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PERSONALISED GENOTYPE MARKERS OF THE ATOPIC DISORDERS PHENOTYPES IN CHILDREN

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Ключові слова: *атопічні хвороби, діти, моноорганні фенотипи, поліорганні фенотипи, однонуклеотидні варіанти*

Abstract. Personalized genotype markers of the atopic disorders phenotypes in children. Dytiatkovskyi V.O. *The goal of the study was to elucidate the impact of the single nucleotide variants rs11466749 of the thymic stromal lymphopoietin gene, rs_7216389 of the orsomucoid-1-like protein 3 gene, and rs10052957 of the human nuclear glucocorticoid receptor subfamily 3, group C, member 1 gene on the development of the mono-organic phenotype "atopic eczema" or the poly-organic "atopic eczema + allergic rhinitis/allergic rhino-conjunctivitis". We recruited 101 patients into the main and 105 into control groups aged from 3 to 18 years old. Patients of the main group suffered from atopic eczema (58 children) and atopic eczema + allergic rhinitis/allergic rhino-conjunctivitis (43 children). Patients of the control group suffered from the digestive tract pathology. Main group patients were genotyped for the A/A, A/G, G/G of rs11466749, C/T, C/C and T/T of rs_7216389 and A/A, A/G and G/G of rs10052957; patients of the control group were genotyped for the A/A, A/G, G/G of rs11466749, C/T, C/C and T/T of rs_7216389 by polymerase chain reaction in real time with restricted fragment length polymorphism. Results: no significant differences in rs11466749 among the main and control groups, the most common variant is A/A – 55.2% (mono-organic) and 55.8% (poly-organic); T/T rs_7216389 is significantly the most common in poly-organic phenotype – 39.5%; rs10052957: A/G variant is significantly most common in mono-organic phenotype – 51.7% and G/G – in the poly-organic phenotype – 62.8%. The G/G rs11466749 variant has a trending to significance direct 0.173 association and increased odds ratio = 5.85 (0.63-54.31) for the poly-organic phenotype and protective impact onto the mono-organic phenotype -0.173 (0.17 (0.02-1.59); T/T rs7216389 variant increases the risk of poly-organic phenotype: 0.227, odds ratio = 2,79 (1.14-6.85) and decreases the risk of mono-organic" phenotype: -0.227, 0.36 (0.15-0.88); A/G rs_10052957 variant significantly increases the risk the mono-organic phenotype: 0.215, odds ratio = 2.5 (1.08-5.56)) and decreases risk of poly-organic phenotype: 0.215, odds ratio = 0.4 (0.18-0.93); G/G rs_10052957 variant significantly increases the risk of the poly-organic phenotype: 0.263, odds ratio = 2.97 (1.31-6.74)) and decreases for the mono-organic phenotype: -0.263, odds ratio = 0.34 (0.15-0.76)). Genotype variant T/T rs_7216389 of the orsomucoid-1-like protein 3 gene significantly increases the risk of developing the poly-organic atopic phenotype by 2.79 times and protects against the mono-organic atopic phenotype by 0.34 times. G/G genotype variant of rs10052957 of the human glucocorticoid receptor subfamily, group C, member 1 gene significantly increases the risk of developing the poly-organic phenotype by 2.97 times, protecting against mono-organic atopic phenotype by 0.34 times.*

Реферат. Персоналізовані генотипні маркери фенотипів атопічних хвороб у дітей. Дитятковський В.О. *Метою дослідження було з'ясувати вплив однонуклеотидних варіантів rs11466749 гена стромального тимічного лімфопоетину, rs_7216389 гена орсомукоїд-1-подібного білка 3 та rs10052957 члена 1 групи С, підродини 3 глюкокортикоїдних рецепторів людини на розвиток моноорганного фенотипу «атопічна екзема» або поліорганного «атопічна екзема + алергічний риніт/алергічний ринокон'юнктивіт». Були набрані 101 пацієнт в основну та 105 у контрольну групи віком від 3 до 18 років. Пацієнти основної групи хворіли на атопічну екзему (58 дітей) та атопічну екзему + алергічний риніт/алергічний ринокон'юнктивіт (43 дитини). Пацієнти контрольної групи мали патологію травного тракту. Пацієнти основної групи були генотиповані на варіанти A/A, A/G, G/G rs11466749, C/T, C/C і T/T rs_7216389 та A/A, A/G і G/G rs10052957; пацієнтів контрольної групи генотипували за A/A, A/G, G/G rs11466749, C/T, C/C і T/T rs_7216389 за допомогою полімеразної ланцюгової реакції в режимі реального часу з обмеженою довжиною фрагмента поліморфізму. Результати: достовірних відмінностей за rs11466749 серед основної та контрольної груп немає, найбільш поширеним є варіант A/A – 55,2% (моноорганний) та 55,8% (поліорганний); T/T rs_7216389 є достовірно найпоширенішим при поліорганному фенотипі – 39,5%; rs10052957: варіант A/G значно*

частіше зустрічається в межах моноорганного фенотипу – 51,7%, G/G – поліорганного фенотипу, 62,8%. Варіант G/G rs11466749 має тенденцію до значущості з прямою асоціацією 0,173 і підвищене співвідношення шансів = 5,85 (0,63-54,31) для поліорганного фенотипу та захисний вплив на моноорганний фенотип: -0,173, співвідношення шансів = 0,17 (0,02-1,59); варіант T/T rs7216389 підвищує ризик поліорганного фенотипу: 0,227, співвідношення шансів = 2,79 (1,14-6,85) і знижує ризик моноорганного: -0,227, співвідношення шансів = 0,36 (0,15-0,88). Варіант A/G rs_10052957 значно підвищує ризик моноорганного фенотипу: 0,215, співвідношення шансів = 2,5 (1,08-5, 56) і знижує ризик поліорганного: 0,215, співвідношення шансів = 0,4 (0,18-0,93); варіант G/G rs_10052957 значно підвищує ризик поліорганного фенотипу: 0,263, співвідношення шансів = 2,97 (1,31-6,74) і знижує для моноорганного: -0,263, співвідношення шансів = 0,34 (0,15-0,76)). Варіант генотипу T/T rs_7216389 гена орсомукоїд-1-подібного білка 3 значно підвищує ризик розвитку поліорганного атопічного фенотипу у 2,79 раза та захищає від моноорганного атопічного фенотипу у 0,34 раза. Варіант генотипу G/G rs10052957 члена 1, групи С підродини глюкокортикоїдних рецепторів людини значно підвищує ризик розвитку поліорганного фенотипу у 2,97 раза, захищаючи від моноорганного атопічного фенотипу в 0,34 раза.

Atopic disorders (AD) are the burden and derivatives of the modern civilization, being on the rise during the last few decades [1]. One of the major problems originating from AD is the progression of the inflammatory process from the skin to the mucosae residing in eye-bulbs and airways, thus transforming into allergic rhinitis (AR), allergic rhino-conjunctivitis (ARC) and bronchial asthma (BA). The bespoke linear progression is called atopic march (AM), allergic march or atopic triad [2]. Presence of any type and localization of allergy in one parent increases the risk of atopic eczema (AE) by 2-3 times in the proband, presence of AE in both – by 5 times [3]. Given the proven fact of the hereditary nature of atopy [5], genetic milieu emerges to be the major target in developing the personalized predictive diagnostics of it. AD background involves single nucleotide variants (SNV), epigenetic defects in methylation, incomplete gene penetration and genomic imprinting breakdowns [5]. Filaggrin – null mutations – are one of the major causes of the early-onset phenotype AE and allergic-atopic march resulting in BA [6].

In the own study dated 2019 [7] there was detected that homozygotic genotype variant T/T SNV rs7216389 of the orsomucoid-1like protein 3 (*ORMDL3*) gene had been significantly frequent among children suffering from AD and increased the risk of seasonal AR/ARC (SARC) by 4.11 times (95% CI 1.55; 16.61), perennial AR (PAR) by 5.07 times (95% CI 1.22; 13.90) and BA by 10.31 times (95% CI 2.50; 42.62). There is a scarce and controversary data on the role of the human glucocorticoid receptors type 3, subfamily C member 1 gene (*hr-NR3C1*) SNVs in the incline to develop the mono-organic or poly-organic AD phenotypes [8]. In the past few decades there was an intensive study of the pro-inflammatory agent thymic stromal lymphopoietin (*TSLP*). The study on Turkish pediatric cohorts has shown the significant linkage of the homozygous A/A and G/G genotypes of the *TSLP* gene SNV rs11466749 in exon 4 with the BA and AR/ARC phenotypes respectively [9]. The linkage disequilibrium, particularly with r11466749, was obtained on Korean cohorts in the study of 9 *TSLP* gene SNV regarding risks of mono- and poly-organic AD phenotypes [10]. In our study the SNV A/G rs11466749 was detected to significantly increase the risks of developing the mono-organic AE and poly-organic AE+AR/ARC phenotypes by 5.88 and 4.17 times respectively related to the full atopic phenotype AE+AR/ARC+BA [11]. Genotype A/A SNV rs11466749 *TSLP* decreased the risk of developing AE phenotype by 0.38 times and the poly-organic AE+AR/ARC by 0.37 times compared to the full atopic phenotype.

Resuming the aforesaid, there emerges the necessity to further elucidate genetic background and SNVs that impact the development of mono-organic and poly-organic AD phenotypes.

Thus **the goal of the present study** was to elucidate the impact of single nucleotide variants rs11466749 of thymic stromal lymphopoietin, rs_7216389 of orsomucoid-1-like protein 3 and rs10052957 of human glucocorticoid receptor subfamily 3, group C, member 1 on the axis of atopic disorders development – whether into the mono-organic atopic eczema or into poly-organic atopic eczema + allergic rhinitis/allergic rhino-conjunctivitis phenotypes.

MATERIALS AND METHODS OF RESEARCH

There were recruited 101 patients into the min group and 105 patients into the control group for the study presented.

Inclusion criteria for the main group were as follows: age between 3 and 18 years old, both genders, officially established diagnosis of the mono-organic atopic phenotype AE (58 patients) or poly-organic AE+AR/ARC phenotype (43 patients) confirmed by the laboratory total and/or increased specific immune globulin E (IgE) testing in blood serum. Exclusion criteria for the main group recruitment were as follows: age younger than 3 and older than 18 years old, absence of the officially diagnosed AD in neither mono-organ nor poly-organ phenotypes.

For the control group there were recruited children by the following inclusion criteria: age from 3 to 18 years old, both genders, officially diagnosed lesions of the digestive system – acute and chronic gastritis, duodenitis, functional dyspepsia, gall bladder and the bile system functional impairments. Exclusion criteria: age below 3 years old or above 18 years old, any signs or officially diagnosed AD in any phenotypes or localization with or without elevated total or specific IgE serum levels.

All the patients have undergone the buccal swab for genotyping the following SNVs: A/A, A/G, G/G SNV rs11466749 of *TSLP* gene, C/T, C/C and T/T rs7216389 of the *ORMDL3* gene. Genotyping for the and A/A, A/G, G/G SNV rs10052957 of the *hr-NR3C1* gene has been performed only to the patients of the main group – the AE and AE+AR/ARC cohorts served as the control ones for each other per the bespoke genotype.

The obtained material was consequently frozen and stored within the temperature of -32°C and then transported with the cold chain maintenance to the certified laboratory of the Department of general and molecular pathophysiology in the Bogomolets Institute of Physiology of the National Academy of Sciences of Ukraine. The delivered swabs were processed by applying the discrimination allele analysis by the means of polymerase chain reaction in the real time with restricted fragment length polymorphism (qPCR). Specifically, we used the following TaqMan kit assays for performing the qPCR as per the bespoke SNVs: C__31152869_10 (rs11466749), C__29062108_10 (rs7216389) and Genotyping Assays 300 rxn (4331349). The entire process has been run on the specified equipment 7500 Fast Real Time PCR System. We considered as significant SNVs with the minor allele frequency >5%.

The design of the current study was approved by the local ethics Committee of Dnipro State Medical University (Minutes` No. 7, October 28th, year 2020). The patients` legal representatives (parents, legal guardians) filled in and signed the informed consents prior to the study start according to the Helsinki declaration updated in the year 2013 in Fortaleza, Brazil and Universal Declaration on Bioethics and Human Rights adopted by UNESCO conference on October 19th, year 2005 in Paris, France.

The results obtained are represented in the format of the mean arithmetic values (M) with the 95% confidence interval (95% CI), validated by the Mann-Whitney-Wilcoxon test (U, $p<0.05$) and relative values (%) for the depiction of the SNV A/A, A/G, G/G SNV rs11466749 *TSLP*, C/T, C/C and T/T rs7216389 *ORMDL3*, A/A, A/G, G/G SNV rs10052957 of the *hr-NR3C1* gene. Associations between the genotypes studied are processed by the Spearman`s rank correlation coefficient ($r_s$) from 1 to -1 depending on the potency and character of associations. The differences in the values of different SNVs in patients` cohorts were validated by Pearson`s chi-squared test ($\chi^2$) for cohorts exceeding 5 patients and Fischer`s exact test (FET) for cohorts under 5 patients. Finally, the odds ratio (OR) or chances of developing the AE mono-organic or AE+AR\ARC poly-organic phenotypes were calculated by applying the logistic regression analysis expressed by the OR value with the 95% CI [12].

The abovementioned statistical computations were performed involving the Statistica v.6.1 software (license No. AGAR909E415822FA, Statsoft Inc., USA).

RESULTS AND DISCUSSION

There were statistically significant differences between the main and control groups in the age distribution (Table 1).

Table 1

Age distribution by the AE and AE+AR/ARC phenotypes of the main and control group

Age, years	AE*° (N, %)	AE+AR/ARC*°° (N, %)	Control group (N, %)
0-3	7	1	2
	12,1%	2,3%	1,9%
4-6	24	8	14
	41,4%	18,6%	13,3%
7-11	20	20	32
	34,5%	46,5%	30,5%
12-18	7	14	57
	12,1%	32,6%	54,3%

Notes: * $p<0.01$ by the $\chi 2$ test between AE and AE+AR/ARC cohorts;° – $p<0.001$ by the $\chi 2$ test collated to the control group; °° – $p>0.05$ compared to the control group.

No gender significant differences between the cohorts of the main group and the control group were detected either (Table 2).

Still, one can see from the data represented in Table 2 that males prevailed in all the cohorts of the main and control group.

Table 2

The gender distribution among the patients of the AE and AE+AR/ARC phenotypes of the main and the control group

Gender	AE*	AE+AR/ARC*	Control group
Females, N	26	17	42
Females, %	44.8%	39.5%	40.0%
Males, N	32	26	63
Males, %	55.2%	60.5%	60.0%

Note. * p>0.05 by the $\chi 2$ test between AE and AE+AR/ARC cohorts and collated to the control group.

In Table 3 there are represented data on the distribution frequency of the genotype variants of rs11466749 *TSLP* in the cohorts of the main and control group.

The Table above clearly depicts the prevalence of the A/A genotype variant rs11466749 *TSLP* within both the AE and AE+AR/ARC phenotypes of the main group, as well in the control group. The A/G genotype happened to be the second most frequent genotype sharing the similar distribution in the patients of the main (both phenotypes) and control group. There were no significant differences detected among the patients of the main and control group.

In Table 4 there are the data of the genotype distribution by the SNV rs7216389 *ORMDL3* in the studied groups.

Table 3

Distribution of the SNV rs11466749 *TSLP* genotype variants in patients of the main and control group

SNV rs11466749 *TSLP*	Groups/Cohorts		
	main: AE	main: AE+AR/ARC	control
A/A*, N	32	24	53
A/A*, %	55.2%	55.8%	50.5%
A/G*, N	25	15	48
A/G*, %	43.1%	34.9%	45.7%
G/G*, N	1	4	4
G/G*, %	1.7%	9.3%	3.8%

Note. * p>0,05 by the $\chi 2$ and FET tests collated to the control group.

Results of genotyping by the SNVs rs10052957 of the *hr-NR3C1* gene are represented in Table 5.

It emerges from Table 5, A/A variant of the SNV rs10052957 *hr-NR3C1* did not reveal any significant differences between the AE and AE+AR\ARC cohorts of the main group. Meanwhile, A/G variant was significantly higher in incidence in patients of the AE cohort and G/G – in patients of the AE+AR/ARC cohort.

Table 4

Distribution of the SNV rs7216389 *ORMDL3* genotype variants in patients of the main and control groups

SNV rs7216389 ORMDL3,	Groups/Cohorts		
	main: AE	main: AE+AR/ARC	control
C/C, N	12*	6**	29
C/C, %	20.7%*	14.0%**	27.6%
C/T, N	35*	20*	60
C/T, %	60.3%*	46.5%*	57.1%
T/T, N	11*	17***	16
T/T, %	19.0%*	39.5%***	15.2%

Notes: * p>0.05 by the $\chi 2$ test collated to the control group; ** p=0.05-0,1 by the $\chi 2$ test collated to the control group; *** p<0.01 by the $\chi 2$ test collated to the control group.

Table 6 represents the associations and OR between the studied SNVs A/A, A/G, G/G SNV rs11466749 *TSLP*, C/T, C/C and T/T rs7216389 *ORMDL3*, A/A, A/G, G/G SNV rs10052957 *hr-NR3C1* and the AE and AE+AR/ARC phenotypes of the main group.

Table 5

Distribution of the SNV rs10052957 of the *hr-NR3C1* genotype variants among the patient cohorts of the main group

SNV rs10052957 *hr-NR3C1*	Groups/Cohorts	
	main: AE	main: AE+AR/ARC
A/A*, N	7	3
A/A*, %	12.1%	7.0%
A/G**, N	30	13
A/G**, %	51.7%	30.2%
G/G***, N	21	27
G/G***, %	36.2%	62.8%

Notes: * p>0.05 by the $\chi 2$ test; ** p<0.05 by the $\chi 2$ test; *** p<0.01 by the $\chi 2$ test.

The results obtained show increased susceptibility to develop mono-organic AE or poly-organic AE+AR/ARC phenotypes in the carriers of the SNVs rs_7216389 *ORMDL3*, rs11466749 *TSLP* and rs10052957*hr-NR3C1*. The aforesaid sometimes matches and, sometimes, mismatches with the global resources data. Thus, the own study as of the year 2019 in children suffering from AD has shown that variant T/T SNV rs7216389 *ORMDL3* is prevalent in all the phenotype cohorts and significantly increases the risk of the isolated mono-organic phenotypes of seasonal AR – by 4.11 times and perennial ARC – by 5.07 times [7]. In the present study, the homozygous genotype T/T rs7216389 *ORMDL3* confirmed the impact of the doubled T/T allele on the AR/ARC clinical profile – it increases the risk of AR/ARC combined into the poly-organic phenotype with AE by 2.79 times and provides protection against the

mono-organic AE phenotype by 0.36 times. C Lou et al. in their study detected the predisposing effect of the SNV rs1898671 *TSLP* with the homozygotic genotype to the development of the AE phenotype, whilst the heterozygotic phenotype revealed the protective effect as for AE [13]. In our study, data obtained show the protective effect of the homozygotic G/G rs11466749 *TSLP* genotype as for the development of the mono-organic AE phenotype. The aforesaid contributes to each other rather than contradicts, indicating a need for the SNV studies for all the culprit genotypes involved in the pathogenesis of different AD clinical phenotypes. In the previous own studies there was detected no significant association between the SNV rs11466749 *TSLP* genotypes and AE and AE+AR/ARC phenotypes [14]. Having increased the number of patients in the aforementioned cohorts, we managed to obtain the trending to significance in positive association of r_b=0.173 with 5.85 OR (95% CI 0.63-54.31) which increases the risk of the AE+AR/ARC phenotype development and, respectively, decreases the risk of the AE phenotype development by 0.17 times (0.02-1.59) with a negative association r_b=-0.173. It clearly points out at the need to study the SNVs rs_7216389 *ORMDL3*, rs11466749 *TSLP* and rs10052957 *hr-NR3C1* in the larger patient cohorts, i.e. >100 patients per phenotype. In their study M. Panek et al. wrote that SNV *Tth111* I (rs10052957), ER22/23EK (rs6189/rs6190), N363S (rs6195) and *Bcl*I (rs41423247) of the *hr-NR3C1* gene increase the risk of BA and cause the resistance to the glucocorticoid therapy, and dicrease control over the disease [15]. The same paper states that heterozygous genotype A/G was the most common SNV of the *Tth111*I (rs10052957) in adults – 57.14% controls, 46.92% BA patients. In our study the aforesaid genotype was the most common within the AE mono-organic phenotype – 51.7%, and homozygous genotype G/G – was the most common SNV in the poly-organic AE+AR/ARC phenotype - 62.8%. The mentioned above points out, first of all, at the scarcity of data regarding the role of SNV rs10052957 *hr-NR3C1* in the genesis of AE and AE combined with AR/ARC, not only BA. So, our original study is the pioneering one to elucidate the mechanism of impact of the SNV rs10052957 *hr-NR3C1* genotype variants in predicting the child to develop either mono-organic AD phenotype, e.g. AE, or a poly-organic one such as AE+AR/ARC.

Table 6

Impact of the genotypes SNV rs11466749 *TSLP*, rs7216389 *ORMDL3* and rs10052957 *hr-NR3C1* on the risk of AE and AE+AR/ARC phenotypes development

SNV	Relation axis	
	AE to AE+AR/ARC	AE+AR/ARC to AE
*G/G rs11466749 *TSLP*, r_s	-0.173	0.173
*G/G rs11466749 *TSLP*, OR (95% CI)	0.17 (0.02-1.59)	5.85 (0.63-54.31)
**T/T, rs7216389 *ORMDL3*, r_s	-0.227	0.227
**T/T, rs7216389 *ORMDL3*, OR (95% CI)	0.36 (0.15-0.88)	2.79 (1.14-6.85)
**A/G, rs_10052957 *hr-NR3C1*, r_s	0.215	-0.215
**A/G, rs_10052957 *hr-NR3C1*, OR (95% CI)	2.5 (1.08-5.56)	0.40 (0.18-0.93)
***G/G, rs_10052957 *hr-NR3C1*, r_s	-0.263	0.263
***G/G, rs_10052957 *hr-NR3C1*, OR (95% CI)	0.34 (0.15-0.76)	2.97 (1.31-6.74)

Notes: * p=0.05-0,1 by the $\chi 2$ test and p>0.05 by FET; ** p<0.05 by the $\chi 2$ test; *** p<0.01 by the $\chi 2$ test.

CONCLUSIONS

1. The single nucleotide variants of rs_7216389 orsomucoid-like-1 protein 3 gene and rs10052957 human nuclear glucocorticoid receptor subfamily 3, group C, member 1 gene have significant impact on the development of the atopic disorders axis.

2. The homozygous genotype variant T/T rs_7216389 of orsomucoid-like-1 protein gene 3 is significantly the most common, directly associated with the patients suffering from the poly-organic atopic eczema + allergic rhinitis/allergic rhino-

conjunctivitis phenotype and significantly increases the risk of its development by 2,79 fold.

3. Consequently, the SNV T/T rs_7216389 of orsomucoid-like-1 protein 3 gene possesses significant negative association and protective features regarding the mono-organic phenotype of atopic eczema.

4. The homozygous G/G genotype variant of rs10052957 human nuclear glucocorticoid receptor subfamily 3, group C, member 1 gene is significantly the most common one in patients suffering from the poly-organic phenotype atopic eczema + allergic rhinitis/allergic rhino-conjunctivitis and, being directly associated, increases the risk of its development by 2.97 fold.

5. Further studies in larger patient cohorts are needed to elucidate the impact of the SNV rs11466749 thymic stromal lymphopoietin genotype variants on the development risks of either mono-organic or poly-organic atopic disorders phenotypes in children.

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

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