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Research article

RISK OF ALLERGY AND ITS IMMUNE PHENOTYPES IN CHILDREN WITH *MMP9 Q279R* GENE POLYMORPHISM

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Scientific research with its focus on allergic diseases relies on up-to-date molecular-genetic methods for identifying individual genetic variability; it seems an important stage in the implementation of programs with their aim to early detect and mitigate risks of such diseases.

In this study, our aim was to identify features of immune regulation associated with Q279R MMP9 gene polymorphism (rs17576) and benzene contamination in biological media in children with allergic diseases.

The test group included 33 children with allergic diseases; the reference group consisted of 40 relatively healthy children. CD-markers were identified with flow cytometry. Genotyping was performed with a real-time polymerase chain reaction.

The research revealed elevated levels of total IgE, IL-4 and TNFalfa under elevated benzene contamination in biological media that were by 1.2–4.2 times higher in the examined children with allergic diseases than in the reference group (p = 0.006–0.03). Q279R MMP9 gene polymorphismin in children from the test group had authentically more frequent occurrence of the GG and AG genotypes, by 1.7 times higher than in the reference group. This allows considering the allele G of the MMP9 gene as a sensitivity marker in children with allergic diseases (OR = 2.34; 95 % CI = 1.17–4.65). We established a growth by 2.8 times in total IgE level and greater IL-4 and TNFalfa expression, by 1.4 and 1.3 times accordingly, in carriers of the allele G against those carrying the homozygote AA genotype among the examined children with allergic diseases (p = 0.020–0.042). Logistic regression analysis established the adequacy of the dominant model (p = 0.01) and revealed a possible association between carriage of the AG and GG genotypes of Q279R MMP9 gene polymorphism and developing allergy (OR = 3.61; 95 % CI = 1.34–9.71).

A risk of developing allergy combined with benzene contamination in biological media and gene polymorphism of matrix metalloproteinase MMP9 (rs17576) is by 2.1 times higher for the allele G carriers against the AA genotype carriers (RR = 2.08; 95 % CI = 1.13–3.83). This allows considering the allele G of the MMP9 Q279R gene as a sensitivity marker in children with allergic diseases.

Keywords: *genetic polymorphism, MMP9 Q279R, hypersensitivity markers, polymerase chain reaction, dominant model, CD-markers, a risk of developing allergy, IL-4, TNFalfa.*

Starting from the beginning of the 20th century, the prevalence of allergic diseases has been constantly growing. Given that, currently sensitization to one or several common allergens approaches 40–50 % among the world population. Allergic (atopic) diseases develop due to interaction between individual genetic predisposition and exposure to environmental

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factors; this interaction has facilitated a rapid growth in this trend over the last five decades. Use of the twin method has revealed that the genetic contribution to allergic diseases is about 50 % with heritability estimates being equal to 33–95 % [1, 2]. Therefore, scientific research with its focus on allergic diseases that relies on up-to-date molecular-genetic methods for identifying individual genetic variability seems an important stage in implementing programs with their aim to early detect and mitigate risks of such diseases [3, 4].

Matrix metalloproteinases belong to the family of zinc-dependent endopeptidases responsible for tissue remodeling and degradation of various proteins in extracellular matrix. They are able to influence biologically active molecules and to regulate cellular and signal pathways both under normal physiological conditions and in case of a developing pathology. Gelatinase B (MMP-9) is a major participant in proteolytic extracellular matrix degradation as well as degradation of multiple non-matrix proteins. It modulates embryonic growth and development, angiogenesis, vascular diseases, inflammation, infectious processes, tumor growth, various aspects of the immune response, apoptosis, cell proliferation, differentiation and migration of immune cells; it releases some cytokines and growth factors [5, 6]. High polymorphism of matrix metalloproteinase genes and carriage of variable allele variants that determine enzymatic activity as well as external factors that can put hereditary information into effect (aromatic hydrocarbons, for example), can be considered potentially able to contribute significantly to pathological processes, allergic (atopic) diseases included [7, 8].

In this study, our aim was to identify features of immune regulation associated with Q279R MMP9 gene polymorphism (rs17576) and benzene contamination in biological media in children with allergic diseases.

Materials and methods. We examined schoolchildren who lived in the Urals region. The test group included 33 children (their average age was 12.0 ± 0.5 years; 15 boys and 18 girls) with diagnosed atopic dermatitis, allergic contact dermatitis, allergic rhinitis, and predominantly allergic asthma. The reference group was made of 40 relatively healthy children (their average age was 12.8 ± 0.45 years; 13 boys and 27 girls). Both groups were comparable as per sex, age, and ethnicity ($p < 0.05$).

All legal representatives of the examined children signed a voluntary informed consent to participate in the study. The study was carried out in accordance with the Declaration of Helsinki by the World Medical Association (revised in 2013) and approved by the Ethics Committee of the FBSI "Federal Scientific Center for Medical and Preventive Health Risk Management Technologies".

Aromatic hydrocarbons (benzene) were identified in children's biological media by using gas chromatography on Kristal 5000 gas chromatographer with plasma ionization detector (Russia). Ratios of basic leukocyte populations were identified with Drew-3 hematological analyzer (USA). Leukocyte fractions as per membrane CD-markers were identified with FACSCalibur flow cytometer (Becton Dickinson, USA) on panels of tagged monoclonal antibodies; the device was controlled by the universal CellQuestPro software with not less than 10,000 events being registered in total. Levels of total IgE, interleukins (IL-1beta, IL-6, IL-4, IL-10), interferon-gamma (IFNgamma), and tumor necrosis factor (TNFalfa) were identified by performing ELISA tests with ELx808IU microplate reader (BioTek, USA) and commercial test-systems (Vektor-Best, Khema, Russia) according to the manufacturer's procedures.

The obtained data were analyzed by using Statistica 10.0 software package (StatSoft, USA). The results were given as the simple mean and the standard error of the mean ($M \pm m$) or quantity (%). Authenticity of intergroup differences was determined as per Student's t-test and the significance was taken as $p < 0.05$.

Biomaterials for further genetic analysis were taken from the oral mucosa. DNA was extracted with the adsorption method. Polymorphism of matrix metalloproteinase-9 *MMP9 Q279R* (rs17576) was identified by performing the real-time polymerase chain reaction with CFX96 detection system (Bio-Rad, USA) and SNP-screen kits (Syntol, Russia). All the obtained data were analyzed with 'Gene Expert' software and genotype frequencies were calculated as per the Hardy–Weinberg equilibrium. Authenticity of intergroup differences was determined with chi-square (χ^2) with its significance taken as $p < 0.05$. Data on allele frequencies were analyzed by using logistic regression with calculating odds ratio *OR* and 95 % confidence interval (95 % CI), as well as a relative risk *RR* (relative risk) and its 95 % confidence interval (95 % CI).

The study was performed in full conformity with the organizational standards and methodical guidelines.

Results. Chemical analysis established elevated benzene contamination in blood of the children from the test group. Benzene levels were by 2.7 times higher in them than in the reference group (0.000566 ± 0.00015 μg/cm^3 against 0.000213 ± 0.00011 μg/cm^3 accordingly; $p = 0.024$). We detected elevated specific sensitivity to benzene as per contents of IgG specific to benzene in 78.8 % of the children from the test group against the reference level ($p = 0{,}000$). This indicator was also by 1.8 times higher than in the reference group (0.378 ± 0.051 AU in the test group; 0.208 ± 0.036 AU in the reference group; the reference level is < 0.015 AU).

The study revealed changes in regulatory immune indicators in the children from the test group (Table 1). These changes were identified as per ratios of major immune-competent cell populations as the total leukocyte counts grew by 1.2 times; eosinophils, by 1.9 times; and the eosinophilic-lymphocytic index also grew by 2.1 times ($p = 0.002$–0.014). We identified an increase in CD3$^+$- and CD4$^+$-populations by 15 % and 11 % accordingly against the reference group ($p = 0.032$–0.043).

We detected elevated total sensitization as per total IgE contents in the children with allergic diseases, which was by 4.2 times higher than in the reference group ($p = 0.006$). Changes in markers of the cytokine immune regulation were identified as per levels of IL-4 and TNFalfa that were on average by 1.6 and 1.2 times accordingly ($p = 0.013$–0.03).

The results obtained by genetic analysis (Table 2) showed some peculiarities of how alleles and genotypes of *Q279R MMP9* gene polymorphism were distributed in the children with allergic diseases. Frequency of variant homozygote *GG* genotype and heterozygote *AG* genotype was by 1.7 higher in the test group than in the reference one ($p = 0.03$). The allele *G* of *Q279R MMP9* gene polymorphism can be considered a sensitivity marker and a risk factor of developing allergic diseases in children *(OR* = 2.34; 95 % CI = 1.17–4.65) whereas the allele *A* acts as a protective factor and is associated with minimization of risks that an allergic diseases would develop (*OR* = 0.43; 95 % CI = 0.22–0.85). Logistic regression analysis established the dominant model to be adequate ($p = 0.01$) and revealed a possible association between carrying *AG* and *GG* genotypes of *Q279R MMP9* gene polymorphism and developing allergic diseases (*OR* = 3.61; 95 % CI = 1.34–9.71). The distribution of allele and genotypes frequencies conformed to the Hardy–Weinberg equilibrium ($\chi^2 = 0.01$–1.16; $p = 0.28$–0.9).

We estimated genotype-associated changes in the immune regulation in the children with allergic diseases (the test group) depending on *Q279R MMP9* gene polymorphism (Table 3). The estimation revealed that a relative eosinophil count was authentically by 1.6 times higher, total IgE as a sensitization marker was by 2.8 times higher, and levels of cytokine mediators IL-4 and

Table 1

Immune profiles of the examined children with allergic diseases

Indicator	Reference level	Test group	Reference group	*p*
Leukocytes, 10^9/dm^3	3.9–6	6.36 ± 0.68	5.41 ± 0.37	0.014
Eosinophils, units	35–350	263.94 ± 78.81	142.18 ± 37.64	0.008
Eosinophils, %	0–3	4.03 ± 0.96	2.6 ± 0.64	0.014
$CD19^+$-lymphocytes, 10^9/dm^3	0.09–0.66	0.29 ± 0.04	0.27 ± 0.03	0.422
$CD19^+$-lymphocytes, %	6–25	12.46 ± 1.39	12.6 ± 1.15	0.874
$CD3^+$-lymphocytes, 10^9/dm^3	0.69–2.54	1.63 ± 0.17	1.42 ± 0.09	0.032
$CD3^+$-lymphocytes, %	55–84	66.7 ± 2.60	66.15 ± 1.983	0.737
$CD3^+CD4^+$-lymphocytes, 10^9/dm^3	0.41–1.59	0.89 ± 0.11	0.76 ± 0.06	0.043
$CD3^+CD4^+$-lymphocytes, %	31–60	36.15 ± 2.48	35.65 ± 2.13	0.760
Total IgE, IU/cm^3	0–99.9	181.39 ± 94.68	43.11 ± 20.82	0.006
IL-10, pg/cm^3	0–20	4.10 ± 1.77	3.16 ± 0.73	0.317
IL-1beta, pg/cm^3	0–11	3.23 ± 1.11	1.87 ± 1.19	0.060
IL-4, pg/cm^3	0–4	1.9 ± 0.36	1.20 ± 0.25	0.013
IL-6, pg/cm^3	0–10	2.50 ± 0.92	1.51 ± 0.41	0.890
INFgamma, pg/cm^3	0–10	3.44 ± 2.41	1.57 ± 0.32	0.126
TNFalfa, pg/cm^3	0–6	2.11 ± 0.26	1.7 ± 0.26	0.030

N o t e : *p* is the significance of intergroup differences between the test and reference group as per Student's t-test.

Table 2

Features of *MMP9 Q279R* gene polymorphism in the examined children with allergic diseases

Genotype, allele	Test group, %	Reference group, %	χ^2	*p*	*OR* (95 % CI)
Codominant model					
AA	27.3	57.5	6.71	0.03	0.28 (0.10–0.75)
AG	51.5	30.0			2.48 (0.95–6.48)
GG	21.2	12.5			1.88 (0.54–6.61)
Multiplicative model					
A	53.0	72.5	5.93	0.01	0.43 (0.22–0.85)
G	47.0	27.5			2.34 (1.17–4.65)
Dominant model					
AA	27.3	57.5	6.71	0.01	0.28 (0.10–0.75)
AG+GG	72.7	42.5			3.61 (1.34–9.71)
Recessive model					
AA+AG	78.8	87.5	1.0	0.32	0.53 (0.15–1.86)
GG	21.2	12.5			1.88 (0.54–6.61)

N o t e : *p* is the significance of intergroup differences; χ^2 is chi-square test; *OR* is odds ratio; 95 % CI is confidence interval.

Table 3

Immune regulation indicators in the examined children with allergic diseases associated with *MMP9 Q279R* genotypes

Indicator	Reference level	Genotype		*p*
		AG+GG	*AA*	
Leukocytes, 10^9/dm^3	3.9–6	6.15 ± 0.62	6.93 ± 2.15	0.440
Eosinophils, units	35–350	292.54 ± 105.68	187.67 ± 70.99	0.098
Eosinophils, %	0–3	4.5 ± 1.26	2.78 ± 0.84	0.023
$CD19^+$-lymphocytes, 10^9/dm^3	0.09–0.66	0.28 ± 0.04	0.33 ± 0.11	0.349
$CD19^+$- lymphocytes, %	6–25	11.79 ± 1.52	14.22 ± 3.41	0.153
$CD3^+$- lymphocytes, 10^9/dm^3	0.69–2.54	1.65 ± 0.17	1.57 ± 0.50	0.750
$CD3^+$- lymphocytes, %	55–84	67.5 ± 2.28	64.56 ± 8.54	0.464
$CD3^+CD4^+$- lymphocytes, 10^9/dm^3	0.41–1.59	0.90 ± 0.12	0.854 ± 0.30	0.769
$CD3^+CD4^+$- lymphocytes, %	31–60	36.63 ± 2.96	34.89 ± 5.56	0.550
Total IgE, IU/cm^3	0–99.9	219.96 ± 128.29	78.55 ± 45.36	0.042
IL-10, pg/cm^3	0–20	4.58 ± 2.46	2.88 ± 1.18	0.207
IL-1beta, pg/cm^3	0–11	3.71 ± 1.57	2.25 ± 1.59	0.117
IL-4, pg/cm^3	0–4	2.08 ± 0.47	1.44 ± 0.29	0.020
IL-6, pg/cm^3	0–10	2.37 ± 0.81	2.91 ± 3.37	0.723
INFgamma, pg/cm^3	0–10	4.05 ± 3.37	1.89 ± 1.26	0.229
TNFalfa, pg/cm^3	0–6	2.24 ± 0.30	1.69 ± 0.45	0.031

N o t e : *p* is the significance of intergroup differences between the test and reference group as per Student's t-test.

TNFalfa were by 1.4 and 1.3 times higher accordingly in carriers of the variant allele *G* against those who carried the homozygote genotype *AA* (p = 0.020–0.042).

We comparatively analyzed indicators of the immune and allergic status in the children with allergic diseases associated with the allele *G* against those who carried the genotype *AA* of *Q279R MMP9* gene polymorphism. The analysis made it possible to verify tests (eosinophils, total IgE, IL-4 and TNFalfa) and a mechanism (extracellular matrix degradation) that underlies developing allergy associated with gene polymorphism of the matrix metalloproteinase *Q279R MMP9* (rs17576). Carriers of the allele G have by 2.1 times higher risks of allergy under elevated benzene contamination in biological media than those who carry the *AA*-genotype (*RR* = 2.08; 95 % CI = 1.13–3.83).

Discussion. Negative effects produced by aromatic hydrocarbons, benzene in particular, on immune reactivity indicators are associated with their immunotoxicity. Its intensity is determined by functional peculiarities of immune-competent cells and a stage in an immune response. Benzene contamination in biological media and further processes of its metabolism can aggravate allergy symptoms when, on one hand, oxidative stress is being activated and, on the other hand, Th-2-mediated processes are being stimulated through increased IgE and IL-4 production [9–11].

A mechanism that underlies developing allergic diseases is known to be associated

with the disrupted immune regulation, imbalanced activation of allergen-specific Th2-clones, IgE synthesis by B-lymphocytes, infiltration and activation of eosinophils, basophils and mast cells in an inflammatory nidus migrating through capillary vessel walls and intersticium. All this makes high demands of extracellular matrix degradation determined by matrix metalloproteinases [12, 13]. *MMP9* is assumed to play a key role in tissue remodeling and recovery by degrading IV and V type collagen and elastin thereby facilitating cell migration. However, at present these enzymes are known to have much wider biological functions.

Matrix metalloproteinases play a key role in the development of immune cells, effector function, migration and receptor-ligand interactions; they influence immune responses through, among other things, regulating the signal pathways of cytokine receptors (TNFalfa, IL-6) associated with inflammatory processes. Experimental studies on mice with *MMP* deficiency show that in particular *MMP9* is secreted by inflammatory cells after a contact with an allergen and as a response to signal stimuli given by Th2-cytokines thereby facilitating recruitment of inflammatory cells through mobilization of anti-inflammatory cytokines, chemokines and growth factors [14, 15]. Thus, these mediators stimulate inflammatory cells to penetrate the airway lumen from tissues in patients with asthma. *MMP* also supports hyperactivity of the airways and extracellular matrix remodeling by influencing contraction of smooth muscles, fibroblast invasion and submucous collagen accumulation. *MMP*-induced regulation of cellular signals transmission through proteolytic detachment and activation of key growth factors such as TGFbeta stimulates proliferation of airway cells and modulates matrix production thereby supporting fibrosis development. In addition, *MMP9* has a key role in infiltration of eosinophils through the basal membrane into airway walls in patients with asthma and in subsequent induction of hyper-reactivity. *MMP9* levels identified in exhaled air condensate of children with asthma are elevated and correlate with a weaker lung function and other inflammation markers such as IL-4 / IL-10 [16, 17].

Some studies show that *MMP9*, given its authentically higher expression and levels in blood plasma, also makes a specific contribution to maintaining allergic inflammation with structural fibrosis-like changes and intensive cellular infiltration in patients with allergic rhinitis and atopic dermatitis [18, 19].

The *MMP9* gene is localized in the 20q11.2-q13.1 chromosome and consists of 13 exons. *Q279R MMP9* gene polymorphism (rs17576) is located in the 6th exon in the collagen-binding domain of the enzyme and is associated with adenine *A* being replaced with guanine *G* in the position 836 (*836 A/G*). As a result, the uncharged amino acid glutamine *Q* is replaced with the positively charged amino acid arginine *R* (*p.Gln279Arg*). This polymorphism potentially has some effects on biological properties of an end protein product since it is able to change a three-dimensional structure of it. This increases affinity to substrate and effectiveness of binding and in case of any changes in *MMP9* enzymatic activity can reinforce developing pathologic processes associated with elevated functional activity of the enzyme [20, 21]. Some research works show that the variant *279R* (*G* allele) makes *MMP9* more active and is associated with growing risks of cardiovascular diseases, asthma and chronic obstructive pulmonary disease [22, 23].

Allergic diseases are becoming one of the most widely spread chronic pathologies in the contemporary society. Their timely diagnostics and selection of adequate treatment strategies is a serious challenge for public healthcare in the 21st century since insufficient therapy leads to a significant decline in work ability thereby influencing people's health and quality of life. It is nec-

essary to perform comprehensive studies with their focus on additional and alternative approaches that will allow implementing patient-specific treatment strategies. Such strategies should rely on profound examinations of specific pathogenetic components and individual sensitivity of the body based on molecular-genetic methods for predicting and monitoring disease development [3, 24–26].

Conclusion. The examination of children with diagnosed allergic diseases revealed some disorders of immune regulatory indicators against elevated benzene contamination in biological media. They were associated with changes in ratios of basic leukocytic fractions, elevated eosinophilic-lymphocytic indexes, growing hypersensitivity and elevated levels of cytokine immune mediators that indicate there has been a Th2-directed shift in immune homeostasis. We showed associations between *MMP9 Q279R* gene polymorphism and a risk of developing allergic diseases; the allele *G* can be considered a sensitivity marker in children with allergic diseases (*OR* = 2.34; 95 % CI = 1.17–4.65) and the *G* allele carriers have by 2.1 times higher risks of allergy than those who carry the *AA* genotype (*RR* = 2.08; 95 % CI = 1.13–3.83). Therefore, *Q279R MMP9* gene polymorphism (rs17576) in children with allergic diseases is accompanied with an imbalanced cytokine profile and its allele *G* is associated with a risk (*RR* = 2.1) of allergy. It can be considered a sensitivity marker and used to solve tasks related to early diagnostics and prevention of atopic diseases in children under benzene contamination in biological media.

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