Published in final edited form as:
Health Aff (Millwood). 2011 May ; 30(5): . doi:10.1377/hlthaff.2011.0078.

Discovering how environmental exposures alter genes and could lead to new treatments for chronic illnesses

Kenneth Olden, PhD, ScD[1,*], **Nicholas Freudenberg, DPH**[1], **Jennifer Beam Dowd, PhD**[1], and **Alexandra E. Shields, PhD**[2]

[1]City University of New York, School of Public Health at Hunter College

[2]Harvard/MGH Center on Genomics, Vulnerable Populations, and Health Disparities, Mongan Institute for Health Policy, Massachusetts General Hospital, Department of Medicine, Harvard Medical School

Abstract

Facilitating translation of basic and clinical discoveries into improved population health has become a national priority. In this commentary, we emphasize the need to expand the "bench to bedside" model to include trans-disciplinary research that integrates knowledge of genomics and epigenetic regulation with information about diverse environmental exposures. Such integrated studies are needed to understand mechanisms underlying human health and disease, and develop novel interventions at the level of the epigenome that might curb the growing global burden of complex chronic illnesses. The completion of the human genome project, as we now know, is only a first step in understanding the etiology of complex disease. Remaining challenges include understanding the role of genetics in controlling susceptibility to environmental exposures and the role of the environment in regulating gene expression and function. Here we emphasize the importance of understanding the crosstalk between the genome, the epigenome, and the environment in coregulating gene expression as key to developing a population health model for the control of chronic diseases. However, this will require developing and integrating new data resources.

New wave of chronic diseases

Chronic complex disorders account for a disproportionate percentage of health care costs and are the primary causes of death in the United States and other industrialized countries. Between 2002 and 2030, the mortality rate for such diseases is expected to increase by 11.5% in high-income countries and by almost 20% worldwide. Given the potential impact of this tsunami of chronic diseases on our economy, health care system, and global community, advancing understanding of the complex pathways leading to chronic illness and developing novel strategies for prevention must be a public health priority. Key to this endeavor is advancing our understanding of environmental and epigenetic contributions to chronic illness and using this information to ameliorate their effects.

The Promise of Genetics Not Yet Realized

Despite ~90% of common genetic variations being shared across human populations of different ancestry, clinically-relevant differences in allele frequencies exist among groups.

Corresponding author: Kenneth Olden, PhD, ScD City University of New York School of Public Health 425 East 25th Street New York, NY 10010 kolden@hunter.cuny.edu Phone: 212-481-4314 Fax: 212-481-5078.
*Kenneth Olden is the former Director of the National Institute of Environmental Health Sciences, National Institutes of Health, U.S. Department of Health and Human Services.

Hypothesizing that genetics can explain differences in disease patterns and disparities in health, huge investments have been made in assessing genetic variation (e.g. haplotype mapping and genome-wide association studies) and genotype-phenotype association in human populations. Despite the expectation that human genome mapping would illuminate simple direct paths from genes to disease, variants identified to date explain only a small portion of disease risk. For the promise of genomics research to be fulfilled, we must move beyond discovery of genetic variants associated with disease to understanding epigenetic regulation of gene expression in the context of complex environmental exposures.

The emerging view is that most, if not all, diseases arise from interactions between the genome, the epigenome, and the environment (broadly defined to include social, behavioral, and physical agents). The timing of environmental exposure with respect to age or stage of development is also a critical factor that influences the magnitude of the gene-environment interaction (GEI). Genetics is just one of several risk factors that contribute to the development of common diseases--environmental context matters! In most cases, genes only "load the gun" or create the potential for adverse health outcomes, while subsequent exposure to environmental triggers is required to initiate physiological or pathological pathways responsible for human health and disease. Failure to account for this additional level of complexity associated with environmental exposure and epigenetic regulation may explain why most of the variance in disease risk has not been explained by genetic analysis alone, and why biologically-strong candidate genetic variants often perform poorly in genotype-phenotype association studies. Phenylketonuria, characterized by mental retardation, is a classic example of a GEI metabolic disorder, caused by the interaction of a rare gene and dietary phenylalanine. Medically significant manifestations of the disorder can be prevented by a low phenylalanine diet for those children with genetic variant. The dramatic increases in obesity and insulin-resistant disorders over the past thirty years are more recent examples of how the environment and genetics interact to impact health.

Epigenetic Regulation of Gene Expression

Epigenetics is the study of heritable changes in gene expression that are not encoded in the nucleotide sequence of DNA. The epigenome refers to chemical modifications of DNA and chromatin (the nucleoprotein around which DNA is coiled in cells). The addition of methyl or other chemical groups to DNA or associated proteins either blocks or promotes binding of the enzyme complex responsible for transcription of DNA into RNA. The net effect of restricting or exposing new DNA binding sites is that gene expression can be turned "off or on" – a process called epigenetic regulation. Exposure to certain environmental chemicals (e.g. heavy metals, endocrine disruptors and dietary substances)[1-3] as well as behavioral exposures during early development (e.g., childhood abuse)[4,5] can lead to epigenetic modification. Epigenetic effects have also been found to exist in animal models. However, studies conducted with cloned animals under identical environmental conditions show that some epigenetic variation is random.[6]

The epigenome controls the differential expression of genes that define tissue specificity. Unlike the genome, which is relatively constant throughout life, the epigenome changes over the life course and is highly variable from developmental phase to developmental phase, and from tissue to tissue. Unlike genes that are inactivated by nucleotide sequence variations, genes silenced by epigenetic mechanisms are still intact, and hence have the potential to be reactivated by environmental or clinical intervention. Furthermore, epigenetic changes occur at a higher rate than mutations and no repair mechanisms comparable to those that protect the integrity of DNA have yet to be described. Genetically identical monozygotic twins are epigenetically very similar at birth, but vary significantly later in life, suggesting that the environment or random variation plays an important role in sculpting the epigenome.[7]

Environment-induced epigenetic changes in gene expression are one possible explanation for the observed discordance in phenotype among genetically-identical twins (approximately 85% for Parkinson's disease,[8] 70% for multiple sclerosis,[9] 40-60% for cancer,[10] 30-50% for diabetes,[11] and 25% for asthma,[12]) and may account for, at least part of the differential risk for chronic diseases across the population.

Epigenome modifications function as a component of cellular memory to maintain the differentiated state of human tissue.[13] Shortly after fertilization, the developing human embryo undergoes massive demethylation to erase most of the information encoded in the epigenome of the sperm and egg. Concomitant with initiation of the formation of specialized or differentiated tissue during embryogenesis, lineage specific epigenetic modifications are reestablished, ostensibly restricting gene expression and developmental fate of different tissue.

To cope with environmental heterogeneity and improve fitness for survival, humans and other living organisms have evolved the ability to alter their phenotype to track changing environments. The phrase “gene-environment interaction” implies that the direction and magnitude of the effect that a genetic variant has on the phenotype can vary as the environment changes; genetic risk may therefore be directly modified by specific environmental factors. Richard Lewontin envisioned the existence of an environmental switch or rheostat that could shift or migrate the phenotype within a defined range specified by the genotype.[14] Such phenotypic plasticity may be viewed as a mechanism to promote adaptation or buffering against environmental variation or heterogeneity. Whereas much of phenotypic plasticity is apparently “hardwired” in the genome to allow the organism to respond or adapt to environmental stress in a matter of hours, epigenetic regulation plays a significant role in long term adaptation to one's environment.[15] Survival is threatened when living cells or organisms lose this ability to change their phenotype in response to internal or external cues (e.g., during aging).

The mechanistic link between environmental exposure and epigenetic states of the genome has been established by analysis of the well-defined and sensitive mouse coat color gene. When methylated, the agout or yellow coat color gene is expressed only in the hair follicles. But when unmethylated, the gene is expressed in the hair. Consistent with this finding, the agout or yellow coat color gene can be prevented by feeding the animals a diet supplemented with methyl donors.[16,17]

It is likely that some genetic variants that once endowed the human species with survival or reproductive advantage and were therefore adaptively selected during the course of human evolution, now increase the risk for disease because of their incompatibility with the modern-day environment. Over the past 100 years, human activity and technology have led to environmental changes that have outpaced evolution of the human genome to the extent that there is now a nature-nurture mismatch. This disconnect appears to be contributing to chronic disease epidemics.

The most definitive data on the link between epigenetic dysregulation and human disease comes from studies of various cancers.[18] Data mining analyses show that abnormal DNA methylation patterns are associated with many other disorders as well, including obesity, type 2 diabetes, anemia, cardiovascular disease, and numerous neurodevelopmental disorders,[19-22] further suggesting the importance of epigenetic regulation in the development of human diseases. The critical question remains as to whether epigenetic changes are the cause or consequence of disease. Studies designed to answer this question, in the context of atherosclerosis showed that epigenetic changes generally precede histological signs of disease.[23] If this finding proves applicable to other complex diseases, it suggests great

opportunities to reduce disease burden by targeting environmental exposures that affect gene expression for complex diseases.

The critical question remains as to whether epigenetic changes are the cause or consequence of disease. Studies designed to answer this question, in the context of atherosclerosis showed that epigenetic changes generally precede histological signs of disease.[23] If this finding proves applicable to other complex diseases, it suggests great opportunities to reduce disease burden by targeting expression for complex diseases.

The dynamic and reversible plasticity of epigenetic modulation provides a template for different environmental exposures to act upon and affect the phenotype, with either adaptive or pathological consequences.[13,29] By delineating the epigenetic changes associated with specific diseases, environmental exposures, lifestyles, and neighborhoods; biological mechanisms amenable to public health or medical intervention may be discovered.

Research on the link between the environment and epigenetic regulation of gene expression and contributions that these interactions may have on human health and disease is in a nascent stage. Even so, human therapeutic intervention trials to reverse deleterious epigenetic changes are underway. Such therapies do not target genes, but rather the enzymes responsible for sculpting the epigenome (e.g., treatment of T-cell lymphoma by reactivation of tumor suppressor genes),[30] and reducing colorectal cancer risk by inhibiting the addition of methyl groups to DNA.[31]

Integration of Genomics and Environmental Health

Disease mechanisms are far more complex than thought when the Human Genome Project (HGP) was conceptualized more than two decades ago. Given the complexity of the regulatory networks involved in human biology, genetic analysis, is unlikely to provide the full insight needed to prevent or cure common diseases. The scope and scale of our effort must be recalibrated to match our current understanding of the complexity of biological and pathologic mechanisms. We need to employ integrative systems and thinking beyond traditional single discipline research strategies. Historical investment policies that pitted genetics against the environment have slowed scientific progress in developing prevention and treatment strategies for common diseases.

There have been some national initiation efforts to spur transdisciplinary approaches to GEI research, most prominently more than a decade ago by the National Institute of Environmental Health Sciences with the development of the Environmental Genome Project (EGP)[32-34] and the National Center for Toxicogenomics.[35,36] With the development of novel tools to discover yet unknown environmental risk factors, a more powerful public health approach would be possible that would include stratifying disease risk based on knowledge of environmental exposures and frequency and distribution of susceptibility alleles (both common and rare) in the population, thus leading to more informed evidence-based environmental health policies.

The above referenced investments, along with the HGP[37,38] the Hap Map project,[39] and Genome-wide association studies,[40] have generated important knowledge and powerful new tools that can be used to unravel complex interactions among genes, the epigenome, and the environment. Furthermore, knowledge generated from these studies can also be used to develop public health prevention strategies to reduce morbidity and mortality from common diseases, reducing the necessity of achieving the more challenging goal of developing curative therapy.

Research and Policy Implications of the Prospect Strategy

The urgency of pursuing an alternative public health prevention strategy was highlighted as we recently celebrated the 10th anniversary of the completion of the HGP.[41] The goal of the HGP was to improve prevention, diagnosis, and treatment of human disease. To date, knowledge of the human genome has led to limited advances in the practice of medicine because genetics is not the sole determinant of human health and disease. Whereas genetic analysis now allow for improved assessment of individual susceptibility, progress in understanding the causes of diseases and disparities among various populations has been limited.

Social and environmental factors are the most powerful predictors of health outcomes, yet medical researchers have largely ignored the potential role of neighborhood social and physical exposures.[42] It is well known that neighborhood characteristics have serious consequences for the well-being of people who live within them. Without objective measures of neighborhood context, one cannot determine how social and physical factors can interact with the genome and epigenome to create a more toxic environment or identify critical windows and intensity of exposure to maladaptive environments that influence disease risk.

Population-based studies aimed at investigating the role of GEI in human health and disease have been hampered by the lack of precise measurement tools for assessing a person's exposure to environmental factors. Since diet, physical activity, behavior, and lifestyle factors play important roles in the etiology, prevention, and treatment of many chronic diseases, accurate data on these factors is critical to understanding of how they influence health. Typically, such data is derived from questionnaire or extrapolated from stationary monitoring devices to assess levels of specific agents in the diet or general environment where people live and work. These methodologies have many limitations, including misclassification errors, temporal uncertainty and relevance, and individual variability. Less often, they are derived from methods such as personal monitoring devices such as portable or wearable sensor badges, clothing, or backpacks to access levels of specific compounds at the point of contact with the body.

The development of the appropriate measurement tools, scalable for use in population-based, genome-wide association studies to track neighborhood exposures will require a cohesive rational strategy. The dearth of data and tools to untangle GEIs leaves researchers and policy makers in the dark about how genetic variation contribute to health disparities and what can be done to eliminate such differences.

The NIH initiative on genes, environment, and health represents an important effort to collect, harmonize, and integrate data from genetic and epigenetic analysis with information on social, behavioral, and environmental exposures. The initiative consists of two components, a genetic program for analyzing genetic variation in populations of patients with specific diseases and an exposure biology program to develop technology for identifying and monitoring environmental exposures that interact with genetic variants to produce disease.[43]

Furthermore, there have been several new approaches to studying the etiology, prevention and health consequences of complex chronic diseases that could potentially elucidate both fundamental and proximal causes and solutions. Social scientists and epidemiologists have demonstrated that social structures, community environment, and public policies help shape the lifestyles and health behaviors that contribute to disparate chronic disease occurrence across populations. Demographers have shown that the changing population profiles caused by increased lifespan, lower fertility rates, urban population density, and high levels of

immigration have changed the populations at risk for chronic diseases, creating new pockets of disease burden and new opportunities for prevention. Other investigators are using the tools of geography and multi-level analysis to examine how neighborhood contextual features, such as air quality, access to healthy food, and "walkability" may affect chronic disease. Life course epidemiology has provided growing evidence that prenatal and early childhood environments can model developing physiological systems in a way that influences future disease risk, possibly mediated by epigenetic changes induced by environmental exposures. Early life experiences may thus mitigate or exacerbate susceptibility to adverse health-related exposures in adulthood. Growing evidence also suggests that all of these factors interact to produce and maintain inequalities in chronic disease outcomes.

Despite these insights, the prospects for near-term reductions in chronic disease and health disparities are daunting. A central challenge is determining optimal strategies for integrating emerging knowledge from historically disparate scientific fields into a coherent and integrated framework, data sits and analytical models. From a public health perspective, these novel transdisciplinary models should focus especially on clinically relevant exposures, environments, and process that are amenable to interruption or change. Translating such research findings into substantive changes in clinical, community, and policy practice has also proved difficult, because scientists, working in isolation within confined disciplines, often lack these translational skills. While most investigators acknowledge that many factors interact in complex ways to produce current patterns of health and illness, few research initiatives have considered a wide enough array of causal factors or characterized their relative contributions over time and place to effectively guide policies and programs towards reversing the growing health trends of chronic diseases and disability.

Conclusions

Genetic polymorphisms and their frequency and distribution in the population may confer small but significant risk for disease. However, genes do not tell the whole story; risk is often linked to the level of exposure to environmental factors. Since most attempts to understand variation in predisposition to disease have not taken environment and epigenetic regulation into account, important sources of variation are yet to be discovered.

Behavioral, dietary and environmental exposures can modify the epigenome causing deviations from the so-called "physiological epigenome."[20] Such exposures over the life course, may lead to accumulation of epigenetic modifications that accelerate manifestation of disease in genetically predisposed individuals. It is therefore crucial to examine how specific environmental exposures, both social and physical, influence epigenetic regulation of gene expression. Studies with cloned animals have shown that small differences in epigenetic patterns can have a significant impact on phenotype.[44] If, as studies indicate, the environment plays a pivotal role in sculpting the epigenome, environmental modification or development of epigenetic therapies to prevent or reverse the deleterious epigenetic regulatory effects of the environment on gene expression offer promising avenues for the prevention and treatment of chronic diseases. In fact, major benefits could be derived long before the specific mechanisms contributing to environmental risks have been identified. For example, improved nutrition and sanitation practices led to significant reduction in death from infectious diseases long before the offending agents were identified and effective drugs or vaccines were developed.[45] Similarly, interventions today will likely include both population-based and personal strategies (e.g., pharmaceuticals to control blood pressure and blood glucose and cholesterol levels). But, to achieve such success we will need to elucidate both the direct and indirect pathways by which the environment can modulate gene

expression and the consequences of gene variants. Such studies will likely provide important insight into the root causes of common diseases, and will complement improved access to health care in making individuals healthier around the globe.

In summary, the key to translation of genomic sciences into prevention and treatment strategies will require integration of knowledge and technologies obtained from multiple disciplines. The integration of such resources from genetics, environmental health, and the social and behavioral sciences will amplify the signal of multiple subtle interactions involved in disease etiology and progression, and will have a transformative effect on translating fundamental discoveries into the practice of public health and medicine.

References

1. Bjornsson HT, Fallin MD, Feinburg AP. An Integrated Epigenetic and Genetic Approach to Common Health Diseases. Trends in Genetics. 2004; 20(8):350–358. [PubMed: 15262407]
2. Poirier LA, Ulasoua TI. The Prospective Role of abnormal methyl metabolism in cadmium toxicity. Environmental Health Perspectives. 2002; 110(Suppl 5):793–795. [PubMed: 12426133]
3. Sutherland JE, Costa M. Epigenetics and the Environment. Annals of the New York Academy of Sciences. 2003; 983:151–160. [PubMed: 12724220]
4. Weaver IC, Meaney MJ, Szyf M. Maternal Care Effects on the Hippocampal Transcriptome and Anxiety-Medication Behavior. Nature Neuroscience. 2009; 12:1559–1566.
5. McGowan PO, Szyf M. The Epigenetics of Social Adversity in Early Life: Implications for Mental Health. Neurobiology of Disease. 2010; 37:13–25. [PubMed: 19664713]
6. Bennett-Boker PE, et al. Age Associated Activation of Epigenetically Repressed Genes in the Mouse. Genetics. 2003; 165:2055–2062. [PubMed: 14704185]
7. Fraga MF, Ballstar E, Paz MF, Ropero S, Setien F, et al. Epigenetic Differences Arise During Lifetime of Monozygotic Twins. Proceedings of the National Sciences. 2005; 102:10604–10609.
8. Tanner CM, Ohtman R, Goldman SM, Langston W. Parkinson Disease in Twins: An Etiologic Study. Journal American Medical Association. 1999; 281:341–346.
9. Baranzini SE, Mudge J, Van Velkinburg JC, Khankhanian P, et al. Genome, epigenome RNA sequences of monozygotic twins discordant for multiple sclerosis. Nature. 2010; 464:1351–1356. [PubMed: 20428171]
10. Lichtenstein P, Niels VH, Verkasala PK. Environmental and Heritable Factors in the Causation of Cancer: Analysis of cohorts of Twins from Sweden. New England Journal of Medicine. 2000; 343:78–85. [PubMed: 10891514]
11. Poulsen P, Kyvik KO, Vaag A. Heritability of Type II (Non-insulin- Dependent) Diabetes Mellitus and Abnormal Glucose Tolerance- a Population-Based Twin Study. Diabetologia. 1999; 42:139–145. [PubMed: 10064092]
12. Sarafino EP, Goldfedder J. Genetic factors in the presence, severity, and triggers of asthma. Archives of Diseases in Childhood. 1984; 75:112–116.
13. Feinberg AP. Phenotypic Plasticity and the Epigenetics of Human Disease Nature. 2007; 447:433–440.
14. Lewontin R. The Adaptations of Populations to Varying Environments. Cold Spring Harbor Symposium on Quantitative Biology. 1957; 22:395–408.
15. Vercelli D. Genetics, epigenetics, and the environment: switching, buffering, releasing. Journal of Allergy Clinical Immunology. 2004; 113:381–386. [PubMed: 15007332]
16. Waterland RA, Jirtle RL. Transposable elements for early nutritional effects on epigenetic gene regulation. Molecular Cell Biology. 2003; 23:5293–5300.
17. Wolff GL, Kodell RL, Moore SR, Cooney CA. Maternal epigenetics and methyl supplements affect agouti gene expression in A^{vy}/a mice. FESEB Journal. 1998; 12:949–957.
18. Szyf M. Epigenomics and its Implications for Medicine. Genomics and Personalized Medicine. 2009; 1:60–73.

19. Wren JD, Garner HR. Data Mining Analysis Suggests an Epigenetic Pathogenesis for Type II Diabetes. Journal Biomedical Biotechnology. 2005:104–115.
20. Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. Annual Review Nutrition. 2007; 27:363–388.
21. Talmud PJ, Humphries SE. Gene-Environmental Interaction in Lipid Metabolism and Effect on Coronary Heart Disease Risk. Current Opinion Lipidology. 2002; 12:149–154.
22. Devaskar SU, Thamotharan M. Metabolic Programming in the Pathogenesis of Insulin Resistance. Review Endocrine Metabolism Disorder. 2007; 8:105–113.
23. Lund G, Anderson L, Lauria M, Lindholm M, Fraga MF, Villar-Garea A, Ballestar E, Esteller M, Zaina S. DNA Methylation Polymorphisms Precede any Histological Sign of Atherosclerosis in Mice Looking Apolipoprotein E. Journal of Biological Chemistry. 2004; 279:29147–29154. [PubMed: 15131116]
24. Wren JD, Garner HR. Data-mining analysis suggests an epigenetic pathogenesis for type 2 diabetes. Journal Biomedicine and Biotechnology. 2005:104–112.
25. Mackey DJ, Boonen SE, Clayton-Smith J, Goodship J, Hahnemann JM, et al. A maternal hypomethylation syndrome presenting as transient neonatal diabetes mellitus. Human Genetics. 2006; 120:262–269. [PubMed: 16816970]
26. Tamashiro KL, Wakayama T, Akutsu H, Yamazak Y, Lachey JL, et al. Cloned mice have an obese phenotype not transmitted to their offspring. Nature Medicine. 2002; 8:262–267.
27. Young LE, Fernandes K, McEvoy TG, Butterwith SC, Gutierrez CG, et al. Epigenetic change in IGF2R is associated with fetal overgrowth after sheep embryo culture. Nature Genetics. 2001; 27:152–154.
28. Petronis A. Human morbid genetics revisited: relevance of epigenetics. Trends Genetics. 2001; 17:142–146.
29. Helden AJ, Hassal M. Phenotypic Plasticity in Growth and Development Rates of Armadillidium Vulgare. Israel Journal of Zoology. 1998; 44:379–394.
30. Workman P. Breaking the Silence: The Rise of Epigenetic Therapy. Journal of the National Cancer Institute. 2002; 94:874–875. [PubMed: 12072537]
31. Kopelovich L, Crowell JA, Fay JR. The Epigenome as a target for Cancer Chemoprevention. Journal of the National Cancer Institute. 2003; 95:1747–1757. [PubMed: 14652236]
32. Kaiser J. Environmental Institute Lays Plans for Gene Hunt. Science. 1997; 278:569–570. [PubMed: 9381162]
33. Brown PO, Hartwell L. Genomics and Human Disease- Variations on Variations. Nature Genetics. 1998; 18:91–93. [PubMed: 9462728]
34. Olden K, Wilson S. Environmental Health and Genomics: Visions and Implications. Nature Review Genetics. 2000; 1:149–153.
35. Olden K, Guthrie J. Genomics: Implications for Toxicology. Mutation Research. 2001; 443:3–10. [PubMed: 11166022]
36. Waters MD, Tennant RW, Olden K. Toxicogenomic approach for Assessing Toxicant Related Diseases. Mutation Research. 2003; 544:415–424. [PubMed: 14644344]
37. Venter JC, et al. The sequence of the Human Genome. Science. 2001; 29:1304–1351. [PubMed: 11181995]
38. Lander ES, et al. Clinical Sequencing and Analysis of the Human Genome. Nature. 2001; 409:860–921. [PubMed: 11237011]
39. International HapMap Consortium. A Haplotype Map of the Human Genome. Nature. 2005; 437:1299–1320. [PubMed: 16255080]
40. McCarthy M, Hirschhorn JN. Genome-Wide Association Studies: Potential Next Steps on a Genetic Journey. Human Molecular Genetics. 2008; 17:R146–165.
41. Wade N. A Decade Later, Gene Map Yields Few New Cures. New York Times. Jun 13.2010 pp1 and 27.
42. Freudenberg N, Olden K. Finding Synergy: Reducing Disparities in Health by Modifying Multiple Determinants. American Journal of Public Health. 2010; 100:S25–S30. [PubMed: 20147690]
43. HHS Secretary Michael O. Leavitt. http://gei.nih.gov/index.asp

44. Rideout WM, Eggan K, Jaemisch R. Nuclear Cloning and Epigenetic Reprogramming of the Genome. Science. 2001; 293:1093–1098. [PubMed: 11498580]

45. Wing S. Environment Justice, Science and Public Health. Environmental Health Perspectives. 2005:54–63. (Special Issue on Future of Environmental Health Research).