

**Report 81:** Environmental Epigenomics and Complex Heritable Disease

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**Brief History:** There is considerable evidence that many complex diseases are heritable and have a genetic basis. However, current evidence suggests that genetic code do not account for all risk of disease. Furthermore, many common complex diseases have alteration in prevalence over decades (for example asthma and obesity) suggesting lifetime environmental exposures (or experience) could modify disease risk. Environmental exposures during vulnerable periods of development can modify the likelihood of development of disease or severity of disease. Emerging evidence supports that epigenomic marks can be modified by exposures (or stress) and are associated with altered disease risk. However, there are limited evidence supporting the mechanistic link between exposure, epigenomic marks, and disease. The NIEHS is uniquely poised to lead the effort to better understand this important relationship between environment, epigenome, and complex human disease.

**Discussion Highlights:** There are considerable interest in the emerging field of epigenomics and disease risk. The NIEHS should lead this effort to understand the important role of environment on modifying epigenomic marks as they relate to disease burden.

Epigenomics for the purpose of this discussion was **defined** as transmissible modifications in DNA and DNA-associated molecules that influence whether genes are turned on or off. These changes include CpG methylation and chromatin/histone modification.

Environmental exposures should be **defined** broadly to include; psycho-social stress, diet, toxicant exposure, obesity, etc....

There are **vulnerable windows** of susceptibility to environmental stress associated with modification in epigenomic marks.

There are limited good mechanistic studies to link exposures with modification of epigenomic marks and disease risk. Basic understanding of this link is required.

Studies of the epigenome require an appreciation for specific tissues and cell types contributing to disease pathogenesis.

The epigenome can be somatically transmitted and could contribute to heritable risk of disease. Further studies should focus on heritable transmission of disease.

Proof-of-principle studies are necessary to move the field forward.

While there is technology available to study epigenetics, this technology should be further developed to facilitate meaningful studies of epigenetics. These include platforms for global methylation and novel technologies that could include in vivo imaging.

Bioinformatics is probably adequate but need to facilitate training of scientist.

A systems biology approach is required to integrate environment, epigenome, genetic code variation, and disease risk.

Timing and dose of exposure are important considerations. There can be considerable lag between relevant exposure and development of disease.

Translational studies should be encouraged but may require further mechanistic insight into targets from mechanistic basic studies from either cell culture or animal models of disease.

Important to integrate studies initiated at the NIEHS with ongoing studies (if possible). Identification or development of adequate human cohorts to study the link between environment, the epigenome, and disease are required (for example, the National Children's Study).

**Recommendations:**

1. Basic mechanistic studies of relationship between environment, epigenome, and disease are necessary. Studies should link the functional consequences of modification of the epigenome on regulation of gene expression.
2. Improved technology will facilitate the field moving forward.
3. Emphasis should be placed on vulnerable windows of susceptibility.
4. Translational studies should be designed to better understand the relationship between environment, epigenome, and disease.
5. A systems biology approach should be encouraged to integrate the environment, epigenome, genetic variation, genomic expression, and disease risk.
6. Biobanks should be established with appropriate protocols to study epigenomic marks. Tissue/cell collection should be protocol-driven.

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