Neighborhood-Specific Epigenome Analysis:
The Pathway Forward to Understanding Gene-Environment Interactions

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Morbidity and mortality associated with complex diseases are expected to increase as the population ages and the number of Americans living in poverty continues to expand. Therefore, improved translation of research findings into clinical practice and public health policy must become a priority. This commentary emphasizes the need for a new research model that accommodates the complex nature of disease etiology.

Complex diseases such as asthma, cancer, diabetes, and cardiovascular disorders account for a disproportionate percentage of health care costs in the United States and other industrialized nations [1]. Furthermore, morbidity and mortality associated with such diseases are expected to increase as the population ages and the number of Americans living in poverty continues to expand. Therefore, improvement in translation of medical research findings into the practice of medicine and public health policy and practice must become a national priority. This commentary emphasizes the need for a new research model that takes into consideration the complex nature of disease etiology. The current "bench to bedside" model must be expanded to include the "community," as well as transdisciplinary research that integrates knowledge of genetics and epigenetic regulation with information about environmental exposures, broadly defined to include social, behavioral, economic, and physical/chemical factors.

We know that the link between the environment and population health is strong. In fact, the World Health Organization estimates that approximately a quarter of the global burden of disease is related to environmental risk factors [1]. Most of the advances in population health during the past 150 years have been due to changes in the physical environment. Measures such as improvements in sanitation, air quality, and food safety and the creation of public drinking water systems have been implemented to address some of the problems introduced by these changes, but many problems persist. We also know, for example, that ambient levels of pollutants in the air we breathe can cause or exacerbate respiratory health problems, cardiovascular disease, and cancer; that water pollution can lead to acute poisonings or have longer-term, chronic effects; and that the environments in which we work, live, and go to school contribute to health disparities. Although researchers and public health practitioners have long known about the links between the environment and population health, insufficient attention has been given to the environmental changes and public health policies necessary to improve both individual health and population health.

A decade after the completion of the Human Genome Project, many disease-susceptibility genes have been discovered, yet the causes of most common diseases still remain unexplained. To date, hundreds of thousands of genetic variants have been examined in disease-association studies. Unfortunately, most of the variants have only modest effects on disease susceptibility. Most of these studies were designed to detect main effects of variant alleles; thus, they are too small to detect gene-environment interactions. Furthermore, the genetic model of disease does not explain several features of complex diseases. These include the high degree of discordance or dissimilarity in susceptibility (often as high as 85%) and variability in age of onset and severity of disease among monozygotic twins, since they share the same genes (both susceptibility and modifier). Moreover, a large body of evidence now exists indicating that environmental, social, behavioral, and economic factors are important determinants of health [2, 3]. The emerging view, from the disparate studies conducted during the past 30 years, is that neither genetics nor environmental factors acting alone cause complex diseases, but rather that they are caused by complex interactions involving the various determinants. Therefore, to improve the health of individuals and populations, research is needed to elucidate gene-environment interactions.

Despite the fact that the concept of gene-environment interaction is now widely accepted, the vast majority of social and behavioral, environmental, and genetic research

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is still conceptualized and conducted within narrow disciplines by investigators with expertise in a single area. Given the complexity of regulatory networks involved in the development of human diseases, it is highly unlikely that standalone disciplinary analysis will provide the insight needed for their prevention or cure. The research approach called for here will require a shift in focus to transdisciplinary teams that involve researchers with expertise in the requisite disciplines needed to develop an integrated, holistic effort to untangle the complex interactions involved in the etiology of complex diseases.

The slow pace of progress in understanding the causes of common diseases is related, at least in part, to the fact that the scope and scale of the models used do not recapitulate the known complexity of disease etiology. For example, most studies designed to understand variation in predisposition to disease have not taken into account the fact that gene expression is regulated by DNA nucleotide sequence and chemical modification of the epigenome and that most, if not all, diseases are caused by interactions between the genome, the epigenome, and the environment. Therefore, an important layer of complexity and a possible source of variation have not been integrated into experimental models.

The epigenome refers to the sum total of all the chemical modifications of DNA and chromatin that are not encoded in the nucleotide sequence of DNA, and epigenetics is the study of such heritable changes. "Epi" is derived from a Greek word meaning "over," "above," or "on top of." Waddington coined the term *epigenome* in 1942, as a conceptual model of how genes, though not yet discovered, might interact with their environment [4]. The epigenome can be viewed as a code that is superimposed on the genetic code, to choreograph gene expression in response to signals derived from the environment. Even though all the information required for the synthesis of all the proteins in the human body is encoded in the DNA, only a small fraction of the total repertoire is expressed at any given time or place.

The epigenome operates at the interface between genes and the environment, playing a pivotal role in mediating cross talk between the environment and the genome. It is now well-established that many environmental exposures (both social and physical) can modify the structure of the epigenome. The most common modifications involve methylation of DNA or histone proteins associated with chromatin. The addition of methyl or other small chemical molecules to DNA or chromatin 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 and predisposition to disease can be altered.

Unlike the genome, which is the same in every cell and tissue in the human body, the epigenome is highly variable over the life course, from tissue to tissue and from environment to environment. Also, unlike genes that are inactivated by nucleotide sequence variation, genes silenced by epigenetic mechanisms are still intact and, thus, retain the potential to be reactivated by environmental or medical intervention.

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. One can envision the existence of a finely tuned epigenetic mechanism that can switch genes "on and off," shifting the phenotype within a genetically defined range as the environment changes [5]. This buffering mechanism allows humans or other organisms to cope with environmental heterogeneity, to improve their fitness for survival. In fact, survival is threatened when living organisms lose their ability to change their phenotype in response to environmental stressors. Whereas epigenetic regulation of gene expression may have evolved to improve fitness for survival in variable environments, changes in gene expression at an inappropriate time or place may lead to disease. Also, the intensity of the environment-induced stress may overwhelm the compensatory capacity of buffering mechanisms. Environment-induced epigenetic changes in gene expression are the most plausible causes for the observed discordance in susceptibility to diseases among genetically identical (monozygotic) twins.

It is likely that human activity and the introduction of new technologies during the past 100 years have led to the build up of harmful by-products in the environment faster than biological systems can evolve buffering or repair systems to ameliorate them. It is also possible 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 risk for disease because of their incompatibility with the modern-day environment. These social and evolutionary trends are likely significant contributors to both the development of the epidemic of chronic diseases and the epigenetic mechanisms to promote adaptation and survival. For example, the rapid increase in the prevalence of type 2 diabetes is surely the result of recent environmental changes (eg, abundance of food) and behavioral changes (eg, sedentary lifestyle) interacting with a relatively constant genetic background that consists of approximately 25 known susceptibility genes.

It is well established that abnormal DNA-methylation patterns are associated with many human diseases and disorders—including cancer, obesity, type 2 diabetes, anemia, cardiovascular disorders, and many neurodevelopmental disorders [6]—further suggesting the importance of epigenetic regulation in the development of human diseases. If environment-induced epigenetic regulation of gene expression proves to play a prominent role in determining susceptibility to common diseases, opportunities to prevent their occurrence would be greatly enhanced by exploiting the dynamic and reversible plasticity of the epigenome.

Even though social and neighborhood factors are among the most powerful predictors of health outcomes, efforts to integrate such knowledge with improved capacity to assess

genetic susceptibility have been limited. The fundamental principle of environmental justice is that social, behavioral, and neighborhood factors matter for health. Neighborhoods are more than groups of people living in a common geographic space—they represent complex environments in which cultural, economic, and physical factors interact in unique ways to influence disease risk. Failure to account for neighborhood differences in study design may account for why most of the variance in disease risk is still unexplained and why strong candidate genes often perform poorly in genotype-phenotype association studies.

We need to take advantage of the much-celebrated neighborhood diversity characteristic of major US cities to develop models of differing exposures. This can be achieved by developing a database consisting of neighborhood-specific epigenetic markers in parallel with genetic, environmental, and gene-expression data. The prediction is that research will detect significant interindividual and neighborhood-specific epigenetic variation that regulates the expression of genes with important roles in disease development and that can be correlated with specific interactions between the genome, the epigenome, and the environment. NCMJ

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