Conceptual Shifts Needed to Understand the Dynamic Interactions of Genes, Environment, Epigenetics, Social Processes, and Behavioral Choices

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Social and behavioral research in public health is often intimately tied to profound, but frequently neglected, biological influences from underlying genetic, environmental, and epigenetic events. The dynamic interplay between the life, social, and behavioral sciences often remains underappreciated and underutilized in addressing complex diseases and disorders and in developing effective remediation strategies.

Using a case-study format, we present examples as to how the inclusion of genetic, environmental, and epigenetic data can augment social and behavioral health research by expanding the parameters of such studies, adding specificity to phenotypic assessments, and providing additional internal control in comparative studies.

We highlight the important roles of gene–environment interactions and epigenetics as sources of phenotypic change and as a bridge between the life and social and behavioral sciences in the development of robust interdisciplinary analyses. (Am J Public Health. 2013;103:S33–S42. doi:10.2105/AJPH.2013.301221)

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EACH DAY, NEW DATA accumulate to provide insights that strengthen the link between the life sciences and the social and behavioral sciences. Phenotypes that are elaborated by the social and behavioral sciences are increasingly being given detail by our enhanced identification and interpretation of the relevant genetic, environmental, and epigenetic factors of influence. The enhancement of social and behavioral science studies with biological data are integrative, 21st century science. This technology-invigorated paradigm shift looks beyond the constricting “nature versus nurture” dichotomy of causation and promises to clarify many of the controversies that emerge when similar phenotypes have diverse underlying mechanisms. Instead of the 2 intellectual traditions of biological orientation and social construction being perceived as being in conflict, we find that greater explanatory power is observed when these traditions are considered together. This kind of integrated thinking is not entirely new because it was evident among such scholars as B. F. Skinner, who saw behavior as a naturally occurring biological phenomenon of interest in its own right, functionally related to surrounding events, and subject to selection by its consequences. In this context, the notion of gene–environment interactions gained significant attention during the last 2 decades, with the development of epigenetics. Epigenetic processes are heritable, and some possibly nonheritable modifications (or patterns) in gene expression that are regulated by mechanisms other than changes in the DNA sequence. However, only recently have we had the necessary computational advances in place and access to raw data to recognize and quantify important genetic, environmental, and epigenetic variables, and then truly conceptualize the balanced and complementary mergers of these diverse databases. Such a merger would be, at its best, one that allows us to address both the structural and functional domains in social and behavioral science research and place this research in both ecological and evolutionary contexts.

Integrative approaches that incorporate genetic and epigenetic evaluations into social and behavioral science research have the potential to tease out cross-cultural differences whose assessments may reflect, in part, the embedded social and cultural values of the researchers. Increasingly, knowledge of genetically and epigenetically based functional and structural alterations can augment and enhance our understanding of the underpinnings of a range of abnormal phenotypes, and clarify the social and situational contexts within which such phenotypes are likely to arise, become reinforced, and acted upon. Disciplinarily integrative approaches can broaden the parameters of social and behavioral research, increase the power of such studies, produce extraordinarily unique and valuable perceptions that would otherwise remain invisible, and develop more sustainable public health interventions.

This article is structured as an analytical essay extended with supportive case studies. We give a general overview of genetics, the environment, and epigenetics, and then emphasize the increasing importance of viewing gene–environment interactions and epigenetics as potential conduits for understanding the links among the life, social, and behavioral sciences in disease expression and its potential remediation. We then provide specific examples from the scientific literature in which genetic, environmental, and epigenetic information can contextualize and enhance our interpretations of the social processes and behavioral choices that modulate diseases and disorders of public health significance. These well-grounded examples are an effort to identify where specific biophysical information has illuminated and often transformed the working assumptions of social and behavioral scientists. Finally, we propose several health-related situations in which new information on the genome, the environment, and epigenome may usefully enhance the explanatory powers of the social and behavioral
dimensions of health and disease, particularly with reference to health disparities.

CENTRALITY OF THE PHENOTYPE

Classically, the phenotype includes the observable properties of an organism that are produced by gene–gene interactions and by the genotype and its interface with the environment. The environment includes all of the social, cultural, psychological, abiotic, and biotic components that surround the individual and to which that individual is responsive. The environment not only includes the sociocultural but also the biophysical factors, and these cumulatively provide the functional programming for gene expression via the epigenome.

Problems have arisen in social and behavioral research when the phenotypes of interest have often been genetically or environmentally complex. In these cases, the impact of the environment on the phenotype has often been inadequately quantified, and in many cases, phenotypes of diverse origins have been lumped together as if they reflected a single mode of causation. However, the phenotype remains the key unit of analysis in many social and behavioral studies of health and disease. It is the phenotype that is the initial focus of evolution. Although the phenotype is easily accessible for most social and behavioral studies, its assessment is often confounded by its own intricacy; most social and behavioral research cannot distinguish, for example, between a phenocopy (an individual resulting from exposure to special environmental conditions) from the mimicked phenotype caused by the expression of a genetic mutation.

In a recent study of the antisocial brain, Gregory et al. characterized a group of men who displayed persistent antisocial and violent behavior. Although they recognized that this group was likely heterogeneous, they identified a distinct subgroup that had callous-unemotional traits in childhood and psychopathic traits in adulthood solely on the basis of the amount of structural gray matter (GM) in areas of their brains associated with empathic processing, moral reasoning, and processing of prosocial emotions such as guilt and embarrassment. The cause of these reduced GM volumes in this subgroup remained unspecified; some of the men may have been the direct products of a constellation of gene mutations with indirect environmental effects, whereas other men could have been directly environmentally produced phenocopies of this pathophenotype. Without this clarification, of course, successful remediation is much more problematic. Other recent studies from Germany have noted that research aimed at identifying structural brain alterations associated with persistent violent behavior or psychopathy often have not adequately accounted for a lifetime history of substance misuse that could produce a phenocopy of the targeted phenotype. Thus, gross alterations in GM volume that have been reported to be correlates of violent behavior or psychopathy may instead be related to lifelong substance use disorders.

A persistent limitation in many social and behavioral research studies is that self-reported or interviewer-based approaches are often used to identify phenotypes without the genetic or epigenetic assessment of those phenotypes at the molecular levels of analysis. Additionally, a number of social and behavioral studies have compromised on the careful attention needed to recognize the long-term environmental influences at specific developmental stages in the lives of affected individuals. Significant environmental effects early in life can trigger certain patterns of gene expression only evident phenotypically later in life. These omissions have handcapped the development of more refined and nuanced investigations and the development of precise, targeted interventions. By putting the findings from brain research, for example, in a wider genetic and environmental context, we can clarify the diversity underlying the antisocial brain in a way that does not neglect the psychological and social aspects of the human mind and behavior.

CONTRIBUTION OF EPIGENETIC MECHANISMS

Two centuries ago Jean-Baptiste Lamarck hypothesized that physiological characteristics acquired in life (caused by environmental exposures) can be passed on to the offspring (i.e., soft inheritance). Until relatively recently, his theory was largely disregarded, especially because of Darwin’s theory of evolution and the extraordinary progress made in the field of genetics, which offered a very compelling rationale supporting the notion of random genetic mutations that induce a competitive advantage, and hence, the process of selection. In this model, the phenotype was solely a reflection of gene–gene interactions. In many cases, the environment was not as rigorously defined as was needed to demonstrate a causal interaction with specific genes and gene products. Additionally, a direct correspondence was presumed between specific gene sequences and the expression of specific gene products. Linear, reductionist thinking dominated these Darwinian (and some neo-Darwinian) models.

However, Lamarck’s theory was recently and partially resurrected as a result of scientific advances in the field of epigenetics, which enabled the understanding of how such acquired traits can be inherited. Epigenetic modifications are defined today, most frequently, as heritable changes in gene expression that are independent of any alteration in the DNA sequence, although other definitions extending the concept to cell development, are also used. Of course, not all Lamarckian theory received acceptance by modern scientists (i.e., the use and disuse component), but modern research demonstrated that environmental triggers can induce changes in phenotypes not only in the exposed individuals, but also in the offspring who were not directly exposed to these influences.

DNA methylation is the chemical modification of nucleotides by the substitution of hydrogen with a methyl group. In eukaryotes, this process occurs most frequently at position 5 within the cytosine ring (5-methylcytosine), when cytosine is followed by a guanine nucleotide (CpG site), but other nucleotides can also undergo methylation. Cytosine methylation is catalyzed by DNA methyltransferases, which participate to either maintain the DNA methylation profile throughout cell replication (inherited methylations) or to establish a new methylation profile (de novo DNA methylation).

DNA methylation can be linked functionally with histone
epigenetic changes revived

interaction between maternal genetic processes such as DNA hydroxymethylation and microRNA expression also contribute to establishing epigenetic patterns.12

During embryonic and fetal development, dynamic changes in DNA methylation allow for the erasure of some parental epigenetic profiles, and the establishment of new patterns that are specific to each cell type and which define the stable cellular phenotypes of cells.10 Other processes such as DNA hydroxymethylation and microRNA expression also contribute to establishing epigenetic patterns.12-15

During embryonic and fetal development, dynamic changes in DNA methylation allow for the erasure of some parental epigenetic profiles, and the establishment of new patterns that are sensitive not only to the maternal environment, but also to the interaction between maternal organisms and environment.16 Interestingly, not all the genes undergo this modification because the epigenetic pattern of some genes is retained from parents (imprinted genes), a process called parent-of-origin effect, and which constitutes the basis for monozigotic expression.17 However, the dynamics of DNA methylation are not confined to early development stages, but are also responsible, in part, for physiological and pathological changes associated with aging.18 So throughout the lifespan, epigenetics can influence the phenotype that is at the foundation of our social and behavioral analyses.

MISMATCH THEORY

The ability of DNA to be subject to epigenetic changes revived Lamarck’s theory of soft inheritance because it indicated that the environment can affect gene expression in both direct and indirect ways, with both immediate- and long-term ramifications. As a consequence, epigenetic patterns in the offspring can be altered by the interactions between the maternal organism and the environment. This led to the theories postulating that (1) many chronic noncommunicable diseases have their origins early in life (Developmental Origins of Health and Disease, or DOHaD), and (2) a causal relationship exists between epigenetic modifications and early exposures to unpredictable environmental conditions.19,20 This has helped us to better understand how genetics and epigenetics interact in an attempt to establish optimal phenotypes that would best fit in predicted environments, and also how the failure to correctly predict environmental exposures leads to pathological consequences (The Mismatch Theory; Figure 1).19,21

PHENOTYPIC DEVELOPMENTAL PLASTICITY

The recognition that our phenotypes can be influenced by early environmental exposures led to the theory of developmental plasticity, which states that epigenetic mechanisms evolved as a strategy to cope with predicted circumstances, to maximize the biological fitness of our genotypes in the context of potential environmental challenges to be met, and in the context of the genetic potential given by a particular genomic structure.21

Epigenetic modifications have been previously reported to be highly associated with risk of disease in both human and animal models.18,22 We have postulated that both genomic and epigenomic structures have to be taken into account when assessing the degree of biological fitness of an individual in the context of specific environmental exposures,23 and that behavioral and decisional consequences can be derived from this interplay.20

One of the best ways to study the importance of epigenetic modifications in shaping the phenotype is using monozygotic

![Image](image.png)

Note. Each individual has a unique genotype because of variations in the DNA sequence and sometimes the inclusion of more than 2 alleles for a given gene (copy number variations [CNVs]). CNVs are abnormal number of copies of a section of DNA that includes both insertions and deletions. This genetic makeup defines, in theory, a unique phenotype (Phenotype 1), if no external influences are considered. In a largely non-optimal environment, with, for example, the stress of food scarcity, evolutionary pressure will select those individuals who are able to more efficiently and more quickly adapt their gene expression patterns (via epigenetic mechanisms) to a fluctuating environment (Phenotype 2). This requires a continuous “returning” of their metabolic needs to the available foods. Maternal dietary intakes influence the offspring in retuning its own epigenetic status to maximize the potential offered by the genetic makeup, in the context of a given (in this case, food scarce) environment. However, in economically developed countries, the presumption of food scarcity is not true, and specific foods can be easily replaced. Therefore, the epigenetic tuning (via maternal nutrition), leads to a mismatch between the predicted conditions (scarce food) and the real food availability (abundant food). The mismatch that occurs between the predicted environment and the existing environment leads to the early development of chronic disease (e.g., childhood obesity, Phenotype 3). The crossed box for Phenotype 1 indicates that such a phenotype cannot be achieved as long as environmental pressures exist.

FIGURE 1—The Mismatch Theory.
twin pairs. During the last decade it has been clearly indicated that the phenotypic differences in monozygotic twins are, in part, associated with epigenetic differences that are, most probably, acquired during postnatal life. An example is the link between the DNA methylation status of the dopamine D2 receptor gene and phenotypes related to schizophrenia in monozygotic twins. In a larger study, Dempster et al. reported that monozygotic twins, who are discordant for schizophrenia or bipolar disorder, also present significant differences in DNA methylation at specific loci across the genome. Although these studies were short of proving causality between epigenetic differences and the discordant phenotypes, biological plausibility exists, because several human and a multitude of animal studies demonstrated that epigenetic changes are drivers for phenotypic discordances among genetically homogenous or isogenic individuals.

**SEASONAL TWEAKING OF THE EPGENETIC MACHINERY**

We know that, in humans, maternal nutrition during pregnancy alters the epigenetic status of their children. Data from the Dutch famine cohort provides very valuable insights as to how children are affected by maternal malnutrition. Mothers who were subjected to famine had children with undernutrition. Mothers who were subjected to famine had children with maternal nutrition during pregnancy. However, as the post-World War II economic and social setting in The Netherlands recovered, food availability increased, and the environmental settings did not fit with the predicted circumstances (as indicated by maternal exposure). The phenotypes of children became, in simple terms, less biologically fit to the new circumstances. Interestingly, the genes that were epigenetically altered in children (e.g., insulin-like growth factor 2 [IGF2] and leptin [LEP]) are involved in the pathogenesis of diabetes and obesity. However, what are the roles of these genes, and how might their epigenetic alterations be involved in the pathogenesis of chronic disease? IGF2, involved in growth, was hypomethylated in children exposed to famine during gestation, which could be interpreted as an attempt to compensate against the predicted food scarcity. By contrast, LEP, which regulates food intake, was hypermethylated, which could lead to its underexpression, and hence, propensity toward compensatory hyperactive eating. However, how does this reconcile with an unpredicted environment where food is abundant? If children were “tuned” toward compensating food scarcity by a hyperactive eating behavior, and food is abundant, this creates the “perfect storm” for the early onset of obesity. However, this hypothetical scenario has to be thoroughly tested, because there are instances when the hypermethylation of a gene is associated with its increased gene expression, as previously indicated.

As mentioned earlier, another aspect is the transgenerational inheritance of such epigenetic alterations. In humans, such studies are in their infancy, but one study, although it did not explore the epigenetic inheritance per se, provided interesting insights. Kaati et al. indicated that mortality rates in grandchildren, because of cardiovascular disease and diabetes, were associated with the nutritional status of their grandparents. Furthermore, this association was gender-specific (grandfathers to grandsons, and grandmothers to granddaughters, respectively).

Additional insights from research in The Gambia (West Africa) shed light onto the role that seasonal environmental changes in food availability have in molding the epigenetic status of children. Using an available local population cohort, Waterland et al. indicated that among a largely agricultural population, seasonal variations in perinatal nutrition could significantly alter the epigenetic status of children. The authors indicated that, during the nutritionally challenging rainy season, the DNA methylation of putative metastable epialleles was increased compared with the epigenetic status of children exposed in utero to the dry season. Two other studies investigated, within the same population, the role that micronutrient supplementation had in the establishment of epigenetic status during conception.

These novel findings enhance our understanding of the role that gene–nutrient interactions have in epigenetic modulation. First, micronutrient supplementation of pregnant mothers induced, in general, DNA hypomethylation of imprinted genes in children. Second, these alterations were gender specific.

**INTEGRATED MODELING**

Recently, an interesting review article published in Science revisited the work of noted evolutionary biologist Ernst Mayr’s proximate-ultimate dichotomy in understanding cause and effect in biological events. Inspired by the evolutionary and developmental diagrams presented in the Laland et al. article, we developed a new and revised diagram to depict how genetics and epigenetics can systemically modulate social and behavioral outcomes, how the environment can regulate the individual’s short-term (developmental) and long-term (evolutionary) fitness, how a series of feedback loops can cause subsequent reciprocal changes in both gene expression and the environment in response to alterations in the viability of the trait in question, and how these changes can influence the biological fitness of future generations. Figure 2 depicts these dynamic interacting relationships over 3 generations.

In Generation One, at node 1, the individual’s genome and epigenome are observed to contribute genes and epigenetic modifications (e.g., changes in methylation status), which at node 2 influence gene expression patterns, in this case, that of a parent. These patterns are, in turn, influenced by a series of environmental factors (node 3), including sociocultural (e.g., dietary exposures to bioactive phytochemicals), psychobehavioral (e.g., levels of neuroendocrine hormones), biotic (e.g., presence of pathogenic microorganisms), and abiotic (e.g., exposure to extreme ambient temperatures). These environmental factors act as filters on the original gene expression signal, further modifying this signal, and at node 4, influencing the viability of a specific social
and behavioral trait. In this model, the phenotypic expression of a specific social and behavioral trait is the reflection of the combined influences of the original gene expression patterns and the salient environmental factors of influence. This trait then becomes one of many traits contributing to the parent’s biological fitness or survival value (node 5). The parent’s biological fitness status also influences their exposure to important environmental factors (node 6), particularly the sociocultural, psychobehavioral, and biotic components of the environment that then go on to influence the genes and epigenetic modifications that the parent passes on to the child. The parent’s biological fitness also influences the child’s gene expression through supplemental epigenetic modification (node 7).

In Generation Two, inherited genes and epigenetic modifications at node 8 are transmitted to the child and influence the child’s gene expression patterns (node 9). These expression patterns are then additionally modified by the child’s exposure to environmental factors. These combined effects (node 10) impact on the expression of the specific social and behavioral trait, which in conjunction with other phenotypic traits in the child, determine the child’s biological fitness status (node 11). As the child matures, the biological fitness status influences exposures to important environmental factors (node 12), which go on to influence the genes and epigenetic modifications that that child, as an adult, passes on to its offspring (the grandchild of the parent, in this model).

In Generation Three, the genes and epigenetic modifications at node 13 go on to influence the grandchild’s gene expression patterns. Together with the influences from the grandchild’s parental fitness status (i.e., that of the child in this model), the grandchild’s gene expression patterns (node 14) are subsequently altered by prompts from salient environmental factors. The phenotypic expression of the specific social and behavioral trait is thus a reflection of gene–gene and gene–environment interactions. In conjunction with other phenotypic traits in the grandchild, the grandchild’s biological fitness status is determined. The biological fitness status of the grandchild modifies the exposures to the environment (node 15). Epigenetic changes in the grandchild that had their genesis in the parent may persist for an unknown number of generations (node 16). Gene expression patterns in the grandchild’s descendants will reflect the influences of the grandchild’s biological fitness status (node 17).

Figure 2 depicts these interactions over 3 generations. The environmental factors 1, 2, and 3 are each generation-specific and modify the individual’s pattern of gene expression, which is itself a reflection, in part, of genes and epigenetic modifications signaled from the environment of the previous generation. In Figure 2, solid arrows represent confirmable changes, whereas dashed arrows indicate likely changes. Environmentally induced epigenetic changes are known to persist, in various mammalian models, at least 3 to 4 generations beyond their initial onset.

**CASE STUDIES**

With this overview in mind, we now present a few specific examples of the ways in which genetics, environment, and epigenetics can expand our research horizons in social and behavioral studies and provide enhanced definition to topics of classical social science interest. The significance of this development is that these new sources of genetic and epigenetic data can begin to empower social and behavioral scientists, allowing this research to detect systemic causality in epidemiological models that in the past may have been restricted to correlation. Furthermore, the importance of considering an evolutionary perspective in these issues of public health importance cannot be underemphasized. Social and behavioral changes can directly and indirectly produce biological changes. The public health implications of biological change,
particularly those associated with health disparities, are best understood within the contexts of population ecology and evolution.

**Chronic Kidney Disease**

Incorporating genomic, environmental and epigenomic considerations into social and behavioral science research can lead to a deeper and broader understanding of disease etiology and diathesis. For example, chronic kidney disease (CKD) and its progression to end-stage renal disease (ESRD), requiring lifelong dialysis or kidney transplant, has become a public health epidemic and a financial burden on health care systems. Some researchers have suggested that the lack of available and appropriately targeted kidney disease education may account for the low awareness of kidney disease, especially among high-risk populations, resulting in late detection of CKD and an increased likelihood of progression to ESRD. People of recent African ancestry develop kidney disease at rates 4 to 5 times higher than most other biosocial groups. This observation holds for kidney disease in African American patients in health disparities, are best understood within the contexts of population ecology and evolution.

The current hypothesis is that these kidney disease genetic risk variants likely rose to high frequency in certain geographic regions of West and West Central Africa because they confer resistance to infection by *Trypanosoma brucei gambiensis*. This genetic association may help researchers understand some proportion of the current excess disparity in nondiabetic nephropathy among African Americans. Additionally, a proportion of the overrepresentation of African American patients in hemodialysis units around the nation likely reflects the high prevalence of genetic risk alleles in individuals of recent West and West Central African ancestry. These alleles provided an adaptive advantage under different environmental conditions in tropical Africa, but now actually reduce biological fitness in the temperate US environment. Without this genetic information and its potential evolutionary context, researchers could overemphasize the issues of access to health education and care in accounting for and (most importantly) attempting to remediate this disparity in ESRD.

**Smoking and Epigenetics**

The social phenomenon of smoking cigarettes has clear multigenerational correlations that go beyond transgenerational behavioral mimicry. A mother’s active smoking during pregnancy has developmental ramifications for herself, her unborn female child, and her grandchildren, even if her child and her grandchildren do not smoke. Research conducted in Zagreb, Croatia (Central Europe), indicates that smoking during pregnancy significantly adversely influences birth weight and birth length. Additional research suggests that parental smoking is implicated in the early onset of childhood obesity and alterations in noncoding RNA (which are important posttranscriptional regulators of gene expression). What emerges from these examples is the notion of genes and environments as malleable, dynamic, and coevolving. This contrasts sharply with the notion of genetic changes as solely as a reflection of hard selective elements of the environment (as in the concept of “nature tooth and claw”). Epigenetic effects counter the misconception of rigid biological determinism in disease onset and expression.

Although there remains a paucity of data regarding changes in DNA methylation in children and adults with in utero exposure to tobacco smoke, by using data from the National Children’s Study, it is clear that methylation status in children exposed in utero to tobacco smoke is significantly lower with the *AluYb8* insertion. This short interspersed nuclear element (SINE) within this gene was also found to be altered in the placenta from exposed fetuses. One of the implications of these alterations in methylation was a slight increase in promoter methylation of a receptor implicated in the development of cancer.

Recently, a study of epigenomic changes associated with smoking identified a single CpG site within the coagulation factor II (thrombin) receptor-like 3 gene (*F2RL3*) that was hypomethylated in peripheral blood genomic DNA from smokers compared with former and nonsmokers. Epigenome-wide association studies of 2 populations of nearly 400 matched pairs of healthy individuals, half of whom went on to develop breast or colon cancer, identified additional loci that were hypomethylated in smokers compared with former and nonsmokers. These changes included an intragenic region of the aryl hydrocarbon receptor repressor gene (*AHRR*), an intergenic CpG island on 2q37.1, and a further intergenic region at 6p21.33. These data show that smoking has a direct effect on the epigenome in lung tissue, which is also detectable in peripheral blood DNA and may contribute to cancer risk.

**Male Infertility**

In the past, the genome has been viewed as an immutable template for the phenotype. This
rigid and uncompromising view has become clearly passé as we now recognize that a single gene can code for a number of different isoforms of a protein and that gene expression patterns are highly influenced by the environmental context, and specifically, the epigenome. This flexibility dramatically enhances the range of possibilities for phenotypic expression and amplifies our adaptive potentials as individuals. One of the most interesting paradigm shifts facing psychosocial researchers is the ability of this new genetic data to provide additional nuance to the origins and classification of the affective changes associated with what was once considered a single phenotype, male infertility. Fifteen of every 100 couples in the world find it difficult to conceive. In about half those couples, the difficulty results from the male partner’s infertility. Male infertility is a common and complex problem affecting 1 in 20 men. Both genetic and nongenetic factors may be implicated in male infertility phenotypes, and an analysis of the genetic basis of the man’s spermatogenic, anatomical, or spermatozoal dysfunction has expanded the range of possible causes for this disorder to include unidentified genetic aberrations, such as chromosomal deletions, translocations, and single nucleotide polymorphisms (SNPs) in many cases of idiopathic male infertility.

Psychosocial issues are often about the perceptions that men and women have regarding androgenic disorders rather than the disorder itself. Male infertility is associated with major social and behavioral ramifications, including feelings of hopelessness, depression (related to the stress of infertility), and feelings of sexual inadequacy. Research concerning the psychosocial aspects of infertility and infertility treatment generally focuses more often on women than men. Infertile, childless men of reproductive age have desires to experience parenthood that are similar to those of their female counterparts. Diagnosis and initiation of treatment of male infertility are associated with elevated infertility-specific anxiety, and unsuccessful treatment can lead to a state of lasting sadness. Psychosocial aspects of androgenic disease, such as infertility, draw out the key areas of psychosocial interest; therefore, a compelling question is whether genetically and epigenetically distinct causes of male infertility are correlated with specific constellations of psychosocial traits. Men with androgenic disease often face problems developing relationships and have psychological problems, such as anxiety, depression, and social phobias. In more serious cases, psychological problems can affect masculinity, selfhood, and identity. Clinical psychologists and other psychotherapists can offer some assistance regarding these perceptions, but where there are problems relating to personality and coping styles, these may be more difficult to overcome. Here, genetic (and epigenetic) information may be of assistance since the genes responsible for male infertility are likely to have multiple effects on the phenotype. Some instances of male infertility may be linked to having a genetic variant of choline dehydrogenase (CHDH), which is associated with human sperm motility. Between 5% and 10% carry this allelic variant, which may result in altered CHDH enzymatic activity. rs126766 (G233T), a nonsynonymous SNP located in the CHDH coding region, is associated with increased susceptibility to dietary choline deficiency and risk of breast cancer. It has recently been reported that this SNP is also associated with altered sperm motility patterns and dysmorphic mitochondrial structure in sperm. A variant of this gene can influence the amount of choline required in an individual’s diet. Choline, a nutrient used to form cell membranes, is found in eggs, meats, and wheat germ, among other foods. Genetic data allow us to recognize a nutrigenetic condition to explain, in part, a disorder with major social and behavioral consequences.

Additionally, epigenetic modifications characterized by DNA methylation, histone modifications, and chromatin remodeling are important regulators in spermatogenesis. Several genes in the testes are regulated epigenetically, indicating a direct influence of these mechanisms on the process of spermatogenesis. In a comprehensive review of the impact of environmental factors on male infertility, epimutations (often hypermethylation) in several genes have been reported in association with poor semen parameters or male infertility, as listed in Table 1.

Exposures to environmental toxins and drugs may also affect fertility via epigenetic modifications. For example, 5-aza-2’-deoxycytidine, an anticancer agent, causes a decrease in global DNA methylation that leads to altered sperm morphology, decreased sperm motility, decreased fertilization capacity, and decreased embryo survival.

While different genes may be able to produce a superficially similar phenotype, generic male infertility, it is also true that the precise combination of genes affecting male infertility may vary among different geographic groups. For example, the polymorphism –9C > T and 368A > G in the H2B histone family, member W, testis-specific H2BFWT gene is associated with male

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<td>Male Infertility-Related Gene</td>
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infertility with idiopathic azoospermia or oligozoospermia, suggesting that the H2BFWT gene may contribute to susceptibility to spermogenesis impairment in Chinese populations. However, this same polymorphism may not be important in a different population group, implying that not only should we be looking for population-specific markers of male infertility but also possibly, population-specific behavioral manifestations of the generic disorder. This level of specificity can only emerge through the analysis and integration of genetic, environmental, and epigenetic data into social and behavioral assessments, thus allowing us to truly explore the depth and breadth of behavioral phenotypes associated with a genetically variable condition.

**Current Challenges**

In this article, we document a few examples that serve to introduce, in a very cursory way, the importance of conceptually increasing our receptivity, as social and behavioral scientists, to the infusion of genetic, environmental, and epigenetic perspectives and data into social and behavioral science research design, analysis, interpretation, and application.

We explore the roles that genes, gene–environment interactions, and epigenetics can play in strengthening the quality and quantity of our social and behavioral analyses, clarify some of the existing ambiguity surrounding variables of cause versus effect, and we provide a series of example-anchored postulates that support the need for a conceptual reorientation.

Because of the previously discussed studies, today we know that the environment, and especially nutrition, past infectious disease exposures, and exposure to environmental toxins, play crucial roles in tweaking our phenotypes by changing the selective advantage of particular genes and stimulating epigenetic modifications. This prompted us to recently argue that, from the social, economic, and ethical standpoints, health can no longer be discussed solely in the simple terms of individual responsibility alone, because the causes of many chronic diseases occur earlier in life, and even in previous generations. Moreover, the implications that gene–environment interactions have upon our health, cannot be truly understood, much less acted upon, unless we consider the genetic, environmental, and epigenetic factors that together drive our phenotypes. Therefore, we postulate that a significant paradigm shift should occur in our conceptualization and implementation of health care policies.

These should take into account, at a minimum, the following premises:

1. Sustainable, long-term disease prevention policies should implement long-term solutions and interventions that are compatible with the ecological context;
2. Fighting against the pervasive causes of chronic diseases requires a unified approach that should be specifically tailored to local environmental pressures; and
3. Policies to be implemented must be ethically sound and accepted by the individuals involved in such programs, in accordance with their particular sociocultural values, beliefs, and practices.

Currently, research in health disparities too often appears partitioned into those studies that look only for a genetic basis for the observed differences (as if such complexity could, at the public health level, be reduced to simple changes in gene sequences in the absence of environmental triggers) and those studies that insist that any differences in health outcomes are attributable solely to adverse aspects in the immediate social environment, independent of intergenerational biological exposures and change (as if social processes can be separated from biological outcomes and vice versa).

It is often difficult to study and interpret genetic data, and there has been a tendency in some quarters to overestimate the predictive power of genetic information with respect to complex phenotypes. There has also been an unfortunate inclination to minimize the ethical concerns of linking genetic data with public health, particularly in vulnerable subgroups. Despite these current important limitations, it is worthwhile for social and behavioral health researchers to make the effort to identify the possible interplay of different gene combinations, expression patterns, and environmental stressor and cues in the health conditions of interest.

New, intentionally interdisciplinary approaches must emerge that begin to fill in the knowledge barriers to our comprehensive understanding of human health and disease. To overcome these barriers, however, researchers will need to retool to increase their basic competence with an ecologically and evolutionarily expanded vision of the health ramifications in social and behavioral research. Researchers will need to seek out collaborators from disciplines that can provide the necessary expertise to aid our understanding of the deeper histories of the populations under study and the extent of population substructure that may limit the utility of uniform interpretations of the causes of health inequities. Broader acceptance and integration of relevant biological phenomena germane to the public health issue at hand will allow us to expand our observational studies to see the possible influence of past environmental impacts, as manifest in the genetic and epigenetic records, on the phenotypes of interest. Such holistic approaches require more genuine interdisciplinary collaboration, more shared vocabulary and overlapping paradigms, and more robust statistical analyses to determine their relevancy to public health. Conceptually shifting from the current “one size fits all” approach permits public health to more smoothly transition to an integrated personalized approach to health and stratified primary prevention strategies. Armed with this broader theoretical base, social and behavioral research on public health issues will be better able to identify salient and sustainable interventions to optimize human phenotypic diversity.

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**Contributors**

F. L. C. Jackson oversaw the initial conceptualization and the anthropological
genetics data of the article M.D. Niculescu oversaw the epigenetics and public health policy implications. R.T. Jackson oversaw the nutritional science data.

**Human Participant Protection**

Human participant protection was not applicable for this article because it did not involve human participants.

**References**


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The Challenge of Causal Inference in Gene–Environment Interaction Research: Leveraging Research Designs From the Social Sciences

The integration of genetics and the social sciences will lead to a more complex understanding of the articulation between social and biological processes, although the empirical difficulties inherent in this integration are large.

One key challenge is the implications of moving “outside the lab” and away from the experimental tools available for research with model organisms. Social science research methods used to examine human behavior in nonexperimental, real-world settings to date have not been fully taken advantage of during this disciplinary integration, especially in the form of gene–environment interaction research.

This article outlines and provides examples of several prominent research designs that should be used in gene–environment research and highlights a key benefit to geneticists of working with social scientists. (Am J Public Health. 2013;103:S42–S45. doi:10.2105/AJPH.2013.301290)

Jason M. Fletcher, PhD, and Dalton Conley, PhD

Since the publication in Science of empirical evidence of gene–environment (G×E) interaction, there has been growing interest in integrating biological and social science approaches, data, and models. The original results by Caspi et al. suggested an important, genetic source of heterogeneity in responses to early life insults, attempting to partially answer the question of why some individuals are resilient to stressors, whereas others experience deleterious psychological sequelae. Although these studies created substantial interest in potential gene-by-environment interactions, they also needed to be replicated and extended by other researchers using alternative data. There are now competing meta-analyses suggesting either that the original results linking differential response to stress by the serotonin transporter gene (5-HTT) is robust or lacks consistent supporting replication.

The discussion generated by this line of research in the biological and social science communities has been valuable in highlighting the shortcoming of the research design by Caspi et al. A key concern that has been the subject of much debate is whether the study (and studies like it) is adequately powered. Pointing to another concern that is the subject of less inquiry. Even with highly powered studies (many current collaborative groups have amassed data sets that include tens of thousands of individuals), an important conceptual (and statistical) issue is the likelihood that the measured environments may be correlated with unmeasured genetic variation, and thus, may be acting as proxy for a gene-by-gene interaction rather than a G×E interaction. As sample sizes continue to get larger, a shift in focus should be from the statistical issue of power to the conceptual issue of modeling interactions between variables that are not themselves correlated (gene–environment correlation [rGE]). Although for studies aiming to detect main effects of genotypes, approaches that try to control for population stratification—such as genomic control, principal components, or family-based analysis—may be adequate to account for rGE, when trying to model G×E interaction effects, the added burden of obtaining exogenous environmental variation is present, lest models become misspecified.

In light of this uncertainty, many researchers have turned to examinations of model organisms to be able to control—through random assignment—the environment as well as the genotype of animal subjects. Because human research focusing on genetic and environmental interactions will be unable to use truly experimental research designs in the near future, this leaves G×E research in a precarious position. On the one hand, results from animal models, where both the genetic and environmental contributions of phenotype can be experimentally altered, will not doubt continue to be used to suggest likely mechanisms involved in similar human phenotypes. However, it is often difficult...