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Molecular Genetic Modifications in the Human Genome: Racial Discrimination as a Biological Stressor

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Abstract

Racial discrimination enhances group separation and places individuals into stereotypical categories based on race and other factors (e.g., gender, behavior, etc.). As seen in studies on physiological diseases and psychological disorders, minority groups (e.g., African Americans) face cellular senescence at an increased risk due to health-related comorbidities and prevalent experiences of racism. This review provides an analysis of modifications within the human genome that may lead to additional insight on the biological stressor: racial discrimination. We focus on how discriminatory practices may alter DNA and histone methylation patterns, leukocyte telomere length, and cognitive behavior specifically among African Americans and other minority groups. Here, the varying studies presented provide insight into the long-term, and sometimes irreversible, immunological effects that racial discrimination induces at the physiological and cellular levels. These findings are supported and summarized through statistically significant data ($p < 0.05$), reflecting that racial discrimination is a key factor and inducer of stress and biological strain in some populations. Yet, it is imperative to note that racial discrimination works in conjunction with other environmental stimuli that individuals are exposed to in society. Thus, this review ultimately aims to uncover and explore a potential underlying mechanism of how racial discrimination affects human physiology at the biological and molecular levels, while supporting the notion that racial discrimination may play a key role in the documented health disparities seen in social settings.

Keywords: racism, racial discrimination, bias, prejudice, leukocyte telomere length, DNA methylation, cognitive development.

Introduction

As a catalyst for systemic oppression, racism increases the rate at which deleterious biological modifications and social interactions manifest in society (Bailey et al., 2017). Categorized as a discriminatory practice, racism aggravates detrimental health outcomes and yields "a fundamental determinant of human traits and capacities [in which] racial differences produce an inherent superiority of a particular race" (Chae et al., 2020; Merriam-Webster, n.d.). In such an event, racism cultivates the establishment of racial preference prompting the favoritism of a single ethnic group (e.g., Caucasians). Consequently, an ethnic group (e.g., African Americans) that exhibits an adverse phenotype faces undue scrutinization and disproportionate gaps in social, economic, and healthcare settings (Bailey et al., 2017; Brody et al., 2016; Harris et al., 2018). Collectively, these societal disadvantages, endured by the alienated race, emanate negative genetic, physiological, and psychological determinants of health and well-being in marginalized people groups (Harris et al., 2018).

Paralleled to racism, both bias and prejudice assist in the advancement of an authoritarian social construct (Bailey et al., 2017; Lin and Alvarez, 2020). Besides promoting exclusivity, bias accelerates "an inclination of temperament or outlook…especially a personal and sometimes unreasoned judgment" (Merriam-Webster, n.d.). Prejudice defined as "injury or damage resulting from some judgment or action of another in disregard of one's rights" (Merriam-Webster, n.d.), expands upon the approval of fundamental beliefs that negate and demean diverse cultural practices amongst members of society (Brody et al., 2016; Cottrell and Neuberg, 2005).

Simultaneously, these behavioral and emotional responses categorize individuals into social groupings, basing classification on alleged actions and bigoted reasoning (Brody et al., 2016; Harris et al., 2018). Thus, at the center of the scheme of systemic oppression, these stimuli serve as reoccurring facets of racial discrimination.

Evolutionary Mechanisms of Social Estrangement and Racial Discrimination

In a population, the method of natural selection enhances biological diversity and drives evolution through both stochastic and defined ecological processes. In most cases, evolution depends on environmental constituents (e.g., natural selection, mutation, sexual selection, genetic drift, and migration). However, in an industrial, well-developed human society, this is not the case. Rather, due to medical and technological advancements, humans have expanded upon the natural realm to establish a dominance hierarchy that operates through modes of artificial selection and collective societal norms (Dreher and Qu, 2018). Described by Dreher and Qu (2018), this dynamic, dominance hierarchy revolves around a pivotal point within the evolutionary paradigm: adaptation.

As stated by Emlen and Zimmer (2020) in a natural population, an adaptation is "an inherited aspect of an individual that allows it to outcompete other members of the same population

that lack the trait (or that have a different version of the trait)." Expanding on this definition, as stated by Foster (2011), in a social setting, adaptations are "phenotypic alterations that arise to ensure that an organism or species can fit a habitual and environmental niche." Thus, based off these facsimiles of adaptation, Emlen and Zimmer (2020), Dreher and Qu (2018), and Foster (2011) note that adaptations can influence both human development and biological interaction. Yet, Foster's application provides insight into how these adaptations may develop within human society. For example, Foster (2011) suggests that the formation of a specialized niche accounts for phenotypic and genotypic variation. Characteristically, when adaptations arise, phenotypic variants are quantified and display morphological, behavioral, and physiological trends within the dominance hierarchy. Therefore, as adaptations accumulate, phenotypic trends arise. In a modern human society these trends progress and display selective biases which build upon factors such as class, status, and race (Dreher and Qu, 2018). As a result, societal niches are selected for and evolve, ensuing the transformation of distinct markers of individual fitness that are contoured by societal and phenotypic predilections (Bailey et al., 2017; Foster, 2011).

Equally, as interconnected processes, preference within the dominance hierarchy produces distinct phenotypic characterization that is synonymous with tribalism. Similar to psychological essentialism (a form of in-group bias that leads to discrimination), tribalism circumvents the notion that the social domain should be based upon out-groupings of individuals, or tribes (Mandalaywala et al., 2018). Tribes, or phenotypically unique individuals, tend to be acknowledged through a refined form of discrimination: stereotyping. Programmed as learned behavioral responses, stereotypes advance tribalism and enforce discrete, discriminatory societal values which place individuals into classifications that promote intergroup attitudes. In order to maintain exclusive networks, studies have uncovered that stereotypes provoke adverse emotions such as resentment, anxiety, and abhorrence among varying out-group individuals (Cottrell and Neuberg, 2005; Mandalaywala et al., 2018).

In a 2005 study, Cottrell and Neuberg found that stereotyping and other sociofunctional behavioral adaptations rely on three interlocked parts. First, humans are extremely reliant on social interactions; humans often look for praise and approval from others to validate an emotional response. Second, groups tend to acquire and favor analogous social domains and practices. That is to say individuals tend to favor others based on collective similarities (e.g., morals, values, lifestyle, etc.). And third, as an adaptation, mutuality protects similar individuals against disastrous environmental events and unfavorable habitual circumstances. Systematically, these three components aid and explain tribalistic tendencies that have emerged across the dominance hierarchy (Cottrell and Neuberg, 2005).

To continue, Cottrell and Neuberg (2005) expanded upon their three-fold hypothesis by conducting a study composed of Caucasians and other ethnic groups. To assess stereotypic inclinations, in- group and out-group effects were measured based on behaviors and observed in-group biases. In the case-setting, two hundred-thirty-five Caucasian undergraduate students with a median age of

20.60 years were asked to rate a set of nine groups: active feminists, African Americans, Asian Americans, European Americans, fundamentalist Christians, gay men, Mexican Americans, Native Americans, and non-fundamentalist Christians (Cottrell and Neuberg, 2005).

Initially, to assess the varying reactions towards these designated groupings, participants reported the extent to which they experienced an emotional response for a certain group. On the questionnaire, a documented score of one reflected a minimal emotional response to a particular group, and a documented score of nine reflected an extremely negative emotional response to a particular group. The data on behavioral reactions among the Caucasian participants showed that Caucasians displayed negative emotional responses (e.g., anger, disgust, and fear) towards African Americans, ranking African Americans as outgroup individuals ($p < 0.001$). Similar statistically significant recordings of prejudicial behavior among Caucasians towards Native Americans and Asian Americans were also noted ($p < 0.001$). Therefore, as perceived threats, Caucasians displayed statistically significant prejudice towards these nine varying ethnic communities ($p < 0.00001$). As suspected and based on elite societal trends, the participatory in-group (i.e., Caucasians) dismissed outgroups (i.e., African Americans, Asian Americans, and Native Americans), ultimately displaying prejudicial predisposition and in-group bias (Cottrell and Neuberg, 2005).

Moreover, a similar study by Mandalaywala et al. (2018) was conducted with one-hundred-fifty-one Caucasian individuals to assess the correlation between two discriminatory practices: racial essentialism and explicit prejudice. Racial essentialism, an example of out-group induction, pertains to the approval or denial of cross-cultural stability. Explicit prejudice, also stemming from out- group bias, relates one's living environment to one's behavioral response towards others. Analyzing these parameters of racial discrimination, preliminary analyses were performed using Implicit Association Testing (IAT) to measure the degree of cognitive impulse between social groupings of Caucasians and African Americans. Upon completion of the study, IAT testing results revealed statistically significant favoring of Caucasians over African Americans ($p \leq 0.001$). Mandalaywala et al. (2018) revealed that essentialism boosts prejudice toward low-ranking groups of individuals, further endorsing the idea that variations in class reflect a subjective social agenda. Interestingly, statistically significant findings revealed that African American in-group devaluation occurred during the IAT as well ($p= 0.004$). These results suggest that African Americans may have developed evolutionary habits that favor interpersonal discrimination or contribute to the idea that the conceptualization of cognitive bias among African Americans has led to lower in-group placement within the dominance hierarchy (Bailey et al., 2017; Mandalaywala et al., 2018).

Increasingly, studies have shown that in comparison to other racial groups, African American males face an unreasonably greater risk for chronic disease development and are more likely to exhibit poor health (Chae et al., 2020). For example, in the United States, the average lifespan of an African American male is between sixty-five to seventy years old, and the average lifespan for a Caucasian male is seventy-five years old. To account for this five to ten-year age difference, scientists have hypothesized that there are ethnic inequalities that mark African American males and lead to biological strain and minority pressures. Scientists have postulated

that factors pertaining to socio- economic status, education, occupation, and lifestyle impact the health of an individual, especially if living conditions are unfavorable (i.e., impoverished conditions). So, in correlation to average lifespan, events that promote biological strain (e.g., racial discrimination) may play significant roles and be key regulators in health outcomes for oppressed people groups (Chae et al., 2014).

Today, in New Zealand, the Maori, are just one modern example of an indigenous people that undergo similar systemic ethnic inequalities comparable to African Americans. Concerning negative health outcomes amongst native individuals, Harris et al. (2018) documented that racism has contributed to a range of mental and physical health discrepancies between the Asian, Maori, and European Ethnic Groups. Based on practices of social intolerance and the ranking of socioeconomic status, the New Zealand Health Survey (NZHS) and the General Social Survey (GSS) documented and analyzed the effects of racial discrimination on health outcomes and cognitive ability among the Asian ethnic group and Maori tribe in New Zealand (Harris et al., 2018).

Launched in 2008, the studies presented by NZHS and GSS aimed to gauge racial favoritism, ethnic background, and livelihood as measures of efficient communal behavior. Surveying through cross- sectional methods, the NZHS measured the prominence of chronic physical conditions and health differences among individuals above the age of fifteen in Maori and European Ethnic Groups (Harris et al., 2018). Comparable to NZHS, GSS gauged social and economic indicators of health and living standards that differentiated human character, civil liberties, and ecological circumstances in individuals above the age of fifteen. Over ten years of continuous surveillance and data collection, negative racial experiences peaked greatly among members who identified as Asian, Maori, or Pacific. Participants that identified as European ranked lower in the total data surveillance. On average, Harris et al. (2018) documented that Asian, Maori, and Pacific Ethnic groups experienced more prevalent racism in both public and work settings, followed by school, health, and housing.

There were also statistically significant findings between health implications and racial experiences, demonstrating the direct role of racial discrimination in reducing the health among individuals in different ethnic groups compared to European Ethnic groups ($p < 0.001$). Mutually, these findings support the notion that an individual's overall health and societal function varies among those who experience more prevalent racial discrimination, suggesting that racial discrimination is a key determinant for wellbeing (Harris et al., 2018).

As a biological stressor and societal catalyst, racial discrimination not only alters an individual's social environment but persists at the biological level as well (Bailey et al., 2017). To examine the stress of racism, studies on telomere length effects, physiological disease, and psychological disorders have become promising topics of interest. This review paper will concentrate on an analysis of biological stressors exacerbated by racism and other discriminatory practices that induce modifications in DNA and histone methylation patterns, leukocyte telomere length, and cognitive development among varying ethnic groups, especially the African American community.

Epigenetic Patterns of Racial Discrimination: An Overview of Chromosomes and Chromatin Structure

Chromosomes are structures composed of DNA and proteins that encompass genetic material (Weaver, 2011). In the cell, these crucial components are responsible for gene expression and regulate the process of transcription. For example, through chromatin-folding, chromosomes securely package the genome into the nucleus, protecting the expression of eukaryotic life. As chromosomes fold and condense, basic (positively charged) histones interact with the acidic (negatively charged) DNA backbone. This interaction induces the formation of a nucleosome, attributes to chromatin structure, and is responsible for directing the mobilization of nucleosomes (Weaver, 2011).

Characteristically, chromatin structure is composed of a euchromatic portion and constitutive and facultative heterochromatin portions. On one hand, in the euchromatic portion, there is great transcriptional activity. Throughout genome sequencing studies, the high transcriptional activity in chromatin has been attributed to large G-C euchromatin regions. Heterochromatin, on the other hand, is tightly packed and transcriptionally inactive. Constitutive heterochromatin is located at and around the centromeres of chromosomes, within vital cellular components (e.g., telomeres), and assists in methylation (Strachan and Read, 2004).

DNA and Histone Methylation Patterns

DNA methylation is a molecular process that marks chromosomal DNA through the addition of a methyl group (Strachan and Read, 2004; Weaver, 2011). As shown in invertebrates, DNA methylation represses both transposon and repeated sequence families, regulating endogenous gene expression and easing transcriptional noise. In transcriptionally active chromatin, the chromatin structure is open, has an expanded conformation, and contains unmethylated DNA portions that lie close to promoter regions. In transcriptionally inactive chromatin, heterochromatin, the DNA is highly condensed and inaccessible (Weaver, 2011).

To continue, transcriptionally inactive chromatin contains methylated DNA that includes a promoter region associated with deacetylated histones. In tandem with chromatin structure, histone acetylation is stimulated through the commencement of acetylated histones at CpG sites.

Through the mediation of repressor binding proteins, methylated CpG sequences within promoter regions bind developmental proteins that play an essential role in the developmental pathway. As a result, when abundant CpG sites accumulate, CpG islands form and operate as transcriptional repressors that induce chromatin remodeling (Strachan and Read, 2004).

In chromatin, CpG islands are located downstream of promoters and assist in transcriptional suppression. Transcriptional silencing occurs as acetyl groups connect to lysine residues on the N- terminal end of histone proteins, forming the open framework necessary for methylation to

proceed through (Strachan and Read, 2004). Additionally, CpG dinucleotides serve as mutation hotspots (Strachan and Read, 2004). In both coding and noncoding vertebrate DNA, there are frequent C to T transitions. Throughout the genome, these alterations arise from the instability between CpG dinucleotides during cytosine methylation at the carbon-atom-5. As a result, CpG to TpG transitions diminish proofreading and DNA polymerase activity (Strachan and Read, 2004).

Notably, these pathogenic mutations have been shown to greatly impact susceptible individuals; current research has shown that individuals who are targets of racial discrimination are more likely to experience epigenetic aging as marked by altered DNA methylation patterns (Chae et al., 2020).

In a 2017 InterGen clinical trial, DNA methylation patterns were studied in a longitudinal cohort of one hundred and fifty-two African American women in Connecticut to observe genetic, epigenetic, and psychological factors influenced by racial discrimination. To note, other factors such as age and lifestyle were controlled. Throughout the study, each of the African American women underwent psychological examination for a total of six months. During this time, clinical data and information on demographics, health history, and psychological measures such as racial experiences, parenting, and depression were gathered. To analyze the results of the InterGen study (2017), a 22-item Race- Related Events (RES) scale scored the responses of the African American women. A response of one on the RES-scale indicated that the individual submitted a response of “yes” to experiencing racism, and zero represented a submitted response of “no.” It is important to note that a majority of the African American women responded “yes” more frequently, suggesting perceived implications of racial discrimination on a minority test group. A Major Life Discrimination (MLD) scale was implemented to assess all experiences of racial discrimination throughout one’s life; the RES scale documented any event or experience related to racial discrimination (Mendoza et al., 2018).

During the study, analysis of DNA extracted from cheek cells present in saliva samples revealed 832,000 autosomal and 19,000 X-chromosomal CpG sites. At these CpG sites, there were statistically significant regions of reduced DNA methylation (i.e., hypomethylation) ($p < 0.05$). Based on the data for the Major Life Discrimination (MLD) scale, these results reflect that African American women who reported greater perceived discrimination had increased hypomethylation at several CpG sites within genes (Mendoza et al., 2018). At these loci, DNA isolated from saliva samples of African American women expressed a reduction in tumor suppression, transcription, neural processing, mitotic arrest, and inflammatory response at pivotal CpG sites. Furthermore, since mutations within these regulatory genes deter physiological function, African American women who endure more prominent racial discrimination may display harmful effects (i.e., diminished CpG activity and cellular function). Thus, additional studies on the stressor, racial discrimination, may further discern how environmental strains interact at the cellular level as modeled in this cohort of African American women (Mendoza et al., 2018).

Supportive Family Environments and Epigenetic Aging

Epigenetics denotes alterations in DNA (e.g., methylation) that are not involved with changes to the sequence of DNA nucleotides (Alvarez and Lin, 2020). Rather, these heritable alterations arise from changes acting upon the genome sequence (Strachan and Read, 2004). Since these modifications can alter normal biological function, it is important to note that compared to other ethnic groups, African Americans face a greater risk for epigenetic aging (Brody et al., 2016). In past studies on African American adults, discrimination has been associated with a range of physiological health markers such as deficient birthing processes, increased amounts of glucocorticoids and C-reactive protein, expression of pro-inflammatory cytokines, and additional inflammatory responses that cause dramatic disorder at the cellular level early on in life (Brody et al., 2016).

As reviewed in Brody et al. (2016) African American adolescents experience racism through two main social methods. First, African American adolescents tend to be exposed to low levels of racial discrimination more frequently, which continues to accumulate throughout their lifespan. Second, African American adolescents are more likely to experience both repetitive and intense levels of racial discrimination that persist throughout maturity (Brody et al., 2016). However, to combat the negative effects of racism in a metropolitan or urban area, studies have shown that a supportive family environment can provide emotional support for African American youth. Specifically, two 2013 studies showed that safe, supportive family environments alleviate the impacts of racial discrimination and prevent negative expression at the cellular level.

In these interconnected 2013 studies conducted by the Strong African American Health Adult Project (SHAPE) and Adults in the Making Project (AIM), three hundred and twenty-two African American individuals in SHAPE and two hundred ninety-four African American individuals in AIM were monitored in household settings. For both studies, the participants were between the ages of sixteen and nineteen and came from diverse economic backgrounds. These participants were asked to rank their racial experiences on a questionnaire over a three-year time span, and blood samples were obtained from each patient to measure methylation patterns and determine epigenetic aging over the three-year span. On the questionnaire, a score of zero indicated that the African American adolescent rarely experienced mistreatment based on race and/or skin color, and a score of two reflected racial mistreatment. On average, a questionnaire score of 0.86 was recorded among the participants, and roughly fifty percent of the African American adolescents in the sample confirmed exposure to racial discrimination (Brody et al., 2016).

To assess the effects of a supportive family environment, an emotional support subscale was used in both studies to explore how positive response (e.g., care from family members) may impact epigenetic aging. In both AIM and SHAPE, once each participant reached twenty years of age, blood samples were collected, and peripheral blood mononuclear cells (PBMCs) were isolated to extract the participant's DNA and interpret methylation patterns. In the SHAPE samples, moderate levels of DNA methylation were recorded. Yet, for AIM, participants that experienced high, persistent levels of racial discrimination had decreased methylation. These findings demonstrate that racism may induce methylation patterns, resulting in a higher

epigenetic score. This could explain how, by the age of twenty-two years old, AIM participants who experienced high levels of discrimination had higher cellular ages compared to their original age.

To continue, participants with less supportive family environments, who also experienced elevated levels of discrimination, had greater epigenetic aging during young adulthood as measured by methylation patterns. These results reflect the idea that exposure to racial discrimination and the varying degree of familial support influences PBMC epigenetic aging. Combined, the AIM and SHAPE studies demonstrate that racial discrimination accumulates over time, and specifically for SHAPE, this led to a statistically significant finding, suggesting that it is highly likely for racial discrimination to activate and enhance negative molecular processes within African American adolescents as they mature ($p < 0.001$) (Brody et al., 2016).

Gene Regulation and Expression

As documented above, the impacts of racial discrimination can be seen at the chromosomal level, specifically within DNA methylation patterns. However, since these processes are coded for and regulated at the genetic level, could a biologicalmechanism be exacerbated by racial discrimination? Generally, in eukaryotes, genes are individually transcribed, and initiation begins at a promoter site. As essential genetic components, promoters are found upstream and control the expression of a single gene at a transcription start point; genes are usually located within 1 kb of the control element, but they can also be found further downstream. Covering large regions, long-range controls coordinate the regulation of gene clusters to create functional domains of gene expression. As an effect, when a gene is turned on for expression, chromatin domains may function as barriers for distal enhancers and silencers. For example, in the diseases aniridia and campomelic dysplasia, the genes PAX6 and SOX9 are both altered, hindering gene expression, and increasing mutation rates within chromosomal regions (Strachan and Read, 2004). Additionally, research on the chromosomal rearrangements found in Drosophila illustrates that within proximity to centromeres, heterochromatic endings called telomeres block gene expression and modify the structure of chromatin domains (Strachan and Read, 2004).

Thus, based on these findings, if racial discrimination can influence telomerase activity, could this mechanistic pathway lead to the identification of racial discrimination as a biological stressor? To provide insight for this question, constitutional and somatic abnormalities serve as two examples of documented mutations that affect telomere function. For instance, constitutional abnormality arises early-on in gestation, resulting from abnormal development during fertilization, and somatic abnormalities transpire when there is variation in cellular tissues, inducing a mosaic structure. Since these abnormalities are dependent on numerical content and structure, both of these factors modify telomerase activity (Strachan and Read, 2004). Thus, in correlation to chromosomal irregularities, detrimental transformations within telomeric regions have the potential to shed further insight into how genetic modifications in the human genome proceed due to the influence of heterochromatic states (Blackburn and Chan, 2002).

Leukocyte Telomere Shortening as a Biomarker for Physiological-Stress Catalyzed by Racial Discrimination

The History of Telomeres and Pivotal Moments in Science

Elizabeth Blackburn was awarded the Nobel Prize for the elucidation of telomere structure and maintenance in 1984. Resolving the end replication problem, Elizabeth Blackburn (2000) documented that telomeres are a nucleoprotein structure with repetitive, noncoding DNA sequences at the ends of chromosomes. Serving as a protective cap between the cellular components and the surrounding subcellular matrix, telomeres are terminal chromosomes that have an RNA-dependent DNA polymerase acting on the leading strand (M. Herrmann and W. Herrmann, 2020; Schutte and Malouff, 2015; Strachan and Read, 2004). Positioned at the 5'-end of chromosomal DNA, telomeres support, assist, and protect against chromosomal fusion and degradation (Blackburn, 1990).

Through the discovery of the enzyme telomerase, Elizabeth Blackburn and Carol Greider (1985) demonstrated that telomerase proceeds through semi-conservative DNA replication, inserting complementary terminal sequences that are removed throughout mitotic cycles. Consisting of heterochromatin, these terminal ends also exhibit abundant DNA folding due to the incidence of telomerase (Blackburn and Chan, 2002). At the terminal end, telomerase adjusts and monitors DNA binding proteins, generating the attachment of telomeric DNA repeats to DNA sequences which ultimately protects the remainder of the chromosome (Blackburn and Chan, 2002). Mechanistically, telomerase expedites DNA replication, blocks chromosomal folding, and sustains the initial conformation of the terminal ends within chromosomes (Blackburn, 1990; Blackburn and Chan, 2002; O'Donovan, 2011; Weaver, 2011).

As demonstrated by Elizabeth Blackburn and Shippen-Lentz (1989), telomerase expands the 3'-end of the G-C rich strand, increasing the synthesis of telomere repeats that are found in DNA. The DNA sequence, which aids in the folding of the three-dimensional structure of telomeres, consists of a 3'-OH overhang and a single strand that is rich in the nucleic acid, guanine. During elongation, the enzyme telomerase synthesizes the guanine-rich strand of telomeric DNA, and the complementary cytosine-base is added and synthesized discontinuously by primase as it replicates along the template strand, forming a T Loop (Blackburn and Greider, 1985; Blackburn, 1990; Herrmann, 2020; O'Donovan, 2011). The T-loop structure is a shelterin complex consisting of six shelterin proteins: TRF1, TRF2, TIN2, POT1, TPP1, and RAP1 which direct the formation of the looped structure found at the end of the chromosome (Weaver, 2011). The looped structure size is reduced at a rate of 50-200 bp of telomeric DNA after cell division (M. Herrmann and W. Herrmann, 2020; Weaver, 2011). As somatic cells continue to divide, telomere lengths continue to decrease, leading to senescence and apoptosis at the end of life (Marieb and Hoehn, 2013; M. Herrmann and W. Herrmann, 2020; Schutte and Malouff, 2017).

To prevent terminal senescence and cellular apoptosis in an extant organism, the enzyme telomerase uses several methods. Through the activation of telomerase, retroviral gene transfer is initiated, decreasing the likelihood for a cell to senesce or grow old (M. Herrmann and W. Herrmann, 2020). However, while this biological activation can be essential for cellular proliferation, overactivation of telomerase can decrease cell viability. For example, the progression of an immortal cell character can result in the development of cancer through means of uncontrollable cellular division (Bowman and Sanders, 2012). Therefore, to combat further replication and the overproduction of telomerase, checkpoints along the DNA strand are programmed into the cellular machinery to detect DNA damage and prevent cells from dividing that have yet to be repaired (Weaver, 2011). Based on these findings and mechanistic discoveries, telomerase is suggested to function as an artifact of the transformation from an RNA to a DNA genome, yielding vital results for eukaryotic life (Blackburn, 1990; Weaver, 2011).

Leukocyte Telomere Composition, Function, and Length

Leukocytes (i.e., white blood cells) are vital cellular components in immunity. As agents of disease prevention leukocytes assist in the removal and processing of pathogens, microbes, and other inflammatory markers (Chae et al., 2014; Hoehn and Marieb, 2013). In correlation to cellular pathology, one key feature of the leukocyte genome is telomere length. Responsible for the development of chronic stress and disease development, leukocyte telomere length alterations, such as telomere shortening, occur as organisms age (Chae et al., 2014; Wolkowitz et al.,2012). During cellular senescence, leukocyte telomere lengths decrease due to low telomerase activity attributed to either an inherited disease or the expression of a mutated gene (Wolkowitz et al., 2012). When these alterations occur, telomerase activity is incapable of adding short telomeres to the ends of DNA leading to reduced cellular viability and additional inflammatory response (O'Donovan, 2012; Wolkowitz et al., 2012). As stated previously, since telomerase extends telomeres, a lack of telomerase activity directly affects and prompts leukocyte telomere shortening (Blackburn, 1990; Wolkowitz et al., 2012).

Leukocyte telomere length (LTL) has also been identified as a symbol of biotic maturation (Chae et al., 2014; Chae et al., 2020; Epel et al., 2004; Lynch et al., 2016; Rej et al., 2020). By analyzing the prevalence of mortality and genetic disparities in humans, shortened leukocyte telomere lengths are markers of health and well-being (O'Donovan et al., 2012). Particularly, as seen in a diverse cohort of older adults, leukocyte telomere length directly impacts the risk of developing an age- related disease. In 2012, O'Donovan et al. scanned inflammatory activities that lead to the formation of threatening illnesses such as cancer, atherosclerosis, and other neurodegenerative disorders (M. Herrmann et al., 2018). At the cellular level, it was determined that these ailments occur from intensified inflammatory responses in common cytokines like tumor necrosis factor-alpha, interleukin-6, and C-reactive protein. Respectively, these cytokines monitor oxidative stressors, osteoclast production, acute phase reactants, and when altered, have been known to accelerate leukocyte telomere shortening in patients with advanced inflammatory conditions (O'Donovan et al., 2012).

Compiling a test group of 1,962 individuals between the ages of seventy and seventy-nine years old, the Health, Aging, and Body Composition Cohort (Health ABC) estimated well-functioning abilities in older individuals. Well-functioning abilities were based on a livelihood parameter that evaluated activity, cognitive function, and physical expenditure. To measure leukocyte telomere length, quantitative polymerase chain reaction (qPCR) was utilized to find the ratio of telomere repeat copy number to single-gene copy number (T/S ratio). In the final analysis, for the 1,962 individuals in the surrounding Pittsburgh and Memphis communities, significant recordings of TNF-alpha, TNF- alpha + CRP, and IL-6 + TNF-alpha, and CRP coefficients were computed ($p<0.01$). Since high levels of these factors correlate to shorter leukocyte telomere length, these data demonstrate that cytokines are capable of inducing senescence and promoting pro-inflammatory factors (Chae et al., 2014; O'Donovan et al., 2012). To conclude, since oxidative stress and inflammation regulate telomere length, there may be varying effects among races (M. Herrmann and W. Herrmann, 2020).

The Role of Leukocyte Telomere Length in Age-Related Processes

As reported by Aviv (2011), at conception, the heritable trait, leukocyte telomere length, impacts telomere dynamics (e.g., cellular proliferation). Mechanistically, the newborn's genome

develops additional hematopoietic stem cell (HSC) reserves due to paternal age at conception (PAC) influences. Ultimately, these PAC factors affect the longevity of the newborn's life span and decrease leukocyte telomere length regulation. Thus, in HSC, reduced cellular proliferation is a marker for leukocyte telomere shortening (Aviv, 2011).

In 2012, Wolkowitz et al. conducted a study that included twenty subjects to assess telomerase activity in individuals diagnosed with depression. Additional factors such as age, lifestyle, and economic standing were evaluated, and statistically significant recordings were documented for these parameters. Economic standing, measured through income, was statistically significant and inversely linked to telomerase activity ($p < 0.005$), and statistically significant recordings of lifestyle were measured for alcohol consumption ($p < 0.02$) and decreased physical activity ($p < 0.01$) compared to the control group. Through experimental assessment, it was concluded that elevated baseline PBMC telomerase activity was seen in samples collected from individuals that experienced greater levels of stress and greater severity of depression ($p= 0.007$). Interestingly, individuals that initially had lower telomerase activity had enhanced telomerase activity accompanied through Sertraline treatment. Still, this only accounted for about seventeen percent of the outpatients (Wolkowitz et al., 2012).

Similarly, Diez Roux et al. (2009) utilized PCR to examine telomeric DNA. Containing nearly one thousand participants, the study included roughly 20% Caucasian, 30% African American, and 50% Hispanic individuals. For each ethnic group, middle-age ranges were noted and parameters such as age, sex, lifestyle, and income were controlled for and assessed. Race and ethnicity were depicted according to the 2000 census, physical activity was assessed with a survey, and BMI was calculated to find links and associations to telomere dynamics as well (Diez Roux, et al., 2009). Initially, it was concluded that individuals who identified as African American or

Hispanic expressed shorter telomeres compared to the Caucasian subject group, limiting significant results. However, statistically significant data was observed and calculated once factors correlating to overall health, economic standing, and BMI were accounted for. With these added parameters, T/S ratios for African Americans (-0.044) and Caucasians (-0.0041) were calculated (Diez Roux, et al., 2009). These results revealed that African American women are six times more likely to exhibit leukocyte telomere shortening compared to Caucasian women, and African American men are three times more likely to exhibit leukocyte telomere shortening compared to Caucasian men based on age and independent of lifestyle. Therefore, while it is important to note that telomere length is a heritable feature, fluctuations in telomere length may occur due to the presence of additional stressors, societal factors, and racial experiences in an environment (Diez Roux, et al., 2009).

Lately, some studies have noted that African American individuals undergo telomere shortening at a swifter pace compared to Caucasian individuals. In a 2014 study, a group composed of ninety-five African American males was selected to inspect telomere length response to racial discrimination. In the experiment, Chae et al. (2014) recorded a minimum telomere length value of 4.80 kb, and a maximum telomere length value of 6.44 kb. An average length of 5.54 kb and a standard deviation equal to 0.38 were also recorded. Out of the entire group, 17% reported experiencing at least one to three events of racial discrimination, 32% reported experiencing at least three to six, and 55% of the participants reported experiencing at least seven to nine events of racial discrimination. Conclusively, a direct association between racial discrimination and implicit racial bias was not mentioned, yet racial discrimination had a significant and direct effect on telomere length ($p= 0.02$) (Chae et al., 2014).

More recently, equivalent to the telomere studies done above, Chae et al. (2020) analyzed data from the Coronary Artery Disease Development in Young Adults (CARDIA) Study. To observe changes in leukocyte telomere length, samples were collected from four hundred and ten African American participants over ten years (Chae et al., 2020). Similar to past studies (Chae et al., 2014; Diez Roux et al., 2009; Wolkowitz et al., 2012), leukocyte telomere length was measured using PCR to compare T/S ratios to identify LTL effects attributed to racial discrimination. Upon completion of the study, it was found that among African Americans, telomeres shortened on average between 4.98 to 5.62 kb each year over a ten-year timespan. Additionally, when the parameter racial discrimination was considered with leukocyte telomere shortening, a statistically significant association was recorded, suggesting that racial discrimination leads to leukocyte telomere shortening ($p= 0.040$). To add, as experiences of racial discrimination accumulate, a statistical calculation of ($p= 0.015$) was recorded, indicating that increasing instances of racial discrimination cause LTL base-pair shortening in African Americans (Chae et al., 2020).

The Correlation Between Depression and Leukocyte Telomere Length

Studies have found a potential correlation between depression and leukocyte telomere length (Chae et al., 2014; Schutte and Malouff, 2015). In a 2015 meta-analysis by Schutte and Malouff (2015), high levels of depression showed an increase in the risk of heart disease, Alzheimer's

disease, diabetes, and cancer by upwards of 29-80% amongst susceptible individuals. Accordingly, it was found that increased rates of developing these life-threatening disorders correlated to a reduction in telomere length. Identified in 21,040 participants, decreased leukocyte telomere length and mental decline are statistically significant and directly related ($p < 0.001$) (Schutte and Malouff, 2015). As a result, the basis of these findings provides strong implications for negative health outcomes of people groups (e.g., African Americans) exposed to high degrees of stress.

Comparably, to Schutte and Malouff (2015), Darrow et al. (2016) examined the association and implication of telomere length on psychiatric development in nearly 15,000 individuals diagnosed with mental illnesses from five varying case studies. As a pre-determinant to disordered cognitive development, meta-analysis evaluation found that physiological disturbances such as oxidative stress and inflammation arose due to leukocyte telomere shortening. The results of the meta- analysis revealed significant values and comparisons between a negative medium effect size and confidence interval, intricately linking short leukocyte telomere length and psychiatric disorders through the Cochran Q Test. The Cochran Q Test showed substantial measures in heterogeneity among each of the studies, indicating that telomere length assays identified statistically significant points for subgroupings of PTSD, depression, and anxiety. A measure of ($p < 0.001$) denoted that psychiatric illness was highly associated with shorter LTL in the 15,000 individuals studied. The parallels between each of the studies present in the meta-analysis suggest that reduced telomere length, excessive cellular proliferation, and increased oxidative stress lead to psychiatric and cognitive decline (Darrow et al., 2016).

Examining accelerated telomere shortening as a response to life stress, Epel et al. (2004) found that telomeres and telomerase play a crucial role in cellular aging and disease prevention in African American women. In a study composed of fifty-eight healthy premenopausal women, women were separated into two groups: a control group (i.e., mothers with health children) and caregiving mothers (i.e., mothers who cared for chronically ill children). Both controls and caregivers filled out a uniform survey to evaluate stress. Blood samples were then acquired from each of the women during stages of pre-ovulation. The PBCMs were collected to analyze the mean telomere length and telomerase activity in each sample. Telomere length was quantified by the use of PCR analysis and calculated as a comparative ratio between telomere repeat copies and single-gene copies. Telomerase activity utilized telomerase replicate amplification to generate a linear scale. Oxidative stress was measured as F2-isoprostane levels in each of the blood samples on a gas chromatogram and a mass spectrometer (Epel et al., 2004).

In the final analysis, it was determined that women in the caregiving group displayed shorter telomere lengths, diminished telomerase movement, and elevated oxidative stress compared to the control group. Indicating that even after maternal age was accounted for, greater BMI and nearly 3,700 shorter telomere base pairs were found in caregiving mothers who endured added stress (i.e., caring for a chronically ill child). Typically, telomere shortening occurs at a rate of sixty bp every year. Yet, in the caregiving group that was under greater stress, a

reduction of 550 bp was seen at the year-mark, displaying a nine-to-seventeen-year biological difference, along with decreased telomerase activity. These results infer that the higher-stressed mothers (i.e., those caring for a chronically ill child) were more susceptible to senescence and had a greater cellular age compared to their actual age. Overall, these data pieces may predict the life outcome of African Americans through cellular aging and provide insight as to the detriments of stress (i.e., racial discrimination) (Epel et al., 2004; Schutte and Malouff, 2015).

Neurological Indicators of Cognitive-Stress Related to Racial Discrimination Skin Tone Bias and Amygdala Activity

Today, several 21st century behavioral studies have aimed to identify the correlation between skin tone bias and differential race-related activity. Studying the amygdala (a subcortical structure that is responsible for processing sensory, social, and emotional stimuli) through magnetic resonance imaging, scientists and researchers have developed and performed experiments on amygdala activity, seeking out potential race-related mechanisms. For instance, in an experiment composed of Caucasian and African American individuals, the amygdala expresses an increase in blood- oxygen-level-dependent (BOLD) based on the perception of the individual being viewed. To note, since an increase in BOLD is indicative of a potential threat to the observer this would reflect uneasiness towards an environmental stimulus (Ronquillo et al., 2007; Telzer et al., 2013). The question that then arises is whether the negative amygdala response is from learned behavior, cultural understanding, or a much deeper biological point of tribalism and out-group bias. To examine and explain both sides of this biological, race-based pendulum, Ronquillo et al. (2007) performed an experiment probing race-related amygdala activity.

In a 2009 clinical trial, eleven Caucasian males were subjected to varying photographs of faces with altered coloring (e.g., one image resembled that of a Caucasian male and the other an African American male). During facial recognition, Echo-Planar Imaging (EPI) and pulse sequencing showed amygdala activity in test-individuals on the right side and left side of the brain. After each trial, it was determined that greater amygdala activity was expressed when individuals looked at the image of an African American male, rather than a Caucasian male. Surprisingly, African American individuals viewed African American counterparts comparably to Caucasian counterparts. African American individuals also had increased amygdala activation when viewing African American or darkened skin tones (Ronquillo et al., 2007). These findings may lead to speculation around the role of interpersonal discrimination acting as a psychosocial stressor, providing insight as to how adverse mental health effects impact the well-being of minority groups, especially African Americans (Bailey et al.,2017).

Following a similar experimental design, McCutcheon et al. (2018) observed amygdala reactivity in twenty African American individuals and twenty-two Caucasian individuals. Each individual underwent a sociodemographic assessment, and an index of segregation was calculated to establish each volunteer's ethnic environment. Analogously, to Ronquillo et al.(2007), MRI and functional magnetic resonance imaging (fMRI) data analysis was employed. In the final analysis,

statistically significant findings (p= 0.01) demonstrated that areas with lower ethnic density experience greater amygdala reactivity to outgroup faces and that both Caucasians and African Americans show significant right amygdala activity, confirming racial bias (McCutcheon et al., 2018).

Relatedly, Telzer et al. (2013) discovered that Caucasian adults have a negative amygdala response towards African Americans, but not to other Caucasians. Telzer et al. (2013) hypothesized that negative, enhanced amygdala response was an unconscious factor, initiated by stereotypic cultural practices that typically view African Americans through a discriminatory scope. Akin to the studies above, Telzer et al. (2013) used fMRI to observe amygdala response as a function of increased racial observations beginning at adolescence and transferring over into young adulthood. Initially, it was hypothesized that if a child were exposed to a diverse background, or grew up in a diverse area, the child would display a moderate amygdala response. This rationale conveys the idea that a child

from a diverse background would view a more phenotypically unique individual as being normal to their environmental setting. In reverse, if a child did not grow up in a diverse community or was not specifically exposed to the African American community at a young age, it was hypothesized that the child would produce a reinforced racial response that would progress into early adolescence (Telzer et al., 2013).

Starting with a pool size of thirty-two adolescents, individuals between the age of four through seventeen years were selected from various upbringings. These individuals identified as members of the African American, Caucasian, Latin American, and Asian American communities. As each individual received an fMRI scan, they were asked to respond to two images showcasing different ethnic individuals with varying emotions. The first image that was shown served as a control; the image had a neutral expression. The remaining images that were shown displayed a scope of emotions (i.e., happy to sad) and amygdala activity was assessed based on individual response (Telzer et al., 2013). Upon the evaluation of the results, the researchers uncovered a substantial effect and correlation with quicker amygdala response time and emotional response. Intriguingly, both Caucasian and African American participants exhibited statistically significant and advanced amygdala response on the fMRI when looking at African American faces ($p < 0.005$). Therefore, regarding racial preference, this study emphasizes a natural, conditioned pattern of response to out-group features and faces. And it is advocated that this racial preference may emerge as an individual is exposed to varying environmental, cultural, and in-group biases (Telzer et al., 2013).

Conclusion

The Impact of Racism on Health

As established throughout the review, factors such as evolutionary predispositions, telomere shortening, changes in DNA methylation patterns, and neurological modifications can arise due to catalyzed, racial discrimination. Organized as a multifaceted unit, these contributors

stimulate detrimental biological and psychological stress in susceptible people groups, especially African Americans. Nevertheless, while these effects are unfavorable, there are several current limitations that have restricted the ability to provide a sole genetic basis for racial discrimination. For instance, other critical applications, especially those relating to allostatic load, have taken a more holistic approach to the underlying function of racial discrimination at the biological level. Allostatic load reflects the biological probability contributing to the formation of the weathering hypothesis and the conceptualization of environmental stresses (Geronimus et al., 2015). Studied by Geronimus et al. (2015), the weathering hypothesis reports the effects of tension on the body. Normally, the sympathetic nervous system induces responses to environmental and physical stressors, which are further expressed through interactions within the hypothalamic-pituitary-adrenal gland. Here, the prevalence of allostatic load can disrupt natural, immunological processes, leading to cellular degradation across the sympathetic nervous system and immunosenescence (Geronimus et al., 2015).

To continue, since studies have attributed telomere size as a biological indicator of environmental stress by evaluating PBMCs, oxidation reactions, aging processes, and inflammation Geronimus et al. (2015) concentrated on a middle-aged subgroup living in the impoverished metropolitan city, Detroit. Habitually, individuals living in poverty express a distinct linear increase between comorbidities and age attributed to racial circumstances, residential dynamics, economic fluctuations, and class systems. Consistent with expectations based on prior research, Geronimus et al. (2015) revealed that telomere size reduces by nearly 17 kb per year in stressed individuals (i.e.,

Caucasian minority individuals). Additionally, when factors such as poverty were incorporated into assessment, it was concluded that for Caucasian individuals, a reduction of approximately three hundred thirty base pairs occurs each year (Geronimus et al., 2015).

In Geronimus et al. (2015), the most prominent variable that remained statistically significant across each model was telomere size, preceded by environmental and comorbidity factors. At large, Geronimus et al. (2015) revealed that, in Detroit, telomere sizes vary and are not consistently ranked based on perceived social class structures, demonstrating that another factor may be present and functioning silently. Therefore, in connection to this review, it is crucial to note that environmental and cultural factors still play a prominent role in health and wellbeing in a characteristic setting. So, while racial discrimination can induce telomere shortening, it is not the sole factor inducing biological deterioration (Geronimus et al., 2015).

As hypothesized earlier, is there potential for racism to have a direct impact on the human genome? As reviewed by Chabris et al. (2013), Genome-Wide Association Studies (GWAS) have expanded the ability to interpret and comprehend psychological traits that are influenced by genes. Specifically, since 1997, studies for the Human Genome Project have targeted TERT (a reverse transcriptase) activity in the human genome through cloning of the hTERT gene, which is a key gene of interest in furthering the understanding of telomere behavior (Aviv, 2011; Blackburn and Chan, 2002; Weaver, 2011). Thus, through the examination of the human

genome and the genetic constitution of the biological makeup of life, genetic variants and associations may be useful tools in examining underlying social and health behaviors in humans. So, could these techniques be applied to study how racial discrimination may obstruct the human genome?

Fundamentally, if a social stressor, such as racial discrimination, could have an impact on the human genome, this effect would need to be traced through familial descent. Therefore, to determine a genetic origin for this type of psychological and biological trait, polymorphic sites and changes in allele frequencies could be examined throughout various lineages of ethnic groups. Yet, as Chabris et al. (2013) describe, there is still a genetic threshold that impedes the formation for an evolutionary model of such a development (Chabris et al., 2013). Consequently, while current Genome-Wide Association Studies (GWAS) have focused on LTL and other potential genetic influences, a direct genetic mechanism attributed to racism as a stressor has yet to be identified (Aviv, 2011).

Combatting Racism Through Scientific Application

Racial discrimination fosters in-group selection, producing detrimental health effects through negative social interactions within minority out-groups (Chae et al., 2014). As reviewed in this paper, aspects of an individual's phenotype (e.g., skin color) direct whether racial discrimination is viewed as a stressor or stereotypic norm. Once individuals who endure racial discrimination begin to adopt an undesirable in-group perspective, these individuals succumb to prejudice and bias which disastrously impact biological measures and markers (i.e., leukocyte telomere length) (Chae et al., 2014). Even so, as seen in the studies reviewed in this paper, while there is a great deal of empirical evidence linking biological, epigenetic, neurological, and evolutionary alterations there is still another salient genetic or environmental factor present (e.g., lifestyle, socio-economic status, etc.) (Geronimus et al., 2015).

To combat the detrimental effects of racism on biological, psychological, and genetic processes, racial practices and tendencies must be addressed head-on by society. By incorporating innovative techniques to expand upon further investigations around race-related issues, studies and clinical

trials should focus on explicitly addressing biological modifications and probable enhancers that point to racial discrimination and strain on ethnic minority groups. Thus, at the forefront of anti- racist efforts, science can pave a path forward to better understand the biological implications of racism that are commonly suppressed or misjudged by society. Nonetheless, while science can create these opportunities, humanity has the responsibility to tackle racism, prejudice, and bias, eradicating past societal norms and accepting all cultures into a progressive society (Bailey et al., 2017).

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