

Understanding the Role of Epigenetics in Adverse Health Outcomes

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ABSTRACT

The term epigenetics refers to a field of study that focuses on modifications to gene expression without directly altering the DNA sequence (NIH Author, 2021). The role of this research project is to investigate the role in processes such as DNA methylation and their long-term effects in producing adverse health outcomes for individuals (CDC Author, 2022). This research project also aims to investigate the environmental conditions, daily habits, and length of time which all contribute towards an epigenetic change. To encapsulate the purpose of this study, a driving question is proposed: How do changes in environmental factors such as prenatal malnutrition, smoking exposure, and psychological stress contribute to epigenetic change and subsequently, adverse health effects? Studies have found some correlation between epigenetic changes and chronic conditions such as cancer, type 2 diabetes, and depression; however, there is much to be explored to completely establish such an association (Dayah et al., 2016). Here, the research project consolidates multiple studies conducted in the realm of epigenetics to determine a cause-and-effect association between environmental factors and finally, specific health outcomes.

Summary of Research

DNA methylation is a heritable process that occurs in the event of an epigenetic change. To elaborate, changes caused by methylation are passed down from parent to offspring. It is crucial in silencing transcription, which produces the primary transcript of RNA. DNA methylation occurs when a methyl group is transferred onto the C5 position of the cytosine, subsequently forming 5-methylcytosine (Moore et al., 2013). There is a common misconception that methylation holds a purely detrimental effect. In most cases, DNA methylation is crucial in development and plays a role in genomic imprinting and X-chromosome inactivation, which ensures offspring cells express genes from both parents (Jin et al., 2011). However, DNA methylation can be associated with an increased risk for certain chronic diseases such as cancer. Exposure to cigarette smoke remains the most definitive environmental factor that can induce DNA methylation (McCartney et al., 2018). An assessment of nearly 16,000 blood-based DNA samples across participants from 16 cohorts (including 2433 current, 6518 former, and 6956 never smokers) found that 7201 of genes associated with CpG islands, sites that are known to regulate gene expression, were differentially methylated in current smokers than in those who never smoked. It can also be noted that the majority of differentially methylated CpG islands returned to normal after 5 years of abstaining from smoking (Zong et al., 2019). Therefore, it is established that smoking cessation can positively impact an individual's health outcomes. The genes associated with the islands represent more than one-third of all known human genes and can be integral in establishing an increased risk factor for chronic diseases such as lung cancer. There is also a significant association between cigarettes per day and duration of exposure in the occurrence of DNA methylation. Two clusters of DNA methylation data for over 4900 individuals were analyzed, where groups of low-dose and high-dose smokers were created. Individuals who were classified as low-dose smokers took 15-19 years to display differentially methylated islands. Individuals who were classified as high-dose smokers took 5-9 years to display similar results (McCartney et al., 2018). As such, the duration of exposure to cigarette smoke as well as the intensity of smoking is associated with differentially methylated CpG islands, which in turn

increase the risk for chronic cardiovascular and pulmonary diseases, as well as cancer. To conclude, smoking in general is a key environmental factor that can cause detrimental DNA methylation, impacting an individual's health outcomes.

Exploring the claim that environmental factors dictate epigenetic changes and adverse health outcomes also entails analyzing one key aspect of epigenetics involving inheritance. Conditions such as type 2 diabetes and rheumatoid arthritis are typically explored while analyzing Mendelian genetics. An individual's environment may not only be capable of influencing their own risk for chronic diseases, but for future generations as well. Knowing how an individual's parent was affected by their environment may explain their current state of health. The Dutch Famine, which occurred from 1944-1945, indicates that epigenetic changes are transgenerational in scope (Roseboom, 2019). Two cohorts of same-sex siblings were tracked using medical birth records, one of which was exposed to famine prenatally while the other was unexposed. Individuals who had been conceived during the famine and consequently exposed to prenatal undernutrition were more obese as adults. Furthermore, this corresponded to an increased risk of type 2 diabetes that resulted from higher glucose levels and insulin resistance (Roseboom, 2019). This study appears to recognize the claim that exposure to detrimental environmental factors during periods of critical physical and cognitive growth has a significant effect on health during adulthood. However, it also presents a new claim: the same exposure also carries over to offspring. Offspring of women who were prenatally exposed to the famine were observed to also have higher insulin resistance, contributing to increased risk of type 2 diabetes (Roseboom, 2019). They were also observed to have higher levels of stress which if experienced long-term contributes to the development of other chronic conditions. As such, it can be concluded from the study that epigenetic changes are heritable traits which may manifest themselves in future generations of offspring. In contrast, when looking purely at DNA methylation patterns in all mammals, offspring typically possessed lower methylation levels than their parents. More specifically, methylation levels were lower in the offspring's embryonic cells than in the mature gametes of the parent (Xavier et al., 2019). This suggests that any epigenetic marks carried by the gametes are replaced by a new methylation pattern. As such, there is not conclusive evidence whether DNA methylation in a parent is passed onto their offspring. Therefore, we cannot assume that adverse health outcomes in an individual may be the result of epigenetic change in their parents.

This research project also examines the role of epigenetics from the perspective of a health professional involved with marginalized populations. The researcher interviewed Dr. Cheryl Ho, a clinician at Santa Clara Valley Medical Center who primarily serves the California Bay Area homeless population. It was found that homeless individuals are more susceptible to mental disorders such as schizophrenia or bipolar disorder. In addition, Dr. Ho claims that such mental disorders are directly related to the various stressors, trauma, and other morbidities that homeless individuals have accumulated. While many homeless individuals do not have a predisposition to conditions such as anxiety, depression, or suicidality, epigenetic changes may result in their higher prevalence. Looking at individual members of the population allows for a more accurate analysis of this claim. Dr. Ho's observations indicate that the social determinants of health play a monumental role in the development of epigenetic change and subsequently, poor health outcomes. Defined as an individual's economic stability, healthcare, community, built environment, and education, these factors coincide directly with a history of abuse, recent incarceration, or social rejection. As Dr. Ho mentions, while they do not have a direct effect on an individual's genome, there are undoubtedly effects on the regulation and expression of genes. Therefore, there is evidence of an association between environmental factors and an individual's health outcomes, brought together by epigenetic change. In this context, the various stressors an individual accumulates influences their risk for physical and cognitive disorders.

Discussion

In this research project, it was established that there is a strong association between environmental factors such as smoking exposure, prenatal malnutrition, and the social determinants of health, and the development of adverse health outcomes. The epigenetic process of DNA methylation was briefly discussed as a key player in gene expression. When looking specifically at DNA methylation levels across two groups of non-smokers and smokers, the group of smokers

had significantly more methylated genes. On the other hand, when smokers began abstaining from the practice, their differential methylation returned to near-normal levels. This result could have implications for rehabilitation efforts relevant to not only victims of nicotine addiction, but also drug abuse. Knowing that rehabilitation reduces the impact of detrimental epigenetic change could push policymakers to institute more aggressive rehabilitation agendas. This is especially relevant for the homeless population, which was discussed previously.

Through two studies by Roseboom et al. and Xavier et al, the claim that changes in the epigenome are transgenerational is not definitively proven. There certainly may be a weak association between DNA methylation levels observed in the parent and health outcomes in the offspring. The Dutch Famine discussed by Roseboom et al. is an extreme environmental event that contributes to this association. This differs from the study conducted by Xavier et al., where previous DNA methylation levels in the parent appeared to be replaced in the offspring. However, it should be noted that no environmental factor such as prenatal malnutrition affected the parent group in the latter study. Therefore, it can be concluded that for epigenetic changes to be observed in offspring, an extreme environmental factor must have affected the parent group.

In conclusion, the research project suggests that epigenetic changes cause differentially methylated CpG islands, which regulate gene expression. Thus, it is inferred that the reason environmental factors cause adverse health effects is due to DNA methylation, among other epigenetic processes. Finally, though the field of epigenetics is a relatively unexplored topic, it has already been established as a key influencer in assessing an individual's risk for chronic conditions.

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