UDC 616-021.5-053.2-07:575.2 https://doi.org/10.26641/2307-0404.2022.1.254378

V.O. Dityatkovsky [1] *,
N.V. Naumenko [1],
O.O. Alifirenko [2],
N.L. Pinaeva [2],
S.T. Taran [2],
I.A. Filatova [2],
O.Ye. Abaturov [1]

SINGLE NUCLEOTIDE VARIANTS OF FILAGGRIN AND GLUCOCORTICOID RECEPTORS GENES IN CHILDREN SUFFERING DIFFERENT PHENOTYPES OF ATOPIC DISEASES

Dnipro State Medical University [1]
V. Vernadskyi str., 9, Dnipro, 49044, Ukraine
**e-mail: 419_04@dmu.edu.ua*
Allergological Center of the Municipal Communal Enterprise "Clinical Hospital of Ambulance" of the Dnipro City Council [2]
Shmidta str., 28, Dnipro, 49000, Ukraine
e-mail: dneprallergy@gmail.com
Дніпровський державний медичний університет [1]
вул. В. Вернадського, 9, Дніпро, 49044, Україна
Алергологічний центр КНП «Клінічна лікарня швидкої медичної допомоги» Дніпровської міської ради [2]
вул. Шмідта, 28, Дніпро, 49000, Україна

Цитування: Медичні перспективи. 2022. Т. 27, № 1. С. 132-139
Cited: Medicni perspektivi. 2022;27(1):132-139

Key words: *atopic diseases, children, single nucleotide variants, filaggrin, glucocorticoid receptors*
Ключові слова: *атопічні захворювання, діти, однонуклеотидні варіанти, філагрин, глюкокортикоїдні рецептори*
Ключевые слова: *атопические заболевания, дети, однонуклеотидные варианты, филаггрин, глюкокортикоидные рецепторы*

Abstract. Single nucleotide variants of filaggrin and glucocorticoid receptors genes in children suffering different phenotypes of atopic diseases. Dityatkovsky V.O., Naumenko N.V., Alifirenko O.O., Pinaeva N.L., Taran S.T., Filatova I.A., Abaturov O.Ye. *Currently, there is an apparent need for genotype-associated personalization of the diagnostic process for atopic diseases (AtD) in children: atopic dermatitis (AD), seasonal allergic rhinitis (conjunctivitis – (SAR(C)), perennial allergic rhinitis (conjunctivitis – (PAR(C)) and bronchial asthma (BA) in different phenotype combinations - monotopic and polytopic. The aim of the study was to identify associations of the genotype variants of SNV rs_7927894 of FLG gene, rs10052957 and rs41423247 of NR3C1 gene in children with AD, SAR(C), PAR(C) and/or BA in mono- and polytopic phenotypes. The study recruited 293 children with AD who were divided into 6 phenotypic clusters: monotopic phenotypes: No. 1 – AD (58 patients); No. 2 – SAR(C)/PAR(C) (71 patients); No. 3 – BA (23 patients); polytopic phenotypes: No. 4 – AD+ SAR(C)/PAR(C) (43 patients), No. 5 – BA+SAR(C)/PAR(C) (72 patients), No. 6-AD+BA+SAR(C)+PAR(C) (26 patients). In patients of all 6 clusters buccal swab of the oral mucosa was taken for genotyping the variants: C/C, C/T, T/T SNV rs7927894 of FLG gene; A/A, A/G, G/G SNV rs10052957 and C/C, C/G, G/G SNV rs41423247 of NR3C1 gene. Heterozygous variant C/T SNV rs_7927894 FLG is the most common, directly associated and significantly increases the risk of polytopic AtD phenotypes: AD+SAR(C)/PAR(C) by 2.47 (95% CI 1.14-5.38, p<0.05) times and AD+BA+SAR(C)+PAR(C) – by 3.13 times (95% CI 1.24-7.95, p<0.05) related to monotopic phenotype SAR(C)/PAR(C). The heterozygous variant A/G SNV rs10052957 of the NR3C1 gene is the most common in all AtD phenotypes, except for monotopic BA and polytopic AD+SAR(C)/PAR(C), and significantly, by 0.40 times (95% CI 0.18-0.93, p<0.05) reduces the risk of the polytopic phenotype related to AD. Homozygous variant G/G SNV rs10052957 of the NR3C1 gene is most common in the monotopic phenotype SAR(C)/PAR(C) and polytopic AD+SAR(C)/PAR(C) as well as in AD+BA+SAR(C)/PAR(C) and significantly increases by 2.97 times (95% CI 1.31-6.74, p<0.05) and decreases by 0.45 times (95% CI 0.21-0.97, p<0.05) the risk of developing AD+SAR(C)/PAR(C) related to AD. Heterozygous variant A/G rs10052957 of the NR3C1 gene significantly reduces by 0.40 times (95% CI 0.18-0.93, p<0.05) the risk of polytopic phenotype BA+SAR(C)+PAR(C) related to AD+SAR(C)/PAR(C). Heterozygous variant C/G SNV 41423247 of the NR3C1 gene was the most common and significantly increased by 2.03 times (95% CI 1.01-4.10, p<0.05) the risk of monotopic AD phenotype related to SAR(C)/PAR(C).*

Реферат. Однонуклеотидные варианты генов филаггрина и глюкокортикоидных рецепторов у детей, больных различными фенотипами атопических заболеваний. Дитятковский В.А., Науменко Н.В., Алифиренко О.А., Пинаева Н.Л., Таран С.Т., Филатова И.А., Абатуров А.Е. *В настоящее время существует актуальная потребность в генотип-ассоциированной персонализации диагностического процесса*

атопических заболеваний (АЗ) у детей: атопического дерматита (АД), сезонного аллергического ринита (конъюнктивита) (САР(К)), круглогодичного аллергического ринита (конъюнктивита) (КАР(К)) и бронхиальной астмы (БА) в различных фенотипных сочетаниях – монотопических и политопических. Цель исследования – выявление ассоциаций генотипных вариантов SNV rs_7927894 гена FLG, rs10052957 и rs41423247 гена NR3C1 у детей, больных АД, САР(К), ЦАР(К), БА в моно- и политопических фенотипах. В исследование было включено 293 ребенка, больных АЗ, которые были распределены на 6 фенотипических кластеров: монотопические фенотипы: № 1 – АД (58 больных); № 2 – САР(К)/ЦАР(К) (71 больной); № 3 – БА (23 больных); политопические фенотипы: № 4 – АД+САР(К)/ЦАР(К) (43 больных), № 5 – БА+САР(К)/ЦАР(К) (72 больных), № 6-АД+БА+САР(К)/ЦАР(К) (26 больных). Пациентам всех 6 кластеров был взят буккальный соскоб слизистой оболочки полости рта для генотипирования по вариантам C/C, C/T, T/T SNV rs7927894 гена FLG; A/A, A/G, G/G SNV rs10052957, C/C, C/G, G/G SNV rs41423247 гена NR3C1. Гетерозиготный вариант C/T SNV rs_7927894 гена FLG наиболее часто встречается, прямо ассоциирован и повышает риски развития политопических фенотипов АЗ: АД+САР(К)/ЦАР(К) в 2,47 раза (95%ДИ 1,14-5,38), p<0,05) и АД+БА+САР(К)/ЦАР(К) в 3,13 раза (95%ДИ 1,24-7,95, p<0,05) относительно монотопического фенотипа САР(К)/ЦАР(К). Гетерозиготный вариант A/G SNV rs10052957 гена NR3C1 наиболее распространён при всех фенотипах АЗ, кроме монотопического БА и политопического АД+САР(К)/ЦАР(К), и достоверно до 0,40 раза (95%ДИ 0,18-0,93, p<0,05) снижает риск развития последнего в отношении АД. Гомозиготный вариант G/G SNV rs10052957 гена NR3C1 наиболее частый при монотопическом фенотипе САР(К)/ЦАР(К) и политопических АД+САР(К)/ЦАР(К) и АД+БА+САР(К)/ЦАР(К) и достоверно повышает в 2,97 раза (95% ДИ 1,31-6,74, p<0,05) и в 0,45 раза снижает (95% ДИ 0,21-0,97) риск развития АД+САР(К)/ЦАР(К) относительно АД. Гетерозиготный вариант A/G rs10052957 гена NR3C1 достоверно снижает до 0,40 раза (95% ДИ 0,18-0,93) риск политопического фенотипа БА+САР(К)+ЦАР(К) относительно АД+САР(К)+ЦАР(К). Гетерозиготный вариант C/G SNV 41423247 гена NR3C1 был наиболее частым и достоверно увеличивает в 2,03 раза (95%ДИ 1,01-4,10, p<0,05) риск заболевания монотопическим фенотипом АД относительно САР(К)/ЦАР(К).

Atopic diseases (AtD) are chronic allergic conditions based on a genetically determined tendency to hyperproduction of class E immunoglobulins. Atopic diseases are characterized by a polymorphism of clinical manifestations in the form of skin lesions (atopic dermatitis – AD), upper respiratory tract and/or eyes (seasonal allergic rhinoconjunctivitis – SAR(C), perennial allergic rhinitis/rhinocconjunctivitis – PAR(C) or lower respiratory tract (bronchial asthma – BA) [4].

The development of atopic diseases is associated with genetic single nucleotide variants (SNVs) of various genes [11]. In particular, SNV rs7927894 of the filaggrin gene (filaggrin – FLG), which is located in the chromosomal region 11q13.5, plays a key role in the development of atopic dermatitis in children, regardless of allergic sensitization [3]. However, the influence of SNV rs7927894 of the *FLG* gene on the development of other atopic diseases in children has not been demonstrated. The clinical significance of SNV of the glucocorticoid receptor gene (nuclear receptor subfamily 3 group C member 1 – NR3C1), whose functional activity determines the course of atopic diseases and individual sensitivity to glucocorticoid (GC) therapy [6], remains practically unexplored in pediatric practice. In the scientific literature, separate works are presented, in which clinical associations of SNVs of the *NR3C1* gene are defined. Thus, SNV rs10052957 of the NR3C1 gene is associated with a low level of response to treatment with GC drugs and an increased level of risk of developing severe forms of atopic diseases [8], and SNV rs41423247 of the *NR3C1* gene is associated with a high risk of developing BA in adults [10]. Other studies indicate the ability of SNV *NR3C1* rs10052957 to cause a reduced ability of GC drugs to inhibit gene expression and, accordingly, the synthesis of transforming growth factor-beta in isoform 1, which increases the frequency and strength of asthma exacerbations due to an increase in the concentration of the indicated inflammatory mediator, enhancing peribronchial and subepithelial fibrosis [9]. In a study of the Han population, a higher frequency of A/A and G/G SNV *NR3C1* rs10052957 genotypes was indicated in adults with BA, but these results were not statistically significant [5].

The aim of our study was to determine the associations and risk of developing different phenotypes of AtD in children with SNV genotypes rs7927894 of the *FLG* gene and rs10052957, rs41423247 of the *NR3C1* gene.

MATERIALS AND METHODS OF RESEARCH

293 children aged from 3 to 18 years (median (interquartile range – IQR) – 9 (6-12) years) were involved in the study. Before the start of the study, the parents or legal representatives of the child patients signed voluntary informed consent for a medical diagnostic examination in accordance with the Declaration of Helsinki (edition dated October 10, 2013, Fortaleza, Brazil). The protocol of this study was approved by the Biomedical Ethics Committee of the Dnipro State Medical University.

The diagnosis of AtD was established clinically and confirmed by additional research methods in the inpatient and consultative-diagnostic children's

departments of the Allergo-Center of the MNE "Clinical Hospital of Emergency Medical Care of the Dnipro City Council", Dnipro, Ukraine.

The patients suffered from AD, SARC, PARC and/or BA in different phenotypes – monotopic with damage to one topographic region and polytopic with damage to several topographic regions. In view of this, we introduced the division of all patients into 6 clusters to establish the associations and risks of the studied genotypes with AtD phenotypes. Monotopic phenotypes: cluster No. 1 – skin lesions, AD (58 patients); cluster No. 2 – lesions of the upper respiratory tract and/or eyes, SAR(C)/PAR(C) (71 patients); cluster No. 3 – lesions of the lower respiratory tract, BA (23 patients). Polytopic phenotypes: cluster No. 4 – lesions of the skin and upper respiratory tract and/or eyes: AD+ SAR(C)/PAR(C) (43 patients); cluster No. 5 – lesions of the upper and lower respiratory tract and/or eyes, BA+SAR(C)/PAR(C) (72 patients); cluster No. 6 – lesions of the skin, upper and lower respiratory tract and/or eyes, AD+SAR(C)/PAR(C)+BA (26 patients). The clusters were compared with each other according to variants of genotypes C/C, C/T, T/T SNV rs7927894 of the *FLG* gene; A/A, A/G, G/G SNV rs10052957, C/C, C/G, G/G SNV rs41423247 of the *NR3C1* gene.

All patients involved in the study underwent buccal scraping, the obtained material was then delivered to storage in refrigeration equipment at a temperature of – 32C. After the collection of the material, it was transported with observance of the temperature chain to the laboratory of the Department of General and Molecular Pathophysiology of the Institute of Physiology named after O.O. Bogomolets National Academy of Sciences of Ukraine. For genotyping, the method of polymerase chain reaction in real time with restriction fragment length polymorphism RFLP-PCR/qPCR) was used.

To carry out this reaction, certified reagents of Applied Biosystems TaqMan SNP Genotyping Assays® C_3243267_10, Custom TaqMan® SNP Genotyping Assays 300 rxn (4331349) and TaqMan® Pre-designed SNP Genotyping Assays, small scale/human (4351379) on the specialized equipment Applied Biosystems 7500 Fast Real Time PCR System were used. For genotyping the sample from each patient, 10-15 μl of extract from the primary sample was used, which was extracted using the NeoPrep100 reagent. SNVs were considered to be made at a minor allele frequency of >0.05 or >5%.

Data on the occurrence of genotypic variants C/C, C/T, T/T SNV rs7927894 of the *FLG* gene; A/A, A/G, G/G SNV rs10052957 and C/C, C/G, G/G SNV 41423247 of the *NR3C1* gene in clusters 1-6 are presented as relative (%) values; descriptive statistics of mean values included median (Me) and interquartile range (IQR). Pearson's $\chi 2$ test ($\chi 2$) was used to assess the reliability of the differences between the relative indicators obtained for clusters 1-6, and the Mann-Whitney test (U) with correction for multiple comparisons was used for average values. Spearman's rank correlation coefficient (r) was used to identify associations (correlations) of the above-mentioned genotypes with different study clusters. To determine the risks of developing mono- and polytopic phenotypes of AtD, logistic regression analysis was used to calculate the odds ratio (OR) with a 95% confidence interval (95% CI). The criterion of $p \leq 0.05$ was established as the degree of statistical reliability [1].

Statistical calculations were performed using the licensed software product Statistica v.6.1 (license number AGAR909E415822FA, Statsoft Inc., USA).

RESULTS AND DISCUSSION

According to gender characteristics, a general predominance of boys was obtained both in the entire sample and in particular clusters (Table 1). Male patients predominated in clusters 2, 3 and 5 ($p \leq 0.05$ compared to cluster 1).

Table 1

Distribution of patients by gender between clusters

Gender	Clusters, No.						Complete group група (n=293)
	monotopic phenotypes			polytopic phenotypes			
	1 (n=58)	2 (n=71)	3 (n=23)	4 (n=43)	5 (n=72)	6 (n=26)	
Girls	44.8	28.2 *	21.7 *	39.5	23.6 *	26.9	31.4
Boys	55.2	71.8 *	78.3 *	60.5	76.4 *	73.1	68.6
Total	100	100	100	100	100	100	100

Note. * – statistical significance ($p \leq 0.05$) compared to cluster 1 (according to Pearson's $\chi 2$ test).

Analysis of the age distribution of patients revealed the following significant differences between the studied clusters: the phenotypic variant of monotopic AD is more common in children aged from 4 to 6 years, the full polytopic phenotype (AD+BA+SAR(C)+PAR(C)) is more common in older age groups from 12 to 18 years old, and monotopic lesions of the upper respiratory tract and eyes – SAR(C)/PAR(C) are more common in children of primary school age from 7 to 11 years (Table 2).

Table 2

Distribution of patients by age in clusters (%)

Age, (years)	Clusters, No.						Complete group (n=293)
	1 (n=58)	2 (n=71)	3 (n=23)	4 (n=43)	5 (n=72)	6 (n=26)	
0-3	12.1	2.8	0.0	2.3	1.4	7.7	4.4
4-6	41.3	29.6	26.1	18.6	6.9	0.0	21.8
7-11	34.5	46.5	52.2	46.5	38.9	38.5	42.0
12-18	12.1	21.1	21.7	32.6	52.8	53.8	31.8
Me (IQR)	6 (4-10)	9 (6-11)	8 (6-11)	9 (7-12)	12 (9-15)	12 (10-14)	9 (6-12)
Difference with cluster*	2.4.5.6	1.5.6	5	1.6	1.2.3	1.2.4	-

Note. * – statistical significance of mean values ($p \leq 0.05$) between corresponding clusters (according to за критерієм Mann-Whitney test).

When determining the spectrum of genotypic variants of SNV rs7927894 of the *FLG* gene, it was established that the C/C genotype was more common in patients with BA phenotype (cluster 3), and the C/T genotype in patients with a combination of AD with other AtD (clusters 4 and 6) (Table 3).

Further analysis of differences according to this genotype made it possible to identify clusters of patients, reliably homogeneous according to its various variants relative to others, and to establish their associations and the risk (chances) of getting sick with certain combinations of nosologies (Table 4).

Table 3

Distribution of genotypes SNV rs7927894 of the *FLG* gene in different clusters of patients with AtD (%)

Clusters, №	Genotype SNV rs7927894 of the *FLG* gene		
	C/C	C/T	T/T
Complete group (n=293)	37.9	45.7	16.4
1 (n=58)	34.5	46.6	19.0
2 (n=71)	43.7	33.8	22.5
3 (n=23)	52.2	39.1	8.7
4 (n=43)	27.9	55.8	16.3
5 (n=72)	38.9	47.2	13.9
6 (n=26)	30.8	61.5	7.7

Table 4 shows that the heterozygous C/T genotype is reliably associated with polytopic phenotypes of AtD – its carriers have a 2.47-fold increase in the risk (chances) of developing AD combined with SAR(C)/PAR(C) (95% CI 1.14-5.38), and for AD, combined with BA and SAR(C)/PAR(C), 3.13 times (95% CI 1.24-7.95) compared to monotopic phenotype of SAR(C)/PAR(C). That is, in the presence of the SNV rs_7927894 SNV rs_7927894 genotype of the FLG gene, the risk of combined damage to the skin and upper and/or lower respiratory tract increases significantly. The homozygous C/C genotype is more associated with the development of a monotopic BA phenotype than with the AD+SAR(C)/PAR(C) phenotype (OR=2.82, 95% CI 1.0-8.10, p=0.05).

Table 4

Associations and risks of developing phenotypes AtD with different genotypes SNV rs7927894 of the *FLG* gene

Ratio of clusters, No.	Genotype SNV rs7927894 of the *FLG* gene	Association, r	Odds ratio, OR (95% CI)
4 to 2	C/T	0.216	2.47 (1.14-5.38)
6 tot 2	C/T	0.250	3.13 (1.24-7.95)
3 to 4	C/C	0.240 *	2.82 (1.0-8.10) *

Note. * – p=0.05, in other cases p<0.05 (according to Pearson's χ2 test).

The distribution of SNV rs10052957 of *NR3C1* gene genotypes in patients is shown in Table 5. The highest frequency of genotype A/A was observed in patients with BA (17.4%), genotype A/G – in patients with AD (51.7%), genotype G/G SNV rs10052957 of the *NR3C1* gene – in patients with polytopic pathology AD+SAR(C)/PAR(C) (62.8%).

Table 5

Distribution of genotypes SNV rs10052957of the *NR3C1* gene in different clusters of patients with AtD (%)

Clusters, №	Genotype SNV rs10052957 of the *NR3C1* gene		
	A/A	A/G	G/G
Complete group (n=293)	9.9	43.0	47.1
1 (n=58)	12.1	51.7	36.2
2 (n=71)	7.0	42.3	50.7
3 (n=23)	17.4	39.1	43.5
4 (n=43)	7.0	30.2	62.8
5 (n=72)	11.1	45.8	43.1
6 (n=26)	7.7	42.3	50.0

Table 6 shows data on significant differences, associations, and the risk of disease for different phenotypes of AtD for SNV rs10052957 of the *NR3C1* gene.

The data in Table 6 indicate reliable associations of hetero- and homozygous genotypes of SNV rs10052957 of the *NR3C1* gene with polytopic phenotypes of AtD: A/G with AD+SAR(C/)PAR(C) with a reduced risk of disease development up to 0.40 times (95% CI 0.18-0.93); G/G – with AD+SAR(C/)PAR(C) with an increase in risk up to 2.97 times (95% CI 1.31-6.74) relative to the monotopic variant of AD. At the same time, this genotype is inversely associated with BA+SAR(C)/PAR(C) (r=-0.191) with a risk reduction up to 0.45 times (95% CI 0.21-0.97) compared to polytopic phenotype AD+SAR(C/)PAR(C).

Table 6

Associations and risks of developing AtD with different genotypes SNV rs10052957 of the *NR3C1* gene

Ratio of clusters, №	Genotype SNV rs10052957 of the *NR3C1* gene	Association, r	Odds ratio, OR (95% CI)
4 to 1	A/G	-0.215	0.40 (0.18-0.93)
4 to 1	G/G	0.263 *	2.97 (1.31-6.74) *
5 to 4	G/G	-0.191	0.45 (0.21-0.97)

Note. * – p<0.01, in other cases p<0.05 (according to Pearson's χ2 test).

Tables 7 and 8 show data on the distribution, associations and risk of morbidity for different phenotypes of AtD in children according to genotypic SNV rs414232477 of the *NR3C1* gene.

The data in Tables 7 and 8 indicate that the heterozygous genotype C/G SNV rs414232477 of the *NR3C1* gene is most frequent in cluster No. 1 (56.9%) and is directly associated with the development of the monotopic AD phenotype (r=0.174, p<0.05), increasing its risk up to 2.03 times (95% CI 1.01-4.10) compared to the SAR(C/)PAR(C) phenotype. That is, this genotype significantly reduces the risk (OR=0.49 (95% CI 0.24-0.99), p<0.05) of developing lesions of the upper respiratory tract in the form of SAR(C)/PAR(C) compared to AD.

Table 7

Distribution of genotypes SNV rs414232477 of the *NR3C1* gene in different clusters of patients with AtD (%)

Clusters, №	Genotype SNV rs41423247 of the *NR3C1* gene		
	C/C	C/G	G/G
Complete group (n=293)	8.2	47.1	44.7
1 (n=58)	6.9	56.9	36.2
2 (n=71)	11.3	39.4	49.3
3 (n=23)	8.7	43.5	47.8
4 (n=43)	7.0	48.8	44.2
5 (n=72)	5.6	47.2	47.2
6 (n=26)	11.5	46.2	42.3

The results obtained in our study coincide with the data of the study by Marenholz I. et al. [6], in which the authors determined the reliable risks of the development of atopic phenotypes "asthma and eczema" and "asthma and hay fever" in carriers of the T-allele variant SNV rs7927894 of the FLG gene among adults and children in the European ALPSAC and GENUFAD cohorts. In their own research, the authors found reliable associations and risks of the development of polytopic phenotypes of AD+SAR(C/)PAR(C) and AD+BA+SARC/PARC compared to the monotopic phenotype of SAR(C)/PAR(C). The main difference is the heterozygous C/T of *FLG* rs_7927894 genotype, which revealed the above-mentioned associations and risks: in the study of Marenholz I. et al. only the T allele was studied.

Table 8

Associations and risks of developing AtD with different genotypes SNV rs414232477 of the *NR3C1* gene

Ratio of clusters, №	Genotype SNV rs414232477 of the *NR3C1* gene	Association, r	Odds ratio, OR (95% CI)
1 to 2	C/G	0.174 *	2.03 (1.01-4.10) *
2 to 1	C/G	-0.174 *	0.49 (0.24-0.99) *

Note. * – p<0.05 (according to Pearson's $\chi 2$ test).

For the first time in Ukraine, a study of clinical associations of SNV rs10052957 and rs41423247 of the *NR3C1* gene in children was conducted. We have demonstrated the distribution of genotypes of SNV data in patients with AtD and the association with the risk of various clinical phenotypes of AtD. In particular, it was established that the A/G SNV rs10052957 genotype of the *NR3C1* gene is most often found in any manifestations of AtD, except for BA and AD+SAR(C)/PAR(C), and the G/G SNV rs10052957 genotype of the *NR3C1* gene was the second in prevalence among children with AtD.

It was established that the G/G SNV rs10052957 genotype of the *NR3C1* gene is associated with an increased risk of the development of the polytopic AD+SAR(C)/PAR(C) phenotype compared to the monotopic variant of AD (the odds ratio is 2.97). At the same time, it significantly reduces the risk of developing another polytopic phenotype BA+SAR(C)/PAR(C) (the odds ratio is 0.45 times) relative to the AD+SAR(C), PAR(C) phenotype. Panek M. et al. [8] in their study obtained a reliable association of homozygous adult carriers of the A/A genotype of SNV rs10052957 of the *NR3C1* gene with the development of AD of a mild degree with a good ability to control – the discrepancy in results is explained by the difference in design, primarily by child cohorts and different phenotypes of AD in their own research

Comparison of SNV rs41423247 *NR3C1* gene association results showed that its C/G genotype is characteristic of all AtD phenotypes, except for diseases with monotopic lesions of the upper or lower respiratory tract, and is associated with an increased risk (2.03) of developing AD. These results are inconsistent with the study by Al-Shami et al. [2], in which an association was established between the C/C genotype in children of the Caucasian population of the Middle Eastern region and the risk of developing BA. In our study, this SNV rs41423247 genotype of the *NR3C1* gene was the rarest, particularly in patients with a monotopic BA phenotype (8.7%).

Personalization of the diagnostic and treatment process in children with AtD, taking into account the SNV genotypes of key genes involved in the development of the aforementioned conditions, will allow to increase the effectiveness of therapeutic measures that allow controlling the pathological process and improve the prognosis of recovery and quality of life in children.

CONCLUSIONS

1. Genotypes S/T SNV rs7927894 of the FLG gene, G/G and A/G rs10052957 and C/G rs41423247 of the NR3C1 gene are reliably associated with the risk of developing various AtD phenotypes.
2. Carriers of the heterozygous S/T SNV rs7927894 genotype of the FLG gene have a 2.47- and 3.13-fold significantly increased risk of developing polytopic phenotypes AD+SAR(C)+PAR(C) and AD+BA+SAR(C)+PAR(C), respectively, compared to the monotopic phenotype of CAR(C)/PAR(C).
3. Carriers of the homozygous genotype G/G rs10052957 of the NR3C1 gene have reliable risks of developing the polytopic phenotype of AD+SAR(C)+PAR(C) – increased by 2.97 times compared to the monotopic phenotype of AD and the polytopic phenotype of BA+SAR(C)+PAR(C) – reduced to 0.45 times relative to the polytopic AD+SAR(C)+PAR(C) phenotype.
4. Carriers of the heterozygous genotype A/G rs10052957 of the NR3C1 gene have a significantly reduced risk of developing the polytopic AD+SAR(C)+PAR(C) phenotype relative to the monotopic AD phenotype.
5. Carriers of the heterozygous C/G rs414232477 NR3C1 gene genotype have a significantly increased 2.03-fold increased risk of developing the monotopic AD phenotype relative to the SAR(C)/PAR(C) phenotype.

Contributors:

Dityatkovsky V.O. – methodology, validation, formal analysis, research, resources, writing – initial project, visualization, finding financial support;

Naumenko N.V. – methodology, validation, research;

Alifirenko O.O. – research, resources;

Pinaeva N.L., Taran S.T., Filatova I.A. – resource;

Abaturov O.Ye. – conceptualization, methodology, data curation, management, writing – reviewing and editing, project administration.

Funding. The research was carried out with the support of the Ministry of Health of Ukraine, within the framework of the GDR, No. 0118U006629.

Conflict of interests. The authors declare no conflict of interest.

REFERENCES

1. Antomonov MY. [Mathematical processing and analysis of medical and biologic data]. Kyiv: IIC «Medinform»; 2018. p. 579. Russian.
2. Al-Shami HM, Al-Awadi SJ, Khaleel KJ. Association of glucocorticoid receptor gene NR3C1 (Tth111I, Bcli) polymorphisms with asthma children in Iraq. Annals of RSCB. 2021;14055-62.
3. Dêbiñska A, Danielewicz H, Drabik-Chamerska A, Kalita D, Boznañski A. Chromosome 11q13.5 variant as a risk factor for atopic dermatitis in children. Postepy Dermatol Alergol. 2020;37(1):103-10. doi: https://doi.org/10.5114/ada.2020.93388
4. Dytiatkovskyi V, Drevytska T, Lapikova-Bryhinska T, Dosenko V, Abaturov O. Genotype associations with the different phenotypes of atopic dermatitis in children. Acta medica (Hradec Kralove). 2021;64(2):96-100. doi: https://doi.org/10.14712/18059694.2021.17
5. Cheng Z, Dai LL, Liu Q, Liu M, Wang Q, Li PF, et al. Correlation between polymorphisms in the glucocorticoid receptor gene NR3C1 and susceptibility to asthma

in a Chinese population from the Henan Province. Genet Mol Res. 2016 Jun 3;15(2). PMID: 27323143.
doi: https://doi.org/10.4238/gmr.15028507

6. Marenholz I, Bauerfeind A, Esparza-Gordillo J, Kerscher T, Granell R, Nickel R, et al. The eczema risk variant on chromosome 11q13 (rs7927894) in the population-based ALSPAC cohort: a novel susceptibility factor for asthma and hay fever. Hum Mol Genet. 2011 Jun 15;20(12):2443-9.
doi: https://doi.org/10.1093/hmg/ddr117

7. Panek M, Jonakowski M, Zioło J, Wieteska Ł, Małachowska B., Pietras T, et al. A novel approach to understanding the role of polymorphic forms of the NR3C1 and TGF-β1 genes in the modulation of the expression of IL-5 and IL-15 mRNA in asthmatic inflammation. Molecular Medicine. Reports 13.6. 2016;4879-87.
doi: https://doi.org/10.3892/mmr.2016.5104

8. Panek M, Pietras T, Fabijan A, Miłanowski M, Wieteska L, Górski P, et al. Effect of glucocorticoid receptor gene polymorphisms on asthma phenotypes. Exp Ther Med. 2013;5:572-80.
doi: https://doi.org/10.3892/etm.2012.809

9. Panek M, Pietras T, Fabijan A, Zioło J, Wieteska Ł, Małachowska B, et al. The NR3C1 glucocorticoid receptor gene polymorphisms may modulate the TGF-beta mRNA expression in asthma patients. Inflammation. 2015 Aug;38(4):1479-92.
doi: https://doi.org/10.1007/s10753-015-0123-3

10. Pietras T, Panek M, Tworek D, Oszajca K, Wujcik R, Górski, et al. The Bcl I single nucleotide polymorphism of the human glucocorticoid receptor gene h-GR/NR3C1 promoter in patients with bronchial asthma: pilot study. Molecular biology reports. 2011;38(6):3953-8. doi: https://doi.org/10.1007/s11033-010-0512-5

11. Tamari M, Hirota T. Genome-wide association studies of atopic dermatitis. J Dermatol. 2014 Mar;41(3):213-20.
doi: https://doi.org/10.1111/1346-8138.12321

Стаття надійшла до редакції
30.11.2021