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ГЕНЕТИЧНІ ПОЛІМОРФІЗМИ ФОЛАТНОГО ЦИКЛУ І ГІПЕРГОМОЦИСТЕЇНЕМІЯ У ДІТЕЙ ІЗ РАЙОНІВ, ЩО МЕЖУЮТЬ З ЧОРНОБИЛЬСЬКОЮ ЗОНОЮ ВІДЧУЖЕННЯ

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GENETIC POLYMORPHISMS OF THE FOLATE CYCLE AND HYPERHOMOCYSTEINEMIA IN CHILDREN FROM AREAS BORDERING THE CHORNOBYL EXCLUSION ZONE

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Hyperhomocysteinemia is an increased content in the blood, in excess of the established physiological level, of the sulfur-containing amino acid homocysteine (H_{cy}), a metabolic product of the essential amino acid methionine (Met).

Elevated levels of H_{cy} in the blood are associated in adults with a number of serious diseases associated with impaired

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***Мета дослідження:** встановлення зв'язку між поліморфізмами фолатного циклу та станом гіпергомоцистеїнемії у дітей, які проживають у районах, що межують з Чорнобильською зоною відчуження (ЧЗВ).*

***Методи дослідження:** лабораторний, генетичний, математико-статистичний.*

***Результати**. Визначено рівні гомоцистеїну (H_{cy}) у крові, а також генетичні поліморфізми фолатного циклу (ФЦ) у 690 дітей (322 хлопчиків та 368 дівчаток) вком 8-17 років, які проживають поблизу ЧЗВ. Встановлено, що у 97,8% випадків діти мали генотипи з алелями ризику поліморфізмів ФЦ. Найчастіше зустрічалися поєднання двох та трьох поліморфних варіантів.*

Питома вага випадків гіпергомоцистеїнемії реєструвалася у 62,5% обстежених дітей і не залежала, як правило, від числа поліморфізмів ФЦ з алелями ризику. У групах дітей, на відміну від їхніх матерів, був відсутній кореляційний зв'язок між концентрацією H_{cy} у крові та кількістю поліморфізмів ФЦ з алелями ризику.

Частота випадків гіпергомоцистеїнемії у хлопчиків була вірогідно вищою, ніж у дівчаток. Стан гіпергомоцистеїнемії виявлено у 40% випадків серед дітей за відсутності алелів ризику генетичних поліморфізмів ФЦ.

Генотипи з алельними варіантами одного поліморфізму ФЦ виявлено у 15% випадків. При цьому висока частота гіпергомоцистеїнемії реєструвалася у підгрупі з геноти-

blood supply to vital organs, cancer, pathology of pregnancy and embryo development, and diseases of the nervous system [1-6].

In children, hyperhomocysteinemia was recorded much less frequently, in particular, with the development of ischemic stroke [7].

However, in the course of the socio-medical project of the European Union in Ukraine «Health and Ecological Programmes around the Chornobyl Exclusion Zone: Development, training and coordination of health-related projects», hyperhomocysteinemia was detected in more than 70% of cases in children living near the Chornobyl Exclusion Zone (ChEZ), under conditions of constant radiation exposure [8].

Given the importance of Met and H_{cy} exchange in human life, it is logical to study the causes of this phenomenon.

In this case, first of all, it is necessary to assess the genetic factor that controls the enzymatic system of the folate cycle (FC).

The most studied genetic polymorphisms in this regard are MTR:A2756G, affecting methionine B_{12} synthase, MTRR:A66G, affecting methionine synthase reductase, MTHFR:A1298C and MTHFR: C677T, affecting methylenetetrahydrofolate reductase activity. All of them, to some extent, are important in the processes of H_{cy} methylation and its transformation into internal Met [9].

Each of these polymorphisms can have three allelic forms: a homozygous variant of risk alleles, a heterozygous variant that includes a risk allele and a neutral allele, and a homozygous variant of neutral alleles.

In one organism, allelic variants of all four of these FC polymorphisms are present simultaneously.

From a scientific and practical point of view, it is important to determine the role of FC genetic polymorphisms, including allelic variants of one polymorphism, as well as combinations of allelic variants of several polymorphisms, in the occurrence of hyperhomocysteinemia.

The aim of the work is to establish a relationship between polymorphisms of the FC and the state of hyperhomocysteinemia in children living in areas bordering the ChEZ.

Material and methods. A genetic and laboratory examination was carried out on 690 children (322 boys and 368 girls) aged 8-17 living near the ChEZ, in the Ivankivskyi and Poliskyi districts of the Kyiv region. The project, agreed with the parents of the children, was supported by the European Commission, the Regional Council of Rhone-Alpes (France), the French public organization «Children of Chornobyl».

When examining children who attended school, in the morning, on an empty stomach, blood was taken from the cubital vein.

The study of blood samples was carried out in a laboratory certified according to international quality standards.

During the genetic study of FC, allelic variants of the genetic polymorphisms MTHFR: C677T and MTHFR:A1298C, MTR:A2756G, MTRR:A66G were determined. At the same time, the following method was used: PCR in Real-time mode. Analyzer and test system detecting cycler «DT-96»; «DNA-Technology» (Russia).

The determination of H_{cy} in the blood was carried out using the immunochemical method with chemiluminescent detection (ECLIA). Analyzer and test system: Architect 1000 (ABBOT Diagnostics (USA). The level of Hcy in the blood of children over 10.0 μmol/l was defined as a state of hyperhomocysteinemia.

Statistical processing of the obtained results was carried out using the IBM SPSS Statistics 22 program (USA). Student's t-test was used to compare relative scores. The critical confidence level of the null hypothesis (p) was taken as 0.05. The hypothesis about the type of distributions was tested (Kolmogorov-Smirnov criterion). All the studied parameters did not correspond to the law of normal distribution.

The relationship between H_{cy} values and the number of genetic polymorphisms with FC risk alleles was determined using the Spearman rank correlation coefficient (r_{xy}). The statistical significance of the indicators was assessed by determining the significance level p using a statistical program. The strength of the cor-

пом T/TMTHFR:677, і у більшості генетичних підгруп. Висока частота гіпергомоцистеїнемії за чотирьох поліморфізмів з алелями ризику була пов'язана з компаунд-гетерозиготами A/CMTHFR:1298 та C/TMTHFR:677 у поєднанні з генотипами A/G MTR: A2756G та G/G A66G.

Гомозиготний варіант нейтральної алелі А генетичного поліморфізму MTRR:A66G, що контролює метіонін синтазу редуктази, сприяв поліпшенню процесів метилювання H_{cy} за алелів ризику трьох поліморфізмів ФЦ.

***Висновки**. Проведені дослідження свідчать про те, що у дітей другого чорнобильського покоління, які від народження проживають в умовах постійного радіаційного впливу у районах, що постраждали від аварії на ЧАЕС, виникнення гіпергомоцистеїнемії не пов'язане з конкретним генотипом та кількістю поліморфізмів ФЦ з алелями ризику. Отримані результати свідчать про участь генетичного і зовнішнього факторів у виникненні гіпергомоцистеїнемії у популяції досліджуваних дітей.*

Ключові слова: гіпергомоцистеїнемія, гени фолатного циклу, алелі ризику, діти, Чорнобильська зона відчуження.

GENETIC POLYMORPHISMS OF THE FOLATE CYCLE AND HYPERHOMOCYSTEINEMIA IN CHILDREN FROM AREAS BORDERING THE CHORNOBYL EXCLUSION ZONE

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The aim *of the work is to establish a relationship between polymorphisms of the FC and the state of hyperhomocysteinemia in children living in areas bordering the ChEZ).*
Research methods: *laboratory, genetic, mathematical-statistical.*
Results: *The levels of homocysteine (H_{cy} in blood and genetic polymorphisms of the folate cycle (FC) were determined in 690 children (322 boys and 368 girls) aged 8-17 years old living near the ChEZ. It was found that 97.8% of the children had genotypes with risk alleles of FC polymorphisms. The most common combinations of 2 and 3 polymorphic variants.*
The proportion of hyperhomocysteinemia cases was recorded in 62.5% of those examined and did not generally depend on the number of FC polymorphisms with risk alleles. Unlike their mothers, there was no correlation between blood H_{cy} concentration and the number of FC polymorphisms with risk alleles in children.
The frequency of hyperhomocysteinemia cases in boys was likely higher than in girls. Hyperhomocysteinemia was detected in 40% of cases among children with no risk alleles for FC genetic polymorphisms. Genotypes with allele variants of one FC polymorphism were found in 15% of cases. High frequency of hyperhomocysteinemia was recorded both in the subgroup with T/T MTHFR:677 genotype and in most genetic subgroups. A high frequency of hyperhomocysteinemia, with four polymorphisms with risk alleles, was associated with compound heterozygotes A/CMTHFR:1298 and C/TMTHFR:677 in combination with A/G MTR genotypes: A2756G and G/G A66G.
The homozygous variant of the neutral allele A of the MTRR:A66G genetic polymorphism, which controls methionine synthase reductase, contributed to the improvement of H_{cy} methylation processes in risk allele variants of three FC polymorphisms.
Conclusions: *The conducted studies indicate that in children of the second Chornobyl generation, who have been living in conditions of constant radiation exposure in areas affected by the Chornobyl accident since birth, the occurrence of hyperhomocysteinemia is not associated with a specific genotype and the number of FC polymorphisms with risk alleles. The results obtained indicate the participation of genetic and environmental factors in the occurrence of hyperhomocysteinemia in the population of children living in areas located near the ChEZ.*

Keywords: hyperhomocysteinemia, folate cycle genes, risk alleles, children, Chornobyl Exclusion Zone.

relation was assessed according to the traditional scale: weak – from 0 to 0.299; medium – from 0.3 to 0.699; strong – from 0.7 to 1.0.

Results and discussion. In the studied groups of school-age children from the Ivankyvskyi and Polyskyi districts of the Kyiv region of Ukraine, the smallest proportion had cases of the absence of risk alleles for all analyzed FC polymorphisms (table 1). A slightly larger proportion were cases of carriage of one polymorphism with a risk allele (table 1). The highest proportion had cases of carriage of risk alleles for two and three polymorphisms (table 1).

The proportion of cases with three polymorphisms with risk alleles in the group of boys was significantly higher than in the group of girls (table 1).

An increase in the level of H_{cy} in the blood above physiological parameters was recorded in 431 out of 690 children (62.5%), while in 425 cases their genome contained risk alleles for genetic polymorphisms of FC (98.6%). In 250 out of 675 children with genetic polymorphisms of the risk alleles of FC, the H_{cy} level did not exceed the upper limit of the physiological level (37.0%).

The smallest proportion of cases of hyperhomocysteinemia was found in subgroup No. 1, in the absence of risk al-

Table 1

The proportion of cases involving genetic polymorphisms of FC with risk alleles in the groups of examined children

Subgroup No	N	Groups of children by gender					
		Both sexes		Boys		Girls	
		n	%	n	%	n	%
1	0	15	2.2	5	1.5	10	2.7
2	1	103	14.9	50	15.5	53	14.4
3	2	313	45.4	138	42.9	175	47.6
4	3	209	30.3	111	34.5	98	26.6*
5	4	50	7.2	18	5.6	32	8.7
6	All cases	690	100.0	322	100.0	368	100.0

Note: N – number of polymorphisms.
** – statistical differences between boys and girls in subgroup No. 4 (t=2.25; p=0.025415).*

leles for all 4 FC polymorphisms. At the same time, an increase in the level of H_{cy} above the physiological level was recorded in 6 girls (table 2).

The proportion of cases of hyperhomocysteinemia, regardless of the number of polymorphisms with risk alleles, in the general group of children exceeded 60%, in the group of boys – 70%, in the group of girls – 50%.

In the general group, in subgroup No. 5, with a combination of risk alleles of 4 polymorphisms, the proportion of cases of hyperhomocysteinemia was significantly more than in subgroup No. 1 with the absence of risk alleles of 4 polymorphisms (tables 2, 3).

In the group of boys, the proportion of cases of hyperhomocysteinemia was statistically more in subgroup No. 5 compared with subgroup No. 3 (tables 2, 3).

In subgroups No. 2-6 of boys, the proportion of cases of hyperhomocysteinemia was significantly more than in similar subgroups of girls (tables 2, 3).

In the analyzed groups, there was no correlation between the number of polymorphisms with risk alleles and the concentration of H_{cy} in the blood (table 4).

In genetic subgroups, the proportion of cases of hyperhomocysteinemia did not depend on the number of FC polymorphisms with risk alleles (tables 5-7).

Previous studies have shown that the most pronounced increase in the level of H_{cy} in the blood, with the lowest content of vitamin B_9, was recorded in children with the T/TMTHFR: 677 genotype [10, 11].

In this study, in the case of risk alleles of one polymorphism, statistical differences were found in the group of boys between subgroups T/TMTHFR:677 and G/GMTRR: 66 (table 6).

In the case of risk alleles of two polymorphisms, statistical differences were found in the general group of children between subgroups T/TMTHFR: 677 and A/GMTR:2756, T/TMTHFR:677 and C/CMTHFR: 1298, and also, in the group of girls between subgroups T/TMTHFR:677 and C/CMTHFR: 1298 (table 5, 7). In the case of risk alleles of the three polymorphisms, statistical differences between subgroups in all groups of children were not identified (tables 5-7).

The combination of risk alleles of all 4 determined FC polymorphisms was distinguished by the absence of T/TMTHFR:677 and C/CMTHFR: 1298 genotypes, and included heterozygous variants C/TMTHFR:677 and A/CMTHFR: 1298 (compound heterozygotes) in combination with risk alleles of MTR polymorphisms: A2756G and MTRR: A66G (tables 5-7). At the same time, the largest proportion of cases of hyperho-

Table 2

The proportion of cases of hyperhomocysteinemia in the groups of examined children

Subgroup No	N	Groups of children by gender					
		Both sexes		Boys		Girls	
		n	%	n	%	n	%
1	0	6	40.0	0	0	6	60.0
2	1	66	64.1	38	76.0	28	52.8
3	2	193	61.7	98	71.0	95	54.3
4	3	132	63.2	81	73.0	51	52.0
5	4	34	70.8	16	88.9	18	56.3
6	All cases	431	62.5	233	72.4	198	53.8

Note: N – number of polymorphisms.

Table 3

Statistical differences in the proportion of cases of hyperhomocysteinemia in the groups of children examined

Comparison groups/subgroups		Student's t-test	Significance level, p
Both sexes № 1	Both sexes № 5	2.16	0.037029
Boys № 3	Boys № 5	2.14	0.034544
Boys № 2	Girls № 2	2.53	0.013741
Boys № 3	Girls № 3	3.10	0.002265
Boys № 4	Girls № 4	3.19	0.001781
Boys № 5	Girls № 5	2.84	0.007910
Boys № 6	Girls № 6	5.16	0.000001

Table 4

The results of the correlation analysis between H_{cy} and the number of genetic

Groups	Correlation coefficient, r_{xy}	Parameters	
		H_{cy}, μmol/l	N
Both sexes	Spearman's	0.003	
	p	0.932	
	N	690	
Boys	Spearman's	0.097	
	p	0.081	
	N	322	
Girls	Spearman's	- 0.093	
	p	0.074	
	N	368	

Note: N – number of polymorphisms of the folate cycle genes with risk alleles.

mocysteinemia was recorded with a combination of genotypes A/GMTR:2756-A/CMTHFR:1298-C/TMTHFR:677-G/GMTRR:66 (table 8).

The presence in the genome of the homozygous variant of the neutral allele of the studied FC polymorphisms did not significantly affect the proportion of cases of hyperhomocysteinemia with 1 or 2 polymorphisms with risk alleles (tables 9, 10).

However, with three polymorphisms with risk alleles, in the subgroup with the homozygous variant of the A allele of the MTRR:66 polymorphism, the proportion of cases of hyperhomocysteinemia was less than in the subgroups with homozygous variants of the neutral alleles of the MTR:2756, MTHFR: 1298, MTHFR:677 polymorphisms (table 11). Statistical differences were traced in the general group and the group of boys (table 12).

The conducted studies showed that the children's population on the territory of the Ukrainian Polissia, near the Chornobyl nuclear power plant (ChNPP), is characterized by a large number of cases with risk alleles for FC polymorphisms. Only 2.2% of children are not carriers of risk alleles for the studied polymorphisms.

The greatest number of children contain risk alleles of two and three FC polymorphisms in their genome.

Among the examined children, cases with risk alleles of one FC polymorphism amounted to about 15%. At the same time, the most common genotypes were A/G MTRR: 66 and G/G MTRR:66.

In 62.5% of cases among all examined children, a state of hyperhomocysteinemia was detected, indicating a violation of the processes of H_{cy} remethylation and the formation of internal Met. The frequency of manifestation of the state of hyperhomocysteinemia, in most cases, was not associated with the number of FC polymorphisms containing risk alleles.

Table 5

The proportion of cases of hyperhomocysteinemia in the general group of children with risk alleles for FC polymorphisms

Subgroup/ main genotype	Genetic polymorphisms with risk alleles											
	1 polymorphism			2 polymorphisms			3 polymorphisms			4 polymorphisms		
	N^1	N^2	%	N^1	N^2	%	N^1	N^2	%	N^1	N^2	%
A/GMTR:2756	4	3	75.0	55	29	52.73	123	75	61.0	44	30	68.2
G/GMTR:2756	2	2	100	10	6	60.0	19	11	57.9	6	4	66.7
A/CMTHFR:1298	18	14	77.8	109	69	63.3	120	74	61.7	50	34	68.0
C/CMTHFR:1298	6	2	33.3	39	18	46.24	20	11	55.0	0	0	0
C/TMTHFR:677	14	8	57.1	120	76	63.3	127	81	63.8	50	34	68.0
T/TMTHFR:677	7	6	85.7	33	25	75.8	19	14	73.7	0	0	0
A/GMTRR:66	26	14	53.9	145	89	61.4	122	84	68.9	35	22	62.9
G/GMTRR:66	26	17	65.4	113	73	64.6	76	45	59.2	15	12	80.0

Note: N^1 – number of children in the subgroup; N^2 – number of cases of hyperhomocysteinemia. N^3 – statistical differences in subgroups A/GMTR:2756 and T/TMTHFR:677 with two polymorphisms (t=2.30; p=0.025625); N^4 – statistical differences in subgroups C/CMTHFR:1298 and T/TMTHFR:677 (t=2.71; p=0.009755).

Table 6

The proportion of cases of hyperhomocysteinemia in the group of boys with risk alleles for FC polymorphisms

Subgroup/ main genotype	Genetic polymorphisms with risk alleles											
	1 polymorphism			2 polymorphisms			3 polymorphisms			4 polymorphisms		
	N^1	N^1	%	N^1	N^2	%	N^1	N^2	%	N^1	N^2	%
A/GMTR:2756	2	2	100	25	15	77.9	68	48	70.6	16	14	87.5
G/GMTR:2756	2	2	100	4	2	50.0	10	7	70.0	2	2	100
A/CMTHFR:1298	10	8	80.0	47	33	70.2	58	43	74.1	18	16	88.9
C/CMTHFR:1298	2	1	50.0	23	12	52.2	12	8	66.7	0	0	0
C/TMTHFR:677	8	5	62.5	49	39	79.6	66	47	71.2	18	16	88.9
T/TMTHFR:677	2	2	100	12	10	83.3	13	10	76.9	0	0	0
A/GMTRR:66	9	7	77.8	68	47	69.1	68	53	77.9	12	10	83.3
G/GMTRR:66	15	11	73.33	48	38	79.2	38	27	71.1	6	6	100

Note: N^1 – number of children in the subgroup; N^2 – number of cases of hyperhomocysteinemia. N^3 – statistical differences in subgroups G/GMTRR:66 and T/TMTHFR:677 with one polymorphism (t=2.34; p=0.0414).

Only in the subgroup of boys with a combination of four polymorphisms with risk alleles, the proportion of cases of hyperhomocysteinemia was significantly higher than in the subgroup of boys with a combination of two polymorphisms with risk alleles.

Also, in groups of children, no correlation was found between the concentration of H_{cy} in the blood and the number of polymorphisms with risk alleles.

At the same time, in mothers, examined children, there was a direct relationship between the number of genetic polymorphisms of FC with risk alleles and indicators reflecting the content of H_{cy} in the blood (r=0.336*, p=0.006, n=66), as well as the proportion of cases of hyperhomocysteinemia (Fig. 1) [12].

The largest and smallest proportion of cases of hyperhomocysteinemia accounted for, respectively, in subgroups of children with risk alleles for all four FC polymorphisms and without them.

In the absence of polymorphisms with risk alleles, the state of hyperhomocysteinemia was recorded only in the group of girls.

However, the proportion of cases of hyperhomocysteinemia in the same subgroups with different numbers of risk alleles in the group of boys was significantly higher than in the group of girls.

In certain genetic subgroups, there was no relationship between the proportion of cases of hyperhomocysteinemia and the number of polymorphisms with risk alleles. At the same time, a high frequency of hyperhomocysteinemia was recorded.

Table 7

The proportion of cases of hyperhomocysteinemia in the group of girls with risk alleles for FC polymorphisms

Subgroup/ main genotype	Genetic polymorphisms with risk alleles											
	1 polymorphism			2 polymorphisms			3 polymorphisms			4 polymorphisms		
	N^1	N^2	%	N^1	N^2	%	N^1	N^2	%	N^1	N^2	%
A/GMTR:2756	2	1	50.0	30	14	46.7	55	27	49.1	28	16	57.1
G/GMTR:2756	0	0	0	6	4	66.7	9	4	44.4	4	2	50.0
A/CMTHFR:1298	8	6	75.0	62	36	58.1	62	31	50.0	32	18	56.3
C/CMTHFR:1298	4	1	25.0	16	6	37.53	8	3	37.5	0	0	0
C/TMTHFR:677	6	3	50.0	71	37	52.1	61	34	55.7	32	18	56.3
T/TMTHFR:677	5	4	80.0	21	15	71.4	6	4	66.7	0	0	0
A/GMTRR:66	17	7	41.2	77	42	54.5	54	31	57.4	23	12	52.2
G/GMTRR:66	11	6	54.5	65	35	53.8	38	18	47.4	9	6	66.7

Note: N^1 – number of children in the subgroup; N^2 – number of cases of hyperhomocysteinemia. N^3 – statistical differences in subgroups T/TMTHFR:677 and C/CMTHFR:1298 with two polymorphisms (t=2.17; p=0.04347).

Table 8

The proportion of cases of hyperhomocysteinemia in groups of children with an association of risk alleles of 4 FC polymorphisms

Genotypes	Groups of children by gender								
	Both sexes			Boys			Girls		
	N^1	N^2	%	N^1	N^2	%	N^1	N^2	%
A/GMTR:2756-A/CMTHFR:1298-C/TMTHFR:677-A/GMTRR:66	29	18	62.1	10	8	80.0	19	10	52.6
G/GMTR:2756-A/CMTHFR:1298-C/TMTHFR:677-A/GMTRR:66	6	4	66.7	2	2	100	4	2	50.0
G/GMTR:2756-A/CMTHFR:1298-C/TMTHFR:677-G/GMTRR:66	0	0	0	0	0	0	0	0	0
A/GMTR:2756-A/CMTHFR:1298-C/TMTHFR:677-G/GMTRR:66	15	12	80.0	6	6	100	9	6	66.7

Note: N^1 – number of children in the subgroup; N^2 – number of cases of hyperhomocysteinemia.

It should be noted the influence on the processes of H_{cy} methylation of the genetic polymorphism MTRR:A66G, the homozygous variant of the neutral allele of which significantly reduces the proportion of cases of hyperhomocysteinemia in the group of children with risk alleles of three FC polymorphisms.

Genotypes with a risk allele of one polymorphism are of interest in terms of identifying the role of one specific element of the FC enzyme system in the etiology of hyperhomocysteinemia. First of all, this concerns the T/TMTHFR:677 genotype.

In the examined groups of boys and girls of the second Chornobyl generation, a high frequency of hyperhomocysteinemia was recorded, not

only in the subgroup with the T/TMTHFR:677 genotype, but also in most genetic subgroups with risk alleles for both one and several FC polymorphisms.

The presence in the genome of children with risk alleles for FC polymorphisms did not necessarily lead to an increase in the level of Hcy in the blood. In 37 % of children with risk alleles for FC polymorphisms, the level of H_{cy} in the blood did not go beyond the physiological parameters.

The conducted studies showed the absence of a close relationship between the number of FC genetic polymorphisms with risk alleles and an increase in the H_{cy} level in the analyzed group of children.

The absence of a significant statistical difference in the proportion of cases of hyperhomocysteinemia in most genetic subgroups of boys and girls, with a different number of FC polymorphisms, indicates an external environmental reason for this phenomenon.

The negative environmental impact on H_{cy} remethylation is also evidenced by the fact that the state of hyperhomocysteinemia was determined in children whose genome did not contain risk alleles for FC polymorphisms.

Thus, in children of the second Chornobyl generation, permanently residing in the territory affected by the accident at the ChNPP, the occurrence of hyperhomocysteinemia is due to the combined effect of internal (the state of the genetic apparatus of FC) and external environmental (radiation) factors.

Conclusions

School-age children permanently residing in the areas of Ukrainian Polissia bordering the ChEZ in 97.8% of cases had genotypes with risk alleles for PC polymorphisms. The most common combinations of 2 and 3 polymorphic variants.

The proportion of cases of hyperhomocysteinemia was

Table 9

The proportion of cases of hyperhomocysteinemia in groups of children with risk alleles of one FC polymorphism

Subgroup/ main genotype	Groups of children with risk alleles of one polymorphism								
	Both sexes			Boys			Girls		
	N^1	N^2	%	N^1	N2	%	N^1	N^2	%
A/AMTR:2756	97	61	62.9	46	34	73.9	51	27	52.9
A/AMTHFR:1298	79	50	63.3	38	29	76.3	41	21	51.2
C/CMTHFR:677	82	52	63.4	40	31	77.5	42	21	50.0
A/AMTRR:66	51	35	68.6	26	20	76.9	25	15	60.0

Note: N^1 – number of children in the subgroup;
N^2 – number of cases of hyperhomocysteinemia.

Table 10

The proportion of cases of hyperhomocysteinemia in groups of children with risk alleles of two FC polymorphisms

Subgroup/ main genotype	Groups of children with risk alleles of two polymorphisms								
	Both sexes			Boys			Girls		
	N^1	N^2	%	N^1	N^2	%	N^1	N^2	%
A/AMTR:2756	248	158	63.7	109	81	74.3	139	77	55.4
A/AMTHFR:1298	165	106	64.2	68	53	77.9	97	53	54.6
C/CMTHFR:677	160	92	57.5	77	49	63.6	83	43	51.8
A/AMTRR:66	55	31	56.4	22	13	59.1	33	18	54.5

Note: N^1 – number of children in the subgroup;
N^2 – number of cases of hyperhomocysteinemia.

Table 11

The proportion of cases of hyperhomocysteinemia in groups of children with risk alleles of three FC polymorphisms

Subgroup/ main genotype	Groups of children with risk alleles of two polymorphisms								
	Both sexes			Boys			Girls		
	N^1	N^2	%	N^1	N^2	%	N^1	N^2	%
A/AMTR:2756	67	46	68.7	33	26	78.8	34	20	58.8
A/AMTHFR:1298	69	47	68.1	41	30	73.2	28	17	60.7
C/CMTHFR:677	63	37	58.7	32	24	75.0	31	13	41.9
A/AMTRR:66	11	3	27.3	5	1	20.0	6	2	33.3

Note: N^2 – number of children in the subgroup;
N^2 – number of cases of hyperhomocysteinemia.

Table 12

Statistical differences in the proportion of cases of hyperhomocysteinemia in subgroups of children

Comparison subgroups		Student's t-test	Significance level, p
A/AMTR:2756 – Both sexes	A/AMTRR:66 – Both sexes	2.84	0.006699
A/AMTHFR:1298 – Both sexes	A/AMTRR:66 – Both sexes	2.80	0.007329
C/CMTHFR:677 – Both sexes	A/AMTRR:66 – Both sexes	2.12	0.040528
A/AMTR:2756 – Boys	A/AMTRR:66 – Boys	3.05	0.005459
A/AMTHFR:1298 – Boys	A/AMTRR:66 – Boys	2.77	0.009758
C/CMTHFR:677 – Boys	A/AMTRR:66 – Boys	2.83	0.009820

recorded in 62.5 % of the examined children and did not depend, in most cases, on the number of FC polymorphisms with risk alleles. In the general group of children, it exceeded the level of 60%, in the group of boys – 70%, in the group of girls – 50%.

However, in the subgroup of boys with a combination of four polymorphisms with risk alleles, the proportion of hyperhomocysteinemia was significantly higher than in the subgroup of boys with a combination of two polymorphisms with risk alleles.

In the groups of children, unlike their mothers, there was no correlation between the concentration of H_{cy} in the blood and the number of FC polymorphisms with risk alleles.

In the group of boys, the proportion of cases of hyperhomocysteinemia was significantly higher (72.4%) than in the group of girls (53.8%), while differences persisted in subgroups with a different number of genetic polymorphisms with risk alleles.

The state of hyperhomocysteinemia was detected in 40% of cases among children with no risk alleles for FC genetic polymorphisms.

The level of H_{cy} in the blood did not exceed the upper limit of the physiological level in 37.0% of children with risk alleles for FC genetic polymorphisms. In individual genetic subgroups of FC, the proportion of cases of hyperhomocysteinemia did not depend on the number of polymorphisms with risk alleles.

Genotypes with allelic variants of one FC polymorphism were found in 15% of cases. At the same time, a high frequency of hyperhomocysteinemia was recorded both in the subgroup with the T/TMTHFR:677 genotype and in most genetic subgroups.

A high frequency of hyperhomocysteinemia, with four polymorphisms with risk alleles, was associated with compound heterozygotes A/CMTHFR1298 and C/TMTHFR: 677 in combination with A/G MTR genotypes: A2756G and G/G A66G.

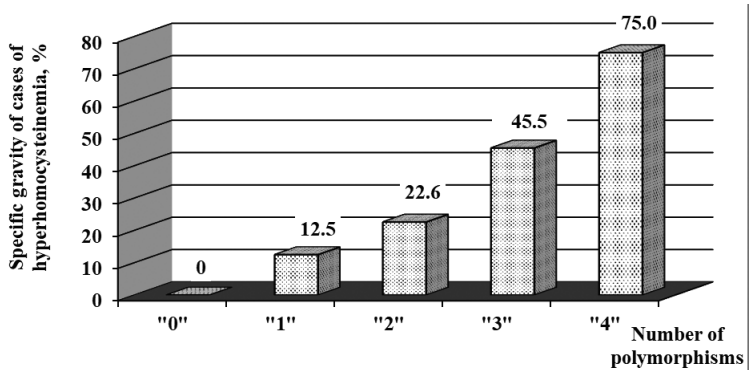
The homozygous variant of the neutral allele A of the genetic polymorphism MTRR:A66G, which controls methionine synthase reductase, contributed to the improvement of H_{cy} methylation processes in the risk alleles of three FC polymorphisms.

The conducted studies indicate that in children of the second Chornobyl generation, permanently living under conditions of constant radiation exposure in areas affected by the Chornobyl accident, the occurrence of hyperhomocysteinemia is not associated with a specific genotype and the number of FC polymorphisms with risk alleles.

The results obtained indicate the participation of genetic and environmental factors in the occurrence of hyperhomocysteinemia in the population of children living in areas located near the ChEZ.

Fig. 1

The proportion of cases of hyperhomocysteinemia depending on the number of genetic polymorphisms with risk alleles in the group of mothers of the examined children [12]



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HYGIENE PLANNING AND BUILDING OF POPULATED CITIES AS A SAFE DETERMINANT OF PUBLIC HEALTH UNDER THE CONDITIONS OF MARITAL STATE

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ГІГІЄНА ПЛАНУВАННЯ ТА ЗАБУДОВИ НАСЕЛЕНИХ МІСЦЬ ЯК БЕЗПЕКОВА ДЕТЕРМІНАНТА ГРОМАДСЬКОГО ЗДОРОВ'Я В УМОВАХ ВОЄННОГО СТАНУ

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В Україні продовжує діяти воєнний стан, в умовах якого першочерговим завданням держави є питання збереження здоров'я і життя населення [1]. Пріоритетним є попередження шкідливого впливу воєнного стану на формування дитячого організму та створення умов для виховання і навчання дітей [2]. Зважаючи на це, вирішення питань щодо колективного цивільного захисту має здійснюватися шляхом будівництва/реконструкції споруд цивільного захисту з урахуванням потреб дорослих і дітей [3-5].

Метою роботи є розробка санітарно-гігієнічних вимог до споруд цивільного захисту громадської та житлової забудови під час воєнних дій та їх використання у повоєнний період як споруд подвійного призначення.

ГІГІЄНА ПЛАНУВАННЯ ТА ЗАБУДОВИ НАСЕЛЕНИХ МІСЦЬ ЯК БЕЗПЕКОВА ДЕТЕРМІНАНТА ГРОМАДСЬКОГО ЗДОРОВ'Я В УМОВАХ ВОЄННОГО СТАНУ
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