Genetic Imprints of Environments: DNA Methylation as a mediator between Childhood Stress and Mental Health Development

Eve Yiran Zheng

Abstract
Stressful experiences in childhood are known to be related to increased risks of various mental disorders. Epigenetic modification, particularly DNA methylation, is one of the mechanisms that biologically encodes the long-term impacts of experiences on individuals. This article summarizes empirical research of DNA methylation in response to two kinds of stressful events early in life: childhood abuse and low childhood socioeconomic status (SES), and how these changes in methylation patterns are associated with mental health development. Alterations in DNA methylation were observed following experiences of childhood abuse and low childhood SES, both on specific loci and on a genome-wide level. The down-stream effect of these alterations led to increased risks of stress-related disorders as well as neuropsychiatric diseases. Overall, evidence from the literature suggest that DNA methylation is an important biological mediator underlying the long-term effect of childhood stressful experience on mental health development.

Stressful early life events are believed to be significant risk factors for multiple mental disorders (Ventura-Junca & Herrera, 2012; Yang et al., 2013). However, the mechanism underlying the long-term impact that childhood experience could have on an individual remains obscure. It is commonly accepted that the interaction between nature and nurture determines the life outcome of an individual (Ventura-Junca & Herrera, 2012). The best-known candidate that connects nature and nurture is epigenetic modification. Epigenetic modification refers to a functional alteration of gene expression without changing the DNA sequence (Gräff & Mansuy, 2008). According to Fraga et al. (2005), monozygotic twins who have more different life histories showed more epigenetic differences. Given that monozygotic twins share the same genetic profiles, this suggests epigenetic modification as an important mechanism that encodes environmental impacts on individuals.

Among various forms of epigenetic modification, DNA methylation is one of the most prevalently studied mechanisms in the developmental literature (IJzendoorn, Bakermans-Kranenburg & Ebstein, 2011). DNA methylation refers to the addition of a methyl group to a cytosine molecule at specific sites in the DNA sequences. The addition of a methyl group leads to the condensation of chromatin structures, and thus inhibits the transcription of methylated sites (Szyf, 2011). The primary function of DNA methylation is to modulate cell differentiation. It is hypothesized that DNA methylation might also function as an adaptation mechanism, which modulates cell function in response to environmental pressures. The down-stream effect of DNA methylation may underlie a number of physical as well as mental disorders. Here, I will summarize research evidence to argue that DNA methylation plays a critical role in mediating childhood stress and risks in mental disorders.

Childhood Abuse and DNA Methylation
The high prevalence of child abuse makes it one of the risk factors for multiple mental disorders (Yang et al., 2013). A range of studies have examined the association between abusive experiences in childhood and DNA methylation. McGowan et al. (2009) examined the levels of hippocampal glucocorticoid receptor (GR) expression in brain samples of individuals who committed suicide with a history of child abuse (Suicide-abused group), individuals who committed suicide without a history of child abuse (Suicide-nonabused group), and non-suicidal control samples with no abusive history. GR expression in hippocampus was related to the control of stress responses; a higher level of DNA
methylation could result in a lower level of GR expression, which in turns result in poorer stress regulations. Results revealed a significant reduction of hippocampal GR expression in suicide-abused group comparing to suicide-nonabused group and controls, but no difference was found between the latter two groups. This indicates that the reduction of GR expression is more closely related to the history of childhood abuse instead of the suicide behaviour per se. They further examined the two possible reasons that could be responsible for this reduction of GR expression: neuron-specific glucocorticoid receptor (NR3C1) promoter nucleotide sequence variation or NR3C1 promoter methylation, since the expression of NR3C1 genes determines the tissue-specific hippocampal GR expression. They found that NR3C1 nucleotide sequence showed no differences among groups, whereas NR3C1 promoter DNA methylation was significantly higher in Suicide-abused group than either the Suicide-nonabused group or the control group, with no significant differences between Suicide-nonabused group and controls. This finding suggests that the hippocampal GR expression in Suicide-abused group was more likely to be caused by increased methylation of the NR3C1 promoter area. The overall findings suggest that the history of childhood abuse was closely associated with changes in GR expression, and this changes in GR expression were due to increase in DNA methylation.

In a more recent study, Mehta et al. (2013) examined differences in DNA methylation patterns among individuals with PTSD who have history of childhood abuse, individuals with PTSD who have a history of trauma not involving childhood abuse, and control individuals who have a history of trauma, but are not clinically diagnosed with PTSD. While McGowan et al. (2009) focused on a specific genetic site, Mehta et al. (2013) looked at DNA methylation at a genome-wide level using peripheral blood cells. Both PTSD groups showed significantly different methylation patterns compared to the control. Interestingly, there was very little overlap (2%) of DNA methylation patterns between individuals with PTSD and history of childhood abuse and individuals with PTSD, but no history of childhood abuse. Among the subjects within groups, the methylation patterns of individuals with PTSD and history of childhood abuse matched 12-folds higher than individuals with PTSD, but no history of childhood abuse. These results suggest that childhood abuse may be one of the main reasons that lead to pathological differences among PTSD individuals, established by differences in DNA methylation patterns. Again, these findings provide a better understanding of how experiences of childhood abuse influence the pathological process of psychiatric disorders.

The previous two studies focused on adult samples, and on a specific disease or outcome. In contrast, Yang et al. (2013) studied child samples with more recent experiences of maltreatment. The saliva samples were obtained from children with and without abusive histories, and examined their genome-wide DNA methylation patterns. They discovered, on average, a 17% methylation difference between children with and without abusive histories. The general pattern of methylation indicated that children with abusive history have higher methylation values at CpG sites with low to medium-range methylation, and lower methylation values at CpG sites with high-range methylation. The findings provide further evidence for the linkage between the history of childhood abuse and changes in DNA methylation at a genome-wide level.

**Early-life Socioeconomic Status and DNA Methylation**

Low socioeconomic status (SES) in early life is another childhood stressor that increases an individual’s vulnerability to various diseases. Miller et al. (2009) found an up-regulation of genes involved in catecholamine-mediated pathways and down-regulation of genes bearing glucocorticoid-mediated pathways among individuals with low SES in childhood. Although the researchers did not examine the molecular process in an epigenetic level, the changes in the regulation of genetic expression suggested a high possibility of epigenetic involvement, because the primary function of epigenetic modification is to regulate gene expression.

Later, Borghol et al. (2011) examined DNA methylation using blood samples from adults with different SES levels in childhood or in adulthood. They discovered that compared to SES levels in adulthood, DNA methylation profiles were more closely associated with the levels of SES in childhood. More specifically, a more pronounced clustered methylation pattern corresponded with differences in SES levels in childhood.
Moreover, individuals with high or low SES levels in childhood have different methylation patterns in gene promoters associated with functional signalling pathways. Similarly, Tehranifar et al. (2013) examined DNA methylation of three repetitive elements in adult women blood samples with varied childhood and adulthood SES. They found two repetitive elements having elevated methylation level associated with lower SES in childhood, yet only one element had lower methylation level associated with higher SES in adulthood, suggesting a greater association between changes in methylation levels and SES in childhood than SES in adulthood. Taken together, there is a clear association between childhood SES and DNA methylation values.

DNA Methylation and Mental Health
Studies by McGowan et al. (2009) and Yang et al. (2013) also investigated the association between epigenetic methylation and mental health. In McGowan et al.’s (2009) study, an increased level of methylation of NR3C1 promoter interferes with transcription factor binding and down-regulates the level of glucocorticoid receptor mRNA, resulting in a lower level of GR expression. Hippocampal GR expression controls the hypothalamic-pituitary-adrenal (HPA) responses to stress, in which lower GR expression level will result in a greater HPA stress response. Abnormal HPA axis responses are believed to be associated with a variety of psychiatric diseases, including depressive disorders and stress disorders (Ventura-Junca & Herrera, 2012). History of childhood abuse was associated with an increased methylation level of NR3C1 promoter, which in turns lowered the GR expression, results in abnormal HPA axis controls and increased likelihood to develop stress-related disorders later in life. Together, the results propose DNA methylation as one of the major mediators underlying the long-term effect of childhood stressful experience on mental health development.

Another study examining the epigenetic effect of child abuse identified 2868 significant CpG methylation sites and eight significant methylated genes (Yang et al., 2013). 20% of the methylation sites are intergenic regions that are associated with neuropsychiatric diseases, cardiovascular diseases and cancer (Yang et al., 2013). The remaining 80% are intragenic regions altering genes associated with cortical development, depression, and substance dependence (Yang et al., 2013). In addition, a recent study found that methylation values of three genes (ID3, GRIN1, and TPPP) act as significant predictors of depression in children (Weder et al., 2014). These experimental results suggest that DNA methylation is an important factor triggering a variety of health problems.

Limitations and Future Direction
As an emerging area, current studies on life experience and DNA methylation do have their limitations. One major limitation across most studies is the lack of longitudinal data. A very limited number of studies examined the variation of DNA methylation in a sample population from childhood to adulthood, and the majority of the existing data is collected at only one point of an individual’s life span. This limitation exists because of the recent and on-going development of methylome measurement technologies (Borghol et al., 2011). Methylome refers to the patterns of methylation modifications in the genome an organism. Methods of methylome measurement are relatively new-established, providing a relatively narrow time span for tracking the developmental path of individuals. Longitudinal studies are helpful in terms of revealing the changes of methylation patterns over time. In the future, research should focus on the formation of longitudinal DNA methylation data set, which facilitates a more extensive understanding of changes in methylations over time, and helps to establish a more explicit interaction mechanisms among experiences, DNA methylation and pathological outcomes.

Another limitation is the use of various tissue types in DNA methylation investigations. The majority of studies used blood samples or saliva samples, with only one group (McGowan et al. 2009) examining brain samples. The advantage of using blood or saliva samples is that these methods are non-invasive, and because the DNA methylation variability is relatively new-established, providing a relatively narrow time span for tracking the developmental path of individuals. Longitudinal studies are helpful in terms of revealing the changes of methylation patterns over time. In the future, research should focus on the formation of longitudinal DNA methylation data set, which facilitates a more extensive understanding of changes in methylations over time, and helps to establish a more explicit interaction mechanisms among experiences, DNA methylation and pathological outcomes.

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with experience-triggered methylation is largely unknown. The use of brain tissues provide less ambiguous evidence in studies regarding mental disorders. Given the limited access to brain tissue, one possibility is to further develop the human brain database, especially for individuals with childhood aversive experiences and mental disorders.

In conclusion, epigenetic changes such as DNA methylation provided biological linkage between childhood stressful experiences on mental health development. Epigenetic research inspired a deeper understanding of the nature-nurture interaction. More importantly, epigenetic research findings suggested that chromatin structure manipulation could potentially become a new possible therapeutic intervention for psychological abnormalities induced by childhood aversive experiences, proving a possible direction for more advanced psychopathological assessments or interventions.

References


