

# The Magic of Epigenetics

*Recipes for a Healthier Life*

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## ABSTRACT

Genetics has long been accepted as a deterministic factor that shapes our psychosomatic features and characteristics. But recent data show that genes are not our destiny and we are the masters of our heredity. Unmistakably, modern genetics proves the fact that by the way we eat, the way we breathe and treat ourselves, we regulate the activity of our genes and their outcomes. New genetic data link education, intelligence, food, and lifestyle as powerful factors that shape our genes. By inducing chemical modifications on the molecule of DNA and the proteins that organize it in the nucleus, factors like stress, lack of physical activity, and chronic illness change the way genes work. The science that studies the molecular mechanisms by which the environment inherently drives the work of our genes is called epigenetics. Epigenetic inheritance, just like genetic inheritance, goes beyond our time and is transmitted to our descendants. Here, we summarize one of the most canonical mechanisms of epigenetics, and link it with certain types of human metabolism, disease, and psychosomatics. The bond between our lifestyle and the choices we make in our daily life with the way genes work is as dominant as genetics per se. Epigenetics holds the key to a healthier and smarter way of living.

**Keywords:** genetics, epigenetics, psychosomatics, brain, stress, environment, food, DNA methylation, PTMs, folic acid

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e often hear that “it’s all in the genes.” In general, this paradigm is true, and the fact is that the program of our biological life is encoded in the tiny DNA structure we inherited from our parents. However, strictly speaking, besides our genes, in our DNA we also inherit an unknown amount of additional information that is not encoded in our genes. Therefore, regardless of the enormous amount of information gathered about our inheritance, we feel just like Alice. We feel like we are in the “wonderland” called human inheritance, where “still we don’t know who we are, and that’s the great puzzle!”

## The Puzzle of Epigenetics

The concept of epigenetics can be traced back to 350 BC when the Greek philosopher Aristotle proposed that the individual development of the organic form is generated from unformed matter by a “vital cause.” Nowadays we assume that the idea of this “vital cause” is covered by the term “epigenetics.” Dr. C. H. Waddington (1905-1975), who in the first half of the last century was interested in the developmental events leading from the fertilization of the oocyte to its transformation into a whole organism, is generally accepted as the “father” of epigenetics. As Waddington proposed, these events are regulated processes that begin with the genetic material and shape the final step by which every living organism is born (Waddington, 1963, 2012). Nowadays, it is commonly assumed

*Who in the world am I?  
Ah, that’s the great puzzle.*

Lewis Carroll,  
Alice in Wonderland

that epigenetics represents the execution of complicated programs that serve to finely tune gene expression, thus enabling cells and the whole organism to cope with changes in the environment. Importantly, a process can be epigenetic only when it is inherited without being coded in the DNA sequence. Epigenetics literally means “above” or “on top of” genetics. It refers to processes that regulate the level of gene activity, including the possibility to turn genes “on” and “off.” In other words, these processes are not encoded in the DNA sequence, but instead, they affect how cells “read” genes.

*Epigenetics is the study of heritable changes in the level of gene expression that do not involve changes to the underlying DNA sequence, i.e., epigenetics leads to a change in the phenotype without a change in the genotype – which in turn affects how the genes are expressed.*

It is appreciated that the activity of genes, i.e., how genes work, can be affected by environmental factors. Therefore, we can state that the environment strongly influences the epigenetic regulation of the organism (Marsit, 2015). The environmental effects on gene activity, especially on the process of embryo development, have been actively studied. The reason for this is that during embryonic development, genes are dynamically switched on and off, reminiscent of a “real storm of changes.” However, the environmental factors, which can be different pollutants, changes in temperature and behavior, but also psychological stress, influence the epigenetics of the early years after birth, as well as the entire life of an organism. Notably, special attention should be given to the effects of the individual’s behavior on his/her epigenetic mechanisms and vice versa. This line of investigation flourished in a set of data called behavioral epigenetics (Lester et al., 2011).

From the point of view of epigenetics, the term “behavior” is understood as the whole amalgam of human activities like eating habits, physical activity, bad habits like smoking, drug, and alcohol addiction, etc. Therefore, knowledge of epigenetic mechanisms is very important in order to understand the so-called universal and specific laws of healthy living. In summary, behavior in accordance with these laws can lead to a long and healthy life (Young, 2014). As of now, mechanisms of epigenetics encompass several more-or-less understood processes and dynamic changes of genetic structures. In order of their recognition, these processes include methylation of DNA, histone modifications, small ncRNAs (non-coding RNAs), and higher-order chromatin organization. To a greater extent, epigenetic processes also determine phenotypic characteristics. In general, epigenetic mechanisms and processes regulate the accessibility of genes to cellular enzyme complexes, which in turn regulate transcription, and thus determine where and when a gene will be activated, as well as the level of its activity. Epigenetic mechanisms play a central role in the regulation of gene expression, and thus enable the body to adapt to its environment. Recently, there has been evidence

that multiple environmental factors such as nutrition, body structure, and social environment can influence epigenetic processes, often with long-lasting effects on the whole physiology of the organism including metabolism, and currently leading to various diseases.

## Smart Strategies for Healthier Life

In our daily lives, we are all confronted with people, situations, and factors that affect us and determine the choices we have to make every day. Small choices at first glance, like what to wear, where to go on our way to work, or what to eat for lunch. But could it be those little pebbles that predetermine our whole destiny? What happens when we chronologically arrange in a general context a series of these small, insignificant choices and situations we fall into daily? Moreover, what happens if we develop different reactions to seemingly banal everyday situations? Have you ever considered what would happen to you if, in a given situation, a conflict on the road, for example, you approached with calmness and respect for your opponent? How would this affect your emotional state? What if you reacted violently, being intolerant, experiencing stress: wouldn’t that hurt you? How about if all those little situations you get into every day, and even more the way you respond to each one of them, leave a mark not only on your current mental state but also on your genes? What’s more, do these small situations that lead to stress, aggression, or pleasure leave a mark not only on your genes but also on the genes of your future children?

It is good to know that every emotional state is controlled by hormones. Genes in the cells of different organs synthesize hormones. In other words, our ability to express, understand, and to some extent control the various types of emotional responses in our daily lives depends on our genetics. And not only!!! It depends on how the genes work (Nicoglou & Merlin, 2017; Rusconi & Battaglioli, 2018).

## Can we Develop Smart Strategies for Being Healthier by Modulating the Way our Genes Work?

The answer is first, we have to know the logic behind these epigenetic mechanisms in order to understand them. Many mental health difficulties have developmental origins. Understanding these mechanisms is a turning point for many mental health disciplines. In recent years, epigenetic processes have emerged as a potential mechanism mediating the long-lasting weakness following the experience of misfortune (Kumsta, 2019). Second, it is good to feel and understand our bodies. It is well-known that meditation, healthy food, and moderate physical activity are the foundation of healthy epigenetics (Allis, Jenuwein, & Reinberg, 2007; Wolffe, 1998). And although we live in a stressful world, through modern techniques for mental health treatment and for alleviating signs of stress and mental fatigue like psychotherapy, for example, one can very proficiently

modulate the way his/her own genes work. This, together with healthy habits, can completely change our way of reacting to stress. Canonical techniques for psychotherapy, together with modern fields like psychosomatic psychotherapy, are those priceless little nuggets that could very masterfully change our whole life. This is a smart strategy for a healthier life. So let's see how we can do it.

## The Colors of DNA

We should not forget that the eukaryotic genome is represented by a DNA molecule with a size of approximately 2 meters. On the other hand, the size of the nucleus is 10  $\mu\text{m}$ , and DNA is compacted 1700 times to fit in this tiny nucleus. Compaction is achieved by contacts of DNA with positively charged proteins called histones. The strength of histone contacts with DNA is modulated by specific enzymes, which add specific chemical moieties to the molecules of histones and DNA, which in turn changes the access to DNA, and hence leads to differences in gene activity (Turner, 2001). Both DNA methylation and histone modifications are the most common and best-studied epigenetic mechanisms that alter the accessibility of transcription enzymes to DNA, and thereby provide a possibility for dynamic modulation of gene activity.

DNA methylation uses enzymes called DNA methyl transferases, which covalently add methyl groups to the cytosine bases of eukaryotic DNA. Methylated cytosines are called CpG dinucleotides (CpGs). They form clusters called CpG islands. The genome consists of 1–2% CpG islands, most of which are located in the promoters of different types of genes, where they play an important role in regulating gene expression. Over the years it has become known that CpG islands can be either hypomethylated or hypermethylated. Many cancer genes have been found to have a high percentage of hypomethylated genomes (Asadollahi, Hyde, & Zhong, 2010). DNA methylation has significant physiological consequences when it is on a cytosine in CpG dinucleotide (Youn, 2017). The 5-Methyl-cytosine obtained by this methylation can be 2 to 5% of all cytosines in mammalian genomes. Cytosine methylation is often found in the promoters of the genes and is associated with repression of these genes (Orphanides & Reinberg, 2002). Importantly, improper DNA methylation can be induced by environmental factors such as pollutants, cigarette smoking, and psychological stress (Philibert, Beach, & Brody, 2014; Rusconi & Battaglioli, 2018). At present, the mechanism by which DNA methyl transferases target sites is not well understood. However, some of these DNA-methyl transferases have been found to be part of chromatin-remodeling complexes, and play a role in chromatin remodeling processes (Burgers, Fuks, & Kouzarides, 2002).

Recent studies show a link between nutrition and DNA methylation. Polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene has been observed in many people with colorectal cancer. A methionine-rich diet leads

to increased methylation in this gene. Accordingly, patients with such a diet have a lower incidence of cancer. On the other hand, increased alcohol consumption is associated with a decrease in MTHFR levels and hypomethylation, which can lead to the development of colon cancer (Feinberg & Tycko, 2004).

## The Epigenetic Regulation of Genes

Besides DNA methylation, histone modifications are the next level for the epigenetic regulation of gene expression. Histones are the proteins that organize DNA in chromatin, thus allowing its compaction and spatial organization. These protein molecules are the playground for numerous post-translational epigenetic modifications like methylation, acetylation, ubiquitination, phosphorylation, and many others (Allis et al., 2007; Nicoglou & Merlin, 2017). Histone post-translational modifications (PTMs) are involved in all processes with molecules of DNA and RNA (Dhanasekaran, 2012; Kurdistani, 2011), and have implications throughout the whole life of the organism. The growing list of histone PTMs has exploded in the last several years due to the considerable advances in modern science technologies, available antibody reagents, peptide and modern protein array procedures, and mass spectrometry-based proteomics (Zhao & Garcia, 2015). These technologies allowed identification of histone PTMs at specific chromatin sites, as well as throughout the whole genome. The combination of different PTMs along the chromatin fibre is thought to form the so-called "histone code" (Jacobs, Fischle, & Khorasanizadeh, 2003).

The histone code is accepted as a secondary hereditary code that is formed on top of the genetic backbone. It governs and masters the way the genetic information is expressed. On the surface of our genes, we have additional colors formed by these PTMs together with the DNA methylation. These combinations are innumerable. Thanks to billions of years of evolution, epigenetic mechanisms are realized through the use of complex and highly specialized systems of enzymes, enzyme complexes, and protein factors. These enzyme systems can change the epigenetic profile of cells, tissues, or even organs for a very short time (on the order of seconds and minutes). This altered epigenetic profile can very quickly be "deleted" and "erased," or, under certain conditions, preserved for life and even passed down through generations. This is what arouses great interest in epigenetic studies. All of these mechanisms have evolved, and are applied to cells to rapidly adapt the body to changes in environmental conditions.

In 1965, it was first hypothesized that histone modifications could regulate transcription (Littau, Burdick, Allfrey, & Mirsky, 1965). Important components of these reactions are the enzyme complexes like histone-acetyltransferases (HAT) enzymes, histone deacetylases (histone deacetylases – HDAC), histone methyltransferases (HMT), and histone-demethylases (HDMT). The function of these

complexes is to modify chromatin, and thus to suppress or stimulate transcription (Taby & Issa, 2010). Histone acetylation was originally discovered in 1968 (Yang & Seto, 2007). This type of modification is part of processes such as DNA repair, transcription, and chromatin structure remodeling. There are two major enzyme components in the histone acetylation process – histone acetyltransferases and histone deacetylases. They were first described in the mid-1990s (Yang & Seto, 2007), with two different types of histone deacetylases – cytoplasmic and nuclear. For example, when lysine residues are deacetylated in the N-terminal tails of the H3 and H4 dimers of DNA nucleosome complex, they become positively charged. This results in chromatin condensation. Conversely, chromatin structure becomes less compact when these residues are acetylated. Histone deacetylation is performed by histone deacetylases (HDACs). They are divided into two families – classic HDACs and Sir2 HDACs families. The function of histone deacetylases is to remove acetyl groups, resulting in a more compact chromatin structure and gene silencing. They also act on non-histone proteins, and are classified as nuclear or cytoplasmic (Taby & Issa, 2010; Yang & Seto, 2007). In some types of cancer, mutations in the histone deacetylases lead to abnormal expression of genes controlling cell proliferation, apoptosis, and cell cycle. Histone deacetylase inhibitors have been the topic of research in the development of drugs for the treatment of cancer. The American Food and Drug Administration (FDA) has already approved compounds such as trichostatin A (TSA) for the inhibition of certain histone deacetylases in various diseases, including cancer (Fraga, Ballestar, Villar-Garea et al., 2005; Ropero & Esteller, 2007).

Histone methylation is a chemical modification discovered in the 1980s. Essentially, histone methylation is carried out on the lysine residues at the N-terminus of their molecules (Feinberg & Tycko, 2004). The significance of this modification depends on the particular amino acid involved, and can lead to both silence and activation of gene expression. The methylation reaction can be reversible, and is also regulated by specific enzymes (Taby & Issa, 2010). The two major enzymes that carry out methylation or demethylation of histones are histone methyltransferases (HMTs) and histone demethylases (HDMTs). The latter are divided into two families: lysine specific demethylase 1 (LSD1) and Jumonji domain-containing enzymes.

All environmental factors are relevant to our epigenetics. Epigenetic markers, although more stable during adulthood, remain dynamic, and can be modified by lifestyle choices and environmental influences. Therefore, the epigenetic profile is formed not only in the womb, but throughout the entire scope of human life. In other words, epigenetic changes can be reversible. There are numerous studies showing how different lifestyle choices and environmental factors can alter markers on DNA, and be determinative of human health (Mario F. Fraga, Ruben Agrelo,

& Manel Esteller, 2007; Fraga, Ballestar, Paz et al., 2005; Heyn, Moran, & Esteller, 2013).

## The Environment and our Lifestyle Can Modulate our Epigenetics and Control our Genes

The term lifestyle is extensively used to describe the typical lifestyle or basic habits and practices specific to an individual or group. Many aspects of a person's lifestyle have been identified as factors that can modify the epigenome. These are diet, all behavioural habits, any types of stress – mechanical, psychological, lack of physical activity, obesity, work habits (especially night shifts), smoking, alcohol consumption, taking certain medications, and aging. Starting from the conditions in which the fetus develops in the womb (maternal diet, smoking) and continuing with food (selenium, EGCG green tea folates), high alcohol intake, physical activity, environmental pollutants (such as arsenic, chromium, benzene, long-lived organic pollutants, etc.), stress, night-shift work, and aging are all factors that can affect and alter DNA methylation, and hence the expression of underlying genes (Fuso et al., 2008; Fuso, Seminara, Cavallaro, D'Anselmi, & Scarpa, 2005; Sapienza & Issa, 2016; Wolfram, 2007).

Two major groups of factors can have a very strong influence on epigenetic mechanisms, and they are the environment and our lifestyle (Georgieva, Staneva, & Miloshev, 2016; Gravina & Vijg, 2010). A growing body of research has shown the relationship between exposure to potential toxic chemical agents and the occurrence of pathological changes in DNA methylation and histone modifications (Bollati & Baccarelli, 2010). The environmental pollutants most commonly regarded as epigenetic toxins are arsenic, polluted air, aromatic hydrocarbons, and other organic pollutants. Two different studies found that DNA isolated from the blood of individuals chronically exposed to toxic levels of arsenic had both global DNA hypermethylation and significant hypermethylation in the promoter regions of the p.53 and p.16 protein genes, compared to controls. Moreover, this effect is not only dependent on the dose of arsenic found in plasma, but also on the folate present in plasma, indicating that arsenic-induced increased methylation of DNA is directly dependent on the presence of methyl groups (Chanda et al., 2006; Pilsner et al., 2007). Exposures to polluted air, especially dust particles, is associated with increased morbidity and mortality due to cardiorespiratory diseases, as well as an increased risk of lung cancer. In a human study, methylation in the promoter of the iNOS gene (inducible nitric oxide synthase) was found to decrease in the blood samples of casting workers taken after exposure to dust particles for a four-day working week, compared with baseline samples (Tarantini et al., 2009). As a result of the demethylation of the iNOS gene, the expression and activity of the iNOS protein, which is

one of the key players in the processes of inflammation and oxidative stress, is expected to increase, and thus the acute health problems observed during breathing in polluted air. Long-term exposure to both dust particles and black carbon correlates with reduced methylation of Alu and LINE-1 (Castro et al., 2003). Because hypomethylation of LINE-1 has been found in the blood samples of patients with various types of cancer or cardiovascular disease, this change in DNA methylation status, on the one hand, reproduces the epigenetic processes associated with the development of these diseases, and on the other, explains the mechanisms by which airborne dust contaminates human health. Another group of epigenetic toxins are aromatic hydrocarbons. A recent DNA test from the blood samples of traffic police officers and gas station employees who regularly inhale gasoline (benzene) vapor through their breathing showed decreased methylation of Alu, LINE-1, as well as hypomethylation of the *MAGE-1* (cancer-antigen) gene and tumor hypermethylation of the *p15* suppressor gene (Bollati & Baccarelli, 2010). A number of other organic pollutants such as polyaromatic hydrocarbons, bisphenol A, have also been found to influence epigenetic mechanisms (Rusiecki et al., 2008).

## Food as a Powerful Epigenetic Factor

Food is a powerful epigenetic factor. On a daily basis every one of us eats at least two, three, or even more times. Thus, over 10,000 different types of biologically active compounds accumulate and begin to circulate freely in our bodies. They are the result of our daily intake of food, drinks, and medicines. Anything we consume can enter the cells and contact the DNA, resulting in chemical modifications on our genome, thus modeling and changing it epigenetically. Covalent modifications of histones can be modified by food (zinc, iron, selenium, polyphenols in vegetables, etc), which in turn affects the chromatin structure, and ultimately affects the regulation of transcriptional activity. In turn, physical activity and smoking influence the regulation of expression of a number of miRNAs by DNA methylation of miRNA loci, resulting in repression of translation or degradation of the transcripts (M. F. Fraga, R. Agrelo, & M. Esteller, 2007; Fraga, Ballestar, Paz et al., 2005; Georgieva et al., 2016; Nicoglou & Merlin, 2017).

Food and its active ingredients leave marks on DNA. This is how they affect our genes and those of our future generations. It is no coincidence that the mother's diet influences future generations very extensively and thoroughly. Now this is a very hot topic not only for scientists, but also for women who are mothers or will be. Of course, this also excites their relatives and friends. We have to realize that diet and the type and quality of food affect not only our metabolism, but even the way our genes work. And the way our genes work determines not only us, but also what we pass on to our children: their susceptibility to diseases, allergies, and even certain psychological traits. A typical

example of the importance of nutrition for gene expression is the agouti mouse and the female bees from a hive. The agouti mice are a gold standard for studying the way diet influences the epigenome. These mice have a different methylation of the *ASIP* gene (agouti-signaling protein) in comparison to the wild type, which is responsible for the distribution of melanin pigment in mammals and rigorously controls the metabolism, results in its silencing and all subsequent changes in the overall metabolism (Wolff, Kodell, Moore, & Cooney, 1998). In one beehive, in the time span of individual development, some bees turn into worker bees and others into mother bees (Kucharski, Maleszka, Foret, & Maleszka, 2008). The diet of the latter, fed mainly on royal jelly, results in a change in the methylation status of more than 500 genes. This process affects the external morphology of the mother bees, their brain development, and completely different behavior later on during their individual life.

DNA methylation plays a role in cancer development, too. Scientific evidence shows that tumor cells have low levels of DNA methylation, which explains the global high level of gene activity in these cells (Ali Khan et al., 2015; Khan et al., 2015). Between diet and cancer, although not yet fully understood, there is a link that is subject to serious research. The EPIC (<https://epic.iarc.fr/>), a European scientific consortium with the aim of seeking to find the link between food and cancer, was recently created. The tasks of this grand project are to explore how lifestyle – diet, diet, exercise and stress – affect the incidence of cancer and various other chronic conditions. The survey is scheduled to be conducted over a period of 15 years on a large group of people: half a million. The research group is widely represented by ten different European countries. Primarily, the connection between food and the onset and type of tumor diseases is sought. All these efforts are not in vain, and even less accidental. As a result of human and animal studies, data have been accumulated suggesting a link between food and a large number of human diseases. A long list of various foods and nutrients (from alcohol to zinc) has been created, and has been shown to influence DNA methylation, and hence the onset and development of various diseases. Folic acid-poor diets, for example, lead to a decrease in DNA methylation levels, and to various diseases like head or neck cancer, stomach cancer, etc. (Newberne, 1986; Pogribny, Tryndyak, Muskhelishvili, Rusyn, & Ross, 2007). A well-known fact is that folic acid is not naturally produced in the body. It is a water-soluble form of Vitamin B9. Its biological activity only manifests itself after being metabolized in the body (mainly in the liver) to Vitamin B9 (folate) (Zeisel, Mar, Howe, & Holden, 2003). It plays an important role in the production of nucleic acids (DNA and RNA), and is involved in cell division processes. It is necessary for the formation of the placenta and for the construction of the bone marrow of the embryo. Consumption of folic acid reduces the risk of birth defects

in the baby. It also has a positive effect on the body of the expectant mother; it regulates and lowers the level of stress hormones. The fact that the human body cannot produce folate necessitates its supply through food.

## Folic Acid – the Miraculous Substance that Marks our Genes

There is a very complex and well-controlled mechanism for the metabolism of folic acid in the human body. Vitamin B6 and B12 are included in this cycle (Fuso et al., 2005; Giles, Kittner, Anda, Croft, & Casper, 1995). Together with folate, they are involved in controlling the body's levels of homocysteine and converting it to methionine. Methionine, for its part, is a major source of methyl groups that can bind to specific stretches of DNA, leading to their methylation and, in general, to the silencing of genes located in these regions. In other words, folate, methionine, homocysteine, vitamins B6 and B12 as well as zinc (the major transport molecule in the folate metabolism cycle) are the leading molecules that are actively involved in DNA methylation processes. Methionine-rich foods are green leafy vegetables (cabbage, spinach, broccoli, Brussels sprouts, lettuce, iceberg lettuce, etc.). They are followed by legumes, sunflower seeds, liver, whole grain bread, and nuts. They are all known for their rich folic acid content. There are over 1,000 different species of green leafy vegetables alone. To improve the levels of methionine in our bodies, it is good to consume spinach, garlic, and tofu. Fish is also rich in Vitamin B12 (Obeid et al., 2009; Pilsner et al., 2007; Wolff et al., 1998; Zeisel et al., 2003).

Still, DNA methylation is not so straightforward in the cell at all; things are never just black and white. Depending on which genes will be methylated, this can both prevent the body from developing cancer, and (in the case of excess) lead to the onset of other diseases. For example, people suffering from epilepsy should be careful with folic acid, as high levels of methylation in DNA can lead to increased brain reactivity and increased seizure frequency. Therefore, folic acid and foods that are rich in it should not be abused. Particular care should be taken when folic acid is taken by pregnant women. The right quantities are extremely important. Specific changes can be detected in the new-born's DNA that indicate the mother's feeding patterns before, at, and after conception (Georgieva et al., 2016). Some authors point to the fact that the mother's nutrition around the time of conception may affect some regulatory areas of the child's DNA, even during its development in the womb. The study was conducted on women from West Africa (Gambia) and their children (Waterland et al., 2010). The weather in West African countries is divided into two distinct periods – rainy and dry. These two periods divide very precisely the diet of people in these countries. This is because they eat products directly from nature. Therefore, the foods they consume during these

two periods are different. Scientists at the London Institute of Hygiene and Tropical Medicine have examined how different eating patterns affect the DNA of children conceived at one time or another. These scientists examined the DNA of both mother and baby blood, looking for specific changes in DNA methylation. Moreover, DNA methylation levels have been shown to be highly influenced by maternal nutrition. This level of DNA methylation is transmitted to newborn infants (Dominguez-Salas et al., 2014). But it also means inheriting the way genes work in children, which is the result of the type of food that mothers ate. This study proves that the level of DNA methylation is important for the amount of homocysteine, folate, and vitamins B absorbed. Changes in the profile of DNA methylation are known to lead to the development of diabetes and cardiovascular disease (Fetita, Sobngwi, Seradas, Calvo, & Gautier, 2006). These and similar other studies prove that women's nutritional diet is important for their future children not only during their pregnancy, but rather before and during conception.

## The Way Epigenetics Functions in Reality

Recent studies on identical twins have shown that although they carry genes responsible for the onset and onset of a specific type of disease (rheumatoid arthritis or schizophrenia), one twin never develops the disease unlike the other (Felson et al., 2000; Pallister, Spector, & Menni, 2014). The reasons for this lie in the epigenetic profile of these individuals, i.e. not in the hereditary information, but in the factors and events that control its functioning. Most identical twins have been shown to differ in their epigenetics even at the time of birth. In the course of their prenatal development, they receive different stimuli from the mother, the intake of nutrients is not exactly the same, and the location in the womb and the size of the placenta are factors act differently (Metrustry et al., 2018). All these differences during prenatal development lead to differences in their epigenetic profile (Pallister et al., 2014; Starnawska et al., 2019). Moreover, twins differing in height and weight show epigenetic differences in the genes responsible for a particular type of metabolism (Pallister et al., 2014).

These and other scientific data underline the importance of environmental factors for the way genetic information is implemented, i.e., which genes to include, which ones to exclude, how to work, when and at what intensity. All this seriously influences the further development of the human body. In other words, epigenetics is the bridge between our life and the way our genome works.

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In a series of subsequent articles, we shall dive into the world of epigenetics and its mechanisms for control of our genes. Our intention is to discover the mechanisms through which we influence our genes through our daily choices and activities. We shall unveil the role of psychotherapy and body psychotherapy for maintaining our mental health on a sensible and well-balanced level where our stress response is maintained by our mindful behavior. And this conscious behavior is sustained by the knowledge of epigenetics in behavior and our mental health, epigenetics in aging and age-associated diseases, and epigenetics and stress.

“What a journey!” Alice would have exclaimed...



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Associate Professor of Molecular Biology. Her current work investigates the interplay between DNA and the environment during normal development, aging and age-associated diseases. As a specialist in Molecular Biology, Genetics, and Epigenetics, Milena believes that in modern biomedicine we can now very clearly distinguish between the time “before” and “after” the project “The Human Genome.” The time “after” not only marks the beginning of the new millennium but also highlights the beginning of a turning point in modern medicine, where the handwriting of our genes and the specificity of our DNA are studied in the light of epigenetics. As a zealous communicator of science, Milena strives to present trends in modern science in accessible and interesting language.

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**Professor George Miloshev**, PhD, Head of the Laboratory of Molecular Genetics, Institute of Molecular Biology, Bulgarian Academy of Sciences. Professor Miloshev is a full professor of Molecular Genetics, and head of the laboratory. His main interests are in the field of chromatin, with special emphasis on the interplay between the environment and chromatin structure and dynamics. His scientific interests and research efforts are aimed at gaining deeper understanding of general cellular mechanisms, specifically about epigenetic phenomena. The intention of his work is to acquire information for practical use in medicine, criminology, and ecology. The areas of his research include epigenetic mechanisms, nuclear organization, and chromatin structure and dynamics, especially at higher order levels of organization.

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## REFERENCES

- Ali Khan, M., Kedhari Sundaram, M., Hamza, A., Quraishi, U., Gunasekera, D., Ramesh, L., . . . Hussain, A. (2015).** Sulforaphane Reverses the Expression of Various Tumor Suppressor Genes by Targeting DNMT3B and HDAC1 in Human Cervical Cancer Cells. *Evid Based Complement Alternat Med*, 2015, 412149. doi:10.1155/2015/412149
- Allis, C. D., Jenuwein, T., & Reinberg, D. (2007).** *Epigenetics*. Cold Spring Harbor Laboratory Press
- Asadollahi, R., Hyde, C. A., & Zhong, X. Y. (2010).** Epigenetics of Ovarian Cancer: from the Lab to the Clinic. *Gynecol Oncol*, 118(1), 81-87. doi:10.1016/j.ygyno.2010.03.015
- Bollati, V., & Baccarelli, A. (2010).** Environmental Epigenetics. *Heredity (Edinb)*, 105(1), 105-112. doi:10.1038/hdy.2010.2
- Burgers, W. A., Fuks, F., & Kouzarides, T. (2002).** DNA Methyltransferases Get Connected to Chromatin. *Trends Genet*, 18(6), 275-277. doi:10.1016/s0168-9525(02)02667-7
- Castro, R., Rivera, I., Struys, E. A., Jansen, E. E., Ravasco, P., Camilo, M. E., . . . Tavares de Almeida, I. (2003).** Increased Homocysteine and S-Adenosylhomocysteine Concentrations and DNA Hypomethylation in Vascular Disease. *Clin Chem*, 49(8), 1292-1296. doi:10.1373/49.8.1292
- Chanda, S., Dasgupta, U. B., Guhamazumder, D., Gupta, M., Chaudhuri, U., Lahiri, S., . . . Chatterjee, D. (2006).** DNA Hypermethylation of Promoter of Gene p53 and p16 in Arsenic-Exposed People with and without Malignancy. *Toxicol Sci*, 89(2), 431-437. doi:10.1093/toxsci/kfj030

- Dhanasekaran, K., Arif, M., Kundu, T. K. (2012).** Cancer: An Epigenetic Landscape. In: T. K. Kundu (Ed.), *Epigenetics: Development and Disease* (Vol. 61): Springer Netherlands
- Dominguez-Salas, P., Moore, S. E., Baker, M. S., Bergen, A. W., Cox, S. E., Dyer, R. A., . . . Hennig, B. J. (2014).** Maternal Nutrition at Conception Modulates DNA Methylation of Human Metastable Epialleles. *Nat Commun*, 5, 3746. doi:10.1038/ncomms4746
- Feinberg, A. P., & Tycko, B. (2004).** The History of Cancer Epigenetics. *Nat Rev Cancer*, 4(2), 143-153. doi:10.1038/nrc1279
- Felson, D. T., Lawrence, R. C., Dieppe, P. A., Hirsch, R., Helmick, C. G., Jordan, J. M., . . . Fries, J. F. (2000).** Osteoarthritis: New Insights. Part 1: The Disease and its Risk Factors. *Ann Intern Med*, 133(8), 635-646. doi:10.7326/0003-4819-133-8-200010170-00016
- Fetita, L. S., Sobngwi, E., Serradas, P., Calvo, F., & Gautier, J. F. (2006).** Consequences of Fetal Exposure to Maternal Diabetes in Offspring. *J Clin Endocrinol Metab*, 91(10), 3718-3724. doi:10.1210/jc.2006-0624
- Fraga, M. F., Agrelo, R., & Esteller, M. (2007).** Cross-Talk between Aging and Cancer. *Ann N Y Acad Sci*, 1100(1), 60-74. doi:10.1196/annals.1395.005
- Fraga, M. F., Agrelo, R., & Esteller, M. (2007).** Cross-Talk between Aging and Cancer: the Epigenetic Language. *Ann N Y Acad Sci*, 1100, 60-74. doi:10.1196/annals.1395.005
- Fraga, M. F., Ballestar, E., Paz, M. F., Ropero, S., Setien, F., Ballestar, M. L., . . . Esteller, M. (2005).** Epigenetic Differences Arise during the Lifetime of Monozygotic Twins. *Proc Natl Acad Sci U S A*, 102(30), 10604-10609. doi:10.1073/pnas.0500398102
- Fraga, M. F., Ballestar, E., Villar-Garea, A., Boix-Chornet, M., Espada, J., Schotta, G., . . . Esteller, M. (2005).** Loss of Acetylation at Lys16 and Trimethylation at Lys20 of Histone H4 is a Common Hallmark of Human Cancer. *Nat Genet*, 37(4), 391-400. doi:10.1038/ng1531
- Fuso, A., Nicolia, V., Cavallaro, R. A., Ricceri, L., D'Anselmi, F., Coluccia, P., . . . Scarpa, S. (2008).** B-Vitamin Deprivation Induces Hyperhomocysteinemia and Brain S-Adenosylhomocysteine, Depletes Brain S-Adenosylmethionine, and Enhances PS1 and BACE Expression and Amyloid- $\beta$  Deposition in Mice. *Mol Cell Neurosci*, 37(4), 731-746. doi:10.1016/j.mcn.2007.12.018
- Fuso, A., Seminara, L., Cavallaro, R. A., D'Anselmi, F., & Scarpa, S. (2005).** S-Adenosylmethionine/Homocysteine Cycle Alterations Modify DNA Methylation Status with Consequent Deregulation of PS1 and BACE and Beta-Amyloid Production. *Mol Cell Neurosci*, 28(1), 195-204. doi:10.1016/j.mcn.2004.09.007
- Georgieva, M., Staneva, D., & Miloshev, G. (2016).** Epigenetic Significance of Chromatin Organization During Cellular Aging and Organismal Lifespan. In: D. Hollar (Ed.), *Epigenetics, the Environment, and Children's Health across Lifespans* (pp. 21-66). Cham: Springer International Publishing.
- Giles, W. H., Kittner, S. J., Anda, R. F., Croft, J. B., & Casper, M. L. (1995).** Serum Folate and Risk for Ischemic Stroke. First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Stroke*, 26(7), 1166-1170
- Gravina, S., & Vijg, J. (2010).** Epigenetic Factors in Aging and Longevity. *Pflugers Arch*, 459(2), 247-258. doi:10.1007/s00424-009-0730-7
- Heyn, H., Moran, S., & Esteller, M. (2013).** Aberrant DNA Methylation Profiles in the Premature Aging Disorders Hutchinson-Gilford Progeria and Werner Syndrome. *Epigenetics*, 8(1), 28-33. doi:10.4161/epi.23366
- Jacobs, S. A., Fischle, W., & Khorasanizadeh, S. (2003).** Assays for the Determination of Structure and Dynamics of the Interaction of the Chromodomain with Histone Peptides. In: *Methods in Enzymology* (Vol. 376, pp. 131-148): Academic Press
- Khan, M. A., Hussain, A., Sundaram, M. K., Alalami, U., Gunasekera, D., Ramesh, L., . . . Quraishi, U. (2015).** (-)-Epigallocatechin-3-Gallate Reverses the Expression of Various Tumor-Suppressor Genes by Inhibiting DNA Methyltransferases and Histone Deacetylases in Human Cervical Cancer Cells. *Oncol Rep*, 33(4), 1976-1984. doi:10.3892/or.2015.3802
- Kucharski, R., Maleszka, J., Foret, S., & Maleszka, R. (2008).** Nutritional Control of Reproductive Status in Honeybees via DNA Methylation. *Science*, 319(5871), 1827-1830. doi:10.1126/science.1153069
- Kumsta, R. (2019).** The Role of Epigenetics for Understanding Mental Health Difficulties and its Implications for Psychotherapy Research. *Psychol Psychother*, 92(2), 190-207. doi:10.1111/papt.12227
- Kurdistani, S. K. (2011).** Histone Modifications in Cancer Biology and Prognosis. *Prog Drug Res*, 67, 91-106
- Lester, B. M., Tronick, E., Nestler, E., Abel, T., Kosofsky, B., Kuzawa, C. W., . . . Wood, M. A. (2011).** Behavioral Epigenetics. *Ann N Y Acad Sci*, 1226, 14-33. doi:10.1111/j.1749-6632.2011.06037.x
- Littau, V. C., Burdick, C. J., Allfrey, V. G., & Mirsky, S. A. (1965).** The Role of Histones in the Maintenance of Chromatin Structure. *Proc Natl Acad Sci U S A*, 54(4), 1204-1212
- Marsit, C. J. (2015).** Influence of Environmental Exposure on Human Epigenetic Regulation. *J Exp Biol*, 218(Pt 1), 71-79. doi:10.1242/jeb.106971
- Metrustry, S. J., Karhunen, V., Edwards, M. H., Menni, C., Geisendorfer, T., Huber, A., . . . Valdes, A. M. (2018).** Metabolomic Signatures of Low Birthweight: Pathways to Insulin Resistance and Oxidative Stress. *PLoS One*, 13(3), e0194316. doi:10.1371/journal.pone.0194316
- Newberne, P. M. (1986).** Lipotropic Factors and Oncogenesis. *Adv Exp Med Biol*, 206, 223-251. doi:10.1007/978-1-4613-1835-4\_18
- Nicoglou, A., & Merlin, F. (2017).** Epigenetics: A Way to Bridge the Gap between Biological Fields. *Stud Hist Philos Biol Biomed Sci*,

66, 73–82. doi:10.1016/j.shpsc.2017.10.002

**Obeid, R., Schadt, A., Dillmann, U., Kostopoulos, P., Fassbender, K., & Herrmann, W. (2009).** Methylation Status and Neurodegenerative Markers in Parkinson Disease. *Clin Chem*, 55(10), 1852–1860. doi:10.1373/clinchem.2009.125021

**Orphanides, G., & Reinberg, D. (2002).** A Unified Theory of Gene Expression. *Cell*, 108(4), 439–451. doi:10.1016/s0092-8674(02)00655-4

**Pallister, T., Spector, T. D., & Menni, C. (2014).** Twin Studies Advance the Understanding of Gene–Environment Interplay in Human Nutrigenomics. *Nutr Res Rev*, 27(2), 242–251. doi:10.1017/s095442241400016x

**Philibert, R. A., Beach, S. R., & Brody, G. H. (2014).** The DNA Methylation Signature of Smoking: an Archetype for the Identification of Biomarkers for Behavioral Illness. *Nebr Symp Motiv*, 61, 109–127. doi:10.1007/978-1-4939-0653-6\_6

**Pilsner, J. R., Liu, X., Ahsan, H., Ilievski, V., Slavkovich, V., Levy, D., . . . Gamble, M. V. (2007).** Genomic Methylation of Peripheral Blood Leukocyte DNA: Influences of Arsenic and Folate in Bangladeshi Adults. *Am J Clin Nutr*, 86(4), 1179–1186. doi:10.1093/ajcn/86.4.1179

**Pogribny, I. P., Tryndyak, V. P., Muskhelishvili, L., Rusyn, I., & Ross, S. A. (2007).** Methyl Deficiency, Alterations in Global Histone Modifications, and Carcinogenesis. *J Nutr*, 137(1 Suppl), 216s–222s. doi:10.1093/jn/137.1.216S

**Ropero, S., & Esteller, M. (2007).** The Role of Histone Deacetylases (HDACs) in Human Cancer. *Mol Oncol*, 1(1), 19–25. doi:10.1016/j.molonc.2007.01.001

**Rusconi, F., & Battaglioli, E. (2018).** Acute Stress-Induced Epigenetic Modulations and their Potential Protective Role toward Depression. *Front Mol Neurosci*, 11, 184. doi:10.3389/fnmol.2018.00184

**Rusiecki, J. A., Baccarelli, A., Bollati, V., Tarantini, L., Moore, L. E., & Bonfeld-Jorgensen, E. C. (2008).** Global DNA Hypomethylation is Associated with High Serum-Persistent Organic Pollutants in Greenlandic Inuit. *Environ Health Perspect*, 116(11), 1547–1552. doi:10.1289/ehp.11338

**Sapienza, C., & Issa, J. P. (2016).** Diet, Nutrition, and Cancer Epigenetics. *Annu Rev Nutr*, 36, 665–681. doi:10.1146/annurev-nutr-121415-112634

**Starnawska, A., Tan, Q., Soerensen, M., McGue, M., Mors, O., & Børghlum, A. D. (2019).** Epigenome-Wide Association Study of Depression Symptomatology in Elderly Monozygotic Twins. 9(1), 214. doi:10.1038/s41398-019-0548-9

**Taby, R., & Issa, J. P. (2010).** Cancer Epigenetics. *CA Cancer J Clin*, 60(6), 376–392. doi:10.3322/caac.20085

**Tarantini, L., Bonzini, M., Apostoli, P., Pegoraro, V., Bollati, V., Marinelli, B., . . . Baccarelli, A. (2009).** Effects of Particulate Matter on Genomic DNA Methylation Content and iNOS Promoter Methylation. *Environ Health Perspect*, 117(2), 217–222. doi:10.1289/ehp.11898

**Turner, B. M. (2001).** Higher-Order Chromatin Structures and Nuclear Organization. In: *Chromatin and Gene Regulation* (pp. 75–100): Blackwell Science Ltd.

**Waddington, C. H. (1963).** Ultrastructure Aspects of Cellular Differentiation. *Symp Soc Exp Biol*, 17, 85–97

**Waddington, C. H. (2012).** The Epigenotype. 1942. *Int J Epidemiol*, 41(1), 10–13. doi:10.1093/ije/dyr184

**Waterland, R. A., Kellermayer, R., Laritsky, E., Rayco-Solon, P., Harris, R. A., Travisano, M., . . . Prentice, A. M. (2010).** Season of Conception in Rural Gambia Affects DNA Methylation at Putative Human Metastable Epialleles. *PLoS Genet*, 6(12), e1001252–e1001252. doi:10.1371/journal.pgen.1001252

**Wolff, G. L., Kodell, R. L., Moore, S. R., & Cooney, C. A. (1998).** Maternal Epigenetics and Methyl Supplements Affect Agouti Gene Expression in Avy/a Mice. *FASEB J*, 12(11), 949–957

**Wolffe, A. P. (1998).** Epigenetics. Introduction. *Novartis Found Symp*, 214, 1–5

**Wolfram, S. (2007).** Effects of Green Tea and EGCG on Cardiovascular and Metabolic Health. *J Am Coll Nutr*, 26(4), 373s–388s. doi:10.1080/07315724.2007.10719626

**Yang, X. J., & Seto, E. (2007).** HATs and HDACs: from Structure, Function and Regulation to Novel Strategies for Therapy and Prevention. *Oncogene*, 26(37), 5310–5318. doi:10.1038/sj.onc.1210599

**Youn, H. D. (2017).** Methylation and Demethylation of DNA and Histones in Chromatin: the most Complicated Epigenetic Marker. *Exp Mol Med*, 49(4), e321. doi:10.1038/emm.2017.38

**Young, S. (2014).** Healthy Behavior Change in Practical Settings. *Perm J*, 18(4), 89–92. doi:10.7812/tpp/14-018

**Zeisel, S. H., Mar, M. H., Howe, J. C., & Holden, J. M. (2003).** Concentrations of Choline-Containing Compounds and Betaine in Common Foods. *J Nutr*, 133(5), 1302–1307. doi:10.1093/jn/133.5.1302

**Zhao, Y., & Garcia, B. A. (2015).** Comprehensive Catalog of Currently Documented Histone Modifications. *Cold Spring Harb Perspect Biol*, 7(9), a025064. doi:10.1101/cshperspect.a025064