CHAPTER 1

Behavioral Genetics

STEPHEN C. MAXSON

INTRODUCTION

Behavioral genetics is a science with dual origins and goals. The study of behavioral genetics that originated in psychology is primarily concerned with the causes of individual variation. The Behavior Genetics Association and its journal, *Behavior Genetics,* have this as their focus. The emphasis is mainly on the genetics of human behavior and mind. Nonhuman animal, mainly rodent, studies of genes and behavior are of interest for their contribution to human behavior genetics. Behavioral genetics that originated in biology is primarily concerned with genetics as a tool to study behavior. The International Behavioral and Neural Genetics Society and its journal, *Genes, Brain, and Behavior*, have this as their focus. Here the genetics of behavior and mind of a wide range of animals as well as humans are of interest in themselves and in relation to each other. Regardless, evolution is an essential context for both subfields of behavioral genetics.

Both subfields of behavioral genetics are well-established. The long history of behavior genetics and its many contributions to psychology and biology have been reviewed by Maxson (2007), Lohelin (2009), and Dewsbury (2009). The literature of both subfields of behavioral genetics is now so large that even multiauthor texts (e.g., Plomin, DeFries, McClearn, & McGuffin, 2008) or monographs with multiauthor articles (e.g., Jones & Mormede, 2007; Kim, 2009) do not cover the vast range of methods and findings across many species. Thus, it is impossible to do so in this short review. Rather, the coverage in this chapter must be selective. The topics to be considered derive from the seminal paper of Ginsburg (1958), *Genetics as a Tool in the Study of Behavior*. In this paper, he cogently argued that in the context of evolution, genetics is a way of defining natural units of behavior, of analyzing the underlying biological mechanisms of behavior, and of studying the effects of environmental and experiential variables on behavior. He illustrated each of these with findings from his research programs on mouse seizures and aggression and from canid reproduction and sociality. This paper was published 5 years after those on Watson and Crick's model of the structure of DNA and its implications for gene replication, mutation, and function. This was also many years before Sydney Brenner (1973) and Seymour Benzer (1971) made similar proposals for genetic studies of behavior respectively in *Caenorhabditis elegans* and in *Drosophila melanogaster*.

SUBJECTS

The main animal subjects for behavior genetics are roundworms (*C. elegans*), fruit flies, zebrafish, mice, rats, canids, primates, and humans. This review will focus on mice, other rodents, primates, and humans. The interested reader may want to consult these reviews, articles, or books on the genetics of behaviors in *C. elegans* (Jansen &

Segalat, 2007), fruit flies (Belay & Sokolowski, 2007; Bellen, Tong, & Isuda, 2010; Comas, Guillame, & Preat, 2007; Dickson, 2008; Vosshall, 2007), honeybees (Smith, Toth, Suarez, & Robinson, 2008), zebrafish (Norton & Bally-Cuif, 2010; Rinkwitz, Mourrain, & Becker, 2011), rats (Brush & Driscoll, 2002, Driscoll, Fernandez-Teruel, Corda, Giorgi, & Stelmer, 2009), canids (Scott & Fuller, 1965; Wayne & Ostrander, 2007; Parker, Shearin, & Ostrander, 2010), and primates (Lesch, 2003; Weiss & King, 2007). The interested readers may also want to consider a review of selective breeding and behavior studies mostly in fruit flies, mice, and rats (Greenspan, 2003), the chapter on other creatures in the text by Ehrman & Parsons (1981), and a review comparing genetic issues and findings for animal and human behaviors (Kendler & Greenspan, 2006).

GENOME PROJECTS

An individual's nuclear genome consists of the DNA found in all the chromosomes in the nucleus of its cells. There is one molecule of DNA for each chromosome. The goal of a genome project is to determine the sequence of the nucleotide bases—adenine, cytosine, guanine, or thymine (A, C, G, or T)—of the nuclear genome of one or more individuals of the species. After the entire sequence is known for a species, it is possible to estimate the number of protein-coding genes in its genome. Also, the amino acid sequence in each protein can be deduced from the coding nucleotide triplets in the gene's structural region. Other DNA sequences of a gene bind proteins known as *transcription factors.* These factors and sequences together are involved in controlling when and where a gene is transcribed as RNA (ribonucleic acid). A small fraction of the transcribed RNA is processed into a messenger RNA (mRNA), and the mRNA is then translated into the sequences of amino acids in its protein. Other transcribed RNA may regulate gene transcription or mRNA translation. There is also DNA in the mitochondria; this DNA codes amino-acid sequences of some of the proteins involved in energy metabolism. This DNA has been sequenced in many organisms.

The DNA sequence of the human genome was initially published in 2001. To date, the DNA sequence of the following animal species by common names have also been partially or wholly published: hydra, round worms (two species), sea urchin, sea hare, fruit fly (two species), flour beetle, honeybee, wasp, aphid, mosquitoes, zebrafish, stickleback fish, green puffer fish, Japanese puffer fish, frog (two species), chicken, zebra finch, duckbill platypus, opossum, mouse, rat, cat, dog, horse, sheep, cattle, pig, giant panda, marmoset, macaque monkey, chimpanzee, and orangutan (www.genomenewsnetwork.org/ resources/ sequenced_genomes/ genome_guide_p1.shtml). In progress are programs for some degree of DNA sequencing for 5,000 insect species (Robinson et al., 2011) and 10,000 vertebrate species (Hausler, O'Brien, & Ryder, 2009). The complete or partial DNA sequence of these species has facilitated or will facilitate the genetic analysis of behaviors in these species and a comparative genetics of behaviors across these species. A comparative analysis of genetics of behavior will eventually be firmly based on findings for the effects of homologous genes across species as considered by Robinson, Fernals, & Clayton (2008) for social behavior and by Maxson (2009) for aggression.

METHODS

There are essentially four approaches to finding and studying genes with effects on behavior. The first is based on linkage or association of naturally occurring genetic variants with behavior. The second is based on effects on behavior of induced genetic mutations. The third is based on effects on behavior of reducing or blocking the translation of a gene's mRNA into its protein. The fourth is based on behavioral correlations with transcription into mRNA of one or more genes.

Natural Genetic Variants and Behavior

There are two approaches to finding and studying effects of naturally occurring genetic variants on behavior. These two approaches can be used with both animals and humans.

The first maps quantitative trait loci (QTLs) with behavioral effects to regions of specific chromosomes. Within the QTL are one or more genes with effects on behavioral variation. This approach depends on well-spaced DNA markers across all the chromosomes, such as single nucleotide polymorphisms (SNPs). Once a replicable QTL is identified, the next step is to find the DNA variants of the gene or genes underlying the QTL. Some recent reviews on QTLs and behavior are: Cherny (2009), Molson (2007), MacKay, Stone, and Ayroles (2009), and Haworth and Plomin (2010). QTLs are considered further in the section on genetics and behavioral taxonomy.

The second correlates DNA sequence variants in regulatory or coding or noncoding regions of a gene with

behavior. This approach depends on knowing some, if not all, of the DNA sequence of the gene and identifying DNA sequence variants of the gene. Some recent reviews on this approach include: Caspi and Moffit (2006) for genotype by environment interactions, Epstein and Israel (2009) for human personality, and Rhee and Waldman (2009) for conduct and antisocial personality disorders. DNA variants of known genes are considered further in the section on Genetics and Behavioral Development.

Gene Mutations and Behavior

There are two approaches to induced mutations in single genes with large effects on behavior in animals but not humans.

In the first, chemical mutagens are used to cause DNA changes at random across the genome. Often the mutations are in single base pairs. They may be in regulatory or coding or noncoding regions of the gene. Mutations of a gene's coding region can cause the gene's protein to be nonfunctional, to decrease its function or increase its function. Some reviews on this approach for mice are Goldowitz et al. (2004), Godinho and Nolan (2006), van Boxtel and Cuppen (2011), and, for rats, van Boxtel and Cuppen (2010). This approach has the potential to identify all the genetic variants with effects on a behavior of a species.

In the second, the coding region of specific genes is targeted for a mutation that renders the gene's protein inactive. These are sometimes referred to as knockout mutations. A gold standard for confirming the effect of a gene mutation on behavior is to replace the mutated gene with a functional copy of it and to assess whether or not this rescues the behavioral effects of the knockout mutation. These functional replacements are sometimes referred to as transgenes. A combination of a knockout mutant and temporal or tissue specific activation of its transgene can be used to identify when and where a gene has its initial effects. For mice, this knockout approach is reviewed by Crawley (2007). For rats, a knockout approach is reviewed by Jacob, Lazar, Dwinell, Moreno, and Geurts (2010). Also, knockout approaches useable with many other animals are reviewed by Remy, Tesson, Menoret, Usal, Scharenberg, and Anegon (2010). Knockout mutants are considered further in the section Genetics and Biological Mechanisms of Behavior.

Translational Knockdowns and Behavior

The effect of a gene's protein on brain and behavior can also be assessed by attenuating or blocking the translation of its messenger RNA into its protein. There are two approaches for doing this.

The first approach involves antisense RNA. DNA has two strands with complementary base pairing. One strand is transcribed as sense mRNA. This mRNA is translated into the amino-acid sequence of the gene's protein. Transcripts from the other DNA strand are antisense mRNA. The base pair sequence of the antisense mRNA is complementary to the sense mRNA. If both DNA strands are transcribed, then the sense and antisense mRNA can hybridize into a double stranded DNA that cannot be translated. The sense strand of mRNA is usually the only transcript from a gene's DNA. However, transgenes with transcription of antisense mRNA can be inserted into genomes or brains of some animals and behavioral effects assessed. An application of this approach is considered further in the section on genetics and biological mechanisms of behavior.

The second approach for blocking translation is RNAi or interference RNA. RNAi are short sequences of RNA (about 22 bp). When combined with specific proteins, they can degrade a gene's mRNA or attenuate or block a gene's mRNA translation into its protein (Mattick, 2004; Sandy, Ventura, & Jacks, 2005). For mice, this approach is reviewed by Kuhn, Streif, and Wurst (2007) and Delic et al. (2008), and for rats, it is considered by Petit and Thiam (2010).

Gene Expression Correlates With Behavior

This approach correlates quantitative variation in mRNA transcription in brain or brain regions of one or many genes across variation in genotype or development or phenotype. mRNA levels are assessed postmortem. The level of more than one mRNA can be assessed with RNA microarrays (Johnson, Edwards, Shoemaker, & Schadt, 2005). RNA microarrays have been used to detect gene expression associated with psychopathologies in humans (Konradi, 2005), and gene expression differences between male and female brains of songbirds (Naurin, Hansson, Hasselquist, Kim, & Bensch, 2011). RNA microarrays and behavior are considered further in the section on genetics and biological mechanisms of behavior.

GENETICS AND BEHAVIORAL TAXONOMY

A genetic variant can have effects on multiple traits. Such multiple effects of a genetic variant are known as pleiotropy. For example, there are pleitropic effects in homozygotes of the sickle-cell variant of the hemoglobin

beta gene on mental function, heart failure, rheumatism, abdominal pain, and enlarged spleen. Such pleiotropic effects of genes are the fundamental basis for using genetics to identify natural units of behavior. This is exemplified for four complex behaviors: mouse aggression, mouse emotionality, mouse cognition, and human psychopathology.

Male Mouse Aggression

Five aspects of mouse aggression taxonomy will be considered. The first is unique and common genetic effects on offense and defense types of aggression. The second is unique and common genetic effects on two aspects of offense. The third is genetic correlations for measures of offense. The fourth is the genetic relationship of coping strategies and aggression. The fifth concerns the distinction between adaptive aggression and maladaptive violence.

Offense and Defense

Offense and defense aggression differ in motor patterns and in attack target (Maxson, 2009). Two studies have assessed the effect of the same gene on offense and defense. Male mice with functional and nonfunctional monoamine oxidase A (MAOA) differ in measures of offense but not defense (Chen et al., 2007) whereas male mice with functional and nonfunctional alpha calcium/calmodulin kinase II (alpha CamK II) differ in measures of both offense and defense (Chen, Rainnie, Greene, & Tonegawa, 1994). Also, overexpression of alpha CamK II in mouse forebrain increased offense but had no effect on defense (Hasegawa et al., 2009). These findings suggest that there are both unique and common behavioral domains for offense and defense aggression.

Two Types of Offense

Whether a genetic variant has an effect on offense in male mice depends on life history and test situation (Roubertoux, Le Roy, Mortaud, Perez-Diaz, & Tordjman, 1999; Roubertoux et al., 2005). Life history includes whether the subject male is housed alone or housed with a female prior to the aggression test (Maxson, 1992; Roubertoux et al., 1999). Being housed alone is often referred to as isolation. Test situation includes the type of test arena (Maxson, 1992; Roubertoux et al., 1999). Tests can occur in the subject's home cage. This is known as a resident-intruder test. In this test, the offense behaviors of the resident are scored. Tests can occur in an arena that is not the subject's home cage. This is known as a neutral cage test. In this test, offense of the subject is scored. These parameters were varied in two studies of the genetics of offense by Roubertoux et al. (1999, 2005).

In a first study, there were 11 inbred strains of mice, and there were five combinations of life history and test arena. Four of these were: (1) nonisolated and neutral cage, (2) isolated 1 day and neutral cage, (3) isolated 13 days and neutral cage, and (4) isolated 13 days and home cage. The behavioral index was the percent of males attacking in a strain. The rank order correlations between strains for any condition were always positive but always less than one. Furthermore, a principal component analysis identified two factors. The first weighted heavily the first two conditions, and the second weighted heavily on the second two conditions.

In the second study, QTLs were mapped in the F2 population descended from a cross of NZB and C57BL6 mice. There were two life history and test conditions. These were no isolation and a neutral cage arena versus isolation and home cage arena. There were four measures of offense. These were latency to tail rattle, tail rattle frequency, latency to attack, and attack frequency. Some but not all QTLs were the same for both life history and test conditions. Also, within a life history and test condition some but not all QTLs were the same for all measures of offense. For example, a QTL variant identified as the gene for steroid sulfatase had effects on latency to tail rattle, latency to attack, and frequency of attack, but not frequency of tail rattle for nonisolated, neutral cage, but not for the isolated, home cage test conditions.

Elsewhere I have suggested on the basis of the findings in these studies that there may be distinct biology underlying offense that is dependent on life history and test arena and a common biology underlying offense that is independent of life history and test arena (Maxson, 2009; Maxson & Canastar, 2007).

Measures of Offense

In genetic studies of mouse offense, composite or single scores are often used. Composite scores often reflect the latency, frequency, or duration of fighting. Single scores include the latency, frequency, or duration of one of the motor patterns of offense. The use of either type of measure assumes that they will detect all genes with effects on offense. For this to be valid, all composite and single scores must be fully correlated. But they aren't. For example, the number of chases and attacks are partially correlated across 11 inbred strains in a neutral cage test with no isolation (Roubertoux et al., 1999). Similar partial correlations among the 11 inbred strains were seen across

several behaviors: number of tail rattles, number of chases, number of attacks, and latency to attack. Also, for both a neutral cage test with no isolation and a resident-intruder test with isolation, some QTLs influenced one or more but not all of the following measures of offense: number of tail rattles, latency to tail rattle, number of attacks, and latency to attack (Roubertoux et al., 2005). Other QTLs acted on all of them. Thus, from a genetic perspective, these measures of offense do not index a unitary trait of offense.

Offense and Coping Strategies

Two lines of mice were selectively bred from wild mice for short and long attack latencies in a resident-intruder test (van Oortmerssen & Bakker, 1981). The lines are respectively known as SAL and LAL. The SAL and LAL lines differ in a consistent way for active avoidance, defensive burying, nest building, routine formation, cue dependence, conditioned immobility, and flexibility (Koolhaas, de Boer, Buwalda, & van Reenen, 2007; Veenema & Neumann, 2007; Koolhaas et al., 1999). It has been suggested that these consistent behavioral strain differences reflect an underlying difference in coping strategies. Coping strategies are ways of responding to environmental challenges. In this context, the SAL mice would be proactive copers that are not guided by environmental stimuli and have rigid routines, whereas the LAL mice would be reactive copers that are guided by environmental stimuli and have flexible repertoires. With regard to aggression, SAL mice would develop routines to control territory, leading them to be more likely to attack an intruder, whereas LAL mice would not develop such rigid routines to control territory, leading them to be less likely to attack an intruder. This hypothesis is based on behavioral differences between two strains. Such strain association may be accidental rather than genetic. This is especially of concern in selected strains where there were only two selected strains and where limitations on colony size inevitably leads to some degree of inbreeding. Regrettably, it has never been determined whether or not these behaviors are correlated in F2 populations of SAL and LAL mice and whether or not the same QTLs affect these behaviors as determined from F2 populations of SAL and LAL mice.

Yet there is partial support in mice and rats for the hypothesis that there is a genetic correlation between offense and coping strategies. As predicted by this hypothesis there is a negative correlation between attack latency and time spent burying a shock probe in an outbred population of wild derived rats (deBoer, Caramaschi, Natarajan, & Koolhaas, 2009). SAL mice show less defensive burying than LAL mice (Sluyter, Korte, & Van Oortmerssen, 1996). Also, as predicted by this hypothesis, mice selected for building large nests were more aggressive than mice selected for building small nests (Sluyter, Bult, Lynch, van Oortmerssen, & Koolhaas, 1995). SAL mice build larger nests than LAL mice. However, there is also evidence that offense and coping behavior are not perfectly correlated (Sluyter, Bult, Lynch, Meeter, & van Oortmerssen, 1997). Genes of the Y chromosome contribute to the attack latency and defensive burying but not to the difference in nest building between SAL and LAL mice (Sluyter et al., 1997; Sluyter, Korte, Van Baal, De Ruiter, & Van Oortmerssen, 1999).

Adaptive Aggression and Maladaptive Violence

Most aggression in animals is adaptive, and most genetic analyses in mice have been of adaptive aggression. In humans, some types of aggression have been labeled as maladaptive violence. This is usually considered as excessive aggression resulting in severe injuries or death to others. A recent attempt to distinguish adaptive aggression from maladaptive violence in animals was based on studies of three strains of mice selected for high levels of offense type aggression (Natarajan & Caramaschi, 2010; Natarajan, de Vries, Saaltink, de Boer, & Koolhaas, 2009). There are the SAI, TNA, and NC900 strains. Although the three strains were similar in high levels of offense against opponents, they differed qualitatively in dimensions of aggression. SAL and TA males were similar in structure and different in context. Structure refers to aggressive interactions with the opponent (presence or absence of ritualistic threat, pronounced aggressive escalation, post-conflict appeasement, and sensitivity to the opponent's submission cues). Context refers to effects of opponent by state (free-moving or anesthetized, sex, and home versus neutral territory) on aggressive behavior. With regard to structure, SAL mice were less likely to investigate opponents than TA or 900 mice. Also, TA and NC900 but not SAL mice displayed ritualistic and preescalatory behaviors, and attacks by TA and NC900, but not SAL mice, were inhibited by opponent's submissive behavior. With regard to context, SAL but not TA or NC900 mice attacked anesthetized males and freely moving females. On this basis, it was suggested that the SAL but not TA or NC900 mice show maladaptive violence similar to that seen in some humans.

The association of these structural and contextual aggressive traits has also been reported for WTG rats (de Boer et al., 2009; Natarajan & Caramaschi, 2010). This strengthens the possibility that these are correlated traits

for a dimension of adaptive aggression versus maladaptive violence. However, this hypothesis needs to be rigorously tested with factor analyses in an F2 of the SAL and TA or NC900 mice and QTL analyses for the SAL and TA or NC900 mice such as those used for offense in mice by Roubertoux et al. (2005), for emotionality in mice by Turri, Datta, DeFries, Henderson, and Flint (2001a) and for cognition in mice by Galsworthy et al. (2005).

Mouse Emotionality

In rodents, emotionality is often assessed by ambulation and defecation in an open field. An open field is a brightly lit, inescapable arena that initially is novel to the individual. Such novel situations are potentially threatening to rodents and decreases in ambulation and increases in defecation in the open field by rodents may be indicators of fear or anxiety. However, there has been much debate as to whether or not open field activity and ambulation index a unitary trait of fearful or anxious emotionality in mice and rats.

One approach to this issue has been genetic analyses of strains of mice selected for open-field activity. Two high-activity lines (H1 and H2), two low-activity lines (L1 and L2), and two control lines (C1 and C2) were bred from an F3 population derived from crosses of the BALBc and C57BL6 inbred strains of mice (DeFries, Gervais, & Thomas, 1978). In the open field, the C57BL6 strain is much more active than the BALB/c strain. After 30 generations of selection, the high lines were 3 times more active than the low lines in the open field. There was also a correlated response to selection with the high lines having low defecation and low lines having high defecation in the open field. QTL mapping studies have been done in F2 crosses of the H1 and L1 lines and H2 and L2 lines not only for open field activity and defecation, but also behavior in the elevated plus maze, elevated square maze, light-dark box, and mirror chamber (Turri et al., 2001a, b). Each of these behaviors has been proposed to index a unitary trait of emotionality.

In their first genetic analysis (Turri, Henderson, & Flint, 2001b), the QTLs on Chromosomes 1, 7, and X had opposite effects on open field activity and defecation in both the H1 by L1 and H2 by L2 crosses. There were also QTLS for open field activity on Chromosomes 4, 12, 15, and 18, and there were also a QTL on Chromosome 14 for open field defecation. For elevated plus maze, there were QTLs on Chromosomes 1, 15, and 18, and for light-dark box, there were QTLs on Chromosomes 1, 14, and 15. In the second genetic analysis (Turri et al., 2001a), QTLs on Chromosomes 1, 4, 15, and 18 had effects on at least one measure in the open field, elevated plus maze, elevated square maze, light-dark box, and mirror chamber tests. There were also QTLs on some but not all tests on Chromosomes 7, 8, 11, 12, 14, and X. For defecation, there were QTLs on Chromosomes 1 and X for every test and QTLs on Chromosomes 8, 12, and 14 for at least one test. These findings support in part the hypothesis that emotionality as assessed by these tests indexes a unitary behavioral dimension.

Rat and Mouse Learning and Cognition

Some of the earliest behavior genetic analyses were focused on rat learning of mazes. For example, Tryon (1929) selectively bred two lines of rats that differed in errors in a simple maze. The line with few errors was known as the maze-bright rats, whereas the line with much error was known as the maze-dull rats. Later, rats were selectively bred for avoidance learning (Brush, 2003; Driscoll et al., 2009). Also, there have been many studies of different types of learning in inbred strains of mice (Bovet, 1977). There is some evidence that in rodents, performance on one learning task is correlated with performance on other learning tasks, especially for complex "cognitive" tasks.

For example, learning in a T-maze, Morris water maze, a puzzle box, Hebb-Williams maze, object exploration, water plus-maze, and syringes was assessed in the CD-1 outbred stock of mice (Galsworthy et al., 2005). In this study, a common factor accounted for 36% of the variance in the test scores.

In another study, CD-1 outbred mice were assessed for six learning tasks (Lashley II maze, Morris water maze, spatial plus maze, passive avoidance, odor discrimination, fear conditioning, as well as tests of sensory-motor function and fitness, exploration, emotionality, and stress-reactivity (Matzel et al., 2006). Across tasks, the scores of individuals were correlated. A common factor also accounted for 32% of the variance across animals and tasks. This common factor was also involved in the variance across exploratory but not sensory motor behaviors, emotional responses, or stress-reactivity. It has been suggested that working memory capacity is the common factor correlating performance across these mouse learning tasks (Kolata et al., 2005).

There needs to be QTL studies of mouse cognition similar to those on aggression and emotionality to further assess the common dimensions of mouse learning and memory.

Human Psychopathology

Schizophrenia and manic depression are diagnostically distinct. Regardless, there is genetic evidence suggesting that they are etiologically related. First, there are the findings from family studies (Lichtenstein et al., 2009). On the one hand, relatives of probands with schizophrenia were at increased risk for manic depression. There were similar findings for both maternal and paternal half-siblings. On the other hand, relatives of probands with manic depression were at increased risk for schizophrenia. There were similar findings for both maternal and paternal half-siblings. Second, some genetic variants affect both the risk for schizophrenia and manic depression (O'Donovan, Craddock, & Owen, 2009; Williams et al., 2011). These include the genes for the zinc finger-binding protein 804A, calcium channel voltage dependent L-type alpha 1C subunit, transcription factor 4, neurogranin, MHC antigens, ankyrin 3, node of Ranvier, and polybrom-1. Other genetic variants are specific to each of these psychopathologies. Similar findings have also been reported for genetic overlap of schizophrenia with neurodevelopmental disorders such as autism spectrum disorders, learning disabilities, and attention-deficit/hyperactivity disorder (Owen, O'Donovan, Thapar, & Craddock, 2011).

Summary

Phenotypic and QTL correlations have been used to assess whether or not variation of conceptually related tests are due to one or more common factors. For aggression, emotionality, and cognition in mice and psychopathology in humans there is genetic evidence for both common and unique factors. There are two limitations to these approaches and to these findings. The first is that the identified common and unique factors are a function of the genetic variants included in a study. The second is that the phenotypic correlations and QTL correlates are due to pleiotropic effects of genes. These pleiotropic effects of genes may or may not cause correlated variation in phenotype by a common factor other than genotype.

GENETICS AND BIOLOGICAL MECHANISMS OF BEHAVIOR

Pedigree of Causes

There is a pedigree of causes tracing a gene's effect on behavior from DNA sequence to its transcription into RNA to its translation into protein to its molecular and cellular function and to its neural function. Two approaches are key to tracing the pedigree of causes for a gene from its DNA to behavior. The first identifies where and when a gene's DNA is transcribed into RNA and then processed into mRNA. This specifies the time(s) and place(s) of the initial steps in the pedigree of causes. The second determines whether or not more mutants and transgenics of a gene or translational knockdowns of a gene affect one or more behaviors. In these ways genetics can be used as a tool to investigate the biological mechanisms of behavior.

Mouse Olfaction

All mammals except the old-world primates, apes, and humans have two olfactory systems (Dulac & Wagner, 2006). The chemosensory neurons of these are in the main olfactory epithelium (MOE) and the vomeronasal organ (VNO). The chemosensory neurons of the MOE project to the main olfactory bulb (MOB) and of the VNO project to the accessory olfactory bulb (AOB). The neurons from the MOB project to many brain areas but primarily to cortical regions, whereas the neurons from the AOB project directly to the amygdala and other limbic areas. Both olfactory systems ultimately project to the same and to different hypothalamic areas.

The MOE and VNO also have distinct genetics (DuLac & Wagner, 2006). In each, a chemosensory neuron expresses a single chemo-receptor protein. For the mouse, there are about 1,035 genes coding for the olfactory receptor proteins (OR) of the MOE neurons, and there are about 300 genes coding for the vomeronasal type 1 and type 2 receptor proteins (V1R and V2R) for the VNO neurons. V1R sensory neurons respond with high specificity to low molecular weight organic molecules, and V2R sensory neurons respond with high specificity to peptides. Coexpressed with the V2Rs are M1 and M10 major histocompatibility complex molecules and beta2-microblobulin.

Homozygous null mutant mice for beta2-microglobin have a defect in V2R receptor localization in VNO chemosensory neurons (Loconto et al., 2003). Male mice mutant for this gene were nonaggressive in a resident-intruder test. The residents were isolated for 7 to 10 days before the aggression test. The intruder was a gonadectomized male with male urine swabbed on his back and anogential region. However, these mutant males can discriminate between males and females. The mutant and wild-types males mount females but do not mount males. Thus, it appears that the V2R receptors and MHC

molecules have some role in effects of pheromones on some behaviors.

There were similar behavioral effects for male mice homozygous for a deletion of a 600-kilobase genome region that contains 12 of the V1R receptor genes (Del Punta et al., 2002). In a resident-intruder test, lactating females homozygous for the deletion were less aggressive toward an intruder male than were lactating females without this deletion. The mutant females had longer latency to attack, lower attack duration, fewer tail rattles, fewer attacks, and fewer fights than wild-type females. However, mutant and wild-type females did not differ in infanticide. In contrast to females, there were no differences between mutant and wild-type males in a resident-intruder test of aggression, but there were differences between mutant and wild-type males in mounting males and females. More wild-type than mutant males mounted males on the first of three tests and mounted females on the last three of five tests. Wild-type and mutant males had essentially the same adult concentrations of plasma testosterone, indicating that the mutant did not act via adult testosterone concentrations. Also, both mutants and wild types could find a hidden cookie, indicating that theV1R mutant had no effect on the function of the MOE. Thus, it appears that the V1R receptors have a role in effects of pheromones on some behaviors.

The role of the VNO in effects of pheromones has also been further confirmed with a knockout mutation of *Trp2* (Stowers, Holy, Meister, Dulac, & Koentges, 2002). TRP2 is a cation channel that is expressed exclusively in the chemosensory neurons of the VNO. Homozygous null mutant male mice are not aggressive in a resident-intruder test, but they mount intact male intruders, gonadectomized male intruders with male urine swabbed on back and anogenital areas, gonadectomized male intruders with no male urine swabbed on them, and female intruders in estrus. Wild-type and mutant males had essentially the same adult levels of plasma testosterone, indicating that the mutant did not act via adult levels of testosterone. Also, homozygous null mutant female mice are not aggressive in a resident-intruder test (Hasen & Gammie, 2009; Kimchi, Xu, & Dulac, 2007; Stowers et al., 2002). The female mice were lactating and the intruders were male. The null mutant females also displayed mounting, pelvic thrusts, anogenital sniffing, and complex ultrasonic vocalizations toward both male and female mice. However, homozygous null mutant mice could find a hidden cookie, indicating that the *Trp2* mutant does not affect the function of the MOE. Behaviors of male and female mice with ablations of the VNO were essentially the same as male and female mice homozygous for this null mutant (Kimchi et al., 2007). The findings described in this paragraph and the previous two paragraphs are consistent with a role of the VNO in behavioral responses to pheromonal chemosignals.

It also appears that the MOE is also involved in behavioral responses to pheromonal chemosignals. CNGA2 (cyclic nucleotide-gated channel $\alpha 2$) is expressed exclusively in MOE neurons and is essential for odor-elicited responses in MOE neurons (Mandiyan, Coats, & Shah, 2005). In a resident-intruder test, homozygous null mutant males had lower frequency and duration of sniffing the opponent, chasing the opponent, and attacking the opponent than wild-type homozygotes. Also, homozygous null mutant males had lower frequency and duration of sniffing, mounting, and intromitting with an estrus female than did wild types. The behavioral deficits of the null mutant males resemble those of mice with olfactory bulbectomy. These findings are consistent with a role not only of the VNO but also the MOE in behavioral responses to pheromonal chemosignals.

Dulac & Wagner (2006) have proposed an interesting model of how input from the MOE and VNO influence gender discrimination, mating, and aggression in males. In this model, VNO cues identify the sender as male or female and stimulate aggression. MOE cues stimulate mating and inhibit aggression. The VNO cues that stimulate aggression also inhibit the inhibitory effects of MOE cues on aggression. Also in the model, the VNO cues identifying a male stimulate mounting and intromitting and the VNO cues identifying a female inhibit mounting and intromitting.

Rodent Social Recognition

Chemosignals that act on MOE and/or VNO have a role in social recognition in rodents. Social recognition refers to the ability of animals to identify and recognize other members of the same species, and has a role in affiliation, aggression, mating, pair bonding, parenting, social learning, and social anxiety.

Two approaches have been used to assess this ability in rodents. One of these is a habituation paradigm. First, there are a series of habituation tests with repeated presentation of the same individual to the subject. Across habituation trials, the time spent investigating the same individual decreases. At the end of the habituation tests, the subject is presented with a novel individual. If the time spent investigating the novel individual increases (dishabituation), this is taken as evidence that that subject is

familiar with the habituated individual and can tell it apart from others. The second approach is a social discrimination paradigm. The subject is presented with one individual or a pair of individuals on one or more trials. It is then presented with a pair of individuals, one familiar and one novel. If the subject investigates the novel individual more than the familiar one, this is taken as evidence that the subject recognizes the familiar individual.

Gene Micronet

A four-gene micronet has been proposed to be involved in performance on these tests of social recognition (Choleris, Clipperton-Allen, Phan, & Kavaliers, 2009; Choleris, Kavaliers, & Pfaff, 2004). The genes are those for the α estrogen receptor (ER-α) and oxytocin receptor (OTR) expressed in neurons of the medial amygdala, and those for the β estrogen receptor (ER-β) and oxytocin (OT) expressed in hypothalamic paraventricular nucleus (PVN). Neurons from the PVN project to the medial amygdala. Homozygous null knockout mutants of the ER-α, ER-β, OT, and OTR show habituation to repeated exposure to a conspecific, but do not show dishabituation to a novel conspecific (Choleris et al., 2003; Ferguson et al., 2000). On the basis of these and gene expression data, it was concluded that the estrogen/receptor complex is required for the synthesis of OT in the PVN and of the OTR in the medial amygdala, and that OT input from the PVN to OTR in the medial amygdala is required for social recognition as measured in habituation/dishabituation tests.

A slightly different pattern is seen in social discrimination paradigms. Homozygous null knockout mutants of the ER-α gene and OT gene fail to show social discrimination, and of the ER-β gene show reduced social discrimination (Choleris et al., 2006). It was suggested from these data that the ER-α gene is necessary for social discrimination via its effect on oxytocin receptor synthesis in the medial amygdala and that the ER-β gene has modulatory roles in social discrimination by upregulating existing baseline levels of OT in the PVN.

In addition, an OTR knockout expressed in forebrain after postnatal day 21 did not show a failure in social recognition in the habituation/dishabituation test (Lee, Cladwell, MacBeth, & Young, 2008). The OTR KO had normal levels of OTR in the olfactory bulb, olfactory nucleus, medial amygdala, and neocortex, and reduced levels of OTR in the lateral septum, ventral palladium, and hippocampus. These data are consistent with the previous studies showing that social recognition depends on OT acting on OTR in the medial amygdala. Two additional experimental studies are also consistent with this neural basis for social recognition in these tests.

In the first study, OT injected into the medial amygdala of OT KO mice before but not after the initial exposure to a stimulus mouse restored social recognition (Ferguson. Aldaq, Insel, & Young, 2001). In this test males are presented with an overiectomized female for 5 minutes. Thirty minutes later, wild-type males investigate the same female, doing so less on the second exposure. OT KO males investigate the same female on the second exposure just as much as on the first exposure. If OT KO males are injected with OT into the medial amygdala just before the first exposure, then they behave like wild types on the second exposure to the female. There was no effect on social recognition of OT KO mice when the OT was injected into the olfactory bulb before the initial exposure to the stimulus mouse. When an OTR antagonist was injected into the medial amygdala of wild-type mice before but not after the initial exposure to a stimulus mouse, they did not show social recognition, just as the OTKO mice did not show social recognition.

In the second study, an shRNA of ER-α encoded in an AAV viral vector was injected into the medial amygdala (Spiteri et al., 2010). This attenuated translation of the ER-α mRNA in the medial amygdala and thereby decreased the level of ER-α in the medial amygdala. Control mice were injected with just the AAV viral vector. This did not affect the level of ER-α in the medial amygdala. In a habituation/dishabituation test, the translations knockdown, but not the control mice, failed to show social recognition with juvenile stimulus mice. Injections of the shRNA of ER-α into the ventromedial nucleus of the hypothalamus educed translation of ER-α mRNA in this area but had no reduced effect on social recognition.

Individual Chemosignals and Social Recognition

It is likely that odors and pheromones are the stimuli for social recognition in rodents and many other mammalian groups, and that genetic variants are the basis of some if not all social recognition chemosignals. On the one hand, the VNO has direct input to the medial amygdala, and the MOE has indirect input to it. On the other hand, genetic variants of the major histocompatability complex (MHC) and of the Y chromosome can be discriminated in mouse urine (Monahan, Yamazaki, Beauchamp, & Maxson, 1993; Yamazaki, Beauchamp, Bard, Thomas, & Boyse, 1982). In mice, there are also the highly polygenic and highly polymorphic major urinary proteins that may be individual recognition chemosignals (Brennan & Kendrick, 2006).

In mice and humans, the MOE, but not VNO, mediates effects of the MHC chemosignals. Mice with lesions of the VNO can still discriminate MHC genetic variants (Wysocki, Yamazaki, Curran, Wysocki, & Beauchamp, 2004). Although humans do not have a functional VNO, they can still discriminate mouse MHC variants (Gilbert, Yamazaki, Beauchamp, & Thomas, 1986). In contrast, the VNO, but not the MOE, mediates the effects of MUP chemosignals (Chamero et al., 2007).

Some studies suggest that MUP rather than MHC chemosignals are the basis of social recognition (Cheetham et al., 2007). Female mice prefer male mice that have countermarked another male's scent mark. In the first scent preference test, a female was presented with mark and countermark of brothers from an outbred strain that either had the same or different MHC type. When males differed in MHC type and when the males were identical in MHC type, the females had the same preference for the countermark owner. In the second scent test, a female was presented with a mark and countermark from brothers that had the same or different MUP genotype. When the males differed in MUP genotype, the females preferred the countermarking male. It appears that in this test individuals are recognized by MUP genotype and not by MHC genotype. Whether or not this is the chemosensory basis of social recognition in habituation/dishabituation tests or social discrimination tests remains to be directly determined.

However, there is indirect evidence that genotype may not be the basis of social recognition in the previously described studies involving the social discrimination test and knockouts. In a study by MacBeth and colleagues social discrimination was assessed in wild-type, OT knockout, and OTR knockout mice (MacBeth, Lee, Edds, & Young, 2009). The novel and familiar mice were either of the same inbred strain or different inbred strains and therefore respectively either genetically identical or genetically different. The inbred strains were BALB/c and C57BL/6. OT and OTR knockouts could not discriminate between novel and familiar mice of the same strain as previously reported, but they could discriminate between novel and familiar mice of different strains. Novel and familiar mice within an inbred strain are genetically identical and their social discrimination must be by environmentally based olfactory cues. Thus, it may be that the four-gene micronet previously described is essential for social recognition based on environmental but not genetic olfactory cues. In those studies, familiar and novel mice were of the same strain.

Mouse Offense

Genetic Variants

Over 80 genes have been shown to affect male offense in a resident-intruder test with the resident isolated or housed with a female, and there is at least one gene that affects offense on each mouse chromosome except for 13, 14, and 16 (Maxson, 2009). The primary biological effects of these genes are on urinary chemosignals, olfactory systems, hormonal systems (androgen receptor, aromatase, α and β estrogen receptors, corticotrophin releasing hormone receptor), neurotransmitter systems (acetylcholine, adenosine, argenine-vasopressin, cannabinoids, dopamine, enkephalin, GABA, glutamate, histamine, nitric oxide, norepinepherine, neuropeptide Y, oxytocin, serotonin, and substance P), second messenger systems, neurotrophins, neural development, and neural structures.

Six of these genes act on the serotonin system (Cases et al., 1995; Hendriks et al., 2003; Holmes, Murphy, & Crawley, 2002; Kulikov, Osipova, Naumenko, & Popova, 2005; Saudou et al., 1994; Young et al., 2008; Zhuang et al., 1999). (1) PET-1 acts on the development of serotonergic neurons. Most serotonin neurons fail to develop in mice with the knockout for the PET-1 gene. These male mice show an increase in offense. (2) GTF2IRD1 is a transcription factor. Knockout mice for its gene have elevated levels of 5HIAA in frontal cortex, parietal cortex, and amygdala. These male mice show a decrease in offense. (3) TPH2 is the enzyme in serotonin cells that catalyzes the conversion of tryptophan to 5-hydroxytryptophan and it is the rate-limiting step in the synthesis of serotonin. TPH2 activity is higher in midbrain of mice homozygous for the 1473C allele than mice homozygous for the 1473G allele. Mice homozygous for the 1473C allele have more offensive attacks. (4) 5HT1AR and 5HT1BR are 2 of the 13 serotonin receptors. Male mice homozygous for a knockout of the 5HT1BR have increased offense, whereas male mice homozygous for a knockout 5HT1AR have decreased offense. (5) MAOA is a mitochondrial enzyme that degrades biogenic amines including serotonin, dopamine, and norepinepherine. It is found in the presynaptic terminals where it degrades the transmitter taken back up into the presynaptic neuron. Male mice with a knockout of MAOA have increased offense. (6) 5HTT is found in the presynaptic terminal of serotonergic neuron, where it acts to take up serotonin from the synaptic space back into the presynaptic serotonergic neuron. Mice homozygous and heterozygous for

a 5HTT knockout have reduced offense. The remainder of this section will focus on determining the pedigree of causes for the effect of the MAOA knockout on male offense.

There are two null mutations of *Maoa* in mice. The first mutation occurred as the consequence of the insertion of a transgene in exon III of the *Maoa* gene in C3H/HeJ mice (Cases et al., 1995). This insertion results in a hybrid MAOA protein with no enzymatic activity. In a 10-minute resident intruder test, the latency to attack was shorter in the null mutant than in wild types for both resident males that had been isolated or that had been paired with a female. The second mutation occurred as a result of a single base pair change in the exon VIII of the *Maoa* gene in 129/SvEvTac mice (Scott, Bortolato, Chen, & Shih, 2008). This mutation truncates translation with the consequence that the MAOA protein had no enzymatic activity. In a 5-minute resident intruder test with 129 intruders, the *Maoa* mutant males had shorter latency to attack, more tail rattles, and more fight bouts than wild-type males. It is worth noting that two independent null mutations of the same gene had the same effects on offense. However, the latency to attack, attack frequency, and the percentage of mice attacking for the null mutant depends on the genotype of the intruder (Vishnivetskaya, Skrinskay, Seif, & Popova, 2007).

A human transgene for MAOA was inserted into the genome of knockout null mutants (Chen et al., 2007). The transgenes were expressed postnatally, but not prenatally, and the transgenes were expressed in forebrain and not in hindbrain or cerebellum. Significant MAOA activity was detected in the frontal cortex, hippocampus, and striatum, but the MAOA activity was only 2 to 5% of that in wild-type mice. This postnatal expression of transgenic MAOA in the forebrain rescues the effect of MAOA knockout on offense. It may be concluded from this that the increase in aggression seen in the MAOA knockout is due to absence of MAOA postnatally in the forebrain.

The absence of MAOA activity in biogenic amine neurons leads initially to an increase of the biogenic amine in the neurons presynaptic terminal and eventually in the synaptic space. This can be seen in whole brain and in regional increases in the biogenic amines. In the first study, the levels of dopamine, norepinepherine, and serotonin of knockout males were higher in whole brain at postnatal days 1 to 90 (Cases et al., 1995). In the second study, the levels of serotonin in knockout males were higher in frontal cortex, striatum, and hippocampus, whereas the levels of norepinepherine in knockout males were higher in frontal cortex and striatum, but not hippocampus. Levels of dopamine in knockout males were higher in striatum, but not in frontal cortex or hippocampus (Chen et al., 2007). The insertion of the human transgene into the knockout reduced the level of the biogenic amine in the relevant forebrain. Thus postnatal elevation of one or more of the biogenic amines in the forebrain is the initial cause of the increase in offense in the null mutants and postnatal decrease of one or more of these biogenic amines in the forebrain is the cause of the decrease in offense of the rescue transgenics. Knockouts for the respective synaptic uptake transporters provide evidence for the role of one or more of their biogenic amines in the effects of the MAOA knockout on offense.

A knockout of the serotonin transporter gene not only elevates brain levels of serotonin but also reduces offense (Holmes et al., 2002). In a resident-intruder test, the serotonin knockout mice had longer latency to attack on the second but not the first test, and fewer attacks on both the first and second tests. The residents were isolated, the intruders were DBA2 males, and the tests lasted for 15 minutes. Similarly, a null mutant of the serotonin transporter in rats elevates brain serotonin and decreases offense (Homberg et al., 2007). The residents had lower latency to attack over four tests. These tests were stopped after the intruder was attacked. A fifth test was allowed to go for 10 minutes after the first attack. On the fifth test, the null mutant had a lower percentage of time displaying offense behavior than the wild types. The residents were pair-housed with a female prior to the aggression test.

Because both the MAOA knockout mouse and 5HTT knockouts in mice and rats had elevated brain levels of serotonin but differed in effect on offense, the elevated levels of brain serotonin in the MAOA null mutant cannot be the cause of its increased offense behaviors. Similarly, because both the MAOA and 5HTT knockout mutants in mice had disrupted barrel fields in somatosensory cortex but differed in offense, the disrupted barrel fields in the somatosensory cortex in MAOA null mutants cannot be the cause of its increased offense behaviors (Murphy et al., 2003). However, there is evidence that disrupted barrel fields of the sensory cortex in both MAOA and 5HTT null mutants is due to the elevated levels of brain serotonin. Barrel fields of the sensory cortex are restored in mice homozygous for double MAOA and 5HT1B null mutants and in mice homozygous for MAOA, 5HTT, and 5HT1B triple null mutants. Mice homozygous for the

double MAOA and 5HTT null mutants have disrupted barrel fields of the somatosensory cortex.

A knockout of the norepinephrine transporter has elevated brain levels of norepinephrine and may have increased offense behavior (Haller et al., 2002). However, the knockout and wild-type mice were intruders rather than residents in resident-intruder tests. In this test, the intruder usually shows defense rather than offense behaviors. When attacked by the resident, the norepinephrine transporter knockout had more attacks than wild types on the first of 10 encounters. The two genotypes did not differ in defensive upright posture on any encounter, suggesting that the observed attacks were offense behaviors. Thus it is possible but not proven that in MAOA knockout mice, the increase in brain levels of norepinephrine is casual to the increased offense behaviors in this null mutant. Mice homozygous for the knockout of dopamine β-hydroxylase have a deficit in norepinephrine and have no offense behavior in a resident intruder test (Marino, Bourdelat-Parks, Cameron Liles, & Weinshenker, 2005). Dopamine β-hydroxylase converts dopamine to norepinephrine.

Knockout mice lacking the dopamine transporter had elevated brain levels of dopamine and increased offense behaviors in both resident-intruder and neutral cage tests (Rodriguez et al., 2004). Both threat postures and attacks were higher in the null mutant than in the wild types. Intruders were C3H/He males, and test duration was 5 minutes. However, although a knockout of COMT increases dopamine in the frontal cortex of mutant homozygotes, it does not increase offense behaviors in mice homozygous for the knockout (Gogos et al., 1998). The findings with these knockouts and the MAOA knockout imply that the increase in offense behavior of the MAOA knockout may be due to the increase in dopamine in the striatum but not frontal cortex. Furthermore, the MAOA knockout upregulates the A_{2A} receptors in the basal ganglia, whereas the 5HTT knockout downregulates A_{2A} receptors in the basal ganglia (Mossner et al., 2000). Thus, the MAOA and 5HTT knockouts not only have opposite effects on offense but also opposite effects on levels of A_{2A} receptors in the basal ganglia. Since mice homozygous for a knockout of the A_{2A} receptor gene have increased offense behaviors in a resident-intruder test (Ledent et al., 1997), it is uncertain as to whether or not the up regulation of the A_{2A} receptors in the basal ganglia mediates the effect of the MAOA knockout on offense. The knockout A_{2A} mice have shorter attack latencies and more tail rattles and attacks than wild-type mice. In this case, the residents were isolated, the intruders were CD1 males, and the test duration was 10 minutes.

This section has reviewed how the pedigree of causes for effects of a gene's mutant on behavior can be traced by comparing and contrasting its effects with those for mutants of other genes.

Gene Expression

Gene expression profiles are another approach to identifying genes with effects on behavior and can be an initial step in tracing the pedigree of causes. Gene mutant methods identify individual genes with effects on a behavior. In contrast, gene expression profiles can find many genes with effects on a behavior. Here, two gene expression profile studies on maternal aggression are described. In the resident-intruder test, lactating female mice will attack male intruders (Gammie et al., 2007). On postpartum day 5, the duration of attacks is higher in lactating than in nonlactating females.

In one study, gene expression in the hypothalamus was compared for lactating and virgin females (Gammie et al., 2005). A DNA microarray representing 1904 genes was used and mRNA was extracted from the hypothalamus, preoptic region, and nucleus accumbens of ICR mice. Gene transcription levels were significantly different for 92 genes. Among these, mRNA levels were higher in lactating than virgin females for neuropeptide Y, neuropetide Y receptor, proenkaphalin, and pololike kinase and were lower in lactating than virgin females in POMC and endothelial receptor type B. This study illustrates the detection of gene expression differences for behavioral state (i.e., lactating versus nonlactating females).

In another study, gene expression in hypothalamus and preoptic area was compared for mice from a line selected for high maternal aggression (S) and a control line selected for neither high nor low maternal aggression (C) (Gammie et al., 2007). A DNA microarray representing over 40,000 genes was used and mRNA was extracted from the hypothalamus and preoptic area of females from the S and C lines. Gene transcription levels were significantly different for 200 genes. Among these, the S line had higher mRNA levels for neuronal nitric oxide synthase, K+ channel subunit Kcna1, corticotrophin-releasing factor-binding protein, GABA A receptor subunit 1A, adenosine A1 receptor, Fos, and Erg-1. Conversely, the S line had lower mRNA levels for neurotensin and neuropeptide Y receptor Y2. This study illustrates the detection of gene expression differences for populations differing in genotype.

Both studies illustrate how gene expression studies of populations differing in either phenotype or genotype can detect a large number of candidate genes for a behavior.

These candidate genes can then be assessed with studies of their knockouts on behavior.

Summary

This section has demonstrated how gene expression, gene knockouts, transgenics, and translational knockdowns can be used to study the biological mechanisms of olfaction, social recognition, and aggression in mice. The approaches described in this section are also being applied to other behaviors, including: nocioception (Mogil, Yu, & Basbaum 2000), circadian rhythms (Bell-Pedersen et al., 2005), sleep (Cirelli, 2009), feeding (Bell, Walley, & Froguel, 2005), mating (Jazin & Cahil, 2010; Pfaff, Waters, Khan, Zhang, & Numan, 2011), emotionality (Gorden & Hen, 2004), learning and memory (Lee & Silva, 2009), and drug/alcohol effects (Hyman, Malenka, & Nestler, 2006). There are several methodological concerns for both the knockout and the gene expression approaches.

For knockout studies, these are:

- Differences between knockouts with knockout parents and wild types with wild-type parents may be due to maternal effects. To avoid maternal effects, the mother of the two genotypes must be the same, and the offspring should be the result of the mating of a heterozygous female to a heterozygous male.
- Some knockout strain pairs are coisogenic, differing only in the normal and mutant alleles of a single gene, but others are only congenic, differing not only in the mutant and normal alleles of genes of interest, but also in alleles of genes linked to it. For congenic strains, any differences may be due to the genes linked to the knockout rather than due to the knockout itself, as discussed by Gerlai (1996). Rescue experiments with the transgenic genes are essential to differentiate between effects of the knockout and genes linked to it.
- Often the knockout is made in one inbred strain, such as one of the 129 inbred strains, and then transferred to another strain. Sometimes the effect of a knockout seen in one strain background is not detected in another. For example, the effect of the knockout for the NOS-l (nitric oxide synthase-I) gene, which increases attacks, is lost after many generations of backcrossing to C57BL6 inbred strain of mouse (LeRoy et al., 2000).
- For knockouts, the mutant gene is present from the time of conception. Thus, it is not possible to tell when or where in the mouse the gene was expressed with consequent behavioral effect. Tissue and temporal specific transgenics or knockouts should be used to determine when and where a knockout acts.

For microarray gene expression studies, limitations are:

- The microchip DNA arrays will not detect genes with low levels of mRNA. It is currently limited to detecting genes expressed at a relative abundance of 1/100,000 mRNAs.
- There may be false positives with this technique. For this reason, findings on gene expression should be confirmed with other techniques for detecting mRNAs such Northern blots, RT-PCR (revere transcription polymerase chain reaction), or in situ hybridization.

Genotype by Genotype Interactions

The effect of a single gene variant on biology and behavior can often depend on the other genetic variants present in the individual. Two examples of this are described in this section. First, there is the interaction of the Y chromosome and autosomes with effects on aggression. These may be due to differential regulation by SRY of tyrosine hydroxylase or MAOA or β-endorphin gene expression. Second, there are interactions of variants of the serotonin transporter gene, of the DRD4 dopamine receptor gene, and of the COMT gene for human personality.

Mouse Aggression

There are two parts to the Y chromosome of all eutherian mammals, including mice. One part of the Y chromosome is male-specific. It is passed strictly from father to son. The other part pairs with and recombines with a homologous part of the X chromosome. It is not passed strictly from father to son.

It was first shown that the male-specific part of the DBA1 and C57BL10 Y chromosomes differed in effects on several measures of offense and that the differential effect of this pair of Y chromosomes depends on one or more genes on the autosomes. Across several measures of offense, the DBA1 males are more aggressive than C57BL10 males and F1 males with the DBA1 Y chromosome are more aggressive than F1 males with the C57BL10 Y chromosome (Selmanoff, Maxson, & Ginsburg, 1976). Males were isolated from weaning until testing, and the test area was a neutral cage. These findings were confirmed with a tetrad of Y chromosome congenics. Y congenic strains are identical in mitochondria, maternal environments, autosomes, X chromosomes, and recombining parts of the Y chromosome, but differ in nonrecombining parts of the Y chromosome. On a DBA1 background,

males with the DBA1 Y chromosome are more aggressive than those with the C57BL10 Y chromosome (Maxson, Didier-Erickson, & Ogawa, 1989), whereas on a C57BL10 background, males with the DBA1 Y chromosome and males with the C57BL10 Y chromosome are equally pacific (Maxson, Ginsburg, & Trattner, 1979).

It has been proposed that this genotype-by-genotype interaction involves the *Sry* gene on the Y chromosome (Maxson, 1996). *Sry* codes for the SRY transcription factor. SRY is necessary for the primordial gonad to differentiate as a testis. *Sry* is also transcribed in mouse, rat, and human brains (Dewing et al., 2006; Lahr et al., 1995; Mayer, Mosler, Just, Pilgrim, & Reisert, 2000). In mouse brain, it is transcribed in cortex, medial mammilary bodies, other areas of the hypothalamus, and the midbrain (notably substantia nigra and ventral tegmentum). In cell cultures, SRY has been shown to regulate the expression of genes for tyrosine hydroxylase (Milsted et al., 2004) and MAOA (Wu, Chen, Li, Lau, & Shih, 2009). Also, in rats, *Sry* transcript is found in the cell bodies of dopaminergic neurons of the substantia nigra, and antisense DNA for *Sry* messenger RNA-reduced levels of tyrosine hydroxylase in the substantia nigra (Dewing et al., 2006). SRY may also regulate the transcription of the proopiomelanoocortin gene and thereby the levels of β-endorphin in the brains of mice (Botbol et al., 2011).

If the SRY proteins of DBA1 and C57BL10 males differed in their binding to regulatory sites for tyrosine hydroxylase or MAOA or proopiomelanocortin genes, this may account for the interaction of Y chromosome and autosomes with regard to offense behaviors. The differential binding of SRY from these two Y chromosomes would be due to DNA sequence difference in the proteins coding part of the Sry genes of the D1 and B10 Y chromosomes and to DNA sequence differences in the regulatory part of tyrosine hydroxylase or MAOA or proopiomelanocortin genes of the D1 and B10 autosomes. Increased transcription of tyrosine hydroxylase and/or decreased transcription of MAOA leading to increased synaptic dopamine might be a cause of the increased offense behaviors in male mice with the DBA1 Y chromosome and autosomes.

Regardless, six other Y chromosomal genes are expressed in mouse brain. These are *Ddx3y, Ube1y, Kdm5d, Eif2s3y, Utf,* and *Usp9y* (Xu et al., 2002). The temporal and spatial expression of these genes is now documented in the Allen Brain Atlas. One or more of these may vary between the DBA1 and C57BL10 mice and be involved in the interaction of Y chromosome and autosomes with regard to offense behaviors.

Mouse Emotionality

The behavioral effect of the 5HTT null mutant was assessed in the C57BL6 and 129S6 genetic background (Holmes, Lit, Murphy, Gold, & Crawley, 2003). The mice were tested in the elevated plus maze and the light-dark box. On the C57BL6 but not the 129 background, the homozygous null mutants spent less time in the aversive light compartment of the light-dark box than the homozygous wild types. Similarly, on the C57BL6 but not the 129 background, the homozygous null mutants spent less time in the aversive open arms of the elevated plus maze than did the homozygous wild types. These findings are consistent with an effect on these behaviors of genotype-by-genotype interaction between the 5HTT null mutant and other genes in the two strains. Regardless, these genotype-by-genotype interactions were not due to effects on levels of serotonin or 5HT1A receptor binding in the null mutant.

However, there are genotype-by-genotype interactions that can affect the level of serotonin in the 5HTT null mutant (Murphy, 2003). First, 5HTT and DAT double null mutants had one-third less brain serotonin than wild types. Second, mice homozygous for the 5HTT null mutant and heterozygous for brain-derived neurotrophic factor (BDNF) null mutant had less serotonin in brain stem, hypothalamus, striatum, and hippocampus than mice homozygous for 5HTT null mutant and homozygous for BDNF wild types.

Personality

Genotype-by-genotype interactions have also been reported for novelty-seeking scores on the Tridimensional Personality Questionnaire (Benjamin et al., 2000; Strobel et al., 2003). Three polymorphic genes were assessed. These were the genes for serotonin transporter (5HTT), catechol-o-methyl transferase (COMT), and dopamine receptor D4 (DRD4). These polymorphisms are for 5HTT in the promoter with either 14 (s) or 16 (l) copies of a 22bp sequence, for the DRD4 in exon VIII with either 7 (+) or less than 7 (−) copies of a 28bp sequence and for COMT in an SNP coding either for a valine or methionine. If the COMT genotype is homozygous for Val/Val individuals with the ll genotype for 5HTT and with – genotype for DRD4 have higher novelty-seeking scores than those with the ll genotype for 5HTT and with the + genotype for DRD4, whereas individuals with the sl or ss genotype for 5HTT and with the + genotype for DRD4 have higher novelty-seeking scores. The same pattern is seen for those with the Met/Met genotype. However, if the COMT

genotype is Val/Met genotype, those with the ll genotype for 5HTT have lower novelty-seeking scores than those with the sl or ss genotypes, regardless of their DRD4 genotype.

Summary

Two types of genotype-by-genotype interactions have been described. On the one hand there are interactions involving gene regulation. These may be said to be at the genetic level. They are exemplified by possible explanations for the interaction of Y chromosome and autosomes with effects on offense. On the other hand, there are interactions of gene effects on one or more neural systems. The interactions may be said to occur at the neural phenotypic level. They are exemplified by interaction of two or possibly three neurotransmitter systems with regard to personality. Regardless, for both, the finding of the interaction and its analysis contribute to an understanding of the biological mechanisms for these behaviors.

GENES, ENVIRONMENT, AND BEHAVIORAL DEVELOPMENT

Genotype by Environment Interactions

Some effects of a gene on phenotype depend on specific environments, and some effects of environment on phenotype depend on specific genotypes. These are known as genotype by environment interactions. They can be of value in determining the effects of environments on behavioral development and expression. The earliest studies of genotype by environment interactions were, in fact, strain by environment interaction. These are considered for rat cognition and mouse aggression. More recent studies of genotype by environment interactions have focused on specific genes. These are considered here for MAOA and 5HTT. The distinction between risk and plasticity genotypes will also be considered in relation to genotype by environment interactions (Belsky et al., 2007).

Rats Cognition

Maze-dull and maze-bright rats were raised in restricted, normal, or enriched environments (Cooper & Zubek, 1958). Restricted environments were small gray rat cages. Normal environments were standard rat cages. Enriched environments were large cages with "toys." In the normal environment, the maze-bright rats made fewer errors than the maze-dull rats. The enriched environment reduced the error scores of the maze-dulls to that of the maze-brights, but it had no effect on the error scores of the maze-brights. The restricted environment increased the error scores of the maze-brights to that of the maze-dulls but it had no effect on the error scores of the maze-dulls. This appears to be a strain by environment interaction. Alternatively, it may reflect floor and ceiling effects. That is to say, error scores cannot be lower than those of the maze-brights, and they cannot be higher then those of the maze dulls. The issue of floor and ceiling effects in reported strain by environment effects on behavior was critically evaluated by Henderson (1968).

Mouse Aggression

Sixty-nine years ago the first studies of aggression in inbred strains of mice were reported by Scott (1942) and Ginsburg and Allele (1942). Both assessed aggression in males of the C57BL10, C3H, and BALB/c inbred strains. Scott's most pacific strain was Ginsburg and Allele's most aggressive stain. Scott obtained the same strain rank order of these strains in both his laboratory and that of Ginsburg and Allele. Ginsburg and Allele obtained the same rank order of these strains in a first and second study. Many years later, an examination of the meticulously kept animal husbandry record revealed that Scott used a forceps to pick a mouse up by the tail to transfer it from cage to cage, and that Ginsburg transferred the mice from cage to cage in a small box. Later experimental studies showed that this experience affects the aggressive behavior of the C57BL10 males, but not that of the C3H and BALB/c males (Ginsburg, 1967).

Human Personality and Psychopathology

MAOA and Antisocial Behavior

A polymorphism in the promoter of the human MAOA gene interacts with childhood maltreatment to affect antisocial behaviors (Caspi et al., 2002). A 30 base pair sequence in a promoter of the MAOA gene is repeated 2, 3, 3.5, 4, or 5 times. The common alleles have either 3 or 4 repeats. In-vitro studies of transfected cell lines have shown that there is more transcription of the 3.5- and 4-repeat alleles than of the 2- and 3-repeat alleles and higher MAOA activity for the 3.5- and 4-repeat alleles than of the 2- and 3-repeat alleles. The alleles are frequently referred to respectively as high MAOA activity and low MAOA activity alleles. This was the genotypic variable.

In the Dunedin Longitudinal Study, abuse was assessed from 3 to 11 years in 499 males. Abuse included rejecting mother, harsh discipline, changes in primary caregiver, physical abuse, and sexual abuse. Individuals were than sorted into no maltreatment, probable maltreatment, and severe maltreatment groups. This was the environmental variable.

The dependent variables were conduct disorder assessed according to DSM-IV criteria, antisocial personality disorder assessed in a questionnaire by someone well-known to the individual, disposition to violence assessed by the Aggression scale of the MPQ, and police records in New Zealand and Australia of conviction for a violent crime. The four outcomes were correlated and a composite index of antisocial behavior was derived from the four dependent measures.

In this study, there was no main effect of genotype on the individual antisocial behaviors and on the composite index of antisocial behavior. However, there was a main effect of childhood abuse on both the individual antisocial behaviors and the composite index as well as interaction of genotype and abuse for both the individual antisocial behaviors and the composite index. Individuals with both the low activity genotype and severe maltreatment/abuse were more at risk for antisocial behaviors than those with both the high activity allele and severe maltreatment and abuse. An additional intriguing finding of this study was that in a sample of girls with high MAOA activity, severe maltreatment did not increase the risk for adolescent conduct disorder.

Since the report by Caspi and colleagues (Caspi et al., 2002), there have been at least 25 studies on the potential interaction of these MAOA genotypes, abuse, and antisocial behaviors (Gunter, Vaughn, & Philibert, 2010). Most, but certainly not all, studies have replicated the initial findings of Caspi and colleagues. However, a meta-analysis of five of these studies was consistent with an MAOA by maltreatment interaction for antisocial behavior (Kim-Cohen et al., 2006). The criteria for choosing the five studies in the metaanalysis were: (a) study published in a peer-reviewed journal, (b) included data on number of repeats of 30bp sequence in MAOA promoter, (c) included a measure of severe maltreatment known to have a main effect on the dependent variable, and (d) sampled from a nonclinical population. Such genotypes by environment interactions have the potential to identify biological mechanisms mediating the effects of environment on behavioral development. Here are some issues that need to be considered in attempting to identify the biological mechanisms mediating the effects of environment on behavioral development from genotype by environment interaction studies.

In vitro and *in vivo* transcription levels of the 3- and 4-repeat allele of MAOA may not be the same. In fact, there was no difference in MAOA activity for the 3- and 4-repeat alleles in adult male cortex, basal ganglia, thalamus, or pons as measured by positron emission tomography with [^{11}C] clorgyline (Fowler et al., 2007). Similarly, there was no association of MAOA promoter polymorphism with MAOA activity in postmortem cortical tissue (Balciuniene, Emilsson, Oreland Pettersson, & Jazin, 2002). Also, allele-specific expression studies of postmortem frontal cortex, temporal cortex, occipital cortex, and cerebellum in mature females did not find any association of the MAOA promoter polymorphisms with MAOA transcription levels (Cirulli & Goldstein, 2007). There are three conclusions from these studies. First, the effect of the polymorphism in the MAOA promoter on its transcription depends on the cellular environment. Second, a cellular environment supporting effects of the MAOA promoter polymorphisms on MAOA transcription levels are found in some transfected cell lines but not in many regions of adult brain. Third, since there are behavioral effects of the promoter polymorphisms on MAOA, it is likely that differences in MAOA activity for the 3- and 4-repeat alleles occur in other regions of adult brain or occur in some brain regions in fetuses or children rather than in adults.

In mice and in humans, null mutants of MAOA have effects on urinary or CSF levels of serotonin, dopamine, and norepinephrine metabolites (5HIAA, HVA, and MHPG, respectively). If adult males with the 3- and 4-repeat alleles of MAOA differed in one or more of these, it would indicate differential transcription and activity of MAOA in one or more regions of the adult nervous system. In two studies, there are higher CSF levels of HVA but not 5HIAA or MHPG in adult males with the 4-repeat allele than in those with the 3-repeat allele (Ducci et al., 2008; Zalsman et al., 2005). These findings are consistent with (a) higher MAOA transcription and activity for the 4-repeat alleles than for the 3-repeat alleles in dopaminergic neurons of adult males, and (b) the effects on antisocial behavior of MAOA polymorphism by maltreatment interaction being mediated by dopaminergic rather than serotonergic or adrenergic interactions. This is similar to how the knockout of the MAOA genes affects offense behaviors in mice via dopamine neurotransmission.

In humans, there are MRI and fMRI studies of normal (no maltreatment) individuals with 3-, 3.5-, 4-, and 5-repeat alleles of the MAOA gene (Buckholtz &

Meyer-Lindenberg, 2008, Meyer-Lindenberg et al., 2006). The 3.5- and 4-repeat alleles had smaller cingulate cortex, amygdala, and hypothalamus than those with the 3-repeat allele. They also had greater activation in the amygdala to emotional stimuli, and a stronger functional connection between the prefrontal cortex and the amygdala. These may be developmental or functional consequences of the difference in dopaminergic metabolism in subjects with the 3 versus 3.5/4 repeats.

There is also a promoter polymorphism in the MAOA gene of rhesus monkeys (Newman et al., 2005). There is an 18 bp sequence in this MAOA promoter with 5, 6, or 7 repeats. In human neuroblastoma cells, those with 5 and 6 repeats have more MAOA transcription than those with the 7 repeats. Monkeys were either mother- or peer-reared. For mother-reared monkeys, those with the 7-repeat allele showed more food competition aggression and social aggression than those with the 5-repeat allele. The reverse pattern was seen for peer-reared monkeys.

In both humans and monkeys, there is a genotype by environment interaction with effects on behavior. In both, there are multiple alleles for a repeat sequence in the promoter with effects of this repeat on transcription in cell line. For both, it is possible that an increase in presynaptic dopamine in the low-activity variants is a critical step in the development of brain structure and function, putting an individual at risk for effects of adverse environments on behavior. In the monkeys, this behavior is clearly aggression. In humans, the trait is better characterized as antisocial behavior that may have an aggressive component.

5HTT, Stress, and Depression

A polymorphism in the promoter of the human 5HTT gene interacts with both childhood maltreatment and with life stress events to affect depression (Caspi et al., 2003). A 20–23bp sequence in the promoter is repeated with 14 (s or short allele) or 16 (l or long allele) times. This is the genotypic difference.

In this study, one of the environmental variables was maltreatment as described for the study by Caspi et al. (2002) with individuals classified again as having no maltreatment, probable maltreatment, and severe maltreatment. The other environmental variable was the number of stressful life events from 21 to 26. Stressful employment, financial, housing, health, and relationship events were included.

The dependent variables were self-reported depression symptoms, informant reports of depression, probability of major depressive episode, and probability of suicidal ideation/attempts. There was no main effect of genotype on any of these. But there was a main effect of number of stressful life events and of childhood maltreatment on each of these. Also, there was a genotype by environment interaction for each of these. Individuals with ss or sl genotype and more than four stressful life events or severe maltreatment/abuse had higher scores for each of the measures of depression.

Since the original report by Caspi et al. (2003) there have been more than 40 studies of these genotypes, stressors, and depression. Most but not all have replicated the original findings of Caspi et al. (2003). Also, it has recently been suggested that convergent evidence approaches support an interaction of 5HTT genotype and stress on depression (Caspi et al., 2003; Hariri, Holmes, Uher, & Moffitt, 2010; Wankerl, Wüst, & Otte, 2010). The convergent evidence comes from the G by E replications in humans, effects of the 5HTT polymorphism on human brain, 5HTT polymorphism and stress in nonhuman primates, and 5HTT knockouts and stress in mice and rats.

In lymphoblastoma cell lines, the s allele is associated with lower transcription of the 5HTT gene, lower 5HTT protein concentration, and lower serotonin uptake than is the l allele. This may mean that there is less transporter in the presynaptic terminal of serotonin neurons for the ss than the sl or ll genotypes, and that there is a higher level of serotonin in the synaptic space for ss than sl or ll genotypes. However, transcription of the 5HTT gene is the same for both s and l alleles in the postmortem pons of adult humans. The pons contains the serotonergic neurons of the dorsal and median raphe (Lim, Papp, Pinsonnealt, Sadé, & Saffen, 2006). The dorsal and median raphe are the primary sites for synthesis of the serotonin transporter. Consequently, it may be that in adults there is no effect of the s versus l allele on the serotonin transporter or on reuptake of serotonin into the presynaptic neuron. But there may still be developmental effects on the brain of the 5HTT polymorphism (Gaspar, Cases, & Maroteaux, 2003). Healthy human carriers of the s allele have smaller gray matter volume of the anterior cingulate cortex and amygdala than ll homozygotes (Pezawas et al., 2005).

There is also a promoter polymorphism in the 5HTT gene of rhesus monkeys (Bennett et al., 2002). There is a 21 bp sequence in this promoter that occurs in one or two copies. In cell lines, those with 42 bp (l allele) have more 5HTT transcription than those with the 21 bp (s allele). For peer-reared monkeys, those with the s/l genotype had higher ACTH levels in response to a stressor than those with the s/s genotype (Barr et al., 2004). For

mother-reared monkeys, the ACTH response to a stressor was the same for s/l and l/l genotypes.

In mice, the 5HTT genotype moderates the effect of maternal behavior on anxiety and depression related behaviors (Carola et al., 2008). F1 females had either C57BL6 or BALB/c mothers. Females with C57BL6 mothers lick their own progeny more from day 1 to day 13 postpartum than females with BALB/c mothers. There was no effect of this treatment on behaviors of wild-type mice in an open field test, elevated plus maze test, and tail suspension test. In contrast, there were effects of this treatment on behaviors in these tests of mice heterozygous for the null mutant of 5HTT. Heterozygotes that had been licked more by their mothers spent more time in the center of the open field, spent more time in the open arms of the elevated plus maze, and had longer latency to immobility in the tail suspension test than those that had been licked less. There was also less binding of GABA to $GABA_A$ receptors in the amygdala, decreased serotonin turnover in the hippocampus and increased brain-derived neurotrophic factor mRNA in the hippocampus of knockout heterozygotes whose mothers spent less time licking them.

In humans, monkeys, and mice, there is a genotype by environment interaction with effect on behavior. In humans and monkeys, there are short and long alleles for sequences in the promoter of 5HTT with effects on transcription in cell lines and perhaps at some time in development. There is also a null mutant of 5HTT in mice. Wild-type and mice heterozygous for this null mutant differ in 5HTT activity. For all of these there are effects on brain structure and function that interact with stressful environments with effects on depression or depression-related behaviors.

Risk Versus Plasticity Genotypes

It has been proposed that the 5HTT, MAOA, and other genetic variants are plasticity rather than vulnerability genes (Belsky et al., 2009; Dick et al., 2011). Such genes increase vulnerability to negative effects of risky environments and increase the beneficial effects of supportive environments. Plasticity genes would have statistical crossover. In vulnerable environments, one allele of a gene would be associated with high values of a trait and the other allele with low values of the trait. In supportive environments, the effects of the alleles would be reversed. Two examples of this are: (1) interaction effects on depression of 5HTT genotypes and being caregiver or not of an Alzheimer's patient (Belsky et al., 2009), and (2) interaction effects on adolescent externalizing behavior of CHRMS (cholinergic muscariic 2 receptor) genotypes and parental monitoring (Dick et al., 2011).

Summary

It is obvious now that there are genotype by environment effects on behavior in animals and humans. These have two implications for the study of behavior. On the one hand, these have small effects on variance in a behavioral phenotype. On the other hand, they have the potential to identify the biological bases for environmental effects on behavior. There are at least two ways that such interactions could occur. In the first, the gene has a developmental effect on neural or biological systems and the environment has its effects on behavior via this neural or biological system. Different outcomes occur for behavior because the neural or biological phenotypes differ. This may be what occurs in the genotype and environment interactions described in this section for the 5HTT and MAOA polymorphisms. In the second, the environment acts on a gene's transcription or translation. Here genotype by environment interactions occur because the genotypes differ based on whether or to what degree an environmental variable affects the gene's transcription or translation.

Epigenetics

Gene Regulation and Behavior (the Encoded and the Expressed Genomes)

Individuals have both an encoded and an expressed genotype. The encoded genotype is the inherited DNA sequence. The expressed genotype is the RNA transcripts from the encoded genotype. Just as cells in the body have the same encoded genotype but different expressed genotypes, so can individuals have the same encoded but different expressed genotypes. Differences in expressed genotype are due to interactions of transcription factors with response elements of a gene that affect its transcription. There are two ways that the environment or experience can have transynaptic effects on the transcription of one or more genes. On the one hand, experience can transynaptically activate a transcription factor and thereby influence a gene's transcription. Here there is no change to the ability of the response element to bind the transcription factor. On the other hand, experience can modify the response elements ability to bind the transcription factor. Here there is a change in the transcription factor's accessibility to the response element. This involves either chemical changes to the DNA of the response element

and/or to the histone proteins associated with the DNA. The changes in the DNA involve either methylation or demethylation of cytosines in the promoter and in the associated histones involving acetylation or deacetylation of lysine. These chemical changes are said to be epigenetic in that they are functional changes in the genome without changes in the DNA sequence.

Rats, Maternal Behavior, Glucocorticoid Receptor, and Stress

Some mother rats lick and groom their pups more than others. If this occurs during the first 7 days postpartum, the pups of high licking and grooming mothers have as adults lower levels of the mRNA for CRH (corticotropin releasing hormone) in neurons of the hypothalamus and higher levels of mRNA for glucocorticoid receptor (GR) in neurons of the hippocampus than do the pups of low licking and grooming mothers (Meaney & Szyf, 2005). This acts to dampen hypothalamic pituitary adrenal (HPA) axis response to stress.

Subsequent studies focused on the mechanism for the effect of maternal licking and grooming of pups on adult levels of mRNA for GR in hippocampal neurons. It has been shown that tactile stimulation from the mother increases serotonin turnover in the hippocampus, and that this activated $5HT_7$ receptors on hippocampal neurons. This in turn induces the synthesis of the transcription factors, NGF1-A and CBP. These bind to the promoter of the GR gene. Subsequent demethylating the promoter DNA and acetylating of associated histones has long-term effects on the transcription of the GR genes in adults (Bagot & Meaney, 2010).

Humans, Abuse, and Glucorticoid Receptor

There is a similar effect in humans of early life experience on hippocampal GR mRNA and demethylation of the GR promoter (McGowan et al., 2009). In postmortem hippocampus from suicide victims, there was less GR mRNA and higher methylation of cytosines in the GR promoter of individuals with childhood abuse and neglect than in those with no childhood abuse or neglect. In vitro, this methylation of cytosines in the human GR promoter was associated with lowered binding of the NGF-1A transcription factor to the human GR promoter.

Rats, Maternal Behavior, and Estrogen Receptor

The daughters of high licking and grooming mothers show high licking and grooming of their own pups; conversely, daughters of low licking and grooming mothers show low licking and grooming of their pups (Champagne, 2008). Cross-fostering studies have demonstrated that this trait is transmitted to daughters via nongenetic mechanisms. The daughters of high licking and grooming mothers have more mRNA for ERα in the medial preoptic area of the hypothalamus than daughters of low licking and grooming mothers (Champangne et al., 2006). Also, levels of cytosine methylation across the promoter of the ERα gene was higher in the daughters of low licking and grooming mothers than of high licking and grooming mothers.

Epigenetics and Learning

DNA methylation in the adult forebrain may also have a role in learning and memory (Korzus, 2010). Dnmt1 and Dnmt3a are methyl transferases, and they are expressed in postmitotic neurons. There are effects on learning and memory in double conditional knockouts restricted to the postnatal forebrain (Feng et al., 2010). The double conditional knockout has impaired spatial learning and memory in the Morris water maze test and impaired memory consolidation in contextual fear conditioning tests.

Summary

Epigenetic regulation may have a role in effects of many kinds of experience on behavior in animals and humans. It may also account for behavioral differences between genetically identical individuals such as monozygous twins or mice from an inbred strain. There is also much speculation about the role of epigenetic regulation in the origin and treatment of psychiatric disorders (Bredy, & 2010; Tsanova, Renthal, Kumar, & Nestler, 2007).

Further progress in this area will be made as the epigenome is mapped for mice, rats, other animals, and humans. The epigenome consists of the parts of the genome and associated histones that can be altered by experience. This mapping project is especially important as specific experiences may act on more than one gene. Maternal care in rats has recently been shown to affect methylation of DNA and acetylation of histones across a 7 million base pair segment of rat Chromosome 18 (McGowan et al., 2011).

There is also speculation that epigenetic changes could be transmitted from parents to offspring (Crews, 2010; Jirtle & Skinner, 2007; Nadeau, 2009). In essence, this requires that somatic and gametic cells change in a parallel fashion. If this is ever validated, it would support a Lamarkian compliment to Mendelian inheritance and fundamentally affect our views on behavioral inheritance, development, and evolution.

FUTURE DIRECTIONS

The following extract is taken from the previous edition of this chapter (Maxson, 2003):

> The completion of the respective genome projects in nematodes, fruit flies, mice, and humans will make it possible to identify all the protein coding genes of these species as well as where and when the genes are transcribed, and the new protein initiative will eventually identify the structural conformation as well as metabolic or cellular function of each protein. This will greatly ease the task of identifying all the genes that can and do cause a behavior to vary in these four species, as well as that of tracing the pathways from gene to behavior. The great challenge will then be to understand how genes interact with each other, how they interact with the environment in the development and expression of behaviors, and how they relate to behavioral evolution.
>
> The study of the genetics of behaviors in animals can and should be for more than just the development of models relevant to human behaviors. The genetics of animal behaviors should also be researched in order to discover general principles relating genes to behavior across animal species and to have a comparative genetics of adaptive behaviors within related species. For this, there will need to be genome projects in other taxonomic groups; such work is already taking place on bees and other insects, many farm animals, domestic dogs, domestic cats, other rodents, and many primates; I believe that this process represents the future of behavior genetics.

As can be seen in the present review, much progress has been made in achieving the past goals for behavior genetics. Regardless, what was stated in 2003 remains a vision for the future of behavior genetics. As envisioned by Ginsburg (1958), a comparative approach and an evolutionary context is very much part of the vision for genetics as a tool in the study of behavior.

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