Hindawi Publishing Corporation
Nursing Research and Practice
Volume 2013, Article ID 410395, 9 pages
http://dx.doi.org/10.1155/2013/410395

Review Article

A Framework to Examine the Role of Epigenetics in Health Disparities among Native Americans

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Received 13 September 2013; Revised 6 November 2013; Accepted 19 November 2013

Academic Editor: Ida J. Spruill

Background. Native Americans disproportionately experience adverse childhood experiences (ACEs) as well as health disparities, including high rates of posttraumatic stress, depression, and substance abuse. Many ACEs have been linked to methylation changes in genes that regulate the stress response, suggesting that these molecular changes may underlie the risk for psychiatric disorders related to ACEs. *Methods*. We reviewed published studies to provide evidence that ACE-related methylation changes contribute to health disparities in Native Americans. This framework may be adapted to understand how ACEs may result in health disparities in other racial/ethnic groups. *Findings*. Here we provide evidence that links ACEs to methylation differences in genes that regulate the stress response. Psychiatric disorders are also associated with methylation differences in endocrine, immune, and neurotransmitter genes that serve to regulate the stress response and are linked to psychiatric symptoms and medical morbidity. We provide evidence linking ACEs to these epigenetic modifications, suggesting that ACEs contribute to the vulnerability for developing psychiatric disorders in Native Americans. *Conclusion*. Additional studies are needed to better understand how ACEs contribute to health and well-being. These studies may inform future interventions to address these serious risks and promote the health and well-being of Native Americans.

1. Introduction

Reservation-based Native Americans live in pervasively adverse social and physical environments that place them at increased risk of exposure to a myriad of stressors during childhood which impact their psychological and physical health over their lifetimes [1]. About 1 of 2.9 million Native Americans that identify as Native American alone resides on reservations [2]. Indian reservations were established by treaty during the Removal and Relocation (1827–1887) period and are lands set aside for tribes in exchange for ceded land and resources. Today there exist 275 Indian land areas in the USA administered as Indian reservations [3]. Of the ten poorest counties in America, five are home to an Indian reservation [4]. Concentrated poverty results in higher crime rates, underperforming public schools, poor housing, and poor health and limits access to many services and job opportunities [5]. Adverse childhood experiences (ACEs) that are substantial contributors to health disparities include childhood physical and sexual abuse, witnessing violence, poverty, and racism. The concept that these experiences become biologically embedded has gained substantial support and provides an explanatory mechanism for health disparities [6]. ACEs are linked to differences in the function of the stress-response system including the neuroendocrine system, the parasympathetic nervous system, and the immune system. These changes likely have substantial long and short term impacts on health and well-being [7]. It is likely that these changes are shaped by epigenetic modifications which alter the function but not the structure of the gene. Epigenetic modifications are considered to be an individual's molecular response to the environment and occur in an effort to preserve the health of the individual by increasing the accessibility of genes for transcription and translation that relate to immediate survival [8]. These genes code for proteins that prepare the individual to be able to respond to the stressor

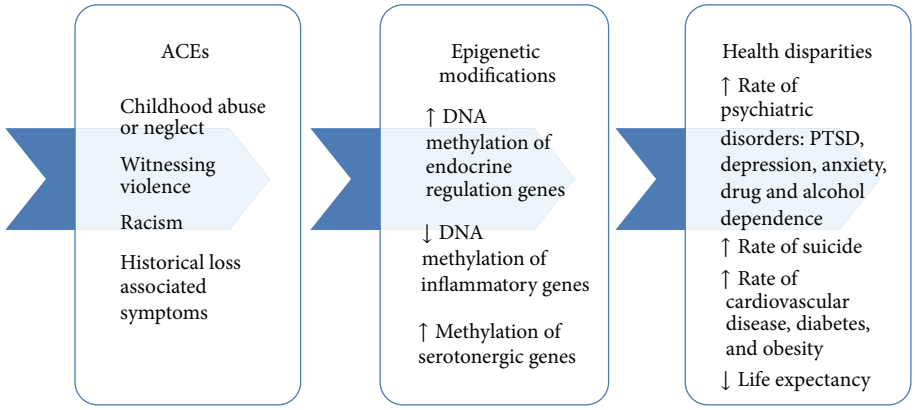

Figure 1: The mediating relationship of epigenetics on the risk for health disparities in Native Americans with childhood adversity.

through a fight or flight response; yet, in Native Americans living on reservations, the stressors most encountered are chronic, not acute. Thus, this adaptive response likely results in overactivation of this stress-response system, and this excessive activity has substantial negative consequences on the health and well-being of Native Americans, individually and across generations. Here we provide a conceptual review of how nurses and other health care professionals can examine health disparities in Native Americans through epigenetic modifications that likely result from ACEs (see Figure 1), including historical trauma, the residual of which is assumed to be historical loss associated symptoms. We expect this conceptual framework to have implications for or be relevant to the mechanisms of health disparities in other racial or ethnic groups.

2. ACEs and Psychiatric Risks in Native Americans

A neighborhood's safety and access to quality health care, economic opportunities, social connections, and social capital are all key determinants of the health of its residents over time [9–12]. Reservations are often characterized by low economic status and segregation, both of which limit access and are risk factors for higher rates of morbidity and mortality [13, 14]. Chronic stress such as that which accompanies experiences of racism and poverty over a lifetime places individuals at risk for posttraumatic stress disorder (PTSD). This vulnerability can be solved in part by ethnic connectedness [15].

Unique to Native Americans is the race-based stress associated with historical trauma [16], as well as discrimination [17–20]. Historical trauma is defined here as the "collective experience of violence perpetrated against Indigenous Peoples in the process of colonizing the Americas resulting in an unresolved humanitarian crisis for reservation communities." The effects of historical trauma are proposed as being transmitted across generations with historical loss associated symptoms currently exhibited [21–23] and include symptoms of complicated bereavement and complex PTSD [24]. This type of trauma has been linked to impaired individual and collective tribal identity [16, 24], which likely also relates to stress and morbidity risk. Over 50% of Native Americans indicate that they think about loss related to historical trauma, such as loss of language, loss of culture, and loss of land, at least occasionally, and which caused them psychological distress [17, 25]. Discrimination has been associated with early substance use among Native American children, and suicidal behavior, and anger, and aggression among adolescents [18, 20, 26]. Thus, this stress combined with other ACEs may be a significant contributor to health disparities.

Native Americans are disproportionally affected by trauma in childhood, including abuse, neglect, and exposure to intimate partner violence (IPV) [27–29]. Approximately half of Native American adolescents and young adults have been exposed to one or more severe traumatic events [30], and 98% have experienced a traumatic event of any severity [31]. Native American adolescents are more likely than other adolescents to witness violence or to have been physically abused, sexually abused, or neglected as a child, resulting in rates of PTSD that are twice that of the estimated rates in the general U.S. population [31].

Assaultive trauma in childhood is linked to the highest risk for PTSD, suggesting that this ACE is specifically linked to this high risk for psychiatric disorders [31]. Specifically, trauma that involves physical or sexual assault prior to adolescence places an individual at five to ten times the risk for PTSD onset compared to an individual without this experience [32, 33]. Witnessing abuse during childhood, as well as residing in a high-crime area, is also linked to a far greater risk for PTSD [34, 35]; however, assaultive trauma at an early age is the ACE most linked to PTSD onset.

ACEs have also been linked to increased risk of depression onset [36–38]. These studies link physical abuse, witnessing domestic violence, and parental alcohol and drug abuse to a vulnerability for depression symptom onset [36, 37]. In addition, residing in an urban, socioeconomically disadvantaged area has also been linked to risk of depression onset as well as drug use [39]. Exposure to trauma also increases the risk for the early onset of substance use and the onset of substance use disorder [40]. Other studies have found similar results, including that ACEs increase the risk for drug use and early alcohol abuse and increased the rates

of initiating these behaviors during adolescence by a factor of two to four [41, 42]. Thus, ACES in general are linked to psychiatric disorder vulnerability, with high degree of comorbidity among these disorders.

3. Health Disparities in Native Americans

Reservation-based Native Americans die at higher rates than other Americans from tuberculosis (750% higher), alcoholism (524% higher), diabetes (293% higher), unintentional injuries (153% higher), homicide (103.3% higher), and suicide (66% higher) (2002–2004, rates adjusted for misreporting of race on state death certificates) [43]. Not only do Native Americans bear a disproportionate burden of disease, but they also experience a lower life expectancy. Life expectancy is an overall measure of quality of life [44] and is one of the indicators used to measure the magnitude of the burden of health disparities [45]. In general, Native Americans born in 2000–2002 have a life expectancy that is about 2.4 years less than the overall US population rate: 76.9 years compared to 74.5 years for Native Americans [43]. However, when this average is disaggregated by IHS Area, the life expectancy ranges from 64.8 years (11 years less than for the U.S.) in the Aberdeen Area to 76.4 years (greater than the U.S. average of 75.8 years) in the California Area (adjusted for race miscoding) using 1994–1996 data [46]; thus highlighting the within group differences. Additionally, the Indian Health Service, using 2000 census data, found 25.7% of all Native Americans were living below the poverty level, compared to 12.4% of the U.S. population overall [43]. The Bureau of Justice, in the first comprehensive statistical analysis of "American Indians and Crime," reports Native American are the victims of violent crimes at two times the rate of the U.S. population overall, and about 7 in 10 violent victimizations involved an offender who was reported by the victim to be a person of another race [47]. However, this may not apply to all communities, especially those that are more remote and isolated where few non-Native American people live. Another report by the Department of Justice, disclosed Native Americans sustain rates of violent victimization (rape, sexual assault, robbery, aggravated assault, and simple assault) at rates that are 2 times higher than African Americans, 2.5 times that of Hispanics, 3 times that of Caucasians, and 6.5 times that of Asians [48]. PTSD is the anxiety disorder most linked to trauma and its prevalence in Native Americans adults is 4.4 times the national average [25, 49]. There is little research regarding the impact that adversity has on tribal communities, so it remains poorly understood.

The adverse childhood experiences (ACE) study suggests that certain adversities are major risk factors for morbidity and mortality [50]. The study established a relationship between adversity in childhood and suicide attempt [51], prescription drug use [52], alcoholism and alcohol abuse [53, 54], illicit drug use [42], obesity [55], and depressive disorders [38]. Among adolescents and young adults, childhood adversity was also associated with a greater risk for interpersonal violence perpetration [56], poor perceived health, more medical care visits, and additional somatic concerns [57]. Therefore, current studies link ACEs to risks to health and well-being; however, the mechanisms underlying these risks have not yet been well described.

4. Genetic Inheritance and Influences on ACEs and Health

In some cases, genetic predisposition may explain some of the enduring effects of ACEs; however, the evidence for this link remains poorly understood. Genetic inheritance provides information encoded in DNA which is transcribed to various types of RNA molecules which likely shape the response of the individual to stressors such as ACEs. One important concept related to phenotypic variation is heritability, which estimates the extent of which genetic inheritance contributes to the phenotypic variance in a population [58]. Heritability is the percent of variation in the genome responsible for the difference in the phenotype. Another parameter used to estimate the contribution of genomic factors in phenotypes is relative risk, which refers to an individual's risk of developing a condition with a family history compared to those without a history [58]. When the heritability estimate or relative risk of a phenotype is low, the influence of the genome sequence is considered to be relatively smaller than the influence of other factors such as environment, and the genomic influence can be easily masked or have a negligible impact. Since most human diseases involve many genes, their interactions, and nongenetic factors, an approach termed "endophenotypes" is used to characterize the disease in a molecular or genetic manner, rather than using a clinical diagnosis to define the phenotype.

Polymorphisms in Native Americans have been linked to a greater vulnerability for alcohol abuse [59], as well as obesity [60]. In general, U.S. samples of trauma exposed participants link endocrine gene (FKBP5) polymorphisms to a greater risk for PTSD development [59, 61]; yet, these are small and do not include Native Americans. Thus, it is essential to consider unique genetic inheritance features in Native Americans which interact with epigenetic modifications and likely contribute to health disparities.

4.1. ACEs and the Biological Stress Response. The stress-response system provides the individual protection from acute stressors through an activation of interactive biological systems [6]. One biological system that is central to this response and is linked to ACEs is the hypothalamic-pituitary-adrenal (HPA) axis, with the end result of activation of this system being the production of cortisol. In addition to playing a pivotal role in activating the stress response, the HPA axis also influences biological functions related to mood, growth, immune function, metabolism, and regulation of biological systems on circadian rhythm [62]. The sympathetic nervous system (SNS) also is activated by stress providing neuronal focus and energy to muscles in order to escape the stressor. Although these systems are effective in adapting to acute stress, chronic activation is linked to negative consequences. Both the HPA axis and SNS impact immune function, and chronic stress is linked to a risk for inflammation [62].

Overactivation of the HPA axis results in disruptions of functioning at rest and following stressors, and these changes have been linked to ACEs. HPA axis alterations are linked to health disparities through mechanisms that include impaired neuronal growth and survival, inflammation, reductions in neuropeptide activity, and accelerated cellular aging [63–65]. SNS function changes have also been linked to health disparities, with one of the most pivotal mechanisms being a lack of circadian variation in blood pressure, a key risk factor for myocardial infarctions [66].

5. Epigenetic Modifications Resulting from ACEs

Evidence is accumulating that environmental influences early in development remain pervasive into adulthood, a relationship that is attributed to an interaction of gene function and environment. Both genetic and environmental factors are critical to developmental processes and even minor changes in either type of factor can result in trajectories of resilience or vulnerability [67]; however, it is the interaction between these factors that may provide the most vital information to understand the heterogeneous response to trauma. This leads us and others to question how future research can address this critical issue.

Epigenetics refers to changes in an individual's phenotype independent of genotype. These changes occur through mechanisms such as histone modification, methylation, acetylation, and noncoding ribonucleic acids which alter the accessibility of genes for transcription. The resulting transcription modifications and protein production result from factors such as environmental challenges including, but not limited to, ACEs [68, 69]. An individual's genome interacts with internal and external factors to create phenotypes such as height, physical appearance, personality, and alterations in the stress-response system [70].

Preclinical models illustrate how ACEs result in epigenetic modifications in neurons, thereby increasing the risk for psychiatric symptoms. To illustrate this link, a study reports that the offspring of high-licking canine mothers exhibit reduced methylation of the glucocorticoid receptor gene [71] and endocrine regulation of a subsequent stressor [72]. In contrast, offspring that face early adversity exhibit endocrine dysregulation [73], as well as reductions in neuronal plasticity in the prefrontal cortex (PFC) that persist into adulthood [74]. In studies of rats who exhibit PTSD-like behavior, there is evidence of increased methylation of stress-response genes including brain-derived neurotrophic factor and nuclear protein phosphate-1 [75] in neurons [76]. Although these studies provide additional evidence linking ACEs to methylation changes in neurons, these studies are not able to clearly determine psychiatric symptoms. Therefore, these studies are limited by not being able to determine the comprehensive risks that relate to ACEs.

The ACE most linked to epigenetic differences and vulnerability for health disparities is that of child abuse. To illustrate this link, in a hallmark study by Labonté in suicide completers, ACEs were linked to increased DNA methylation of the glucocorticoid receptor in the hippocampus, and this differential methylation was particularly linked to childhood abuse [77]. This study provides further support for the McGowan et al. study, whose subject group was also suicide completers, which reported that childhood abuse was associated with greater methylation levels at CpG sites in the exon1_F of the promoter region of the glucocorticoid receptor gene [78]. These studies had the distinct advantage of examining epigenetic modifications in neurons, which is not available in other studies. Epigenetic patterns differ among cell types, even differing among brain regions [79, 80]. Thus, an additional challenge to understanding the impact of ACEs on health disparities is to determine how epigenetic alterations in the brain differ from those in peripheral tissues and how to advance despite this methodological challenge. In addition, these few studies are not able to determine the role of preexisting methylation in this risk or to measure other factors that may contribute to methylation changes.

Epigenetic changes resulting from ACEs can also be observed in studies that use peripheral blood in living participants, which show that HPA-regulating genes are often impacted. A study by Klengel et al. linked ACEs to reduced methylation of the FKBP5 gene, an essential regulator of the stress response, as well as to changes in the function of the HPA axis under stress, and to reduced cognitive ability [81]. Direct physical abuse and observing the abuse of a mother have also been associated with greater methylation levels at CpG sites in the exon1_F of the promoter region of the glucocorticoid receptor gene in leukocytes [82]. Similar methylation profiles are also reported in the peripheral blood of babies whose mothers were depressed during the third trimester of pregnancy, and these methylation changes were related to salivary cortisol elevations at three months of age [83]. Although glucocorticoid receptors in peripheral tissue may differ from those on the HPA axis, the link between methylation of the glucocorticoid gene in the periphery and the function of the HPA axis has been demonstrated in multiple studies in addition to those of Oberlander et al., 2008. Additional studies that include analysis of blood samples collected closer to the time of the ACE may provide additional insights into the individual variation in response to ACEs.

Other studies link ACEs to hypomethylation of inflammatory genes, suggesting that these experiences result in a greater inflammation later in life. In a recent study of children who were removed from their parents due to abuse or neglect, a reduction in methylation of NR3C1, an inflammatory regulation gene, as well as differential methylation of cancer related pathways was found in children with ACEs compared to controls [84]. A study of adults linked child abuse to reduced methylation of IGF2AS, an antisense transcript of the insulin-like growth factor gene, which encodes for the inflammatory cytokine family of growth factor beta [85]. Borghol et al. linked childhood poverty to differential methylation of genes related to metabolism and inflammation, and these changes were different from those in participants who experience poverty only during adulthood [86]. Together these studies provide evidence that a variety of ACEs result in methylation changes, suggesting that these

molecular changes likely contribute to health disparities; however, additional, larger, and more representative studies are needed to determine relationships.

Altered serotonergic neurotransmission is also postulated to result from ACEs and provides a mechanistic link to increased vulnerability for psychiatric disorders. The Iowa adoption study demonstrated a link between hypermethylation of the serotonin gene SLC64A to childhood sex abuse [87], and this molecular change mediated the development of antisocial personality disorder [88]. This group was also able to relate differences in gene expression of serotonin related genes to methylation, and that genotype influenced methylation at cg22584138 [89]. Additional studies are needed to determine the role of other ACEs in serotonergic gene methylation and to determine how ACEs contribute to psychiatric risks.

6. Methylation Changes Associated with ACEs Increase the Risk for Psychiatric Disorder Onset

Clinical studies are restricted to examining differential methylation in samples of peripheral fluids, but these studies do provide some key insights into how these molecular changes relate to PTSD, depression, and drug abuse risk. For instance, PTSD is associated with changes in the methylation of inflammatory (toll-like receptors 1 & 3, IL-8, chemokine ligand 1, and others) and endocrine genes FK506 binding protein-5 (FKBP5) [90]. Another study that measured DNA methylation reported that postdeployment hypomethylation of LINE-1 was associated with PTSD onset following deployment [91]. Differential methylation of neurotransmitter genes is also linked to PTSD risk. Two studies utilized samples of civilians from the Detroit Neighborhood Health Study. One study determined that serotonin transporter gene (SLC6A4) methylation levels were modified by the effect of the number of traumatic events on PTSD after controlling for SLC6A4 genotype, such that persons with more traumatic events were at increased risk for PTSD, but only at lower methylation levels [92]. The other study found that the candidate gene MAN2C1 showed a significant methylation × trauma experience interaction, such that those with both higher MAN2C1 methylation and greater exposure to traumatic events showed an increase in risk of lifetime PTSD [93]. Thus, there is evidence that PTSD is associated with similar methylation differences in immune, endocrine, and neurotransmitter genes to those linked to ACEs; suggesting that these chronic differences may be a result of ACEs, yet additional prospective studies are needed to better describe these relationships.

Studies in individuals with depression have also shown differential DNA methylation. Sabunciyan et al. carried out the first genome-wide DNA methylation scan in major depressive disorder patients. The study pinpointed 224 candidate regions, primarily involved in neuronal growth and development genes, which showed differential methylation; PRIMA1 showed the greatest differences [94]. Specific genes that have been shown to be differentially methylated in individuals with depression include those that code for angiotensin converting enzyme [95], brain-derived neurotrophic factor [96], orexin A [97], and gamma-aminobutyric acid receptor alpha1 [98].

In addition to observing differential DNA methylation in PTSD and depression, many studies have observed methylation differences in those that suffer from drug abuse as compared to healthy controls. Increases in DNA methylation of the OPRM1 gene that codes for opioid receptors have been reported in individuals with chronic opioid use [99–102] and alcohol dependence [103], and global methylation differences have also been reported for these two populations [99, 104]. The proopiomelanocortin gene promoter [105], dopamine transporter gene promoter [106], homocysteine-induced endoplasmic reticulum protein promoter [107], and alpha synuclein promoter [108] were found to be differentially methylated in individuals with alcoholism compared to healthy controls. Methylation at the monoamine oxidate A locus was also significantly associated with nicotine and alcohol dependence in women, but not in men [109]. Together these studies show that psychiatric disorders related to ACEs are associated with methylation changes that may be reflective of ACEs or psychiatric symptoms; however, there are no prospective studies to elucidate the possible mediating role of methylation on these psychiatric risks in individuals that experience ACEs.

7. Conclusion

Reservation-based Native Americans disproportionately experience ACEs and health disparities, significantly impacting long-term physical and psychological health. In addition to these experiences, the persistence of stress associated with discrimination and historical trauma converges to add immeasurably to these challenges. Here we provide evidence to suggest that ACEs result in methylation differences in genes that regulate the stress response and that these changes may contribute to an increased vulnerability for developing psychiatric disorders, as depicted in Figure 1. Although we postulate these relationships, the lack of prospective studies in this at-risk group prevents us and others from concluding this causality, as well as more studies that include Native Americans. Thus, additional studies are needed to better understand the mechanisms through which ACEs contribute to health and well-being. These studies may inform future interventions to address these serious risks and promote the health and well-being of Native Americans.

Conflict of Interests

All authors have no conflict of interests.

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