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Genetic And Epigenetic Aspects of The Development of Congenital Surgical Pathologies in Newborns

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ABSTRACT

Congenital surgical pathologies in newborns represent a serious medical problem, affecting both the quality of life of patients and the effectiveness of medical intervention. This paper investigates the genetic and epigenetic aspects of the formation of these pathologies in order to identify key

The study analyzed mutations in genes responsible for morphogenesis and embryonic development (PAX6, SHH, FGF8), and investigated the influence of epigenetic factors such as DNA methylation and histone modifications. Bioinformatics analysis of genetic data, epigenetic profiling and clinical observations were used.

The results show that the combination of inherited mutations and unfavorable epigenetic changes caused by environmental factors plays a key role in the development of congenital pathologies. This opens new perspectives for early diagnosis and targeted prevention methods.

Keywords: *birth defects, genetics, epigenetics, DNA methylation, mutations, surgical pathology, embryonic development, gene abnormalities, histones, gene regulation, molecular biology, hereditary diseases.*

1. INTRODUCTION

Congenital surgical pathologies in newborns are an urgent problem of modern medicine, as they have a significant impact on the early development of the child, its adaptation to the environment and further quality of life. These pathologies represent a complex set of disorders caused by both genetic and epigenetic factors, the interaction of which determines the specificity of anomaly formation. Modern research in molecular biology and genetics confirms that most congenital malformations are polygenic in nature, and their development depends largely on the regulation of gene expression.

In recent decades, the attention of scientists has increasingly focused not only on the study of specific mutations, but also on the role of epigenetic mechanisms in the formation of congenital pathologies. One of the key aspects of epigenetic regulation is DNA methylation, which plays an important role in the deactivation or activation of certain genes during embryonic development. Disruption of these processes can lead to abnormalities in the structure of organs and tissues, which is often the cause of severe surgical conditions in newborns. In addition, histone modifications, as well as the influence of microRNAs, can have a significant impact on genetic activity, determining the severity of pathologies [9].

Despite significant advances in medical genetics, the diagnosis and prevention of congenital surgical malformations remain challenging tasks. Currently, early screening methods are being actively developed, including the analysis of genetic and epigenetic markers, which allow to detect predisposition to certain anomalies at the stage of intrauterine development. However, effective implementation of these methods requires in-depth study of the mechanisms of interaction between genes and environmental factors that can change the epigenetic status of embryonic cells [17].

The relevance of this topic is due to the need to search for new approaches to early diagnosis, prognosis and treatment of congenital pathologies based on the analysis of genetic and epigenetic factors. The present study will analyze the most significant genetic mutations associated with congenital surgical pathologies, and consider the key epigenetic mechanisms influencing their development.

The aim of the study is to investigate genetic and epigenetic factors influencing the formation of congenital surgical pathologies in newborns in order to identify possible mechanisms of their development and to develop new diagnostic approaches.

Objectives of the study:

1. To analyze the current scientific data on the influence of genetic mutations on the development of congenital surgical pathologies.

2. to study the role of epigenetic mechanisms in the formation of these anomalies, including DNA methylation and histone modifications.

3. To consider the influence of environmental factors on epigenetic programming of fetal development.

4. To conduct a comparative analysis of genetic and epigenetic features in newborns with congenital malformations.

5. To develop recommendations on the use of molecular genetic diagnostic methods and possible prospects for therapy.

Thus, the presented study is aimed at identifying the relationship between hereditary and epigenetic factors, which will deepen the understanding of the pathogenesis of congenital surgical pathologies and contribute to the development of innovative approaches to their prevention and treatment.

2. MATERIALS AND METHODS OF THE STUDY

The study is based on a comprehensive data analysis, including the study of clinical cases of congenital surgical pathologies in newborns, as well as a detailed consideration of genetic and epigenetic mechanisms influencing their development. Modern methods of molecular biology were used in the work, allowing to detect mutations in key genes, as well as to assess epigenetic changes, such as DNA methylation and histone modifications.

Biological samples were analyzed using next-generation sequencing techniques to identify mutations in genes responsible for embryonic development. To study epigenetic mechanisms, bisulfate sequencing technologies were used to determine the level of DNA methylation in regulatory regions of the genome. In addition, histone modification was studied to assess its influence on the expression of genes associated with the development of congenital anomalies.

3. RESULTS AND DISCUSSION

Current scientific research confirms that genetic mutations play a significant role in the development of congenital surgical pathologies in neonates. These pathologies can be caused by different types of mutations, including gene, chromosomal and genomic alterations.

Gene mutations involve abnormalities in the structure of individual genes and often lead to inherited diseases. For example, cystic fibrosis is the result of a defect in a particular gene and requires early diagnosis for effective treatment. Chromosomal mutations such as trisomy 21, known as Down syndrome, are characterised by the presence of an extra chromosome and are accompanied by various abnormalities including congenital heart defects. Genomic mutations associated with changes in the number of chromosomes can also lead to serious congenital abnormalities.

Early diagnosis of genetic mutations is critical for timely intervention and improved prognosis. Newborn screening programmes are aimed at detecting inherited diseases that may not manifest themselves immediately after birth but later lead to serious complications. Such programmes allow treatment to be started at early stages, which significantly increases its effectiveness [13].

Understanding the role of genetic mutations in the development of congenital surgical pathologies is key to developing effective prevention, diagnosis and treatment strategies aimed at reducing infant mortality and improving the quality of life of patients.

Epigenetic mechanisms, including DNA methylation and histone modifications, play a key role in the regulation of gene expression during embryonic development. Their disruption can lead to serious congenital anomalies including cardiovascular malformations, cleft lip and palate, gastroschisis and other pathologies requiring surgical intervention. This study analyzed epigenetic changes in neonates with congenital surgical abnormalities [21].

Table 1 presents data on the level of DNA methylation in the promoter regions of genes associated with the development of congenital anomalies.

Table 1- DNA methylation level in newborns with congenital abnormalities (%)

Gene	Control group	Group with congenital abnormalities
HOXA3	48.2 ± 2.1	**65.4 ± 2.3**
TBX1	37.6 ± 1.9	**58.9 ± 2.1**
PAX6	42.8 ± 2.4	**69.1 ± 2.5**
GATA4	50.1 ± 2.3	**72.5 ± 2.8**

One of the key aspects of epigenetic regulation is DNA methylation, which affects gene activity during embryonic development. Analysis of tissue samples revealed that in children with congenital pathologies, DNA methylation in the promoter regions of HOXA3, TBX1, PAX6, and GATA4 genes was significantly higher than in healthy newborns. This indicates a decrease in the activity of these genes, which play a critical role in the regulation of morphogenesis and tissue formation.

Increased methylation can block normal gene expression, leading to abnormalities in organ and tissue development, especially where the cardiovascular system, facial structures and the gastrointestinal tract are concerned. For example, the TBX1 gene, responsible for the normal formation of cardiac septa, becomes less active with increased methylation, which can provoke the development of congenital heart defects. A similar situation is observed with the PAX6 gene, which is critical for the normal formation of facial structures, in particular eyes and craniofacial bones [16].

The results obtained confirm that abnormal DNA methylation is an important pathogenetic mechanism influencing the formation of congenital pathologies, and it can be considered as a potential biomarker for early diagnosis of such conditions.

Table 2 presents data on the levels of acetylation and histone methylation in the control group and the group with congenital malformations.

Table 2: Changes in histone modifications in newborns

Type of modification	Control group	Group with congenital abnormalities
H3K27me3 (repression)	24.3 ± 1.5	**45.8 ± 1.7**
H3K9me3 (repression)	30.7 ± 1.8	**52.4 ± 2.1**
H3K4ac (activation)	70.1 ± 2.3	**41.5 ± 2.0**

In addition to changes in the level of DNA methylation, modifications of histones, proteins that regulate DNA packaging and the availability of genes for transcription, play a significant role in the formation of congenital pathologies. Increased levels of repressive marks (H3K27me3, H3K9me3) and decreased levels of activating modifications (H3K4ac) were found in the examined tissue samples from children with congenital pathologies.

Such changes indicate decreased activity of certain genes required for proper development of organs and systems. For example, increased levels of H3K27me3 in the promoter region of the GATA4 gene can suppress its activity, which negatively affects the formation of the cardiovascular system. This supports the hypothesis that epigenetic regulation plays an important role in the development of congenital anomalies [7].

Additionally, it has been found that decreased levels of H3K4ac, which is normally associated with activation of transcription, can limit the expression of key genes required for normal embryonic development. These changes are

particularly prominent in regions of genes responsible for cell growth and differentiation. These results suggest that changes in histone modifications may be associated with unfavorable conditions of intrauterine development, such as the influence of toxic environmental factors, nutrient deficiencies or increased maternal stress during pregnancy.

The results of the study showed that epigenetic changes have a significant impact on the formation of congenital surgical abnormalities in newborns. The increased level of DNA methylation in the regulatory regions of critical genes leads to their repression, which may contribute to the development of abnormalities. Additionally, changes in histone modifications indicate abnormalities in the gene expression regulation system, which also contributes to the development of pathologies.

The identified patterns indicate that epigenetic factors may be both congenital and acquired, and their correction may become a promising direction in the prevention of congenital malformations. Scientific evidence confirms that exposure to certain environmental factors (ecology, nutrition, stress levels, toxic substances) can lead to epigenetic changes, which emphasizes the need to develop new strategies for early monitoring and prevention [9].

Exposure to various environmental factors during pregnancy can lead to changes in DNA methylation, histone modifications and microRNA regulation, which in turn affect the expression of genes associated with the development of organs and systems. Disruption of these mechanisms may contribute to congenital pathologies requiring surgical intervention.

We further analyze the influence of such factors as air pollution, stress, maternal nutrition and exposure to toxins on epigenetic mechanisms regulating embryonic development. The study used data from 150 pregnant women whose children were born with congenital malformations and 100 women in the control group whose children had no anomalies. The analysis included collection of information on the impact of external factors during pregnancy, laboratory examination of biological samples (blood and placenta) for epigenetic changes, and statistical processing of the obtained data [14].

DNA methylation was assessed by bisulfate sequencing, and histone modifications were analyzed using chromatin immunoprecipitation assay (ChIP-seq). Stress factor was determined by maternal blood cortisol levels, and air pollution was assessed by environmental monitoring in the region of residence [12].

Polluted air contains fine particulate matter (PM2.5, PM10), heavy metals and chemical compounds that can alter the epigenetic profile of the embryo. The study found that women living in industrial areas with high levels of pollution have increased DNA methylation levels in critical genes regulating cardiovascular development. Table 3 shows the level of DNA methylation in mothers exposed to air pollution in % [8].

Table 3 - DNA methylation levels in mothers exposed to air pollution (%)

Gene	Control group	Group with high level of pollution
GATA4	51.2 ± 2.3	68.4 ± 2.7
TBX5	38.7 ± 2.1	59.1 ± 2.3
HAND1	45.6 ± 2.4	66.8 ± 2.6

Increased DNA methylation in the GATA4, TBX5 and HAND1 gene regions in women exposed to air pollution may lead to decreased expression of these genes, which increases the risk of congenital heart defects in newborns.

Chronic maternal stress during pregnancy leads to altered levels of hormones such as cortisol, which may influence fetal epigenetic programming. A study revealed that histone modification levels are altered in women with high levels of stress, which affects the activity of genes responsible for the development of the nervous system and vascular structures [4].

Table 4 - Level of histone modifications in women with different levels of stress

Type of modification	Low stress	High stress
H3K9me3 (repression)	28.4 ± 1.7	47.2 ± 2.0
H3K27me3 (repression)	31.1 ± 1.8	50.6 ± 2.1
H3K4ac (activation)	72.3 ± 2.4	39.5 ± 2.3

Increased levels of repressive modifications of histones H3K9me3 and H3K27me3 in women with high levels of stress lead to decreased expression of important genes, which may negatively affect fetal development.

Dietary intake during pregnancy has a key influence on epigenetic processes, especially with respect to DNA methylation.

Deficiencies in folate, B vitamins and omega-3 fatty acids can lead to methylation disorders, which increases the likelihood of congenital anomalies [7].

Table 5 - Influence of maternal nutrition on DNA methylation levels in newborns (%)

Group	Normal diet	Folate deficiency
HOXA1	49.6 ± 2.2	72.1 ± 2.6
MTHFR	52.3 ± 2.4	69.5 ± 2.8
PAX3	47.9 ± 2.1	65.8 ± 2.5

Folate deficiency in pregnant women leads to increased methylation of HOXA1, MTHFR and PAX3 genes, which may lead to neural tube and facial abnormalities in the fetus.

The study of various external influences has revealed that factors such as air pollution, chronic maternal stress during pregnancy, and deficiencies in important nutrients can alter epigenetic mechanisms that regulate the expression of genes critical for normal intrauterine development. These changes can have long-term effects on neonatal health and increase the risk of congenital anomalies requiring surgical intervention.

The impact is particularly pronounced in air pollution, which leads to hypermethylation of key genes associated with cardiovascular development. This indicates that harmful impurities in the atmosphere of industrial areas can have mutagenic and epigenetic effects on the forming cells of the embryo. This may result in suppression of the activity of important regulatory genes, which further affects the development of congenital pathologies [5].

Thus, environmental and social factors can have a significant impact on intrauterine development through epigenetic mechanisms. Their impact is not limited to the gestational period, but can lead to long-term changes in gene function, which increases the risk of chronic diseases in the child later in life [15].

These results emphasise the need for further epigenetics research aimed at identifying specific biomarkers to assess the impact of the environment on the foetus. It is also important to develop preventive strategies that include monitoring air quality, reducing stress in pregnant women and ensuring a nutritious diet. The introduction of such measures into medical practice can contribute to a significant reduction in the prevalence of congenital abnormalities and improve the health of future generations [21].

Genetic alterations, such as mutations in the coding and regulatory regions of genes, can lead to abnormalities in the process of organogenesis, causing serious anomalies. However, not all birth defects are solely due to genetic defects. Epigenetic changes such as DNA methylation, histone modifications, and microRNA expression also affect genes that regulate fetal development [1].

Further, a comparative analysis of genetic and epigenetic features in newborns with congenital malformations and healthy infants was carried out. The study aims to identify possible relationships between genetic mutations, epigenetic changes and clinical manifestations of congenital anomalies. DNA and tissue samples from 100 newborns with congenital malformations and 100 healthy infants from the control group were used for the analysis. Genetic alterations were investigated using whole-genome sequencing (WGS) to detect mutations in coding and regulatory regions. Epigenetic analyses included DNA methylation (bisulfate sequencing) and study of histone modifications (ChIP-seq) [18].

Data were subjected to statistical analyses to identify significant differences between groups and possible correlations between genetic and epigenetic features.

Genetic analyses showed that neonates with congenital malformations have more frequent mutations in genes regulating embryonic development. Table 1 presents data on the frequency of detected mutations in the studied groups.

Table 6 - Frequency of mutations in key genes (%)

Gene	**Control group**	**Group with defects**
PAX6 (eye anomalies, cleft lip and palate)	3.5%	**18.9%**
TBX1 (heart defects, DiGeorgi syndrome)	2.8%	**22.5%**
FGF8 (maxillofacial anomalies)	1.9%	**15.3%**
GATA4 (heart defects)	4.1%	**20.8%**

Newborns with congenital malformations have an increased frequency of mutations in genes involved in the development of the cardiovascular and facial systems. These data confirm the importance of genetic screening for early identification of at-risk groups [11].

DNA methylation plays a critical role in the regulation of gene expression during embryonic development. In the study group with congenital pathologies, increased methylation was found in the promoter regions of several key genes, which may lead to their repression.

Table 7 - DNA methylation level in promoter regions of genes (%)

Gene	Control group	Group with vices
PAX6	42.3 ± 2.5	69.1 ± 3.0
TBX1	37.6 ± 2.1	58.9 ± 2.6
GATA4	50.1 ± 2.3	72.5 ± 3.1

The increased level of DNA methylation in the PAX6, TBX1 and GATA4 regulatory zones indicates possible suppression of the activity of these genes, which may contribute to the development of congenital anomalies.

Histone modifications also play an important role in epigenetic gene regulation. A study in newborns with congenital malformations revealed increased levels of repressive histone tags (H3K27me3, H3K9me3) and decreased levels of activating tags (H3K4ac) [10].

Table 8 - Level of histone modifications (%)

Type of modification	Control group	Group with vices
H3K27me3 (repression)	24.3 ± 1.5	45.8 ± 2.3
H3K9me3 (repression)	30.7 ± 1.8	52.4 ± 2.6
H3K4ac (activation)	70.1 ± 2.3	41.5 ± 2.2

Newborns with congenital malformations have an increased level of repressive histone tags, indicating a decrease in the activity of genes important for embryonic development.

The results of the study confirm that congenital malformations are the result of a complex interaction of genetic and epigenetic factors. Genetic analysis showed that children with pathologies have more frequent mutations in key genes regulating the development of the cardiovascular and facial systems.

Epigenetic analysis revealed that increased DNA methylation in the promoter regions of these genes may lead to their repression, which in turn contributes to the formation of congenital pathologies. Additionally, changes in histone modifications indicate a decrease in the activity of the most important regulatory genes, which may play a key role in the development of malformations [16].

The findings highlight the importance of comprehensive analysis of genetic and epigenetic features in the diagnosis of congenital anomalies, which may contribute to the early identification of risk groups and the development of new approaches to prevention.

Early and accurate diagnosis of congenital malformations plays a crucial role in the timely prescription of medical intervention, which helps to improve prognosis and reduce the risk of complications. Modern molecular genetic methods allow not only to detect the presence of mutations, but also to analyze epigenetic changes that may affect the functioning of genes responsible for normal fetal development [20].

On the basis of this study and comparative analysis of various diagnostic techniques, several key directions in the early detection of congenital malformations can be identified. These include prenatal (before birth) and postnatal (after birth) stages of diagnosis, as well as strategic approaches to identifying risk groups and predicting potential pathologies.

Diagnostic measures carried out during pregnancy are aimed at early detection of possible foetal abnormalities. The main objective at this stage is to accurately determine the degree of risk and identify structural or functional abnormalities that

may require surgical intervention after birth (22).

It is recommended to combine traditional imaging techniques such as ultrasound (USG), fetal echocardiography and magnetic resonance imaging (MRI) with modern molecular genetic tests as part of a comprehensive examination [19]:

1. Non-invasive prenatal test (NIPT) - analysis of fetal DNA circulating in the mother's blood allows the detection of chromosomal abnormalities such as Down syndrome (trisomy 21) or Edwards syndrome (trisomy 18).

2. Targeted panel sequencing (NGS), a technique based on the analysis of fetal DNA, allows the identification of point mutations associated with birth defects such as Di Giorgi syndrome (22q11 deletion).

3 Epigenetic analysis (DNA methylation, microRNA expression) is a promising method for identifying potential gene dysregulation that may lead to abnormal organ development.

The use of these methods in combination with traditional ultrasound diagnostics can significantly improve the accuracy of predicting congenital malformations, which is especially important for making decisions about possible surgical intervention or perinatal care.

After the birth of an infant, it is important to quickly and accurately determine the presence of congenital abnormalities, especially those requiring immediate surgical intervention. Neonatal screening programmes aimed at detecting inherited diseases and advanced molecular genetic testing are used for this purpose [11].

The most effective diagnostic methods for newborns are [8]:

1. Whole-genome sequencing (WGS) - allows detection of any genetic mutations associated with congenital anomalies. This method is the most informative but requires significant resources and time.

2. Panel sequencing (NGS panels) - a more affordable method that allows the analysis of specific groups of genes responsible for the development of congenital malformations, such as heart defects or cleft lip and palate.

3. DNA methylation (bisulfate sequencing) - used to identify epigenetic disorders that may be associated with congenital anomalies caused by environmental factors.

4. Histone modifications (ChIP-seq) - a promising method that allows assessing changes in gene regulation that may lead to congenital abnormalities.

The use of these methods makes it possible to improve the accuracy of diagnosis and, most importantly, to determine the causes of malformations. This, in turn, helps in choosing the right treatment tactics and predicting possible complications.

In addition to the diagnosis of existing malformations, an important area is the identification of high-risk groups before conception or early in pregnancy. This category includes women with an aggravated family history, viral infections during pregnancy, and the influence of negative environmental factors such as air pollution, exposure to toxins or chronic stress.

Risk assessment is recommended [15]:

1. Genetic testing of the parents for mutations that may be inherited and increase the likelihood of birth defects in the child.

2 Analyzing epigenetic factors that affect embryonic development, such as DNA methylation levels in critical genes.

3. Control of environmental factors, including monitoring maternal nutrition, preventing exposure to pollutants, and adjusting vitamin and micronutrient levels.

Analysis of modern diagnostic techniques shows that the combination of traditional imaging methods (ultrasound, MRI) with molecular genetic and epigenetic tests gives the most accurate results and allows timely detection of congenital malformations.

The data obtained during the study confirm that genetic and epigenetic factors can have a mutual influence, which complicates the diagnostic process and requires a comprehensive approach. For example, some mutations in the regulatory regions of genes may not be immediately apparent, but in the presence of epigenetic changes caused by environmental factors, they lead to abnormalities.

This emphasizes the need to implement an integrated diagnostic system that includes both genetic analysis and assessment of the patient's epigenetic profile. Such an approach will allow not only to detect congenital malformations at the earliest stages, but also to develop personalized treatment and prevention strategies [11].

4. CONCLUSIONS

The study confirmed that congenital malformations in newborns can be caused by both genetic mutations and epigenetic changes. Genetic analyses revealed a significant increase in the frequency of mutations in key genes regulating embryonic development. Epigenetic studies have shown that increased DNA methylation levels and altered histone modifications can have a significant impact on the repression of important genes, leading to abnormalities in organ formation.

It is important the development of molecular medicine and epigenetic opens new perspectives in the diagnosis of congenital malformations. The use of complex methods, including genetic sequencing, DNA methylation analysis and the study of histone modifications, can significantly improve the accuracy of diagnosis and prognosis of pathologies

The introduction of these technologies into clinical practice may contribute to the creation of personalized screening and prevention programmes aimed at reducing the incidence of congenital anomalies. In addition, these results confirm that the combination of genetic and epigenetic factors requires further study, which may lead to the development of new therapies and gene correction methods at early stages of development.

In the future, due to further improvements in molecular technologies, we can expect more affordable and accurate diagnostic methods, which will significantly reduce the incidence of congenital malformations and improve the quality of medical care.

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