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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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ER22/23EK AND TTH111I POLYMORPHISMS IN THE GLUCOCORTICOID RECEPTOR GENE IN PATIENTS WITH BRONCHIAL ASTHMA WITH REGARD TO THE AGE OF ONSET

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Abstract.

Objective: The objective of the study was to evaluate the frequency of the ER22/23EK and Tth111I polymorphisms in the glucocorticoid receptor gene (GR) in patients with early-onset and late-onset asthma (BA) and to assess the risk of its phenotype's development.

Materials and Methods: We examined 553 BA patients and 95 apparently healthy individuals. The patients were divided into 2 groups depending on the age of BA onset: Group I included 282 patients with late-onset asthma, and group II included 271 patients with early-onset asthma. The ER22/23EK (rs 6189/6190) and Tth111I (rs10052957) polymorphisms in the GR gene were determined using polymerase chain reaction-restriction fragment length polymorphism analysis. Statistical analysis of obtained results was performed using SPSS–17 program.

Results: The analysis of frequency of genotypes and alleles for the ER22/23EK polymorphism in the GR gene with regard to the age of BA onset demonstrated a significant difference between patients with early-onset and late-onset asthma ($p = 0.035$). A significant difference was revealed in the distribution of alleles and genotypes for the Tth111I polymorphism in the GR gene between patients with early-onset BA and late-onset BA ($p = 0.006$). No correlation was found between the ER22/23EK polymorphism in the GR gene and late-onset BA in all genetic models; also, there was a reduction in the risk of early-onset BA observed in the dominant and additive models. No association was demonstrated between the Tth111I polymorphism in the GR gene and late-onset asthma, while a statistically significant correlation was shown with the risk of early-onset asthma in the dominant and super-dominant models.

Conclusions: We established a significant difference in the distribution of alleles and genotypes for the ER22/23EK and Tth111I polymorphisms in the GR gene with regard to onset age; also, we found no association between these polymorphic variants and the development of late-onset asthma, but revealed a protective role of the ER22/23EK polymorphism in the GR gene in the dominant and additive inheritance models and of Tth111I polymorphism in the GR gene – in the dominant and super-dominant models.

Key words. Bronchial asthma, onset, ER22/23EK and Tth111I polymorphisms in the glucocorticoid receptor gene.

Introduction.

Bronchial asthma (BA) is a chronic inflammatory respiratory disease that affects 1 to 18% of population in various countries. The incidence of BA in developed countries is constantly growing. According to the GINA guidelines (2020), BA is a complex heterogeneous disease which is influenced by genetic factors. Due to polygenic nature of BA, the age of onset is of great importance in terms of diagnosis, prognosis, and treatment [1-3]. The differences known to date in the etiology, pathogenesis, and clinical manifestations of early-onset and late-onset asthma involve different genetic factors depending on the age of onset. Several studies on genetic factors in patients with early-onset and late-onset asthma identified specific variants of genetic risk factors for these asthma variants [4], which partly explains the differences in their pathogenesis [1-3].

Research on the ER22/23EK and Tth111I polymorphisms in the glucocorticoid receptor (GR) gene is attributable to the fact that the gene is located on the long arm of chromosome 5 (5q31-q32) which is associated with asthma risk and suggests its participation in the pathogenesis of this disease. More than 2,500 single-nucleotide substitutions were identified in the GR gene, of which only the following were observed in the Caucasian population with a frequency of > 1%: rs6190 (Arg23Lys), rs6195 (N363S), rs41423247 (BclI, C/G), and rs10052957 (-3807 C/T or Tth111I) [5]. Due to the high polymorphy of the GR gene, the frequency of alleles and genotypes differs statistically among different ethnic groups [6]. The involvement of some of its polymorphic variants in the development of asthma [7-9], obesity, and metabolic syndrome was demonstrated [10,11]. According to the results of a meta-analysis by Fu G., which included 4 studies on ER22/23EK polymorphism and 2 studies on Tth111I polymorphism in the GR gene, no association of these polymorphic variants with asthma was found [12]. However, some studies reported the association of these polymorphisms with the development of asthma, its course severity, and disease control [9]. Due to the lack of consistent data on the effect of the ER22/23EK and Tth111I polymorphisms in the GR gene on the risk of asthma, we aimed to study the association between these SNPs and the risk of different phenotypes of BA depending on the age of onset.

The objective of the study was to evaluate the frequency of the ER22/23EK and Tth111I polymorphic variants in the GR gene in patients with early-onset and late-onset BA and to assess the risk of BA phenotypes development.

Materials and Methods.

We examined 553 BA patients (experimental group) and 95 apparently healthy individuals (control group); all participants had previously signed an informed consent form. The patients were divided into 2 clinical groups depending on the age of BA onset. Group I included 282 patients with late-onset asthma

(late-onset asthma phenotype) and group II included 271 patients with early-onset asthma (early-onset asthma phenotype). Based on the absence of exact guidelines for asthma early and late-onset definitions, we use stratifications from the previously published data and consider asthma onset before the age of 12 as early and after the age of 12 as late [13].There was no significant difference in gender, age, severity, or control level between the groups ($p > 0.05$). BA was diagnosed according to the 2016 GINA recommendations and its later versions.

The study was approved by the Bioethics Committee of Medical Institute of Sumy State University and complied with the Declaration of Helsinki. The ER22/23EK (rs 6189/6190) and Tth111I (rs10052957) polymorphisms in the GR gene were determined using polymerase chain reaction-restriction fragment length polymorphism analysis. Statistical analysis of obtained results was performed using SPSS–17 program. We used Pearson's chi-squared test; the P-value of <0.05 was considered statistically significant. Binary logistic regression was used for risk assessment; analysis-of-variance method and F-test were also used in the study.

Results.

Given the fact that early-onset and late-onset asthma has its own phenotypic differences, we analyzed the frequency of alleles and genotypes for the ER22/23EK and Tth111I polymorphisms in the GR gene depending on the onset age in order to check for the association between the studied polymorphic variants and different phenotypes (Table 1).

The analysis of distribution of genotypes and alleles for the ER22/23EK and Tth111I polymorphisms in the GR gene with regard to the age of BA onset showed a significant difference between patients with early-onset and late-onset asthma ($p = 0.035$; $p = 0.006$). As can be seen from the table above, the frequency of GG-genotype for the ER22/23EK polymorphism in the GR gene was higher in the patients with early-onset asthma compared to late-onset asthma, while AG heterozygotes were more common with late-onset asthma. G-allele was more frequently observed in patients with early-onset asthma, while A-allele was more common among late-onset BA patients. The results of the study of the Tth111I polymorphism in the GR gene concerning the age of onset along with significant difference in the distribution of genotypes showed a higher frequency of TT homozygotes in patients with early-onset asthma compared to late-onset asthma.

Given the significant difference in the distribution of genotypes for the ER22/23EK and Tth111I polymorphisms in the GR gene depending on the age of onset, we performed a statistical analysis to identify a possible association between genetic markers and relative risk of early-onset and late-onset asthma (Table 2, 3).

No association was established between ER22/23EK polymorphism in the GR gene and the risk of late-onset asthma in any genetic model. However, there was a reduction in the risk of early-onset BA observed in the dominant, super-dominant, and additive models.

Analysis of the risk of late-onset and early-onset asthma depending on the Tth111I polymorphism in the GR gene showed no association between the development of late-onset asthma and Tth111I polymorphism in the GR gene but demonstrated a statistically significant association with the risk of early-onset asthma in the dominant ($p = 0.02$) and super-dominant ($p = 0.001$) models.

Table 1. *Distribution of genotypes and alleles for the ER22/23EK and TTH111I polymorphisms in the glucocorticoid receptor gene in patients with bronchial asthma with regard to the age of onset.*

Parameter	**Late onset, n = 282**		**Early onset, n = 271**	
Genotype	n	%	n	%
ER22/23EK polymorphism in the glucocorticoid receptor gene				
GG	244	86.5	252	93.0
AG	36	12.8	17	6.3
AA	2	0.7	2	0.7
$\chi^2 = 6.72$; $p = 0.035$				
Allele	%		%	
G	92.9		96.1	
A	7.1		3.9	
TTH111I polymorphism in the glucocorticoid receptor gene				
Genotype	n	%	n	%
CC	103	36.5	125	46.1
CT	141	50.0	99	36.5
TT	38	13.5	47	17.3
$\chi^2 = 10.2$; $p = 0.006$				
Allele	%		%	
C	61.5		64.4	
T	38.5		35.6	

Table 2. *The risk of early-onset and late-onset asthma with regard to the ER22/23EK polymorphism in the glucocorticoid receptor gene.*

Model	**P_{obs}**	**OR_{obs} (95% CI)**	**AIC**
Late onset			
Dominant	0.42	0.77 (0.41–1.49)	16.84
Recessive	0.27	0.33 (0.04–2.8)	16.34
Super-dominant	0.62	0.85 (0.44–1.7)	17.24
Additive	0.3	0.74 (0.43–1.34)	16.46
Early onset			
Dominant	0.01	0.37 (0.18–0.77)	15.82
Recessive	0.29	0.35 (0.04–2.91)	21.84
Super-dominant	0.01	0.39 (0.18–0.83)	17.05
Additive	0.01	0.44 (0.23–0.81)	16.18

Table 3. *The risk of early-onset and late-onset asthma with regard to the Tth111I polymorphism in the glucocorticoid receptor gene.*

Model	**P_{obs}**	**OR_{obs} (95% CI)**	**AIC**
Late onset			
Dominant	0.43	1.21 (0.75–1.94)	21.65
Recessive	0.07	2.31 (1.01–6.25)	18.22
Super-dominant	0.66	0.9 (0.56–1.43)	21.98
Additive	0.13	1.32 (0.92–1.92)	19.87
Early onset			
Dominant	0.02	0.67 (0.48–0.94)	25.65
Recessive	0.21	1.35 (0.85–2.15)	29.33
Super-dominant	0.001	0.58 (0.41–0.81)	20.67
Additive	0.34	0.89 (0.7–1.13)	30.01

Discussion.

The objective of our study was to provide supplementary modern knowledge about genetic aspects of BA with regard to

the age of onset taking into account the ER22/23EK and Tth111I polymorphisms in the glucocorticoid receptor gene. The study was performed by estimating the frequency of genotypes for the studied polymorphisms and assessing the risk of developing phenotypes of early-onset and late-onset BA. Taking into account the age of BA onset, we revealed a significant difference between early-onset and late-onset asthma in terms of the frequency of genotypes and alleles for the ER22/23EK polymorphism in the GR gene ($p = 0.035$). The frequency of GG-genotype was higher in the patients with early-onset asthma, while AG heterozygotes were more common with late-onset asthma. G-allele was more frequently observed in patients with early-onset asthma (96.1%) compared to late-onset asthma (93.1 %), while A-allele was observed in 3.9% and 6.9%, respectively. Preliminary we found no difference in the distribution of alleles and genotypes for the ER22/23EK polymorphism in the GR gene in patients with asthma with no regard to age of onset and in apparently healthy individuals ($\chi 2 = 4.14$; $p = 0.126$); apart from that, we revealed no statistically significant association with BA risk in all models of inheritance. Differentiated analysis of the association between the ER22/23EK polymorphism in the GR gene and different BA phenotypes demonstrated no correlation in patients with late-onset asthma, while patients with early-onset asthma revealed decreased BA risk in the dominant and recessive models ($p = 0.01$).

Taking into account the clinical and laboratory phenotypic peculiarities of early-onset asthma and late-onset asthma, we analyzed the distribution of alleles and genotypes for the Tth111I polymorphism in the GR gene with regard to onset age in order to check for the possible association between the studied polymorphic variant and these phenotypes. Preliminary analysis of BA risk with no regard to age of onset in recessive homozygotes showed a 2.69-fold increase vs. major allele homozygotes ($p = 0.02$). Taking into account the age of BA onset, we found a significant difference in the distribution of alleles and genotypes for the Tth111I polymorphism in the GR gene with regard to onset age ($p = 0.006$); also, we revealed no association between the development of late-onset asthma and Tth111I polymorphism in the GR gene, but demonstrated a statistically significant association with the risk of early-onset asthma in the dominant ($p = 0.02$) and super-dominant ($p = 0.001$) models.

The study of Szczepankiewicz A. (2008) did not find any association of the Tth111I polymorphism in the GR gene with asthma and an increased need for high doses of inhaled GC [14,15].

The inconsistency of findings that were obtained in different studies related to the role of the ER22/23EK and Tth111I polymorphisms in the GR gene in BA development and course and involving BA patients with and without regard to onset age can be attributable to the clinical heterogeneity of this disease, different age of onset, and pathogenetic differences among different phenotypes of the disease. Our findings show the differences in genetic factors in patients with early-onset and late-onset asthma. Therefore, an in-depth study of pathogenesis mechanisms and genetic factors causing the disease in adults and children will help to develop strategies for BA prevention and treatment.

Conclusion.

A significant difference was observed in the distribution of genotypes and alleles for the ER22/23EK and Tth111I polymorphisms in the GR gene between patients with early-onset and late-onset asthma.

No correlation was found between late-onset BA and the ER22/23EK polymorphism in the GR gene in all genetic models; also, there was a reduction in the risk of early-onset BA observed in the dominant and additive models.

No association was reported between late-onset asthma and the Tth111I polymorphism in the GR gene, while a statistically significant association was shown with the risk of early-onset asthma in dominant and super-dominant models.

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