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A post-genomic view of behavioral development and adaptation to the environment

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ABSTRACT

Recent advances in molecular genetics and epigenetics are reviewed that have major implications for the bio-behavioral sciences and for understanding how organisms adapt to their environments at both phylogenetic and ontogenic levels. From a post-genomics perspective, the environment is as crucial as the DNA sequence for constructing the phenotype, and as a source of information in trying to predict phenotypes. The review is organized with respect to four basic processes by which phenotypes adapt to environmental challenges, with an emphasis on the data for humans: (1) developmental plasticity, (2) epigenetic mechanisms, (3) genotype-environment correlations, and (4) gene × environment interactions.

Introduction

Two landmark events in the history of genetics that occurred during the lifetime of many working scientists have each heralded paradigm shifts with broad implications for the bio-behavioral sciences. The discovery of the molecular structure of DNA in 1953 by Watson and Crick ushered in a fertile period of research generated by the successful integration of molecular genetics within the paradigm of the Modern Synthesis. This perspective viewed natural selection as the key mechanism for the evolution of new life forms from within-species variation generated principally from random mutations of structural DNA, the sole biological agent involved in heritability. Fifty years later momentum would build for a new paradigm that would call into question and eventually overturn this dominant paradigm. Completed in 2003, the Human Genome Project (HGP) was a principal catalyst in this

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genetics revolution. This 13-year, $3 billion project, coordinated by the US Department of Energy and the National Institutes of Health, with additional contributions coming from the UK, Japan, France, Germany, China, remains one of the largest single investigative projects in modern science. Once the principal goal of sequencing the three billion chemical units in the human genome was accomplished, the next step was to identify the genetic variants that increase the risk for common diseases.

In announcing on June 26, 2000, that the first draft of the human genome project had been achieved, then US President Clinton said it would "revolutionize the diagnosis, prevention and treatment of most, if not all, human diseases." This statement accurately reflected the optimistic consensus among scientists at that time. Instead, after another decade of research the results of the HGP have yielded very little gain in medical practice, as the common disease variants investigated have turned out to explain just a tiny fraction of the genetic risk (Goldstein, 2009). However, if the project did not revolutionize medicine, it did revolutionize science. The HGP, and the research directions it stimulated in molecular genetics, epigenetics, and genomics, have led to a radically new understanding of the fundamental relationship between genotype and phenotype that was largely unanticipated by most scientists at the inception of the HGP and still poorly understood today.

For example, one of the primary goals of the Human Genome Project was to identify all the genes in human DNA. Before the HGP, some scientists had estimated that the known three billion or so DNA letters necessitated a hundred thousand or more genes, to match the one million or so proteins in the human organism (Bernot, 2004). Some scientific estimates of the number of genes in the human genome at the start of the project were as high as 200,000. In 2004, researchers from the International Human Genome Sequencing Consortium (IHGSC) of the HGP shocked the scientific community with a new estimate of just 20,000–25,000 genes in the human genome. This is the same range as in mice and roundworms, and considerably less than the 32,000 genes found in an ear of corn (Schnable et al., 2009). Such a wildly miscalculated prediction necessitated a rethinking of the basic assumption that each protein was produced by a specific gene, with each gene containing the instructions for making just one protein. These assumptions created the expectation of a near perfect correlation between level of anatomical complexity in a species and the degree of complexity in their DNA. However, we now know that there is no such correlation. The genetic complexity of many simpler organisms like algae, mosses and salamanders exceeds that of many complex species of birds and mammals, including humans, a situation known as the *C*-value paradox. This would prove to be just one of many assumptions of the previous paradigm that would fall in the face of strong counter evidence.

The goal of this paper is to review more recent advances in molecular genetics that have major implications for the bio-behavioral sciences informed by genetics. In particular, we consider how to accommodate this body of research into a general framework for understanding how organisms mesh with environments. From a post-genomics perspective, the environment is as crucial as the DNA sequence for constructing the phenotype, and as a source of information in trying to predict phenotypes. Matching phenotypes with their environments is the critical adaptive problem, at both phylogenetic and ontogenic levels. After a brief summary of the assumptions of evolutionary models of development, we organize our discussion with respect to the basic processes by which phenotypes become adapted to their environments, with an emphasis on the data for humans.

Basic concepts: The perspective of evolutionary psychology

The basic evolutionary model of development emphasizes the smooth, reliable development of adaptations—mechanisms designed to solve problems that were recurrent over evolutionary time. The current view of evolutionary psychology is that these problems were solved by evolving a set of psychological mechanisms designed to deal with these specific recurrent problems. A key point for development is reliability across the range of environments that constitutes the evolutionarily expected range of environmental variation. That is, no matter how complex the transactions between genes and environments, ultimately adaptations must be reliably evolving across the range of evolutionarily expected environments.

An important general issue therefore is whether the environment being matched is an environment that is part of the evolutionary history of the organism—implying the concept of an evolutionarily

expected environment (EEE) and the closely related concept of the Environment of Evolutionary Adaptedness (Bowlby, 1969). These concepts highlight the idea that species are designed to solve the problems encountered in the environments in which they evolved, and animals are designed to expect the range of environments typically encountered during their evolution. Evolutionary approaches suppose that it is meaningful and important to speak of a universal, species-typical environment: the environmental invariance that combines with normal human genetic commonality to result in reliably developing human phenotypes. Recurrent environmental events are a critical force in evolution: "It is only those conditions that recur, statistically accumulating across many generations, that lead to the construction of complex adaptations. . . . For this reason, a major part of adaptationist analysis involves sifting for these environmental or organismic regularities or invariances" (Tooby & Cosmides, 1992, p. 69).

While this statement overestimates the importance of environmental invariance for designing adaptations, the important exceptions being domain general mechanisms of learning and intelligence, (Chiappe & MacDonald, 2005; MacDonald, 2009, in press), there is no question that a fundamental aspect of evolution is the design of adaptive systems in response to longstanding environmental regularities.

Although there are indeed stochastic phenomena that must be accommodated to an evolutionary account (see below), an evolutionary theory of development must ultimately have a strong deterministic core. The development of an oak tree, a dung beetle, or a child must be conceptualized as the predictable consequence of the interplay between genomes specific to each species and environments that are normally encountered by these species. If development were truly as contingent and unspecified genetically as claimed by some authors (Gottlieb, Wahlsten, & Lickliter, 2006), there would be no way to explain the overwhelming regularity of developmental outcomes: the fact that development within the normal range of human environments reliably results in normally formed, psychologically functioning children (Bjorklund & Pelligrini, 2002). In traditional developmental theory, the organismic perspective comes closest to this perspective. For example, Piaget (1952) viewed development as directional—that children go through predictable stages and that an adult human is the normal result of children interacting with environments that are universal to humans. We will consider further the question of *how* development keeps the organism true to type in our discussion of epigenetics.

The evolutionary psychology of individual differences

As a first cut, therefore, normal development is conceptualized as the result of species-specific, universal genetic endowments interacting with the range of environments universally encountered by individual members of the species that were recurrent over evolutionary time. However, many important human adaptations such as intelligence and personality systems show genetic variation. Genetic variation is ubiquitous, even for adaptations (e.g., West-Eberhard, 2003), leading to the evolution of appraisal mechanisms in which the value of different personality traits and physical features may be appraised differently depending on the perceived interests of evaluators—potential spouses, lovers, employees, employers, friends, leaders, etc. (e.g., Lusk, MacDonald, & Newman, 1998; Singh, 1993). From an evolutionary perspective, individual differences within the normal range are seen as variation in evolved systems. The most accepted proposal for why genetic and phenotypic variation in adaptive systems remains in populations is environmental heterogeneity (MacDonald, 1995; Nettle, 2006), which is well established in animal research that demonstrate that traits that are beneficial in some environments impose costs in others, depending on local environmental conditions.

Much of the genetic variation for fitness characters is additive—that is, it has a consistent effect on the phenotype independent of genetic background. Hill, Goddard, and Visscher (2008) summarize data from animal and human genetics indicating that for fitness-related traits typically around 50% of the phenotypic variation is due to additive genetic variation and that about 80% of genetic variation is additive. The standard view is that continuously distributed quantitative traits typically depend on a large number of genes, each making a small contribution to measurable variation in the trait. In general, the smaller the effects, the more nearly additive they are (Crow, 2010). There is a gradation between genes with large effects and genes with small effects, with a very large preponderance of genes

with small effects. For example, Crow (2010) estimates that well over 600 genes affect human height. Populations contain a great deal of variance that may be brought out in selection experiments. Selection for oil and protein content in corn over 100 generations has not exhausted genetic variation and continues to yield positive results. In general, the response to selection by a trait correlated with fitness can be predicted from knowing the additive genetic variance of the trait or covariance of the character and fitness. Epistatic effects are important for individual genes with large effects but can be safely ignored for quantitative traits for which there are no genes with large effect (Hill et al., 2008).

Adaptation: Matching organisms to environments

It cannot be overstated that being able to match organisms with their environments is the critical adaptive problem, at both phylogenetic and ontogenic levels. It was Darwin's particular genius to grasp the full significance of natural selection as an answer to this central phenomenon of adaptive design in nature, and the origin of species-specific characteristics of living organisms that enable them to survive and reproduce in a particular environment. Just as each species become adapted to a particular niche, individuals within a species may be better adapted to a particular aspect of the normal environmental range than others. We organize our discussion with respect to four basic processes by which phenotypes become adapted to their environments, with an emphasis on the data for humans.

1. developmental plasticity,
2. epigenetic mechanisms,
3. genotype-environment correlation, and
4. gene $\times$ environment interaction.

Developmental plasticity

Developmental plasticity refers to the process by which a given genotype can give rise to a range of different phenotypes in response to different environmental inputs during development. Plasticity may be described at different levels of organization arranged hierarchically from the behavioral to the neural and ultimately to the molecular level. It is quite probable that epigenetic processes underlie many different forms of plasticity, although we reserve detailed discussion of this to the next section in which epigenetic processes are documented at the molecular level of analysis.

At the organismic level, plasticity is a critical feature of life history strategies and a key mechanism for achieving an adaptive fit between phenotypes and their environments. From an evolutionary perspective, developmental plasticity is conceptualized as a series of "if–then" rules linking environments that were recurrent in the evolutionary past to phenotypes that were successful in those environments. When the environment presents long-standing problems and recurrent cues relevant to solving them, the best solution is to evolve modules specialized to handle specific inputs and generate particular solutions (Geary, 2005; Tooby & Cosmides, 1992). Such mechanisms fulfill the typical definition of module—that is, mechanisms that respond automatically to domain-relevant information (Stanovich, 2004). The epigenetic mechanisms discussed later are prime examples of this modular type of plasticity designed to cope with recurrent types of environmental variation.

Variation in nutrition is attractive for studying plasticity because variation in nutritional quality is a recurrent environmental feature for the vast majority of organisms and thus likely to result in phylogenetic adaptations designed to cope with it. A well-known example in humans is the developmental-origins hypothesis, sometimes called the Barker hypothesis after David J.P. Barker, a researcher at the University of Southampton (Barker, 1992; Barker, 1997). Barker theorized that under poor nutritional conditions, a pregnant female can modify the development of her unborn child to prepare for survival in an environment in short supply of resources, resulting in a thrifty phenotype (Hales & Barker, 1992). Individuals with a thrifty phenotype have a smaller body size, slower metabolic rate and are less active, which may be seen adaptations to an environment that is chronically short of food (Bateson & Martin, 1999).

This phenomenon whereby the adult phenotype can be cued by specific features of the early environment in order to match the expected adult environment can also produce a mismatch when humans dramatically change their environment during adulthood. In the case of reduced fetal growth due to an early nutritionally deprived environment, the individual who is subsequently exposed to an abundant food supply is strongly predisposed towards a number of health problems (obesity, coronary heart disease, stroke, diabetes, and hypertension) later in life. Barker theorizes that this increased susceptibility results from accommodations made by the fetus in an environment limited in its supply of nutrients. In adapting to a low-quality nutritional environment, the fetus is ill-prepared for an environment of abundance later in life. Barker initially supported his theory with epidemiological data linking low birth weight with late-onset cardiovascular disease. Further empirical support was provided by the Dutch famine of 1944, which allowed scientists to document the effects of famine on human health. The Dutch Famine Birth Cohort Study found that the children of pregnant women exposed to famine were more susceptible to diabetes, obesity, cardiovascular disease and other health problems, depending on the timing and extent of the food shortage (Hart, 1993; Stein, 1975).

Another example of an evolved adaptive response to early environmental conditions involves the development of sweat glands. Humans are born with the same number of sweat glands, none of which initially function. Rather the glands are activated during the first 3 years after birth due to their innervation by the axons of the sympathetic nervous system, according to temperature the child experiences during this period (Stevens & Landis, 1988). If the child is exposed to higher temperatures, a higher percentage of the sweat glands become functional. Such a high degree of plasticity generally confers an adaptive advantage by matching the individual to his environment. Such an adaptation that can be re-programmed in a single generation may have allowed for the rapid migration of early *Homo sapiens* into quite different climate zones (Gluckman & Hanson, 2005). However, after the critical period of developmental programming, an individual's ability to sweat efficiently becomes fixed and cannot be further modified. This can present a problem as it did for Japanese soldiers during WW II working in the heat of southeast Asia. Many of the soldiers from the northern provinces of Japan suffered from heatstroke because of their inability to sweat efficiently.

In both of these examples of developmental programming of the phenotype we see that flexible adaptations can evolve when the organism is faced with recurrent, but fluctuating, problems posed by environmental conditions (availability of food resources, variation in temperature). While natural selection will favor the developmental fine-tuning of the phenotype, it also works against phenotypic mismatches, as both of the above examples demonstrate.

Brain development and plasticity

Brain development clearly illustrates the adaptive logic of plasticity. A brain that is built up and wired by individual cells following self-regulating recipes has a greater capacity to adapt itself to different environmental demands. "Wiring the mind" is a demanding and specialized task and genes have evolved to read internal as well as external signals indiscriminately to guide the process. By guiding the development of the brain using both genetic and environmental signals, which are relative rather than absolute, plasticity emerges as an inherent feature of the human brain (Marcus, 2004).

From the moment the human brain begins its prenatal growth (about 25 days after conception) it increases at the rate of a million neurons every 4 min, reaching approximately 100 billion neurons at birth. At birth, each neuron in the cerebral cortex has approximately 2500 synapses. By the time an infant is 2 or 3 years old, the number of synapses is approximately 15,000 synapses per neuron (Gopnick, Meltzoff, & Kuhl, 1999). This amount is about twice that of the average adult brain. As we age, old connections are deleted through the process of synaptic pruning. The amount and type of stimulation influences the structure of the cortex, in the number of synapses and their pruning. Neurons with the strongest patterns of innervation retain their connections and the other cells die off. Two types of innervation are relevant:

(1) endogenous neural firings,
(2) exogenous neural firings produced by sensory inputs.

To illustrate the latter, imagine that one eye is kept closed during the development of the visual system. This would result in the individual's becoming functionally blind in that eye. Even though cells projecting from the retina produce normal outputs, the area in the cortex to which they feed will not respond appropriately to visual inputs. One reason for this relatively high degree plasticity in the visual cortex is that the development of depth perception must be "fine-tuned" by experience. The brain's response to the partially-overlapping images seen by the two eyes provides the basis of depth perception. However this function cannot be hardwired into the brain at birth because the brain's response must take into account the distance between the eyes, which is smaller in the newborn than it will be later. Instead the brain modifies its connections over time in response to many experiences with images that the child sees. The brain manages this adaptive task by creating extra synapses between neurons and then by selectively pruning those that are not being used.

The Baldwin effect and genetic assimilation

Plasticity is also implicated in traits produced by environmental induction as a result of extreme or unusual environmental influences, as in genetic assimilation and similar phenomena (West-Eberhard, 2003). For example, in the Baldwin effect, there is a phenotypic response to variable or extreme environments made possible by plasticity. The Baldwin effect, named after its originator, James Mark Baldwin, postulates that the recurring behavior of individual members of a species can shape the evolution of that species via the differential survival of individuals who learn to respond appropriately to novel, adverse, and recurring environment conditions (Baldwin, 1902). Phenotypic changes can be gradually assimilated into the organism's genetic/epigenetic repertoire via natural selection on "variation in the regulation, form or side effects of the novel trait" (West-Eberhard, 2003, p. 140). In other words, genetic changes accommodate to the new phenotype, for example, by making it function more smoothly; but the original alteration of the phenotype occurs as the result of plasticity. As a result, the new trait becomes heritable.

Rather than always viewing the organism as passively shaped by the environment, it is important to note that it is often the behavior of the organism that actively *creates* the environmental conditions under which morphological traits are then selected (Wcislo, 1989). The origins of human language, and other complex human adaptations may reside in processes of genetic assimilation that were set in motion by the behavior of the organism. Innovative behaviors by juveniles provide the raw material from which an organism generates pathways of response that could become independent of environmental triggers and become the normative phenotype of the species – referred to as genetic assimilation by Waddington (1942, 1956).

Besides facilitating adaptation of the organism to specific environmental niches developmental plasticity has important consequences for the evolvability of a phylogenetic lineage. If the generation of phenotypes is conditional and dependent on external or environmental inputs, evolution can proceed by a "phenotype-first" route with genetic change following, rather than initiating, the formation of morphological and other phenotypic novelties (West-Eberhard, 2003). Moreover, environmentally induced traits may be immediately recurrent because of the prevalence of the inducing feature of the environment, and more likely to spread than mutations that can be quickly eliminated by natural selection. As a result of modularity and plasticity, the organism has the capacity to respond to new situations that recur with a novel trait, which then is able to spread throughout a population via selection for the ability required to produce the trait. In this view, evolution begins with a recurrent developmental change brought about either by a mutation or (more commonly) by environmental induction. Selection then consolidates the trait by modifying genes influencing the regulation of the trait. Jacob (1977) eloquently described how evolution proceeds by "tinkering", shuffling the deck of genetic material and recombining what is already available in novel ways. Rather than relying primarily on mutations to structural genes within the DNA, evolution more often simply rearranges developmental regulatory genes to create novel structures, often conserving a similar program or module in a host of organisms.

The discovery of the homeotic Hox gene family in vertebrates in the 1980s further consolidated this view and allowed researchers in evolutionary developmental biology to empirically assess the relative

importance of gene regulation to the evolution of morphological diversity. Only a small fraction of genes are involved in development, principally as components of signaling pathways. Hox genes determine where limbs and other body segments will grow in a developing embryo or larva. In addition, the organism's developmental history conditions the impact of later developmental inputs. Hox genes act as switches for other genes, and can be induced by other gene products such as morphogens. These discoveries drew biologists' attention to the fact that hox genes can be selectively turned on and off, rather than being always active, and that highly disparate organisms (for example, fruit flies and human beings) use the same basic set of hox genes for embryogenesis, but regulating them differently. Evolutionary developmental biologists are now finding that variations in the level, pattern, or timing of gene expression may provide more variation for natural selection to act upon than changes in the gene product alone (Carroll, 2005). The implication that major evolutionary changes in body morphology are associated with changes in gene regulation, rather than the evolution of new genes, suggest that the action of natural selection on promoters responsive to Hox and other "switch" genes may play a major role in evolution. We discuss this type of developmental plasticity involving specific regulatory mechanisms of gene activity in the following section.

Epigenetics and maternal effects

Some adaptations function as contingent strategies in which organisms mesh with their environments as a result of different genes being expressed in different environments (e.g., different qualities of early maternal care). This results in adaptive responses to expected environmental variation. This environmental variation is expected in the sense that the environments must be recurrent over evolutionary time to produce these adaptations. A paradigmatic example is maternal grooming of offspring in rats where different patterns of licking are linked with different epigenetic outcomes (reviewed in Belsky & Pluess, 2009; Charney, 2012; Meaney, 2010).

The term 'epigenetics' was originally suggested by Waddington (1956), combining aspects of epigenesis and genetics. For Waddington, epigenetics referred to all interactions of genes with their environment that bring the phenotype into being. At the same time Waddington emphasized the evolutionary importance of the epigenotype as a species-specific network of developmental interactions that has important consequences for the evolvability of a phylogenetic lineage. He coined a number of concepts to address these developmental and evolutionary mechanisms, such as the "epigenetic landscape," "canalization" and "genetic assimilation." Most authors in the second half of the twentieth century referred to these concepts when they spoke of epigenetics, and the prevailing usage in some developmental texts to some extent still reflects this earlier meaning.

The meaning of the term began to change toward the end of the twentieth century by an increasing association of the term 'epigenetics' with molecular mechanisms of selective gene regulation and non-DNA-based forms of inheritance. Although a certain notion of developmental context has remained, the prevailing emphasis now is on the regulatory mechanisms of gene activity, and current definitions of epigenetics provided in mainstream developmental journals like *Child Development* are formulated in the vocabulary of genetics and evolutionary developmental biology (e.g. Meaney, 2010). Following recent usage, we use the term 'epigenetic' to refer to functional modifications of gene activity that are not based on alterations of DNA sequence and reserve the broader term 'developmental plasticity' to refer to environmentally induced phenotypic variation for which no epigenetic mechanism has been demonstrated.

At a molecular level structural modification of the chromatin can be achieved by a variety of mechanisms including cytosine methylation, histone hypoacetylation, RNA silencing and other forms of posttranscriptional modification. DNA methylation, primarily of cytosine, is essential for the normal control of gene expression in development and is the best-understood mechanism of the silencing of gene transcription. Methylation at regulatory regions, especially within the promoter regions sensitive to switch genes, prevents the binding of regulatory factors at these sites, with a strong positive correlation between the extent of methylation and the degree of silencing.

For our purposes three striking features of the epigenetic control of gene expression are most relevant: (1) the altered gene expression is stable and for the most part irreversible; (2) it is often directly

influenced by environmental agents; and (3) the alterations in gene expression are heritable. We discuss each of these features in turn.

Initially researchers only observed DNA methylation very early in embryonic development. However, later research revealed that DNA methylation patterns can be modified in mature cells, particularly neurons, in response to environmental events (Bird, 2007). These environmentally induced epigenetic modifications lead to a fundamental change in our understanding of genotype–phenotype relations. One commonly studied realm involves maternal effects on gene expression and stress responses in the rat.

The focus of these studies has been the effects of maternal care in the first week of life on the development of individual differences in offspring involving the transcription of the glucocorticoid receptor that regulates the HPA response to stress. An important feature of these maternal effects in rats is that the effects persist into adulthood even though the differences in maternal care, assessed as frequency of licking and grooming (LG) are limited to the first week after birth. Brief, daily handling of rat pups for the first 21 days was found to permanently increase glucocorticoid receptor (GR) concentrations within the hippocampus (Meaney & Aitken, 1985), as well as altering serotonin (5-HT) turnover and 5-HT2 receptor binding in selected brain regions and reducing the HPA stress response (Weaver et al., 2001). Thus, the development of this system is modifiable by environmental stimulation. The handling effect on hippocampal GR concentrations is apparent as early as 1 week after birth. Moreover, handling in the first week of life shows the largest increase in GR concentrations and the most pronounced behavioral changes; handling in the 2nd week is somewhat less effective, and handling during the 3rd week is without effect. Thus, the sensitivity of the hippocampal GR system to this early manipulation wanes through the first 3 weeks of life as GR concentrations reach adult levels (Weaver et al., 2001, 2004). In summary, early experience (an increase in LG in the first week) appears to be the critical mechanism for altering the intracellular signals in hippocampal neurons that, in turn, produces a stable imprint on the adult genome responsible for an adaptive response to stress in the adult rat. Below we discuss the inter-generational transmission of these effects under the heading of epigenetic inheritance.

Although research in this area is just beginning, results suggest that a wide range of environmental stimuli may result in epigenetic reprogramming of a wide range of changes in neural function. Current rodent research indicates that epigenetic modifications of histone proteins are linked to drugs, physical abuse, and other stressors (Renthal & Nestler, 2008). Recent research in humans modeled after the epigenetic findings in rodents have established a similar relationship between adversity in the social environment and brain epigenetic changes. Adaptive responses to adversity may help individuals become more vigilant and actively prepared to confront risks, but over the long term the cost of such adaptations may lead to increased vulnerability to stress, psychiatric disorders, and even suicide. In the first study of its kind, McGowan et al. (2009) found that DNA methylation levels at the *NR3C1* gene resulted in lower glucocorticoid receptor expression in brains of suicide victims with a history of childhood abuse as compared with controls. Highly stressful experiences in early development trigger methylation differences in hippocampal genes and in gene expression that lead to increased glucocorticoid secretion as well as stress-related behavioral outcomes in individuals who had experienced severe childhood abuse and died by suicide (Labonte & et al., 2012). Other studies have identified several individual genes on the HPA axis that appear to moderate the effects of psychosocial stressors, such as child abuse, on risk for suicide attempt: *FKBP5* (Roy, Gorodetsky, Yuan, Goldman, & Enoch, 2010), *FKBP5* & *CRHBP* (Roy, Hodgkinson, Deluca, Goldman, & Enoch, 2012), and *CRHR1* Ben-Efraim, Wasserman, Wasserman, & Sokolowski, 2011).

While precise mechanisms are currently unknown, the hope is that once epigenetic pathways are identified, it will be possible to prevent or reverse the emergence of associated disorders later in life. However, without replication of these effects of specific genes there is little basis for moving on towards potential application. Moreover, the primary prevention of child abuse should be our first priority, since detailed prospective-longitudinal studies have already firmly established both abuse and neglect as risk factors for a number of disorders that may be manifest in childhood, adolescence and beyond (Sroufe, Egeland, Carlson, & Collins, 2005).

Similar epigenetic mechanisms that mediate the effects of maternal care on the development of individual differences in stress response in rodents may underlie the development of attachment in

human infants. Indirect evidence is provided by behavior genetic studies. If infant attachment classification is primarily influenced by variation in sensitive and responsive mothering rather than rooted in the genome, then behavior genetic studies should reveal substantial shared environmental influence and low heritability of quality of attachment. Indeed, recent studies of attachment in human infants show strong effects of shared maternal environment, a result that is atypical of the vast majority of behavior genetics research (Bakermans-Kranenburg, van Uzendoorn, Bokhorst, & Schuengel, 2004; Bokhorst et al., 2003; Roisman & Fraley, 2008). For example, Roisman and Fraley found that shared environment explained 53% of the variance in attachment security, unshared environment explained 30%, with the remaining 17% due to additive genetic variance. A model with the additive genetic component of the model constrained to equal 0 was able to explain the data just as well as the full model.

Lack of maternal effects would be surprising given evolutionary and life history perspectives on the importance of maternal care, particularly in mammals. Maternal effects are expected to be critically important for mammals because female investment is high due to internal gestation and a high degree of postnatal maternal care. In resource-rich human environments, characteristics such as intimate pair bonding between parents, relatively low fertility, high-investment parenting, secure attachment with offspring, and delayed maturation of the young are likely to be adaptive. Substantiating this view, researchers report large inter-correlations among these characteristics, with parenting variables accounting for 20– 50% of the variance in child outcomes (Belsky, Steinberg, & Draper, 1991; Maccoby, 2000).

This type of phenotypic plasticity makes great adaptive sense. The developmental process grants the genome a much greater level of flexibility than previously assumed with a rigid DNA code and little environmental intervention between the genotype and phenotype. Developmental plasticity allows certain types of information to be passed to offspring without having to go through the vastly slower processes of random mutation and natural selection. Its great adaptive advantage stems for its sensitivity to fluctuating environmental conditions. In the end it is nature and nurture in concert that shape developmental pathways and outcomes, resulting in a "blurring of boundaries" between genes and environment.

Epigenetic inheritance

In evolutionary biology, epigenetic inheritance refers to the transmission of epigenetic states from one generation to the next, via the germ line, without a change in DNA sequence. This second inheritance system is based on the same mechanisms as the passing on of gene deactivation patterns in cell lineage propagation. Although differential methylation states are generally erased during sexual reproduction through reprogramming in the germ cell (Reik, 2001), certain epigenetic marks seem to be able to escape erasure.

DNA methylation is one type of chemical modification of DNA that can be inherited without changing the original DNA sequence. As part of the epigenome, it can eliminate or cause diseases associated with environmental agents to be transmitted across generations. Epigenetic inheritance raises the controversial issue of the transmission of individually acquired, functional states from one generation to the next. Because it is known that methylation and other forms of epigenetic chromatin marking can stem from environmental influences, epigenetic inheritance has been argued to represent a kind of neo-Lamarkian mechanism in evolution (Jablonka & Lamb, 2005).

That epigenetic effects are heritable was first demonstrated in mammals by Jirtle and colleagues in a groundbreaking experiment in 2000 (Waterland & Jirtle, 2003). Mice that carried a gene called the agouti gene that made their fur yellow and rendered them susceptible to particular diseases were fed a diet containing methyl groups. The methyl molecules, commonly found in foods such as soy and leafy vegetables, attached to the agouti gene and switched it off. Their offspring were born with the agouti gene still in their DNA but silenced. They had brown fur and were no longer susceptible to the same diseases. The parent mice had passed on not only their DNA, but also the epigenetic switches attached to it.

Recent research has led to a more detailed understanding of the chemical scaffolding that supports DNA and activates or deactivates genes. For example, Crews and et al. (2007) demonstrated that

female rats exposed to high levels of the fungicide vinclozin had male offspring who were likely to be sterile and to develop various diseases, including cancer, as adults. What makes the study noteworthy is that the propensity for diseases persisted in the male rats over four generations. The rats' genes had not been altered by the fungicide and no genetic change occurred. Rather the fungicide altered the chemistry of early development by influencing gene expression. It was this epigenome – the chemical scaffolding surrounding and interacting with the DNA – that was inherited.

In the case of the epigenetically programmed patterns of stress response in rodents discussed above, cross-fostering studies reveal that individual differences in maternal care and stress reactivity are transmitted from mother to daughter, regardless of their biological origins. Thus the female offspring of fearful, low-LG mothers show the same pattern of behavior as their foster mothers (for a detailed review, see Meaney, 2010). These findings indicate that early experience can modify both gene expression at the molecular level and complex behavior that is mediated by the HPA system.

Several recent studies have suggested that transgenerational epigenetic inheritance may occur in humans. Some of the more convincing evidence thus far comes from research on the effects of (1) maternal nutrition and (2) synthetic forms of estrogen like bisphenol A (BPA). While human exposure to artificial substances like BPA is quite recent, variation in nutrition in human populations from feast to famine has always been a recurrent environmental feature and thus likely to result in adaptations designed to cope with it, as discussed earlier in Barker's developmental-origins hypothesis. In addition, diet is one of the more easily measured and best understood environmental factors in epigenetic change, compared to more complex variables like attachment or stress. Nutrients from the food we eat enter metabolic pathways where they are modified into molecules that can silence genes. Diets high in methyl-donating nutrients can modify gene expression, especially during early development when the epigenome is first being established.

Recent findings document transgenerational effects of maternal diet and suggest the presence of underlying epigenetic mechanisms. For example, historical records of harvests and food prices dating from the 19th century obtained from Överkalix, a small town in northeast Sweden, showed that the paternal (but not maternal) grandsons of Swedish men who were exposed during preadolescence to famine were less likely to die of cardiovascular disease. But if food was later plentiful, then diabetes mortality in the grandchildren increased, suggesting transgenerational epigenetic inheritance. However the opposite effect was observed for females: paternal (but not maternal) granddaughters of women who experienced famine while in the womb (and therefore while their eggs were being formed) lived shorter lives on average (Kaati, Bygren, Pembrey, & Sjostrom, 2007; Pembrey et al., 2006).

Such sex-specific effects are due to parental imprinting, a process that results in allele-specific differences in transcription, DNA methylation, and DNA replication timing. The establishment of parental imprints occurs during gametogenesis – i.e., the formation of the male and female gametes. Subsequently during embryogenesis and into adulthood, alleles of imprinted genes are maintained in two epigenetic states: paternal or maternal. Thus, genomic imprints act as templates for their own replication, are heritable, can be identified by molecular analysis, and serve as markers of the parental origin of genomic regions.

A second example of adverse environmental effects that may be mediated by epigenetic mechanisms is the case of Bisphenol A (BPA), widely used to make plastics and epoxy resins. Because it is also a synthetic estrogen it can act as an endocrine disruptor that may lead to negative health effects (Rubin, 2011). In 2010 the Environmental Protection Agency reported that over one million pounds of BPA are released into the environment annually. The primary human exposure route to BPA is diet, including ingestion of contaminated food and water. A 2011 study that investigated the number of chemicals pregnant women are exposed to in the US found BPA in 96% of women (Science Daily, 2011). Such widespread exposure of humans to BPA, together with its estrogen-like properties, raised concern about its suitability in consumer products and food containers.

The biomedical research community responded by conducting a large number of government-funded experiments exploring the health effects of low doses of BPA on lab animals. Of these studies, 153 found adverse effects and 14 did not. In contrast, all 13 studies of BPA funded by chemical corporations reported no harm (Chemical & Engineering News: Government & Policy, 2007). Early developmental stages appear to be the period of greatest sensitivity to its effects. Prenatal exposure is linked to later abnormal weight gain, insulin resistance, prostate cancer, and excessive mammary gland

development (O'Connor and Chapin, 2003). The mechanism responsible for these effects is not yet clear, but at least one study has shown that BPA suppresses DNA methylation, which is involved in normal epigenetic regulation (Dolinoy, Huang, & Jirtle, 2007).

Because BPA causes adverse effects in rodents that are almost identical to some of the health problems that have recently increased in human populations (cancer, diabetes, obesity, heart disease), researchers have begun studies exploring possible effects of BPA in humans. In 2008 the first large epidemiological study in humans found that higher BPA levels were associated with heart disease and diabetes (Lang et al., 2008). Subsequently a 2010 report from the FDA warned of possible hazards to fetuses, infants, and young children (USFDA, 2010) and, in the same year, Canada became the first country to declare BPA a toxic substance. For an older, but more comprehensive, review of the adverse effects of artificial endocrine-active substances on reproduction and development, see O'Connor and Chapin (2003).

In conclusion, current scientific understanding of the causal chain resulting in epigenetic changes in humans is quite limited compared to research done on animals, mostly rodents. Despite decades of investigation, scientists can still only speculate on the importance of epigenetic processes to human health. But with the alarming increase in the prevalence of conditions such as obesity, diabetes and autism, which often have no clear genetic etiology, the probability that these complex conditions are affected by epigenetic processes seems likely. Certainly the dramatic increase of these disorders over the past 50 years is not being caused by genetic changes in the human population. We currently know that a number of environmental factors, like nutrients and chemicals, are capable of altering gene expression, and those factors that manage to penetrate germline chromatin and escape reprogramming could, in theory, be passed on to our progeny. As scientists continue to search for definitive evidence of transgenerational epigenetic inheritance in humans, the implications thus far suggest that the quality of the food we eat, the water we drink, and the air we breathe may directly affect the genetic health of our children and possibly our grandchildren.

Gene-environment correlations

Thus far we have emphasized a causal chain from parent to child. However, it would be misleading to view the child as merely a passive agent in the developmental process. When parents and their children are conceptualized as a dynamic, co-evolving system, genotype-environment correlations arise (*r*GE) in which heritable characteristics of children can influence their environments (Plomin, DeFries, & Loehlin, 1977; Scarr, 1992; Scarr & McCartney, 1983). This perspective recognizes the child as an active agent in his or her own development, in addition to the genetic contributions of both parents, and the shaping influence of the environment that they create for their child.

There are three types of genotype-environment effects: active, passive, and evocative, each type involving genetic differences in exposure to environments. An active effect refers to the child's own genetically influenced choices to seek out and selectively attend to a specific aspect of the general environment, in effect creating their own environment out of a myriad of choices available to them. It is well known that animals engage in a great deal of active "niche-picking", and "niche construction", which in turn influences the course of their development. Scarr proposes that the child's genotype leads them to seek out and prefer certain types of stimulation from their environment. For example, if a child who is naturally active watches more aggressive TV programming and video games than a less active sibling, this would result in an active genotype-environment correlation. The environmental influence of regularly watching violent programming was not independent of the child's genotype.

A passive effect refers to the rearing environment provided by genetically related parents. Findings indicate that the parents' genetic characteristics influence what type of environment they create for themselves and their children. For example, intelligent parents have children with a high genetic potential for intelligence, but they also provide optimal environments for the facilitation of their children's intelligence. This could be expressed by providing a stimulating home environment with physical resources (lots of books and stimulating toys) and social resources (reading to the child, answering questions thoughtfully, etc.). Children would be expected to differentially benefit from

the environments provided by high-investment parents depending on their genotype. In early childhood at least, passive genotype-environment correlations are more important contributors to the correlations between measures of IQ and the HOME and FES measures of the environment than are active or evocative genotype-environment correlations (Plomin, 1994).

Evocative effects refer to the various responses by a child's parents, teachers, peers and others that are elicited by the child because of some aspect of his or her genotype. For example, if a child who is naturally shy by temperament is overprotected by well-intentioned parents, that child's environment may be substantially different from that of a bold child whose parents provide a wide range of social experiences, or an aggressive child whose parents escalate the type of control they use.

Recent findings, reviewed by Horwitz and Neiderhiser (2011) indicate an important role for both evocative and passive *r*GE in parenting. For example, mothers' positivity and monitoring are heritable and an aspect of passive *r*GE for children; on the other hand, mothers' negativity and control were found to be the result of evocative *r*GE in which the child's genotype was driving the interactions. There are similarities and differences between mothers and fathers on how these variables operate, and at times (as with negativity) both passive and evocative effects are found for the same variable.

Behavior geneticists propose that the use of DNA markers should greatly enhance our understanding of G E correlations. As an example, Plomin and Rutter (1998) review research on the behavioral correlates of the DRD4 dopamine receptor gene. Previous research had indicated that the 7-repeat allele of this gene is a risk factor for ADHD and has been associated with the personality trait of novelty-seeking. Plomin & Rutter speculate that children who have inherited this allele could experience more chaotic family environments created by parents whose own novelty-seeking leads them to construct a less ordered family climate. These same children could also evoke different reactions from others based on their more intrepid behavior, or actively construct a social environment by selecting thrill-seeking peers as friends. DNA markers provide an excellent means of testing such hypotheses. For example, Rowe (2003) tested the hypothesis of association between the DRD4 dopamine receptor gene and divorce, as indexed by number of marriages. Rowe found that the mean number of marriages was greater in the 7-repeat carriers compared with all other groups. He interprets the finding as either an evocative or active GE correlation "to the extent that these mothers evoke conflict from their husbands or select husbands who are psychologically unstable and less able to maintain a marriage" (Rowe, 2003, p. 83). Unlike correlations between psychological and environmental variables, the result establishes a causal direction because a greater number of marriages cannot cause a woman's DRD4 gene to change in any way.

In the past, demonstrating heritability in childhood outcomes did not actually rule out environmental influences, because in behavior genetics research *r*GE were always subsumed under genetic effects, thereby ignoring feedback effects on the child resulting from environments that are actively sought out (the active *r*GE), evoked (the evocative *r*GE), or passively experienced (the passive *r*GE). "This is misleading because risk environments that are genetically influenced may still create risks that are truly environmentally mediated" (Plomin & Rutter, 1998, p.1235). While the use of DNA markers may help to alleviate this situation, we believe that there is no substitute for directly studying how the environment affects the individual (LaFreniere & MacDonald, 2008).

Gene × environment interactions

Further evidence that the genotype–phenotype relation may be influenced by early experience is provided by a growing literature on gene × environment interactions. As used here, G × E interactions occur when a subset of individuals, identified either phenotypically or by a genetic marker, respond to different environments differently than others do, for genetic reasons. This implies a statistical interaction (Rowe, 2003). As with all genes, in order to be an aspect of the adaptive architecture of the organism, one must suppose that the effects on the phenotype are the result of natural selection in the organism's EEA; however, in the case of G × E interactions that are part of the adaptive architecture of the organism, one must suppose that the genomic variants are under selection in at least two different environments, that the genomic variants influence the construction of quite different phenotypes, and that these phenotypes are adaptive in each of these environments.

Of course, the genes resulting in G × E interactions may not be part of the adaptive architecture of the organism. Among the possibilities are that the range of environments includes environments not encountered in the EEA. For example, as a result of improvements in technology, there is a G × E interaction for the PKU gene such that its effects depend on whether the person with the condition has a diet from which phenylalanine has been removed—not a condition that would have obtained in the EEA. Or the gene may be a mutation that is in the process of being removed from the population because it has a negative effect on fitness in some environments normally encountered by the organism but does not affect fitness in others. With some exceptions (see below), researchers have generally not been interested in whether the G × E interactions discovered are part of the adaptive architecture of the organism.

A general caveat regarding the practical importance of G × E interactions involving single genes is the robust finding in population genetics that genes with small effects are much more likely than genes associated with large effects (hopeful monsters) (Charlesworth, 1982). Flint and Mackey (2009; see also, Crow, 2010) review data indicating small effect sizes for quantitative trait loci (QTL's) across three species, the laboratory mouse, the fruit fly, and humans. For example, 54 genes have been discovered that influence height, but together they account for < 5% of the variance. Although epistatic interactions and GXE interactions are common for QTL's, when discovered, they also have small effect sizes.

Consistent with the above, four "Perspective" articles published in the *New England Journal of Medicine* in 2009 indicates that, while some common genetic variants have been found, in almost all cases they carry such a modest risk for the disease that they are of little or no practical importance for diagnosis or treatment. Now after 5 years of investigation, the search for common variants has been widely judged a failure.

Goldstein (2009) concludes that if there were any common gene variants responsible in a major way for chronic diseases, they would have been found already. He assumes that all single nucleotide polymorphisms (one-base variations in the genome) yet to be discovered will have even weaker effect sizes than the weakest so far found. In his view the search for a genetic basis of common diseases must be shifted to identifying rare genetic variants. Schizophrenia, for example, would be caused by combinations of 1000 rare genetic variants, not 10 common genetic variants. Such circumstances would undermine the position of those who argue that the common variants detected so far, even if they explain only a small percentage of the risk, will nonetheless identify the biological pathways through which a disorder emerges, and hence point to corrective drugs.

Even the defenders of such studies do not dispute that, thus far, they have failed to realize the widely broadcast promise that genomics would revolutionize clinical medicine. Kraft and Hunter (2009) argue that genome-wide association studies remain valuable, but they acknowledge that those polymorphisms discovered to date do not have much diagnostic utility, since the great majority of the newly identified risk-marker alleles confer very small relative risks and are found in only small portions of the population. In principle, their effects on personality traits and various disorders are likely to be important, but findings to date are inconsistent and at best account for a tiny percentage of the individual variation, a situation that suggests that their effects on the phenotype may be dependent upon environmental risk factors and triggers that are not assessed in genome-wide association studies.

The expectation of finding single genes with large effects for psychiatric disorders perhaps stems from the tradition of the qualitative classification scheme common in psychiatry. Qualitative schemes divide people into sharp categories, so that it is natural to suppose that people with and without the diagnosis are different in some fundamental way. However, there is a great deal of evidence that the common psychiatric categories may be conceptualized as extremes on personality systems (MacDonald, 1995, 2012; Widiger & Trull, 1992). For example, individuals who are extreme on the Behavioral Inhibition System (BIS) are prone to fears and phobias (Gray, 1987); individuals who are extreme on the Behavioral Approach System (BAS) are prone to disinhibited pleasure seeking, dangerous sensation seeking, and aggression; individuals who are low on the Nurturance/Love system are prone to victimizing others and show no empathy or guilt (MacDonald, 2012). Given that personality systems are quantitative traits influenced by many genes, it is thus not surprising that few genes with large effects on personality disorders have been found. Individuals who are extreme on personality systems and

thus prone to psychopathology are likely to have a great many genes with small effects that make them prone to being extreme on a particular system.

In general, complex traits are typically influenced by a great many genes with small effects; these additive genes have similar effects on a wide range of normal genetic backgrounds and across a wide range of normal environments. The evolutionary logic of such genes is that when a trait such as cranial capacity or intelligence is under directional selection, there is selection for genes that provide a general positive effect on the trait that is more or less independent of genetic background and a wide range of normal environmental rearing conditions. For example, the genes for intelligence are predominantly additive (e.g., Plomin, 2003). Given that intelligence (or increased lung capacity or increased oxygen efficiency) is a valuable trait, genes that contributed to intelligence in one commonly encountered environment but lowered intelligence in another commonly encountered environment would be at a disadvantage. The presence of complex, unpredictable, and idiosyncratic interactions would make it very difficult for natural selection to construct complex adaptations.

Nevertheless, Gottlieb et al. (2006) propose that different individuals subjected to a range of environments increasing in value may have radically different responses to this range of environments. Empirical evidence for such a model is lacking; moreover, in such a model there would there be no predictable patterns of environmental effects in environments of different quality—for example, no predictable beneficial effects from enriched environments versus deprived environments. Genes promoting such unpredictable effects would violate a fundamental aspect of evolutionary adaptations: that they be reliably developing in the environments normally encountered by the organism.

In contrast, models stressing additive genes and additive environmental effects propose that genes that are most easily incorporated into complex adaptations are selected (a) because they result in reliably developing phenotypes across a wide range of environments, (b) because they have predictable effects on the phenotype independent of genetic background, and (c) because, since naturally occurring environments vary in quality, they are often structured to result in additive increments to the phenotype for genetically normal people. For example, as noted above, nutritional variation is a recurrent environmental feature and thus likely to result in adaptations designed to cope with it. This does not imply that there are no interactions at all or that individual differences would be absolutely preserved over a wide range of normalenvironments (Turkheimer, Goldsmith, & Gottesman, 1995). It does mean that such interactions are unlikely to have large effects and are not expected to disrupt the design plan of complex adaptations.

Despite the general failure to find powerful single gene effects on psychiatric disorders, an influential literature on gene $\times$ environment interactions has emerged in biological psychiatry over the past decades involving the effects of genomic variants on dopamine and serotonin metabolism (e.g., Caspi et al., 2003; Meaney, 2010; Suomi, 2000, 2006). While promising, the findings of powerful interactive effects of particular combinations of genes and environments conflict with the previously discussed evolutionary logic favoring large numbers of additive genes with small effects. Moreover, findings of G $\times$ E interaction effects have been questioned because of disturbingly low rates of successful replication (Duncan & Keller, 2011), leading to a policy in the journal *Behavior Genetics* that in most cases such findings should be replicated in order to be considered for publication (Hewitt, 2012).

Nevertheless, findings to date suggest possibly important pathways whereby certain genes and environments combine to produce adaptive or maladaptive phenotypes in contemporary environments. Here we limit our discussion to two of the most intensively studied genomic variants: (1) the serotonin transporter gene (5-HTTP); and (2) the dopamine D4 receptor gene (DRD4).

Serotonin is implicated in the regulation of emotion and is a major target for medications designed to treat a range of affective disorders, including depression and anxiety. A polymorphism in the serotonin transporter gene (5-HTTP) in humans has long been a focus of research in biological psychiatry. Two common alleles are found in humans: a short (S) variant (14 copies of a 20–23 base-pair sequence) and a long (L) variant (16 copies). Individuals with at least one copy of the S allele have been shown repeatedly to be at risk for depression and anxiety disorders. These individuals show increased activation of the amygdala while processing fearful or anxious faces (Hariri et al., 2002, 2005) and decreased functional connectivity between the amygdala and the anterior cingulated cortex (Pezawas et al., 2005), a possible mechanism for this increased response to negative stimuli. Pezawas et al.

(2005) suggest that the vulnerability to depression found in S-allele individuals could be triggered by periods of stress that result in an impaired capacity to regulate negative affective states, whereas in adversity-free environments individuals with the S allele are not prone to depression.

Research at NIMH has consistently demonstrated stable individual differences in biobehavioral responses to stress in rhesus monkeys depending on which genomic variant of the 5-HTTP polymorphism they had (Suomi, 2006). The 5-HTTP polymorphism in rhesus monkeys is comparable in form and function to that in humans and the S allele is associated with deficits in serotonin metabolism, impulsivity, and aggression (Bennett et al., 2002; Suomi, 2006). However this finding is only apparent in monkeys who were separated from their mothers and reared with peers. Suomi and colleagues report findings involving a G × E interaction in HPA responsiveness to short-term social separation at 7 months. Specifically, monkeys with the "short" (LS) 5-HTTP allele exhibited heightened ACTH responsiveness compared with those with the "long" (LL) allele, but only if the animals had been peer-reared. In contrast, LS monkeys reared by their biological mother did not differ in ACTH responsiveness from mother-reared LL subjects, suggesting a "buffering" effect of maternal rearing similar to that discussed previously in rodents.

Finally, cross-fostering studies in rhesus monkeys reveal that individual differences in maternal care and stress reactivity are transmitted from mother to daughter, regardless of their biological origins. Again, deficits in serotonin metabolism, impulsivity, aggression, and excessive alcohol consumption were evident in monkeys who experienced insecure early attachment relationships, but not in monkeys who developed secure attachment relationships with their cross-fostered mothers during infancy. According to Suomi (2005), daughters tend to develop the same type of attachment relationships with their own offspring that they experienced with their mothers early in life. He concludes that early experience in attachment quality provides a possible nongenetic mechanism for transmitting these patterns to subsequent generations.

Studies of the 5-HTTP polymorphism in humans reveal that childhood maltreatment increases the risk of an episode of major depression, but only in individuals with the S allele (Caspi et al., 2003). The greatest impact was observed on those homozygous for the short serotonin-transporter allele and least for those homozygous for the long allele, with those heterozygotes carrying one of each allele falling in between. Subsequent research has yielded inconsistent results (for a review, see Caspi & Moffit, 2006). Such inconsistency is not surprising given that interaction effects are quite difficult to detect due to the low statistical power of most research designs (McClelland & Judd, 1988). Another potential source for these discrepant findings is likely due to inconsistency in the measurement of depression. While the liability of developing depression resulting from childhood maltreatment is life-long, the manifestations of depression are often episodic. Chronic or recurrent depression is more heritable and is more strongly associated with childhood maltreatment than depression diagnosed at one point in time. These observations led Brown and Harris (2008) to hypothesize that genetic sensitivity to childhood maltreatment should be specific to depression that is chronic or recurrent. A more recent study by Uher et al. (2011) has confirmed this hypothesis. In two cohorts, statistical tests of G × E interactions were significant for persistent depression, but not single-episode depression. Individuals with two short 5-HTTLPR alleles and childhood maltreatment had an elevated risk for chronic, but not episodic, depression.

Another widely studied genomic variant is the dopamine D4 receptor (DRD4), a critical gene in biological psychiatry because of its neuro-anatomical connections and its involvement in the physiology of behavior, pharmacological response and psychopathology. The DRD4 gene codes for a protein that is distributed in the frontal cortex, striatum, hypothalamus and hippocampus. The DRD4 polymorphism has been studied in association with disorders like schizophrenia, attention deficit hyperactivity disorder (ADHD), obsessive–compulsive disorder, bipolar disorder, and avoidant personality disorder. In developmental research it has been associated with differences in infant response to novelty and attachment quality (LaKatos et al., 2002), which in turn influence the child's responsiveness to parental socialization. Further study has also shown G × E interaction effects with respect to parent-training interventions (Bakermans-Kranenburg, Van IJzendoorn, Pijlman, Mesman, & Juffer, 2008). As a whole these results suggest that children can be expected to respond differently to the same environmental input as a function of their genotype. While research in biological psychiatry over the past decade involving the G × E interaction effects of genomic variants involving dopamine and serotonin

metabolism hold great promise for the future, questions remain to be clarified by further research concerning the practical importance of genomics with respect to intervention.

The widespread difficulty of detecting reliable associations between genomic variants and various psychiatric disorders (see above) has led to increasing acceptance of genetic investigations of endophenotypes (or biological markers) that can be defined more precisely. The purpose of introducing the intermediate concept of endophenotype is to divide behavioral symptoms into more stable phenotypes with clearer genetic connections (Gottesman & Gould, 2003). For example, in schizophrenia the overt phenotypic symptom could be a psychosis, but underlying endophenotypes might be a lack of sensory gating and a decline in working memory, since both have a clear genetic component and are systematically linked to schizophrenia.

Another question that is currently debated is the evolutionary basis for the persistence of genomic variants that predispose individuals toward greater risk for a variety of illnesses. Within the general model of Darwinian medicine and evolutionary psychiatry genomic variants will persist in the general population only if they confer relative advantages in survival and reproductive success as indexed by inclusive fitness, at least in certain recurrent environments (Nesse & Williams, 1994). This principle is clearly illustrated in the classic case of the context-specific heterozygous advantage that results in the retention of a high frequency of the allele that causes sickle-cell anaemia in African populations that live in areas where malaria is prevalent. Heterozygous individuals are protected against malaria because the sickle cell allele can speed the removal of infected cells. However, homozygote individuals get sickle-cell anaemia, which usually leads to an early death before reaching reproductive age. The protection conferred by the allele against the prospect of death by malaria outweighs the real costs of sickle-cell anaemia, but only where malaria is a pervasive threat. Thus the allele is maintained only in those populations, though it may also reside in those African–Americans who have inherited it from their West African ancestors. Thus, the possibility exists in other contexts that certain genomic variants that were formerly adaptive still exist in modern environments where they no longer provide substantial benefits. That is, they have not yet been winnowed down by natural selection.

More recently, theorists have suggested that variation in susceptibility to environmental influence may be similarly strategic—that parents may hedge their bets by having children that vary in their susceptibility to environmental influences such that highly plastic children may benefit disproportionately from positive environments but suffer disproportionately from negative environments (Belsky et al., 2009). This theory, labeled Differential Susceptibility Theory (DST), is based on data showing that plasticity is heritable, as well as data showing that environmental stressors experienced *in utero* appear to act by making children more reactive to environmental stimulation. This bet hedging argument postulates that parents can better maximize inclusive fitness by having the development of some children be more canalized than others. Parents may then benefit if some of their children adopt "conditional strategies" in which different strategies are triggered by different environments.

Boyce and Ellis (see Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011) provide a somewhat different evolutionary theory for explaining the phenomenon whereby highly reactive children have the worst outcomes in poor environments and the best outcomes in positive environments, while non-reactive children have adequate outcomes in all environments typical for the species. Their theory, labeled Biological Susceptibility to Context (BSCT), proposes that highly reactive phenotypes emerge in both highly stressful and in highly protected environments. Highly reactive children are highly sensitive to context whether positive or negative, while children who are not highly reactive are buffered against typical stressors.

Both DST and BSCT challenge prevailing developmental psychopathological analysis of maladaptive outcomes within adverse settings by emphasizing that both stressful and supportive environments have been part of human experience throughout our evolutionary history, and that developmental systems shaped by natural selection respond adaptively to a normal or expected range of environments. More controversially, both theories claim that the highly reactive phenotype is adaptive in both positive and negative environments. According to Ellis et al. (2011), the fact that highly reactive individuals typically have worse outcomes in contemporary Western societies obscures the fact that "even though susceptible individuals in negative environments may be especially vulnerable to poor mental health outcomes (as defined by dominant Western values), they may still be acting in ways that promote or once promoted status and reproductive success in dangerous environments (e.g., gang

membership in bad neighborhoods: see Palmer & Tilley, 1995; advantage taking, sexual promiscuity, limited parental investment" (p. 14). Nevertheless, their hypotheses 1) that the highly reactive phenotype is biologically adaptive in negative environments, or 2) that the highly reactive phenotype is more biologically adaptive than the less reactive phenotype in positive environments are largely speculative at this point.

Conclusion

The accumulation of new genetic data made possible by the technological advances in the post-genomic era has led to fundamental changes in the working paradigm of the genotype-to-phenotype relationship. Rather than separate forces acting on the organism, genes and the environment act together, often in highly complex ways. Rather than immutable, DNA is subject to some, perhaps substantial, environmental influence. Rather than the sole biological agent of heritability, it is now clear that the epigenome can also be inherited.

A key change involves a new understanding of how the dynamics of development and early experience influence gene expression and determine phenotypic variation. Identical DNA sequences can exist in phenotypically different cell types due to epigenetic programming that determines which genes are transcribed and which proteins are synthesized in any given cell. The realization that much biodiversity is not due to differences in genes, but rather to alterations in gene regulation, has fundamentally changed the working paradigm (Carroll, Jennifer, Grenier, & Weatherbee, 2004). Such changes in gene regulation are "second-order" effects of genes, resulting from the interaction and timing of activity of gene networks, as distinct from the functioning of the individual genes in the network. It is worth emphasizing that these new epigenetic findings should not result in a view of development that is dominated by random, stochastic effects. The most basic postulate of developmental theory is that development itself is lawful rather than unpredictable. And the most basic observation of development is that it proceeds by invariant sequences and with great regularity within a given species. At the level of epigenetic systems, Ho (1984) discusses how it is that development remains lawful and predictable:

> Stability and repeatability reside in the dynamics of the epigenetic system in two senses. First, it is the automatic result of physiochemical reactions of which the system is composed — and the physicochemical environment in which the system is in turn embedded. Second, it is due to assimilated experiences held jointly in the nucleus and cytoplasm. These introduce regular biases into developmental reactions, which may otherwise behave in a non-committal or unpredictable way. Assimilated experiences therefore anticipate the environments to be experienced (HO, 1984, p. 285).

In other words, epigenetic mechanisms are similar to developmental plasticity in implying "if p, then q" mechanisms such that there is a predictable outcome given an environmental contingency.

Because the action of genetic material is involved in the metabolic processes of every cell, genetic influence is relevant to every developmental process. Epigenetic phenomena are particularly prevalent in the human brain, and thus can be expected to influence much of human behavior, and they play a critical role in development during the perinatal period where they enable phenotypic plasticity (Charney, 2012; Meaney, 2010). Such profound conceptual changes in molecular genetics affect all of biology, but are especially important in the human context because of societal implications regarding the epistemology of genetic causation and applications in public health.

For example, the emerging field of social genomics, which combines measures of health, behavior and cognition with molecular data, will allow researchers to study how, at a molecular level, early life conditions relate to health and behavior (Azar, 2011). One of its leading proponents, Stephen Suomi, says "We started off with showing that the environment creates behavioral differences. Now we are looking at biological factors and finding that this early experience is affecting virtually every aspect of behavior and biology, including gene expression." (in Azar, 2011, p. 7). Researchers will be able to ask new questions such as how exposure to an environmental trigger causes changes in gene expression and whether interventions can reverse them.

As the natural heir to the Human Genome Project, the Human Epigenome Project was recently established with the goal of identifying DNA methylation patterns of all human genes in all major

tissues. Because methylation can change genome function under environmental influence, it constitutes a vital, but currently missing, link between genetics, disease and the environment. As epigenetic markers, methylation variable positions, much like single nucleotide polymorphisms, promise to significantly advance our ability to understand and diagnose human disease.

The paradigm shift in genetics has already impacted medical practice and education since understanding the origins of health and disease requires an understanding of the interaction of the individual's genome and the environment. For example, the Dr. John T. Macdonald Foundation Department of Human Genetics has now initiated a 2-year residency in Medical Genetics. In the human behavioral sciences, innovative training programs will also need to be initiated and nurtured. The biological sciences have begun to pave the way for this via innovative textbooks in evolutionary developmental biology and ecological developmental biology (e.g. Gilbert & Epel, 2009). From this biological foundation, textbooks in evolutionary developmental psychology will need to incorporate an understanding of uniquely human developmental and ecological factors, including culture, into an expanded synthesis (e.g. LaFreniere, 2010). Cross-disciplinary integration and consolidation of the new paradigm will be greatly enhanced by precise concepts and common terminology, rather than a proliferation of terms for the same concept, or, more insidiously, the use of the same term for different concepts. Hence our attention to defining terms, and noting different historical usage of them, throughout this review.

References

Azar, B. (2011). Social Genomics: The psychology of cells. *Monitor of Psychology, 42*(5).

Baldwin, J. M. (1902). *Development and evolution*. New York: Macmillan.

Bakermans-Kranenburg, M. J., van Uzendoorn, M. H., Bokhorst, C. L., & Schuengel, C. (2004). The importance of shared environment in infant-father attachment: A behavioral genetic study of the attachment Q-sort. *Journal of Family Psychology, 18*(3), 545–549.

Bakermans-Kranenburg, M. J., van IJzendoorn, M. H., Pijlman, F. T., Mesman, J., & Juffer, F. (2008). Experimental evidence for differential susceptibility: Dopamine D4 receptor polymorphism (DRD4 VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. *Developmental Psychology, 44*, 293–300.

Barker, D. J. P. (Ed.). (1992). *Fetal and infant origins of adult disease*. London: BMJ Books.

Barker, D. J. P. (1997). Maternal nutrition, fetal nutrition, and disease in later life. *Nutrition, 13*, 807.

Bateson, P., & Martin, P. (1999). *Design for a life: How behaviour develops*. London: Jonathan Cape.

Belsky, J., & Pluess, M. (2009). Beyond diathesis–stress: Differential susceptibility to environmental influence. *Psychological Bulletin, 135*, 885–908.

Belsky, J., Steinberg, L., & Draper, P. (1991). Childhood experience, interpersonal development, and reproductive strategy: And evolutionary theory of socialization. *Child Development, 62*(4), 647–670.

Ben-Efraim, Y. J., Wasserman, D., Wasserman, J., & Sokolowski, M. (2011). Gene-environment interactions between CRHR1 variants and physical assault in suicide attempts. *Genes, Brain and Behavior, 10*(6), 663–672.

Bennett, A. J., Lesch, K.-P., Heils, A., Long, J. C., Lorenz, J. G., Shoaf, S. E., et al (2002). Early experience and serotonin transporter gene variation interact to influence primate CNS function. *Molecular Psychiatry, 7*, 118–122.

Bernot, A. (2004). *Genome, transcriptome, and proteome*. West Sussex: John Wiley & Sons.

Bird, A. (2007). Perceptions of epigenetics. *Nature, 447*, 396–398.

Bokhorst, C. L., Bakermans-Kranenburg, M. J., Pasco Fearon, R. M., van Ijzendoorn, M. H., Fonagy, P., & Schuengel, C. (2003). The importance of shared environment in mother-infant attachment security: A behavioral genetic study. *Child Development, 74*, 1769–1782.

Bowlby, J. (1969). *Attachment and loss: Vol. I. Attachment*. New York: Basic Books.

Brown, G. W., & Harris, T. O. (2008). Depression and the serotonin transporter 5HTTLPR polymorphism: A review and a hypothesis concerning gene – Environment interaction. *Journal of Affective Disorders, 111*, 1–12.

Bjorklund, D. F., & Pelligrini, A. D. (2002). *The origins of human nature: Evolutionary developmental psychology*. Washington, DC: American Psychological Association.

Carroll, S. B. (2005). *Endless forms most beautiful: The new science of Evo Devo and the making of the animal kingdom*. New York: Norton.

Carroll, S. B., Jennifer, K., Grenier, S. D., & Weatherbee (2004). *From DNA to diversity: Molecular genetics and the evolution of animal design* (2nd ed.). Norton.

Caspi, A., & Moffit, T. E. (2006). Gene–environment interactions in psychiatry: Joining forces with neuroscience. *Nature Reviews Neuroscience, 7*, 583–590.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301*, 386–389.

Charlesworth, B. (1982). Hopeful monster cannot fly. *Paleobiology, 8*, 469–474.

Charney, E. (2012). Behavior genetics and post genomics. *Behavioral and Brain Sciences, 35*(6), 1–80.

Chemical and Engineering News: Government and Policy (2007). Bisphenol A on trial. *Vol, 85*(16), 38.

Chiappe, D., & MacDonald, K. B. (2005). The evolution of domain-general mechanisms in intelligence and learning. *Journal of General Psychology, 132*, 5–40.

Crews, D. et al (2007). Transgenerational epigenetic imprints on mate preference. *Proceedings of the National Academy of Sciences, 104*, 5942–5946.
Crow, J. F. (2010). On epistasis: Why it is unimportant in polygenic directional selection. *Philosophical Transactions of the Royal Society B, 365*, 1241–1244.
Dolinoy, D. C., Huang, D., & Jirtle, R. L. (2007). Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. *Proceedings of the National Academy of Sciences, 104*, 13056–13061.
Duncan, L. F., & Keller, M. C. (2011). A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *American Journal of Psychiatry, 168*(10), 1041–1049.
Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary-neurodevelopmental theory. *Development and Psychopathology, 23*, 7–28.
Flint, J., & Mackay, J. F. C. (2009). Genetic architecture of quantitative traits in mice, flies, and humans. *Genome Research, 19*, 723–733.
Geary, D. C. (2005). *The origin of mind: Evolution of brain, cognition, and general intelligence*. Washington, DC: American Psychological Association.
Gilbert, S. F., & Epel, D. (2009). *Ecological developmental biology: Integrating epigenetics, medicine, and evolution*. Sunderland, Mass.: Sinauer Associates.
Gluckman, P. D., & Hanson, M. A. (2005). *The fetal matrix: Evolution, development, & disease*. Cambridge, Mass.: Cambridge University Press.
Goldstein, D. B. (2009). Common genetic variation and human traits. *New England Journal of Medicine, 360*(17), 1696–1698.
Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry, 160*(4), 636–645.
Gottlieb, G., Wahlsten, D., & Lickliter, R. (2006). The significance of biology for human development: A developmental systems view. In W. Damon & R. Lerner (Eds.). *Handbook of child psychology* (Vol. 1, pp. 210–257). New York: Wiley.
Gopnick, A., Meltzoff, A. N., & Kuhl, P. K. (1999). *The scientist in the crib: Minds, brains, and how children learn*. NY: William Morrow and Company.
Gray, J. A. (1987). *The psychology of fear and stress*. Cambridge, UK: Cambridge University Press.
Hariri, A. R., Drabant, E. M., Munoz, K. E., Kolachana, B. S., Mattay, V. S., Egan, M. F., et al (2005). A susceptibility gene for affective disorders and the response of the human amygdala. *Archives of General Psychiatry, 62*, 146–152.
Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., et al (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science, 297*, 400–403.
Hales, C. N., & Barker, D. J. (1992). Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis. *Diabetologia., 35*, 595–601.
Hart, N. (1993). Famine, maternal nutrition and infant mortality: A re-examination of the Dutch hunger winter. *Population Studies, 47*(1), 27–46.
Hewitt, J. S. (2012). Editorial policy on candidate gene association and candidate gene-by-environment interaction studies of complex traits. *Behavior Genetics, 42*, 1–2.
Hill, W. G., Goddard, M. E., & Visscher, P. M. (2008). Data and theory point to mainly additive genetic variance for complex traits. *PLoS Genet, 4*(2), e1000008. http://dx.doi.org/10.1371/journal.pgen.1000008.
Ho, M.-W. (1984). Environment, heredity and development. In M.-W. Ho & P. T. Sanders (Eds.), *Beyond Neo-Darwinism: An introduction to the new evolutionary paradigm* (pp. 267–289). London: Academic Press.
Horwitz, B. N., & Neiderhiser, J. M. (2011). Gene-environment interplay, family relationships, and child adjustment. *Journal of Marriage and Family, 73*(4), 804–816.
Jablonka, E., & Lamb, M. J. (2005). *Evolution in four dimensions: Genetic, epigenetic, behavioral, and symbolic variation in the history of life*. Cambridge, MA: MIT Press.
Jacob, F. (1977). Evolution and tinkering. *Science, 196*, 1161–1166.
Kaati, G., Bygren, L. O., Pembrey, M., & Sjostrom, M. (2007). Transgenerational response to nutrition, early life circumstances and longevity. *European Journal of Human Genetics, 15*, 784–790.
Kraft, P., & Hunter, D. J. (2009). Genetic risk prediction–are we there yet? *New England Journal of Medicine, 360*(17), 1701–1703.
Labonte, B. et al (2012). Genome-wide epigenetic regulation by early-life trauma. *Archives of General Psychiatry, 69*, 722.
LaFreniere, P. J. (2010). *Adaptive origins: Human evolution and development*. New York: Psychology Press/Taylor & Francis.
LaFreniere, P. J. & MacDonald, K. (2008). *An evolutionary perspective on the effects of parenting on attachment*. Paper presented at the International Society for Human Ethology, Bologna, Italy.
Lakatos, K., Nemoda, Z., Toth, I., Ronai, Z., Ney, K., Sasvari-Szekely, M., et al (2002). Further evidence for the role of the dopamine D4 receptor (DRD4) gene in attachment disorganization: Interaction of the exon III48- bp repeat and the-521C/T promoter polymorphisms. *Molecular Psychiatry, 7*, 27–31.
Lang, I. A., Galloway, T. S., Scarlett, A., Henley, W. E., Depledge, M., Wallace, R. B., et al (2008). Association of urinary bisphenal A concentration with medical disorders and laboratory abnormalities in adults. *JAMA, 300*(11), 1303–1310.
Lusk, J., MacDonald, K., & Newman, J. R. (1998). Resource appraisals among self, friend and leader: Implications for an evolutionary perspective on individual differences and a resource/reciprocity perspective on friendship. *Personality and Individual Differences, 24*, 685–700.
Maccoby, E. (2000). Parenting and its effects on children: On reading and misreading behavior genetics. *Annual Review of Psychology, 51*, 1–27.
MacDonald, K. B. (1995). Evolution, the five factor model, and levels of personality. *Journal of Personality, 63*, 525–567.
MacDonald, K. (2009). Evolution, psychology, and a conflict theory of culture. *Evolutionary Psychology, 7*(2), 208–233.
MacDonald, K. B. (2012). Cutting nature at its joints: Toward an evolutionarily informed theory of natural types of conduct disorder. *Journal of Social, Evolutionary, and Cultural Psychology, 6*(3), 260–291.
MacDonald, K. B. (in press). Human General Intelligence as a Domain General Psychological Adaptation. In J. Kush (Ed.) *Intelligence quotient: Testing, role of genetics and the environment and social outcomes*. Hauppauge, NY: Nova Science Publishers.
Marcus, G. (2004). *The birth of the mind: How a tiny number of genes creates the complexities of human thought*. New York: Basic.

McClelland, G. H., & Judd, C. M. (1988). Statistical difficulties of detecting interaction and moderator effects. *Psychological Bulletin, 114*, 376–390.
McGowan, P. O., Sasaki, A., D'Alessio, A. C., et al (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience, 12*(3), 342–348.
Meaney, M. J. (2010). Epigenetics and the biological definition of gene x environment interactions. *Child Development, 81*(1), 41–79.
Meaney, M. J., & Aitken, D. H. (1985). The effects of early postnatal handling on hippocampal glucocorticoid receptor concentrations: Temporal parameters. *Developmental Brain Research, 22*(2), 301–304.
Nesse, R. M., & Williams, G. C. (1994). *Why we get sick*. New York: Times Books Random House.
Nettle, D. (2006). The evolution of personality variation in humans and other animals. *American Psychologist, 61*, 622–631.
O'Connor, J. C., & Chapin, R. E. (2003). Critical evaluation of observed effects of endocrine active substances on reproduction and development. *Pure Applied Chemistry, 75*.
Palmer, C. T., & Tilley, C. F. (1995). Sexual access to females as a motivation for joining gangs: An evolutionary approach. *Journal of Sex Research, 32*, 213–217.
Pembrey, M. E., Bygren, L. O., Kaati, G., Edvinsson, S., Northstone, K., Sjöström, M., et al (2006). Sex-specific, male-line transgenerational responses in humans. *European Journal of Human Geneticss, 14*(2), 159–166.
Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B. S., et al (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: A genetic susceptibility mechanism for depression. *Nature Neuroscience, 8*, 828–834.
Piaget, J. (1952). *The origins of intelligence in children*. New York: Routledge & Kagan Paul.
Plomin, R. (1994). *Genetics and experience: The interplay between nature and nurture*. Thousand Oaks, CA: Sage Publications.
Plomin, R. (2003). Genes, genomics, and *g*. *Molecular Psychiatry, 8*, 1–5.
Plomin, R., DeFries, J. C., & Loehlin, J. C. (1977). Genotype-environment interaction and correlation in the analysis of human behavior. *Psychological Bulletin, 84*, 309–322.
Plomin, R., & Rutter, M. (1998). Child development, molecular genetics, and what to do with genes once they are found. *Child development, 69*, 1223–1242.
Reik, W. J. (2001). Genomic imprinting: Parental influence on the genome. *Nature, 293*, 1089–1096.
Renthal, W., & Nestler, E. J. (2008). Epigenetic mechanisms in drug addiction. *Trends in Molecular Medicine, 14*, 341–350.
Roisman, G. I., & Fraley, R. C. (2008). A behavior–genetic study of parenting quality, infant attachment security, and their covariation in a nationally representative sample. *Developmental Psychology, 44*, 831–839.
Rowe, D. (2003). Assessing genotype–environment interactions and correlations in the postgenomic era. In R. Plomin, J. C. DeFries, I. W. Craig, & P. McGuffin (Eds.), *Behavior genetics in the post-genomic era*. Washington, DC: American Psychological Association.
Roy, A., Gorodetsky, E., Yuan, Q., Goldman, D., & Enoch, M. A. (2010). Interaction of FKBP5, a stress-related gene, with childhood trauma increases the risk for attempting suicide. *Neuropsychopharmacology, 35*(8), 1674–1683.
Roy, A., Hodgkinson, C. A., Deluca, V., Goldman, D., & Enoch, M. A. (2012). Two HPA axis genes, CRHBP and FKBP5, interact with childhood trauma to increase the risk for suicidal behavior. *Journal of Psychiatric Research, 46*(1), 72–79.
Rubin, B. S. (2011). Bisphenol A: An endocrine disruptor with widespread exposure and multiple effects. *The Journal of Steroid Biochemistry and Molecular, 127*, 27–34.
Scarr, S. (1992). Developmental theories for the 1990's: Development and individual differences. *Child Development, 63*, 1–19.
Scarr, S., & McCartney, K. (1983). How people make their own environments: A theory of genotype-environment effects. *Child Development, 54*, 425–435.
Schnable, P. S., Ware, D., Fulton, R. S., Stein, J. C., Wei, F., Pasternak, S., et al (2009). The B73 maize genome: Complexity, diversity, and dynamics. *Science, 326*, 1112–1115.
Science Daily (2011). *99% of Pregnany women in the US test positive for multiple chemicals including banned ones, study suggests*.
Singh, D. (1993). Adaptive significance of waist-to-hip ratio and female physical attractiveness. *Journal of Personality and Social Psychology, 65*, 293–307.
Sroufe, L. A., Egeland, B., Carlson, E. A., & Collins, W. A. (2005). *The development of the person: The Minnesota Study of risk and adaptation from birth to adulthood*. New York: Guilford Press.
Stanovich, K. E. (2004). *The robot's rebellion: Finding meaning in the age of Darwin*. Chicago: The University of Chicago Press.
Stein (1975). *Famine and human development: The Dutch hunger winter of 1944–1945*. NY: Oxford University Press.
Stevens, L. M., & Landis, S. C. (1988). Developmental interactions between sweat glands and the sympathetic neurons that innervate them: Effects of delayed innnervation on neurotransmitter plasticity and gland maturation. *Developmental Biology, 130*, 703–720.
Suomi, S. J. (2006). Risk, resilience, and gene environment interactions in rhesus monkeys. *Annals of the New York Academy of Sciences, 1094*, 83–104.
Suomi, S. J. (2000). A biobehavioral perspective on developmental psychopathology: Excessive aggression and serotonergic dysfunction in monkeys. In A. J. Samaroff, M. Lewis, & S. Miller (Eds.), *Handbook of developmental psychopathology*. New York: Springer.
Suomi, S. J. (2005). Mother-infant attachment, peer relationships, and the development of social networks in rhesus monkeys. *Human Development, 48*, 67–79.
Tooby, J., & Cosmides, L. (1992). Psychological foundations of culture. In J. Barkow, L. Cosmides, & J. Tooby (Eds.), *The adapted mind* (pp. 19–136). New York: Oxford University Press.
Turkheimer, E., Goldsmith, H. H., & Gottesman, I. I. (1995). Commentary—Some conceptual deficiencies in 'developmental' behavior genetics. *Human Development, 38*, 142–153.
Uher, R., Caspi, A., Houts, R., Sugden, K., Williams, B., et al (2011). Serotonin transporter gene moderates childhood maltreatment's effects on persistent but not single-episode depression: Replications and implications for resolving inconsistent results. *Journal of Affective Disorders, 135*, 56–65.
USFDA (2010). *Update on Bisphenol A for use in food contact applications*.
Waddington, C. H. (1942). Canalization of development and the inheritance of acquired characters. *Nature, 150*, 563–565.

Waddington, C. H. (1956). Genetic assimilation. *Advances in Genetics, 10*, 257–290.
Waterland, R. A., & Jirtle, R. L. (2003). Transposable elements: Targets for early nutritional effects of epigenetic gene regulation. *Molecular Cell Biology, 23*, 5293–5300.
Wcislo, W. T. (1989). Behavioral environments and evolutionary change. *Annual Review of Ecology and Systematics, 20*, 137–169.
Weaver, I., La Plante, P., Weaver, S., Parent, A., Sharma, S., et al (2001). Early environmental regulation of hippocampal glucocorticoid receptor gene expression: Characterization of intracellular mediators and potential genomic target sites. *Molecular and Cellular Endocrinology, 185*(1–2), 205–218.
Weaver, I. C. G., Cervoni, N., D'Alessio, A. C., Champagne, F. A., Seckl, J. R., Szyf, M., et al (2004). Epigenetic programming through maternal behavior. *Nature (Neuroscience), 7*, 847–854.
West-Eberhard, M. J. (2003). *Developmental plasticity and evolution*. New York: Oxford University Press.
Widiger, T. A., & Trull, T. J. (1992). Personality and psychopathology: An application of the five-factor model. *Journal of Personality, 60*, 363–393.