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Review Article

Can Your Genes Change??

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Abstract

There is a famous saying which goes as 'nothing is permanent except change'. We are all aware that the way our genes are expressed remains unchanged for a lifetime. Now, then why do we talk about change in genes, isn't it strange? Yes! Let's read more about this interesting topic, 'EPIGENETICS'. Changes in genetic sequence or in other words, genetic variations resulting in inter-individual differences in a particular trait is something we all know about. Unlike this, epigenetic changes refer to addition of chemical compounds to single genes which can potentially regulate their activity. Identified triggers of epigenetic changes are tobacco smoke, pesticides, diesel exhaust, heavy metals, polycyclic aromatic hydrocarbons, radioactivity, hormone therapy and exposure to certain bacteria or virus. Nutrients have a potential role in modifying epigenetic mechanisms [1,2].

Keywords: Nutrients; Smoke; Pesticides

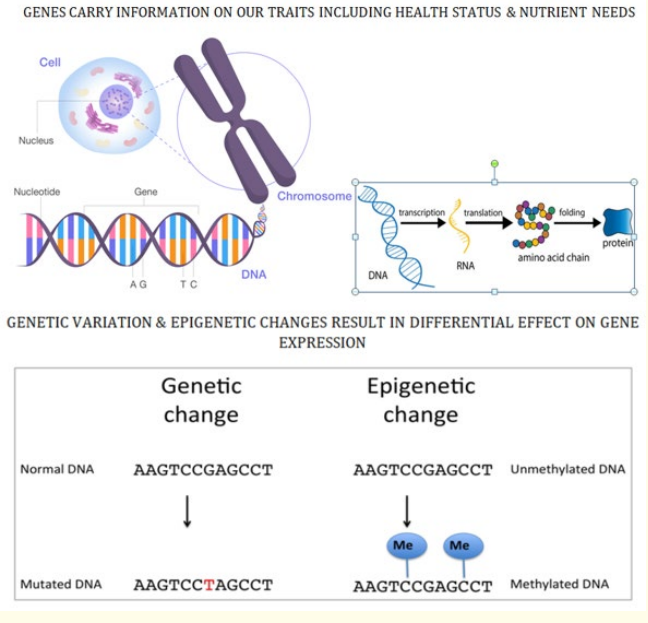

Figure 1

Types of epigenetic processes

Deoxyribonucleic Acid (DNA) modifications can affect gene activity without altering the DNA sequence. Epigenetic changes in a gene are modifications that affect its activity through addition of chemical compounds. Epigenetic changes transform a genome into an epigenome as adjuncts (chemical compounds) are on or attached to a gene within a genome. These chemical compounds of the epigenome are not part of the DNA sequence. Diet and exposure to pollutants are environmental influencers of an epigenome [3].

Epigenetic processes which alter gene activity without changes in DNA sequence, are capable of transmission to daughter cells (eventhough some epigenetic changes can be reversed). Epigenetic processes are natural and essential to a number of cellular functions, but if they occur improperly, there can be major adverse health and behavioural effects [1].

The most significant epigenetic mechanisms include DNA methylation, histone modifications, and the non-coding RNAs [4-6]. Epigenetic processes mainly DNA methylation and histone modifications lead to persistent effects on the availability of DNA for transcription [7].

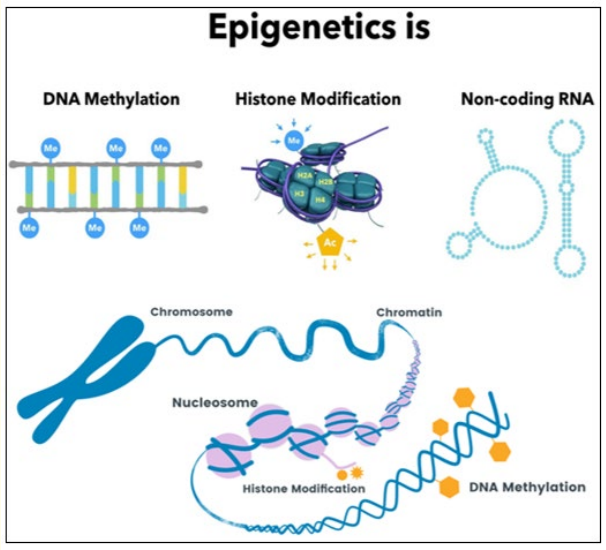

Figure 2

DNA methylation is the epigenetic process of converting a cytosine (within a CpG dinucleotide) into '5-methylcytosine' through the addition of a methyl group. DNA methylation is generally associated with gene silencing, and DNA demethylation is usually connected with gene activation. Appropriate DNA methylation is necessary for the normal regulation and development of genome function [8-14].

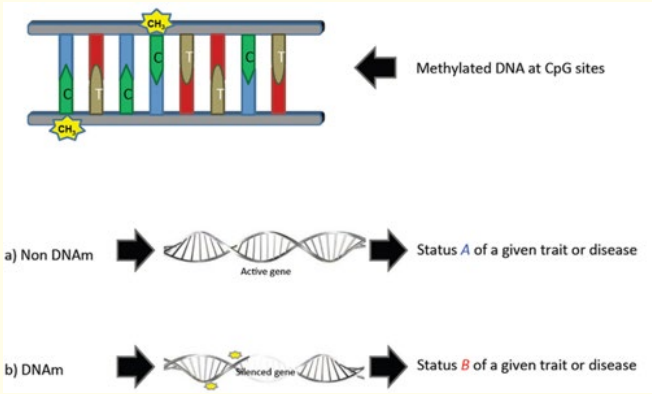

Figure 3

Possible role of nutrition in DNA methylation [15-18]

- An appropriate DNA methylation is crucial for normal genome function, and hence aberrant DNA methylation can be considered as an epigenetic indicator of happenings such as disruptions in DNA integrity and stability, unusual chromosomal modifications, and mutation onset.
- Aberrant DNA methylation patterns and dysregulation of DNA methylation are present in many human diseases, including cancer, imprinting disorders, and developmental disabilities.
- Folate, a B vitamin, is the main source of one-carbon group in DNA methylation. It also serves as the one-carbon source for other cellular methylation pathways (RNA, protein) and vital DNA processes such as synthesis and maintenance.
- Rapidly dividing tissue tumors may be susceptible to low folate availability, resulting in hypomethylation. Low folate status is associated with decreases in DNA methylation, which in some studies has been associated with an increased risk of cancer, especially when tumor-suppressor genes are silenced because of this epigenetic change.
- The extent of folate deficiency and the efficacy of its supplementation on DNA methylation are precisely dependant on the gene and its site of epigenetic change. While other crucial factors such as the cell type, target organ, stage of transformation, and the degree and duration of folate depletion also have a significant role.
- Folate depletion can result in a destabilized DNA replication, as inadequacy of folate during cell division can compromise thymidine production substituting it with uracil in the DNA sequence. Such a mutagenic episode demands repair attempts which hike the incidence of chromosomal breaks. This concept has been proven in tissue culture studies wherein folate depletion has led to chromosomal breakage evidenced through micronuclei formation. The 'TT' genotype of MTHFR gene (rs1801133) might lead to increased micronuclei formation under low folate conditions, implying higher susceptibility to the detrimental effects of this epigenetic change.
- Low folate-mediated aberrant DNA methylation is a potential epigenetic contributor of Alzheimer's disease and autism.

Histone modification refers to the post-translational enzymatic modification of histone proteins through methylation, acetylation, phosphorylation, and ubiquitination. During gene expression, the extent of chromatin compactness is reliable on histone modification. Acetylation which usually occurs in the lysine residues conserved to N-terminal vitally modifies the histone proteins. For instance, acetylations of histone H3 at lysine residues 9 and 14, and of histone H4 at lysine residues 5, 8, 12, and 16 are associated with the activation or opening of the chromatin. However, de-acetylation of the lysine residues leads to chromatin compression and inactivation of gene transcription [19-25].

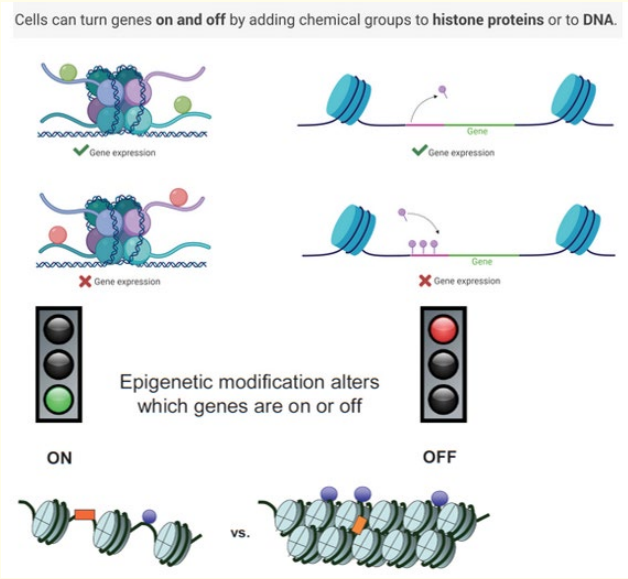

Figure 4

Possible role of nutrition in Histone modification

- Sulforaphane (SFN) is an isothiocyanate obtained from cruciferous vegetables like broccoli, cauliflower and Brussels sprouts. Sulforaphane has anticarcinogenic properties by potentially inducing Phase 2 detoxification enzymes. The SFN also has a protective role against epigenetic changes by inhibiting histone deacetylase/HDAC activity in human cancer cell lines of colon and prostate (with increased global and local histone acetylation status). In a research study, healthy subjects consumed a single serving (68 g) of broccoli sprouts. Nearly 3–6 hours after consumption, their circulating peripheral blood mononuclear cells showed an inhibition in histone deacetylase activity, alongside a concurrent induction of histone H3 and H4 acetylation [26].
- An *in-vitro* study on human colon cell lines with tumor showed an increase in histone H3 and H4 acetylation with high consumption of diallyl-disulfide from garlic [27].
- Both these studies suggest the positive effect of nutrients on epigenetic change, favouring activation of gene transcription.
- Other dietary agents such as butyrate, biotin, lipoic acid, and metabolites of vitamin E have structural features compatible with HDAC inhibition [2].

Other important nutrients that take part in DNA methylation and Histone modification

- Selenium has anti-cancer effects in the cell owing to its role in epigenetic modifications. Epigenetically, selenium activates methylation-silenced genes by modulating DNA and histones. Selenium has been shown to directly inhibit DNA methyltransferases (DNMT) expression and activity. Selenium potentially restores the expression of hypermethylated genes in human prostate cancer cells through down-regulation of DNMTs and inhibition of HDAC activity [28-35].
- Polyphenols can impact DNA methyltransferases, Histone acetylases and Histone deacetylases inducing reversibility of epigenetic dysregulation.
- Green tea contains EGCG or epigallocatechin-3-gallate; EGCG inhibits the activity of DNA methyltransferase and reactivates methylation-silenced genes in cancer cell lines. Supporting evidence from *in-vitro* experiments with various cancer cell lines (prostate, esophageal, breast and colon), showed that numerous CpG islands of several loci were efficiently demethylated by EGCG, and consequently expressed previously silenced genes [36-39].
- Soy beans are also extremely rich in polyphenols (phytoestrogens like genistein, biochanin A, and daidzein) [40]. Soy polyphenols effectively inhibit DNA methyltransferases and histone deacetylases in cancer cell lines and potentially reverse aberrant CpG island methylation [41,42].
- In human endothelial cells, incubation with arachidonic acid modulated gene methylation, promoting an up-regulated pro-angiogenic mechanism. On the contrary, polyunsaturated fats might suppress tumorigenic processes through dampening of inflammation and NF-kappaB pathway [43,44].

Non-encoding Ribonucleic Acid (non-coding RNAs) aren't translated into proteins. They are capable of dividing into housekeeping non-coding RNAs and regulatory non-coding RNAs. Ribonucleic acid with a regulatory role is predominatly divided based on its size, as either short chain non-coding RNAs (such as siRNAs, miRNAs, and piRNAs) or long chain non-coding RNA/ lncRNAs). Non-encoding RNAs are crucial players in epigenetics owing to their regulation at the gene expression level and at the level of chromosome to control cell differentiation [45-50].

Impact of physical activity on epigenetic changes

- Epigenetic mechanisms may be involved in mediating effects of physical activity.
- Physical activity is shown to be associated with higher methylation in peripheral blood lymphocytes of LINE-1 elements (a class of repeated sequences highly repeated in the human genome). While a low methylation in LINE-1 repetitive elements is linked with inflammation and chromosomal instability.
- Elderly individuals who show high LINE-1 methylation in peripheral blood lymphocytes may experience lower incidence and mortality from ischemic heart disease and stroke. Implying this positive epigenetic change could be mediated by adequate physical activity.
- Exercise increases histone acetylation and alters non-coding RNA (miRNA) in such a way that it brings down inflammation [51-55].

Along with their susceptibility to external influences, epigenetic patterns are internally subjective with pivotal control centres predisposing to higher or lower capabilities in physical performance. Epigenetic effects may also play a considerable role in the determination of athletic potential.

Epigenetics and the circardian rhythm

CLOCK gene regulates circadian rhythm through a histone-acetyltransferase activity. This promotes chromatin-remodelling events implicating circadian control of gene expression. The adjustment in circadian rhythm might get affected by factors like shift-work. Epidemiological studies have shown a negative impact of night-shift on the health and well-being of workers probably because of a mismatched endogenous circadian timing system and its environmental synchronizers such as the light/dark cycle. An epigenetic reprogramming of circadian genes probably alters endogenous circadian rhythms. A current research work in night-shift workers illustrated alterations in blood DNA methylation, indicative of aberrant DNA methylation in inflammatory genes [56-61].

Epigenetics relates with a change in gene function caused by alterations in the DNA (addition of chemical compounds, such as methylation, acetylaion, etc..) unaccountable for sequence change. This change is applauded if it enhances gene function favourably, promoting good health. Nutrients modify epigenetic mechanisms, suggesting a scope for teering epigenetics in a health-promoting way.

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