodents have revealed intrinsic genetic variation for an equally wide range of behaviors, including maze learning (17), aggression (18), ethanol preference (19) and withdrawal (20), anxiety (21), and response to stress (22).

In summary, as with psychiatric disorders, individual differences in virtually all behavioral traits examined in simpler organisms are influenced by genetic factors. Heritability estimates both for psychiatric disorders in humans and behaviors in lower organisms vary widely, although most traits appear to fall in the range of 10%–50% for the population tested.

The Multigenic Nature of Natural Variation

Psychiatric Disorders in Humans

Although twin and adoption studies provide strong evidence for the existence of aggregate genetic effects for psychiatric disorders, several lines of evidence suggest that these effects are the result of multiple genes, each of small to modest effect. First, individual genes that strongly influence a phenotype produce a characteristic pattern of illness in pedigrees (e.g., autosomal dominant, sex-linked recessive, etc.). Despite efforts by many researchers to find pedigrees in which psychiatric disorders segregate like classic or "Mendelian" traits, these efforts have to date been largely unsuccessful. Second, linkage studies can "sweep" the human genome looking for genomic regions that impact strongly on disease risk. In such studies, genes of large effect size have a typical "signature," which has not been found to date in any of the psychiatric disorders studied by linkage including schizophrenia, bipolar illness, panic disorder, or eating disorders. Third, a recent careful meta-analysis of 20 genome scans for schizophrenia suggests that at least 10 genomic regions are likely to contain susceptibility genes (23). In addition, current evidence of bipolar disorder, the next most studied psychiatric disorder by linkage scans, also suggests multiple loci (24, 24a).

Behavior in Simpler Organisms

Much has been learned about the number and effect size of the genes that influence behavior in simpler organisms. Most of these advances come from the application of linkage methods to the study of naturally occurring genetic variation. In linkage analysis of psychiatric disorders, the focus is typically on diseases. However, in animal linkage studies a quantitative behavior (such as motor activity or emotionality) is more commonly used. Genes that influence such traits are called "quantitative trait loci" or QTLs. In QTL analysis, a phenotypic difference between two strains is mapped against an extensive set of genetic markers that also differ between them, and chromosomal regions mediating significant effects are mapped. The power of QTL analysis in simpler organisms often substantially exceeds that available in humans because of the possibility of designing specific crosses to provide maximal linkage information.

Flint has thoroughly reviewed the literature on QTL studies of behavior in rodents, with the most commonly studied traits being circadian rhythm, drug preference or response, emotionality, motor activity, and learning (21). He concludes that such behaviors are typically influenced by many genes of small effect. While an accurate estimation of the number of QTLs involved is problematic (and available estimates are likely to be too low), current evidence suggests that most behavioral traits in rodents are influenced by six to 24 QTLs.

In QTL studies, effect size is typically measured as the proportion of variance in the trait that results from variance at the particular QTL. (The available effect sizes are probably overestimates, since large effect genes are the ones to be first detected.) Flint concludes that—while there are exceptions—most behavioral traits are influenced by genes that account for 10% or less of the total phenotypic variance. More typically, detected genes have effect sizes of less than 5%.

In a recent, thorough QTL analysis of five anxiety-related measures in the mouse, Henderson et al. (25) found a total of 17 QTLs across all the traits and typically four to six per individual measure. While over half of the 17 loci discovered accounted for less than 1% of phenotypic variance, at least one QTL accounting for 5% of total variation was found for each of the five measures. Using a different technical approach (chromosomal substitution strains), Singer et al. (26) confirmed the presence of multiple loci influencing models of anxiety in mice. In a recent genome-wide association study in genetically heterogeneous mice, Valdar et al. (26a) examined seven behavioral phenotypes divisible into 21 more specific measures. Using a plausible statistical model, they detected a mean of nine QTLs per measure. On average, these QTLs individually accounted for 2.1% of the variation in these behaviors.

Fewer QTL studies of behavioral traits have been conducted in other organisms (27). Two recent examples explored variation in a key feature of the courtship song of *Drosophila*—the mean interpulse interval—and reported results similar to those found for behaviors in the rodent, i.e., multiple QTLs each accounting for 3%–10% of the phenotypic variance (28, 29).

A different approach toward identifying genes involved in behavioral traits in simpler organisms has come with the advent of DNA microarray technology. With these methods, it is possible to directly examine differences in expressed levels of mRNA between strains selected for behavioral differences. This approach does not directly measure the number of allelic differences giving rise to the behavioral difference. Instead, it reveals the set of genes whose expression is changed as a result of those allelic differences. These two sets of allelic differences are surely overlapping, but not likely to be identical. This method was, for example, applied to *Drosophila* strains selected for differences in geotaxis and found approximately 250 genes whose expression differed in the two selected lines (30).

The number of individual genes influencing a behavioral trait can also be estimated from surveying experimental studies of individual genes. Such studies are carried out with induced mutations (e.g., "knockouts") or genetically engineered strains (transgenics) in which expression of the gene is altered. While not designed as a direct measure of the number of loci involved, these studies can provide a different sort of sampling than that obtained from more directed gene searches. Furthermore, such a list, if complete, will be considerably larger than that obtained from QTL studies, since many of the genes so identified would not have trait-relevant variations in natural populations. Although far from complete, recent surveys have enumerated 33 genes identified since 1995 that influence aggressive behavior in the male mouse (31) and 14 loci from mutations that altered odor-guided behavior in *Drosophila* (32).

Combining these two approaches may provide the most complete picture of the multigenic foundations for behavior. In a comprehensive study of genes affecting long-term memory in *Drosophila*, Dubnau et al. (33) combined a large-scale mutation screen with an analysis of gene expression patterns. The mutant screen identified 60 new mutants that are selectively defective in long-term memory, and in parallel, the DNA microarray analysis identified 42 genes expressed in the brains of flies under conditions that produce long-term memory. Both sets of genes run the gamut of biological functions—transcription, translation, signal transduction, cytoskeleton, and metabolism.

How far down the phylogenetic scale of complexity does the multigenic influence over behavior extend? In the nematode *C. elegans*—which contains only 302 neurons—mutations in over 100 different genes impair locomotion while mutations in at least 18 genes are involved in the response to light touch (34). Many genes appear to be able to influence behaviors in even the simplest organisms.

In summary, three distinct methods—QTL linkage analysis, examination of knockout and transgenic animals,

and comparison of expression arrays in selected lines—all suggest that in simpler organisms most behavioral traits are influenced by a relatively large number of genes. Variants in these genes that exist in natural populations tend to have modest effects on the phenotype.

The Impact of Individual Genes on Multiple Traits

Psychiatric Genetics in Humans

In twin and adoption studies, genetic risk factors are often not specific for individual psychiatric or drug abuse conditions but rather influence liability for a range of disorders. One recent large-scale twin study of seven psychiatric and substance use disorders found one common genetic risk factor that increased risk for drug abuse, alcohol dependence, antisocial personality disorder, and conduct disorder and a second common genetic factor influencing liability to major depression, generalized anxiety disorder, and phobia (35). Other twin studies have also found evidence for genetic factors that have an impact on risk for multiple disorders (e.g., references 36–38). This relationship is often quantified by a statistic called the "genetic correlation," which reflects the degree of overlap of the genetic risk factors for two traits or disorders.

Using the methods of linkage and association, evidence has also accumulated for genomic regions or individual genes that convey risk to more than one disorder. A number of overlapping positive regions in linkage genome scans for bipolar illness and schizophrenia have led some to argue that this reflects shared genes between these two disorders (39). A pair of overlapping genes on chromosome 13q (termed G30 and G72) may be associated with risk for both schizophrenia and bipolar illness (40). Claims have been made that several functional candidate genes (e.g., serotonin transporter, dopamine transporter, D_2 receptor) are associated with a wide range of psychiatric disorders and/or psychiatrically relevant traits (41, 42).

Behavior in Simpler Organisms

Thirty years of analyzing genes affecting behavior in mice, fruit flies, and nematodes have consistently supported the contention that genes influencing behavior are pleiotropic—that is, they affect more than one trait (43, 44). In studies most closely analogous to human investigations, genetic correlations can be calculated between two traits when both are studied in animals that are genetically related to one another—such as parents and offspring or siblings. Reviewing such studies, Roff (45) found reports on 166 genetic correlations between behaviors from six different animal species. The mean and median absolute value of these genetic correlations were +0.59 and +0.56, respectively, indicating that most of the examined pairs of behaviors were substantially influenced by common sets of genes.

A second approach to studying pleiotropy is through selection studies. Over and over again, studies have found that, in selecting for one trait, changes are also seen in other traits. While some of these results will not always be due to pleiotropy (selection can carry along linked variants at other loci that affect the different phenotypes), when suitably analyzed, such correlated traits are often found to arise from pleiotropic effects. For example, flies selected for geotaxis preference also displayed increased behavioral stereotypy (46), altered egg-laying behavior (47), and altered mating preference (48). In the many selection experiments performed on courtship and mating behavior in *Drosophila*, correlated responses have also been found for open field behavior (analogous to the test for emotionality in rodents) (49, 50), general locomotor activity (51), and increased sensitivity to disturbance (49). An example with more cognitive phenotypes comes from experimental selection for an increase in sensitization ("central excitatory state") in the blowfly *Phormia regina*. These flies showed correlated responses in both associative conditioning (52) and in food search behavior (53).

The pleiotropic effects of individual genes can be most powerfully demonstrated by the study of individual mutants where a diversity of phenotypic effects has been shown to be the rule rather than the exception (43, 44). We list several examples in Table 1, exploring two additional cases here in a bit more detail. A locus in the nematode *C. elegans* encoding a protein similar to the vertebrate neuropeptide-Y receptor originally identified through effect on feeding behavior (54, 55) was subsequently found to display hyperactivity on food, burrowing into agar, accumulation on the border of a bacterial lawn, and greater resistance to ethanol (56). The *dunce* gene in *Drosophila* epitomizes pleiotropy. First identified in a screen for flies defective in learning, as assayed by olfactory avoidance conditioning (57), and subsequently shown to encode one of several forms of cAMP-phosphodiesterase (58), the dunce phenotype was initially thought to be "clean," having an impact solely on learning. However, further examination showed effects on female fertility, biological rhythms (59), female mating receptivity (60), abnormal embryonic development (61), decreased longevity (60), and defects in synaptic transmission (62).

In summary, evidence from breeding studies, selection experiments, and single gene mutants all suggest that genes that alter behavior in simpler organisms frequently influence a variety of often quite disparate behaviors.

Gene-Environment Interactions

Psychiatric Genetics in Humans

Commonsense etiologic models in psychiatry assume that genetic and environmental risk factors add together to produce disease liability. However, classical genetics and biomedicine provide many examples where genetic effects are modified by environmental exposure, thereby

TABLE 1. Pleiotropy of Behavioral Mutants in *Drosophila*

Mutant	Initial Specific Phenotype	Gene Product	Ultimate Extent of Pleiotropy
Dunce	Associative conditioning	cAMP phosphodiesterase	Embryonic patterning; female fertility; biological rhythms; longevity
Cacophony	Male courtship song	Calcium channel	Visual acuity; convulsions
Latheo	Associative conditioning	ORC (origin of replication) homolog	Imaginal disc formation; cell proliferation in CNS
Optomotor-blind	Optomotor response, development of motion detecting neurons	T-box transcription factor	General optic lobe development; wing, leg, and abdominal patterning
No-action-potential	Nerve conduction	RNA-helicase homolog	Male viability; regulation of X-linked genes
No-receptor-potential-A	Photoreceptor potential	PI-phospholipase C	Circadian rhythms; olfaction

producing "gene-environment interaction." Twin and adoption studies have produced evidence for such interactions for major depression with exposure to stressful life events (63, 64), and schizophrenia, conduct disorder, and aggression with exposure to a dysfunctional rearing environment (65, 66). Genotype-environment interactions have also been shown in twin studies for a range of psychiatrically relevant traits including aggression, disinhibition, and smoking (3). In many of these studies, heritability of traits increases in more permissive environments. Caspi and colleagues have found evidence for interactions between environmental factors and polymorphisms in the association of monamine oxidase with risk for antisocial behavior (67) and the association of serotonin transporter with risk for depression (68).

Behavior in Simpler Organisms

Clear examples of genotype-environment interaction have emerged in studies of the genetics of behavior in simpler organisms. In contrast to the foregoing examples, many of these have come from work in behavioral ecology on various species studied initially in the field and then brought into the laboratory.

For example, a range of hybrid strains of the paradise fish *Macropodus opercularis* were exposed to four environments that differed in their level of novelty and threat, which provided an ethologically valid test of "anxiety." Significant gene-by-environment interactions were observed, with the ordering of the strains (from most to least "anxious") varying widely across the different environments (69).

In a similar test in mice, Wahlsten et al. (70) systematically examined eight different strains on five behavioral tests in three laboratories. Of these tests, three produced robust evidence for genotype-environment interaction—meaning that the genetic differences between strains varied as a function of the laboratory in which the tests were performed. In the detailed study of genetically heterogeneous mice noted above, Valdar et al. (70a) examined interactions on the behaviors examined between background genetic liability and 10 environmental covariates. Six percent of the interactions tested (10 in total) met rigorous criteria for statistical significance.

Two sets of rodent studies of genotype-environment interaction have particularly close analogies with human studies (63, 66). Investigations with both Y-chromosomal variants and the oxytocin gene show that their phenotypic effect on aggressive behavior in mice was substantially modified by the maternal environment (31). The effects of the social stress of crowding and frequent cage reassignment on both aggression and hypertension varied dramatically between different rat strains (71).

Henderson (72) studied the heritability of a complex motor food-seeking task for mice raised in standard or enriched laboratory cages. Heritability was much higher in the enriched (40%) than standard conditions (10%), perhaps because the enriched environment was more "permissive," i.e., permitting mice with high innate skills to practice the needed complex motor behaviors.

As has been seen in a more limited range of conditions in human studies of psychiatric disorders, the examination of behavior in simpler organisms suggests that genetic effects can frequently be modified by environmental exposure.

Genetic Effects on the Environment

Psychiatric Genetics in Humans

In the traditional view of gene action, genetic expression takes place entirely in a physiological "internal milieu," or "inside the skin." The environment, by contrast, exists outside the skin with the causal relationship between organism and environment flowing only from environment to organism. When considering behavior, however, a revised view of gene action is indicated. Through an influence on behavior, genes can also have an impact on the external milieu. In humans, this effect is seen in the social environment from which emerge a number of risk factors for psychiatric and substance use disorders. Studies in twin populations have now suggested that genetic factors, through "outside the skin" pathways, influence exposure to a range of environmental risk factors, including stressful life events (73–75), low levels of social support and marital quality (76, 77), both the elicitation and provision of poor parenting (78–80), and deviant peer groups in adolescence (81). For psychiatric and substance use disorders, one pathway from gene to illness involves self-selec-

tion into high-risk environments that then feed back to increase risk of illness.

Behavior in Simpler Organisms

In what is called "niche construction," animals modify their physical environment through building burrows, webs, and dams and constructing nursery environments for their offspring (82). While there are well demonstrated strain and species differences in such behaviors, few have been analyzed genetically. In addition to the physical environment, in social animals, an organism's genes can, through behavior, also have an impact on key aspects of the social environment such as parent-offspring, mate and adult-peer relations.

Lynch (83) performed a selection study for nest construction in female mice and achieved nearly a 10-fold divergence in behavior after 15 generations, with a realized heritability of 28%. Maestripieri et al. (84) found that infant abuse "ran in families" in pigtail macaques but could not discriminate genetic from familial-environmental transmission. In rodents, genetic effects are seen with both the provision and elicitation of parental care. Hurnik et al. (85) performed a selection experiment for the speed of maternal retrieval behavior in two inbred mouse strains. Over only five generations, substantial divergence was seen in the groups selected for slow and fast retrieval, respectively. Eisen et al. (86) conducted a selection experiment for 12-day litter weight and concluded that 11% of the variance in this trait was due to genes in the mother which, via quality of care and feeding, influenced weight gain in her offspring. Roubertoux et al. (87) studied genetic influences on vocalizations in newborn mice, a primary method by which newborns communicate distress to their mother. Substantial differences in a range of vocalizations were found among seven inbred strains. Single gene effects have also been seen on maternal behavior. For example, female mice homozygous or heterozygous for knockout of their prolactin receptor exhibit relatively specific impairment in maternal behavior (88).

The effect of individual genes on affiliative behavior has been studied in two species of voles. The prairie vole *Microtus ochrogaster* is monogamous, biparental, and highly social. By contrast, the montane vole *Microtus montanus* is promiscuous, maternal, and minimally social (89). The hormones oxytocin and vasopressin exert complementary effects on these behaviors in the prairie vole, as they appear to do in rats and mice. Moreover, the anatomical distribution of oxytocin and vasopressin receptors in the brain differs markedly between the two vole species (90).

Vasopressin administration stimulates affiliative behavior in prairie voles but neither in montane voles nor in mice. When a prairie vole vasopressin receptor gene (V_{1a}) was transferred into mice, thereby creating an anatomical distribution similar to that of the prairie vole, the mice began to exhibit affiliative behavior in response to vasopressin. This result argues that changing the pattern of V_{1a} distribution is sufficient to alter this social behavior. This interpretation is further supported by the fact that the V_{1a} receptor genes are virtually identical between the two vole species that differ in affiliative behavior, except for the presence in prairie voles of a small segment in the region of the gene that is likely to regulate its expression. The presence of this DNA segment correlates well with behavioral and anatomical features of two other species, the pine vole *Microtus pinetorum*, which is like the prairie vole behaviorally as well as in its anatomical and molecular characteristics of V_{1a}, and the meadow vole *Mictotus pennsylvanicus*, which is like the montane vole in all of these respects. Thus, it appears that subtle changes in the expression pattern of the vasopressin receptor V_{1a} may account for these substantial differences in social behavior in these rodent species.

This interesting case is an exception to our earlier assertion that natural genetic variants tend to have modest effects on a phenotype and tend to act in concert with many other genes. The large preponderance of studied examples is consistent with our earlier statement but, as in all things biological, there are exceptions. Two other examples of large single gene effects on complex behavior are the neuropeptide-Y-receptor-like gene in the nematode *C. elegans* and the cGMP-dependent protein kinase gene in *Drosophila*, both of which affect foraging behavior (54, 91).

Aggression is another important social behavior that has been shown, in simpler organisms, to be influenced by genetic factors. Enhanced aggression has been achieved through selection experiments in *Drosophila* (92) and mice (18). Finally, variation in a gene influencing eye color in *Drosophila* influences preference of flies for different microenvironments differing in ambient light conditions (93). This study shows how genetic variation can have an impact on the active selection of environments.

In summary, given prior strong evidence for genetic influences on a wide range of behavior, it is not surprising that increasing evidence in both human and nonhuman animal populations suggests that genes also influence an organism's social and physical environment. With respect to behavior, gene action does not stop at the physiologic boundary of the organism, the skin.

Gene-by-Sex Interactions

Psychiatric Genetics in Humans

Twin studies have suggested that the aggregate genetic risk factors for major depression (94), some forms of phobias (95), and alcoholism (96) are not entirely the same in males and females. Of two genome scan linkage studies for major depression, one presented evidence for a male-specific locus (97) while a second revealed several loci specific in their effect on women (98). A genome scan for the personality trait of neuroticism—closely related genetically to risk for major depression (99)—revealed three loci

on chromosomes 1q, 12q, and 13q that appeared to be female specific (100).

Behavior in Simpler Organisms

Since sexual differences start out developmentally as differences in gene expression in the sex determination pathway, it is not surprising that many genetic influences on behavior also have differential effects on females and males. Initially, in selection experiments on behavioral traits, sex-specific results were obtained. One sex was found to respond more to selection than the other, and in some cases that differential response was true at one phenotypic extreme and not the other. This is illustrated in two different experiments, one in *Drosophila* selecting for differential geotaxis response (101), and one in the blow fly *Phormia* selecting for the conditioned response to a sucrose stimulus (102). When such selected strains are bred to produce various classes of progeny, sex-by-gene interactions can often be seen at the aggregate gene level, as seen in a *Drosophila* study of response to an unconditioned stimulus (103).

Sex-specific behavioral responses have been shown, in several instances, to reflect underlying differences in gene expression. This is merely a more restricted aspect of the emerging data from whole-genome expression analysis, which has shown that 50%–60% of all genes are differentially expressed between the sexes (104, 105). In one study, sex was shown to have the strongest single effect on the variance in gene expression (106). Whereas many of these are genes directly involved in sex determination and sex-specific development and show an all-or-none difference, many more are not. Fruit flies also show sexually dimorphic responses to cocaine (107, 108), and this is reflected in a differential sensitivity to the induction of stereotypical locomotor behavior.

Such sex-specific effects are by no means confined to the fruit fly. For example, studies have shown sex-specific QTLs for several different alcohol-related traits in mice including preference (109), duration of loss of righting reflex (110), and severity of withdrawal (111). Other studies in the mouse have shown sex-specific effects on basal gene expression in brain (112, 113) as well as in response to caffeine administration (114).

In summary, evidence on psychiatric and substance use disorders in human populations and a range of behavioral phenotypes in simpler animals suggest that modification of genetic effects by sex is probably a common phenomenon.

Gene-Gene Interactions

Psychiatric Genetics in Humans

We now turn to two areas where clear findings in psychiatric genetics have yet to emerge. The first of these, termed gene-gene interaction or "epistasis," occurs when two alleles at different genetic loci interact in a nonadditive fashion on a phenotype (115). While widely suspected to be important in psychiatric genetics, gene-by-gene interactions have been little studied. In part this is because the standard "work horses" of genetic epidemiology—twin and adoption studies—are very weak at detecting such effects (116).

While methods have been developed for linkage studies to detect gene-gene interactions (117), they have not been widely validated, may have quite low power, and have been applied only rarely to human behavioral traits (118). Theoretically, association studies provide substantially greater power to detect such interactions. However, all the difficulties with association studies of the main effect of genes (e.g., low a priori probabilities, multiple testing, liberal alpha values, and false positive rates [119, 120]) are further exacerbated in studying interactions. A number of association studies have reported interactions, but we are unaware of any that have been widely replicated or supported by meta-analyses. Applying statistical models to risk of illness in various classes of relatives, Risch suggests that gene-by-gene interactions are important in the etiology of schizophrenia (121).

Behavior in Simpler Organisms

In contrast to human studies, robust methods are available in simpler organisms to detect gene-gene interactions. One powerful approach is to observe the effects of induced mutations that influence behavior in different laboratory strains. These strains provide varying "genetic backgrounds" that could modify the effects of the mutated gene.

Mouse geneticists have long noted the sensitivity of mutations to genetic background (122). In one striking example, a mutation in the serotonin transporter (5-HTT) showed dramatically different effects when placed in two different strains. In B6 mice, the 5-HTT mutation produced increased anxiety-like behavior and reduced exploratory locomotion. However, the same mutation in 129S6 mice produced no change in either measure (123). (Of note, the 5-HTT mutation in the 129S6 strain was shown to produce expected changes in serotonin receptor binding and function, thus proving that the mutation was "active" but its behavioral effect was "suppressed" by the genetic background of 129S6 mice.) Similarly, a knockout of the nitric oxide synthase 1 (NOS1) enzyme increased attack behavior in one mouse strain (C57BL/6By) but not in a related substrain (C57BL/6J) (31). The effect of NOS1 inactivation on agonistic behavior must depend critically on one or more of the rather small number of genes that distinguish the two mouse substrains.

Epistasis can also be examined using a defined set of mutant genes. Such an approach was illustrated for odor-guided behavior in *Drosophila*. Fourteen distinct smell-impaired mutant lines were isolated (124). Interactions among the 14 genes were assessed by constructing pairwise combinations of the mutants and testing them for their olfactory responsiveness. The majority of pairwise

combinations showed gene-gene interactions in which the combination of the two mutations produced a greater phenotypic effect than would have been predicted from the average effect of each mutation on its own (125).

The molecular basis of gene-gene interactions is illustrated in the following example. Beginning with the cAMP phosphodiesterase gene *dunce*, introduced here as having pleitropic effects on both learning and egg-laying, mutations were screened to find one that would suppress the effects of *dunce*. One was found in the gene encoding the synthetic enzyme for cAMP: adenyl cyclase (61), which was already known as the learning mutant *rutabaga* (126, 127). One mutant gene could mask the effect of the other, apparently due to a restoration of a balance between the level of cAMP synthesis and degradation when mutations impaired the function of both enzymes.

In conclusion, the impact of gene-gene interactions on behavior is much more easily studied in simpler organisms than in humans. The available evidence suggests that such interactions certainly occur and may be relatively common. Available human data, however, indirectly suggest that for psychiatric disorders, genetic effects will not be limited to only gene-gene interactions. This inference is based on the following line of thought: Every time an egg or sperm is made, specific set of genes that might be interacting on a trait will commonly be broken up by recombination. If most genetic effects were mediated by such gene-gene interactions, resemblance in relatives for psychiatric disorders would be restricted to monozygotic twins who share all their genes in common. However, all well studied psychiatric disorders robustly "run in families." This pattern of findings suggests that at least a reasonable proportion of genetic effects are what statistical geneticists call "additive," which means that genes have reliable average effects that are not highly dependent on the presence or absence of other genes.

What Sits Under Linkage Peaks

Psychiatric Genetics in Humans

For complex human syndromes like psychiatric disorders, linkage "peaks" are large, often spanning tens of millions of base pairs and hundreds of possible genes (128). The last several years have seen some initial success—most notably in schizophrenia—in what has been called "fine mapping": using different techniques to localize a specific susceptibility gene under the linkage peak (40, 129). However, this task has proven more difficult than might have been initially thought. Furthermore, some of the genes found may not account for the entire linkage signal.

Behavior in Simpler Organisms

Further progress has been made, in simpler organisms, in the fine mapping of QTL peaks (analogous to linkage peaks in human research). In many cases, on closer examination, a single QTL fractionates into multiple tightly linked QTLs. In a recent review, Mackay (130) notes QTL studies with just this result for the *Drosophila* traits of "starvation resistance," "olfactory behavior," and longevity. In one study, two QTLs influencing longevity resolved, on fine mapping, into eight distinct peaks. Yalcin et al. (131) have fine mapped in the mouse a QTL shown to influence anxiety-related behaviors and found that it too "broke apart" into three discrete peaks. If true, these results have two implications. First, prior QTL and linkage studies may have substantially underestimated the number of loci that have an impact on behavioral phenotypes. Second, the task of fine mapping traits in humans under linkage peaks, where we have fewer and less powerful methods than in lower animals, may be even more difficult than we have previously estimated.

Conclusions

In the spirit of Darwin's "Descent of Man," we set ourselves the task in this essay of trying to determine the level of continuity in the broad patterns of the genetic influences on behavior from "simpler organisms" to humans. We framed for ourselves the question of the degree of similarity in general outline of results obtained in psychiatric genetics and in the behavior genetics research in simpler organisms. On the basis of this review, our response to this question would be "Quite similar." An analogous answer would have been obtained had we examined complex nonbehavioral traits such as blood pressure or immune function. Throughout the animal kingdom, individual differences in behavior are, almost without exception, influenced by genetic factors. Most commonly, these genetic effects are of moderate rather than overwhelming importance and sometimes genetic influences are quite modest in magnitude. Across a wide variety of species, including humans, the genetic influences on behavior are typically the result of a moderate to large number of individual genes each of which, on its own, has a rather small effect on the behavior. In both humans and simpler organisms, the interrelationship between genes and the environment in their impact on behavior is, at least for a number of traits, likely to be complex. Gene-environment interaction, while still much underresearched, may be widespread in its effects. It is equally likely that genes, through "outside the skin pathways" play critical roles in influencing important aspects of the social environment to which the organism is exposed. For a number of behaviors across most organisms, the pathway from genes to behavior may differ meaningfully in males and females.

Studies in simpler organisms suggest that gene-gene interactions may play an important etiologic role for many behavioral traits. Whether this also holds for genetically influenced traits in humans remains an open question; it seems a reasonable expectation, given all of the other similarities between genetics of behavior in humans and model organisms, but the data are lacking. Studies in

Drosophila and mice suggest that our prior assumption that linkage or QTL peaks are the result of a single susceptibility gene is likely to be incorrect for a substantial number of such peaks.

Given that Darwin was correct when he argued over 130 years ago that "man is the modified descendent of some preexisting form" (1), our results are not surprising. They should, however, further encourage dialogue and collaboration between those trying to understand the genetic basis of psychiatric disorders and those studying the genetic influences on behavior in "simpler" organisms.

Received Aug. 28, 2004; revisions received Dec. 31, 2004, and April 11, 2005; accepted April 28, 2005. From the Virginia Institute for Psychiatry and Behavioral Genetics and the Departments of Psychiatry and Human Genetics, Medical College of Virginia, Virginia Commonwealth University; and The Neurosciences Institute, San Diego. Address correspondence and reprint requests to Dr. Kendler, Department of Psychiatry, Medical College of Virginia of Virginia Commonwealth University, P.O. Box 980126, Richmond, VA 23298-0126; kendler@vcu.edu (e-mail).

Dr. Kendler and Dr. Greenspan report no competing interests.

Supported by the Fritz Redlich Fellowship at the Center for Advanced Study in the Behavioral Sciences to Dr. Kendler. Dr. Greenspan is the Dorothy and Lewis B. Cullman Fellow at The Neurosciences Institute, which is supported by the Neurosciences Research Foundation.

The authors thank Jonathan Flint, M.D., and Robert Karp, Ph.D., for their comments on an earlier version of this manuscript.

References

1. Darwin C: The Descent of Man, and Selection in Relation to Sex. London, J Murray, 1871
2. Plomin R, DeFries JC, Craig IW, McGuffin P (Eds.): Behavioral Genetics in the Postgenomic Era. Washington, DC, American Psychological Association, 2002
3. Kendler KS: Twin studies of psychiatric illness: an update. Arch Gen Psychiatry 2001; 58:1005–1014
4. Loehlin JC, McCrae RR, Costa PT Jr, John OP: Heritabilities of common and measure-specific components of the big five personality factors. J Res Pers 1998; 32:431–453
5. Krueger RF, McGue M, Iacono WG: The higher-order structure of common DSM mental disorders: internalization, externalization, and their connections to personality. Pers Individ Dif 2001; 30:1245–1259
6. Hettema JM, Neale MC, Kendler KS: A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am J Psychiatry 2001; 158:1568–1578
7. Sullivan PF, Neale MC, Kendler KS: Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000; 157:1552–1562
8. Heath AC, Bucholz KK, Madden PAF, Dinwiddie SH, Slutske WS, Bierut LJ, Statham DJ, Dunne MP, Whitfield JB, Martin NG: Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. Psychol Med 1997; 27:1381–1396
9. Prescott CA, Kendler KS: Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. Am J Psychiatry 1999; 156:34–40
10. Sullivan PF, Kendler KS, Neale MC: Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry 2003; 60:1187–1192
11. Craddock N, Jones I: Genetics of bipolar disorder. J Med Genet 1999; 36:585–594
12. Bespalova IN, Buxbaum JD: Disease susceptibility genes for autism. Ann Med 2003; 35:274–281
13. Roff DA, Mousseau TA: Quantitative genetics and fitness: lessons from drosophila. Heredity 1987; 58(part 1):103–118
14. Mousseau TA, Roff DA: Natural selection and the heritability of fitness components. Heredity 1987; 59(part 2):181–197
14a. Meffert LM, Hicks SK, Regan JL: Nonadditive genetic effects in animal behavior. American Naturalist 2002; 160(suppl):S198-S213
15. Lewontin RC: The Genetic Basis of Evolutionary Change. New York, Columbia University Press, 1974
16. Greenspan RJ: The varieties of selectional experience in behavioral genetics. J Neurogenet 2003; 17:241–270
17. Tryon RC: Genetic differences in maze-running ability in rats. Yearbook of the National Society for the Study of Education 1940; 39:111–119
18. Miczek KA, Maxson SC, Fish EW, Faccidomo S: Aggressive behavioral phenotypes in mice. Behav Brain Res 2001; 125:167–181
19. Grahame NJ, Li TK, Lumeng L: Selective breeding for high and low alcohol preference in mice. Behav Genet 1999; 29:47–57
20. Crabbe JC, Phillips TJ: Selective breeding for alcohol withdrawal severity. Behav Genet 1993; 23:171–177
21. Flint J: Analysis of quantitative trait loci that influence animal behavior. J Neurobiol 2003; 54:46–77
22. Harshfield GA, Grim CE: Stress hypertension: the "wrong" genes in the "wrong" environment. Acta Physiol Scand Suppl 1997; 640:129–132
23. Lewis CM, Levinson DF, Wise LH, Delisi LE, Straub RE, Hovatta I, Williams NM, Schwab SG, Pulver AE, Faraone SV, Brzustowicz LM, Kaufmann CA, Garver DL, Gurling HM, Lindholm E, Coon H, Moises HW, Byerley W, Shaw SH, Mesen A, Sherrington R, O'Neill FA, Walsh D, Kendler KS, Ekelund J, Paunio T, Lonnqvist J, Peltonen L, O'Donovan MC, Owen MJ, Wildenauer DB, Maier W, Nestadt G, Blouin JL, Antonarakis SE, Mowry BJ, Silverman JM, Crowe RR, Cloninger CR, Tsuang MT, Malaspina D, Harkavy-Friedman JM, Svrakic DM, Bassett AS, Holcomb J, Kalsi G, McQuillin A, Brynjolfson J, Sigmundsson T, Petursson H, Jazin E, Zoega T, Helgason T: Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: schizophrenia. Am J Hum Genet 2003; 73:34–48
24. Mathews CA, Reus VI: Genetic linkage in bipolar disorder. CNS Spectr 2003; 8:891–904
24a. McQueen MB, Devlin B, Faraone SV, Nimgaonkar VL, Sklar P, Smoller JW, Abou Jamra R, Albus M, Bacanu SA, Baron M, Barrett TB, Berrettini W, Blacker D, Byerley W, Cichon S, Coryell W, Craddock N, Daly MJ, Depaulo JR, Edenberg HJ, Foroud T, Gill M, Gilliam TC, Hamshere M, Jones I, Jones L, Juo SH, Kelsoe JR, Lambert D, Lange C, Lerer B, Liu J, Maier W, Mackinnon JD, McInnis MG, McMahon FJ, Murphy DL, Nothen MM, Nurnberger JI, Pato CN, Pato MT, Potash JB, Propping P, Pulver AE, Rice JP, Rietschel M, Scheftner W, Schumacher J, Segurado R, Van Steen K, Xie W, Zandi PP, Laird NM: Combined analysis from eleven linkage studies of bipolar disorder provides strong evidence of susceptibility loci on chromosomes 6q and 8q. Am J Hum Genet 2005; 77:582-595
25. Henderson ND, Turri MG, DeFries JC, Flint J: QTL analysis of multiple behavioral measures of anxiety in mice. Behav Genet 2004; 34:267–293
26. Singer JB, Hill AE, Burrage LC, Olszens KR, Song J, Justice M, O'Brien WE, Conti DV, Witte JS, Lander ES, Nadeau JH: Genetic dissection of complex traits with chromosome substitution strains of mice. Science 2004; 304:445–448
26a. Valdar W, Solberg LC, Gauguier D, Burnett S, Klenerman P, Cookson WO, Taylor MS, Rawlins JN, Mott R, Flint J: Genome-wide genetic association of complex traits in heterogeneous stock mice. Nat Genet 2006; 38:879-887

27. Anholt RRH, Mackay TFC: Quantitative genetic analyses of complex behaviours in Drosophila. Nat Rev Genet 2004; 5:838–849
28. Gleason JM, Ritchie MG: Do quantitative trait loci (QTL) for a courtship song difference between Drosophila simulans and D sechellia coincide with candidate genes and intraspecific QTL? Genetics 2004; 166:1303–1311
29. Gleason JM, Nuzhdin SV, Ritchie MG: Quantitative trait loci affecting a courtship signal in *Drosophila melanogaster*. Heredity 2002; 89:1–6
30. Toma DP, White KP, Hirsch J, Greenspan RJ: Identification of genes involved in *Drosophila melanogaster* geotaxis, a complex behavioral trait. Nat Genet 2002; 31:349–353
31. Maxson SC, Canastar A: Conceptual and methodological issues in the genetics of mouse agonistic behavior. Horm Behav 2003; 44:258–262
32. Anholt RR, Dilda CL, Chang S, Fanara JJ, Kulkarni NH, Ganguly I, Rollmann SM, Kamdar KP, Mackay TF: The genetic architecture of odor-guided behavior in Drosophila: epistasis and the transcriptome. Nat Genet 2003; 35:180–184
33. Dubnau J, Chiang AS, Grady L, Barditch J, Gossweiler S, McNeil J, Smith P, Buldoc F, Scott R, Certa U, Broger C, Tully T: The staufen/pumilio pathway is involved in *Drosophila* long-term memory. Curr Biol 2003; 13:286–296
34. Segalat L: Genetic analysis of behavior in the nematode Caenorhabditis, in Neurobehaviroal Genetics: Methods and Applications. Edited by Jones BC, Mormede P. New York, CRC Press, 1999, pp 373–381
35. Kendler KS, Prescott CA, Myers J, Neale MC: The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Arch Gen Psychiatry 2003; 60:929–937
36. Kendler KS, Jacobson KC, Prescott CA, Neale MC: Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. Am J Psychiatry 2003; 160: 687–695
37. Slutske WS, Eisen S, True WR, Lyons MJ, Goldberg J, Tsuang M: Common genetic vulnerability for pathological gambling and alcohol dependence in men. Arch Gen Psychiatry 2000; 57: 666–673
38. Scherer JF, True WR, Xian H, Lyons MJ, Eisen SA, Goldberg J, Lin N, Tsuang MT: Evidence for genetic influences common and specific to symptoms of generalized anxiety and panic. J Affect Disord 2000; 57:25–35
39. Berrettini W: Review of bipolar molecular linkage and association studies. Curr Psychiatry Rep 2002; 4:124–129
40. Owen MJ, Williams NM, O'Donovan MC: The molecular genetics of schizophrenia: new findings promise new insights. Mol Psychiatry 2004; 9:14–27
41. Ueno S: Genetic polymorphisms of serotonin and dopamine transporters in mental disorders. J Med Invest 2003; 50:25–31
42. Noble EP: D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. Am J Med Genet 2003; 116B:103–125
43. Greenspan R: A kinder, gentler genetic analysis of behavior: dissection gives way to modulation. Curr Opin Neurobiol 1997; 7:805–811
44. Sokolowski MB: Drosophila: genetics meets behaviour. Nat Rev Genet 2001; 2:879–890
45. Roff DA: The evolution of genetic correlations: an analysis of patterns. Evolution 1996; 50:1392–1403
46. Murphey R, Hall C: Some correlates of negative geotaxis in *Drosophila melanogaster*. Anim Behav 1969; 17:181–185
47. Pyle DW: Correlated responses to selection for a behavioral trait in *Drosophila melanogaster*. Behav Genet 1978; 8:333–340
48. Lofdahl K, Hu D, Ehrman L, Hirsh J, Skoog L: Incipient reproduction isolation and evolution in laboratory *Drosophila melanogaster* selected for geotaxis. Anim Behav 1992; 44:783–786
49. Manning A: The effects of artificial selection for mating speed in *Drosophila melanogaster*. Anim Behav 1961; 9:82–92
50. Manning A: Selection for mating speed in *Drosophila melanogaster* based on the behaviour of one sex. Anim Behav 1963; 11:116–120
51. McDonald J, Crossley S: Behavioural analysis of lines selected for wing vibration in *Drosophila melanogaster*. Anim Behav 1982; 30:802–810
52. Tully T, Zawistowski S, Hirsch J: Behavior-genetic analysis of phormia regina, III: a phenotypic correlation between the central excitatory state (CES) and conditioning remains in replicated F2 generations of hybrid crosses. Behav Genet 1982; 12: 181–191
53. McGuire TR, Tully T: Food-search behavior and its relation to the central excitatory state in the genetic analysis of the blow fly phormia regina. J Comp Psychol 1986; 100:52–58
54. de Bono M, Bargmann C: Natural variation in a neuropeptide Y receptor homolog modifies social behavior and food response in C elegans. Cell 1998; 94:679–689
55. de Bono M: Molecular approaches to aggregation behavior and social attachment. J Neurobiol 2003; 54:78–92
56. Davies AG, Bettinger JC, Thiele TR, Judy ME, McIntire SL: Natural variation in the npr-1 gene modifies ethanol responses of wild strains of C elegans. Neuron 2004; 42:731–743
57. Dudai Y, Jan YN, Byers D, Quinn WG, Benzer S: Dunce, a mutant of Drosophila deficient in learning. Proc Natl Acad Sci USA: 1976; 73:1684–1688
58. Byers D, Davis RL, Kiger JA Jr: Defect in cyclic AMP phosphodiesterase due to the dunce mutation of learning in *Drosophila melanogaster*. Nature 1981; 289:79–81
59. Levine JD, Casey CI, Kalderon DD, Jackson FR: Altered circadian pacemaker functions and cyclic AMP rhythms in the drosophila learning mutant dunce. Neuron 1994; 13:967–974
60. Bellen HJ, Kiger JA Jr: Sexual hyperactivity and reduced longevity of dunce females of *Drosophila melanogaster*. Genetics 1987; 115:153–160
61. Bellen HJ, Gregory BK, Olsson CL, Kiger JA Jr: Two Drosophila learning mutants, dunce and rutabaga, provide evidence of a maternal role for cAMP on embryogenesis. Dev Biol 1987; 121: 432–444
62. Zhong Y, Wu CF: Altered synaptic plasticity in Drosophila memory mutants with a defective cyclic AMP cascade. Science 1991; 251:198–201
63. Kendler KS, Kessler RC, Walters EE, MacLean C, Neale MC, Heath AC, Eaves LJ: Stressful life events, genetic liability, and onset of an episode of major depression in women. Am J Psychiatry 1995; 152:833–842
64. Eaves L, Silberg J, Erkanli A: Resolving multiple epigenetic pathways to adolescent depression. J Child Psychol Psychiatry 2003; 44:1006–1014
65. Tienari P, Wynne LC, Sorri A, Lahti I, Laksy K, Moring J, Naarala M, Nieminen P, Wahlberg KE: Genotype-environment interaction in schizophrenia-spectrum disorder: long-term follow-up study of Finnish adoptees. Br J Psychiatry 2004; 184:216–222
66. Cadoret RJ, Yates WR, Troughton E, Woodworth G, Stewart MA: Gene-environment interaction in genesis of aggressivity and conduct disorders. Arch Gen Psychiatry 1995; 52:916–924
67. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R: Role of genotype in the cycle of violence in maltreated children. Science 2002; 297:851–854
68. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R: Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003; 301:386–389

69. Gerlai R, Csanyi V: Genotype-environment interaction and the correlation structure of behavioral elements in paradise fish (Macropodus opercularis). Physiol Behav 1990; 47:343–356
70. Wahlsten D, Metten P, Phillips TJ, Boehm SL, Burkhart-Kasch S, Dorow J, Doerksen S, Downing C, Fogarty J, Rodd-Henricks K, Hen R, McKinnon CS, Merrill CM, Nolte C, Schalomon M, Schlumbohm JP, Sibert JR, Wenger CD, Dudek BC, Crabbe JC: Different data from different labs: lessons from studies of gene-environment interaction. J Neurobiol 2003; 54:283–311

70a. Valdar W, Solberg LC, Gauguier D, Cookson WO, Rawlins NJ, Mott R, Flint J: Genetic and environmental effects on complex traits in mice. Genetics 2006 Aug 3; [Epub ahead of print; doi: 10.1534/genetics.106.060004]

71. Mormede P: Genetic influences on the responses to psychosocial challenges in rats. Acta Physiol Scand Suppl 1997; 640:65–68
72. Henderson ND: Genetic influences on the behavior of mice can be obscured by laboratory rearing. J Comp Physiol Psychol 1970; 72:505–511
73. Plomin R, Lichtenstein P, Pedersen N, McClearn GE, Nesselroade JR: Genetic influences on life events during the last half of the life span. Psychol Aging 1990; 5:25–30
74. Foley DL, Neale MC, Kendler KS: A longitudinal study of stressful life events assessed at personal interview with an epidemiologic sample of adult twins: the basis of individual variation in event exposure. Psychol Med 1996; 26:1239–1252
75. Lyons MJ, Goldberg J, Eisen SA, True W, Tsuang MT, Meyer JM, Henderson WG: Do genes influence exposure to trauma? a twin study of combat. Am J Med Genet 1993; 48:22–27
76. Bergeman CS, Plomin R, Pedersen NL, McClearn GE, Nesselroade JR: Genetic and environmental influences on social support: the Swedish Adoption Twin Study of Aging (SATSA). J Gerontol 1990; 45:101–106
77. Kendler KS: Social support: a genetic-epidemiologic analysis. Am J Psychiatry 1997; 154:1398–1404
78. Hur YM, Bouchard TJ Jr: Genetic influences on perceptions of childhood family environment: a reared apart twin study. Child Dev 1995; 66:330–345
79. Kendler KS: Parenting: a genetic-epidemiologic perspective. Am J Psychiatry 1996; 153:11–20
80. O'Connor TG, Hetherington EM, Reiss D, Plomin R: A twin-sibling study of observed parent-adolescent interactions. Child Dev 1995; 66:812–829
81. Rose RJ: How do adolescents select their friends? a behavior-genetic perspective, in Paths to Successful Development: Personality in the Life Course. Edited by Pulkkinen L, Avshalom C. Cambridge, UK, Cambridge University Press, 2002, pp 108–128
82. Odling-Smee FJ, Laland KN, Feldman MW: Niche Construction: The Neglected Process in Evolution. Princeton, NJ, Princeton University Press, 2003
83. Lynch CB: Response to divergent selection for nesting behavior in *Mus musculus*. Genetics 1980; 96:757–765
84. Maestripieri D, Wallen K, Carroll KA: Infant abuse runs in families of group-living pigtail macaques. Child Abuse Negl 1997; 21:465–471
85. Hurnik JF, Bailey ED, Jerome FN: Divergent selection for retrieving behavior in mice. Can J Zool 1973; 51:21–26
86. Eisen EJ, Legates JE, Robison OW: Selection for 12-day litter weight in mice. Genetics 1970; 64:511–532
87. Roubertoux PL, Martin B, Le Roy I, Beau J, Marchaland C, Perez-Diaz F, Cohen-Salmon C, Carlier M: Vocalizations in newborn mice: genetic analysis. Behav Genet 1996; 26:427–437
88. Lucas BK, Ormandy CJ, Binart N, Bridges RS, Kelly PA: Null mutation of the prolactin receptor gene produces a defect in maternal behavior. Endocrinology 1998; 139:4102–4107
89. Young LJ, Wang Z, Insel TR: Neuroendocrine bases of monogamy. Trends Neurosci 1998; 21:71–75
90. Young LJ, Nilsen R, Waymire KG, MacGregor GR, Insel TR: Increased affiliative response to vasopressin in mice expressing the V1a receptor from a monogamous vole. Nature 1999; 400: 766–768
91. Osborne KA, Robichon A, Burgess E, Butland S, Shaw RA, Coulthard A, Pereira HS, Greenspan RJ, Sokolowski MB: Natural behavior polymorphism due to a cGMP-dependent protein kinase of Drosophila. Science 1997; 277:834–836
92. Dierick HA, Greenspan RJ: Molecular analysis of flies selected for aggressive behavior. Nat Genet 2006 Aug 13; [Epub ahead of print; doi: 10.1038/ng1864]
93. Jones JS, Probert R: Habitat selection maintains a deleterious allele in a heterogeneous environment. Nature 1980; 287: 632–633
94. Kendler KS, Gardner CO, Neale MC, Prescott CA: Genetic risk factors for major depression in men and women: similar or different heritabilities and same or partly distinct genes? Psychol Med 2001; 31:605–616
95. Kendler KS, Jacobson KC, Myers J, Prescott CA: Sex differences in genetic and environmental risk factors for irrational fears and phobias. Psychol Med 2002; 32:209–217
96. Prescott CA, Aggen SH, Kendler KS: Sex-specific genetic influences on the comorbidity of alcoholism and major depression in a population-based sample of US twins. Arch Gen Psychiatry 2000; 57:803–811
97. Petronis A, Macciardi F, Athanassiades A, Paterson AD, Verga M, Meltzer HY, Cola P, Buchanan JA, Van Tol HH, Kennedy JL: Association study between the dopamine D4 receptor gene and schizophrenia. Am J Med Genet 1995; 60:452–455
98. Zubenko GS, Maher B, Hughes HB III, Zubenko WN, Stiffler JS, Kaplan BB, Marazita ML: Genome-wide linkage survey for genetic loci that influence the development of depressive disorders in families with recurrent, early-onset, major depression. Am J Med Genet 2003; 123B:1–18
99. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ: A longitudinal twin study of personality and major depression in women. Arch Gen Psychiatry 1993; 50:853–862
100. Fullerton J, Cubin M, Tiwari H, Wang C, Bomhra A, Davidson S, Miller S, Fairburn C, Goodwin G, Neale MC, Fiddy S, Mott R, Allison DB, Flint J: Linkage analysis of extremely discordant and concordant sibling pairs identifies quantitative-trait loci that influence variation in the human personality trait neuroticism. Am J Hum Genet 2003; 72:879–890
101. Erlenmeyer-Kimling L, Hirsch J, Weiss JM: Studies in experimental behavior genetics, III: selection and hybridization analyses of individual differences in the sign of geotaxis. J Comp Physiol Psychol 1962; 55:722–731
102. McGuire TR, Hirsch J: Behavior-genetic analysis of Phormia regina: conditioning, reliable individual differences, and selection. Proc Natl Acad Sci USA 1977; 74:5193–5197
103. Vargo M, Hirsch J: Biometrical and chromosome analyses of lines of *Drosophila melanogaster* selected for central excitation. Heredity 1986; 56(part 1):19–24
104. Ranz JM, Castillo-Davis CI, Meiklejohn CD, Hartl DL: Sex-dependent gene expression and evolution of the Drosophila transcriptome. Science 2003; 300:1742–1745
105. Arbeitman MN, Fleming AA, Siegal ML, Null BH, Baker BS: A genomic analysis of Drosophila somatic sexual differentiation and its regulation. Development 2004; 131:2007–2021
106. Jin W, Riley RM, Wolfinger RD, White KP, Passador-Gurgel G, Gibson G: The contributions of sex, genotype and age to transcriptional variance in *Drosophila melanogaster*. Nat Genet 2001; 29:389–395
107. McClung C, Hirsh J: Stereotypic behavioral responses to free-base cocaine and the development of behavioral sensitization in Drosophila. Curr Biol 1998; 8:109–112

108. Yellman C, Tao H, He B, Hirsh J: Conserved and sexually dimorphic behavioral responses to biogenic amines in decapitated Drosophila. Proc Natl Acad Sci USA 1997; 94:4131–4136
109. Gill K, Desaulniers N, Desjardins P, Lake K: Alcohol preference in AXB/BXA recombinant inbred mice: gender differences and gender-specific quantitative trait loci. Mamm Genome 1998; 9: 929–935
110. Radcliffe RA, Bohl ML, Lowe MV, Cycowski CS, Wehner JM: Mapping of quantitative trait loci for hypnotic sensitivity to ethanol in crosses derived from the C57BL/6 and DBA/2 mouse strains. Alcohol Clin Exp Res 2000; 24:1335–1342
111. Buck KJ, Rademacher BS, Metten P, Crabbe JC: Mapping murine loci for physical dependence on ethanol. Psychopharmacology (Berl) 2002; 160:398–407
112. Yonehara K, Suzuki M, Nishihara M: Sex-related differences in gene expression in neonatal rat hypothalamus assessed by cDNA microarray analysis. Endocr J 2002; 49:131–137
113. Dewing P, Shi T, Horvath S, Vilain E: Sexually dimorphic gene expression in mouse brain precedes gonadal differentiation. Brain Res Mol Brain Res 2003; 118:82–90
114. Stonehouse AH, Adachi M, Walcott EC, Jones FS: Caffeine regulates neuronal expression of the dopamine 2 receptor gene. Mol Pharmacol 2003; 64:1463–1473
115. Cordell HJ: Epistasis: what it means, what it doesn't mean, and statistical methods to detect it in humans. Hum Mol Genet 2002; 11:2463–2468
116. Neale MC, Eaves LJ, Kendler KS: The power of the classical twin study to resolve variation in threshold traits. Behav Genet 1994; 24:239–258
117. Blangero J, Williams JT, Almasy L: Variance component methods for detecting complex trait loci. Adv Genet 2001; 42:151–181
118. Cloninger CR, Van Eerdewegh P, Goate A, Edenberg HJ, Blangero J, Hesselbrock V, Reich T, Nurnberger J Jr, Schuckit M, Porjesz B, Crowe R, Rice JP, Foroud T, Przybeck TR, Almasy L, Bucholz K, Wu W, Shears S, Carr K, Crose C, Willig C, Zhao J, Tischfield JA, Li TK, Conneally PM: Anxiety proneness linked to epistatic loci in genome scan of human personality traits. Am J Med Genet 1998; 81:313–317
119. Sullivan PF, Eaves LJ, Kendler KS, Neale MC: Genetic case-control association studies in neuropsychiatry. Arch Gen Psychiatry 2001; 58:1015–1024
120. Little J, Bradley L, Bray MS, Clyne M, Dorman J, Ellsworth DL, Hanson J, Khoury M, Lau J, O'Brien TR, Rothman N, Stroup D, Taioli E, Thomas D, Vainio H, Wacholder S, Weinberg C: Reporting, appraising, and integrating data on genotype prevalence and gene-disease associations. Am J Epidemiol 2002; 156:300–310
121. Risch N: Genetic linkage and complex diseases, with special reference to psychiatric disorders. Genet Epidemiol 1990; 7:3–16
122. Gerlai R: Gene-targeting studies of mammalian behavior: is it the mutation or the background genotype? Trends Neurosci 1996; 19:177–181
123. Holmes A, Lit Q, Murphy DL, Gold E, Crawley JN: Abnormal anxiety-related behavior in serotonin transporter null mutant mice: the influence of genetic background. Genes Brain Behav 2003; 2:365–380
124. Anholt RR, Lyman RF, Mackay TF: Effects of single P-element insertions on olfactory behavior in *Drosophila melanogaster.* Genetics 1996; 143:293–301
125. Fedorowicz GM, Fry JD, Anholt RRH, Mackay TFC: Epistatic interactions between smell-impaired loci in *Drosophila melanogaster.* Genetics 1998; 148:1885–1891
126. Livingstone MS, Sziber PP, Quinn WG: Loss of calcium/calmodulin responsiveness in adenylate cyclase of rutabaga, a Drosophila learning mutant. Cell 1984; 37:205–215
127. Feany MB: Rescue of the learning defect in dunce, a Drosophila learning mutant, by an allele of rutabaga, a second learning mutant. Proc Natl Acad Sci USA 1990; 87:2795–2799
128. Roberts SB, MacLean CJ, Neale MC, Eaves LJ, Kendler KS: Replication of linkage studies of complex traits: an examination of variation in location estimates. Am J Hum Genet 1999; 65:876–884
129. Kendler KS: Schizophrenia genetics and dysbindin: a corner turned? (editorial). Am J Psychiatry 2004;161:1533–1536
130. Mackay TF: The genetic architecture of quantitative traits: lessons from Drosophila. Curr Opin Genet Dev 2004; 14:253–257
131. Yalcin B, Willis-Owen SA, Fullerton J, Meesaq A, Deacon RM, Rawlins JN, Copley RR, Morris AP, Flint J, Mott R: Genetic dissection of a behavioral quantitative trait locus shows that Rgs2 modulates anxiety in mice. Nat Genet 2004; 36:1197–1202