ГЕНОТИП MTHFR:677TT І СТАН ГІПЕРГОМОЦИСТЕЇНЕМІЇ У ДІТЕЙ ІЗ РАЙОНІВ, ЩО ПОСТРАЖДАЛИ ВНАСЛІДОК АВАРІЇ НА ЧОРНОБИЛЬСЬКІЙ АТОМНІЙ ЕЛЕКТРОСТАНЦІЇ

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MTHFR:677TT GENOTYPE AND HYPERHOMOCYSTEINEMIA IN CHILDREN FROM AREAS AFFECTED BY THE CHORNOBYL NUCLEAR POWER PLANT ACCIDENT

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Mutations in folate metabolism genes are one of the main causes of abnormal metabolism of methionine — an essential amino acid for the human body.

This may result in excessive formation of homocysteine, which is associated with malignant tumors, changes in rheological properties of blood and congenital defects [1-9].

Studies carried out in 2015 within projects of the European Commission and the Rhone-Alpes Region (France) showed that hyperhomocysteinemia was observed in the majority of examined adolescent children living in areas of Ukraine affected by the Chornobyl nuclear power plant accident [10-11].

The TT homozygous variant of MTHFR:C677T genetic polymorphism is associated with an almost complete loss of activity of methylenetetrahydrofolate reductase, a key enzyme of folate metabolism [12, 13]. The degree of manifestation of the genetic polymorphism is linked to the effect of an external factor.

In order to develop effective preventive measures, it is important to identify the phenotypic manifestation of this genetic defect in the form of increased formation of a sulphur-containing amino acid homocysteine in children living in areas contaminated with radioactive substances as a result of the Chornobyl nuclear power plant accident.

The aim of the study was to identify the phenotypic manifestation of the MTHFR:677TT genotype in groups of children from districts contaminated with radioactive agents due to the Chornobyl nuclear power plant accident and having different levels of socioeconomic development with the use of blood homocysteine values and hyperhomocysteinemia rate figures.

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Гомозиготний варіант ТТ генетичного поліморфізму MTHFR:C677T асоціюється з майже повною втратою активності метілентетрогідрофолатредуктази — основного ферменту фолатного циклу. Ступінь прояву генетичного поліморфізму пов'язана з впливом факторів зовнішнього середовища.

***Мета роботи** — визначити фенотипічний прояв генотипу MTHFR:677TT у групах дітей із районів, територія яких забруднена радіоактивними агентами внаслідок аварії на Чорнобильській атомній електростанції, які мають різний рівень соціально-економічного розвитку, використовуючи показники вмісту гомоцистеїну у крови і частоти поширеності стану гіпергомоцистеїнемії.*

***Методи дослідження.** Імунохімічний, математико-статистичний.*

***Результати**. У підгрупі дітей-носіїв генотипу MTHFR:677TT із районів, що постраждали від аварії на Чорнобильській атомній електростанції, вміст гомоцистеїну у крови був достовірно більшим порівняно з підгрупами дітей, які не є носіями даного генотипу.*

Присутність алелі ризику Т поліморфізму MTHFR:C677T у гомозиготному стані зумовлює у дітей, які проживають на території, забрудненій радіоактивними елементами внаслідок аварії на Чорнобильській атомній електростанції, підвищене утворення гомоцистеїну, порівняно з дітьми, які не мають у складі свого генома генотип MTHFR:677TT.

Фенотипічний прояв генотипу MTHFR:677TT у вигляді підвищеного утворення гомоцистеїну в організмі (стан гіпергомоцистеїнемії) більш виражений у дітей із районів, що мають гірші соціально-економічні умови після аварії на Чорнобильській атомній електростанції.

Ключові слова: гіпергомоцистеїнемія, генотип MTHFR:677TT, поліморфізм фолатного циклу, алель ризику Т, території, забруднені радіонуклідами, аварія на Чорнобильській атомній електростанції, діти.

MTHFR: 677TT GENOTYPE AND STATE OF HYPERHOMOCYSTEINEMIA IN THE CHILDREN OF REGIONS SUFFERED AS A RESULT OF THE ACCIDENT AT THE CHORNOBYL NUCLEAR POWER PLANT

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TT homozygous variant of MTHFR: C677T genetic polymorphism is associated with almost full loss of methylene tetrahydrofolatreductasa, the main enzyme of folate cycle. A degree of the manifestation of genetic polymorphism is connected with the external impact.
***Objective**. We determined the phenotypical manifestation of MTHFR: C677T genotype in the groups of the children from the regions, contaminated with the radioactive agents as a result of the accident of the Chornobyl nuclear power plant and having a different level of social-and-economic development, using the parameters of the content of homocystein in blood and frequencies of the occurrence of the state of hyperhomocysteinemia.*
***Methods:** immunochemical, mathematical-and-statistical.*
***Results**. In the subgroup of the children-carriers of MTHFR:677TT genotype, suffered from the accident at the Chornobyl nuclear power plant, a content of homocystein in blood was authentically larger in comparison with the subgroups of the children that were not the carrier of given genotype.*
The presence of risk allele of MTHFR:677TT T polymorphism predetermines the elevated homocystein formation in the children residing at the territory, contaminated with radioactive elements as a result of the accident at the Chornobyl nuclear power plant, in comparison with the children not having MTHFR:677TT genotype in the content of their genome.
Phenotypic manifestation of MTHFR:677TT genome as elevated formation of homocystein in the organism (state of hyperhomocysteinemia) is more expressed in the children from the regions that are in worse social-and-economic conditions after the accident at the Chornobyl nuclear power plant.

Keywords; hyperhomocysteinemia, MTHFR:677TT genotype, polymorphisms of folate cycle, T risk allele, areas contaminated with radionuclides, accident at the Chornobyl nuclear power plant, children.

Material and methods. 179 children from Ivankiv district and 84 children from Polesie district, Kiev region, Ukraine, whose average age was (14.7 ± 0.1) years (95% CI 14.6-14.9 years), living permanently since birth in rural localities affected by the CNPP accident (with a ^{137}Cs soil contamination density of <2 Cu/km^2 [14]) were studied.

All the children had blood drawn from the ulnar vein on an empty stomach in the morning to determine homocysteine levels and carry out genetic analysis of folate metabolism. All the children at the time of blood draw attended school.

The blood samples were analysed in a laboratory certified under quality standards within the project of the European Commission in Ukraine «Health and ecological programmes around the Chornobyl Exclusion Zone: Development, training and coordination of health-related projects» with the financial support of the Rhфne-Alpes Regional Council (France) and agreed with the parents in 2015.

Blood homocysteine levels were determined using an immunochemical method with chemiluminescent detection (CLIA). An analyser and a test system: Architect 1000 (ABBOT Diagnostics, USA).

In the children, blood homocysteine levels of over 10 μmol/L were defined as hyperhomocysteinemia.

The allelic variants C677T and A1298C of the MTHFR gene (methylenetetrahydrofolate reductase), A2756G of the MTR gene (B_{12}-dependent methionine synthase) and A66G of the MTRR gene (methionine synthase reductase) were determined during genetic analysis of folate metabolism.

A real-time PCR method was used. An analyser and a test system: the DT-96 detecting thermocycler, DNA-Technology (Russia).

An assessment of degree of phenotypic manifestation of the MTHFR:677TT genotype was carried out by comparing the percentage of hyperhomocysteinemia cases and blood homocysteine levels in genetic subgroups having and not having the MTHFR:677TT genotype in the children from two districts with different socioeconomic levels.

The comparison groups included the children with the same genotype of one of the four genetic polymorphisms of folate metabolism.

The statistical processing of the obtained results was performed using the IBM SPSS Statistics 22 software (USA). The arithmetic mean (M) ± standard error of mean (m), confidence

Table 1

Percentage of hyperhomocysteinemia cases in groups of children from Ivankiv and Polesie districts

Genotype	Ivankiv district			Polesie district		
	Number of cases	Hyperhomo-cysteinemia		Number of cases	Hyperhomo-cysteinemia	
		Absolute number	%		Absolute number	%
Homozygous TT	15	12	80.0	11	11	100.0
Other variants	164	119	73.0[1]	73	56	76.7[2]

Note: 1 — statistical differences, Ivankiv district (— t = 0.68; p = 0.497577);*
*2 — statistical differences, Polesie district (** — t = 4.6; p = 0.000017).*

interval for the average value (95% CI), median (Me), interquartile range (IR), minimum and maximum parameter values and percentiles were calculated for the variables analysed. The distribution hypothesis was tested (a Kolmogorov-Smirnov test). All the parameters under study did not conform to the normal distribution law, thus, a non-parametric U Mann-Whitney test was used to compare values. The statistical significance of variables was assessed by determining a significance level for p with the help of the statistical software programme. The Student's t-test was used to compare relative values. The critical level of significance for the null hypothesis (p) was set at 0.05.

Results and discussion. The MTHFR:677TT genotype was present in 8.4% of cases (15 out of 179 cases) in the group of children from Ivankiv district and in 13.1% of cases (11 out of 84 cases) in the group of children from Polesie district.

The proportion of hyperhomocysteinemia cases was statistically higher in the group of children from Polesie district in the subgroup of carriers of the MTHFR:677TT genotype than in the subgroup of subjects from the same district who do not have this genotype. No such association was noticed in the group of children from Ivankiv district (table 1).

A similar situation was observed when comparing the proportion of hyperhomocysteinemia in the subgroups with the MTHFR:677TT genotype and other folate metabolism genotypes. Unlike the group of children from Ivankiv district, the proportion of hyperhomocysteinemia was statistically lower in most subgroups of children from Polesie district compared to that with the MTHFR:677TT genotype (table 2).

Blood homocysteine levels were statistically significantly higher in the group of children who are carriers of the MTHFR:677TT genotype than in the general group of children as well as in other genetic subgroups who do not have this genotype (tables 3-6), except for the subgroup of children with the MTR:2756GG genotype from Polesie district, where no statistically significant differences were detected (tables 4, 6).

The studies conducted showed that under conditions of permanent living in the areas contaminated with radioactive substances as a result of the Chornobyl nuclear power plant accident, the children – carriers of the MTHFR:677TT genotype have higher levels of homocysteine in the blood compared to the children who are not carriers of this genotype.

All cases of carriership of the MTHFR:677TT genotype in the children from Polesie district were accompanied by hyperhomocysteinemia, while it did not occur in the children from Ivankiv district.

A statistically significant difference in the proportion of hyperhomocysteinemia cases was found between the subgroup of

Table 2

Percentage of hyperhomocysteinemia cases in groups of children from Polesie district

Group №	Polymorphisms, genotypes	Number of children in groups	Number of hyperhomocysteinemia cases		
			Absolute number	Percentage among children in a group, %	Statistical differences with a group № 9
1	MTR:2756 AA	48	38	79.17	t = 3.55; p = 0.000889
2	MTR:2756 AG	23	16	69.57	t = 3.17; p = 0.004132
3	MTR:2756 GG	2	2	100	-
4	MTHFR:1298A A	36	30	83.33	t = 2.68; p = 0.010707
5	MTHFR:1298A C	25	19	76.00	t = 2.81; p = 0.009098
6	MTHFR:1298C C	12	7	58.33	t = 2.93; p = 0.010381
7	MTHFR:677 CC	44	31	70.45	t = 4.30; p = 0.000112
8	MTHFR:677 CT	29	25	86.21	t = 2.15; p = 0.038581
9	MTHFR:677 TT	11	11	100	
10	MTRR:66AA	15	11	73.33	t = 2.34; p = 0.030642
11	MTRR:66AG	33	25	75.76	t = 3.25; p = 0.002662
12	MTRR:66GG	25	20	80.00	t = 2.50; p = 0.018551

*Note: * — statistically significant differences between values of all groups and that of a group № 9 (MTHFR:677TT genotype).*

Table 3

Statistical characteristics of blood homocysteine levels in children from Ivankiv and Polesie districts (μmol/L)

Genotype	Number of cases	Ivankiv district		Number of cases	Polesie district	
		Me	IR		Me	IR
Homozygous TT	15	16.6	12.1-26.7	11	15.0	13.2-22.1
Other variants	164	11.6	9.7-13.2[1]	73	11.7	10.1-13.8[2]

Note: Me — median, IR — interquartile range;
1 – statistical differences: Ivankiv district, TT variant: average rank – 127.8; variant without TT – 86.5; U Mann-Whitney test – 662.5; p=0.003; 2 — statistical differences: Polesie district, TT variant: average rank – 39.0; variant without TT – 65.7; U Mann-Whitney test – 146.5; p=0.001.

children from Polesie district who are carriers of the MTHFR:677TT genotype and the subgroups of children who are not carriers of this genotype.

Thus, the presence of the T risk allele of the MTHFR:C677T polymorphism in a homozygous state predetermines increased homocysteine formation in the children living in the areas contaminated with radioactive elements as a result of the Chornobyl nuclear power plant accident in comparison with the children who do not have the MTHFR:677TT genotype as part of their genome.

Taking into account the results of comparison of figures of the percentage of hyperhomocysteinemia in genetic subgroups, it can be concluded that the phenotypic manifestation of the MTHFR:677TT genotype in the group of children from Polesie district was more effective than in the group of children from Ivankiv district. Perhaps this is due to the fact that inhabitants of Polesie district live in worse socioeconomic conditions after the Chornobyl nuclear power plant accident than those in Ivankiv district [15] and do not have the opportunity to receive vital nutrients, including folic acid, in an adequate amount.

At the same time, they are forced to consume locally produced foodstuffs, forest gifts, wild animal meat and fish from local water bodies containing radioactive elements.

Conclusions

1. Blood homocysteine levels in the children – carriers of the MTHFR:677TT genotype from the districts affected by the Chornobyl nuclear power plant accident are significantly higher than in the children who are not carriers of this genotype.

2. Carriership of the T risk allele of the MTHFR:C677T polymorphism in a homozygous state is an internal risk factor for abnormal folate metabolism and hyperhomocysteinemia in the children living in the areas contaminated with radioactive elements as a result of the Chornobyl nuclear power plant accident.

3. The phenotypic manifestation of the MTHFR:677TT genotype in the form of increased homocysteine (hyperhomocysteinemia) formation is more pro-

Table 4

Statistical characteristics of homocysteine levels within genetic groups in children from Ivankiv and Polesie districts (μmol/L)

Polymorphism, genotype	Ivankiv district		Polesie district	
	Me	IR	Me	IR
MTR:A2756G				
AA	11.7	9.7 -13.7	12.4	10.8-15.0
AG	11.4	10.1 -13.3	10.6	9.8-12.3
GG	9.5	8.5 – 11.6	13.0	12.97-12.99
MTHFR:A1298C				
AA	11.2	9.6 – 12.7	11.8	10.6-13.4
AC	11.9	10.4 – 13.3	12.0	10.1-14.4
CC	9.1	7.9 – 12.6	10.8	9.4-16.9
MTHFR:C677T				
CC	11.3	9.4 – 12.9	11.4	9.7-14.1
CT	11.6	9.9 – 13.3	12.0	10.6-13.4
TT	16.6	12.1 – 26.7	15.0	13.2-22.1
MTRR:A66G				
AA	10.7	8.9 – 11.8	11.2	9.3-12.6
AG	11.3	9.5 – 12.9	12.0	10.0-13.4
GG	12.1	10.6 – 13.8	12.8	10.2-16.8

Note: Me — median, IR — interquartile range.

Table 5

Results of quantitative comparison (Ivankiv district) of populations (nonparametric analysis)

Polymorphism, genotype		Hc, μmol/L		
		Number of cases	Average rank	U Mann-Whitney test, statistical significance, p
MTR:A2756G MTHFR:C677T	AA	96	52.8	411.0, p=0.008
	TT	15	76.6	
MTR:A2756G MTHFR:C677T	AG	57	33.0	225.5, p=0.005
	TT	15	50.0	
MTR:A2756G MTHFR:C677T	GG	11	8.4	26.0, p=0.003
	TT	15	17.3	
MTHFR:A1298C MTHFR:C677T	AA	75	42.1	307.0, p=0.006
	TT	15	62.5	
MTHFR:A1298C MTHFR:C677T	AC	80	44.6	326.5, p=0.005
	TT	15	66.2	
MTHFR:A1298C MTHFR:C677T	CC	9	8.2	29.0, p=0.022
	TT	15	15.1	
MTHFR:C677T MTHFR:C677T	CC	81	44.7	299.0, p=0.002
	TT	15	69.1	
MTHFR:C677T MTHFR:C677T	CT	83	46.4	85.0, p=0.011
	TT	15	66.8	
MTRR:A66G MTHFR:C677T	AA	24	16.0	102.5, p=0.006
	TT	15	26.3	
MTRR:A66G MTHFR:C677T	AG	84	46.2	313.5, p=0.008
	TT	15	71.1	
MTRR:A66G MTHFR:C677T	GG	56	34.1	264.0, p=0.028
	TT	15	48.1	

nounced in the children from the areas being in worse socioeconomic conditions after the Chornobyl nuclear power plant accident.

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Table 6

Results of quantitative comparison (Polesie district) of populations (nonparametric analysis)

Polymorphism, genotype		Hc, μmol/L		
		Number of cases	Average rank	U Mann-Whitney test, statistical significance, p
MTR:A2756G MTHFR:C677T	AA	48	26.9	116.5, p=0.004
	TT	11	43.4	
MTR:A2756G MTHFR:C677T	AG	23	13.3	26.0, p=0.00001
	TT	11	26.6	
MTR:A2756G MTHFR:C677T	GG	2	3.5	4.0, p=0.231
	TT	11	7.6	
MTHFR:A1298C MTHFR:C677T	AA	36	20.3	65.0, p=0.001
	TT	11	36.1	
MTHFR:A1298C MTHFR:C677T	AC	25	15.2	54.5, p=0.004
	TT	11	26.1	
MTHFR:A1298C MTHFR:C677T	CC	12	8.8	27.0, p=0.016
	TT	11	15.6	
MTHFR:C677T MTHFR:C677T	CC	44	24.5	89.0, p=0.001
	TT	11	41.9	
MTHFR:C677T MTHFR:C677T	CT	29	17.0	57.5, p=0.002
	TT	11	29.8	
MTRR:A66G MTHFR:C677T	AA	15	9.2	18.0, p=0.001
	TT	11	19.4	
MTRR:A66G MTHFR:C677T	AG	33	18.7	55.0, p=0.001
	TT	11	34.0	
MTRR:A66G MTHFR:C677T	GG	25	15.9	73.5, p=0.028
	TT	11	24.3	

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ALLELIC POLYMORPHISM OF THE GENES OF DNA REPARATION AND LIKELIHOOD OF BRONCHOPULMONARY PATHOLOGY DEVELOPMENT IN MINERS AND WORKERS OF ASBESTOS CEMENT PLANTS IN UKRAINE

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АЛЛЕЛЬНЫЙ ПОЛИМОРФИЗМ ГЕНОВ РЕПАРАЦИИ ДНК И ВЕРОЯТНОСТЬ РАЗВИТИЯ БРОНХОЛЕГОЧНОЙ ПАТОЛОГИИ У ШАХТЕРОВ И РАБОТНИКОВ АСБЕСТОЦЕМЕНТНЫХ ЗАВОДОВ УКРАИНЫ

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Ключевые слова: молекулярно-генетические маркеры, XRCC1, XRCC3, бронхолегочная патология.

Заболевания органов дыхания от воздействия промышленных аэрозолей занимают центральное место в структуре профессиональной патологии и продолжают оставаться приоритетной проблемой медицины труда [1].

Важным направлением молекулярной биологии и медицины на современном этапе развития является разработка молекулярных основ профилактической медицины, фундаментом которой есть генетический полиморфизм. Известно несколько десятков генных полиморфизмов, вовлеченных в разные виды системы репарации [2]. Установлено, что нарушения в системе контроля над процессами репарации ДНК и апоптоза вызваны не только генетическими и эпигенетическими нарушениями, но и вариабельностью функционирования генов, обусловленной генетическим полиморфизмом [6].

АЛЕЛЬНИЙ ПОЛІМОРФІЗМ ГЕНІВ РЕПАРАЦІЇ ДНК ТА ВІРОГІДНІСТЬ РОЗВИТКУ БРОНХОЛЕГЕНЕВОЇ ПАТОЛОГІЇ У ШАХТАРІВ І ПРАЦІВНИКІВ АЗБЕСТОЦЕМЕНТНИХ ЗАВОДІВ УКРАЇНИ
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У статті представлено результати дослідження поліморфізму генів репарації ДНК у шахтарів і працівників азбестоцементних заводів з професійно зумовленою бронхолегеневою патологією.
***Мета роботи** — вивчити розподіл частот генотипів генів XRCC1 (rs25487) і XRCC3 (rs861539) у працівників азбестоцементних заводів та шахтарів для виявлення маркерів ризику розвитку бронхолегеневої патології.*
***Матеріали та методи.** Обстежено працівників азбестоцементних заводів і шахтарів. Методом полімеразної ланцюгової реакції у реальному часі визначали генотипи генів репарації ДНК.*
***Результати дослідження.** Встановлено, що генотип XRCC1*AA асоційований з ризиком розвитку бронхолегеневої патології у популяції працівників азбестоцементних заводів і шахтарів України. Встановлено протективну роль генотипу XRCC1*GA щодо ризику розвитку захворювань бронхолегеневої системи у працівників азбестоцементних заводів України.*

Ключові слова: молекулярно-генетичні маркери, XRCC1, XRCC3, бронхолегенева патологія.