POLYMORPHISM OF PROINFLAMMATORY CYTOKINE GENES IN GIRLS PREDISPOSED TO RECURRENT RESPIRATORY INFECTIONS

Kazakova AV1, Uvarova EV2, Limareva LV3, Lineva OI1, Svetlova GN2, Trupakova AA1

1 Samara State Medical University, Samara
2 Kulakov National Medical Research Center for Obstetrics, Gynecology, and Perinatology, Moscow
3 Kulakov National Medical Research Institute for Obstetrics, Gynecology and Perinatology, Moscow

Acute respiratory infections (ARI) are very common in children and often prompt parents to seek medical advice. Increased susceptibility to ARI is caused by a number of factors, including genetically determined imbalances in cytokine production. The aim of this study was to analyze the frequency of 6 clinically relevant polymorphisms of proinflammatory cytokine genes in girls predisposed to recurrent respiratory infections. The study was conducted in girls aged 7–17 years who were undergoing a routine medical checkup. A group of children with frequent respiratory infections was identified. The following polymorphisms were analyzed for possible associations with predisposition to frequent respiratory infections: IL-1β T-31C (rs1143627), IL-1β T-511C (rs16944), IL-1β C-2953T (rs1143634), IL-1β G-1473C (rs1143623), IL-6 C-174G (rs1800795), and TNFα G-308A (rs1800629). For polymorphism detection, PCR and gel electrophoresis were used. The following alleles were found to be associated with an increased risk for recurrent respiratory infections in girls aged 7–17 years: C-31 (rs1143627) (OR = 2.05; CI: 1.16–3.64; p = 0.013) and C-511 (rs16944) (OR = 3.11; CI: 1.25–7.76; p = 0.013) of the IL-1β gene.

Keywords: recurrent respiratory infections in children, pro-inflammatory cytokines, gene polymorphism

Author contribution: Kazakova AV — conception and design of the study; data acquisition and statistical analysis; Uvarova EV — conception and design of the study; manuscript preparation; Limareva LV — conception and design of the study; statistical analysis; manuscript preparation; Trupakova AA — data acquisition; Svetlova GN, Lineva OI — manuscript preparation.

Compliance with ethical standards: the study was approved by the Ethics Committee of Samara State Medical University (Protocol № 5 dated April 20, 2018). Informed consent was obtained from the parents.

ОБЩЕСТВЕННОСТЬ ПОЛИМОРФИЗМА ГЕНКОВ ПРОВОСПАЛИТЕЛЬНЫХ ЦИТОКИНОВ У ДЕВОЧЕК, ПРЕДРАСПОЛОЖЕННЫХ К ЧАСТЫМ РЕСПИРАТОРНЫМ ЗАБОЛЕВАНИЯМ

А. В. Казакова1, Е. В. Уварова2, Л. В. Лимарева1, О. И. Линева1, Г. Н. Светлова2, А. А. Трупакова1

1 Самарский государственный медицинский университет, Самара, Россия
2 Научно-исследовательский медицинский центр акушерства, гинекологии и перинатологии имени академика В. И. Кулакова, Москва, Россия

Респираторные заболевания (ОРЗ) относятся к числу наиболее распространенных заболеваний детского возраста и служат поводом частого обращения за медицинской помощью. Повышенная заболеваемость детей определяется целым рядом факторов, в том числе нарушением баланса в системе цитокинов, уровень синтеза которых генетически детерминирован. Целью работы было проанализировать особенности распределения шести клинически значимых полиморфных локусов в генах провоспалительных цитокинов у девочек с частыми респираторными заболеваниями. Среди девочек 7–17 лет, проходящих плановый профилактический осмотр, на основании анализа была выделена группа часто болеющих детей. Проведен анализ ассоциации полиморфных вариантов генов провоспалительных цитокинов IL-1β T-31C (rs1143627), IL-1β T-511C (rs16944), IL-1β C-2953T (rs1143634), IL-1β G-1473C (rs1143623) в гене интерлейкин-1β; IL-6 C-174G (rs1800795) — в гене интерлейкин-6 и TNFα G-308A (rs1800629) — в гене фактора некроза опухоли альфа с предрасположенностью к частым респираторным заболеваниям. Полиморфные варианты генов выявлялись методом ПЦР с электрофоретической детекцией. Показано, что с повышенным риском рецидивирующих респираторных заболеваний у девочек 7–17 лет ассоциированы аллели C-31 (rs1143627) (ОШ = 2.05; ДИ: 1.16–3.64; p = 0.013) и C-511 (rs16944) (ОШ = 3.11; ДИ: 1.25–7.76; p = 0.013) гена IL-1β.

Ключевые слова: часто болеющие дети, провоспалительные цитокины, полиморфизм генов

Информация о вкладе авторов: А. В. Казакова — концепция и дизайн исследования, сбор и обработка материала, статистический анализ, написание и редактирование текста; Е. В. Уварова — концепция и дизайн исследования, редактирование текста; Л. В. Лимарева — концепция и дизайн исследования, статистический анализ, написание и редактирование текста; А. А. Трупакова — сбор и обработка материала; Г. Н. Светлова, О. И. Линева — написание текста.

Соблюдение этических стандартов: исследование одобрано этическим комитетом СамГМУ (протокол № 5 от 20 апреля 2018 г.). Родителями участников исследования были подписанные добровольные информированные согласия на участие в исследовании и публикацию результатов.
has more than 6 episodes of ARI a year; this definition refers to repeated or recurrent viral, bacterial or mixed infections of ear, nose and throat (adenoiditis, tonsillitis, otitis), upper (laryngitis) or lower respiratory tract (tracheitis, bronchitis, pneumonia) developing as a result of compromised immunity or inadequate therapy for ARI [13–15]. Increased susceptibility to ARI is determined by a few factors, including genetic ones. There is an ongoing search for possible immunogenetic markers of such predisposition.

The aim of our study was to explore possible associations between the polymorphisms of genes coding for key proinflammatory cytokines and predisposition to frequent respiratory infections in girls aged 7 to 17 years.

METHODS

We examined 116 girls aged 7 to 17 years residing in Samara who visited a pediatric/adolescent gynecologist for a routine checkup in 2014–2016. The following inclusion criteria were applied: age between 7 and 17 years; the absence of severe organic pathology; normal physical, sexual and cognitive development. Exclusion criteria: age outside the specified range; severe organic pathology; developmental abnormalities. We analyzed the medical history of the patients (frequency of respiratory infections and their course) and allele and genotype frequencies for proinflammatory cytokine genes using PCR with gel electrophoresis (SNP-EXPRESS assay; Littech; Russia). We searched for the following SNPs: IL1β T-31C (rs1143627), IL1β T-511C (rs16944), IL1β C-3953T (rs1143634), IL1β G-1473C (rs1143623); IL6 C-174G (rs1800795), and TNFa G-308A (rs1800629). DNA was isolated from the buccal mucosa using an express DNA isolation kit (Littech; Russia). SNPs selected for our study are associated with human immune status and were proposed as clinically and diagnostically relevant at the 15th International Histocompatibility and Immunogenetics Workshop in Brazil in 2008 [16].

DNA was amplified in a DTitle-4S1 thermocycler (DNA-Technology; Russia). We measured positive associations and assessed the significance of differences in the distribution of categorical variables (odds ratios and 95% confidence intervals). Statistical analysis was performed online on the website of the Institute of Human Genetics (Munich, Germany) using DeFinetti software [17]. The minor alleles were hypothesized to be risk alleles and were analyzed in all combinations.

RESULTS

The analysis of clinical data and medical histories revealed that 56.9% of the participants had ARI 6 to 10 times a year. Of them, 10.6% had a chronic ENT pathology (tonsillitis, pharyngolaryngitis) with frequent relapses (4 to 6 times a year) in the setting of acute viral and/or bacterial infection. The girls were divided into 2 groups: 65 girls constituted the group of children with recurrent respiratory infections and 51 girls made up the group without recurrent ARI.

The genotype frequency of 5 out of 6 analyzed SNPs conformed to the Hardy-Weinberg equilibrium. The only exception was TNFa (G-308A); therefore, this polymorphism was excluded from further analysis (see Table).

The analysis of allele/genotype frequencies of the genes encoding proinflammatory cytokines demonstrated that the general sample was dominated by the carriers of the alleles T-31, G-1473 and C-3953 in the IL1β gene (p < 0.05) determining the high levels of the encoded cytokines. In the case of IL1β (T-511C) and IL6 (C-174G), the alleles associated with high and low levels of IL1β and IL6 were distributed in our sample relatively equally.

Comparison of individual polymorphisms occurring at the clinically relevant loci of the studied cytokine genes and associated with high/low levels of their expression revealed that homozygous and heterozygous C alleles at positions 31 and 511 of the IL1β gene were significantly more frequent in the group of girls suffering from recurrent infections. The presence of the C-31 allele increased the risk of frequent respiratory infections twofold (OR = 2.05; CI: 1.16–3.64) in comparison with the T-31 allele. The highest risk of recurrent infections was detected in the carriers of the CC genotype in comparison with heterozygous CT carriers (OR = 2.58; CI: 1.14–5.85) and the pooled CT and TT genotypes (OR = 2.65; CI: 1.25–5.63). The presence of any C-511 allele variant also indicated a high risk of recurrent respiratory infections (OR = 1.68; CI: 0.99–2.83; p = 0.053). The risk of frequent respiratory infections increased more than threefold in the carriers homozygous for CC and CT alleles compared to heterozygous CT (OR= 3.28; CI: 1.22–8.79), homozygous TT (OR = 2.9; CI: 1.98–8.17) and the pool of children with CT or TT (OR = 3.11; CI: 1.25–7/76) at -511C/T of the IL1β gene.

We failed to establish a statistically significant association between recurrent respiratory infections and the IL6 (C-174G) polymorphism, but the girls suffering from recurrent infections were homozygous for the G allele associated with high levels of IL6 1.5 times as rare as the girls without recurrent respiratory infections (OR = 0.57; CI: 0.20–1.59; p = 0.77).

DISCUSSION

Long-lasting and frequent respiratory infections, especially at early age, present a medical challenge yet unsolved, creating a serious social and economic burden for the family and the society in general. The contemporary view on the problem is that the primary causes of high susceptibility to infection in children are the immaturity of the immune system and genetic predisposition [18, 19]. Cytokines play an important role in defense against pathogens: they regulate response to infection not only at the immune system level but also at the level of the whole organism. So far, extensive evidence has been accumulated suggesting that SNPs of cytokine genes can be functional and alter expression of the latter. Such functional polymorphisms hereditarily determine the levels of cytokine production in an individual, affecting the progression and outcome of infectious diseases and immunopathological processes [20]. Anti-inflammatory cytokines play a central role in the formation and regulation of inflammatory response in both innate and adaptive immunities. Therefore, research into the polymorphisms of genes coding for key proinflammatory cytokines can result in the emergence of new diagnostic and therapeutic approaches [21, 22].

In this study, we analyzed associations between polymorphisms of genes coding for key proinflammatory cytokines and predisposition to recurrent respiratory infections in 7 to 17-year-old girls. Clinically relevant functional polymorphisms were assessed, including IL1β (T-31C), IL1β (T-511C), IL1β (C-3953T), IL1β (G-1473C), IL6 (C-174G), and TNFa (G-308A).

In the first stage of the study, we analyzed allele/genotype frequencies of polymorphic variants of the genes encoding proinflammatory cytokines in all study participants regardless of their predisposition to frequent API and tested the conformity of the observed data to the Hardy-Weinberg equilibrium. This is an
Table. Polymorphic allele and genotype frequencies for the genes encoding proinflammatory cytokines in girls aged 7 to 17 years

| Gene polymorphism | Allele, genotype | Frequency, abs / % | Odds ratio (Confidence interval) |
|-------------------|------------------|--------------------|----------------------------------|
|                   |                  | All girls n = 116  | Without recurrent ARI n = 51     | With recurrent ARI n = 65 | (minor allele dominating) |
| IL1B (G–308A)     | T                | 100/67.0 ± 3.3*    | 46/75.0 ± 4.7                   | 54/60.0 ± 4.4             | [1]<–>[2]**: 2.05 (1.16–3.64), χ² = 6.18, p = 0.013 [1]<–>[12]**: 2.58 (1.14–5.88), χ² = 5.28, p = 0.022 [1]<–>[22]: 2.84 (0.87–9.28), χ² = 5.28, p = 0.077 [11]<–>[12 + 22]**: 2.65 (1.25–5.63), χ² = 6.53, p = 0.011 |
|                   | C                | 61/33.0 ± 3.3      | 20/25.0 ± 4.7                   | 41/40.0 ± 4.4             | |
|                   | TT               | 55/47.4            | 31/60.8                         | 24/36.9                   | |
|                   | CT               | 45/38.8            | 15/29.4                         | 30/46.2                   | |
|                   | CC               | 16/13.8            | 5/9.8                           | 11/16.9                   | |
| IL1B (T–31C)      | T                | 78/45.0 ± 3.4      | 36/52 ± 5.5                     | 42/39 ± 4.1               | [1]<–>[2]: 1.68 (0.99–2.63), χ² = 3.74, p = 0.053 |
|                   | C                | 90/55.0 ± 3.4      | 34/48 ± 5.5                     | 56/61 ± 4.1               | [1]<–>[12]: 3.28 (1.22–8.79), χ² = 5.80, p = 0.016 |
|                   | TT               | 26 / 22.4          | 17/33.3                         | 9/13.8                    | |
|                   | CT               | 52/44.8            | 19/37.3                         | 33/50.8                   | |
|                   | CC               | 38 / 32.8          | 15/29.4                         | 23/35.4                   | |
| IL1B (G–1473C)    | G                | 94 / 57.0 ± 3.3    | 40/59.0 ± 5.3                   | 54/55 ± 4.1               | [1]<–>[2]: 1.15 (0.68–1.94), χ² = 0.28, p = 0.600 [11]<–>[12]: 2.00 (0.86–4.63), χ² = 2.65, p = 0.104 [11]<–>[12 + 22]: 1.11 (0.39–3.18), χ² = 0.04, p = 0.844 [11]<–>[12 + 22]: 1.69 (0.77–3.68), χ² = 1.72, p = 0.189 |
|                   | C                | 78 / 43.0 ± 3.3    | 31/41±5.3                       | 47/45 ± 4.1               | |
|                   | GG               | 38 / 32.7          | 20/39.2                         | 18/27.7                   | |
|                   | GC               | 56 / 48.3          | 20/39.2                         | 36/55.4                   | |
|                   | CC               | 22 / 19.0          | 11/21.6                         | 11/16.9                   | |
| IL1B (C–385T)     | G                | 109/78.0 ± 2.8*    | 48/80.4 ± 4.2                   | 51/77 ± 3.8               | [1]<–>[2]: 0.28 (0.65–2.33), χ² = 0.41, p = 0.524 [11]<–>[12]: 1.37 (0.61–3.09), χ² = 0.58, p = 0.447 [11]<–>[12]: 1.16 (0.24–5.57), χ² = 0.54, p = 0.691 [11]<–>[12 + 22]: 1.33 (0.62–2.87), χ² = 0.54, p = 0.461 |
|                   | C                | 43 / 22.0 ± 2.8    | 17/20.0 ± 4.2                   | 26/23.0 ± 3.8             | |
|                   | CC               | 73 / 62.9          | 34/46.7                         | 39/60.0                   | |
|                   | TC               | 36 / 31.0          | 14/27.5                         | 22/33.9                   | |
|                   | TT               | 7 / 6.0            | 3.5/9                           | 4/8.2                     | |
| IL6 (C–511T)      | C                | 79 / 45.0 ± 3.4    | 31/40.0 ± 5.2                   | 48/48.0 ± 4.3             | [1]<–>[2]: 0.72 (0.42–1.21), χ² = 1.58, p = 0.209 [11]<–>[12]: 1.05 (0.40–2.78), χ² = 0.01, p = 0.925 [11]<–>[22]: 1.15 (0.20–1.59), χ² = 1.18, p = 0.277 [11]<–>[12 + 22]: 0.81 (0.33–2.00), χ² = 0.20, p = 0.652 |
|                   | G                | 91 / 55.0 ± 3.4    | 41/60.0 ± 5.2                   | 50/52.0 ± 4.3             | |
|                   | CC               | 25 / 21.5          | 10/19.6                         | 15/23.1                   | |
|                   | CG               | 54 / 46.5          | 21/41.2                         | 33/50.8                   | |
|                   | GG               | 37 / 31.9          | 20/39.2                         | 17/26.2                   | |
| TNFa (C–308G)     | G                | 32 / 18.0 ± 2.9    |                                 |                           | Does not conform to the Hardy–Weinberg equilibrium (p = 0.0001) |
|                   | A                | 106/92.0 ± 2.9     |                                 |                           | |
|                   | GG               | 10 / 8.6           |                                 |                           | |
|                   | GA               | 22 / 19.0          |                                 |                           | |
|                   | AA               | 84 / 72.4          |                                 |                           | |

Note: ARI — acute respiratory infections; * — statistically significant differences in the allele frequency at the given locus (p < 0.05); ** — statistically significant associations with increased risk of respiratory infections.

Important stage because if observed frequencies are consistent with those predicted by the Hardy–Weinberg equation, it means that patient selection for a genetic study is adequate. The frequencies of 5 out of 6 analyzed polymorphisms was consistent with the Hardy–Weinberg equilibrium, except for TNFa (G-308A). For the G-308A polymorphism of the TNFa gene, the frequency of the heterozygous genotype observed in the general sample was different from the predicted frequency. This could be explained by the insufficient number of observations and the character of allele distribution for this locus in the studied group. Therefore, TNFa (G-308A) was excluded from further analysis.

The analysis of allele and genotype frequencies of IL1B and IL6 revealed that the general sample was dominated by the carriers of the T-31, T-1473 and C-3953 polymorphisms of the IL1B gene and the G-174 polymorphism of the IL6 genes. The distribution of IL1B (T-511C) alleles was relatively even. The pattern of allele/genotype distribution for this polymorphism was similar to that observed in the European female population [23] and Russian females residing in Moscow [24], which may indicate the evolutionary advantage of the alleles that determine high levels of proinflammatory cytokines in the Caucasian population.

The subsequent analysis of the associations between predisposition to frequent ARI and the carriership of the studied alleles at the polymorphic loci of the genes encoding proinflammatory cytokines demonstrated that the presence of the C-31 and C-511 alleles in the IL1B gene significantly increased the risk of recurrent respiratory infections (2- to 3-fold), especially in the homozygous patients. In the girls with recurrent respiratory tract infections, the G allele in locus 174 of the IL-6 gene was 1.5 times rarer (p > 0.05). The discovered association between the polymorphic C-31 and C-511 alleles of the IL1B gene and frequent respiratory infections is consistent with the literature: IL-1β plays a central role in the generation and regulation of immune response against infection; carriership of polymorphic variants at positions 31T and 511T in most cases leads to an increase in the production of this cytokine in vivo.
and in vitro in comparison with C alleles, whose carrier increases the severity and frequency of respiratory infections in children and adults [25–27].

For some European populations, IL1B (T-31C) is in 100% linkage disequilibrium with IL1B (T-511C) [28], which seems to explain similar risks associated with this pair of SNPs. The fact that only 2 SNPs of the ILB gene were significantly associated with frequent respiratory infections suggests the need for identifying the subgroups with high prevalence of bacterial/viral infections, the presence/absence of allergies, etc. in the general sample of children predisposed to recurrent ARI, as well as the need for a larger patient sample. At the same time, the cytokine system is a polymorphic, highly reliable pleiotropic regulatory network of mediators whose biological effects are exerted in a cascade manner, are very diverse and sometimes excessive [29]. Therefore, a decrease in the expression of one or several cytokine genes and the resulting low production of the peptide mediator will not always be accompanied by a pronounced pathology. This means that research into the effects of polymorphisms in the cytokine genes should not be limited to the analysis of carrierhip of individual polymorphic variants occurring in a few cytokine genes. It is important to consider linked inheritance, mutual effects, interactions with receptors and other factors affecting the cytokine status in health and pathology.

CONCLUSIONS

1. The studied group of 7 to 17-year old girls residing in Samara was dominated by the carriers of the alleles T-31, G-1473, C-3053 in the ILB gene and the G-174 allele in the IL6 gene.
2. The presence of the alleles C-31 and C-511 in the ILB gene was associated with the increased risk of recurrent respiratory infections. 3. The established association between the studied gene variants and respiratory infections dictates the need for further research into the functional polymorphisms of cytokine genes aiming at developing new diagnostic approaches, prevention measures and personalized therapies. 4. The analysis of carrierhip of individual polymorphic gene variants in the cytokine system is not enough for the comprehensive assessment of individual immunogenetic features and the search for genetic markers for prediction, prevention and personalized treatment; it is important to account for linked inheritance, mutual effects, interactions with receptors and other factors affecting the cytokine status in health and pathology.

References

1. Sepiashvili RI, Sliyanskaya TA. Strategiya i taktika kompleksnoy immunoreabilitatsii bol'nykh s zabolayveniyamim sistemy. Allergologiya i immunologiya. 2015; 16 (1): 51–7. Russian.
2. Ketlinska SA, Simbirsev AS. Tsitokinov. SP.: Foklan, 2008; 552 s. Russian.
3. Gulomov ZS, Simbirsev AS, Yanuk YV, Varyushina EA, Tymova EV. Rol' tsitokinov pri lechenii ostryx i kronicheskikh zabolayveniy verkhnikh dykhatel'nyx putey (Ozobor literature). Rossisskaya otorinolaringologiya. 2008; 37 (6): 200–5. Russian.
4. Prilepskaya VN, Letunovskaya AB, Domnikov AE. Mikrobiotsnoe vival'galischa i polimorfizm genov tsitokinov kak marker zdorov'ya. Zabolayveniya, 2015; 17 (2): 4–13. Russian.
5. Bodenyenkova GM, Timova ZhV. Rol' polimorfizm i ekspresssii otdel'nykh genov tsitokinov v formirovanii patologii (Ozobor). Uspeshnye sovremennoy estestvoznaniya. 2015; (1): 616–20. Russian.
6. Nesterova IV, Kovalева SV, Kleshchenko EI, Shinkareva ON, Golovanova OV, Zonova EV, Abramova DA, Savenkova MS. Rol' sotsial'nykh i ekologicheskikh faktorov v formirovanii gruppy chasto boleyushchikh detey v sotsial'no blagopoluchnykh sem'yakh g. Moskvy. Det'skiye infektsii. 2013; (4): 52–7. Russian.
7. Shchevchenko AV, Golovanova OV, Konenko VI. Osobennosti polimorfizma promotornykh regionov genov tsitokinov IL1, IL4, IL5, IL6, IL10 i TNF-α v evropeoidnogo naseleniya Zapadnoy Sibir. Immunologiya. 2010; 9 (4): 176–81. Russian.
8. Abramov DD, Kofladi IA, Khaltov MR, Sergeev IV, Tirofiev DYU, Gudima GO, i dr. Osobennosti polimorfizma genov, reguliruyushchikh razlichnye komponenty immunnogo otveta, v russkoy populatii. Rossissky gliallogicheskaya zhurnal. 2012; (6): 62–7. DOI:10.24110/0031-403X-2014-93-2-62-67. Russian.
9. Shevchenko AV, Golovanova OV, Konkeno VI. Osobennosti polimorfizma promotornykh regionov genov tsitokinov IL1, IL4, IL5, IL6, IL10 i TNF-α u evropeoidnogo naseleniya Zapadnoy Sibir. Immunologiya. 2010; (4): 176–81. Russian.
10. Abramova NA, Savenkova MS. Rol' sotsial'nykh i ekologicheskikh faktorov v formirovanii gruppy chasto boleyushchikh detey v sotsial'no blagopoluchnykh sem'yakh g. Moskvy. Det'skiye infektsii. 2013; (4): 52–7. Russian.
11. Kutkhin AG, Brusina EB, Volkov AN, Yuzhalin AV, Zhivotovskiy AS. Correlation between genetic polymorphisms within IL-1B and TLR4 genes and cancer risk in a Russian population: a case-control study. Tumor Biol. 2014; 35 (5): 4821–30.
12. Zhu Q, Sun J, Chen Y. Preterm birth and single nucleotide polymorphisms in cytokine genes. Transl Pediatr. 2014; 3 (2): 120–134. DOI: 10.3978/j.issn.2224-4336.2014.03.02.
13. Abramova NA, Savenkova MS. Rol' sotsial'nykh i ekologicheskikh faktorov v formirovanii gruppy chasto boleyushchikh detey v sotsial'no blagopoluchnykh sem'yakh g. Moskvy. Det'skiye infektsii. 2013; (4): 52–7. Russian.
14. Yuliish EI, Yaroshenko SYa. Chasto boleyushcheye deti i taktika pediatrii. Zabolayveniy. 2013; 49 (6): 70–6. Russian.
15. Kriyinya YuO, Krmar LV, Sovremennyye podkhody k profilaktike i lecheniyu ORZ u chasto boleyushchikh detey. Lekarnyy meditsinskyy vestnik. 2015; (59): 40–5. Russian.
16. Marsh SG, Albert ED, Bodmer WB, Bontrop RE, Dupont B, Erlich HA, et al. An update to HLA nomenclature, 2010; 10:45 (5): 846–8. Available from: http://www.hla.org.tw/cisi-bin/hla/hla1w1.html.
17. levina AS, Babachenko IV, Skripchenko NV, Imyanitov EN. Ekologicheskaya struktura zabolayveniy u chasto boleyushchikh detey v zavisimosti ot vozrasta. Rossissky vestnik perinatologii i pediatrii. 2017; 62 (2); 72–7. Russian.
18. Esposito S, Bianchini S, Bosis T, Tagliabue C, Corio I, Argentiero A, Principi N. A randomized, placebo-controlled, double-blinded, single-centre, phase IV trial to assess the efficacy and safety of OM-85 in children suffering from recurrent respiratory tract infections. J Transl Med. 2019 Aug 23; 17 (1): 284. DOI: 10.1186/s12967-019-2040-y. PMID: 31443716 Free PMC Article.
19. Simbirsev AS, Tolotyan AA. Tsitokinov v laboratornoy diagnostike. Infektsionnye bolezni: novosti, mneniya, obucheniye. 2015; (2): 82–98. Russian.
Литература

1. Сергишина Р. И., Славянская Т. А. Стратегия и тактика комплексной иммунологической помощи больным с заболеваниями иммунной системы. Алергология и иммунология. 2015; 16 (1): 51–7.
2. Китченко С. С., Сымбирцев А. С. Цитокины. СПб.: Фолиант, 2008; 552 с.
3. Гулюмов З. С., Симбирцев А. Е., Коненков В. И. Роль цитокинов в лечении острых и хронических заболеваний верхних дыхательных путей (Обзор литературы). Российская онкологическая литература. 2008; 37 (6): 200–05.
4. Прилепская В. Н., Летуновская А. В., Донников А. Е., Гуломов З. С., Симбирцев А. С., Янов Ю. К., Варюшина Е. А., Кетлинский С. А., Симбирцев А. С. Цитокины. СПб.: Фолиант, 2010; 552 с.
5. Нестерова И. В., Ковалева С. В., Бодиенкова Г. М., Зуевой Г. Н., Яковлев В. Г. и др. Полиморфизм и экспрессия отдельных генов цитокинов в формировании патологии (Обзор). Успехи современного естествознания. 2015; (1): 616–20.
6. Артюшкин С. А. Генетический полиморфизм цитокинов. Комплексный анализ клинической эффективности коротких курсов интерферона в лечении ОРВИ у иммунокомпетентных и длительно болеющих детей. Педиатрия. Журнал имени Г. Н. Сперанского. 2014; 93 (2): 62–7. DOI: 10.24110/0031-403X-2014-93-2-62-67.
7. Шевченко А. В., Голованова О. В., Коненков В. И. Особенности полиморфизма промоторных регионов генов цитокинов IL-4, IL-5, IL-6, IL-10 и TNF-α у европеоидного населения Западной Сибири. Иммунология. 2011; (2): 3–10. Russian.
8. Абрамов Д. Д., Кофирди И. А., Хайтов М. Ф., Сереев И. В., Трофимов Д. Ю., Гудима Г. О. и др. Особенности полиморфизма генов, регулирующих различные компоненты иммунного ответа, в русской популяции. Российский аллергологический журнал. 2012; (6): 72–5.
9. Королев М. А., Леонова Ю. Б. Комплексный анализ цитокинов, регулирующих экскрецию опухолевых клеток дефектных, в формировании болезни. Медицинская иммунология. 2010; (4): 361–74.
10. Новоселова М. В., Сымбирцев А. С., Симбирцева А. С. Полиморфизм генов цитокинов при атопической бронхиальной астме. Сибирское медицинское обозрение. 2013; (2): 62–98.
11. Артюшкин С. А. Генетический полиморфизм цитокинов в формировании патологии у иммунокомпетентных и длительно болеющих детей. Педиатрия. Журнал имени Г. Н. Сперанского. 2014; 93 (2): 62–7. DOI: 10.24110/0031-403X-2014-93-2-62-67.
12. Казакова А. В., Уварова Е. В., Лимарева Л. В., Трупакова А. А., Симбирцева А. С. Полиморфизм генов, регулирующих различные компоненты иммунного ответа, в русской популяции. Российский аллергологический журнал. 2012; (6): 72–5.
13. Казакова А. В., Уварова Е. В., Лимарева Л. В., Трупакова А. А., Симбирцева А. С. Полиморфизм генов, регулирующих различные компоненты иммунного ответа, в русской популяции. Российский аллергологический журнал. 2012; (6): 72–5.
14. Марш С. Г., Алберт Э., Боглер В., Бонторп Р., Дюплон Б., Эрlich А., и др. An update to HLA nomenclature, 2010. 2010; 45 (5): 846–8. DOI: 10.1186/s12268-010-0115-2.
15. Шинкарева О. Н., Малиновская В. В., Выжлова Е. Н. Стратегия и тактика профилактики и лечения ОРЗ у часто болеющих детей. Вестник российского медицинского обозрения. 2008; (6): 200–5.
16. Юлиш Е. И., Ярошенко С. Я. Часто болеющие дети и тактика педиатра. Здоровье ребенка. 2013; 49 (6): 70–4.
17. Симбирцева А. С., Тотолян А. А. Цитокины Цитокины в лабораторной практике и лечении ОРЗ у часто болеющих детей. Вестник Российской военно-медицинской академии. 2010; (30): 2; 211–9. Russian.
18. Юлиш Е. И., Ярошенко С. Я. Часто болеющие дети и тактика педиатра. Здоровье ребенка. 2013; 49 (6): 70–4.
19. Королев М. А., Леонова Ю. Б. Комплексный анализ цитокинов, регулирующих экскрецию опухолевых клеток дефектных, в формировании болезни. Медицинская иммунология. 2010; (4): 361–74.
20. Литература