DRUGS & BEYOND
JOURNAL

# EPIGENETICS

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*June 2023 - Issue 8*

# Letter to the community.

Dear HPPS community,

Welcome to the Eighth issue of HPPS journal!

This issue's topic is epigenetics, in which we will provide you with interesting facts and recent research about this innovative subject. Like always, an introduction to the subject is added, this will give you the basic knowledge needed for understanding the more advanced articles. These are about reversing epigenetic changes, epigenetics in health and disease, nutrition during pregnancy, epigenetics and trauma, environmental factors and its influence on epigenetics. Besides that, interviews with experts, PhD student Ifigeneia Thomopoulou, and Dr. Hanneke Vlaming are included where we can see how it is to be a researcher in the field of epigenetics. If you are more interested, at the end of our journal you can find more recommended readings to dive deeper into the topic of epigenetics.

As a fun closing of our new issue we added a journal journey quiz, this time it's in the format of a crossword puzzle. We hope you are all as excited as we are about this subject and that you will learn a lot of new things. Enjoy reading and until next time!

Rody van der Veer,

**On behalf of the HPPS journal team: Emilija Radonić, Nienke van der Plaats, Sofieke Rot, Kristian Kissyov, Lara Cerezin, Nikola Todorov**

**Special thanks to our supervisor Gert Folkerts for reviewing issue 8.**

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## EPIGENETICS



## EXTRAS

# Introduction to Epigenetics

*Lara Cerezin & Nikola Todorov*

Epigenetics refers to the study of how one's behavior and environment can cause changes in how their genes work. While genetic changes can alter which protein is made, epigenetic changes affect gene expression to turn genes "on" and "off." Contrary to genetic alterations, epigenetic changes do not alter the DNA sequence but are heritable and reversible changes in gene function. Epigenetic modifications control fundamental, but distinct biological processes like malignant transformation, cell differentiation, cell division, and aging.

Epigenetic changes can be induced by a variety of factors, including diet, stress, and exposure to environmental toxins. Stress is an especially prominent environmental cue that exerts changes in the epigenome and also phenotypic modifications. For example, studies have shown that the children of mothers who were exposed to famine during pregnancy are more likely to have certain epigenetic modifications that affect their metabolism and cardiovascular health (1). Similarly, exposure to chemicals such as bisphenol A (BPA) has been shown to alter DNA methylation patterns and gene expression in a way that may increase the risk of obesity, diabetes, and other health problems (2).
DNA wraps around proteins called histones. Proteins that read genes can't access DNA easily when histones are tightly packed together, so they turn the genes off. A loosely packed histone exposes more DNA, so proteins that read it are able to access it, thus activating the gene. Chemical groups can be added or removed from histones to make the histones more tightly or loosely packed, influencing the gene expression. (1) This happens because histone modifications alter the structure of chromatin, which in turn leads to changes in transcription. These epigenetic events are usually studied using high-throughput sequencing chromatin immunoprecipitation (ChIP-seq) assays (3).

The alterations in gene expression due to environmental factors are mainly influenced by epigenetic changes. Such changes mainly impact DNA methylation, non-coding RNA and histone modification with the latter including various modifications such as phosphorylation, ADP ribosylation, sumoylation, acetylation and methylation. Epigenetic processes, including DNA methylation and histone modification,

are thought to influence gene expression mainly at the level of transcription. However, other steps in the process, such as splicing and translation, may also be regulated epigenetically. (3) DNA methylation, the addition of a methyl group to the DNA molecule, is the most extensively studied epigenetic modification. Typically, this group is added to specific places on the DNA, namely the 5-position of the cytosine ring in CpG dinucleotides, where it blocks the proteins that attach to DNA to “read” the gene. The most popular techniques used for detection of DNA methylation include bisulfite conversion-based methods, restriction enzyme-based approaches, and affinity enrichment-based assays. This chemical group can be removed through a process called demethylation, reversing the epigenetic process. Typically, methylation turns genes “off” and demethylation turns genes “on” (4).
Other important epigenetic codes implicated in physiological and pathological processes are non-coding RNAs (ncRNAs). Coding RNA is used to make functional proteins, while non-coding RNA helps control gene expression by attaching to coding RNA, along with certain proteins, to break down the coding RNA so that it cannot be used to make proteins. Non-coding RNA may also recruit proteins to modify histones to turn genes “on” or “off” (3).

Before you are born, epigenetic changes begin. Your cells all have the same genes, but act differently. During your growth and development, epigenetics determines what function cells will perform, such as a heart cell, liver cell or nerve cell. Epigenetics change throughout your life. At birth, your epigenetics are different from that during childhood or adulthood. For example, researchers measured DNA methylation in newborns, 26-year-olds, and 103-year-olds, and found that methylation levels decreased as people aged. The results indicated that the level of DNA methylation in the body decreases with age. A newborn had the highest DNA methylation, whereas the 103-year-old had the lowest DNA methylation, which correlates to lower transcription (1).

Are epigenetic changes reversible? Not all epigenetic changes are permanent, meaning that sometimes, as a result of changes in behavior or environment, epigenetic changes can be added or removed. For instance, in smoking, at certain parts of the aryl hydrocarbon receptor repressor (AHRR) gene, which might have a function of a tumor suppressor, smokers tend to have less DNA methylation than non-smokers. This difference is larger for heavy smokers and long-term

smokers. After quitting smoking, former smokers can once again begin to exhibit increased DNA methylation at this gene. Eventually, they can reach levels similar to those of non-smokers. (1)

In summary, epigenetics is a rapidly growing field that has the potential to provide important insights into how our environment and lifestyle choices can influence our health and well-being. By understanding how these epigenetic mechanisms work, we may be able to develop new strategies for preventing and treating diseases in the future.


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# Reversing Epigenetic Changes

*Nikola Todorov*

Introduction

Epigenetic changes are often linked to aging, thus also to many types of diseases that humans are more prone to later in life. Reversing these changes is a challenge that researchers in the medical sphere are trying to explore further. Solutions for the case are sought in the context of alleviating disease states, slowing down the biological aging of individuals, and improving public health.

Advanced age is the most significant risk factor for the deterioration of mental and physical function and the development of a number of non-communicable diseases such as cancer, neurodegeneration, type 2 diabetes, and cardiovascular disease (1). These health impairments put a large strain on our economy. If aging could be delayed in a way that ensures that everyone gets an extra 2.2 healthy years, it could save 7 trillion dollars over fifty years (1). This approach, based on extending a person's healthy life span is much broader than disease-specific work and thus this is a much better investment (1). Thus, if ways through which we can extend health span even modestly can be found, benefits for public health and healthcare economics will be considerable (1).

DNA Methylation & the DNAmAge Clock

One of the mechanisms through which epigenetics affect human health is DNA methylation. DNA methylation refers to the addition of a methyl group to cytosine residues at specific places on a human chromosome (e.g. CpG islands, shelf/shore, exons, open sea) (1). Methylation is currently the best-studied mechanism which plays a role in the control of gene expression (1). It has also shown the biggest therapeutic potential. As DNA methylation is a unique genetic marker, it can be readily and cheaply mapped from tissue samples of patients (1). Consequently, researchers hypothesize that aging itself is based on epigenetic changes (among which also methylation changes) over time (1). Methylation levels at a few thousand sites within the human genome are tightly correlated with age (1). Methylation patterns currently constitute the best biochemical markers of an individual's age (1).

The current best-studied methylation-based clock is the multi-tissue DNA methylation age (DNAmAge) clock (1). Developed by Horvath, the DNAmAge clock is used to biologically predict the causes of mortality and multiple morbidities with better accuracy than just chronological age (1). All methylation clocks (including the DNAmAge one) are based on systematic methylation changes occurring with age (1). The DNAmAge clock provides a specific statistic - around 60% of cytosine residues lose methylation, and 40% of the residues gain methylation with advancing age (1). A pattern of systematic methylation changes can be observed, where the promoter regions of tumor suppressor genes are hypermethylated, leading to their expression being inhibited, while the inflammatory cytokines are hypomethylated, promoting their expression (1). Saliva is a viable source of high-quality DNA as it contains both white blood cells and buccal cells, making it a suitable tissue type for DNAmAge clock assessment (1).

The Effect of Diet on Epigenetics

The main ways through which epigenetic changes could be reversed studied so far include a balanced and nutrient-rich diet, regular exercise, reduction of stress through allocation of relaxation time and proper sleep, and the use of supplements.

A number of associations between diet and the DNAmAge clock have been established. Research has shown that individuals who consume a diet consisting of lean meat, fish, and plant-based foods experience a slight, but still significant decrease in DNAmAge (as measured by blood carotenoids) (1). For changes of a greater magnitude, a more specific and targeted dietary approach is likely required (1). In the dietary intervention mentioned above, the focus was on a plant-centered diet that included high levels of nutrients serving as substrates or cofactors in methylation biosynthetic pathways (such as folate and betaine), cofactors and modulators of ten-eleven translocation (TET) demethylases (such as alpha-ketoglutarate, vitamin C, and vitamin A), and polyphenolic modulators of DNA methyltransferases (such as curcumin, epigallocatechin gallate, rosmarinic acid, quercetin, and luteolin) (1). In addition to the plant-centered components, the aforementioned dietary intervention also incorporated limited intake of nutrient-dense animal proteins (such as liver and egg) (1). Carbohydrates were restricted, and mild intermittent fasting was implemented to lower glycemic cycling. Furthermore, the diet was supplemented daily with fruit and vegetable powder (1).

The Effect of Exercise on Epigenetics

Exercise is widely recognized for its extensive health benefits and has been demonstrated to increase mean lifespan in animal models (1). In human, in a study that involved 500 women regular practice of tai chi was found to be associated with a deceleration of age-related DNA methylation losses (2). Another study, involving 647 women, revealed that a lifetime of regular exercise was associated with a similar outcome (3). According to a systematic review of human studies, engaging in regular daily physical activity is linked to lower blood levels of homocysteine, with elevated homocysteine levels indicating insufficient methylation capacity (4). It has been suggested that excessive exercise may accelerate methylation aging, but this risk appears to be limited to elite, competitive athletes, based on available observations (1).

To alleviate stress, individuals were prescribed twice-daily breathing exercises that induce the Relaxation Response, a state of deep physical relaxation that prompts the body to release chemicals, slowing down breathing and heart rate (1). A recent study showed that practicing relaxation techniques twice a day for 20 minutes each time over a period of 60 days, designed to induce the Relaxation Response, led to a significant reduction in DNAmAge (1).

The Effect of Stress on Epigenetics

Approximately one-fourth of the DNAmAge CpG sites (85 out of 353) are situated in glucocorticoid response elements, which suggests a probable association between stress and accelerated aging (1). Research has demonstrated that the cumulative impact of lifetime stress is linked to accelerated aging of the methylome (1). Studies have reported that dexamethasone, a synthetic glucocorticoid agonist, can accelerate the DNAmAge clock and bring about associated transcriptional alterations (1). The genes regulated by dexamethasone were found to have a higher association with aging-related conditions, such as coronary artery disease, arteriosclerosis, and leukemia (1). Further studies have demonstrated that PTSD (post-traumatic stress disorder) can accelerate methylation aging, while greater infant distress, such as a lack of caregiver contact, is linked to a less developed and younger epigenetic age (1).

The Effect of Sleep on Epigenetics

Although seven hours of sleep per night is generally considered to be healthy, the limited available data on accelerated aging has only focused on the extremes of sleep deprivation (1). Research has shown that sleep deprivation can have a transient effect on genome-wide methylation patterns in blood, but it is not clear how this effect contributes to accelerated aging (1). Insomnia has been associated with acceleration of the DNAmAge clock in a sample of 2078 women (5). A small study of 12 female college students found an association between poor sleep quality and fewer hours of sleep with age acceleration (5).

Conclusion

In summary, epigenetic changes often drive the aging and development of diseases in people as they get older. Some general lifestyle improvements have already proven to have a positive effect in terms of avoiding harmful epigenetic modifications. Finding a concrete, scientific-based way to reverse epigenetic changes that have already occurred in some, or even to stop them from happening altogether in others, has the potential to significantly improve the health of the general population and decrease the occurrence of many debilitating diseases.


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# Epigenetics and Health

*Lara Cerezin & Christian Kissyov*

Environmental epigenetics is defined by the ability of the environmental factor to influence the spatial conformation of chromatin and thus influence the regulation of genes. Environmental factors might include the effects of behavior, nutrients, and pollutants, which can all influence human health. Therefore, with better understanding of the importance of epigenetics to human health, we could use it to our own advantage and exploit its benefits.

Nutritional Epigenetics and health

The relationship between nutrition and health has long been studied (1). For instance, the Dutch famine, hunger winter, of 1944-1945 was used as a study to examine the effects of starvation to development of the fetus during pregnancy. This resulted in smaller-than-usual offspring indicating that the fetus epigenetically adapts to the low amounts of nutrients. This is due to long exposure to famine being associated with a lower degree of methylation of the gene IGF2 which is responsible for insulin metabolism (2). The IGF2 gene is an insulin-like growth factor II which is maternally imprinted (inherited from the mother). Its imprinting is maintained through the methylation of the DMR region (2). Hypomethylation of this region thus leads to silencing of this gene (3). Although the exact relationship between famine and the lower degree of methylation of the IGF2 gene is still poorly understood, it is thought to be epigenetic in nature. Whatever the reason might be, this indicates that lower food supply directly influences the regulation of genes responsible for the conversion of food into energy that the body can use for its various functions. That is a product of a change in insulin regulation. Moreover, it has been demonstrated that nutrition is capable of inducing long-term changes in DNA methylation by directly inhibiting epigenetic enzymes like DNA Methyltransferases (DNMTs), Histone Deacetylases (HDACs), or Histone Acetyltransferases (HAT), which then alter the expression of genes critical for our complete well-being and longevity (2). Nutrients and bioactive food components can therefore reversibly alter the DNA methylation status, histone modifications, and chromatin remodeling, subsequently altering gene expression and having an impact on overall health. Therefore, by deciphering the epigenetic signatures triggered by bioactive food components we might pave the way for personalized nutritional interventions.

## Epigenetics and diseases

Epigenetic modulations include alteration in DNA methylation, histone modifications and modifications undertaken by non-coding RNA (4). Collectively, these three mechanisms together ascertain the regulation of gene expression. Epigenetic variations pertain to alterations in DNA methylation, changes made to histones and modifications undertaken by non-coding RNA. Due to their importance in regulating the expression of genes, epigenetics is firmly linked with many diseases. For example, some changes are notoriously associated with the increased risk of cancer development. Having a mutation in the *BRCA1* gene that prevents it from working properly makes you one more likely to get breast cancer and other cancers. Conversely, increased DNA methylation that results in decreased *BRCA1* gene expression increases the risk for breast cancer and other cancers.While certain genes of cancer cells stand out due to their atypical levels of DNA methylation, overall DNA methylation levels are lower in cancer cells compared with normal cells that maintain regular DNA methylation patterns. Hence, the application of epigenetics can be utilized for identifying the classification of cancer in an individual. By coupling this technique with additional screening procedures, it is plausible to leverage epigenetics as a valuable asset towards improving cancer diagnosis methods (4).

Histone modifications are another type of epigenetic modulations that include acetylation, methylation, and phosphorylation (4). Dysregulation of histone modifications has been implicated in a variety of diseases, including asthma, autoimmune disorders, and cancer. In asthma, for example, histone acetylation levels are altered in airway smooth muscle cells, leading to changes in gene expression that contribute to airway hyperresponsiveness. (5)

The third example of epigenetic modulation is performed by the non-coding RNA, such as microRNA and long non-coding RNA, again playing a crucial role in the genetic readout (4). The non-coding RNA, for example, are reported to be able to target mRNA molecules and inhibit their translation. The dysregulation of microRNA has been observed in a variety of diseases, including cancer, cardiovascular disease, and neurological disorders. (5)

## Conclusion

The health of each individual depends on the interaction of their genetics with many different environmental factors. Our lifestyle choices directly influence our own health via epigenetic mechanisms. The epigenetic marks can be passed on to the next generation but can also be reversed. Because of their reversible nature, epigenetic modifications are becoming an attractive target for therapeutic intervention. Many drugs such as DNA methyltransferases and histone deacetylase inhibitors, have been used for the treatment of cancer and many other diseases. Thus, by understanding the role and importance of epigenetics on our health, we can induce the necessary changes in our lifestyle that will decrease the risk of some vicious diseases and will increase our quality of life.


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# Nutrition, Pregnancy, and Epigenetics

*Rody van der Veer and Emilija Radonić*

Nutrition is a crucial part of health and development. Nutrition is related to improved infant, child and maternal health, stronger immune systems, safer pregnancy and childbirth, lower risk of non-communicable disease (diabetes, cardiovascular disease) and longevity. (1) In this review we will focus on nutrition during pregnancy and how nutrition has an effect on the epigenome of the offspring at birth.

Pregnancy is a vital time of growth and development during which maternal nutrition significantly influences the future health of both the mother and the baby. During pregnancy, the fetus experiences a critical period of plasticity. Epigenetics, specifically DNA methylation, plays an important role here (2). As nutrition has an impact on DNA methylation, then can maternal nutrition during pregnancy modify the offspring's epigenome at birth (2). Evidence from the study of Geraghty et al. shows that maternal nutrition does not largely influence global methylation patterns, particularly in nutrient-replete populations. (2)

The research of Geraghty et al, focuses on micronutrients and methyl donors such as folate and B vitamins. They found out these particular nutrients are known to impact DNA methylation due to their interaction with the one-carbon metabolism cycle. This cycle results in the formation of methyl groups that are required for the methylation of DNA. Folate feeds into this cycle and has been shown to alter the levels of DNA methylation in women of childbearing age. To date has found no association between folic acid intake during pregnancy and global methylation or long interspersed nucleotide element-1 (LINE-1) methylation status in the offspring. A decrease in the level of dietary folate has been found to decrease genomic DNA methylation levels. With respect to specific genes, folate intake during pregnancy has been shown to have an impact on the infant.

Other nutrients, including vitamins B12, B6, and B2, choline, and betaine, are required to provide the cofactors that are used to make the methyl groups (2). Maternal serum vitamin B12 was shown to be inversely correlated with offspring's global methylation status at birth. Another study found that early pregnancy intakes of methyl donors, including vitamins B12, B2, and B6, did not impact infants' global methylation status. However, they did find that intake of choline and betaine in early pregnancy was inversely associated with global cord blood methylation among male infants only. (3)

Last but not the least, the offspring's genetics cannot be observed only by the nutrition of the mother. In the study of Finer et al, maternal weight during pregnancy was also associated with altered methylation patterns in the child's DNA and later infant adiposity. Offspring in both underweight and overweight mothers were also reported to have altered DNA methylation patterns (4).

Recent epigenetic studies suggest an association between maternal nutrient intake during pregnancy and the epigenetic patterns of the offspring at birth. Methyl donor nutrients, such as folate, appear to affect the offspring's pattern of DNA methylation. Up until now, the studies can only be done clearly when examining gene-specific methylation levels rather than overall global methylation levels. There are a lot of unclear genetics questions left to be answered. The first years of life are a critical period of development, and advancements in this area of research could influence advice and guidelines regarding maternal nutrition during pregnancy and lactation. The potential in this research is that later on, the use of DNA methylation patterns at birth to predict health and growth of the child in later life, further epigenetic research is required.


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# Epigenetics & Trauma

*Nienke van der Plaats & Kristian Kissyov*

Some individuals are more susceptible to the effects of trauma and stress. Not so long ago, the reason for this varying susceptibility was mainly attributed to genetic factors and predisposition. However, new evidence highlights the importance of epigenetics processes in the biological response to trauma and a potentially new biomarker for stress-associated disorders.

## Epigenome

The epigenome comprises different modifications that regulate the expression of genes without interfering with the genetic sequence of DNA (1). This flexibility has biological importance since it enables the optimal adaptation to the various conditions within the environment. Every individual experiences the stress of a traumatic event at some point of their lives, and epigenetics changes have shown to be tightly associated with dealing with these events.

Trauma is caused by a combination of nature and nurture and epigenetics can change the way genes work. For instance, trauma has shown to alter DNA methylation patterns (1). An effect of DNA methylation is to modify or suppress the binding of transcription factors to regulatory sequences, resulting in changes to the expression of gene products (1). The time of the traumatic event in the life development of the person is also important for the final outcome, with early life showing to be a particularly sensitive period of biological vulnerability. Many studies have demonstrated that early-life trauma has an effect on the DNA-methylation in central tissue in the hippocampus- a brain region with direct involvement in stress signaling (1). One such study proved that the hippocampal NR3C1 methylation is increased in severe suicide victims with a history of childhood abuse (2). The NR3C1 gene is associated with the regulation of the hypothalamic-pituitary-adrenal (HPA) axis by modulating the availability of the stress hormone cortisol. Therefore, this increase in the hippocampal NR3C1 methylation is linked with trauma and many mental disorders such as major depression, post-traumatic stress disorder, anxiety, and personality disorders.

## Children of patients with post-traumatic stress disorder

It is remarkable that not only the Holocaust survivors, but also some of their children experienced some kind of trauma in their lives. Apparently,

this phenomenon is also present in some children of PTSD patients, like descendants of war veterans, refugees and many others. That population of people is more prone to stress and in them mental problems are also more common. The epigenetic changes the parents acquired during their life can possibly be passed, in the same way as genetic characteristics, to their children (3).

However, this is not completely confirmed in humans, only in mice and rats is evidence found for the inheritance of effects of physiological stress. In fact, a study was once done on mice that when they notice the odor of cherries, they directly receive an electric shock. The children and grandchildren of those mice also showed signs of anxiety when exposed to the odor, even though they had never "learned" the painful association (4). For humans it is more difficult to do research for this subject, because there may be many more factors involved in this process. Something we definitely know is that epigenetic marks can dispose one towards developing some behaviors, but the specific behavior depends on specific inputs the person gets in its own lifetime.

For the future, being able to reverse epigenetic changes could be a potentially great research project. After all, if we could reverse these changes, some people will experience fewer mental problems in their lives.


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# Influence of toxic factors on epigenetics

*Emilija Radonić & Nienke van der Plaats*

## Introduction

Genetic aspects of environment-related disease have been considered as one of the most important causes of disease. Vast majority of diseases are influenced by environmental and genetic factors, some are common and others are specific (1). Asthma, diabetes, and smoking are specific examples of these diseases, and will be further discussed in this article. Beyond the current knowledge, the present review briefly outlines some chief challenges and priorities for better understanding of this field.

## Asthma

Recently, there has been some research in the role of epigenetics in the complex gene-by-environment interactions that can lead to asthma. In vitro, there is some data indicating that DNA methylation of genes critical to T-helper cell differentiation may induce polarization toward or away from an allergic phenotype. For example, demethylation at the proximal promoter of the proallergic IL-4 gene and hypermethylation of sites in the counterregulatory IFN-y promoter, result in greater IL-4 production and Th2 differentiation, both probable causes of asthma (2).

However, that is not the only mechanism, cigarette smoke also modulates DNA methylation, demonstrated by differential fetal lung tissue and placental methylation in association with cigarette smoke exposure. Smoking can cause asthma and also makes the symptoms of asthma a lot worse (3).

## Diabetes

The prevalence of type 2 diabetes is increasing rapidly worldwide, partly due to the epidemic in obesity seen among most ethnic groups. Obesity can be influenced by epigenetics. For example, leptin expression in human adipocytes is regulated by the leptin promoter embedded within a CpG island. Normally, leptin makes you feel satiated after eating something. DNA methylation of the leptin promoter leads to a decrease in the expression of leptin, so even after eating a whole meal, there is less

feeling of satiety. However, this hypothesis is not yet entirely certain and more research needs to be done on the epigenetic regulation of leptin expression in adipocytes to explain its relationship with food intake (4).
In addition to type 2 diabetes, there is of course also the mostly hereditary variant, type 1 diabetes. In diabetes type 1 is dysfunction of the islet of Langerhans the cause of glucose intolerance. An increased promoter DNA methylation of the gene coding for the islets has been investigated in animal models. So, that could be a link between epigenetic silencing of the islet of Langerhans gene and type 1 diabetes.
Evidence shows that hyperglycemia (HG) can induce epigenetic changes to the chromatin structure through activation of signaling (5). Therefore, HG could impact the epigenetics of your genes. However, diabetes is a complex disease and other factors, such as dyslipidemia and nutrient status, can cooperate with HG to influence the epigenetic state of target cells in damaged tissues.

Smoking

Tobacco-smoking, causing many factors of cardiovascular disease, is partially determined by genetic background and is associated with altered epigenetic patterns (6). Genetic predisposition to nicotine dependence has been firmly established. In the study of Jennifer J. et al, the knockout mouse models were used and the importance of alpha5 nAChR subunits were highlighted in regulating nicotine intake, particularly those localized to the habenula-interpeduncular nucleus pathway (connection between dopaminergic striatum and the limbic forebrain, act as modulator of the cross talk between these brain regions) (6). Their challenge was to evaluate the effect of nicotine on brain activation as a function of certain genotypes using neuroimaging technologies, which may lead to novel smoking cessation therapies (6).

On the other hand, environmental factors, such as the availability of nicotine, play a role in each stage in the development of cardiovascular disease (3). The accessibility of a substance is relatively more important in the initiation of substance use (1). The development of substance dependence requires the initiation of substance use and the conversion from experimental use to established use before development of dependence. Many studies have indicated contribution to this process, then genetic factors would identify genetic factors that influence the transition from regular use to dependence (1). However, very few studies contributed to specific genetic contributions of illicit drug use, even though there is a strong correlation of genetic components involved in smoking (1).

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# Role of epigenetics in mammalian puberty onset

*Sofieke Rot*

Puberty is a process in which a mammal goes from childhood to adulthood via a series of developments and processes. Puberty is regulated by molecular and genetic underpinnings and initiated at the onset of the - previously absent - gonadotropin-releasing hormone (GnRH) secretion, together with the reactivation of the hypothalamic-pituitary-gonadal (HPG) axis (1). The sexual maturation will then begin to transition the person into an adolescent. While all go through puberty, the age can differ drastically between individuals, and sexes. Females are known to initiate going through puberty at an earlier age than males. While sex is an important factor, it is also of interest to explore the other causes of variation of puberty timing, as the timing is associated with later life outcomes.

It is found that children with early puberty are at risk for various prospects, such as short adult height, psychosocial difficulties and accelerated skeletal maturation to name a few (2). Altered timing can also affect the development of reproductive tract cancers later in life. Recent evidence suggests that a dual mechanism of epigenetic regulation affecting the transcriptional activity of neurons involved in stimulating gonadotropin-releasing hormone release plays a fundamental role in the timing of puberty (1). In this article we will dive deeper into this role of epigenetics in the onset of puberty.

One might argue that it is genetics, not epigenetics, that largely determines the start of puberty, but even in genetically identical twins, variation in pubertal timing is found, so this is not the only factor. As there is a complex gene network that is involved in regulation of pubertal timing and GnRH secretion, that consists of genes that can function as inhibitory, excitatory and permissive in this process, it becomes clear that the dynamic regulation and balance of these genes will onset puberty. This said, the (de)activation of genes in this network plays a big role in this process. The network changes over time,

as in puberty the GnRH excretion is supposed to be stimulated and before it is prohibited, thus phenotypic plasticity is vital in this network. This means that the transcription of certain regulatory genes is different at different times and thus can be influenced by epigenetically mediated interactions, regulating the pubertal timing and sometimes unexplained variability. The gene expression is changed over time via epigenetic changes, while the DNA stays the same. These epigenetic changes on pubertal timing can be influenced by environmental factors, such as general health, stress and nutrition.

Recent developments in epigenetic research have found that the reactivation of the HPG axis has underlying mechanisms of epigenetically mediated nature: controlling the neuroendocrine-related gene transcription (1). The most important finding is that the factors that were inhibiting the HPG axis neurons during childhood dormancy, were lifted through epigenetic mediation. This change partly mediates the activation of neuroendocrine components involved in the pubertal initiation. So, the next steps are to search for the exact epigenetic changes that regulate this.

There are multiple epigenetic control systems that regulate the mammalian gene expression. These two are the most important regulatory epigenetic systems yet found in mammalian puberty onset:
*DNA Methylation*, where the cytosine residues (5-mC) of DNA is methylated. This is the most common in cytosine guanine dinucleotides. This epigenetic change can lead to silencing of the gene and can be maternally or paternally inherited. It is often associated with lower levels of expression. This methylation can be maintained during replication via certain DNA methyltransferases. DNA demethylation can also occur, either passively - when in DNA replication it is not copied - or actively - through oxidation facilitated by enzymes. This is followed by full demethylation by thymine DNA glycosylase-mediated base excision and, ultimately the regeneration of the cytosine through DNA repair pathways.
*Histone modifications* is the second epigenetic system. Histone modifications are processes such as acetylation and methylation of histones. Histone modifications are one of the crucial processes of epigenetic regulation, as they can aid or obstruct the access to transcriptional start sites for transcriptional machinery. Therefore, they regulate gene expression during development and in response to environmental factors. Histone modifications can also be inherited through mitosis. Histone modifications can be found using chromatin

immunoprecipitation followed by high-through-put DNA sequencing (ChIP-Seq). Researchers found that the polycomb group repressive complex 2, a complex of chromatin-associated proteins, mediates epigenetic silencing of transcription via chromatin compaction and that the epigenetic regulation of this complex is connected to the regulation of the HPG-axis development in puberty (1).

Even though progress has been made in finding the reasons for fluctuation of pubertal onset in mammals through epigenetics, the field is still quite new. Therefore, further research in this area is needed to enhance our understanding of all factors that are involved in gene regulatory networks controlling the HPG-axis and that underlie the variation of pubertal timing observed. Finding these gene regulatory networks will also help understand how pubertal timing affects us later in life, as epigenetic changes can change systems for a long time or affect the regulation in a different way.


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**How would you introduce yourself?**

I am Hanneke Vlaming and I have recently joined Utrecht University as an assistant professor at the faculty of Sciences (department of Biology in the Institute of Biodynamics and Biocomplexity, division of Genome Biology and Genetics).

I studied at the VU University in Amsterdam, I obtained my BSc in Pharmaceutical Sciences and a MSc in Drug Discovery and Safety. There were many different tracks to choose from during my masters where I realized I liked “target finding”. This is basically molecular biology, from which I chose a course called Gene expression that I absolutely loved. After my first internship at the VU, I did a second internship in Barcelona that was in the epigenetics field; DNA methylation, gene expression changes, and some histone marks. Thereafter, I got a PhD position at the Netherlands Cancer Institute in Amsterdam where I worked on a particular histone modification and what was regulating it. I did research using yeast as a model organism, but also mice. For the postdoc, I moved to Boston, where I worked at Harvard Medical School for six years, studying transcription and how it is regulated. Then, I moved back to the Netherlands to start as an assistant professor. Now I am doing science, managing a team, teaching, supervising students; it was fun to make this step and be closer to my family again.

**How would you define epigenetics?**

If you ask different people, you would get different definitions of epigenetics. It was back in the forties that somebody first came up with the term epigenetics. It was really about how you go from gene to phenotype and whatever is in between. He was mainly interested in embryonic development. In the eighties, people started introducing this concept of changes that do not involve DNA. In early 2000, people got excited about histone modifications and DNA methylation and people started calling all of it epigenetics. I think it is a more informal use of the term, but the most common use in this field.

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**Why is epigenetics your topic of interest?**

During my masters I followed a course about epigenetics, where we studied not only the basics of the field but we also had guest lectures on more in depth topics. It fascinated me, and still does, but it is hard to see why exactly. It brings together a lot of different approaches and many information streams coming together at the chromatin.

**What project are you currently working on?**

When you want to transcribe the gene there is an enzyme complex called RNA polymerase II. If you need to transcribe a gene that is like 50kb long, it needs that full length without falling off. Otherwise you can never get your full messenger RNA, thus you cannot get your protein. At the same time there are a lot of bases in the genome that do not encode for proteins which the same RNA polymerase enzyme is also transcribing. This usually stops after a few hundred nucleotides, so what I am trying to understand is: 'How does the polymerase know that at protein coding genes it should keep going, otherwise you are not going to have your messenger RNA, but that at most non-coding regions it should stop very early?'.

**What are your days like as a scientist?**

Right now I spend a lot of time behind the computer, analyzing data from some experiments I did in Boston. Sometimes an experiment gets me data in a few weeks, and data analysis can take months. I am also thinking about a grant that I should apply for and what I should propose for it, to be able to do more science in the lab. Besides that, I am designing a new course in the biology bachelors, which includes planning lectures, assignments, and computer practicals for students.

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**Where is pharmacy/pharmaceutical sciences in epigenetics, is there any opportunity for pharmacists or researchers to work in the epigenetic field?**

There are quite a few molecules targeting different epigenetic enzymes, such as histone modifying enzymes, that are being studied in clinical trials. Sometimes researchers find that they are too toxic, because these processes at the chromatin are often critical to all cells. But, there are opportunities. For example, sometimes healthy cells have two proteins that share a similar function, and a cancer cell could be lacking one of them. In that scenario, the cancer cell is particularly sensitive to inhibiting the remaining protein, so it would be a great treatment option.

It is clear that there are alterations in the chromatin in many important diseases. I think a lot of research still needs to be done to find what to target that cures the disease without too many side effects. But then small molecules need to be found to modulate those targets, their efficacy and specificity needs to be tested, etc.

*Kwesi-Maliepaard EM, Aslam MA, Alemdehy MF, van den Brand T, McLean C, Vlaming H, et al. The histone methyltransferase DOT1L prevents antigen-independent differentiation and safeguards epigenetic identity of CD8+ T cells. Proceedings of the National Academy of Sciences. 2020 Aug 25;117(34):20706–16.*

**You helped in this article, can you explain the process of getting such a research started? What underlying steps do you undertake to accomplish this, and how long does it typically take?**

During my PhD I started working with mice where the DOT1 protein could be taken away. In the genome of these mice, the two DOT1L genes were changed in a way that you could delete the gene in a specific cell. I bred mice in which the DOT1L gene was deleted in the thymus. I used this to answer a specific question on whether DOT1L was important in cancer formation caused by some other gene deletion. However, as a control experiment I looked at thymuses that only lacked DOT1L, and I found that they did not have the same number of cells in a DOT1 knock-out versus wild type. So, something with T cells was happening. Other people continued this project and they wanted to characterize those cells. Characterisation of what type of T cells were present was done using flow cytometry, and they performed different assays to look at T cell function and memory. For this project it probably took

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around 4 years to get published. Now, base on the work done in this paper, there is a lot of research going on to see if modulating DOT1L is useful in immunotherapy.

**You are involved in quite a few research articles, what has been the most memorable one you have worked on? Or alternatively, what are you most proud of?**

Most impactful was the paper I have written in my postdoc. I developed the INSERT-seq methodology to test whether the transcribed sequence affects the elongation potential of RNA Polymerase II, and obtained new insights into the sequence elements that contribute. It was special for me, because it was my project from the very start, having the idea, setting up the experiment and then finishing the project.

**What do you expect to see in the future of Epigenetics?**

There's been a lot of technological development, so people can answer questions which could not be done for many years because of lack of technology. Single cell technology has been highly improved in the last couple of years. They got RNA expression from a single cell, so you can say which cell is expressing which gene and where certain histone modifications are. We are starting to link those data together and whether those things are correlated or not. Another big improvement over the last years is that we can do rapid degradation of proteins now, so we can look at effects after minutes rather than days after the loss of a protein. I think all these technological advances will help us answer cool new questions in the field.

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**Where do you see epigenetics in everyday life?**

A cool example of epigenetics is calico cats. Some back story: females have two X while males have only one, but in the end they still need to express the same level of the proteins that are encoded there. So there are some species, like humans and cats, where females just shut down one of the X chromosomes so in practice they only have the one they express from it. Which copy is shut down is decided randomly in individual cells during early development. So now about those calico cats: the coat color of the cat (black or orange) is encoded on the X chromosome. A female cat can have the black allele on one chromosome and the orange allele on the other chromosome, and through X inactivation patches of the coat will be either orange or black. This makes a tortoiseshell cat, or a calico cat if you add in some white patches too. So, when you see a calico cat, you know this has to be a female cat, male cats could never have both colors on their one X chromosome.

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**How would you introduce yourself?**

I am Ifigeneia Thomopoulou and I come from Greece. I've been living in the Netherlands for a bit less than 4 years. I have a Bachelor's in Biology with a specialization in molecular biology and biotechnology. After my bachelor's which I obtained in Greece at the University of Crete, I did my masters at Erasmus University in Rotterdam. The programme was called "molecular medicine". After I obtained my Master's I worked as a technician in a research lab for a year. Two months ago, I started my PhD at the University of Utrecht, so I'm at the very beginning. During my Master studies, I had some lectures in epigenetics and then I decided to do my Master's thesis in an epigenetic lab. I was very fascinated by epigenetics. I liked the subject, so I wanted to learn more about it. I think a PhD is the best option to do this because you do research on something that you like and to some extent you have the freedom to form your own project.

**How would you define epigenetics?**

The general approved definition is: "The study of heritable DNA modifications that alter DNA expression without changing the sequence." But it is also a very outdated definition. The idea is that in our body, all our cells have the same DNA, but some cells become muscle cells while others become nerve cells, skin cells etc. This happens, because in different cell types, different genes are expressed. So, it is not the DNA that differs between different cells types. There is another layer of information (the epigenetic information) which dictates the destiny of the cell. So, this extra layer of information hasn't been studied well enough yet. Whether a gene is expressed or not, depends on many factors. Even though the genetic information is the same in different cell types, for example some chemical modifications on the DNA can dictate which genes are turned on or off. You can think of these chemical modifications or epigenetic marks as tiny flags on the DNA.

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**Where is pharmacy/pharmaceutical sciences in the field of epigenetics?**

There is a collaboration between the field of epigenetics and immunology where scientists are developing the so-called 'epidrugs'. These are drugs or medicines that target epigenetic marks. Proteins bind to the DNA and either activate or suppress the expression of a gene. The presence or the absence of an epigenetic modification can affect whether these proteins can bind or not onto the DNA. Cancer patients have different epigenetic modifications compared to healthy individuals. When you give those drugs to a cancer patient you can restore normal cell function. I know that there is also a discussion about combining these epi-drugs with chemotherapy. This could potentially make the treatment more effective. So, this is more related to pharmacy and pharmaceutical sciences.

**What project are you currently working on?**

I'm doing fundamental research. As I said before, in different cell types, different genes are expressed. Different kinds of proteins need to be recruited at a specific place on the genome. After they bind on it, they can turn a gene "on" or "off". Some proteins can bind at specific locations on the genome only if there is a specific chemical modification. In my project, I want to identify which are these proteins that are attracted by these modifications and thus regulate gene expression. To investigate that, I use mouse embryonic stem cells.

**What are your days like?**

In the beginning of a PhD your days involve a lot of reading, because you need to know a lot about the topic, what is already known but is also not. You also need to invest some time to understand why you are going to do an experiment. What is the question that you want to answer? What is the most efficient way to answer it? You also need to understand what techniques you will use. I get a protocol, but if something goes wrong, I have to optimize it and figure out myself why the experiment didn't work. Recently, I have also started doing some initial experiments. In the meantime, I also follow some courses and seminars I find interesting. So far, I have followed a course in programming and I'm currently following a masterclass that is about how to present your research topic to the public. Additionally, I believe that connecting with other researchers is also very important. Sometimes you can apply their technique to your own research. It is also insightful to get a different point of view. Every Monday we have a meeting with all PhD students of our building and some of us present our projects and ask for input. We also have a weekly meeting with my research group where we discuss our projects and the problems we encounter. There is a lot of communication between the people in a lab. It is truly helpful to get feedback for your project.

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**What is the main difference between a thesis and a PhD?**

Personally, I did a research Masters so the things that I have to do on a daily basis are not very different compared to my Masters. However, now I have the full responsibility of my own project. During your Bachelor or Master studies usually, you have to report to your supervisor your progress and if you encounter problems she/he will try to solve it for you because she/he has a better knowledge. As a PhD student you learn how to become an expert in your field. Even if you have a supervisor you can form your own project and the emphasis is on the responsibility that you have on that project.

**Where does your PhD exactly take place?**

I work at the Science Park, at the Kruyt building. My research group belongs to the Faculty of Science. Specifically, we are part of the department of Biology, division of Genome Biology and Epigenetics. My lab has just moved from Switzerland to the Netherlands, so it is quite new at this place.

**What do you expect to see in the future of Epigenetics?**

The future of epigenetics is now. Last year I worked in a forensics research lab. In one of the projects there, some researchers were using epigenetic marks to find whether a person was a smoker or not. The field of epigenetics can be helpful in so many other fields in the future. It opens the door for a lot of new projects. Even people from totally different fields, like psychotherapists start to talk about epigenetics. If you just search online for “epigenetics and intergenerational trauma” you will be surprised by the amount of results that you will get. Food scientists can benefit from the fields of epigenetics and of course any kind of lab that works with any kind of disease. In general, I am very optimistic that epigenetics will give insights and will be able to help many other fields.

# *Recommended* readings & websites

***Fragile Nucleosome*** (youtube channel)
Virtual seminars about chromatin.

*The Epigenetics Revolution: How Modern Biology Is Rewriting Our Understanding of Genetics, Disease and Inheritance*
**Book by: Nessa Carey**
Introduction to epigenetics and its result on disease development in humans, animals and plants.

*Epigenetics in Human Disease*
**Book edited by: Trygve Tollefsbol**
Encompasses the role of epigenetics in various diseases, such as cancer, immune disorders, cardiovascular disease etc.

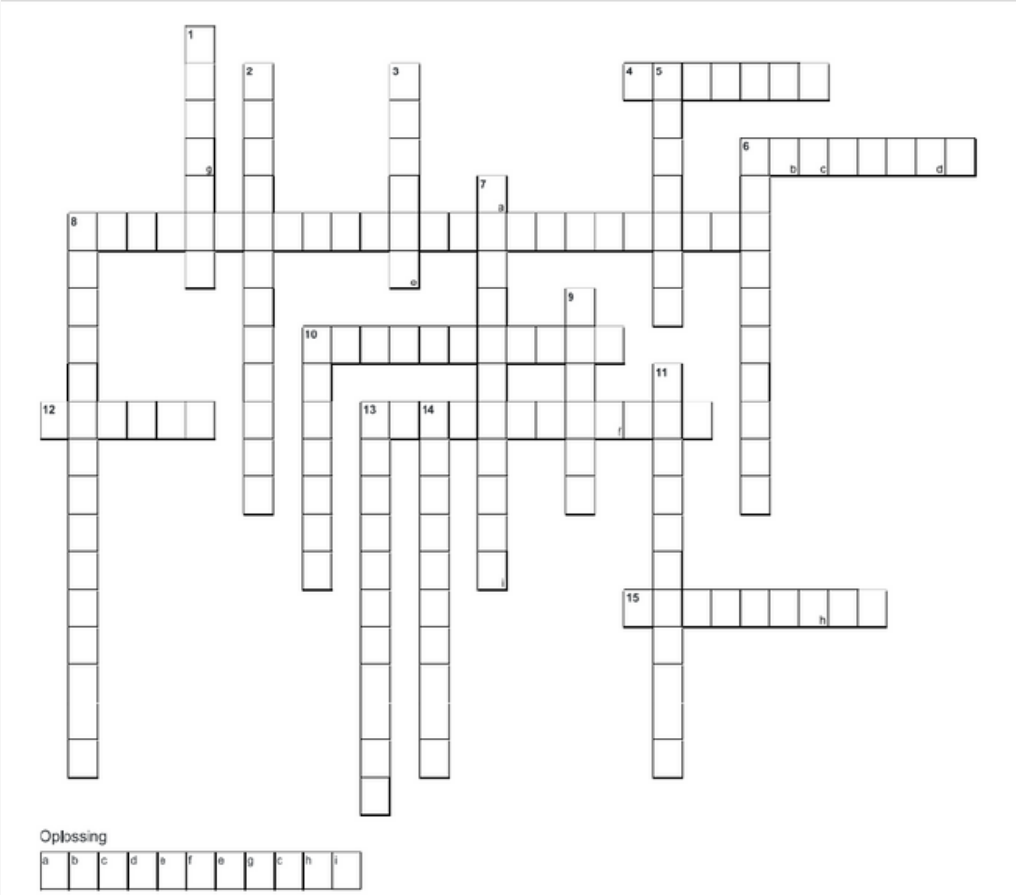
*Epigenetics: How Environment Shapes Our Genes*
**Book by: Richard C. Francis**
Introduction to epigenetics and examines changes in gene function influenced by the external environment.

**Scientific article**
Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, et al. Epigenetic differences arise during the lifetime of monozygotic twins. Proceedings of the National Academy of Sciences. 2005 Jul 11;102(30):10604–9.

University of Utah - Genetic Science Learning Center Website

# JOURNAL JORNEY

# CROSSWORD




## Horizontal

4 best-studies methylation-based clock
6 drugs or medicines working on epigenetics
8 connection dopaminergic striatum-linbic forebrain
10 ...research = why and how things happen
12 hormone which makes you satiated
13 period studied examining effects of starvation
15 kind of cat with cool example of epigenetics

## Vertical

1 the protein where DNA wraps around
2 immunologic cell involved with asthma and allergy
3 vitamin altering DNA-methylation
5 trauma is caused by a combination of nature and...
6 sensitive period of biological vulnerability
7 determination of the function of your cells
8 cause of silencing of the IGF2 gene
9 viable source of high-quality DNA
10 when was the first use of the term epigenetics
11 addition of a methyl group to the DNA
13 brain region involved in stress signaling
14 DNA/RNA playing a crucial role in genetic readout

# my notes