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How Do Interactions Between Early Caregiving Environment and Genes Influence Health and Behavior?

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Abstract

To promote optimal health and behavioral outcomes in children, nurses have long supported parents in providing the best possible care and nurturance to their offspring. A growing body of neuroscience research argues convincingly for the combined influences of genes and early caregiving on producing an individual's unique health and behavioral phenotype. In this article, we systematically review studies that demonstrate the relationship between qualities of early caregiving and genetic propensity to health and behavioral outcomes. From an initial set of 255 articles, 24 articles met our inclusion criteria. The outcomes fall into four distinct groups: hypothalamic-pituitary-adrenal (HPA) response to stress, externalizing behavior, internalizing behavior, and disorganized attachment. In the articles, authors examined genes that code for the *5-hydroxy tryptamine (serotonin) transporter genes linked polymorphic region* [5-*HTTLPR*] serotonin transporter promoter, D4 dopamine receptor, brain-derived neurotrophic factor, and monoamine oxidase A promoter. The reviewed studies suggest that the effect of the early rearing environment on gene expression relates mainly to HPA response to stress, whereas interactions between genes and caregiving mainly relate to behavior and attachment. Findings have implications for nurses focused on advocacy, prevention, and intervention to support the healthy development of children in families faced with adversity.

Keywords

epigenetics, gene expression, Gene-by-Environment interactions, early rearing environments, attachment

In the study of human health and development, there has long been contention between those who ascribe behavioral outcomes to genes and those who ascribe them to environmental influences. These two camps (known as *nature and nurture*, respectively) have often been construed as opposite poles in a continuum. However, a growing body of neuroscience research argues convincingly for an inclusive perspective wherein genes and the environment interact to produce a unique phenotype (Barr et al., 2003; Cirulli et al., 2009; Ellis, Boyce, Belsky, Bakermans-Kranenberg, & Van Ijzendoorn, 2011). The term *phenotype* refers to the observable characteristics of an organism. Unlike genotype, which refers only to an organism's DNA, phenotype encompasses the end product of biological, psychological, and social development.

To nurses specializing in health promotion, treatment, and disease prevention, phenotype can also refer to pathologies such as heart disease, obesity, depression, and reduced ability to cope with stress. Nurses may not recognize the dual contributions of genes and environmental factors to these disease states. Increasingly, international policy organizations trumpet the importance of the early years to long-term human health and developmental outcomes, with an explicit aim of embedding this understanding in the practice of health professionals such as nurses (e.g., Center on the Developing Child at Harvard University, 2007, 2010; McCain, Mustard, & Shanker, 2007). The American Academy of Pediatrics recommends action to prevent the exposure of children to toxic stress, explicitly characterized as adverse or traumatic early rearing experiences at the hands of their caregivers (Garner et al., 2012). Given that nurses have historically supported families to promote optimal children's (and thus population) health and development (U.S. Public Health Service, 1993), nurses need to be aware of and understand the neuroscience supporting and promoting policy shifts in this area. Moreover, such knowledge will ensure that nurses remain at the

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forefront of advocacy efforts to promote population health. Thus, the aim of this article is to summarize the accumulating neuroscientific theory and evidence explaining many of the health and developmental outcomes that nurses confront daily in order to simultaneously inform practice and advocacy to promote human health and prevent disease.

Retrospective studies have reported that stress in early childhood can cause a vast array of adverse conditions, disorders, and diseases. The Adverse Childhood Experiences study, a large-scale investigation examining over 17,000 participants, has produced more than 50 scholarly articles to date connecting childhood stress to conditions as diverse as alcoholism (Dube et al., 2006), drug addiction (Dube et al., 2003), lung cancer (Brown et al., 2010), autoimmune disorders (Dube et al., 2009), obesity (Williamson, Thompson, Anda, Dietz, & Felitti, 2002), and depression (Chapman et al., 2004). These studies provide solid evidence that stress in childhood and poor health outcomes in adulthood are closely linked. Neuroscience literature has begun to reveal that early stress, particularly when associated with alterations in caregiving experienced in infancy, may be the culprit behind many of the adult diseases nurses manage in daily professional practice (Miller, Chen, & Parker, 2011). Thus, to achieve our aim in this article, we systematically reviewed studies that demonstrate how early caregiving and genes interact to produce distinct phenotypic outcomes.

Specifically, we have focused on phenotypic outcomes predicted by both (1) epigenetic changes associated with caregiving (i.e., how environmental factors can alter gene expression) and (2) Gene-by-Caregiving Environment interactions (i.e., how genes modify susceptibility to environmental influences). Previous reviews have focused broadly on early life stressors without specific focus on maternal caregiving as a significant determining factor (Center on the Developing Child at Harvard University, 2010; Hertzman & Boyce, 2010; Schore, 1997). Due to the ethical challenge of manipulating caregiving in humans, much of the research on the effects of maternal care on health and development necessarily stems from nonhuman animal models. Accordingly, our review both (1) narrows the scope to facilitate a better understanding of how early maternal care, particularly with attachment figures, influences development and (2) broadens the scope to include both human and nonhuman (e.g., rodent and primate) literature. We seek to bridge the knowledge gap between neuroscience and nursing by presenting the findings of neuroscience studies and explaining their implications for nursing. Finally, this review is relevant to nurses who work with families in community health settings because recent neuroscience data underscore the value of their efforts to support caregiving and maternal–infant relationships in advocacy, policy, and practice domains.

Background

Epigenetics and Gene-by-Environment Interaction

Of our estimated 20,000 genes, most code for proteins responsible for human biological functions. Historically, changes in the expression of these genes were believed to be due solely to variants (mutations) in DNA. More recently, remarkable data have shown that changes in gene expression can occur without altering the genetic code itself. These findings have spawned the field of epigenetics: The study of how gene expression is influenced by mechanisms other than changes in the underlying genome (the genetic blueprint of DNA present in every cell). As a discipline, epigenetics draws from research in genetics, animal biology, and developmental psychology to explain how environmental influences alter gene expression. The epigenome consists of various molecules that influence the genome by changing the frequency with which genes are transcribed. Transcription is the first stage in the process that converts genes into protein products, giving the epigenome enormous influence over an organism's phenotypic outcome without actually rewriting its genetic code (Francis, 2011). Epigenetic changes occur after conception and can be modified by environmental influences, providing a mechanism by which early caregiving environments may indirectly impact phenotype.

The two most common forms of epigenetic regulation are methylation and histone modification. Methylation involves the conversion of cytosine (one of the four nucleotides comprising DNA, which include adenosine, cytosine, guanine, and thymine) in regions involved in gene regulation into a variant called 5-methylcytosine, which essentially silences the gene. This typically happens at a CpG site, a segment of DNA in which a cytosine occurs next to a guanine in the DNA sequence. Histone modification involves a different process. Histones organize the DNA into structural units and act as spools around which DNA is wound. One example of histone modification is the acetylation of histones, which relaxes the DNA strand so that genes are more available for expression. In contrast, deacetylated histones limit or entirely silence gene expression on the DNA target site. Whether or not a gene is silenced contributes to changes in gene expression and therefore may result in a specific change in phenotype. Although methylation and histone deactylation are two rather different mechanisms for epigenetic regulation, they both influence phenotype by limiting or silencing gene expression.

While epigenetics focuses on how environmental factors can alter gene expression, gene-by-environment ($G \times E$) interaction focuses on how genes modify susceptibility or, more recently, plasticity to environmental influences. The terms *multifactorial* and *polygenic inheritance* describe similar processes but focus mainly on susceptibility (Lewis, 2008). With relevance to caregiving, genes play a role in the relationships between adverse early rearing environments and internalizing (e.g., anxiety and depression) and externalizing (hyperactivity and aggression) behaviors in children (Bakermans-Kranenburg & Van IJzendoorn, 2006; Barr et al., 2003).

Historically, in $G \times E$ interactions, researchers regarded genes as providing a susceptibility to poor outcome characterized by the diathesis stress/dual risk theory (Ellis et al., 2011). From this perspective, the gene acts as a filter and the early environment as the stream of water passing through it. Should the stream contain some detritus (e.g., pseudomonas infection, exposure to tobacco

smoke, or poor caregiving), the filter would effectively strain out these impurities. An imperfect filter was of little consequence should the stream be pristine. However, when the water was murky and the filter malfunctioning, environmental pollutants passed unrestricted, causing trouble for the unlucky individual downstream. Accordingly, the effects of the environment on phenotype are not the same for all genetic variants—some genotypes allow greater susceptibility to the environment than others.

However, recent research and theory (Belsky et al., 2009; Ellis et al., 2011) suggest that some genotypes provide not only susceptibility but also plasticity. To extend the example, the filter (gene) is highly sensitive to the environment; if the water (early environment) passing through the filter is pristine, the filter functions better than in any other condition—the water produced is most potable. If the water passing through is very murky, the filter functions poorly. From this more contemporary perspective, the filter responds to the environment. This perspective is common to both the biological sensitivity to context theory and differential susceptibility theory, as they converge on the hypothesis that some individuals are more susceptible to both negative (risk-promoting) and positive (development-enhancing) environmental conditions (Ellis et al., 2011). In other words, while some genes may be associated with more maladaptive outcomes in negative environmental contexts (e.g., childhood abuse and tobacco smoke), those same genes may provide more adaptive outcomes in positive environmental contexts (e.g., sensitive nurturant caregiving). With respect to caregiving, based on genotype, authors have even described children as orchids (highly sensitive to caregiving stress, so more vulnerable or more successful, depending on the environment) and dandelions (less sensitive to caregiving stress, so less vulnerable yet less successful than orchid children; Ellis & Boyce, 2008).

In summary, in G × E there is no direct change to the expression of the genome. Instead, genomic variation results in a specific phenotype that is influenced by the environment. In epigenetics, environmental exposure changes the epigenetic regulation of specific genes, resulting in an altered phenotypic outcome. These mechanisms have profound implications for understanding how early caregiving influences short- and long-term health outcomes and, more importantly in the present context, how nursing interventions benefit children and families.

Attachment and Caregiving

Though G × E interactions and epigenetics are two different mechanisms of development, both are relevant to attachment theory. First proposed by renowned psychologist John Bowlby, attachment theory draws on evolutionary and developmental biology to describe the importance of attachment, defined as an infant's warm and continuous relationship with a caregiver, in promoting lifelong psychological health and well-being. In collaboration with Ainsworth (1967, 1973), Bowlby proposed that differences in the security of maternal–infant attachment may have significant long-term implications for psychopathology. Chisholm (1996) argued that sensitive and responsive parental care leads to secure infant attachment, while inconsistent or abusive patterns of caregiving lead to attachment insecurity, such as disorganization (Solomon & George, 1999). While a securely attached infant enjoys environmental exploration and is effectively comforted by his or her caregiver when distressed, an insecure infant may display a range of behaviors including anxiety, fear, and ambivalence toward or avoidance of the caregiver (Gervai, 2007; Waters & Valenzuela, 1999).

Most problematic is the disorganized attachment type, in which children engage in erratic and contradictory attachment strategies. Disorganized attachment is displayed by approximately 15% of infants in nonclinical samples; in maltreated samples, the incidence can be as high as 80% (Carlson, Cicchetti, Barnett, & Braunwald, 1989; Main & Solomon, 1990; Van IJzendoorn, Schuengel, & Bakermans-Kranenburg, 1999). Though maltreatment is almost certainly a primary cause of disorganized attachment, researchers have also begun to explore the role of certain polymorphisms as a catalyst for disorganized behavior. For example, Hertzman and Boyce (2010) described a cascade effect, beginning with caregiving quality and leading to changes in brain and body systems associated with mental health problems and chronic disease phenotypes. In particular, they noted the susceptibility of the hypothalamic–pituitary–adrenal (HPA) system, the central component of the body's stress response, to long-term changes in function associated with qualities of early caregiving. These brain and body changes help explain how early caregiving gets under the skin to create phenotypic outcomes.

Method

We conducted literature searches in March 2012 using no date or species restrictions and included the following search terms: genetic transformation, genetic, infants, and (parenting or parenting style or parenting styles or nurturing behavior or caregiving). We included studies in this review if (1) they were peer reviewed, (2) epigenetic or G × E interactions were examined as outcomes, and (3) outcomes were associated with variations in early caregiving. The time period associated with early caregiving was variously defined and species specific. Databases searched included all those available to the EBSCOhost and Ovid aggregator sites. After we removed duplicates, the EBSCO search yielded 195 potential articles and the Ovid search yielded 23 potential articles. We also used the ancestry approach, wherein we searched the reference lists of review articles or articles dealing broadly with pertinent subject matter, uncovering 37 additional papers. In total, we examined 255 unique papers for potential inclusion based on abstracts. Of these, we included 38 based on the abstract alone, 24 of which we finally included based on the full text.

Sample

The 24 studies that met inclusion criteria came from 5 countries: 11 from the United States, 7 from Canada, 4 from the Netherlands, 1 from Germany, and 1 from Hungary. They varied in study

Table 1. Outcomes Associated With Observed Changes in Gene Expression in Studies of Infant Stress Responses to Maternal Behavior in Rats.

	Heightened Sensitivity to Stress (Low LG-ABN Behavior)	Reduced Sensitivity to Stress (High LG-ABN Behavior)
Physical outcomes	Decreased oxytocin receptor binding[a]	Increased oxytocin receptor binding[a]
	Decreased estrogen receptor expression in the MPOA[a]	Increased estrogen receptor expression in the MPOA[a]
	Severe HPA responses to stress[b]:	Modest HPA responses to stress[b]:
	Increased plasma corticosterone responses to stress[b,c]	Reduced plasma corticosterone responses to stress[b,c]
	Increased ACTH responses to stress[b,d]	Reduced ACTH responses to stress[b,d]
	Reduced hippocampal GR expression[e]	Increased hippocampal GR expression[e]
	Poor glucocorticoid feedback sensitivity[e]	Enhanced glucocorticoid feedback sensitivity[e]
Behavioral outcomes	Less inclined to explore during open field test[c]	More inclined to explore during open field test[b]
	More reluctant to eat after food deprivation[c]	Less reluctant to eat after food deprivation[b]
	Inhibited under conditions of novelty[c]	Uninhibited under conditions of novelty[b]
Potential sequelae	Visceral obesity[b]	None noted
	Hypertension and insulin intolerance[b]	
	Diabetes[b]	
	Depression[b]	
	Drug addiction[b]	
	Coronary heart disease[b]	

Note. ACTH = adrenocorticotropic hormone; GR = glucocorticoid receptor; HPA = hypothalamic–pituitary–adrenal; LG-ABN = licking, grooming, and arched-back nursing; MPOA = medial preoptic area.
[a]Champagne, Dorio, Sharma, and Meaney, 2006.
[b]Szyf et al., 2005 (review).
[c]Francis, Diorio, Plotsky, and Meaney, 2002.
[d]Meaney and Szyf, 2005 (review).
[e]Weaver et al., 2005.

design, with 14 focused on humans, 3 on nonhuman primates, and 7 on rodents and 12 using experimental designs and 12 observational. We organized the studies into two broad categories: those that examined influences of caregiving on gene expression and those that examined interactions between caregiving variation and genetic susceptibility to phenotypic outcomes.

Results

The phenotypic outcomes of the studies fell into four distinct groups: HPA response to stress, externalizing behavior, internalizing behavior, and disorganized attachment. In the first section below, in which we discuss the effect of early rearing environment on gene expression (epigenetic change), we draw examples primarily from the first group, while in the second section, in which we explore G × E, the focus is on the latter three.

Caregiving's Effect on Gene Expression (Epigenetic Change)

Evidence shows that, not only are epigenetic changes associated with caregiving in rodents and humans, but also that these changes may be reversed by enrichment. As such, this evidence is particularly relevant to nurses interested in advocacy and clinical practice focused on prevention and intervention for families at risk. Most epigenetic studies have focused on the effect of caregiving on the HPA axis; when confronted with stressful stimuli (e.g., maltreatment), the HPA axis releases hormones including glucocorticoids (Szyf, Weaver, Champagne, Diorio, & Meaney, 2005). Glucocorticoids help to mobilize metabolic resources required for dealing with stress by binding with glucocorticoid receptors (GRs) to upregulate the production of anti-inflammatory proteins and return the organism to an unstressed state. However, epigenetic modification (methylation) in the exon 17 GR promoter prevents this binding, decreasing the facility with which the HPA axis can return to baseline after the threat of danger has passed and leaving the organism in a state of heightened sensitivity to stress. In nonhuman primates, chronic exposure to elevated levels of stress hormones predicts a multitude of deleterious conditions such as heart disease, depression, and a predisposition to substance abuse (for review see Szyf et al., 2005).

The most compelling evidence for caregiving's effect on gene expression comes from research in rats. Studies measuring the chemical and psychological responses of rats to stressful stimuli demonstrated a direct link between maternal behavior and infant stress response. More specifically, a mother's level of licking, grooming, and arched-back nursing (LG-ABN) behavior was correlated to epigenetic modifications resulting in several detectable changes in gene expression. High LG-ABN behavior was positively correlated to GR expression in the hippocampus (Caldji, Dorio, & Meaney, 2003; Francis, Dorio, Liu, & Meaney, 1999; Weaver et al., 2005), medial preoptic area (MPOA), estrogen receptor expression (Champagne, Dorio, Sharma, & Meaney, 2006), and enhanced glucocorticoid negative-feedback sensitivity (Weaver et al., 2005) and negatively correlated to levels of plasma adrenocorticotropic hormone (ACTH), hypothalamic corticotrophin–releasing factor, messenger ribonucleic acid (mRNA), and corticosterone response to stress. In Table 1, we summarize the outcomes associated with the observed changes in gene expression.

Table 2. Genes of Interest for Gene × Environment (G × E) Interactions and Their Associated Sequelae.

Gene	Simple Associations	G × E Associations
5-HTTLPR Serotonin transporter	Alcoholism, depression, anxiety, and affective disorders	Depression[a,b] and behavior problems[c]
Dopamine receptor D4 (*DRD4*)	Depression, anxiety, addictive behavior, ADHD, aggression, risk-seeking behavior, disorganized attachment, anorexia, Parkinson's disease, and schizophrenia	Disorganized attachment[d,e,f], and ADHD[g,h], aggression[g,h]
Brain-derived neurotrophic factor (*BDNF*)	Depression, epilepsy, and Alzheimer's disease	Depression[a]
Monamine oxidase A promoter (*MAOA*)	ADHD, antisocial behavior, aggression, and violent behavior	ADHD[i,j] and antisocial behavior[i]

Note. ADHD = attention-deficit hyperactivity disorder.
[a]Kaufman et al., 2006.
[b]Kaufman et al., 2004.
[c]Champoux et al. 2002.
[d]Bakermans-Kranenburg and Van IJzendoorn, 2006.
[e]Gervai, 2007.
[f]Van IJzendoorn and Bakermans-Kranenburg, 2006.
[g]Bakermans-Kranenburg, Van IJzendoorn, Pijlman, et al., 2008.
[h]Bakermans-Kranenburg and Van IJzendoorn, 2006.
[i]Kim-Cohen et al., 2006.
[j]Li and Lee, 2012.

HPA stress response and LG-ABN behavior passes from a mother to her offspring, making them heritable traits (Caldji et al., 2003; Champagne et al., 2006; Francis et al., 1999; Francis, Diorio, Plotsky, & Meaney, 2002). However, when infant pups of low LG-ABN mothers were cross-fostered to high LG-ABN mothers, their behavior, GR mRNA expression, and ACTH levels matched those of their high LG-ABN adopted mothers not their low LG-ABN biological mothers (Caldji et al., 2003; Francis et al., 1999; Francis et al., 2002; Weaver et al., 2005). The inverse was also true, with biological offspring of high (more nurturant) LG-ABN mothers fostered by low (less nurturant) LG-ABN mothers exhibiting their adopted siblings' predisposition toward heightened ACTH levels (Szyf et al., 2005), lowered GR mRNA gene expression (Weaver et al., 2005), and more anxious behavior (Champagne et al., 2006). Rodents' behavior in response to stressful stimuli is thus ''inherited'' epigenetically from their early rearing environment, not their genes.

This inheritance is caused by epigenetic modification (i.e., methylation or demethylation) of genes affiliated with the stress response, particularly the Neuron Growth Factor 1-A (NGF1-A) exon l7 GR promoter sequence. Prior to birth, the GR promoter sequence was unmethylated in pups of low and high LG-ABN mothers (Weaver, Diorio, Seckl, Szyf, & Meaney, 2004). It became methylated on neonatal Day 1, again in both groups. Between neonatal Days 1 and 6, the 5′ CpG dinucleotide of the NGF1-A-response element became unmethylated in high LG-ABN pups while remaining methylated in low LG-ABN pups. This period was precisely the same in which the difference in high and low LG-ABN mothers' maternal behavior became apparent. Beyond neonatal Day 20, the GR promoter sequence tended to maintain its methylated/unmethylated status for the remainder of the rodent's life. However, changes to this status can be induced, even in fully developed adult rodents. Infusing low LG-ABN rodents with a histone deacetylase inhibitor, called trichostatin A, significantly increased demethylation and binding of protein NGF1-A (a transcription factor associated with increased GR expression on the exon I7 promoter site), augmenting these factors to levels comparable to high LG-ABN rodents. This augmentation in turn improved the function of the hippocampus, a region of the brain associated with converting short-term memory into long-term memory. High LG-ABN rodents' exon I7 promoter sites were already unmethylated, which meant they were unaffected by this treatment.

Less invasive measures also reversed the effects of negligent upbringing. Francis, Diorio, Plotsky, and Meaney (2002) divided rats into two groups based on their stress response. High-stress rats had higher levels of corticosterone than low-stress rats and exhibited more nervous behavior. Investigators then placed a random selection of high- and low-stress rats in ''enriched conditions'' designed to stimulate their emotional and cognitive development. High-stress rats in enriched conditions later developed corticosterone and behavioral responses to stress in line with low-stress rats. Enrichment had little effect on low-stress rats, as their mothers' high LG-ABN behavior provided them with what was effectively an enriched environment immediately after birth. This change in reactivity and disposition, which occurred well after the typical methylation pattern in the rodents had already been set, shows a promising potential for epigenetic change beyond the early formative years, allowing for successful intervention.

Early life stress influenced epigenetic markers in studies involving humans as well. Maternal stress during a child's infancy was associated with increased methylation in 139 CpG sites throughout the genome, while paternal stress during preschool years was linked to similar results in 31 genetic sites

(Essex et al., 2011). As with rodents, intervention has the potential to reverse these effects in humans. Parents of 1- to 3-year-old children who exhibited high levels of externalizing behavior were randomly assigned to an intervention program where professional child care educators guided parents to be sensitively responsive to their infants or to a comparison program. Children in the intervention group exhibited reduced levels of cortisol, signifying that their stress response systems had become less reactive due to the changes in their parental caregiving (Bakermans-Kranenburg, Van IJzendoorn, Mesman, Alink, & Juffer, 2008). However, investigators found this reduction only in children who possessed the 7-repeat polymorphism of the D4 dopamine receptor (*DRD4*) gene. For children with less reactive polymorphisms, the intervention had little effect on cortisol levels.

Gene × Environment Interactions

A growing body of research reveals the interaction between genotype and early environment, in which the two factors jointly contribute to phenotype. Genes that have attracted researchers' interest include the *5-hydroxy tryptamine (serotonin) transporter genes linked polymorphic region* [*5-HTTLPR*] serotonin transporter gene, the *DRD4* gene, the brain-derived neurotrophic factor gene (*BDNF*), and the monamine oxidase A (*MAOA*) promoter polymorphism. See Table 2 for the genes and their associated phenotypes.

Researchers have shown that the *5-HTTLPR* serotonin transporter gene influences the susceptibility of human and nonhuman primates to a number of adverse conditions, including alcoholism, depression, and anxiety (for review see Barr et al., 2003). The short (s) allele of the *5-HTTLPR* polymorphism causes lower transcriptional efficiency in comparison to the long (l) allele (Lesch et al., 1996) and as such is associated with increased environmental susceptibility (Barr et al., 2003). The *DRD4* gene has been considered a contributing factor to depression (Tochigi et al., 2006), anxiety (Tochigi et al., 2006), addictive behaviors (Lerman et al., 1998), attention-deficit hyperactivity disorder (ADHD; Ebstein, Benjamin, & Belmaker, 2002), aggression (Ebstein et al., 2002; Schmidt, Fox, Rubin, Hu, & Hamer, 2002), and attachment disorganization (Lakatos et al., 2000). More specifically, studies investigating G × E interaction have focused on a 48-bp repeating sequence in the third exon of the gene (Van Tol et al., 1992). The sequence can repeat from 2 to 10 times. The 7-repeat allele is less efficient at transcription and translation than the more common 2- or 4-repeat alleles. Outcomes that have been associated with all four of these genes in humans include externalizing behaviors and disorganized attachment.

Externalizing Behavior

Externalizing behavior disorders encompass a range of behavioral phenotypes in which the affected child directs his or her emotions outward in an uncontrolled, disruptive, or violent manner (Liu, 2004). Subgroups of this behavior include aggression, delinquency, and hyperactivity. Most of the research in this area has involved nonhuman primates. McCormack, Newman, Higley, Maestripieri, and Sanchez (2009) examined the effect of mother macaques' abusive parenting on their 6-month-old offspring's behavior as mediated by the *rh5-HTTLPR* gene. They found a significant correlation between the *rh-5HTTLRP* l/s allele and increased behavioral problems in both abused and nonabused infant macaques, though abused l/s infants fared even worse than their nonabused peers. The authors found a similar correlation in the abusive tendencies of the nonhuman primate mothers, with 9 of the 10 mothers in the abusive cohort possessing the l/s allele. Previous studies supported these findings (Bennett, Lesch, Heils, & Linnoila, 1998; Champoux et al., 2002).

Much like the rh-*5HTTLPR* l/s polymorphism in nonhuman primates, research has repeatedly shown the *DRD4* 7-repeat allele in humans to increase susceptibility to poor early rearing environments. Infants with the *DRD4* 7-repeat allele showed significantly more signs of externalizing behavior in environments of low parental sensitivity than those in high-sensitivity homes (Bakermans-Kranenburg & Van IJzendoorn, 2006). Conversely, infants without the 7-repeat allele displayed similar amounts of externalizing behavior regardless of whether they were reared in high-sensitivity or low-sensitivity homes, scoring substantially lower than children with insensitive parents and the 7-repeat allele but higher than 7-repeat-allele children raised in nurturing, sensitive environments. The authors replicated these results in a similar study (Van IJzendoorn & Bakermans-Kranenburg, 2006).

Extrapolating on these findings, Bakermans-Kranenburg, Van IJzendoorn, Pijlman, Mesman, and Juffer (2008) randomized human mothers to either a video-feedback intervention to promote positive parenting and sensitive discipline or a comparison condition and examined the intervention effectiveness on children 1–3 years of age with various *DRD4* exon III polymorphisms. Externalizing behavior decreased in the intervention group but only in children with the *DRD4* 7-repeat allele; children without the 7-repeat allele did not substantively benefit from the program.

Jaffee and colleagues (2005) examined the effect of G × E interactions in a large cohort of 5-year-old monozygotic (MZ) and dizygotic (DZ) twins without focusing on a specific gene. Genetic risk for conduct disorder was established based on the interaction between children's zygosity and the behavior of their twin. MZ children whose twins had been diagnosed with conduct disorder were at the highest risk followed by DZ children with diagnosed twins, DZ children with undiagnosed twins, and, at the lowest risk, MZ children whose twins had not been diagnosed. Children's level of genetic risk corresponded directly with their level of conduct problems, with frequency of conduct disorders ascending along with level of genetic risk. However, the rate of ascension was much steeper in maltreated children (defined by mothers' reports of child physical abuse or corporal punishment) than in children who had not experienced maltreatment. Maltreated children in the lowest risk group were only slightly more likely to exhibit disorderly conduct than children in the same risk

Table 3. Stress Response of Newborn Pups of Type B and Type C Mice Randomly Cross-Fostered to Mothers of the Same or Opposite Strain.

Pup Type	Raised by Type B Mothers	Raised by Type C Mothers
Type B mice (fearful)	Skittish, fearful, and performed poorly on test	Fearless, curious, and performed well on test
Type C mice (fearless)	Fearless, curious, and performed well on test	Fearless, curious, and performed well on test

Note. Data are from Caldji et al., 2004.

group who were not maltreated; by contrast, maltreated children in the highest risk group exhibited disorderly conduct substantially more often than their nonmaltreated peers.

Another study linked genetic risk of externalizing behavior in 7-year-old boys to their *MAOA* promoter polymorphisms (Kim-Cohen et al., 2006). This gene promotes the development of the enzyme called monoamine oxidase A, which breaks down neurotransmitters such as serotonin, dopamine, and adrenaline. Children with the low-activity *MAOA* genotype who had been exposed to familial adversity (e.g., physical abuse or interparental violence) were twice as likely to exhibit mental health problems as children with the high-activity genotype who had been similarly exposed. In a similar study, the probability of conduct disorder in children with low *MAOA* reactivity was positively correlated to their level of exposure to childhood adversity, defined as exposure to interparental violence, parental neglect, or inconsistent discipline (Foley et al., 2004). Each increase in a child's level of exposure exponentially increased that child's likelihood of disorderly conduct. The same was not true of children with high *MAOA* reactivity, where increases in the level of exposure to childhood adversity actually decreased the probability of a child displaying disorderly conduct. Other studies addressing similar criteria, however, have either failed to find a significant link between *MAOA* genotype and sensitivity to context (Haberstick et al., 2005) or found that the low-reactivity *MAOA* polymorphism had a moderating effect on externalizing behavior, while the high-activity polymorphism increased sensitivity (Li & Lee, 2012).

In summary, both nonhuman primate and human research suggest that the early rearing environment has an effect on a child's propensity for externalizing behavior, though the precise nature of this effect will only be revealed upon further study. Moreover, genotypic variation may help explain the variable effect of interventions targeting parenting.

Internalizing Behavior

Internalizing behavior disorders are emotional problems directed inward including depression, anxiety, social withdrawal, and neurosis (Liu, 2004). As with externalizing behavior, researchers have observed interactions among early rearing environment, genotype, and predisposition toward internalizing behavior in human and nonhuman species.

Caldji, Dorio, Anisman, and Meaney (2004) selected two strains of mice, called *Type B and Type C*, for a cross-fostering study. Type B mice display greater fear of novelty and HPA responses to stress than Type C mice. As shown in Table 3, when newborn pups of Type B and Type C strains were randomly cross-fostered to mothers of the same or opposite strain, Type B (fearful) mice raised by Type C (fearless) mothers showed less fearfulness than Type B mice raised by Type B mothers. However, Type C mice displayed low levels of fearfulness regardless of whether they were raised by Type B or Type C mothers.

Tests on humans have yielded similar findings. In a 2004 study, Kaufman et al. found a strong correlation between an abusive rearing environment and high depression scores among children aged 5–15 years with the s/s allele of the *5-HTTLPR* gene. However, nonabused children with the s/s allele achieved depression scores far lower than their counterparts from abusive environments and similar to children with the l/l or l/s allele from both abusive and nonabusive homes. A larger study by the same group affirmed these results (Kaufman et al., 2006). In this later study, the researchers once again found that children from abusive environments with the *5-HTTLRP* s/s allele are more susceptible to depressive behavior than s/s children from nonabusive homes or children from either environment with the l/s or l/l alleles. Interestingly, Bennett, Lesch, Heils, and Linnoila (1998) showed that the more sensitive s/s allele acts as a protective factor in certain environments.

Kaufman et al. (2006) also examined the effects of the *BDNF* gene, which controls levels of BDNF, a protein shown to influence susceptibility to depression. Researchers coded children for either the val/val or val/met *BDNF* polymorphism, with *val* referring to the high-reactive allele and *met* to the low-reactive allele. In terms of genetic susceptibility, the BDNF val/val allele would be equivalent to the *5-HTTLPR* l/l polymorphism, while *BDNF* val/met resembles *5-HTTLPR* l/s. Findings indicated an interaction between maltreatment history, *BDNF*, and *5-HTTLPR* genotype, as at-risk children (those from abusive environments with the s/s allele) who possessed the val/met polymorphism scored higher on depression scales than those who were at risk but possessed the val/val type.

Internalizing behavior disorders, like externalizing behavior disorders, may benefit from treatment informed by children's genotype. Knowledge of the polymorphisms of the genes discussed above, and doubtless many others not yet explored, may improve and customize nursing interventions for children at risk of internalizing behavior disorders. Regardless, across species, it is apparent that more optimal caregiving environments, like those advocated for and promoted by nurses every day, proffer a greater likelihood of a healthy outcome for offspring.

Disorganized Attachment

Certain polymorphisms may increase a child's risk of developing disorganized attachment. Infants with the *DRD4* 7-repeat

allele whose mothers had experienced an unresolved loss, such as the death of a loved one, were 18.8 times more likely to exhibit disorganized behavior than infants raised in similar conditions without the 7-repeat allele (Van IJzendoorn & Bakermans-Kranenburg, 2006). However, the *DRD4* 7-repeat allele did not confer greater risk of disorganized attachment when infants were exposed to maternal behavior that was threatening or frightening. This finding is surprising, since parenting behaviors, at least in theory, are a more proximal risk factor for disorganized attachment. In contrast, Gervai (2007) found that infants without the 7-repeat allele were significantly more susceptible to disruptive parenting, while infants with the 7-repeat allele were, in terms of disorganized attachment, effectively immune. Spangler, Johann, Ronai, and Zimmermann (2009) found that *DRD4* had no influence whatsoever on disorganized attachment, noting instead an association between the *5-HTTLPR* genotype and disorganized attachment. Infants with the s/s allele were four times more likely to exhibit signs of disorganized attachment than infants with the l/l allele if the mothers engaged in low-sensitive maternal behavior. When mothers used a high-sensitive parenting style, this discrepancy disappeared. Luijk et al. (2011) found no significant correlations among the *DRD4* or *5-HTTLPR* genotype, maternal sensitivity, and infant attachment strategy. Considering these contradictory findings, the evidence of G × E interactions influencing disorganized attachment remains equivocal. The evidence that environmental factors influence a child's probability of exhibiting disorganized attachment behaviors, however, is substantial.

Discussion

Nurses engaged in prevention and intervention work targeted at supporting parent–infant relationships will find these studies encouraging. Like other reviews that examine the influence of parenting support in infancy on child health and developmental outcomes (Barlow et al., 2010), the present review also revealed that the quality of a child's caregiving environment impacts his or her chances of experiencing increased internalizing, externalizing, and disorganized attachment behavior. Perhaps the most well-regarded nursing intervention program focused on parenting support, the Nurse–Parent Partnership Program (Olds et al., 2007), similarly demonstrates improvements in multiple domains including child and adolescent mental and physical health. The current review adds to this literature by pointing out mechanisms by which changes in the early caregiving environment, induced by nursing support and care, may produce more optimal outcomes in children. Armed with this knowledge, nurses will be more cognizant advocates for such important services for families at risk.

Nurses have a historical advocacy role in seeking to promote children's health and development. Though the most vital period in determining a child's behavioral outcome may be the first year of his or her life, enrichment studies suggest that, under the right conditions, behaviors can be modified at a later age (e.g., Bakermans-Kranenburg, Van IJzendoorn, Pijlman, et al., 2008; Francis et al., 2002). These findings are supported by studies of Romanian institutionalized adoptees, which revealed the effects of early caregiving deprivation. While institutionally deprived children adopted before the age of 6 months fared quite well, children adopted beyond that age were significantly more likely to suffer negative effects as a result of their deprivation (Fisher, Ames, Chisholm, & Savoie, 1997; Mainemer, Gilman, & Ames, 1998; Marcovitch et al., 1997). However, Fisher, Ames, Chisholm, and Savoie (1997) showed that enrichment reversed some of these effects. Unfortunately, such a reversal is often only partially successful (Beckett et al., 2006), which speaks to the profound importance of nurses' prevention efforts aimed at supporting parent–infant relationships. Nurses can use this knowledge to enhance advocacy efforts and contribute to policy dialogue for enhanced services for at-risk families.

In studies of children in early intervention, more substantive gains appear to be associated with programs that utilize approaches to support parents and promote optimal parent–infant relationships, as opposed to merely emphasizing parental education and parenting behavior (Doherty, 2007; Geddes Haw, & Frank, 2010). Maternal nurturance may be an influential source of resilience, offsetting the risky hormonal, metabolic, inflammatory, and cardiovascular profiles that tend to develop in children exposed to childhood adversity (Miller et al., 2011). However, because the present review is limited by its exclusive focus on the influence of early caregiving on later health and development, we necessarily overlooked other research that has demonstrated, for example, that chronic interpersonal stress in adulthood (not just childhood) mediates the relationship between early caregiving stress and adult recurrent depression (Kessler & Magee, 1994).

Reports of studies of early interventions rarely include genetic markers or examine gene and environment interactions (Bakermans-Kranenburg & Van IJzendoorn, 2006, and Bakermans-Kranenburg, Van IJzendoorn, Mesman, et al., 2008 are notable exceptions). The findings of the present review provide reason to consider the contribution that genetic screening could make to identifying children and families at risk or who may most benefit from nursing intervention. Future research may determine the utility of such additions to standard screening, which traditionally focuses on family history and other psychosocial risk factors for determination of eligibility for public health nursing service provision (Doherty, 2007; Geddes et al., 2010).

The present review shows that adverse conditions in early life can elevate stress reactivity (e.g., HPA axis), and others have suggested that adverse early conditions can lead to a greater risk for a number of poor outcomes (Hertzman & Boyce, 2010). Moreover, some genotypes (i.e., the *DRD4* 7-repeat allele, the *5-HTTLPR* s/s polymorphism, etc.) exacerbate this risk, as they render the carrier particularly susceptible to variations in caregiving. Biological sensitivity to context and differential susceptibility theories provides a more positive framework for these findings. In these theories, heightened sensitivity to early rearing environment (high reactivity) is not

an inherently maladaptive trait. Rather, both high and low reactivity can be advantageous, depending on a child's situation. Though high-reactive children respond poorly to adverse environs, exhibiting greater signs of externalizing and internalizing behavior, they respond especially well to supportive, stable conditions (Boyce & Ellis, 2005). Low-reactive children, on the other hand, are resistant to environmental influences. Their stress responses are less likely to be negatively impacted by adverse early rearing conditions than their high-reactive peers, but they will also benefit less from stable, nurturing environments.

A child's biological sensitivity to context is not randomly determined but rather is calibrated by his or her early rearing environment. Under conditions of great adversity or exceptional security and support, children are disproportionally likely to exhibit high sensitivity to context; when exposed to the occasional and moderate levels of stress typical of an average home, they are more likely to develop low sensitivity to context (Boyce & Ellis, 2005; Ellis, Essex, & Boyce, 2005). At both extremes, high reactivity was once an effective survival strategy. For children subjected to large amounts of stress, high sensitivity would allow them a heightened awareness of danger, potentially increasing their chances of survival; for children in secure, nurturing environments, high sensitivity would allow children to take full advantage of the resources available to them, drawing greater emotional nourishment from their surroundings (Boyce & Ellis, 2005). Children whose early rearing environment fell in the middle of the spectrum, on the other hand, would have benefited more from lower sensitivity to context, as it would have provided greater resilience in the face of changing or uncertain conditions. A number of studies in our review achieved results that fit Boyce's model (Bakermans-Kranenburg & Van IJzendoorn, 2006; Bennett et al., 2002; Ellis et al., 2005; Gervai, 2007; Kim-Cohen et al., 2006; Van IJzendoorn & Bakermans-Kranenburg, 2006). For nurses engaged in advocacy and practice supporting at-risk families and children, it is important to note that the more optimal caregiving environments produced the most optimal outcome, regardless of genotype or biological sensitivity.

In conclusion, both early environment-based modification of gene expression and G × E interaction contribute substantially to the development of the childhood as well as the adult phenotype. Though the precise nature of these contributions may not yet be fully understood, more study of the interaction between caregiving and genetics is warranted, especially to inform the effective use of family nursing interventions to support healthy child development. Moreover, across conditions, sensitive caregiving almost always produces the most optimal outcomes for offspring. Curiously, in a few of the studies we have examined, children with low-reactive genotypes (*5-HTTLPR* l/l allele, 4- or 2-repeat *DRD4* allele, etc.) exhibited lower externalizing or internalizing behavior when raised in less stable conditions (Bakermans-Kranenburg & Van IJzendoorn, 2006; Li & Lee, 2012). However, these discrepant studies did not examine the role of supportive early rearing environments but rather of stabilility of caregiving. Differences were also slight, particularly when compared to the relatively larger magnitude of environmental influence observed in children with high-reactive genotypes.

Future discoveries regarding the effects of epigenetics and G × E interactions on behavioral outcomes may allow us to develop more sophisticated and effective interventions. In the meantime, nursing efforts to provide parental support should strive to provide more nurturant caregiving conditions, as sensitive early caregiving environments are universally beneficial and within the power of nurses to create.

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