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Transgenerational inheritance: understanding the etiology of a disease

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Abstract

Observational results suggest that environment has a great impact on physiology but these phenomena cannot be explained by genetic mechanisms alone. The epigenetic studies broadens our knowledge about development and physiology. Currently, the topical issues are transgenerational effects which imply transmission through generations both genetic and phenotypic adaptive mechanisms. The accumulated data indicate that the influence of environmental factors (bad habits, stress, excessive or insufficient nutrition, microbiota and others) at early stages of development can contribute to the epigenetic transgenerational inheritance of phenotypic variability. Epigenetic processes can alter gene expression, which in turn can either increase vulnerability or contribute to the development of disease tolerance in future generations. Epigenetic biomarker signatures can be considered as a future diagnostic tool for assessing person's specific susceptibility to disease or exposure to environmental toxicants. The current review discusses the molecular genetic mechanisms of transgenerational inheritance and the influence of various risk factors.

Key words: epigenetics, epimutation, epigenetic transgenerational inheritance, generation, risk factors

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Трансгенерационное наследование: современные подходы к поиску причин заболеваний

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Резюме

Результаты большого количества наблюдений позволяют предполагать, что окружающая среда оказывает влияние на организм без вовлечения генетических механизмов. Изучение роли эпигенетики в основных процессах развития и физиологии значительно расширяет наше понимание биологии организма. В настоящее время одной из актуальных тем для изучения возможностей предотвращения развития заболеваний является исследование трансгенерационных эффектов — когда не только генетические, но и фенотипические адаптивные механизмы передаются через поколения. Накопленные данные свидетельствуют о том, что влияние факторов окружающей среды (вредные привычки, стресс, избыточное или недостаточное питание, кишечная микробиота и другие) в период раннего развития может способствовать эпигенетическому трансгенерационному наследованию фенотипической изменчивости. Эпигенетические процессы могут изменять экспрессию генов, что, в свою очередь, может или повысить восприимчивость, или способствовать развитию толерантности к заболеваниям в следующих поколениях. Эпигенетические биомаркерные сигнатуры могут быть использованы в будущем в качестве диагностического инструмента для оценки наличия у человека специфической восприимчивости к заболеваниям или воздействию токсикантов окружающей среды. В настоящем обзоре обсуждаются молекулярно-генетические механизмы трансгенерационного наследования и влияние различных факторов риска.

Ключевые слова: эпигенетика, эпимутация, эпигенетическое трансгенерационное наследование, поколение, факторы риска

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Introduction

Despite the fact that most of the inheritance laws have already been described, recent studies show that inheritance of phenotypic traits can also take place through nongenetic factors. Thus, it can be through epigenetic mechanisms which can manifest their effects across generations (transgenerational inheritance). Epigenetic processes are integral part of normal biology and are critical for the body to be able to respond to its environment with changes in gene expression and also allow stem cells to develop into a differentiated cell type [1].

The influence of environmental factors, such as toxicants, unhealthy diet or stress, can contribute to the epigenetic transgenerational inheritance of phenotypic variability that may promote development of diseases [2]. Epigenetic processes are critical for the body's response to the environment by changes in gene expression, which, in turn, can either increase susceptibility or contribute to the development of tolerance to diseases in future generations [3].

Molecular epigenetic mechanisms of transgenerational inheritance

Epigenetic transgenerational inheritance is the inheritance of epigenetic information, mediated by the germ line, between generations in the absence of constant direct environmental influence leading to phenotypic variability. There are described two types of inheritance. Firstly, intergenerational inheritance, which occurs as a result of direct exposure, when the embryonic cell receives external signals and transfers them into epigenetic changes. The persistence of these changes after fertilization and early development underlies phenotypic or metabolic variability, causing differentiated risk of disease development in the offspring compared to its parents. For example, when a pregnant mother (F0) is exposed to an adverse environmental factor, it can affect the offspring (F1) as well as grandchildren (F2) as a result of intrauterine exposure to the developing embryo (F1) or the developing germ cell (later F2). On the other hand, a direct impact on the father's life (F0) can affect his offspring (F1) through epigenetic changes in his sperm. Secondly, transgenerational inheritance is a phenomenon in which the effects are manifested in the unexposed generation [4]. Under intrauterine exposure the F3 generation will be the first generation to acquire a transgenerational phenotype. Although this mechanism is not yet fully described, epigenetic effects, which are transgenerational, may underlie persistent and evolutionarily important changes.

Epigenetic molecular processes include DNA methylation, histone modifications, non-coding RNA molecules, RNA methylation, and chromatin structure (Fig. 1, [5]). The most studied epigenetic factor is DNA methylation. The methyl group attaches to the cytosine base of DNA [6] to form 5-methylcytosine. The Tet family of enzymes (Ten-eleven translocation) can oxidize 5-methylcytosine to 5-hydroxymethylcytosine and other compounds [7]. Histone proteins that create a nucleosome with DNA can be chemically modified to alter gene expression. It should be noted that acetylation of histones can enhance transcription, while methylation can suppress transcription [8]. Non-coding RNA molecules that act as epigenetic factors are independent of the DNA sequence. Thus, most noncoding RNA molecules do not rely on the presence of a nucleotide sequence complementary to a specific region of DNA or RNA to function [9]. Long noncoding RNAs [10] and RNA-derived short RNAs are present in spermatozoa and can act as epigenetic factors that influence subsequent generations. RNA molecules themselves can also be epigenetically modified, which in this way can affect the translation and expression of genes [11]. The helical, loop, and general structure of DNA is also an epigenetic factor [12]. Due to the three-dimensional structure of DNA some parts of the genome can become accessible for the transcriptional mechanism, for example, the regions of the enhancer are close to the gene promoters, which affect gene expression.

Examples of transgenerational inheritance include observations made with calorie restriction or a high-fat diet. The Överkalix study by L. O. Bygren et al (2014) showed the relationship of cardiovascular mortality with nutrition in childhood and adolescence. While a grandmother experienced prolonged nutritional restriction prior to her puberty, her sons' daughters had an increased risk of cardiovascular mortality [13]. The study found no effect of the maternal grandmother's diet on cardiovascular risk in grandchildren. Another study showed that adult grandchildren whose fathers were starved in the womb had a higher body mass index than a control population [14]. According to the

Figure 1. Epigenetic molecular mechanisms (adapted from [5])

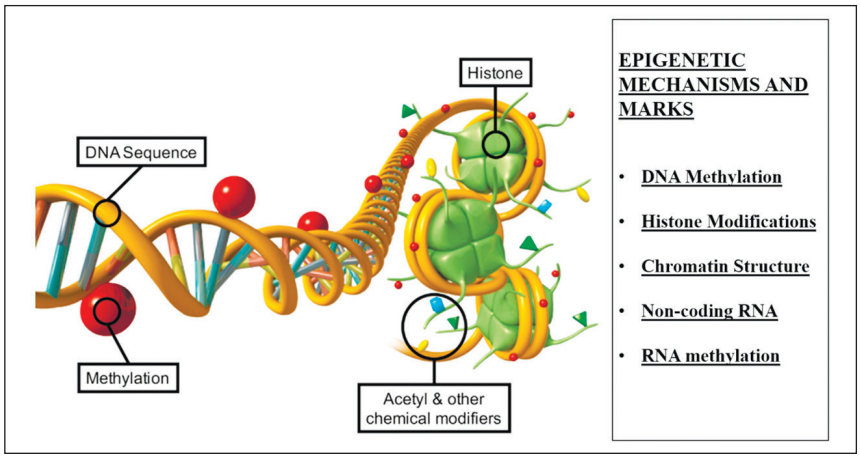
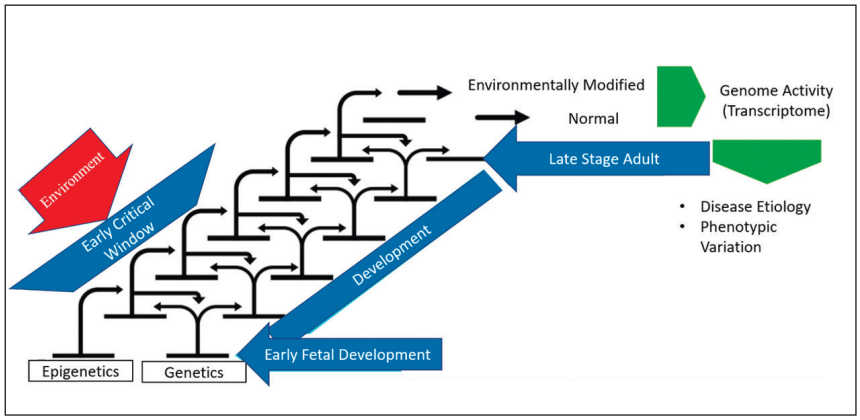


Figure 2. Epigenetic and genetic cascade of events participating in stem-cells development (adapted from [18])



hypothesis of a predictive adaptive response [15], environmental influences such as starvation can epigenetically promote the development of an adaptive (lean) phenotype in subsequent generations. If the living environment of the offspring contains enough nutrients, it contributes to the development of diabetes, cardiovascular disease and obesity.

Environmental exposure can disrupt the normal molecular epigenetic mechanism and lead to stochastic and / or directional epigenetic changes, epimutations. Epimutation is the environmentally induced differential presence of epigenetic changes that can lead to a change in genome activity when compared to unaffected organisms. If they occur in the germ line, it can lead to the transgenerational inheritance of a wider range of phenotypes in the offspring, including those that can contribute to the development of diseases. This explains the increased susceptibility to diseases of organisms whose ancestors were exposed to adverse environmental influences. On the other hand, phenotypic variability can also lead to better adaptation to a changed environment, which promotes natural selection and evolution [16].

There are primary epimutations — epigenetic changes in the absence of genetic changes; and secondary epimutations — changes that form after the initial genetic change. J. R. McCarrey and M. K. Skinner (2016) put forward the idea of tertiary epimutations, which are initial primary epimutations that contribute to genome instability, leading to an accelerated accumulation of genetic mutations [17]. However, it remains unclear why some primary epimutations are only temporary (leading to generational effects) and why in other cases the initial effects can turn into tertiary epimutation (or can cause it), inducing persistent transgenerational phenotypes.

Transgenerational inheritance of environmentally induced epigenetic changes requires germline transmission from parents to future generations. However, epigenetic changes appear as changes

in gene expression, and do not cause the development of diseases. Oncological diseases, pathology of the prostate gland or kidneys, as well as obesity are caused by disturbances in gene expression in the corresponding somatic cells. The hypothesis is that epimutations in the germ line change the epigenome of embryonic stem cells, which affect all subsequent epigenomes and transcriptomes of somatic cells (Fig. 2 [18]) [19]. These cellular and tissue-specific epimutations contribute to tissue-specific changes in transcriptomes that can contribute to the development of disease.

A. Soubry et al (2014) suggested the existence of epigenetic windows of susceptibility to environmental influences during sperm development [20]. Sperm are at a higher risk of epigenetic damage during periods of epigenetic reprogramming, and environmental factors can alter this process. It can be assumed that these changes are likely to be passed on to the next generation (s). Although most of the evidence is based on animal models, some studies show that sperm in men of general human population are susceptible to unhealthy lifestyles or obesity [21] and exposure to pollutants such as organophosphates [22]. The same researchers demonstrated that epigenetic signatures can be passed from father to child [23]. Some intergenerational effects of early exposure have been found in humans in long-term studies. For example, K. Northstone and co-authors (2014) in their study showed that those men whose fathers started smoking at an early age were prone to obesity [24]. It should be noted that the exposure to phthalates in men was associated with poor blastocyst quality in couples attending a fertility clinic [25]. This led to the emergence of a new paradigm of Paternal Origins of Health and Disease (POHaD) [26].

Transgenerational Effects of Various Risk Factors Influence

Stress

Offspring born to mothers who have experienced at least one major stressful / traumatic life event during pregnancy have lower serotonin transporter messenger RNA levels compared to infants without prenatal maternal stress. It is worth noting that the authors found a negative relationship between the number of prenatal stressors / traumas in maternal life and SLC 6A4 messenger RNA [27].

There is a classic example of the stressful impact of severe food shortages, the Dutch famine of 1944–45, known in the Netherlands as the Hongerwinter, its literal translation is hunger winter (November 1944 — April 1945). The Dutch famine studies have observed different effects of maternal and paternal PTSD on both glucocorticoid receptor sensitivity and vulnerability to psychiatric disorders [28]. The observed changes in sensitivity to glucocorticoid receptors in offspring may be due to changes in parental sex methylation in the NR 3C 1 gene encoding the glucocorticoid receptor. Indeed, in the offspring of men who survived the Holocaust, a higher methylation of the NR 3C 1 promoter was noted, while in offspring having post-traumatic stress disorder occurred in both the paternal and maternal lines, a lower methylation of NR 3C 1 was revealed [29].

R. Yehuda, et al (2016) studied transgenerational methylation changes on FKBP5, a moderator of glucocorticoid activity, in Holocaust survivors [30]. FKBP5 intron 7 methylation levels were significantly higher in Holocaust survivors than in their offspring. The authors suggested that this opposite effect, observed at the levels of methylation of intron 7 of FKBP5, may be associated with biological accommodation in the offspring. Among the limitations of this study are the small size of the sample, as well as the presence of other factors that cannot be controlled, such as extreme conditions during the Holocaust, which may have also contributed to the observed effect. Descendants of Holocaust survivors have a higher risk of anxiety, depression, PTSD and cardiovascular events compared to non-Holocaust Jewish populations [31].

Malnutrition

Malnutrition or starvation during pregnancy and early life is one of the most important factors for the development of distant cardiometabolic disorders in adulthood. The most valuable information about the effects of nutrition during pregnancy on the health of children and adults in the long term can be obtained by studying the incidence among cohorts of people born during periods of natural disasters and wars, when entire cities, localities, regions, and even countries were exposed to starvation. Jie Li et al (2015) investigated the effect of prenatal exposure to starvation in 1959–1961 in China on the cognitive function of adults in two

successive generations. The findings suggest that prenatal exposure to severe malnutrition is negatively associated with visual-motor skills, mental flexibility, and selective attention in adulthood. However, these associations are limited to only one generation [32].

Another example is the study of children whose grandmothers fasted during Ramadan during pregnancy [33]. In this study, the grandchildren of these women were noted to have a lower body weight at birth and a lower weight of the placenta was recorded, which increases the likelihood of developing metabolic effects later in life.

In the previously mentioned Dutch cohort, when studying the influence of perinatal starvation, no differences were found in the prevalence of cardiovascular diseases, high cholesterol levels, diabetes and hypertension between the offspring of men and women. But prenatal exposure to starvation in men has been associated with an increase in body mass index in their offspring [34]. In the same group, the length of leukocyte telomeres and the prevalence of short telomeres did not differ between those who underwent intrauterine fasting and did not undergo fasting in early pregnancy. Prenatal exposure to starvation was not associated with telomere shortening in peripheral blood leukocytes at age 68.

A study of seasonal dietary fluctuations in the Gambia [35] showed different levels of DNA methylation in offspring whose mothers were malnourished during pregnancy compared with respondents who did not experience maternal malnutrition in utero.

The siege of Leningrad became another tragic example of the catastrophic malnutrition of the inhabitants of the city, which was in the absence of supplies for two and a half years during the Great Patriotic War (September 1941 — January 1943). When Professor B.M. Rachkov examined the descendants of the besieged Leningrad citizens, diseases of the musculoskeletal system were most often recorded, followed by symptoms of diseases of the cardiovascular system, followed by various diseases of the gastrointestinal tract and respiratory organs [36].

Another historical example of this kind was the brutal communist regime in Romania. After the end of World War II, Romania was under Soviet occupation and the country's resources were depleted. In addition, in 1946–1947, there was a severe drought, which led to severe famine in some parts of Romania. All babies born during such difficult times have health problems later in adulthood. According to the European Obesity Day (EOD), among respondents aged 65 to 74 (Romanians born between 1940 and 1949), the proportion of obese people was 71.2% in 2014, the highest in terms of compared to any other age group in Romania [37]. Another conclusion can be drawn regarding the age group 18 years and older — these are the grandchildren of those who were born in 1946–1947. One of the clinical trials published by S. Popa et al. (2016) (– the PREDATORR study) — showed a high prevalence of obesity / overweight, abdominal obesity and metabolic syndrome among the Romanian adult population. It should be noted the relatively high prevalence of obesity (20.9%) and metabolic syndrome (20%) in the age group 20–39 years old [38]. It is worth noting that over the past 30 years, the total calorie intake in the Romanian population has exceeded the level recommended by the Food and Agriculture Organization (FAO), corresponding to 2,700 calories per day in a temperate climate. The amount of food purchased by Romanians that predispose to the development of diabetes mellitus, fatty liver disease associated with metabolic dysfunction, cardiovascular diseases purchased by Romanians is excessive; this behavior can also be explained by the transgenerational effect of food deprivation in previous periods [39].

Caffeine

Although caffeine is present in coffee, tea, and chocolate, it is also increasingly being added to a variety of foods and beverages, raising both interest and concern about the potential health effects of caffeine in future generations [40]. Many pregnant women around the world consume caffeinated beverages, which can have adverse effects on the fetus, although research results are conflicting. M.C. Cornelis et al (2016) conducted a genome-wide associative study of caffeine metabolites and identified genes encoding proteins with important clinical functions beyond the caffeine metabolism [41].

In a population cohort of 7857 mothers and their children, maternal caffeine intake during pregnancy was assessed using questionnaires. According to E. Voerman et al (2016), children whose mothers consumed 6 or more units of caffeine per day tended to have lower birth weight, higher weight

gain from birth to 6 years, and higher body mass index from 6 months to 6 years. In addition, they had higher total childhood fat mass at age 6. The authors did not observe differences in insulin or C-peptide levels, but this may be due to the limited fasting period before blood sampling [42].

E. Papadopoulou et al (2018) conducted a study within the framework of the Norwegian Maternal and Child Cohort Study (MoBa) [43] — a prospective population-based cohort study of pregnant women conducted by the Norwegian Institute of Public Health [43]. A total of 50,943 mothers and their babies born after singleton pregnancies took part in the study. The mothers were provided with information on the average caffeine intake estimated mid-pregnancy. The authors found that any maternal caffeine intake during pregnancy was associated with a higher risk of overgrowth in infancy and overweight in early childhood. Maternal intake of caffeine above 360 mg / day was associated with higher birth weight to 6 years of age compared to intake below 180 mg / day, but the authors found no association with overweight. Higher caffeine intake (360–540 mg / day) during pregnancy was positively associated with body fat percentage and higher insulin levels in 6-year-old children [44]. Li et al (2015) reported that any maternal caffeine intake was associated with an overall increased risk of obesity between the ages of 2 and 15 years [45]. Combining previous results from the MoBa study, the authors showed that children who were prenatally exposed to high levels of caffeine were smaller at birth, grew faster in infancy, and maintained a higher body weight throughout childhood without significant differences in height, leading to obesity. [44]. These data are consistent with the fetal obesity programming hypothesis [46]. However, the effect of prenatal caffeine exposure on postnatal growth and overweight development was independent of birth weight. Therefore, along with healthy birth weight, it is important to identify modifiable factors (for example, prenatal: excess gestational weight [47], high (> 3 times per week) fish intake and postnatal factors: feeding formula and feeding schedule), which can independently affect excess growth in infancy, regardless of fetal growth.

Obesity

Higher maternal mass index at the beginning of pregnancy and higher gestational weight gain were associated with subsequent obesity in the offspring [48]. Some, although not all [49] studies before and after bariatric surgery show that in cases of extreme maternal obesity, these associations may be caused by intrauterine mechanisms. Taken together, these results suggest that exposure to both undernutrition and overnutrition in utero may lead to more pronounced obesity later in life.

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a population-wide cohort pregnancy study that enrolled 14,541 pregnant women with a due date between April 1991 and December 1992 [50]. This study identified several CpG sites that are differentially methylated in the umbilical cord blood of the offspring of obese or underweight mothers compared to the offspring of normal weight mothers, without overlapping sites associated with maternal obesity and underweight. When assessing epigenetic changes in the offspring of women with underweight and normal body weight, much more differentially methylated regions were revealed (1621) than when comparing the offspring of obese women and ones with normal body weight, which suggests that maternal weight deficit has a greater effect on the epigenome of fetus than maternal obesity. The effect of maternal obesity was stronger than that of paternal obesity, which confirms the underlying intrauterine mechanism. There was also no consistent association of weight gain during pregnancy with DNA methylation.

A general trend shows that areas hypermethylated due to maternal obesity or hypomethylated due to maternal underweight tend to be positively associated with offspring obesity, and areas hypomethylated due to maternal obesity or hypermethylated in associations with maternal underweight are generally inversely associated with obesity in the offspring. This suggests that a linear association (as shown in ALSPAC) between maternal obesity and offspring obesity may be mediated through DNA methylation in the offspring at birth [51].

F. Guénard et al (2013) found 5698 differentially methylated CpG sites in the peripheral blood of children born to morbid obese mothers before bariatric surgery, compared with their siblings born after bariatric surgery on the mother and associated weight loss [52]. Other studies have found little or no association between maternal body mass index and offspring DNA methylation [53]. Only two

studies have examined the relationship between DNA methylation at birth and obesity in later childhood. Both studies used an approach to candidate genes, and each identified a separate associated locus [54, 55].

At the present time, there have been developed no recommendations for a healthy lifestyle for future fathers. However, this may well need to be corrected, given that obesity can act as a factor contributing to the development of diseases in offspring. A meta-analysis published by J. M. Campbell et al (2015) included 30 studies and about 115,000 participants. In obese men, infertility and an increased percentage of spermatozoa with low mitochondrial membrane potential, DNA fragmentation, and abnormal morphology were more often observed [56].

However, when studying DNA methylation at the individual gene level or in genome-wide studies, differential methylation was established according to the status of obesity. For example, in the sperm of 69 young and healthy volunteers, the percentage of DNA methylation in differentially methylated regions of imprinted genes differs significantly in obese or overweight men compared to men with normal body weight [57].

Gut microbiota

In the early postnatal period, the intestines of humans are colonized by symbiotic bacteria, the intestinal microbiota is unstable during the first days of life, and by the age of 3 it acquires an adult-like complexity. Consistent with Barker's hypothesis, one would expect adult metabolic diseases to result from several genes being turned off or on to optimize perinatal and early adult life. Interestingly, the period of life during which epigenetic DNA imprinting is most active coincides with this early three-year period [58].

C. A. Devaux et al (2018) suggested that the microenvironment of the cell (bacterial surface antigens and secreted proteins, low molecular weight compounds of bacteria and biologically active molecules supplied with food and processed by the intestinal microbiota) remains constant from one generation to the next, highlighting a new term — "microbiological memory". Microbiological memory remains stable when diet and microbiota are nearly unchanged. According to this theory, what is currently known as epigenetic programming is likely nothing more than a nongenetic hereditary signature resulting from molecular cross-interactions between gut prokaryotes (microbiota metabolome) and eukaryotic cells. It can trigger continuous changes in cellular genes through the activation of signaling pathways in host cells, thereby controlling the epigenetic signature [59].

The hypothesis of "intrauterine colonization" indicates that the microbiota of offspring lives in the intrauterine environment (in the placenta, amniotic fluid, umbilical cord blood and meconium) before birth and is maternally transferred [60]. It is likely that microbial colonization begins in the amniotic fluid and placenta and that maternal gut microbiota supports the development of prenatal microbiota, but the exact route of transference remains unclear to date [61]. The postnatal stage during lactation, which depends on the types of contact with the mother, the maternal diet, and breastfeeding / infant formula, is also of great importance for establishing the composition of the intestinal microbiota [62]. It is generally accepted that the microbiota of the offspring is of great importance for the establishment and development of the immune, metabolic function and further health of the offspring [63, 64].

Smoking

The mechanisms underlying the different health effects of smoking on the health of adults and infants whose mothers smoked during pregnancy remain largely unknown. In a large-scale meta-analysis of the relationship between current smoking and DNA methylation in the blood of adults in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium, the authors identified numerous differentially methylated cytosine phosphate guanine sites [65].

According to a meta-analysis of studies from the Pregnancy And Childhood Epigenetics (PACE) consortium, widespread differential methylation across the entire genome associated with prolonged maternal smoking during pregnancy was revealed in newborns. However, it should be noted that statistically significant changes in methylation between exposed and non-exposed groups (both neonates and adults) are small [66].

It is also worth noting that many DNA methylation associations related to long-term personal smoking in adults can also be seen in newborns who have been exposed to tobacco smoke in ute-

ro, although their mothers have smoked far fewer cigarettes. S. Sikdar et al (2019) identified differentially methylated CpGs associated with smoking in a meta-analysis of data from the existing PACE and CHARGE consortia [67].

Conclusion

The evolutionary aspects of developing epigenetic transgenerational inheritance of disease are still unclear. It is necessary to consider the potential role of these hereditary influences and epigenetic transgenerational inheritance in the etiology of diseases. In addition, from a clinical point of view, the relationship of epimutation patterns or signatures with a specific disease and / or hereditary effect on human is of interest. Epigenetic biomarker signatures can be used in the future as a diagnostic tool for assessing a person's specific susceptibility to diseases or exposure to environmental toxicants. This can contribute to the development of personalized medicine and new approaches to preventing the negative influence of risk factors across generations.

Conflict of interest

The authors declare no conflict of interest.

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