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Analysis of the association of bronchial asthma clinical course with ER22/23EK and TTH111I polymorphic variants in the glucocorticoid receptor gene**Kachkovska Vladyslava**

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Abstract: bronchial asthma (BA) is one of the important and urgent medical and social problems of our time due to the high incidence and prevalence, which keep increasing. This is a typical multifactorial disease determined by the influence of external factors and genetic predisposition. The combination of these numerous factors determines the phenotypic heterogeneity of bronchial asthma. Identification of asthma phenotypes was based mainly on clinical variables; however, further identification of clinical phenotypes revealed their genetic heterogeneity. Accordingly, the determination of genetic marker data for clinical phenotypes of bronchial asthma will improve the diagnostic capabilities of preventive and evidence-based medicine in the future. The objective of the study was to determine the features of the course of early-onset and late-onset BA depending on the ER22/23EK and Tth111I polymorphisms in the glucocorticoid receptor gene and to supplement modern data on the role of genetic factors in BA onset and the severity for various phenotypes. We examined 553 BA patients and 95 apparently healthy individuals. All of them had previously signed an informed consent form. BA diagnosis, severity, and control level were determined according to the GINA recommendations-2016 and its later versions and the Decree of the Ministry of Health of Ukraine No. 868 issued on 08 October 2013. Respiratory function was studied using Kardioplus diagnostic suite (Ukraine). The patients were divided into two clinical groups according to the BA onset: Group I included 282 patients with late-onset asthma, and Group II included 271 patients with early-onset asthma. The Bioethics Committee of the Medical Institute of Sumy State University approved the study. The ER22/23EK (rs 6189/6190) and Tth111I (rs10052957) polymorphic variants in the glucocorticoid receptor (GR) gene were determined using polymerase chain reaction-restriction fragment length polymorphism analysis. Statistical analysis of obtained results was performed using SPSS-17 program. A statistically significant difference was observed in the distribution of genotypes for the ER22/23EK and Tth111I polymorphisms in the GR gene depending on BA severity, with a higher frequency of minor alleles in both cases in patients with severe BA ($\chi^2 = 6.09$; $p = 0.048$ and $\chi^2 = 15.8$; $p = 0.001$, respectively). The relative risk of severe BA did not depend on the ER22/23EK polymorphism in the GR gene; however, it was 3.63 times higher in the carriers of the TT genotype for the Tth111I polymorphism vs. carriers of the major allele homozygotes. The risk of severe disease in early-onset and late-onset BA depended on the Tth111I polymorphism in the GR gene; in the recessive model, it increased by 3.7 times for early-onset asthma and by 3.5 times – for late-onset asthma. Analysis of ER22/23EK (rs 6189/6190) and Tth111I (rs10052957) polymorphic variants in the GR gene demonstrated their possible correlation not only with the increased risk of BA, but also with certain phenotypes and severity of the disease.

Keywords: [Bronchial Asthma](#), [Clinical Course](#), [Disease](#), [The Glucocorticoid Receptor Gene](#), ER22/23EK and Tth111I polymorphisms

Introduction

Bronchial asthma (BA) is known to be one of the important and urgent medical and social problems of our time due to the high incidence and prevalence, which keep increasing. This is a typical multifactorial disease determined by the influence of external factors and genetic predisposition. The combination of these numerous factors determines the phenotypic heterogeneity of bronchial asthma (Moffatt et al, 2015). Identifying asthma phenotypes was based mainly on clinical variables; however, further identification revealed their genetic heterogeneity (Azim et al, 2020; De Nijs et al, 2013). The structure of genetic factors of BA depends on the age of onset. It is confirmed by the results of genome-wide association studies, which are specific for the phenotypes of early-onset and late-onset BA. The established genetic independent associations were specific for early-onset and late-onset asthma, and only a small amount was shared by these BA types (Ferreira et al, 2019). The genetic predisposition to early-onset and late-onset asthma phenotypes was proven: genes determine the pathogenesis of the immune response, the nature of inflammation, and, accordingly, affect the severity of the disease. A differentiated study of genomic associations with the age of BA onset can help to identify risks for a certain phenotype of the disease, which will generally contribute to understanding the distinctions in pathogenesis, the clinical course of early-onset and late-onset BA, and approaches to treatment (Tan et al, 2015; Tan et al, 2016; Souza et al, 2014).

We chose to study the ER22/23EK and Tth111I polymorphic variants of the glucocorticoid receptor (GR) gene due to the fact that a number of studies demonstrated their role in the development of BA, disease control, airway remodeling, and the effectiveness of background therapy (Fu et al, 2018; Panek et al, 2013). The ER22/23EK polymorphism is always associated with the T allele of the TthIII polymorphism, and this haplotype, in turn, is associated with relative resistance to GCs and a favorable metabolic profile (Van Rossum et al, 2004). However, these associations show low

reproducibility in different studies, and thus, clinical application of the results of genetic testing for these GR gene polymorphisms requires further research (Szczepankiewicz et al, 2008). The main reasons why the clinical significance of this polymorphism has not been confirmed in various studies are the heterogeneity of the population, insufficient sample size, and inappropriate characteristics of the comparison groups (Ilmarinen et al, 2015; Kaur et al, 2019).

It is assumed that common genetic factors and, accordingly, common mechanisms are involved in the formation of certain phenotypes of the disease, i.e., clinical features and severity. A differentiated approach to the study of genomic associations with the age of asthma onset can help to identify risks for a certain phenotype of the disease, which will contribute to determining the clinical course features and treatment approaches (Mohamed et al, 2015).

Aim

The objective of the study was to determine the features of the course of early-onset and late-onset BA depending on the ER22/23EK and Tth111I polymorphisms in the GR gene and to supplement modern data on the role of genetic factors in BA onset and the severity of various phenotypes.

Materials and Methods

553 patients with bronchial asthma were examined. All of them had previously signed an informed consent form. The control group consisted of 95 apparently healthy individuals. BA diagnosis, severity, and control level were determined according to the GINA recommendations-2016 and its later versions and the Decree of the Ministry of Health of Ukraine No. 868 issued on 08 October 2013 (GINA report, 2020). Respiratory function was studied using Kardioplus diagnostic suite (Ukraine). The patients were divided into two clinical groups according to the BA onset: Group I included 282 patients with late-onset asthma, and Group II included 271 patients with early-onset asthma. The Bioethics Committee of the Medical Institute of Sumy State University approved the study. The ER22/23EK (rs 6189/6190) and

Tth111I (rs10052957) polymorphic variants 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

Among the 553 patients examined, 88 (15.9%) subjects had a mild disease, 175 (31.7%) subjects had a moderate disease, and 290 (52.4%) had a severe disease. For further analysis, patients with a mild and moderate BA course were combined into a non-severe BA group (n = 263). Taking into account the results of clinical studies on the association of the GR gene SNPs with asthma onset and severity, as well as with the development of resistance to basic asthma therapy, we investigated the distribution of genotypes for the ER22/23EK and TthIII polymorphisms in the GR gene in non-severe BA group vs. severe BA group (Table 1).

Table 1. Distribution of genotypes for the ER22/23EK and TthIII polymorphisms in the glucocorticoid receptor gene depending on BA severity

Genotype	BA severity			
	Non-severe BA, n = 263		Severe BA, n = 290	
	n	%	n	%
rs 6189/6190				
GG	243	92.4	253	87.2
AG	20	7.6	33	11.4
AA	0	0	4	1.4
$\chi^2 = 6.09; p = 0.048$				
rs10052957				
CC	100	38.0	128	44.1
CT	135	51.3	105	36.2
TT	28	10.6	57	19.7
$\chi^2 = 15.8; p = 0.001$				

A statistically significant difference was observed in the distribution of genotypes for the ER22/23EK and TthIII polymorphisms in the GR gene depending on BA severity (p = 0.048; p = 0.001). Thus, patients with severe disease

had AG and AA genotypes for the ER22/23EK polymorphism in the GR gene more often vs. patients with a non-severe disease. Among the 553 subjects, only 4 homozygous carriers of the minor allele had a severe course. At the same time, we found out that the carriers of the TT genotype for the TthIII polymorphism in the GR gene were twice as many among the patients with a severe disease vs. among the patients with a non-severe disease. Table 2 represents the severe BA risk analysis using a binary logistic regression in four inheritance models.

Table 2. The risk of severe asthma depending on the ER22/23EK and Tth111I polymorphisms in the glucocorticoid receptor gene

Model	Pobs	ORobs (95% CI)	AIC
ER22/23EK			
Dominant	0.32	0.72 (0.39 – 1.4)	16.33
Recessive	0.62	0.65 (0.12 – 4.75)	17.07
Super-dominant	0.39	0.74 (0.39 – 1.5)	16.57
Additive	0.31	0.76 (0.44 – 1.33)	16.31
Tth111I polymorphism			
Dominant	0.6	0.88 (0.55– 1.41)	32.03
Recessive	0.001	3.63 (1.63 – 9.67)	21.35
Super-dominant	0.01	0.51 (0.32 – 0.82)	24.39
Additive	0.23	1.22 (0.88 – 1.7)	30.85

The relative risk estimation of developing severe asthma depending on the ER22/23EK polymorphism in the GR gene revealed no statistically significant correlation in any model of inheritance. At the same time, the TthIII polymorphism in the GR gene was found to have a statistically significant association with severe BA in recessive (p = 0.001) and super-dominant models of inheritance (p = 0.01). The risk of severe BA in the minor allele homozygotes was 3.63 times higher vs. major allele homozygotes.

Analysis of the frequency of genotypes for ER22/23EK and Tth111I polymorphisms in the GR gene with regard to BA severity and the age of onset are shown in Table 3.

To study the association of ER22/23EK and Tth111I polymorphisms in the GR gene with the risk of severe disease in early-onset and late-onset

Table 3. The ER22/23EK and Tth111I polymorphisms in the glucocorticoid receptor gene in BA patients with regard to BA severity and the age of onset

ER22/23EK polymorphism					Tth111I polymorphism				
Early onset									
Parameter	Non-severe BA, n = 91		Severe BA, n = 180		Parameter	Non-severe BA, n = 91		Severe BA, n = 180	
Genotype	n	%	n	n	Genotype	n	%	n	n
GG	89	97.8	163	90.6	CC	51	56.0	74	41.3
AG	2	2.2	15	8.3	CT	30	31.9	70	38.5
AA	0	0	2	1.1	TT	11	12.1	36	21.2
$\chi^2 = 4.98; p = 0.083$					$\chi^2 = 5.92; p = 0.05$				
Allele	%		%		Allele	%		%	
G	98.6		95.2		C	71.7		60.6	
A	1.4		4.8		T	28.3		39.4	
Late onset									
Parameter	Non-severe BA, n = 172		Severe BA, n = 110		Parameter	Non-severe BA, n = 172		Severe BA, n = 110	
Genotype	n	%	n	%	Genotype	n	%	n	%
GG	154	89.5	90	81.8	CC	53	30.8	56	50.9
AG	18	10.5	18	16.4	CT	106	61.6	35	31.8
AA	0	0	2	1.8	TT	13	7.6	19	17.3
$\chi^2 = 6.08; p = 0.05$					$\chi^2 = 24.51; p = 0.001$				
Allele	%		%		Allele	%		%	
G	95.3		87.9		C	59.4		64.9	
A	4.7		12.1		T	40.6		35.1	

BA, a statistical analysis was performed with regard to four models of inheritance (Table 4).

The relative risk estimation for the recessive, super-dominant, and additive models showed no statistically significant correlation between the ER22/23EK polymorphism in the GR gene and the risk of severe course of early-onset BA. In the dominant model, the protective role of this polymorphism was revealed ($p = 0.04$). No association was established between the studied polymorphism and the severity of late-onset BA.

In the recessive model of inheritance, an association was observed between the Tth111I polymorphism in the GR gene and a 3.7-fold increase in relative risk of developing severe early-onset BA ($p = 0.001$) and a 3.5-fold increase in relative risk of developing severe late-onset BA ($p = 0.01$). A reduction in the risk of developing severe disease

in early-onset and late-onset BA was found in the super-dominant model ($p = 0.03$; $p = 0.001$).

Discussion

The objective of the study was to determine the features of the course of early-onset and late-onset BA depending on the ER22/23EK and Tth111I polymorphisms in the GR gene and to supplement modern data on the role of genetic factors in BA onset and the severity of various phenotypes.

Preliminary results of assessing the frequency of genotypes for the ER22/23EK and Tth111I polymorphisms in the GR gene with regard to the age of BA onset and risks of developing early-onset and late-onset BA phenotypes revealed a significant difference in allele and genotype distribution for the ER22/23EK polymorphism between patients with early-onset and late-

Table 4. The risk of severe disease in early-onset and late-onset BA depending on the ER22/23EK and Tth111I polymorphisms in the glucocorticoid receptor gene

Model	P _{obs}	OR _{obs} (95% CI)	AIC	P _{obs}	OR _{obs} (95% CI)	AIC
Early onset			Late onset			
ER22/23EK polymorphism in the glucocorticoid receptor gene						
Dominant	0.04	0.46 (0.22 – 0.97)	15.65	0.38	1,39(0.67 – 2.92)	15.4
Recessive	0.46	0.47 (0.06 – 4.0)	19.26	0.97	1.04 (0.12 – 8.86)	16.18
Super-dominant	0.06	0.47 (0.22 – 1.04)	16.3	0.36	1.43 (0.66 – 3.12)	15.35
Additive	0.05	0.53 (0.28 – 1.0)	15.95	0.44	1.28 (0.68 – 2.44)	15.58
TTH111I polymorphism in the glucocorticoid receptor gene						
Dominant	0.96	0.9 (0.6 – 1.6)	29.47	0.28	0.7 (0.4 – 1.3)	28.36
Recessive	0.001	3.7 (1.6 – 10.2)	19.18	0.01	3.5 (1.4 – 9.8)	21.97
Super-dominant	0.03	0.6 (0.3 – 0.9)	24.47	0.001	0.4 (0.2 – 0.8)	20.93
Additive	0.13	1.3 (0.9 – 1.9)	27.17	0.61	1.1 (0.8 – 1.6)	29.29

onset disease ($p = 0.035$); on the other side, we found no statistically significant difference in the distribution of alleles and genotypes for the ER22/23EK polymorphism in the GR gene in patients with asthma disregarding age of onset and in apparently healthy individuals ($\chi^2 = 4.14$; $p = 0.126$) and no significant association with BA risk in all models of inheritance (Kachkovska et al, 2023). Analysis of the association between the ER22/23EK polymorphism in the GR gene and different BA phenotypes showed no correlation in patients with late-onset asthma, while patients with early-onset asthma had decreased BA risk in the dominant and recessive models ($p = 0.01$). In addition to this, we revealed a statistically significant difference in the distribution of genotypes for the ER22/23EK polymorphism in the GR gene depending on BA severity due to the higher frequency of AG and AA genotypes in patients with severe asthma vs. patients with non-severe asthma. The risk of developing severe asthma did not depend on the ER22/23EK polymorphism in the GR gene. After adjusting by the age of onset, we detected a significant difference in the distribution of genotypes for the ER22/23EK polymorphism in the GR gene depending on BA severity only in patients with late-onset BA, which was confirmed by a higher frequency of AG heterozygotes and the minor AA allele homozygotes in patients with a severe

course of the disease. Along with this, in dominant and recessive models of inheritance, a protective role of the ER22/23EK polymorphism in the GR gene was observed in terms of the risk of severe early-onset BA. At the same time, no correlation was found in terms of late-onset BA in any model of inheritance.

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 ($p = 0.02$) (Kachkovska, 2023). 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. A statistically significant difference was observed in the distribution of genotypes for the Tth111I polymorphism in the GR gene depending on the severity in patients with severe asthma vs. patients with non-severe asthma. At the same time, severe BA risk was 3.63 times higher in the carriers of the TT genotype for the Tth111I polymorphism vs. carriers of the major allele homozygotes. We found a significant difference in genotype distribution for

the Tth111I polymorphism in the GR gene only in late-onset BA patients: there was a 1.9 times higher frequency of homozygous carriers of the minor allele among patients with severe BA vs. patients with non-severe BA. The risk of severe disease in early-onset and late-onset BA depended on the Tth111I polymorphism in the GR gene and in the recessive model, it increased by 3.7 times for early-onset asthma and by 3.5 times – for late-onset asthma.

The Tth111I polymorphism in the GR gene plays an important role in the development of both allergic and non-allergic asthma and correlates with a specific profile of asthma control according to ACT™, which was demonstrated by Panek et al.: the T allele correlated with the risk of developing certain BA phenotypes, i.e., severe allergic and severe non-allergic BA, and the level of its control according to ACT (Panek et al, 2013).

At the same time, no significant difference was found in the distribution of alleles and genotypes for rs6189/90 (Arg23Lys) and rs10052957 (-3807 C/T or Tth111I) polymorphisms in the GR gene in patients with severe BA who were treated with high doses of inhaled glucocorticoids to maintain BA control and in patients with moderate BA who were treated with low doses (Szczeplankiewicz et al, 2008). A study in the Serbian population on the association of the ER22/23EK polymorphism in the GR gene with COPD and the daily dose of inhaled glucocorticoids showed no significant difference in the distribution of genotypes and alleles between patients with COPD and healthy individuals ($p > 0.05$). It was also revealed that the heterozygous genotype was associated with a higher daily dose of inhaled GCs compared to the carriers of the wild-type ER22/23EK polymorphism ($p = 0.047$) (Mohamed et al, 2015). M. Panek studied one of the possible mechanisms of the correlation between the severity of BA, resistance to glucocorticoids and Tth111I and ER22/23EK polymorphisms in the GR gene by assessing the TGF- β 1 mRNA expression level in patients with BA and healthy volunteers (2015). The Tth111I polymorphism in the GR gene was shown to correlate significantly ($p = 0.0115$) with the TGF- β 1 mRNA expression level. In particular, the TT and SS genotypes were associated with an increase and decrease in the level of TGF- β 1 mRNA expression, respectively. In

the case of the occurrence of Tth111I polymorphic forms of the GR gene, a decreased ability of glucocorticoids to inhibit the expression of TGF- β 1 can be observed. ER22/23EK polymorphism did not influence the TGF- β 1 mRNA expression level (Panek et al, 2015).

Conclusions

A statistically significant difference was observed in the distribution of genotypes for the ER22/23EK and Tth111I polymorphisms in the GR gene, depending on BA severity.

The frequency of AG and AA genotypes for the ER22/23EK polymorphism in the GR gene and the TT genotype for the Tth111I polymorphism in the GR gene was higher in patients with severe asthma vs. patients with non-severe asthma.

The relative risk of severe BA did not depend on the ER22/23EK polymorphism in the GR gene; however, it was 3.63 times higher in the carriers of the TT genotype for the Tth111I polymorphism vs. carriers of the major allele homozygotes.

We detected a significant difference in the distribution of genotypes for the ER22/23EK polymorphism in the GR gene depending on BA severity only in patients with late-onset BA, which was confirmed by a higher frequency of AG heterozygotes and the minor AA allele homozygotes in patients with a severe course of the disease. We found a significant difference in genotype distribution for the Tth111I polymorphism in the GR gene only in late-onset BA patients: there was a 1.9 times higher frequency of homozygous carriers of the minor allele among patients with severe BA vs. patients with non-severe BA.

In dominant and recessive models of inheritance, a protective role of the ER22/23EK polymorphism in the GR gene was observed in terms of the risk of severe early-onset BA. For late-onset BA, there was no correlation found in any inheritance model.

The risk of severe disease in early-onset and late-onset BA depended on the Tth111I polymorphism in the GR gene; in the recessive model, it increased by 3.7 times for early-onset asthma and by 3.5 times – for late-onset asthma.

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Conflict of Interest

The authors have no conflicts of interest to declare.

Consent to Publication

The author has obtained consent to publish the results of the study.

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

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Аналіз асоціації клінічного перебігу бронхіальної астми з ER22/23EK і Tth111I поліморфними варіантами гена глюкокортикоїдного рецептора

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Анотація: бронхіальна астма (БА) є однією із важливих і актуальних медико-соціальних проблем сучасності, що зумовлено високою захворюваністю та поширеністю, а також їх зростанням. Це захворювання є типовим мультифакторним, розвиток якого зумовлений впливом зовнішніх чинників та генетичною схильністю. Поєднання даних чисельних чинників зумовлює фенотипову гетерогенність БА. Виділення фенотипів астми ґрунтувалося в основному на клінічних змінних, однак, у подальшому ідентифікація клінічних фенотипів з'ясувала і їх генетичну гетерогенність. Відповідно визначення даних генетичних маркерів клінічних фенотипів бронхіальної астми дозволить покращити діагностичні можливості превентивної та доказової медицини у майбутньому. Мета дослідження полягала у встановленні особливості перебігу ранньої та пізньої БА залежно від ER22/23EK і Tth111I поліморфізму гена глюкокортикоїдного рецептора та доповненні сучасних даних щодо ролі генетичних чинників не лише у виникненні БА, а і у тяжкості перебігу різних фенотипів захворювання. Обстежено 553 хворих на БА та 95 практично здорових осіб, котрі висловили згоду на участь у дослідженні. Діагноз БА, тяжкість перебігу, ступінь контролю встановлювали згідно із рекомендаціями GINA-2016 та її наступних версій та Наказу МОЗ України №868 від 08.11.2013 р. Функцію зовнішнього дихання вивчали за допомогою діагностичного комплексу «Кардіоплюс» (Україна). Пацієнтів розподілено на дві клінічні групи залежно від віку дебюту БА: I група, яка включала 282 хворих із пізнім дебютом астми, II група – 271 хворих із раннім початком. Дослідження було схвалено Комісією з питань біоетики медичного інституту Сумського державного університету. Визначення ER22/23EK (rs 6189/6190) і Tth111I (rs10052957) поліморфних варіантів гена глюкокортикоїдного рецептора (ГР) проводили за допомогою полімеразно-ланцюгової реакції з наступним аналізом рестрикційних фрагментів. Статистичний аналіз отриманих результатів проводили за допомогою SPSS-17 програми. Установлено вірогідну відмінність у розподілі генотипів за ER22/23EK та Tth111I поліморфізмами гена ГР залежно від тяжкості перебігу БА, із вищою частотою мінорних алелей у обох випадках у хворих із тяжкою БА ($\chi^2 = 6,09$; $p = 0,048$, $\chi^2 = 15,8$; $p = 0,001$, відповідно).

Відносний ризик розвитку тяжкої БА не залежить від ER22/23EK поліморфізму гена ГР, але у пацієнтів носіїв TT генотипу за TthIII поліморфізмом гена ГР був у 3,63 рази вищий, ніж у гомозигот за основним алелем. Ризик розвитку тяжкого перебігу БА із раннім і пізнім дебютом залежав від Tth111I поліморфізму гена ГР та зростав щодо ранньої астми у 3,7 рази у рецесивній моделі та у 3,5 рази щодо пізньої БА у рецесивній моделі. Визначення поліморфних варіантів ER22/23EK (rs 6189/6190) і Tth111I (rs10052957) гена ГР продемонструвало їх можливий зв'язок не лише із зростанням ризику виникнення БА, але і зв'язок із визначеними фенотипами та тяжкістю перебігу.

Ключові слова: бронхіальна астма, ген глюкокортикоїдного рецептора, перебіг, ER22/23EK і Tth111I поліморфізми.



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