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რეზიუმე

ფიბროზის მარკერ ST2-ის და ანგიტენზინოგენის პოლიმორფიზმის როლი გულის ქრონიკული უკმარისობის პროგრესირებაში შაქრიანი დიაბეტი ტიპი 2-ის მქონე ავადმყოფებში

ი. რუდიკი, ე. მედენცევა

უკრაინის მეცნიერებათა ეროვნული აკადემიის ლ. მალოის სახ. თერაპიის ეროვნული ინსტიტუტი, ხარკოვი, უკრაინა

გულის ქრონიკული უკმარისობის (გქუ) მეურნალობაში მიღწეული პროგრესის მიუხედავად, მისი პროგნოზი არაკეთილსაიმედო რჩება, იმის გამო, რომ გქუ-ის მნიშვნელოვანი ქვეჯგუფები არასაკმარისადაა გამოკვლეული. ეს ეხება გქუ-ით ავადმყოფებს მეტაბოლური დარღვევების ფონზე, კერძოდ, შაქრიანი დიაბეტი ტიპი 2-ისა. ცნობილია,

რომ ATG M235T გენის rs699 მარკერის პოლიმორფიზმი დაკავშირებულია მიდრეკილებასთან არტერიული ჰიპერტენზიის, გულის იშემიური დაავადების და წინაგულების ფიბრილაციისადმი. დადგენილია კავშირი M235T-პოლიმორფიზმსა და გულის უკმარისობის განვითარების რისკს შორის. ერთ-ერთ პერსპექტულ და ახალ ბიომარკერად ითვლება ფიბროზის მარკერი ST2. კვლევის მიზანს შეადგენდა ბიომარკერ ST2-ის და ATG M235T გენის გენეტიკური პოლიმორფიზმის როლის გარკვევა გქუ-ის პროგრესირებასა და არაკეთილსაიმედო მოვლენების განვითარებაში თანხმლები შაქრიანი დიაბეტი ტიპი 2-ის მქონე პაციენტებში. დადგენილია, რომ, MM გენოტიპის მტარებლებთან შედარებით, გენოტიპ TT+MT-ის მქონე პაციენტებს გქუ-ით, მარცხენა პარკუჭის განდევნის ფრაქციის შენარჩუნებით და შაქრიანი დიაბეტი ტიპი 2-ით, აქვთ ფიბროზის მარკერ ST2-ის უფრო მაღალი დონე და არაკეთილსაიმედო გულ-სისხლძარღვოვანი მოვლენების განვითარების მეტი ალბათობა.

INTERRELATION OF THE GENE CDKN1A (RS 1801270) POLYMORPHIC STATE AND LEVEL OF DEVELOPMENT OF CARIES IN CHILDREN WITH DOWN SYNDROME

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The significant prevalence and high intensity of oral cavity organs' diseases in people, in particular in children, determine the necessity of conducting preventive measures aimed at maintaining dental health that significantly predetermine the whole body's health [3,5,6]. Considering polyetiology of oral cavity diseases, the individual approach to each patient is very important. Timely estimation of pathogenetically determined risk factors of caries development in children with Down syndrome will allow preventing development of pathological process.

The main factors predisposing diseases of periodontal tissues and teeth are the microflora of the oral cavity and dental plaque, uncontrolled use of carbohydrates and poor hygiene of the oral cavity, somatic disorders and reduced immunity. Peculiarities of development of teeth and periodontal tissues also play the key role in developing oral cavity [7,13]. Their full development is ensured through a complex of genes whose protein products control different stages of this complex process. Changes in gene structure as well as their expression's destruction can lead to destruction of development of teeth and periodontal tissues.

CDKN1A gene (also known as p21) which encodes protein p21 is a universal cyclin-dependent kinase inhibitor involved in controlling the cell cycle. The p21 gene-

product is involved in the first stage of the primary enamel knots' development (Primary Enamel Knot) of milk, and then permanent teeth. This process starts on the 8th week of embryogenesis after the formation of the dental plate. The role of gene CDKN1A is shown during enamel tubercle apoptosis [15], there is some positive correlation between the level of CDKN1A gene expression at the primary stages of odontogenesis and the structure and shape of the crown [4].

To date, there is an unexamined question about the relationship of polymorphism of genes that control the cell cycle with the development of pathologies of the dentition and periodontal tissues. Of particular interest is the study of this question in groups of children with an increased risk of developing caries, for example, with chromosome diseases. Genotyping and the formation of groups of risks for subsequent observation based on individual genetic predisposition is the most effective approach to the prevention and timely detection of cariogenic situation.

Thus, the purpose of this work is to analyze the connection of polymorphic status of CDKN1A gene (rs1801270) with the level of intensity of caries development in children with Down syndrome living in Kharkiv region.

Material and methods. The study has been carried out on the basis of the University Dental Center of Kharkiv

National Medical University. The total number of examined patients is 43 children aged from 2 to 17 years. The core group consists of 10 children with Down syndrome which was represented by insomnia of 21 chromosomes with the exception of 1 case. The control group consists of 33 children without chromosomal pathology. To adequately compare the core and control groups, we have divided the control group into 2 age categories: the first one is children from 2 to 10 years (15 people – control 1) and the second one is children from 11 to 17 years (18 people – control 2). The groups are comparable in age and gender. All the examined children and their parents have been informed of the purpose of the study and the methodologies to be applied. The parents have given written consent to participate in the study.

The study of a dental status of children has involved determining the condition of hard tissues of teeth, namely, index of caries intensity (cf, CFR + cf, CFR; c – carious teeth, f – filled teeth, r – removed teeth) and the calculation of caries intensity level – CIL (Leus).

One of the indices determining the level of a carious process in children is index of caries intensity.

For children with temporary bite we have used the following indices:

- cf – a number of carious and filled teeth of a temporary bite;

- cfs – a number of affected surfaces of temporary teeth.

Teeth in a temporary bite removed in result of physiological change have not been taken into account.

For children with mixed dentition we have used the following indices:

- CFR + cf – a number of carious, filled permanent and temporary teeth and removed permanent teeth;

- CFRs + cfs - a number of carious surfaces in permanent and temporary teeth and a number of removed permanent teeth.

For assessment of a permanent bite we have used the following indices:

- CFR – a number of carious, filled and removed teeth;

- CFRs – a number of caries-affected teeth surfaces and removed teeth [3].

The index of caries intensity level – CIL (Leus), which allows determining individual and group levels of caries

intensity by CFR of teeth in any age, has been calculated by the formula:

$CIL = cf / n$; n is age of a child (for children under 8 years old);

$CIL = CFR / n-5$, (from 9 to 19 years old), n-5 is 5 years of life without permanent teeth;

$CIL = CFR / n$, (for children with a permanent bite and adults).

Assessment of caries activity by different indices of CIL has been carried out according to the Table 1 data [9].

To conduct genotyping we have used buccal epithelial cells. The collection of biomaterial for the study has been conducted during the dental examination by using sterile disposable urogenital probe in individual containers marked in accordance with the methodology [1]. DNA has been extracted by using a commercial set of Diatom™ DNA Prep 100 (Russia) in accordance with the instruction of the manufacturer [1]. Typing of SNP polymorphism in codon 31 of *CDKN1A* gene(rs1801270) has been conducted by using the polymerase chain reaction (PCR), PCR products processed by restrictase and subsequent analysis of the polymorphism of the lengths of restriction fragments (PLRF). The necessary conditions for the analysis of the polymorphism of *CDKN1A* gene are shown in Table 2.

The presence of the restriction site (two products of restriction 183 p.n. + 89 p.n.) testifies of the presence of the allele *Cin* the third position of codon 31 *CDKN1A* gene (*Ser* in 31 position of the polypeptide chain). The absence of the restriction site (one fragment 272 p.n.) – the allele (*Arg* in 31 position of polypeptide chain). Thus, *CC* homozygotes (*Ser/Ser*) are characterized by the presence of two DNA fragments with the size of 183 p.n. and 89 p.n.; *AA* homozygotes (*Arg/Arg*) – a fragment with the size of 272 p.n.; heterozygotes *CA* (*Ser/Arg*) are characterized by the presence of three fragments with the size 272 p.n., 183 p.n. and 89 p.n. [1].

To conduct PCR of alleles of *CDKN1A* gene, we have used the automatic thermocycler “Tercik” (Russia) and commercial sets of reagents GenPak™ PCR Core (0.5 ml) (Russia), in accordance with the manufacturer’s instructions. PCR conditions: denaturation within 5 min at 94°C; 35 cycles consisting of denaturation within 20 sec at 94°C, annealing of primers

Table 1. Assessment of caries activity by different indices of CIL

Age	Low caries activity	Average caries activity	High caries activity	Huge caries activity
1-8 years	≤0,4	0,5 – 0,8	0,9 – 1,2	≥ 1,3
9-19 years	≤0,3	0,4 – 0,6	0,7 – 0,9	≥ 1,0
> 20 years	≤0,155	0,16 – 0,3	0,31 – 0,6	≥ 0,6

Table 2. PCR primers, restrictase and sizes of the fragments obtained after restriction necessary for analysis of the polymorphism of *DKN1A* gene

Gene	Genotype	Restrictase	Size of fragments, p.n.	Primers
<i>CDKN1A</i>	<i>Ser/Arg</i>	Bpu1102I (BspI)	272=183+89	F 5’- ACCAGCTGGAAGGAGTGAGA- 3’ R 5’-GTCTTTGCTGCCTACTTGC- 3’

within 20 sec at 58°C, elongation within 20 sec at 72°C; final elongation within 7 min at 72°C [1].

Detection of PCR results has been conducted by dividing the amplification products in 2% agarose gel at constant voltage 70V within an hour. For electrophoresis we have used commercial sets ELA-50 (“Neogene”, Ukraine). Visualization of the fragments has been conducted by ethidium bromide processing of gel and subsequent analysis on a transilluminator in ultraviolet light. The sizes of the fragments have been determined in comparison with a marker of molecular weight of pUC19 DNA/Mspl (HpaII) Marker, 23 (Thermo Fisher Scientific Inc.)

The difference between the control and core groups on alleles available in codon 31 of *CDKN1A* gene has been determined by using the criterion of Kruskal-Wallis. The reliability of differences between the control and core groups has been evaluated by using Student’s F-criterion. Calculation of the frequency of alleles of *CDKN1A* gene is carried out by using GenoMprofessional. Comparison of the theoretically expected and actual frequencies of genotypes has been conducted by using χ^2 criterion. Statistical processing of data and mathematical analysis are carried out by using BioStat 2008 Professional.

Results and their discussion. When assessing the individual genetic characteristics of patients with Down syndrome compared with a group of apparently healthy donors without somatic diseases, we have obtained the following

results. Checking the distribution of genotypes by SNP of *CDKN1A* gene *Ser31Arg* in the control and core groups for compliance with the Hardy-Weinberg equilibrium has shown that the distribution of genotypes not significantly differs from the theoretically expected results (Table 3).

When analyzing the genotypes of polymorphic locus of *CDKN1A* gene in codon 31 in groups of the examined patients, we have received the following data: genotype C/C has been determined more frequently in both groups (average in population – 0.728). Genotypes containing the allele A (heterozygous C/A and homozygous A/A) are present in the population of children of Kharkiv region with frequency 0.251 and 0.022.

Among the examined children, in both groups (diagnosed “Down syndrome”), the dominant allele of *CDKN1A* gene is option C (*Ser*) which is typical for the most populations studied. The frequency of alleles containing triplet AGC (*Ser*) or triplet AGA (*Arg*) in codon 31 of *CDKN1A* gene has not statistically differed in the core and control groups (Table 4), which is confirmed by checking the results of the study by using the Kruskal-Wallis criterion, which has not shown significant differences in the frequency of alleles of *CDKN1A* gene in the control and core groups ($p=0.978$).

Evaluation of the effectiveness level of caries development has shown that there are significant differences in the control (control 1) and core groups in homo- and heterozygotes in the studied allele of *CDKN1A* gene (Fig. 1).

Table 3. Frequency of genotypes of polymorphic locus of *CDKN1A* gene in codon 31 in groups with Down syndrome (core group) and apparently healthy donors (control group)

Genotype	The core group	χ^2 , level p	The control group	χ^2 , level p
C/C (ser/ser)	0.810	0.12, 0.73	0.708	1.29, 0.26
C/A (ser/arg)	0.180		0.267	
A/A (arg/arg)	0.010		0.025	

Table 4. Comparison of frequency of alleles of a polymorphic locus in *CDKN1A* gene in codon 31 in groups of children with Down syndrome and apparently healthy donors

Allele	Patients with Down syndrome	Apparently healthy donors	χ^2 ,	p level
	n = 10	n = 41		
AGC (ser)	0.900	0.841	0.44	0.51
AGA (arg)	0.100	0.159		

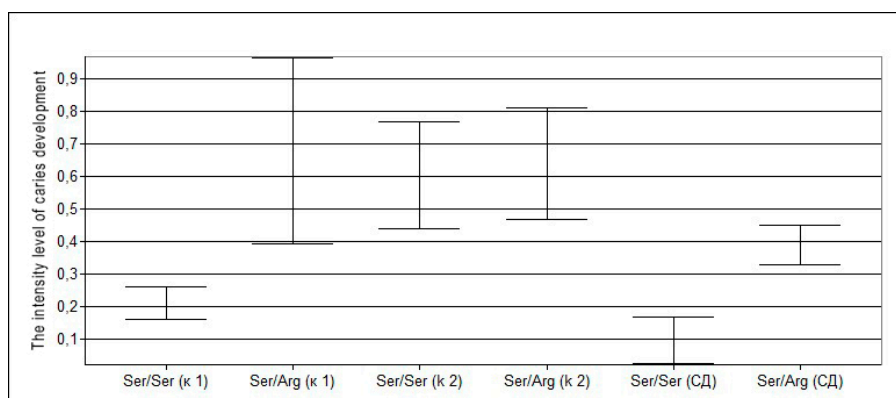


Fig. 1. The intensity level of caries development in the core and control groups (k 1 and k 2) in homo- and heterozygotes in the studied polymorphism *Ser31Arg* of *CDKN1A* gene

So, it is shown that the intensity of caries development (by Leus) is higher in children with heterozygous genotype (*Ser/Arg*) up to the age of 10 years both in the control (k 1) and core (diagnosed “Down syndrome”) groups. The differences between different genotypes are not shown in elder children of the control group (k 1).

Thus, the study has established the association of heterozygous option *C/A* of the studied marker *Ser31Arg* with the intensity level of caries development (by Leus) in children under 10 years old living in Kharkiv region. Unfortunately, we cannot say whether the allele *A* contributes to the formation of the cariogenic situation, since the sample studied in the work is small enough, and homozygotes *A/A* (*Arg/Arg*) detected by genotyping are not enough for a statistical analysis.

CDKN1A gene is located on chromosome 6p21.2 and consists of three exons and two introns. *p21* broadcast area lies mainly in exon 2 that encodes a protein with a molecular weight 21 kDa [16]. This protein is a cyclin-dependent kinase inhibitor (CDKI) which stops the cell proliferation and DNA replication both in physiological conditions and after DNA damage [11]. The complex of p53 protein with *CDKN1A* gene induces mediated G1/S cell cycle arrest, playing a critical role in cellular response to DNA damage. Polymorphism in codon 31 of *p21* gene (rs1801270) is associated with transversion *C* to *A* and replaces the serine (*Ser*) to arginine (*Arg*). It results in a loss of the restriction site that affects the sequence Znfinger which binds with DNA. The study has shown that this polymorphism plays a role in causing cancer. So, there is an association of polymorphism *p21 Ser31Arg* with the risk of cancer of the lungs, breast, neck of uterus [12, 14], tumors of the gastrointestinal tract [2]. Also, it is found that expression of *p21* gene plays an important role in odontogenesis, participating in formation of tooth follicles [4, 15]. Our research has shown that there is a connection between the polymorphism *CDKN1A Ser31Arg* with the intensity level of caries development in children living in Kharkiv region up to the age of 10 years. The lack of detected polymorphism in elder children can be evidently explained by the fact that genes of cell cycle control are difficult to consider as a distinct and unambiguous marker of formation of the cariogenic situation. This is due to the complex multifactorial nature of caries.

A higher level of the intensity of caries development in heterozygotes (*Ser/Arg*) would allow the use of genotyping (in particular rs1801270) when forming risk groups for subsequent monitoring and timely detection of caries status in both groups of children with Down syndrome, characterized by an increased risk of caries, and groups of apparently healthy children without somatic pathologies.

Conclusions. Analysis of the polymorphism of *CDKN1A* gene *Ser31Arg* in children living in Kharkiv region has shown that the frequency of genotypes and alleles corresponds to the theoretically expected distribution by Hardy-Weinberg in the core ($\chi^2 = 0.12$) and control ($\chi^2 = 1.29$) groups. There is no significant differences in the frequency of alleles of *CDKN1A* gene in the group of healthy children and children with Down syndrome ($p = 0.978$).

There is an association of a heterozygous option *C/A* of the studied marker *Ser31Arg* of *CDKN1A* gene with the intensity level of caries development (by Leus) in children under the age of 10 years.

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SUMMARY

INTERRELATION OF THE GENE CDKN1A (RS 1801270) POLYMORPHIC STATE AND LEVEL OF DEVELOPMENT OF CARIES IN CHILDREN WITH DOWN SYNDROME

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Study is devoted for rs1801270 polymorphism of CDKN1A gene due to the level of intensity of caries development in children with Down syndrome.

The full development of oral cavity organs is ensured through a complex of genes whose protein products control different stages of this difficult process. Changes in gene structure, as well as disturbance of their expression may lead to abnormalities of development of teeth and periodontal tissues. Analysis of the polymorphism of CDKN1A gene Ser31Arg in children living in Kharkiv region has shown that the frequency of genotypes and alleles corresponds to the theoretically expected distribution by Hardy-Weinberg in the core ($\chi^2=0.12$) and control ($\chi^2=1.29$) groups. There is no significant differences in the frequency of alleles of CDKN1A gene in the group of healthy children and children with Down syndrome ($p=0.978$). There is an association of heterozygous option C/A of the studied marker Ser31Arg of CDKN1A gene with the level of intensity of caries development (by Leus) in children with Down syndrome under 10 years old.

Keywords: caries, CDKN1A, gene, Ser31Arg, children, Down syndrome.

РЕЗЮМЕ

ВЗАИМОСВЯЗЬ ПОЛИМОРФНОГО СОСТОЯНИЯ ГЕНА CDKN1A (RS 1801270) И УРОВНЯ ИНТЕНСИВНОСТИ РАЗВИТИЯ КАРИЕСА У ДЕТЕЙ С СИНДРОМОМ ДАУНА

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Работа посвящена изучению полиморфизма rs1801270 гена CDKN1A с учетом уровня интенсивности развития кариеса у детей с синдромом Дауна.

Развитие органов полости рта обеспечивается комплексом генов, белковые продукты которых контролируют разные этапы этого сложного процесса. Изменения в структуре генов, а также нарушение их экспрессии, могут привести к нарушению формирования зубов и тканей пародонта. Анализ полиморфизма гена CDKN1A Ser31Arg у детей, проживающих в Харьковской области, показал, что частота генотипов и аллелей соответствует теоретически ожидаемому распределению Харди-Вайнберга в исследуемой ($\chi^2=0,12$) и контрольной ($\chi^2=1,29$) группах. Существенных различий в частоте аллелей гена CDKN1A в группе здоровых детей и детей с синдромом Дауна ($p=0,978$) не выявлено.

Установлена ассоциация гетерозиготного варианта C/A изучаемого маркера Ser31Arg гена CDKN1A с уровнем интенсивности развития кариеса (по Леусу) у детей с синдромом Дауна в возрасте до 10 лет.

რეზიუმე

გენი CDKN1A (RS 1801270)-ის პოლიმორფულ მდგომარეობასა და კარიესის განვითარების ინტენსივობას შორის ურთიერთკავშირი დაუნის სინდრომით ბავშვებში

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ნაშრომი ეძღვნება გენ CDKN1A (RS 1801270)-ი პოლიმორფიზმის კვლევას კარიესის განვითარების ინტენსივობასთან მიმართებით დაუნის სინდრომით ბავშვებში.

პირის ღრუს ორგანოების განვითარება განპირობებულია გენების კომპლექსით, რომელთა ცილოვანი პროდუქტები აკონტროლებს ამ რთული პროცესის სხვადასხვა ეტაპს. ცვლილებებმა გენების სტრუქტურაში, ასევე, მათი ექსპრესიის დარღვევამ, შესაძლოა გამოიწვიოს კბილებისა და პაროდონტის ქსოვილების ფორმირების დარღვევები.

გენი CDKN1A Ser31Arg-ის პოლიმორფიზმის ანალიზმა ხარკოვის ოლქში მცხოვრებ ბავშვებში აჩვენა, რომ გენოტიპების და ალელების სისშირე შეესაბამება ხარდი-ვაინბერგის მოსალოდნელ თეორიულ განაწილებას საკვლევე ($\chi^2=0,12$) და საკონტროლო ($\chi^2=1,29$) ჯგუფებში. არ გამოვლინდა არსებითი განსხვავება გენ CDKN1A-ის ალელების სისშირეში ჯანმრთელ და დაუნის სინდრომის მქონე ბავშვებში ($p=0,978$).

დადგენილია გენ C Ser31Arg-ის შესწავლილი მარკერის C/A ჰეტეროზიგოტური ვარიანტის ასოციაცია კარიესის განვითარების ინტენსივობასთან (ლეუსის მიხედვით) 10 წლამდე ასაკის დაუნის სინდრომის მქონე ბავშვებში.