



Insights from epigenetic studies on human health and evolution

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Epigenetic variation represents a unique aspect of human biological variation that can shed light on our evolutionary history as well as the etiology of human disease. DNA methylation is the most commonly studied type of epigenetic modification and can alter gene expression without changing the underlying DNA sequence. DNA methylation occurs throughout all living organisms although its function seems to have evolved from genome defense in fungi, bacteria and plants to a more complex role in gene regulation and cellular differentiation in animals. Human DNA methylation was originally studied in imprinting diseases and cancer, but more recently has been investigated as a mechanism to mediate the impact of environmental and psychosocial stressors on human health and disease.

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Epigenetics and human evolution

Epigenetic variation has emerged as the latest lens through which to study human evolution and disease. Epigenetic modifications can alter gene expression without changing the underlying DNA sequence and, thus, illuminate a different facet of evolution and adaptation compared to genetic variants [1]. With both genetic and epigenetic variation, one can investigate the evolution of the genome at a molecular level as well as adaptation at individual and population levels. However, genetic change occurs less frequently and is more stable in comparison to epigenetic change, which can occur in response to environmental stimuli experienced during an individual's lifetime. Epigenetic responses to environmental stressors may have evolved to provide rapid, short-

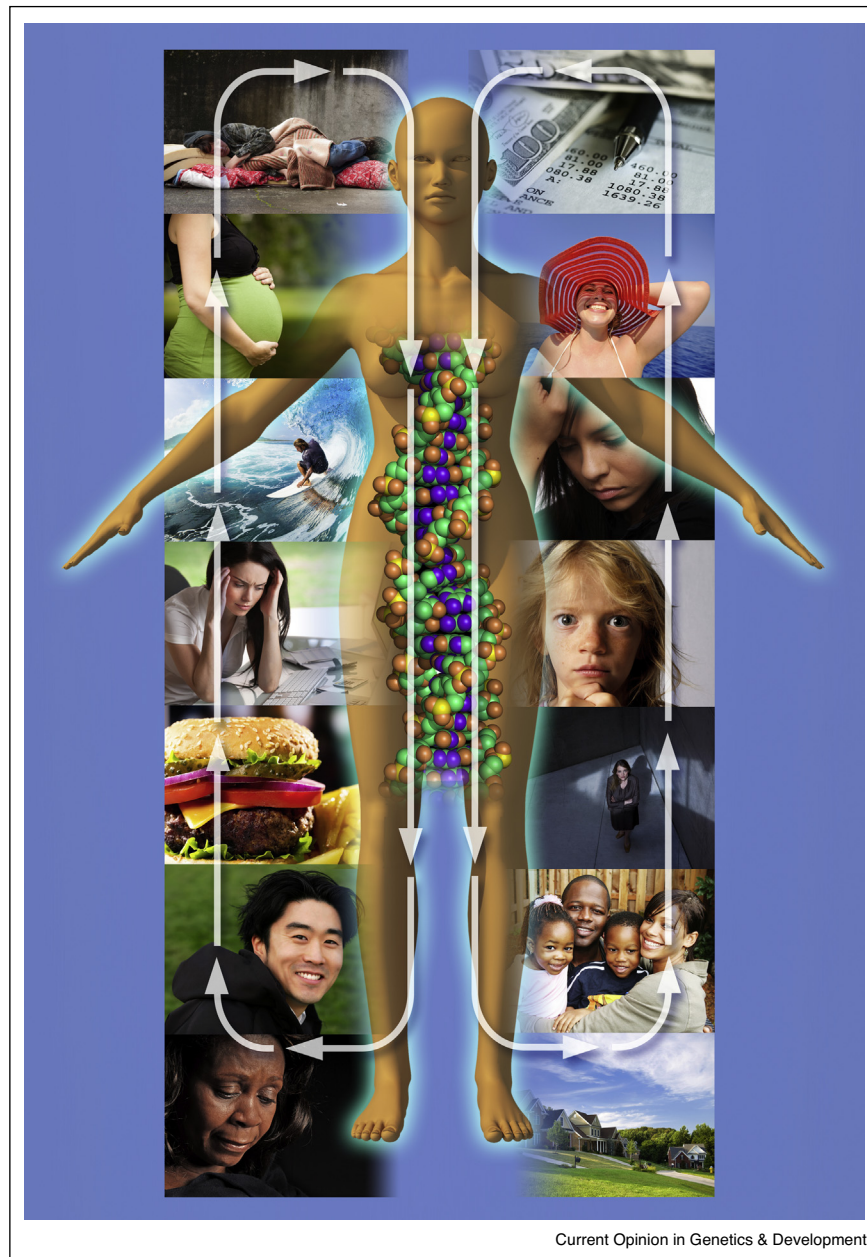
term responses to changes in the environment while genetic changes provided long-term adaptations.

Both epigenetic and genetic variants influence our response to diverse stimuli, ranging from environmental toxins to diet to emotional distress, and those responses can impact our physical and mental health (Figure 1). Epigenetic variants may also be altered by environmental stimuli, in contrast to more stable genetic variants. Moreover, different stimuli may feedback on epigenetic variants in a cyclical manner highlighting the complexity of epigenetic variation and the human condition, for example, exposure to lead or other toxins may create epigenetic modifications that alter the expression of genes involved in cognitive functioning and then lead to increased risk of joblessness, poverty, and continued exposure to environmental toxins. Epigenetic response to biological and psychosocial factors, like those illustrated in Figure 1, may have evolved in humans as an adaptation to increasingly complex stressors that are not experienced in simpler organisms [2].

DNA methylation is one of the most studied types of epigenetic modifications and typically occurs at cytosines followed by guanines, that is, CpG sites. In addition to environmental factors, DNA sequence variants can influence the level of methylation at nearby CpG sites; those genetic variants are called methylation quantitative trait loci, or meQTLs, and have been found to associate with certain complex phenotypes and diseases [e.g. 3]. DNA methylation is one of the main epigenetic factors that controls gene regulation in mammals and plays a critical role in cellular differentiation and reprogramming [4]. Originally, DNA methylation was found to 'silence' genes when methylation occurred in promoter regions. More recently, research has shown that gene expression can be either increased or decreased depending on the region of the gene and genome that is methylated as well as the developmental stage and transcriptional activity of the genome [5–7].

Multiple research groups have assayed DNA methylation in healthy human populations in order to better understand how methylation contributes to natural human variation and to demonstrate how methylation is influenced by both genetic variation (meQTLs and genetic ancestry) and environmental exposures [8–10]. DNA methylation and meQTLs show high population-specificity and associations with complex phenotypes, such as age, can be highly consistent across diverse populations

Figure 1



A wide range of biological and psychosocial factors, both positive and negative, influence our lives (illustrated in the photographs in the figure), including poverty and homelessness, environmental exposures to toxins or irradiation, physical or emotional trauma, psychiatric disorders such as depression or anxiety, our emotional moods, pregnancy and family, our neighborhood, and nutrition and physical activity. Genetic and epigenetic variants may influence how we respond to these factors and how they impact our physical and mental health. Furthermore, these physical/psychosocial factors and genetic/epigenetic variants may feedback on each other in a cyclical manner, for example, exposure to lead or other toxins may create epigenetic modifications that alter the expression of genes involved in cognitive functioning and then lead to increased risk of joblessness, poverty, and further exposure to environmental toxins.

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[11,12^{••},13]. Recently, Carja *et al.* [14^{••}] produced the first worldwide map of human DNA methylation at CpG sites. They found good correlation between population-specific levels of genetic, epigenetic and mRNA variation but

much stronger correlation between genetic and epigenetic divergences suggesting that DNA methylation evolves in a clock-like fashion, similar to genetic variation. Furthermore, they found far greater evolutionary

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