Epigenetics and Understanding the Impact of Social Determinants of Health

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Synopsis

Recently, a new research agenda emphasizing interactions between social factors and health has emerged. The term *social determinant of health* often refers to any nonmedical factor directly influencing health, including: values, attitudes, knowledge, and behaviors. Health across the life span is strongly and adversely affected by social disadvantage. Research in epigenetics indicates that alterations in DNA methylation may provide a causal link between social adversity and health disparity. Likewise, accelerated loss of telomeres (the protective ends of chromosomes) is highly correlated with chronic stress including social stress and aging, and may provide a link between adversity and some of the physiological stigmata associated with health disparities. Considerable research is still required to develop a sound mechanistic understanding of the role of epigenetics and perturbed telomere function in linking social adversity with health outcome.

Social Determinants of Child Health

The health consequences of material deficiency (e.g. extreme malnutrition or lack of water, inadequate clothing and shelter, etc) have been long known [1]. However, recently, a new, more broadly applicable, research agenda emphasizing social factors and health has emerged [2]. The term *social determinant of health* often refers to any nonmedical factor directly influencing health, including: values, attitudes, knowledge, and behaviors. However, it can also refer to more external sources of influence such as family, neighborhood and social network context. A large and convincing literature over the last several decades shows that health across the life span is strongly linked to social disadvantage [1-4].

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For example, neighborhoods can influence health through their physical and geographic characteristics, such as air and water quality, lead paint exposure, proximity to both health promoting and suppressing features (i.e. hospitals and nutritious food stores vs. toxic factories and fast food), access to green space, and so on [2,5,6]. Additionally, more social aspects of neighborhoods such as strong social cohesion show far better health and safety [7,8].

Recent evidence demonstrates that the chronic stress of social disadvantage, socioeconomic inequality, and racial discrimination act through a variety of biological pathways to influence health, including: neuroendocrine, developmental, immunologic, and vascular mechanisms[2,9]. In response to stressful events cortisol, cytokines, and other intermediates are released, and if there is long-term, repetitive or chronic exposure, these substances may damage key physiologic systems[9,10]. It is thought this mechanism of physiological strain results in more rapid onset or progression of chronic illnesses [11].

One of the largest and most consistently replicated literatures demonstrates the negative effects of social disadvantage in childhood on later child and adult health, socio-emotional wellbeing, and cognitive ability[12-16]. This literature shows that childhood social disadvantage works through a variety of complex mechanisms to result in dramatically different developmental outcomes, which are often apparent even in childhood, but which are typically more fully manifest in adulthood. Indeed, there is evidence that early childhood disadvantage appears to leave a "biological residue" which in turn has effects on development, health and wellbeing [16,17].

Social Determinants of Child Mental Health

There is strong evidence that the mental health of children, adolescents, and young adults is affected by social factors at personal, family, community, and national levels [11,18]. In particular, the evidence is good that paired with safe and supportive social environment, such as family and schools, children need positive peer networks in order to have healthy mental health development. Even national level social determinants of health such as national wealth, income inequality, and access to education were associated with a range of mental health outcomes in young people [18].

Social Determinants of Asthma

Lung function, allergy, and asthma appear to have a strong links to early life stress and social disadvantage [19]. Due to the large health inequalities in this area social stressors have been used extensively to explain racial disparities in childhood asthma [20]. Indeed recent research suggests that the social context children are raised in may be equal to the natural environmental effects in asthma disease risk [21].

Biological Underpinnings of Social Determinants

Early life experience "gets under the skin" in ways that affect the health, wellbeing and child development. Although the most extensive research shows strong biological effects of physical and emotional abuse (and other similarly extreme childhood events) on health and developmental consequences, more recent research shows that less obvious but more regular

adversities of early childhood also have a lasting influence on later health and development [22,23]. Recent work has begun to focus on epigenetics as a key biological mechanism linking early life experience and health.

Description of Epigenetics

Despite having the same DNA, different cell types have distinct gene expression (mRNA) patterns in order to perform different functions [24]. One mechanism of this differential gene expression is through epigenetic changes, which some have argued may also explain some of the variation in behavioral phenotypes of humans[25]. One key aspect of the *epigenome* is that, unlike the DNA sequence, it may be modified by environmental and pharmaceutical interventions. This provides the potential for reversing the effect of adverse life events on later health and wellbeing [17]. Epigenetic changes or *marks* refer to alterations in DNA or histone structure that do not affect the sequence of DNA but may affect gene expression and therefore cellular function. The effect on cellular function may be sustained, and under many circumstances, it can be transmitted to subsequent generations of cells.

Recall that DNA is organized as a linear molecule, in which the four nucleotides (adenine, A; thymine, T; guanine, G; cytosine, C) form the core of the DNA molecule, and sugar-phosphates the backbone of the DNA (Figure 1). In humans, nuclear DNA is organized into 46 chromosomes: twenty-two autosomes and 1 sex chromosome from each parent. The flow of information in a cell has been termed the Central Dogma (Figure 2), in which information flows from DNA to messenger RNA (mRNA), to protein. Genes are arrayed along the chromosomes, and a gene can be viewed as consisting of the arrangement of base sequences that specifies a complementary mRNA, and, therefore, a specific protein, together with those nearby DNA sequences that determine when and to what extent the gene is transcribed into RNA.

Figure 3 provides a schematic of a typical gene as it appears in DNA. Bases that code specific amino acids are organized in blocks termed, exons. Between the exons are the introns, which are composed of bases that do not specify specific amino acids but may contain control regions. Due to the orientation of the DNA strands, one side of the gene is termed the 5′ end, and the other, the 3′ end. At the 5′ end of the gene is a sequence of bases termed the *promoter/enhancer*, which is enriched for cytosine and guanine bases. Binding of the promotor by a series of *transcription factors* activates transcription, the process by which *RNA polymerase* syntheses a complementary strand of mRNA. Soon after the new primary RNA copy of the gene is synthesized, the introns are removed and the exons are stitched together. After several more steps, the mRNA is used by the ribosome as a template for synthesis of a polypeptide chain—the basic structure of all proteins.

This arrangement provides for several points at which gene regulation can adjust the synthesis of proteins to meet the needs of the cell. *Transcriptional control* is a key form of regulation, through which the amount of mRNA synthesized from a particular gene is increased or decreased as necessary.

Upon receipt of an appropriate signal, the cell can deploy or withdraw specific transcription factors within minutes, thereby rapidly modulating the transcription of specific genes. This

type of signaling response is rapid, and easily reversible. On the other hand, epigenetic changes to DNA generally take days to years to occur, and as mentioned, they tend to be stable.

DNA Methylation

The promotor regions of genes are enriched for sequences containing cytosine alternating with guanine (5′-CG-3′ abbreviated CpG). Areas in which the proportion of CpG's is greater than statistically predicted are termed CpG islands. Wherever a CpG occurs, the C is susceptible to being modified by the enzyme DNA methyltranferase through the addition of a methyl (CH_3) group (forming 5-methylcytosine) (Figure 4). A promoter containing a group of CpG sequences that have been methylated is less able to bind relevant transcription factors, and this attenuates or halts transcription. Since the addition of a methyl group to cytosine is a covalent reaction, it may be an enduring change; furthermore, the DNA replication apparatus has mechanisms for ensuring that the corresponding CpG is methylated in newly synthesized DNA

Clusters of CpG residues are not only found in promoters, but also interspersed within genes, and along intergenic regions. The role played in cellular physiology by methylation of these other CpG sites is the subject of considerable research, and they may be more important in controlling transcription than the CpG islands.

The methylation of DNA is just one way in which a cell can create an epigenetic mark. DNA is tightly coiled around highly basic proteins called histones. One effect of this winding is to greatly compress the DNA, allowing it to be packaged into a cell nucleus. Fully extended, the DNA of a chromosome would extend about 75 mm but in its coiled state it is about 5 μm (compression of about 15,000 fold!). Often, when DNA is tightly wound on a nucleosome, the DNA regulatory sites (such as the promoter) become inaccessible to transcription signals, and the affected genes become silent. Histone proteins have several sites at which they can be covalently modified, principally by methylation or acetylation. The effect of these covalent changes may be to slightly relax the DNA, thereby freeing regulatory sites for interactions with various transcriptional activator proteins. These histone changes are also termed epigenetic marks. As is the case with DNA methylation, the cell is able to duplicate the histone marks on newly synthesized histones that are destined for daughter cells. Thus, histone-based epigenetic marks are heritable even though they are not coded in the DNA.

It is important to note that while epigenetic marks are heritable from parent cell to daughter cell, this is often misunderstood to mean that in multicellular organisms, such as humans, epigenetic marks are transferred directly from parent to child. Rather, during the process of gamete formation most epigenetic marks are cleared, and each generation develops a new set of epigenetic marks. However, as indicated below, under appropriate circumstances environmental signals (including those supplied through maternal behavior) may result in patterns of epigenetic marks in the offspring that reflect those also found in the parent.

At the biochemical level, epigenetics affects transcription and ultimately the protein repertoire of a cell. The epigenetic mechanism serves four essential cellular roles: *1) X-*

chromosome inactivation; 2) differentiation; 3) imprinting; 4) medium and long-term transcriptional control. This review focuses on how social and environmental signals shape DNA methylation and thereby transcription. Aberrations in DNA methylation are frequently associated with cancer, but this phenomenon is not within the scope of this review.

Measurement of DNA Methylation

Although it is likely that marks based in both DNA and histones are important epigenetic signals of adversity and stress, for technical reasons, most of the social science research to date has involved detecting changes only in DNA methylation. Determining whether a specific CpG site is methylated is relatively simple and several approaches are in routine laboratory use. More recently, chip technology has been applied to determine the methylation state of 500,000 CpG sites per DNA sample. Although the technology is straightforward, early experience suggests that there are significant challenges to analyzing the data, ranging from batch effects (artifacts induced by day to day variation in lab procedures) to the statistical challenges implicit in very large numbers of repeated measures in a limited number of samples. Furthermore, while it is relatively straightforward to identify which CpG sites are hyper- or hypo- methylated under a certain condition, it is much more difficult to associate this observation with a specific functional significance. This is because the biological effect of a change in methylation status at a particular CpG or cluster of CpGs is often unknown or unpredictable. While work with both rodents and humans has demonstrated the value of methylation changes in explaining how environmental inputs are translated to durable behavioral effects, this work has, so far, depended upon measurement of the methylation state of specific sites with known or clearly predictable functions. How methylation profiles across hundreds of thousands of sites should be correlated with underlying social inputs and health or behavior states remains an important topic for research. Furthermore, since the methylation state of differentiated tissues is highly specific, it is not clear how methylation profiles developed in circulating blood cells or saliva cells will provide information about changes in DNA from less accessible tissue such as brain, cells of the autonomic nervous system, or specific immune cells. All of these questions require extensive additional research.

Description of Telomeres

During DNA replication, the fact that DNA is replicated from the 5′ to 3′ direction means that the end of one strand of the chromosome shortens with each cycle of chromosomal replication and cellular division. To prevent loss of genetically important information, chromosomes are capped by repetitive DNA sequences $(TTAGGG)_n$ and associated proteins, termed telomeres[26]. In addition, the presence of the telomere prevents fusion of adjoining chromosomal ends. Over time, with each cell division, the telomere ends become shorter, and so the telomere has been referred to as a "mitotic clock." Associated with progressive telomere shortening, the cell activates pathways that prevent further cell division (replicative senescence). Stem cells maintain telomere length by activating an enzyme, "telomerase." Telomerase consists of both a protein catalytic unit (TERT) and a RNA template unit (TERC), used to specify the sequence of the newly synthesized telomeric

bases. Most specialized cells do not express, or express very low levels of telomerase, so their telomeres progressively shorten with the age of the organism (Figure 5).

Mutations in telomere-associated proteins produce a number of serious hereditary diseases in humans. *Dyskeratosis congenita* (dystrophic nails, oral leukoplakia and skin depigmentation) in infancy is followed by bone marrow failure, occasionally, pulmonary fibrosis, cirrhosis, and increased susceptibility for cancer. First attributed to a mutation in a gene on the X-chromosome, dyskerin (DKC1), a number of other telomere-associated mutations have subsequently been associated with the disorder and related conditions. Patients with *dyskeratosis congenita* have abnormally short telomeres through life[27].

Accelerated telomere shortening is also associated with a number of acquired disease processes, including cancer associated with chronic inflammation, such as esophageal cancer with Barrett's esophagitis, colon cancer with ulcerative colitis, and lung cancer. Several population based and clinical studies have also correlated telomere length shortening with coronary artery disease. Since cancer and coronary disease are the major causes of death in older individuals, and telomere shortening is a consequence of normal aging (Figure 5), some have postulated that aging (or the diseases of aging) is related to telomere shortening. In this model, telomere shortening beyond a critical limit results in senesce of various cell populations, impeding for example, repair, and immune surveillance. Although it is clear that, on average, telomere length decreases as humans age, this association does not establish a cause and effect relationship, and many questions regarding the role of telomere shortening on the age-associated changes in cellularity and reparative ability remain to be elucidated.

As described subsequently, an emerging literature also links accelerated telomere shortening with stress, including both environmental stress such as malnutrition or violence, and social stress, such as perceived racism, depression, and absence of a father. Despite a large literature that replicates this basic observation, it is not clear whether telomere attrition contributes mechanistically to the health effects associated with chronic stress, or whether it is merely a biomarker that reflects these effects.

The mechanism by which stress modulates telomere shortening is not well understood. Some research suggests that the physiological correlates of stress (i.e., activation of the HPA axis, inflammation) impose an increased oxidative burden on the cell, which damages the telomere, resulting in accelerated telomere attrition[28]. Other studies point to depressed telomerase function, also associated with stress, as contributing to reduced average telomere length [29]. The evidence for either mechanism is not strong. Understanding how stress affects telomere length is an urgent research priority, because without better knowledge of the biological mechanisms that link stress and other moderators of wellness and health to telomere length, it is not possible to articulate a convincing model to explain either the causes or the consequences of the observed disparities in telomere length.

Measurement of Telomere Length (TL)

Several approaches are used to determine the average telomere length in a sample of DNA. The classic approach is the terminal restriction fragment (TRF) length Southern blot assay.

In many laboratories a rapid quantitative real time PCR (qRT-PCR) reaction is used to compare the amount of telomere DNA (TTAGGG) in a sample with the amount of another, control gene. Often results are expressed as a ratio of telomere to control DNA (T/S ratio)[30], but more recently investigators have used internal control oligomers to report the length of the telomere in base pairs[31]. Using this method, our laboratory has observed that the average telomere length in a sample of adult females (average age 34.2 years) is 6.12 kb, and in a sample of 2,818 children (average age 9.28 years), it is 9.66 kb. As between boys and girls the telomere length was 9.70 and 9.88 kb, respectively (p = ns)[32]. Several other approaches are occasionally employed, and all produce roughly similar results. Recent reports have used DNA derived from saliva to measurement telomere length. Although saliva TL is significantly longer than TL derived from peripheral blood mononuclear cells (the usual source) across an individual, the two sample types produce highly correlated measurements [16].

Social determinants of epigenetic marks

Research on epigenetic regulation of gene activity related to behavior and the influence of the social environment on epigenetic regulation began about a decade ago[25]. Despite this relative novelty, there is now evidence that life experiences (and especially early life experiences) can directly influence genetic function by altering the epigenetic patterns in specific loci on the genome [33]. It is important to note that the vast majority of work looking at environmental influences on DNA methylation or DNA methylation effects on health has been done on animals (especially mice, rats, and voles). Animals studies have shown that the strong effect of mother's nurturing on rat pups' ability to handle stress and form attachments is associated in part to increases in CpG methylation of the promoters regions of the glucocorticoid and estrogen receptor genes and the BDNF gene[34]. Another line of research shows that animals that have been stressed either through social isolation, nutritional deprivation, or contextual uncertainty also exhibit changes in methylation —typically decreasing methylation at the promoter regions of CNS genes [35].

In addition to parenting quality, other environmental or life experiences are related to methylation. For example, using buccal cells one study recently found that adversity (such as physical abuse) in infancy and preschool was related to methylation pattern differences in adolescents [22]. Adverse early life experiences have also been tied to differences in epigenetic patterns for genes related to mental health, [36] drug addiction [37] and obesity [38].

Social determinants of telomere length

Telomere length appears to be a biomarker of social stress. Telomere shortening has been associated with depression, harsh parenting, paternal absence, and perceived racism. Stress related telomere shortening could evoke physiological weathering in a way similar to aging [39]. Research suggests several possible behavioral mediators of the negative association between stress and TL, including smoking, mental illness (particularly depression), caregiver stress, and obesity[40]. Considering the strong association between social deprivation and these mediators, it is not surprising that some measures of social standing and social deprivation have also been found to be associated with TL [16,41].

The TL literature has focused almost exclusively on adults, although several studies have used retrospective reports to measure childhood conditions, and one prospective study has examined the association between childhood conditions between ages 5 and 10 and TL, and a second study determined that the duration of exposure to institutional care between 22 and 54 months was negatively associated with telomere length [26,40]. Recently, we reported that the association between children's social environment and TL is moderated by specific variants or alleles in dopaminergic or serotonergic pathways. Involved genes associated with serotonergic transmission are HTT and TPH2 and with dopaminergic transmission are COMT, DAT1, DRD2 and DRD4.

Epigenetic Association with Child Mental Health

A growing literature suggests that DNA methylation plays an important role in mental health disorders as well [42]. For example, exposure to third trimester depressed maternal mood is associated with methylation status of a CpG-island of *NR3C1* in newborns and altered hypothalamic-pituitary-adrenal stress reactivity at age three months[43]. The association is indicative of a potential epigenetic mechanism linking maternal depression and newborn physiology. A second example suggests that depression is associated with higher methylation levels in the 5-hydroxytryptamine transporter (5-HTT, or SLC6A4) gene[44]. This work also ties back into the larger work on 5-HTTLPR and depression[45] by showing both genetic (the S allele of 5-HTTLPR) and epigenetic factors (methylation of the 5-HTTLPR promoter) may interact with environmental states to moderate risk of depression. However, this research area topic is still nascent and therefore the mechanisms that lead to changes in methylation or how that methylation modifies biology to influence mental health are still unknown.

Epigenetic Association with Asthma

Like the rest of the epigenetic literature, the work on asthma and allergy exploits both candidate gene and genome-wide approaches[46]. The candidate gene approach was the first method and still most common, but epigenome-wide data are becoming more available. For example, the 17q12-21 locus is one of the most widely replicated genetic loci for asthma. Interestingly, the effect of polymorphisms at this locus seems to be suppressed in females by higher levels of methylation of this locus[47], which would tend to reduce expression of the risk allele. Another interaction between a genetic variant, this time in Il-4R, and the extent of methylation of a related CpG site has recently been described. The Il-4R gene variant (rs rs3024685) is not independently associated with risk of asthma, but the combination of this variant with a high level of methylation increased asthma risk by approximately 47-fold[48]. The biochemical mechanism underlying this effect remains to be better defined, but interactions between genetic variants ('the genome') and the extent of methylation ('the epigenome') may underlie many examples in which conventional rules of genetics fail to account for observed phenotypes. These studies show how polymorphisms and epigenetic regulations are interrelated and how future studies should be structured to examine these interactions. Not surprisingly the majority of the environmental exposures in this literature implicate the natural environment rather than social [46]. However, in many cases, the social

and natural environments are highly correlated—and thus more research is needed to evaluate possible indirect and potentially spurious associations.

Current Recommendations

Substantial evidence indicates that pathways initiated by childhood social adversity can be interrupted. Studies show that high-quality early development interventions—including center-based programs to nurture and stimulate children and to support and educate parents —greatly ameliorate the effects of social disadvantage on children's cognitive, emotional/ behavioral, and physical development; the first five years of life appear to be most crucial, although opportunities for intervention continue throughout childhood and adolescence [49-51]. However, the extent to which these improvements are based on or related to epigenetic changes has not yet been evaluated, although there is great interest in pursuing these mechanisms. Therefore, while the early epigenetic literature cannot support specific recommendations, we expect that in the next few years the mechanistic link between early social adversity, early childhood development, and interventions to enhance development will begin to come into focus. Ideally, this research will be longitudinal, collaborative and may involve very large data sets and new statistical methods based on bioinformatics.

Finally, although not explored in this paper, a major limitation of this area is the lack of integrated research in social and natural environmental effects on epigenetics. Social and natural environment are highly correlated and yet are rarely discussed together. To what extent one might explain the effects of the other environment type on methylation patterns has not fully been explored. This might be a particularly useful way to expand available data and research.

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Key Points

- Epigenetic factors, especially DNA methylation, and telomere length are currently being examined as biological mechanisms linking social factors and health.

- Social deprivation is associated with a wide range of epigenetic change in children and young adults.

- Epigenetic markers are associated with obesity and eating disorders, mental health, and asthma.

- Research is still too new to provide actionable evidence for a causal mechanism linking social experiences and child health through epigenetics and telomere length.

- Research exploring the overlap between social and natural environmental links to epigenetics and health is desperately needed.
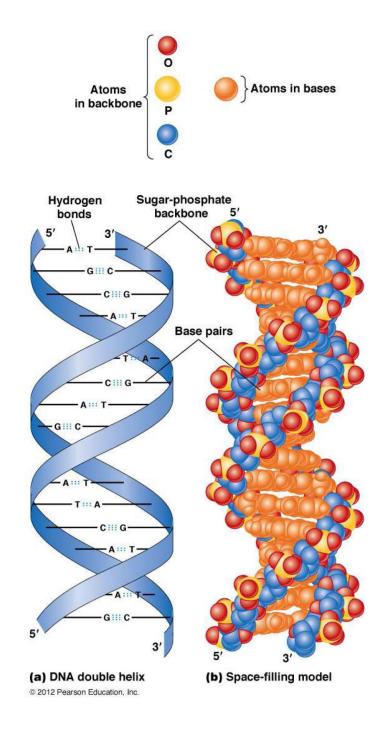
Figure 1.
(a) A schematic representation of the double helical structure of DNA. A = adenosine; T = thymidine; C = cytosine; G = guanine. The strips represent the helical structure formed by the phosphodiester bonds (the "double helix,") and the horizontal bars represent paired bases. (b) A space-filling model of the DNA double helix. The color-coded atoms are shown at the top of the figure.
From Hardin J, Bertoni, G, Kleinsmith, LJ. *Becker's World of the Cell – 8th ed.* San Francisco: Benjamin Cummings; 2006; with permission.
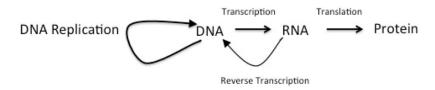
Figure 2.
The Central Dogma of Molecular Biology, modified to include reverse transcription.
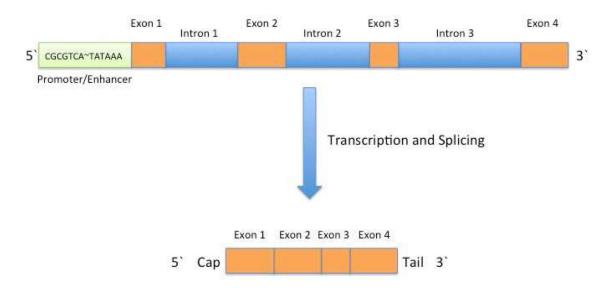
Figure 3.
Schematic of a typical human gene. The 5′ end of the gene contains a promoter/enhancer region that is enriched for CpG sequence. The promoter also contains a special sequence, TATTAAA, which is a target for the transcription factors to bind. Several other sequences may intervene between the CpG island and the TATTAAA. Introns are shown in blue, and exons in orange. During transcription and splicing, an RNA copy of the gene is made, and the introns are excised. A 5′ cap and a 3′ tails are added to the final mRNA copy of the gene.

Figure 7-79 Molecular Biology of the Cell 5/e (© Garland Science 2008)
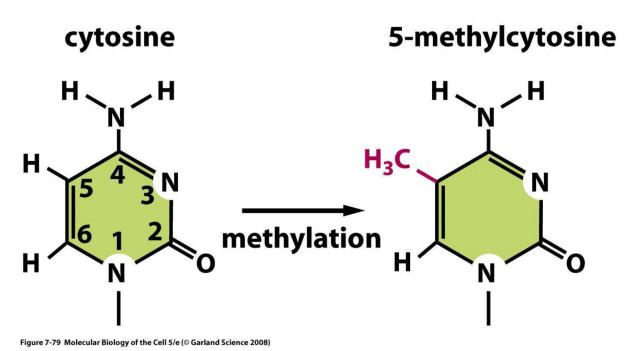
Figure 4.
5-methylcytosine is formed by the addition of a methyl (--CH$_3$) group to cytosine. From Alberts, Bruce, Johnson A, Lewis J, et al. Molecular Biology of the Cell, 5th ed New York: Garland Science, 2008; with permission.
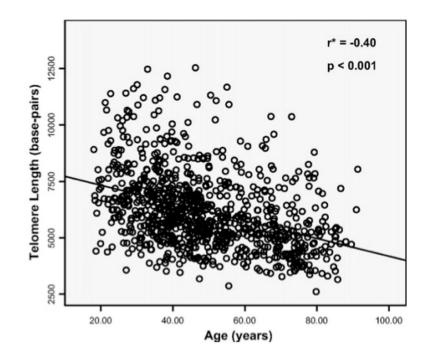
Figure 5.
Correlation between leukocyte telomere length and age. From Njajou OT, Cawthon RM, Damcott CM, Wu SH, et al. Telomere length is paternally inherited and is associated with parental lifespan PNAS 2007;104:12135-12139; with permission.

Figure 6.
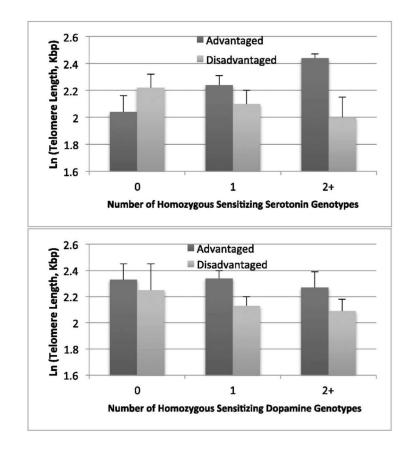
ln(telomere length) by environment type (advantaged vs. disadvantaged) and serotonin
pathway (Upper) and dopamine pathway (Lower) homozygous genotype counts. For the
serotonin pathway genotypes, the environment effect is borderline for 0 genotypes (P =
0.09), not significant for 1 genotype (P = 0.32), and significant for 2+ genotypes (P = 0.02).
For the dopamine pathway genotypes, the environment difference is not significant for 0
genotypes (P = 0.63), significant for 1 genotype (P = 0.05), and borderline for 2+ genotypes
(P = 0.08). This indicates that specific alleles in neurotransmitter pathways moderate the
effect of social stress on telomere length.

From Mitchell C, Hobcraft J, McLanahan, SS, et al. Social disadvantage, genetic sensitivity,
and children's telomere length PNAS 2014; 16: 5944-5949; with permission.