

32. United Nations Office for Disaster Risk Reduction (UNISDR). Chair's summary presented at: Fourth Session of the Global Platform for Disaster Risk Reduction; May 21–23, 2013; Geneva, Switzerland.

33. Oxley MC. A “people-centred principles-based” post-Hyogo framework to strengthen the resilience of nations and

communities. *Int J Disaster Risk Reduction*. 2013;4:1–9.

34. Intergovernmental Panel on Climate Change (IPCC). *Managing the Risks of Extreme Events and Disasters to Advance Climate Change Adaptation: A Special Report of Working Groups I and II of the IPCC*. Field CB, Barros V, Stocker TF,

et al. eds. Cambridge, UK, and New York, NY: Cambridge University Press; 2012.

35. United Nations Office for Disaster Risk Reduction (UNISDR). Summary of country practices and examples. 2005. Available at: <http://www.unisdr.org/2005/mdgs-drr/summary-countries.htm>. Accessed April 24, 2014.

36. The One Health Initiative. Available at: <http://www.onehealthinitiative.com/about.php>. Accessed April 22, 2014.

37. Sustainable Development 2015: advocacy toolkit: influencing the post-2015 development agenda. Available at: <http://www.sustainabledevelopment2015.org/index.php/about/timeline>. Accessed November 1, 2013.

Epigenome: Biosensor of Cumulative Exposure to Chemical and Nonchemical Stressors Related to Environmental Justice

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Understanding differential disease susceptibility requires new tools to quantify the cumulative effects of environmental stress. Evidence suggests that social, physical, and chemical stressors can influence disease through the accumulation of epigenetic modifications.

Geographically stable epigenetic alterations could identify plausible mechanisms for health disparities among the disadvantaged and poor. Relations between neighborhood-specific epigenetic markers and disease would identify the most appropriate targets for medical and environmental intervention. Complex interactions among genes, the environment, and disease require the examination of how epigenetic changes regulate susceptibility to environmental stressors. Progress in understanding disparities in disease susceptibility may depend on assessing the cumulative effect of environmental stressors on genetic substrates.

We highlight key concepts regarding the interface between environmental stress, epigenetics, and chronic disease. (*Am J Public Health*. 2014;104:1816–1821. doi:10.2105/AJPH.2014.302130)

PROFOUND HEALTH DISPARITIES exist between affluent Americans and their socioeconomically disadvantaged and minority counterparts.¹ A landmark study showed that the most significant risk factors accounting for differential health outcomes were related to the environment.² For example, minority communities of color are exposed to more environmental pollutants than are White communities³ because toxic waste sites, landfills, congested roadways, and manufacturing facilities are most often located in such neighborhoods.⁴ The large and disproportionate environmental burden of the broad array of environmental hazards borne by poor and minority communities, labeled environmental justice, is likely to be a major contributor to health disparities.

To date, efforts to link health disparities and environmental justice have been largely observational, and most have focused on single risk factors. In addition to coexposure to multiple chemicals and physical agents, a large body of evidence has emerged indicating that social and behavioral factors moderate an individual's response to hazardous environmental exposures.⁵ Therefore, to elucidate the complex relation

between environmental justice and health disparities, one must develop tools that integrate community characteristics, social conditions, and cultural influences into the risk assessment–risk management paradigm.

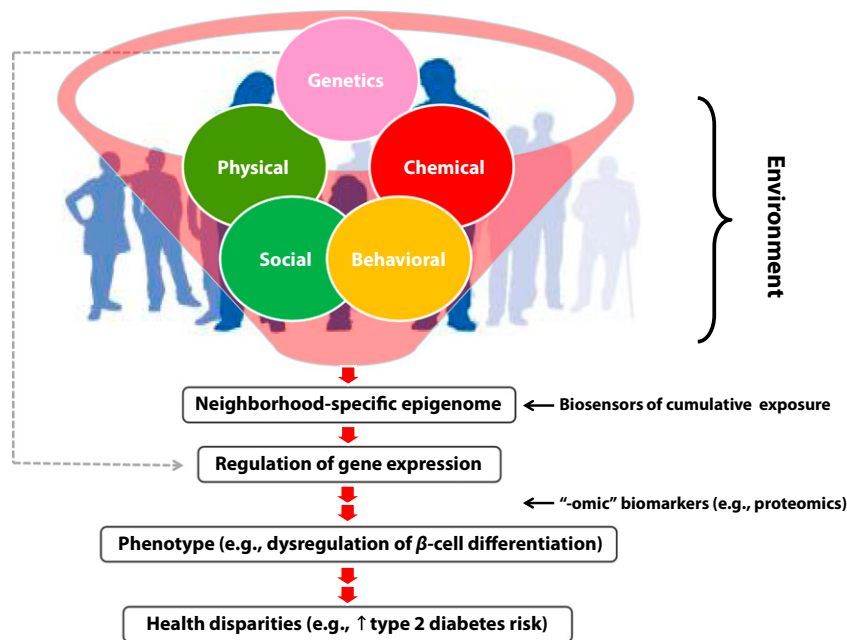
We examine the growing body of evidence suggesting that environmental exposures can influence the development of noncommunicable diseases in human populations through the accumulation of chemical modifications in DNA and chromatin that subsequently alter gene expression in target-specific tissues. Geographic neighborhood-specific epigenetically stable alterations potentially can be used as platforms to investigate the mechanisms accounting for well-documented health disparities (as shown schematically in Figure 1). By characterizing differential epigenetic modifications associated with living in a “disadvantaged” compared with an “advantaged” neighborhood, one can gain a mechanistic understanding of the relation between environmental justice and health disparities. Insight into these epigenetic contributions to health disparities could logically lead to actionable strategies to reduce hazardous exposures and screen for

community-level environmental justice–related exposures.

FROM GENOME TO EPIGENOME

Candidate gene and genome-wide association studies have identified genetic loci for numerous diseases and traits.⁶ However, disease mechanisms are complex, and genetic variations appear to account directly for only a small proportion of disease phenotypes. The phenotypic expression of specific genes varies with environmental conditions and has been attributed to chemical modification of DNA and chromatin, collectively known as the epigenome.^{7–11} Aberrant micro-RNA expression also has been associated with disease such as cancer¹² and may represent another form of epigenetic regulation of gene expression. Epigenetic research, however, has concentrated on methylation of CpG dinucleotides within promoter sequences of DNA and chemical modifications (e.g., acetylation) of histones, the chief protein component of the chromatin.^{13–15} We thus focus primarily on methylation and histones.

Studies have shown that, in most cases, genetic predisposition



Source. Population image was adopted from Centers for Disease Control and Prevention. *Health Disparities and Inequalities Report 2011*. Available at: <http://www.cdc.gov/mmwr>.

FIGURE 1—Framework for proposed neighborhood-specific epigenome analysis for the study of environmental health disparities.

creates the potential for adverse health outcomes only when subsequently exposed to environmental toxicants^{16,17}; colloquially said: “genetics loads the gun, but the environment pulls the trigger.” For the promise of genomics to be realized, one must move beyond the discovery of disease-associated genetic variants to understanding the epigenetic mechanisms by which the environment may modulate gene expression and hence trigger disease.

NEIGHBORHOOD ENVIRONMENT MATTERS

Health disparities have been widely linked to regional variations in exposure to chemical and nonchemical stressors. Because disadvantaged populations often live in close proximity to polluted industrial sites,¹⁸

contaminated drinking water may be responsible for consistent reports of higher arsenic and lead burdens in racial/ethnic minorities than in White individuals.^{19,20} These exposures raise health concerns because arsenic and lead are also recognized risk factors for diabetes, cardiovascular and renal disease, and cancer.^{21–25} Disadvantaged communities and populations are also disproportionately exposed to toxic chemicals such as bisphenol A and traffic-related air pollution (e.g., particles with aerodynamic diameter $\leq 2.5 \mu\text{g}/\text{m}^3$ [$\text{PM}_{2.5}$]).^{18,26}

Exposure to these chemical stressors can cause disease by damaging DNA, disrupting hormones, inhibiting protein synthesis, or abrogating metabolic pathways.^{27,28} In the absence of direct mutations, environmentally induced epigenetic changes represent

alternative pathways for gene–environment interactions capable of significant effects on human health. Toxic metals such as arsenic and lead can modify disease susceptibility by altering DNA methylation and gene expressions.^{29,30} Indeed, evidence suggests that the carcinogenicity associated with these metals results from epigenetic modifications.³⁰ Studies also have linked other environmental chemicals, including bisphenol A and $\text{PM}_{2.5}$, with both gene-specific hypermethylation^{30–33} and global DNA hypomethylation (e.g., decreased long interspersed nucleotide element 1 methylation).^{34–36} These chemical-mediated modifications appear to result from competition for methyl donors during normal metabolic detoxification of metals³² and may persist across successive generations.³⁷

Disadvantaged neighborhoods are often exposed to not only chemical agents but also higher levels of nonchemical stressors, both physical (e.g., noise) and social (e.g., unhealthy food and psychosocial stress).^{18,38,39} Reports suggest that these nonchemical stressors can cause epigenetic changes,^{40,41} although this field of study is still in its early stages. For example, maternal care such as grooming and nursing of rat pups alters the methylation profile within a critical receptor gene in the brain of the pups (e.g., hypothalamus).⁴¹ Similarly, maltreatment, conflict-laden familial relationships, and unhealthy physical and social environments during childhood also can alter the human epigenome in ways that influence brain structure and its functional plasticity.⁴² The prenatal exposure of the developing child to famine (“Dutch Hunger Winter” cohort of 1944–1945⁴³) was associated with hypomethylation of the key growth factor gene for insulin-like growth factor 2 (*IGF2*) and the subsequent expression of *IGF2*.

TYPE 2 DIABETES AND CUMULATIVE EPIGENETIC CHANGES

As indicated earlier, populations living in disadvantaged neighborhoods likely will be compromised regarding their capacity both to detoxify chemicals and to methylate DNA. Once toxicants have entered the body, one mechanism of detoxification involves conjugation with the tripeptide glutathione, a key antioxidant molecule. However, exposure to toxic chemicals can deplete glutathione. Depleting glutathione stores decreases cellular *S*-adenosylmethionine and can contribute to genome-wide DNA hypomethylation.

S-adenosylmethionine is a critical methyl donor for most of the methyltransferases that modify DNA, RNA, histones, and other proteins. Thus, the methylation cycle and glutathione synthesis are biochemically interconnected. Loenen⁴⁴ hypothesized that for populations living in chemically contaminated communities, glutathione depletion results from intense glutathione consumption secondary to conjugation with chemicals or their metabolites. The methyl groups used in DNA methylation are often derived from dietary sources (e.g., fresh vegetables and fruits). Limited access to healthy foods supplemented with folic acid, methionine, and other methyl group donors may result in dietary methyl deficiency and thus exacerbate susceptibility to adverse health risk among those disadvantaged neighborhoods.⁴⁵

Type 2 diabetes is one of the most widely studied health endpoints with respect to epigenetic changes. Diabetes is a complex multifactorial disease and emerging major public health threat in overweight individuals, especially among minorities and the poor.⁴⁶ The underlying mechanisms remain undetermined, but studies have consistently shown an epigenetic link between type 2 diabetes and environmental factors (e.g., physical inactivity and arsenic exposure).^{15,47,48}

Kuroda et al.⁴⁹ reported that the degree of methylation declines within the insulin promoter of murine embryonic stem cells as they differentiate into insulin-expressing cells. Consistent with this observation, the promoter in human pancreatic β cells is similarly demethylated, suggesting that epigenetic influences could moderate insulin secretion. DNA methylation also alters the expression of the murine agouti gene, which is associated

with the subsequent development of obesity and a diabetes-like metabolic condition.⁵⁰ Complementary studies in this regard have shown that intrauterine nutrient deprivation and growth retardation may lead to type 2 diabetes secondary to the epigenetic silencing of a key transcription factor (pancreatic and duodenal homeobox 1) that regulates insulin gene expression and β -cell differentiation.^{51,52} Taken together, these studies support the thesis that environmental context matters and provide the clues that environment-induced epigenetic alterations may be central to the expression of common diseases (e.g., type 2 diabetes).

BEYOND THE SINGLE-STRESSOR ASSESSMENT STRATEGY

As outlined earlier, various environmental exposures have been linked to epigenetic modifications.^{30,47} Nevertheless, most studies on the relation between neighborhood context and health have focused on single stressors: chemical, physical, biological, or social conditions. The cumulative effect of multiple stressors and multiple exposures has received little attention or investigation because of the lack of integrated tools to quantify effects of such exposures and link them to health outcomes. Yet recent technology advancement (see the following section) has now made it possible to examine a broader and more complex array of neighborhood effects on human health.

Given the complexity of the gene–environment interactions, no single disciplinary approach alone could provide sufficient insight into either prevention or intervention strategies for elimination of health disparities. Thus,

the key to translating genomic science into public health practice is to develop tools to assess the cumulative effect or epigenetic load resulting from environmental justice–related differential exposures and subsequent disease risk. A new paradigm is apparently needed to establish the link between environmental influence as a whole and health disparities associated with disproportionate environmental exposures.

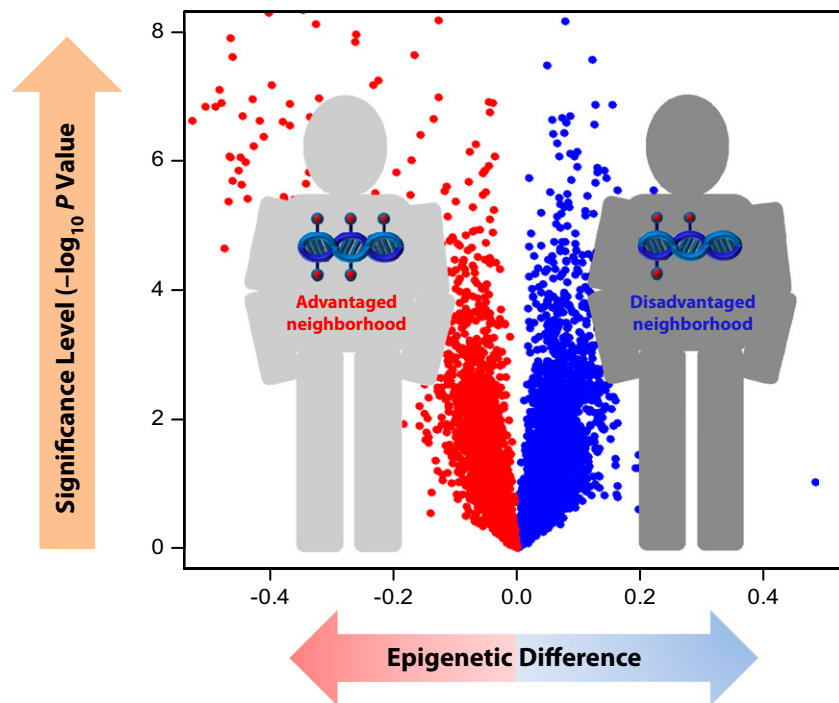
Epigenome programming can serve as a tool to monitor efforts to ameliorate environmental justice or neighborhood disadvantage. Neighborhood disadvantage is a powerful predictor of health outcomes, yet the effect of variations in neighborhoods on health has received little attention until recently.⁵³ It is intriguing to speculate that the accumulated extent and character of epigenetic markers resulting from exposure to a broad spectrum of environmental risk factors may be a predictive biomarker of susceptibility to chronic illnesses. Furthermore, finely tuned epigenetic mechanisms may operate to switch genes on and off, shifting the phenotype within genetically controlled limits. Such a buffering mechanism allows humans and other organisms to adjust their traits to cope with environmental heterogeneity, perhaps to improve their fitness for survival. Of course, not every adjustment is beneficial to the organism. Epigenetic regulation of gene expression may improve survival in one environment but increase vulnerability to disease in another time and place. Thus, this provides a strong rationale to elucidate the role of environmental justice–related unequal exposures in producing a differential neighborhood epigenome and its resultant health disparities. Understanding epigenetic pathways

could provide key insight for the targeted intervention and elimination of health disparities.

THE FUTURE OF EPIGENETIC ANALYSIS

Until recently, epigenetics could be examined only in a descriptive manner. With advancement in scientific technology (e.g., whole genome bisulfite sequencing), epigenetic marks, with respect to extent and location, can be easily identified. Once identified, the activation and inactivation of specific genes can be evaluated by microarray technology. The most definitive mechanistic link between environmental influence and epigenetic status to date was established by the well-defined and sensitive mouse coat color gene.^{54,55} Despite this predictive success in experimental animals, limited progress has been made in establishing causative links between environmentally induced epigenetic processes and diseases in humans.

To date, most of these human epigenetic studies used cross-sectional design and have examined particular genomic loci in only a limited sample size. Still lacking is the direct evidence of a temporal relation that is needed to link environmental justice, epigenetic alterations, and adverse health outcomes. Additional studies are needed on effects of environmental factors at specific stages in gestational development that may propagate onward to produce long-term phenotypic changes. Also, the timing of environmental exposure with respect to age or stage of human development is a critical factor that influences the magnitude of gene–environment interactions and warrants further investigation. This raises the question of a tipping point—the point beyond which the collected



Note. The x-axis denotes the relative fold change of DNA methylation, and the y-axis is the significance level of the result ($-\log_{10} P$ value) for each genetic loci interrogated on the microarray platform used.

FIGURE 2—Conceptual representation of differential epigenetic patterns between “advantaged” and “disadvantaged” neighborhoods, as illustrated by the volcano plot of DNA methylation.

duration or composition of neighborhood risk factors can no longer be individually tolerated, and health is compromised. It is also important to note that the epigenetic modification operates at the interface between genes and the environment and is a dynamic process that varies with age, a phenomenon also known as epigenetic drift.⁵⁶ One of the best examples of epigenetic drift is that considerable differences are found in both global and locus-specific DNA methylation and histone acetylation in identical twins across ages,⁵⁶ a finding that again substantiates the earlier argument that neighborhood environment matters.⁵⁷

Longitudinal studies are even better suited to investigate this type of age-related epigenetic changes.^{56,58} This approach could

be a reasonable solution to estimate the contribution of heritable and environmental factors to variation in a quantitative trait such as DNA methylation. In longitudinal analysis, one can estimate to what extent DNA methylation is influenced by environmental stressors associated with environmental justice (e.g., lead),^{19,30} because although both the epigenome and the environment are dynamic,^{58,59} the underlying genome is relatively constant. Nevertheless, not all epigenetic changes are environmentally mediated, and dynamic changes in DNA methylation do occur in conjunction with normal age-associated developmental processes.

Another major challenge is to develop precise tools and dynamic capabilities of evaluating environmental justice effects. Typically,

such data are derived from questionnaires or extrapolated from stationary monitoring devices. These methodologies have inherent limitations, including misclassification errors and individual variability. The advancement in high-throughput technology allows the incorporation of emerging “-omic” approaches: RNA expression (transcriptomics), protein expression (proteomics), and metabolites (metabolomics) as advocated in Wild’s “exposome” to characterize total past exposure.⁶⁰ The resulting “-omic” profiles can complement epigenome analysis by characterizing the downstream biological events associated with each epigenetic pattern in the exposure–disease continuum. With these relationships in hand, one can improve exposure assessment

and therefore better predict disease risk related to environmental justice.

As stated earlier, the recent advances in epigenetic technology (e.g., longitudinal analysis and “-omic” biomarkers) have made the proposed neighborhood-specific epigenomic approach feasible to examine the relation between health disparity and environmental justice. For instance, one may perform an exploratory analysis like the volcano plot of the differential DNA methylation analysis (Figure 2) or heat map or hierarchical clustering analysis^{61,62} to examine epigenetic profiles between neighborhoods. Once these profiles are identified, one can focus on candidate epigenetic alterations and further perform the functional annotation analysis of these differentially methylated genes⁶³ to enrich these identified genes in gene ontology biological processes such as transcription regulation or cell surface receptor–linked signal transduction.

Despite the promise, several critical issues remain to be addressed such as the development of technologies to assess the functional relation among individual methylated components (e.g., promoters) and to cope with the small effect size of epigenetic changes.⁶⁴ Hence interdisciplinary efforts are needed, including exposure assessment, bioinformatics, biostatistics, epidemiology, social sciences, and clinical medicine, to tackle the complex issues associated with health disparities.

CONCLUSIONS

In summary, the synthesized evidence cited earlier suggests that disproportionate environmental burdens, referred to as environmental justice, can lead to differential epigenetic changes including

chemical modification of DNA and chromatin. These epigenetic modifications can alter gene expression to enhance susceptibility or resistance to the cumulative effect of multiple environmental stressors. Neighborhood-level analyses, which go beyond chemical-by-chemical approaches to risk evaluation, are needed to identify the interactive effects of chemical and nonchemical stressors to develop effective and sustainable environmental health interventions.

Insight into epigenetic regulation of gene expression may lead to identification of novel targets for population-based prevention efforts, and by comparing neighborhood-specific epigenomic profiles, one can then identify and address the most promising remedies. For instance, one may consider intervention with inhibitors of enzymes involved in the chemical modifications of DNA or chromatin (e.g., dietary supplements) and modifiers of DNA methylation and histone deacetylation to reactivate epigenetically silenced genes and thus to restore normal cell function. Thus, characterization of metabolic pathways affected by epigenetic modifications may provide considerable insight into the possible role of environmental justice in health disparities. ■

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Contributors

K. Olden conceptualized and supervised the work. Y.-S. Lin, D. Gruber, and B. Sonawane conducted a systematic literature review and co-wrote the article.

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References

- Office of Minority Health. Health and Human Services fact sheet: minority health disparities at a glance. Washington, DC: US Department of Health and Human Services. Available at: <http://www.minorityhealth.hhs.gov>. Accessed August 7, 2013.
- Murray CJ, Kulkarni SC, Michaud C, et al. Eight Americas: investigating mortality disparities across races, counties, and race-counties in the United States. *PLoS Med*. 2006;3(9):e260.
- Clark LP, Millet DB, Marshall JD. National patterns in environmental injustice and inequality: outdoor NO₂ air pollution in the United States. *PLoS ONE*. 2014;9(4):e94431.
- Bullard RD. *Dumping in Dixie: Race, Class, and Environmental Quality*. 3rd ed. Boulder, CO: Westview Press; 2000.
- Institute of Medicine (IOM). *Genes, Behavior, and the Social Environment: Moving Beyond the Nature/Nurture Debate*. Washington, DC: National Academies Press; 2006.
- Stranger BE, Stahl EA, Raj T. Progress and promise of genome-wide association studies for human complex trait genetics. *Genetics*. 2011;187(2):367–383.
- Ramsahoye BH, Biniszkiewicz D, Lyko F, Clark V, Bird AP, Jaenisch R. Non-CpG methylation is prevalent in embryonic stem cells and may be mediated by DNA methyltransferase 3a. *Proc Natl Acad Sci U S A*. 2000;97(10):5237–5242.
- Lister R, Pelizzola M, Dowen RH, et al. Human DNA methylomes at base resolution show widespread epigenomic differences. *Nature*. 2009;462(7271):315–322.
- Clark SJ, Harrison J, Frommer M. CpNpG methylation in mammalian cells. *Nat Genet*. 1995;10(1):20–27.

- Beck S, Rakan VK. The methylome: approaches for global DNA methylation profiling. *Trends Genet*. 2008;24(5):231–237.
- Irizarry RA, Ladd-Acosta C, Wen B, et al. The human colon cancer methylome shows similar hypo- and hypermethylation at conserved tissue-specific CpG island shores. *Nat Genet*. 2009;41(2):178–186.
- Jiang Q, Wang Y, Hao Y, et al. miR2Disease: a manually curated database for microRNA deregulation in human disease. *Nucl Acids Res*. 2009;37(suppl 1):D98–D104.
- Talmud PJ, Humphries SE. Gene: environment interaction in lipid metabolism and effect on coronary heart disease risk. *Curr Opin Lipidol*. 2002;13(2):149–154.
- Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. *Annu Rev Nutr*. 2007;27:363–388.
- Wren JD, Garner HR. Data-mining analysis suggests an epigenetic pathogenesis for type 2 diabetes. *J Biomed Biotechnol*. 2005;2005(2):104–112.
- Olden K. Commentary: from phenotype, to genotype, to gene-environment interaction and risk for complex diseases. *Int J Epidemiol*. 2007;36(1):18–20.
- Olden K. Human health and disease: interaction between the genome and the environment. In: Huntington WF, Ginsburg GS, eds. *Genomic and Personalized Medicine*. Vol 1. San Diego, CA: Academic Press; 2009:47–59.
- Gee GC, Payne-Sturges DC. Environmental health disparities: a framework integrating psychosocial and environmental concepts. *Environ Health Perspect*. 2004;112(17):1645–1653.
- National Center for Environmental Health. *The Fourth National Report on Human Exposure to Environmental Chemicals*. Centers for Disease Control and Prevention. 2013. Available at: <http://www.cdc.gov/exposurereport>. Accessed May 1, 2013.
- Balazs CL, Morello-Frosch R, Hubbard AE, Ray I. Environmental justice implications of arsenic contamination in California's San Joaquin Valley: a cross-sectional, cluster-design examining exposure and compliance in community drinking water systems. *Environ Health*. 2012;11:84.
- Schober SE, Mirel LB, Graubard BI, Brody DJ, Flegal KM. Blood lead levels and death from all causes, cardiovascular disease, and cancer: results from the NHANES III mortality study. *Environ Health Perspect*. 2006;114(10):1538–1541.
- Guo HR. Cancer risks associated with arsenic in drinking water. *Environ*

- Health Perspect*. 2007;115(7):A339–A340; author reply A340–A341.
- Baastrop R, Sørensen M, Balstrøm T, et al. Arsenic in drinking-water and risk for cancer in Denmark. *Environ Health Perspect*. 2008;116(2):231–237.
- Moon K, Guallar E, Navas-Acien A. Arsenic exposure and cardiovascular disease: an updated systematic review. *Curr Atheroscler Rep*. 2012;14(6):542–555.
- Chung CJ, Huang YL, Huang YK, et al. Urinary arsenic profiles and the risks of cancer mortality: a population-based 20-year follow-up study in arseniasis-endemic areas in Taiwan. *Environ Res*. 2013;122:25–30.
- Nelson JW, Scammell MK, Hatch EE, Webster TF. Social disparities in exposures to bisphenol A and polyfluoroalkyl chemicals: a cross-sectional study within NHANES 2003–2006. *Environ Health*. 2012;11:10.
- Alonso-Magdalena P, Ropero AB, Carrera MP, et al. Pancreatic insulin content regulation by the estrogen receptor ER alpha. *PLoS ONE*. 2008;3(4):e2069.
- Bromer JG, Zhou Y, Taylor MB, Doherty L, Taylor HS. Bisphenol-A exposure in utero leads to epigenetic alterations in the developmental programming of uterine estrogen response. *FASEB J*. 2010;24(7):2273–2280.
- Litt JS, Tran NL, Burke TA. Examining urban brownfields through the public health "macroscopic." *Environ Health Perspect*. 2002;110(suppl 2):183–193.
- Hou L, Zhang X, Wang D, Baccarelli A. Environmental chemical exposures and human epigenetics. *Int J Epidemiol*. 2012;41(1):79–105.
- Chanda S, Dasgupta UB, Guhamazumder D, et al. DNA hypermethylation of promoter of gene p53 and p16 in arsenic-exposed people with and without malignancy. *Toxicol Sci*. 2006;89(2):431–437.
- Chen H, Li S, Liu J, Diwan BA, Barrett JC, Waalkes MP. Chronic inorganic arsenic exposure induces hepatic global and individual gene hypomethylation: implications for arsenic hepatocarcinogenesis. *Carcinogenesis*. 2004;25(9):1779–1786.
- Rossman TG. Mechanism of arsenic carcinogenesis: an integrated approach. *Mutat Res*. 2003;533(1–2):37–65.
- Mass MJ, Wang L. Arsenic alters cytosine methylation patterns of the promoter of the tumor suppressor gene p53 in human lung cells: a model for a mechanism of carcinogenesis. *Mutat Res*. 1997;386(3):263–277.
- Reichard JF, Schnekenburger M, Puga A. Long term low-dose arsenic exposure induces loss of DNA

- methylation. *Biochem Biophys Res Commun*. 2007;352(1):188–192.
36. Sciandrello G, Caradonna F, Mauro M, Barbata G. Arsenic-induced DNA hypomethylation affects chromosomal instability in mammalian cells. *Carcinogenesis*. 2004;25(3):413–417.
37. Fry RC, Navasumrit P, Valiathan C, et al. Activation of inflammation/NF-kappaB signaling in infants born to arsenic-exposed mothers. *PLoS Genet*. 2007;3(11):e207.
38. Wilhelm M, Ritz B. Residential proximity to traffic and adverse birth outcomes in Los Angeles county, California, 1994-1996. *Environ Health Perspect*. 2003;111(2):207–216.
39. Perera FP, Rauh V, Whyatt RM, et al. Molecular evidence of an interaction between prenatal environmental exposures and birth outcomes in a multiethnic population. *Environ Health Perspect*. 2004;112(5):626–630.
40. Zhang FF, Cardarelli R, Carroll J, et al. Physical activity and global genomic DNA methylation in a cancer-free population. *Epigenetics*. 2011;6(3):293–299.
41. Meaney MJ, Szyf M. Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. *Dialogues Clin Neurosci*. 2005;7(2):103–123.
42. McEwen BS. Brain on stress: how the social environment gets under the skin. *Proc Natl Acad Sci U S A*. 2012;109(suppl 2):17180–17185.
43. Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A*. 2008;105(44):17046–17049.
44. Loenen WA. S-Adenosylmethionine: jack of all trades and master of everything? *Biochem Soc Trans*. 2006;34(pt 2):330–333.
45. Burdge GC, Lillycrop KA. Nutrition, epigenetics, and developmental plasticity: implications for understanding human disease. *Annu Rev Nutr*. 2010;30:315–339.
46. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care*. 1998;21(9):1414–1431.
47. Ling C, Groop L. Epigenetics: a molecular link between environmental factors and type 2 diabetes. *Diabetes*. 2009;58(12):2718–2725.
48. Bailey KA, Wu MC, Ward WO, et al. Arsenic and the epigenome: interindividual differences in arsenic metabolism related to distinct patterns of DNA methylation. *J Biochem Mol Toxicol*. 2013;27(2):106–115.
49. Kuroda A, Rauch TA, Todorov I, et al. Insulin gene expression is regulated by DNA methylation. *PLoS ONE*. 2009;4(9):e6953.
50. Morgan HD, Sutherland HG, Martin DI, Whitelaw E. Epigenetic inheritance at the agouti locus in the mouse. *Nat Genet*. 1999;23(3):314–318.
51. Gallou-Kabani C, Junien C. Nutritional epigenomics of metabolic syndrome: new perspective against the epidemic. *Diabetes*. 2005;54(7):1899–1906.
52. Park JH, Stoffers DA, Nicholls RD, Simmons RA. Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of Pdx1. *J Clin Invest*. 2008;118(6):2316–2324.
53. Freudenberg N, Olden K. Finding synergy: reducing disparities in health by modifying multiple determinants. *Am J Public Health*. 2010;100(suppl 1):S25–S30.
54. Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Mol Cell Biol*. 2003;23(15):5293–5300.
55. Wolff GL, Kodell RL, Moore SR, Cooney CA. Maternal epigenetics and methyl supplements affect agouti gene expression in Avy/a mice. *FASEB J*. 1998;12(11):949–957.
56. Fraga MF, Ballestar E, Paz MF, et al. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci U S A*. 2005;102(30):10604–10609.
57. Olden K, Isaac L, Roberts L. Neighborhood-specific epigenome analysis: the pathway forward to understanding gene-environment interactions. *N C Med J*. 2011;72(2):125–127.
58. Madrigano J, Baccarelli A, Mittleman MA, et al. Aging and epigenetics: longitudinal changes in gene-specific DNA methylation. *Epigenetics*. 2012;7(1):63–70.
59. Lin YS, Kupper LL, Rappaport SM. Air samples versus biomarkers for epidemiology. *Occup Environ Med*. 2005;62(11):750–760.
60. Wild CP. The exposome: from concept to utility. *Int J Epidemiol*. 2012;41(1):24–32.
61. Subramanian A, Tamayo P, Mootha VK, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A*. 2005;102(43):15545–15550.
62. Slonim DK. From patterns to pathways: gene expression data analysis comes of age. *Nat Genet*. 2002;32(suppl):502–508.
63. Huang da W, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat Protoc*. 2009;4(1):44–57.
64. Mill J, Heijmans BT. From promises to practical strategies in epigenetic epidemiology. *Nat Rev Genet*. 2013;14(8):585–594.