Alergologia Polska – Polish Journal of Allergology 2026; 13, 3: 189-195
DOI: https://doi.org/10.5114/pja.2026.165156
Received: 27.06.2025, accepted: 3.05.2026, online publication: 28.09.2026.

Alergologia POLSKA
Polish Journal of Allergology

ORIGINAL PAPER

Integral model of personalised diagnostics of the clinical profiles of atopic march in children

Volodymyr Dytiatkovskyi, Olexander Abaturov, Olena Rusakova

Department of Paediatrics 1 and Medical Genetics, Dnipro State Medical University, Ukraine

ABSTRACT

Introduction: There is a strong need for the personalised precise genotype-associated diagnostic tools to detect the probability (P) of the poly-organ clinical profiles (CP) of atopic march (AM) in children.

Aim: To develop the integral model (IM) of the personalised precise genotype-associated diagnostics (PPGAD) of the poly-organ CPAM development probability in children.

Material and methods: We recruited 21 patients into the study group – children with poly-organ CP comprising atopic dermatitis (AD), bronchial asthma (BA), allergic rhinitis or rhino-conjunctivitis (AR/ARC): AD + AR, AD + ARC, AD + AR + ARC, AD + BA. We recruited 47 patients into the control group – children without any atopic disorders, suffering from digestive tract disorders (DTD). All the patients underwent the genotyping for the single nucleotide variants (SNV) of the filaggrin gene (rs7927894 *FLG*) and orosomucoid-1-like protein 3 (rs7216389 *ORMDL3*) along with detection of the serum concentration levels of total immune globulin E (IgE) and cutaneous T-cell attracting chemokine (CTACK/CCL27).

Results: The integral model (IM) of the personalised precise genotype-associated diagnostics (PPGAD): cut-off value for the increased probability (P) of the poly-organ CP of AM development > 0.403, area under the curve = 0.961 ($p < 0.001$); specificity = 95.7% (95% CI: 85.5–99.5), sensitivity = 85.7% (95% CI: 63.7–97.0). We developed the designed PPGAD IM on 4 clinical cases. Of the study group patients: with mono-organ CP of AD $p = 0.118$, with the CP AD + AR + ARC $p = 0.986$. In the control group patients with DTD: $p = 0.027$ and $p = 0.403$.

Conclusions: PPGAD integral model of development probability of the poly-organ CP of AM comprises genotyping the child for the SNV C/T rs7927894 *FLG*, T/T rs7216389 *ORMDL3*, detecting serum levels of CTACK/CCL27 and total IgE. It needs further validation in longitudinal studies on larger patients' cohorts.

KEY WORDS

children, filaggrin, atopic march, orosomucoid-1-like protein 3, personalised precise genotype-associated diagnostics

ADDRESS FOR CORRESPONDENCE

Volodymyr Dytiatkovskyi, Department of Paediatrics 1 and Medical Genetics, Dnipro State Medical University, Ukraine, e-mail: ditiatkovskyvo@gmail.com

Copyright © Polish Society of Allergology. Creative Commons licenses: This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY -NC -SA 4.0). License (http://creativecommons.org/licenses/by-nc-sa/4.0/).

INTRODUCTION

At present, the risks of transformation of the paediatric atopic dermatitis (AD) into the so-called atopic triad or atopic march (AM) remain not fully detected and managed. AM represents the linear progression of AD into its combinations with other atopic disorders (ADis) – allergic rhinitis (AR), allergic rhino-conjunctivitis (ARC) and bronchial asthma (BA). Referring to one of the recent studies of the AM multi-morbidity and epidemiology conducted by Choi *et al.* [1], increased hazard ratios were detected for the development of different atopic multi-morbidities in children suffering from the early-onset AD (before 1 year old) compared to controls without the early-onset AD (after 1 year old): 19.21% vs. 8.65%, $p < 0.001$, to develop BA, 28.27% vs. 12.62%, $p < 0.001$, to develop AR, and the complete AM comprising the whole triad – AD + AR + BA: 10.69% vs. 0.71%, $p < 0.001$. Furthermore, the AD patients had developed AR with the 20.1% incidence in the overall cohort.

The pathogenetic mechanisms of AD are complex and reveal by interconnections between the genotype markers, biomarkers (cytokines, chemokines) to manifest clinically in common AD signs. Particularly, specific diagnostic biomarkers were detected to distinguish AD from psoriasis and other pruritic disorders: carbonic anhydrase II, neuron-specific NELL-like protein 2, cutaneous T-cell attracting chemokine (CTACK/CCL27) and matrix metalloproteinases [2]. The upregulated CTACK/CCL27 in psoriasis could yield some possible prognosis of developmental risk for the entire AM, not just separately within AD and other atopic disorders (ADis). The above emerges from the recent review of biomarkers within AD on behalf of the International Eczema Council [3].

Additionally, AD being based on the food allergy pathophysiology, is closely associated with the hyperproduction of immunoglobulin E (IgE) against the food and aeroallergens [4]. The multiple studies of recent decades had yielded understanding that AD comprises different endo- and phenotypes or clinical profiles (CP) based on the filaggrin gene (*FLG*) variations, total and specific IgE serum levels, ethnicity and age [5]. Since AD to date is classified into endotypes as well as phenotypes, there is an emerging need to reveal the new features of the well-investigated IgE and its role in the precise personalised diagnostics of AD and its other atopic co-morbidities which comprise the different CP of AM in children.

In respect of the genotype predisposition, one of the basic markers is, particularly, the filaggrin gene (*FLG*) deviations – loss-of-function mutations and single nucleotide variants (SNV). They were discovered a few decades ago and remain the basic predictors in patients' developing AD, other ADis and, finally, AM itself [6]. Thus, in our own studies the C/T SNV rs7927894 *FLG* genotype variant had been detected as the culprit marker of developing both mono-organ AD, AR/ARC and BA CP along with the poly-organ combinations of AD + AR/ARC, BA + AR/ARC and the complete CP of AM AD + AR/ARC + BA [7].

Another significant genotype marker of the BA onset within the AM course is the orosomucoid-1-like protein 3 gene residing at chromosome region 17q21 (*ORMDL3*) – its SNV rs7216389 *ORMDL3* had already been detected as the most strongly BA-associated one [8, 9].

Still, to date the diagnostic tools, which would enable the efficient prognosing and thus, prevention of AM in children are limited. So, we have focused our research also on the bespoke SNV to include them in the attempt of creating an integral model of the genotype-associated diagnostics – thus, more personalised and precise.

AIM

Hence, the aim of this study was to develop the integral model (IM) of the personalised precise genotype-associated diagnostics (PPGAD) of the poly-organ CP of AM development probability in children.

MATERIAL AND METHODS

We recruited 21 patients into the study group and 47 – into the control group with the age span from 4 up to 18 years old. The study group was composed of the children meeting the following inclusion criteria: common clinical signs of ADis in poly-organ CP – AD + AR, AD + ARC, AD + AR + ARC and AD + BA (Table 1); these clinical signs had been confirmed by the levels of total IgE above the reference interval. The final diagnosis of all the ADis had been established according to the national guidelines for the primary, secondary (specialised) and tertiary (highly specialised) medical aid for AD (Ukraine Health Ministry (UHM) Order No. 670 issued on 16.07.2016) and BA (UHM Order No. 868 issued on 08.10.2013).

The control group was composed of the children meeting the following inclusion criteria: no clinical complaints or signs of ADis, suffering from the digestive tract disorders – chronic gastritis, chronic duodenitis, peptic ulcer, biliary tract disfunctions. The mentioned diagnosis of the control group patients had been established according to the "Unified clinical protocols of medical aid for children with the digestive tract disorders" issued by UHM Order No. 59 as of 29.01.2013.

The groups were collatable by the gender distribution and differed significantly by age (Table 2).

The genotype variants were detected by means of polymerase chain reaction in real time with the restricted

TABLE 1. Distribution of poly-organ clinical profiles diagnoses in the study group

Diagnostic combination	Number of patients, *n*	Percentage of patients, %
AD + AR	6	28.6
AD + ARC	9	42.8
AD + AR + ARC	5	23.8
AD + BA	1	4.8

TABLE 2. The age-gender distribution in the study and control groups

Value/Cohort	Study group	Control group	*P*-level
Mean age [years] (Me [LQ; HQ]	8 [7; 11]**	11 [8; 14]	0.043*
Gender – females, *n* (%)	8 (38.1%)*	26 (55.3%)	0.189*
Gender, males, %	13 (61.9%)*	21 (44.7%)	

Me – median, LQ – lower quartile, HQ – higher quartile; *Mann-Whitney test; **Pearson's χ^2-test.

polymorphism length – qPCR. The qPCR had been carried out on the specified apparatus for the discrimination analysis in a certified laboratory based in the Department of General and Molecular Pathophysiology at the Bogomolets Institute of Physiology of the National Academy of Sciences of Ukraine. The material with patients' DNA was obtained by means of buccal swab, subsequently frozen at –32°C and transported with the cold chain maintained. We had used the specified genotyping kits to perform discrimination allele analysis – predesigned SNP Genotyping Assays rs7927894 and rs_7216389 on the specified apparatus Applied Biosystems 7500 Fast Real Time PCR System.

The serum concentration levels of the total IgE in patients of the study and control groups were measured by means of the immune-enzyme analysis using the Cobas Elecsys 2010 IGE II specified kits with the peripheral blood obtained from the patients, subsequently frozen and transported to the certified laboratory. The serum concentration of CTACK/CCL27 in the patients of the study and control groups was measured by means of enzyme-linked immunosorbent assay using the specified kits – Human CTACK Elisa Kit (ISO 13485) in the peripheral blood of the patients subsequently frozen and transported to the certified laboratory.

To process the data retrieved we had applied the following statistic tools:

- The multiple logistic regression analysis with detecting the regression coefficients (x_1, x_2, x_3, x_4 validated by the Wald test) and the odds ratio (OR) along with the 95% confidence interval (95% CI) with the step-by-step inclusion of the studied marker factors into the formula (forward procedure with $p < 0.2$ to include the variable into the designated model) – to quantitatively assess the impact each studied factor carries to predict the development of poly-organ AM CP;
- The quality of the designated model was assessed by the following tools: the regression adequacy (likelihood ratio χ^2), the goodness of fit, Hosmer-Lemeshow test (χ^2), Nagelkerke pseudo-coefficient of determination, receiver operator characteristic (ROC) analysis with detecting the area under the curve (AUC), specificity (Sp), sensitivity (Se), prognosis accuracy (PA), prognostic significance of the negative result (PSNR) and prognostic significance of the positive result (PSPR) – all the ROC-values assessed by the 95% CI; the AUC values' quality had been interpreted as follows: AUC 0.9–1.0 – excellent, AUC 0.8–0.9 – very good, AUC 0.7–0.8 – good, AUC 0.6–0.7 – moderate, AUC 0.5–0.6 – unsatisfactory, 0.5 pointed at the method's mismatching.

All the methods used had been approved by the local biomedical ethics committee of the Dnipro State Medical University which is stipulated in the following Minutes: No. 6 of 07.02.2018, No. 7 of 28.10.2020 and No. 19 of 15.05.2024. The parents or legal guardians of all the children recruited into the study had signed the informed written consent to carry out all the laboratory examinations and data processing according to the UNESCO Universal Declaration on Bioethics and Human Rights (issued at the UNESCO General conference in October 2005, Paris, France) and the World Medical Association Declaration of Helsinki (last amended at the 64th WMA General Assembly in October 2013, Fortaleza, Brazil).

STATISTICAL ANALYSIS

The statistical significance of the results obtained had been set as $p < 0.05$, its value $0.05 < p \leq 0.1$ was interpreted as the trend to statistical significance. The statistical calculations and computations were carried out using the Statistica v.6.1 (StatSoft Inc., USA, license No.

AGAR909E415822FA) and MedCalc Software trial version 23.5.2 (MedCalc Software Ltd, Ostende, Belgium; https://www.medcalc.org; 2026).

RESULTS

Based on the results of our research there were 4 predictor factors to be used in the equation of the multiple logistic regression, which had emerged as follows: $P = 1/(1 + e^{-z})$; $z = -10.3912 + 2.2473 \times x_1 + 1.5077 \times x_2 + 0.001538 \times x_3 + 0.003585 \times x_4$ (Formula 1), where: x_1 – presence (1)/absence (0) of the genotype SNV C/T rs7927894 *FLG*; x_2 – presence (1)/absence (0) of the genotype SNV T/T rs7216389 *ORMDL3*; x_3 – serum level of the CTACK/CCL27, pg/ml; x_4 – serum level of the total IgE, IU/ml.

The mentioned personalised precise genotype-associated diagnostic integral model based on the above formula is presented below (Table 3).

It shows the values and their figures of the AM progression chances in children from the mono-organ into poly-organ CP with high possibility when $p > 0.40$ and the quality characteristics of that model – PA, Se, Sp, PVNR, PVPR – which are shown in Table 4.

Within the internal validation of the IM by the Leave-One-Out Cross-Validation method (LOOCV) we had obtained similar results: AUC = 0.903 (95% CI: 0.806–0.961), Sp = 91.5 (95% CI: 79.6–97.6), Se = 85.7 (95% CI: 63.7–97.0), $p < 0.001$. Difference between ROC-curve AUC – 0.058 (95% CI: 0.0035–0.114), $p = 0.037$ (Table 5).

To validate the proposed PPGAD IM of the AM poly-organ CP, we had applied it to the respective clinical cases in the study and control group patients.

Clinical case 1. Patient M., 4 years old, female, with the established clinical diagnosis: atopic dermatitis, generalised, exudative-squamous form with lichenification, moderate severity degree, exacerbation period. Genotyping results: SNV rs_7927894 *FLG* – C/T, SNV rs_7216389 *ORMDL3* – C/T; blood test for the serum concentrations of CTACK/CCL27 = 3902.3 pg/ml, total IgE = 36.0 IU/ml. The risk assessment of the AM progression into the poly-organ CP AD + AR/ARC or BA + AR/ARC by the PPGAD proposed IM yields the low-risk ratio in this patient as follows in the LR equation: $z = -10.3912 + 2.2473 \times 1 + 1.5077 \times 0 + 0.001538 \times 3902.3 + 0.003585 \times 36.0$, $z = -2.0131$, $p = 1/(1 + e^{+2.0131}) = 0.118$.

The obtained probability figure of 0.118 is below the detected cut-off one of 0.403, so this patient experiences a low risk of developing the poly-organ CP of AM out of mono-organ CP of AD.

Clinical case 2. Patient M., 7 years old, female with the established clinical diagnosis: seasonal allergic rhino-conjunctivitis, persistent form, severe degree, remission phase; comorbid diagnosis: perennial allergic rhinitis, intermittent form, mild degree, exacerbation phase; atopic dermatitis, diffuse, moderate severity degree, exacerbation phase. Genotyping results: SNV rs_7927894 *FLG* – C/T, SNV rs_7216389 *ORMDL3* – T/T; blood test for the serum concentrations of CTACK/CCL27 = 3739.73 pg/ml, total IgE = 1437.0 IU/ml. Application of the proposed IM of the PPGAD yields the following results $z = -10.3912 + 2.2473 \times 1 + 1.5077 \times 1 + 0.001538 \times 3739.73 + 0.003585 \times 1437$, $z = 4.26715$, $p = 1/(1 + e^{-4.26715}) = 0.986$.

Thus, we have detected an extremely high probability of such markers' combination to predispose their carrier to the developmental risk of the AM poly-organ CP, particularly, to AD + AR + ARC.

Clinical case 3. Patient Z., aged 4 years old at examination, with the established clinical diagnosis: functional dyspepsia; comorbid diagnosis: gall bladder dysmotility. Genotyping results: SNV rs_7927894 *FLG* – C/C, SNV rs_7216389 *ORMDL3* – C/T; blood test for the serum concentration of CTACK/CCL27 = 4105.51 pg/ml, total IgE = 137.6 IU/ml. Applying the equation of the IM of PPGAD developed to foresee the AM poly-organ CP of AM development probability yielded the following results: $z = -10.3912 + 2.2473 \times 1 + 1.5077 \times 0 + 0.001538 \times 4105.51 + 0.003585 \times 137.6$, $z = -3.58363$, $p = 1/(1 + e^{+3.58363}) = 0.027$.

The above calculated data evidence the very low probability of the AM poly-organ CP within patients carrying the combination of C/C SNV rs_7927894 FLG and C/T SNV rs_7216389 *ORMDL3* genotypes and similar to patient Z. serum figures of the CTACK/CCL27 and total IgE.

Clinical case 4. Patient A., 9 years old at examination, with the clinical diagnosis: functional dyspepsia; comorbid diagnosis: gall bladder dysmotility, sphincter of Oddi dysfunction, pancreatic type. Genotyping results: SNV rs_7927894 *FLG* – C/C, SNV rs_7216389 *ORMDL3* – C/C; blood test for the serum concentration of CTACK/CCL27 = 6178.29 pg/ml, total IgE = 138.5 IU/ml. Applying the developed IM of PPGAD equation to foresee the poly-organ CP of AM development probability yielded the following results: $z = -10.3912 + 2.2473 \times 0 + 1.5077 \times 0 + 0.001538 \times 6178.29 + 0.003585 \times 138.5$, $z = -0.39247$, $p = 1/(1 + e^{+0.39247}) = 0.403$.

The probability of developing the poly-organ CP of AM in this clinical case is balancing on the cut-off figure ($p = 0.403$), thus increased despite carrying the combination of homozygous genotype variants C/C of SNV rs_7927894 *FLG* and heterozygous C/T SNV rs_7216389 *ORMDL3* and due to the elevated concentrations of CTACK/CCL27 and total IgE.

TABLE 3. The integral model of the poly-organ clinical profiles of atopic march development probability assessment in children

Model values				
The multiple logistic regression equation to assess the illness development probability (P)	$P = 1/(1 + e^{-z})$; $z = -10.3912 + 2.2473 \times x_1 + 1.5077 \times x_2 + 0.001538 \times x_3 + 0.003585 \times x_4$			
AM development markers	Regression coefficients		*P* (Wald test)	aOR (95% CI)
rs7927894 FLG (C/T -1, other genotype variants -0)	x_1	2.2473	0.078	9.46 (0.78–114.8)
rs7216389 ORMDL3 (T/T –1, other genotype variants -0)	x_2	1.5077	0.150	4.52 (0.58–35.25)
CTACK/ CCL27 [pg/ml]	x_3	0.001538	0.021	1.002 (1.0002–1.003)
IgE [IU/ml]	x_4	0.003585	0.001	1.002 (1.0001–1.006)

aOR (95% CI) – adjusted odds ratio with a 95% confidence interval.

TABLE 4. The quality parameters of the integral model to assess the developmental risk of the combined poly-organ clinical profiles of atopic march in children

Model quality values	
Model adequacy (χ^2 test)	$\chi^2 = 52.72$, $p < 0.001$
Goodness to fit (Hosmer-Lemeshow test)	$\chi^2 = 0.95$, $p = 0.999$
Nagelkerke pseudo-coefficient of determination	$R^2 = 0.76$
Prognostic quality (by the ROC-analysis)	
Area under the ROC-curve	AUC = 0.961 (0.884–0.993), $p < 0.001$
Cut-off value as of/for the high risk (P)	> 0.403
Sensitivity	Se = 85.7% (70.7–100)
Specificity	Spe = 95.7% (90.0–100)
Prognostic accuracy, prognostic value of the negative and positive result	PA = 92.6% (86.4–98.9), PVNR = 93.8% (86.9–100), PVPR = 90.0% (76.9–100)

TABLE 5. Comparison of the original and validation models regarding the coincidence of results with actual data

Parameter	Original model	Validation model
Predictive quality (by the ROC-analysis):		
Area under the ROC-curve	AUC = 0.961; 95% CI (0.884–0.993)[a]; 95% CI (0.891–0.989)[b]; $p < 0.001$	AUC = 0.903; 95% CI (0.806–0.961)[a]; 95% CI (0.778–0.967)[b]; $p < 0.001$
Cut-off value as of/for the high risk (P)	> 0.403; 95% CI (> 0.115 to > 0.495)[b]	> 0.435; 95% CI (> 0.262 to > 0.670)[b]
Sensitivity	Se = 85.7%; 95% CI (63.7–97.0)	Se = 85.7%; 95% CI (63.7–97.0)
Specificity	Spe = 95.7%; 95% CI (85.5–99.5)	Spe = 91.5%; 95% CI (79.6–97.6)
Difference between areas under the ROC curve	0.058; 95% CI (0.0035–0.114); $p = 0.037$	
Concordance correlation coefficient	$r_c = 0.993$; 95% CI (0.989–0.996)	

95% CI[a] – 95% confidence interval by Binomial exact test; 95% CI[b] – bootstrap CI.

DISCUSSION

In this study we have designed and developed the integral models of the PPGAD to detect the developmental probabilities of the poly-organ CP comprising the AD combinations with AR/ARC and/or BA in children. This personalised diagnostic tool allows to screen children both with mono-organ ADis (AD or BA) and without them, thus, to prognose the probability of developing the linear AM progression. The limitation which still impacts the predictive features of the developed IM of PPGAD is embedded in the retrospective nature of our study – it had used the already existing ADis/AM diagnoses, without the follow-up observation. Along with that, the age-related differences of the biomarkers' levels are the possible limitation for the elaborated PPGAD IM performance.

However, this approach had not been developed so far both in domestic and foreign studies. The recent one conducted by Indolfi *et al.* mentions that CTACK/CCL27 is a significant biomarker to distinguish AD from psoriasis, being specific for psoriasis [2]. A systemic review made by Mastraftsi *et al.* had supported the clinical significance of the thymus- and activation regulated chemokine (TARC/CCL17) as the basic cytokine biomarker for evaluating both the severity of AD and its course, still not CTACK/CCL27 [10]. Simultaneously, it had been stipulated as the diagnostic serum biomarker for AD. In our study, we had obtained different results – CTACK/CCL27 and its serum concentrations have been evidenced as a reliable biomarker in combination with the genotype markers and the total IgE serum levels. The same study indicates the necessity to develop a combined (i.e. integral) biomarkers' panel to better predict disease development and progression what had been initiated in our research.

The special attention should be focused on the total serum IgE – it had been numerously stated that it has poor diagnostic evidence as a biomarker, though it is the most studied of them in allergy, particularly in AD and other ADis [10, 11]. For instance, patients suffering from the intrinsic AD do not have elevated levels of the tota IgE in the serum. In our study, we have evidenced a significant, still limited by the lowest OR, role of the total IgE as the component of the integral PPGAD model for prognosing the poly-organ CP development probability within the AM progression in children. The formula matrix designed for the developed model yields that the higher the levels of the total IgE, the higher the probability of developing those CP – it corresponds to current knowledge of total IgE. The perspective of expanding the limitations of total IgE in the risk assessment of ADis could be realised by investigating the poly-genic predisposition to its hyper-production as the predictor of AD and AM start [12].

Regarding the genetics of AM, the low levels of filaggrin and elevated levels of the total IgE make the patients prone to developing the comorbid AM manifestations of the food allergy paving the way to the development of its poly-organ CP [13]. The low filaggrin could result not just of the *FLG* gene null or loss of function mutations, but of the numerous SNV, particularly of the rs7927894 *FLG*. The aforesaid fact is supported by results of our study, which had revealed the C/T heterozygous variant as culprit in the development of the AD comorbidities as the part of developing the poly-organ CP of AM. Its carriage by the patients adds by the 9.46-fold to the mathematic chances of developing the mentioned CP. Other culprit variant is the homozygous T/T variant of the SNV rs7216389 *ORMDL3* which contributes – according to our study – by the 4.52-fold into the formula of calculating the AM poly-organ CP developmental risk. This genotype variant, as well as the SNV rs8076131, had been shown to be associated with a higher whole-blood plasma levels of dihydroceramides, ceramides, and sphingomyelins within children with allergic BA collated with the ones with non-allergic BA and the healthy controls [14]. In our study we had evidenced that the homozygous variant T/T SNV rs7216389 *ORMDL3* is one of the risk predictors not only for BA development, but also for the poly-organ CP of BA and AD. Our study partly correlates with the findings on the Japanese adult populations that SNV rs7216389 *ORMDL3* is significantly associated with the development (onset) of BA – as the part of the AM linear progression, in the respective study of Kitazawa *et al.* – with the both childhood-onset BA as well as the elevated total IgE levels [15]. Furthermore, the aforesaid study had confirmed the association of the T-allele SNV rs7216389 *ORMDL3* with the total serum IgE elevation that increased its association with with BA regardless of the onset age.

However the excellent quality of the elaborated IM of PPGAD – AUC = 0.961 (0.884–0.993), $p < 0.001$, it still has to be validated in larger cohorts of patients suffering from the mono-organ CP of AD with the follow-up observation from 3 to 10 years to elaborate its prediction capability as well as to secure the results' performance in the various risk cohorts. The larger cohorts' dataset of the AM patients should increase the statistical significance and stability of the bespoke IM. Other potential bias of the control group clinical composition could be amended by recruiting healthy peers, with no exacerbations of any disorders, into that cohort. This will broaden the limits of its predictive potential and efficacy. Although, total IgE is not known as a specific or sensitive biomarker for DTD; and CTACK/CCL 27 had not been reported as such in the study of adult patients suffering the eosinophilic es-

ophagitis [16]. Thus, the recruitment of the patients suffering from DTD is eligible for our study provided above.

Removing the above-mentioned limitation bias should strengthen the predicative features of the developed IM of PPGAD and enable its implementation into the clinical practice.

CONCLUSIONS

The integral model of personalised precise genotype-associated diagnostics of the poly-organ CP of AM – AD + AR, AD + ARC, AD + AR + ARC, AD + BA development probability had been designed and validated. The reliable markers were detected to be the heterozygous genotype C/T SNV rs_7927894 *FLG*, homozygous genotype T/T SNV rs7216389 *ORMDL3*, the cut-off serum concentrations of CTACK/CCL27 and total IgE. The cut-off value for the increased probability of the poly-organ CP of AM development according to the proposed model formula is $p > 0.403$. The future of managing the progression of AM is, particularly, in the application of the integral personalised precise models comprising the maximal number of culprit genotype variants and biomarkers.

FUNDING

The conducted study was partly funded in the framework of the research activity of the Department of paediatrics 1 and medical genetics of the Dnipro State Medical University "The genotype-associated personalisation of the diagnostic and therapeutic process in children suffering the disorders of the respiratory, endocrine and digestive systems (state registration number 0118U006629) and "The precise approaches to diagnosing and managing the somatic and endocrine disorders in children" (state registration number 0123U105100). The other part of the conducted study was financed from personal funds.

ETHICAL APPROVAL

All the methods used had been approved by the local biomedical Ethics Committee of the Dnipro State Medical University which is stipulated in the following Minutes: No. 6 of 07.02.2018, No. 7 of 28.10.2020 and No. 19 of 15.05.2024.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Choi UE, Deng J, Parthasarathy V, et al. Risk factors and temporal associations of progression of the atopic march in children with early-onset atopic dermatitis. J Am Acad Dermatol 2025; 92: 732-40.
2. Indolfi C, Grella C, Klain A, et al. Biomarkers in atopic dermatitis in children: a comprehensive review. Life 2025; 15: 375.
3. Renert-Yuval Y, Thyssen JP, Bissonnette R, et al. Biomarkers in atopic dermatitis – a review on behalf of the International Eczema Council. J Allergy Clin Immunol 2021; 147: 1174-90.e1.
4. Peters N, Peters AT. Atopic dermatitis. Allergy Asthma Proc 2019; 40: 433-6.
5. Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol 2019; 143: 1-11.
6. Paternoster L, Standl M, Waage J, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. Nat Genet 2015; 47: 1449-56.
7. Dytiatkovskyi V, Abaturov O. Filaggrine genotype associations with atopic march at children. Pol J Allergol 2019; 6: 24-9.
8. Moffatt M.F., Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature 2007; 448: 470-3.
9. Ntontsi P, Photiades A, Zervas E, et al. Genetics and epigenetics in asthma. Int J Mol Sci 2021; 22: 2412.
10. Mastraftsi S, Vrioni G, Bakakis M, et al. Atopic dermatitis: striving for reliable biomarkers. J Clin Med 2022; 11: 4639.
11. Thijs JL, de Bruin-Weller MS, Hijnen D. Current and future biomarkers in atopic dermatitis. Immunol Allergy Clin N Am 2017; 37: 51-61.
12. Sutoh Y, Hachiya T, Otsuka-Yamasaki Y et al. Genetic predisposition for immunoglobulin E production explains atopic risk in children: Tohoku Medical Megabank cohort study. Am J Hum Genet 2025; 112: 1852-63.
13. Tham EH, Leung DY. Mechanisms by which atopic dermatitis predisposes to food allergy and the atopic march. Allergy Asthma Immunol Res 2019; 11: 4-15.
14. Ono JG, Kim BI, Zhao Y, et al. Decreased sphingolipid synthesis in children with 17q21 asthma-risk genotypes. J Clin Invest 2020; 130: 921-6.
15. Kitazawa H, Masuko H, Kanazawa J, et al. ORMDL3/GSDMB genotype as a risk factor for early-onset adult asthma is linked to total serum IgE levels but not to allergic sensitization. Allergol Int 2021; 70: 55-60.
16. Ishihara S, Shoda T, Ishimura N, et al. Serum biomarkers for the diagnosis of eosinophilic esophagitis and eosinophilic gastroenteritis. Intern Med 2017; 56: 2819-25.