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Meta-Analysis of the association of FCER1B, FCER2, and ADAM33 gene polymorphisms with asthma

Abstract. *Asthma is a complex heterogeneous disease, the development of which is determined by the complex interaction of many predisposition genes and environmental factors. Many epidemiological studies have shown that single nucleotide polymorphism (SNP) in the FCER1B (rs1441586), FCER2 (28364072), and ADAM33 (rs528557) genes are associated with the risk development of asthma. However, the results are inconsistent and inconclusive. The aim of this study was to determine whether the FCER1B (rs1441586), FCER2 (28364072), and ADAM33 (rs528557) polymorphisms confer susceptibility to asthma. To derive a more precise estimation, a meta-analysis was performed. Meta-analysis was conducted with the data from case-control association studies (20 studies with 9954 controls and 8261 cases). Comprehensive Meta-Analysis software was used for statistical analysis. A random-effects model was used to calculate summary odds ratios (ORs). The meta-analysis showed no association between asthma and the FCER1B rs1441586 variant under any genetic model. A noticeable association of FCER2 (rs28364072) polymorphism with susceptibility to asthma in overall pooled subjects was observed under dominant, recessive, and allele contrast models. Moreover, statistically significant results were obtained for the ADAM33 polymorphism in the allele contrast model. This meta-analysis illustrates that the FCER2 (rs28364072) and ADAM33 (rs528557) polymorphisms may increase susceptibility to asthma.*

Keywords: *asthma, SNPs, FCER1B, FCER2, ADAM33, meta-analysis.*

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Introduction

Asthma is a heterogeneous disease, usually characterized by chronic inflammation of the respiratory tract. This is determined by the presence of a history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, which vary over time and intensity, as well as variable restrictions of airflow when exhaling [1]. According to estimates by the World Health Organization (WHO), more than a third of billions of people have suffered from asthma worldwide and up to half a million people die every year around the world precisely because of this disease [2].

The etiopathogenesis of asthma results from intricate interactions between genetic factors and exposure to numerous environmental agents [3].

Nowadays, it is widely accepted that asthma susceptibility has a strong genetic component, as shown by multiple studies. In the last decade, several genome-wide association studies (GWAS) have identified numerous genetic variants responsible for asthma susceptibility [4]. These mainly non-coding variants play a regulatory role in gene expression and asthma heritability [5]. And such kind of genetic variations in various loci and genes are important in asthma pathogenesis. Regardless of the severity of atopic bronchial asthma, its pathogenetic basis is allergic inflammation, the peculiarity of which is a hereditary predisposition and hyper production of immunoglobulins IgE and IgG4 [6]. In the regulation of IgE secretion, various immunological pathways are of great importance. Alterations in any of the major pathways can greatly increase the risk of developing asthma. Variant polymorphisms of some genetic markers can predict susceptibility to asthma.

The high-affinity receptor IgE 1 (FCER1) gene is located on chromosome 11q13, a region that is

involved in the induction of immune responses in atopic disease, contributing to the IgE-dependent activation of mast cells and basophils. It encodes the beta chain of the high-affinity receptor for IgE (FceRI-β gene, FCER1B), which in combination with one alpha subunit binding IgE and the dimer of the gamma subunit forms the FceRI tetramer. It is believed that FCER1B functions as an enhancer of FceRI expression and signaling, which enhances the activation of mast cells and basophils and enhances IgE-mediated inflammatory reactions [7].

Taking into account the importance of FCER1B in the immunopathogenesis of bronchial asthma, multiple epidemiological studies have been conducted to identify potentially important single-nucleotide polymorphisms (SNP) in the FCER1B gene associated with the risk of developing asthma. Two functionally important SNPs in this gene were the polymorphism of the promoter C109T (rs1441586) and the 7th exon E237G (rs569108). Although several studies have shown no significant differences in the distribution of -109 C/T polymorphism between asthma patients and healthy control subjects, the data were still contradictory [8-11].

Low-affinity immunoglobulin E receptor gene (FCER2), is a protein-coding gene that is located on chromosome 19. It is one of the key molecules in the regulation of IgE production. Gene variant rs28364072 of the FCER2 is presumably related to the severity of asthma [12,13] and the duration of hospitalization [12,13, 14]. K. G. Tantisira et al. [13] established the effect of three SNPs of the FGFR2 gene on an increase in serum IgE levels and the deterioration of asthma in European Americans. The authors demonstrated the association of rs 28364072 (T2206C) polymorphism with severe asthma exacerbations in children [15, 16].

Relatively recently asthma gene A disintegrin and metalloprotease 33 (ADAM33) [17] located on chromosome 20p13 was characterized. Analysis of 135 SNPs of the ADAM33 gene showed the most significant association with asthma. These data indicate the important role of ADAM33 in the functions of the respiratory tract. Currently, the role of these genetic variations associated with susceptibility to asthma has been confirmed in Saudi Arabia and China populations [18]. However, the data on polymorphism rs528557 were contradictory.

Therefore, we aimed to perform a meta-analysis based on the studies of the association between FCER1B, FCER2, and ADAM33 gene variants to asthma susceptibility.

Materials and methods

Strategy for literature search. In this meta-analysis collected all the case-control studies using Scopus, PubMed, Web of Science, Medline, and other databases until March of 2022. The databases were searched for the keywords: FCER1B, FCER2, ADAM33, polymorphism, single nucleotide variant, C109T, E237G , rs1441586, rs28364072, rs528557, SNP and asthma.

Inclusion and exclusion criteria. For inclusion in the meta-analysis, the studies must have the following criteria: (1) the study association between FCER1B, FCER2, ADAM33 polymorphisms, and asthma; (2) should have a case-control design; (3) the study must offer the sample size, distribution of alleles and genotypes.

Studies identified from the searches were screened and excluded from further analysis if one of the following reasons was satisfied: a review article, lack of information, animal research, not case-control or nested case-control study design, or unreported genotype frequencies.

For each publication included in the meta-analysis, the following information was obtained: author's first name, year of publication, SNP, quantitative and qualitative characteristics of asthmatic patients and control group, and genotyping data.

Statistical analysis. In the control population, the Hardy–Weinberg Equilibrium (HWE) was

evaluated using the online software "Calculation of the Chi-square criterion for deviation from the Hardy-Weinberg equilibrium" (https://gene-calc.pl/hardy-weinberg-page). The statistical analysis was carried out using Comprehensive Meta-Analysis Version 3.0 (Biosta, Englewood, NJ, USA). We used ORs and 95% CIs to summarize the tightness of the connection between FCER1B, FCER2, and ADAM33 polymorphisms and asthma. The heterogeneity was estimated by using the I^2 index. If I2 > 50%, it indicates that there was high heterogeneity, and the random-effects model was used to calculate the association of OR. In other respects, the fixed-effects model was applied (19). Publication bias was measured via "Begg's funnel plot" and "Egger's linear regression" methods [20]. A two-tailed p-value < 0.05 implied a statistically significant publication bias.

Results

Studies included in the meta-analysis

A total of 213 potential articles were identified from the database search. After 171 duplicate records were removed, a total of 42 potential articles were reviewed. Amongst these articles, 18 were excluded after the titles and abstract review. Four others were excluded for lacking controls. Finally, 20 studies with a total of 9954 controls and 8261 cases that met the inclusion criteria were included in this meta-analysis (Fig. 1). The characteristics and genotype frequencies and HWE examination results of each study included in this meta-analysis are listed in Table 1, Table 2 and Table 3.

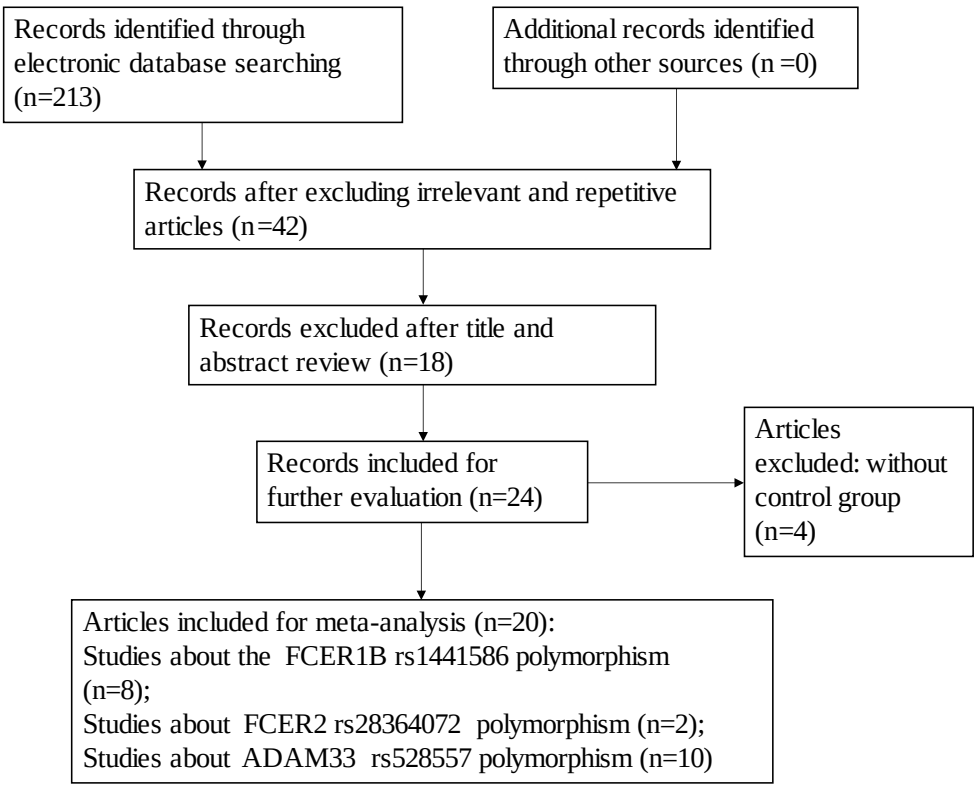

Figure 1. Flow diagram of the study selection process

Table 1

Characteristics of the studies of FCER1B (rs1441586) polymorphism included in the meta-analysis

First author, year	Case			Control			p (HWE) Control
	TT	CT	CC	TT	CT	CC	
Li Hua, 2021[21]	108	125	31	317	329	74	0,66
Li Hua, 2015[22]	416	436	148	406	470	124	0,64
V. Tikhonova, 2010[23]	53	69	18	48	70	18	0,61
E.S. Kim, 2009[24]	159	167	20	140	135	28	0,68
H. Li, 2009[25]	110	24	58	78	24	90	0,46
D.P. Potaczek, 2007[26]	57	72	25	57	70	27	0,59
S. H. Kim, 2006[27]	67	65	8	113	128	23	0,67
N. Hizawa, 2000[28]	85	123	18	108	99	19	0,69

Table 2

Characteristics of the studies of FCER2 (rs28364072) polymorphism included in the meta-analysis

First author, year	Case			Control			p (HWE) Control
	TT	TC	CC	TT	TC	CC	
Fayzullina, 2019[29]	51	34	7	41	47	11	0,65
Ly, 2016[30]	58	39	10	5	11	7	0,45

Table 3

Characteristics of the studies of ADAM33 (rs528557) polymorphism included in the meta-analysis

First author, year	Case			Control			p (HWE) Control
	GG	GC	CC	GG	GC	CC	
Thongngarm, 2022[31]	182	60	8	148	82	20	0,75
Shen, 2017[32]	48	78	24	39	41	20	0,59
Miyake, 2012[33]	10	28	50	94	506	681	0,27
Tripathi, 2011[34]	20	67	88	159	79	15	0,78
Jie, 2011[35]	92	52	6	43	28	3	0,77
Awasthi, 2010[36]	18	85	108	72	51	14	0,71
Blakey, 2009[37]	46	319	472	458	2682	3726	0,26
Thongngarm, 2008[38]	114	77	9	72	21	7	0,82
Hirota, 2006[39]	299	159	24	354	251	39	0,74
Howard, 2003[40]	85	55	10	68	42	13	0,72

Data analysis

Meta-analysis of the relationship between the FCER1B (rs1441586) gene polymorphism and risk of asthma

Meta-analysis has shown, that FCER1B (rs1441586) gene polymorphism was not associated with asthma (TT+CT versus CC: OR = 1.175, 95 % CI 0.815-2.039, p = 0.269; CT+CC versus TT: OR = 0.957, 95 % CI 0.815-1.518, p = 0.648; CC versus TT: OR = 1.171, 95 % CI 0.813-2.188, p = 0.306). All data of meta-analysis concerning associations between the FCER1B (rs1441586) polymorphism and risk of asthma is shown in Table 4.

Table 4

Meta-analysis of the association between FCER1B (rs1441586) polymorphism and risk of asthma

Polymorphism	OR	95 % CI	P-value	I^2	Egger P
Dominant model TT+CT vs. CC	1.175	0.815-2.039	0.269	59.483	0.11
Recessive model CT+CC vs. TT	0.957	0.815-1.518	0.648	59.251	0.35
Additive model CC versus TT	1.171	0.813-2.188	0.306	59.017	0.2

Meta-analysis of the relationship between the FCER2 (rs28364072) gene polymorphism and risk of asthma

Meta-analysis has shown, that FCER2 (rs28364072) gene polymorphism was associated with asthma in dominant, recessive and allele contrast model (TT+TC versus CC: OR = 2.408, 95 % CI 1.518-4.244, p = 0.020; TC+CC vs. TT: OR = 0.411, 95 % CI 0.235-0.568, p = 0.037; T allele versus C allele: OR = 2.139, 95 % CI 1.482-3.128, p = 0.042; C allele versus T allele: OR=0.468, 95 % CI 0.320-0.675, p = 0.042) (Fig. 2-4). Moreover, there is a trend of rs28364072 association with asthma under additive model (TT versus CC: OR=3.737, 95 % CI 1.955-8.120, p=0.063). All data of meta-analysis concerning associations between the FCER2 (rs28364072) polymorphism and risk of asthma is shown in Table 5.

Table 5

Meta-analysis of the association between FCER2 (rs28364072) polymorphism and risk of asthma

Polymorphism	OR	95 % CI	P-value	I^2	Egger P
Dominant model TT+TC vs. CC	2.408	1.518-4.244	0.020	45.836	-
Recessive model TC+CC vs. TT	0.411	0.235-0.568	0.037	51.569	-
Additive model TT versus CC	3.737	1.955-8.120	0.063	63.617	-
Allele contrast model T allele versus C allele	2.139	1.482-3.128	0.042	61.955	-
Allele contrast model C allele versus T allele	0.468	0.320-0.675	0.042	61.955	-

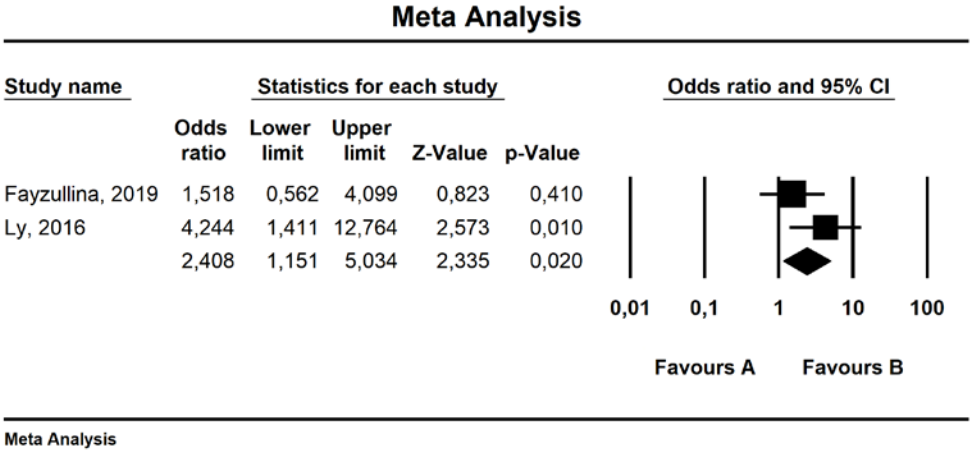

Figure 2. Forest plot of the association between FCER2 rs28364072 and risk of asthma: TT+TC vs. CC

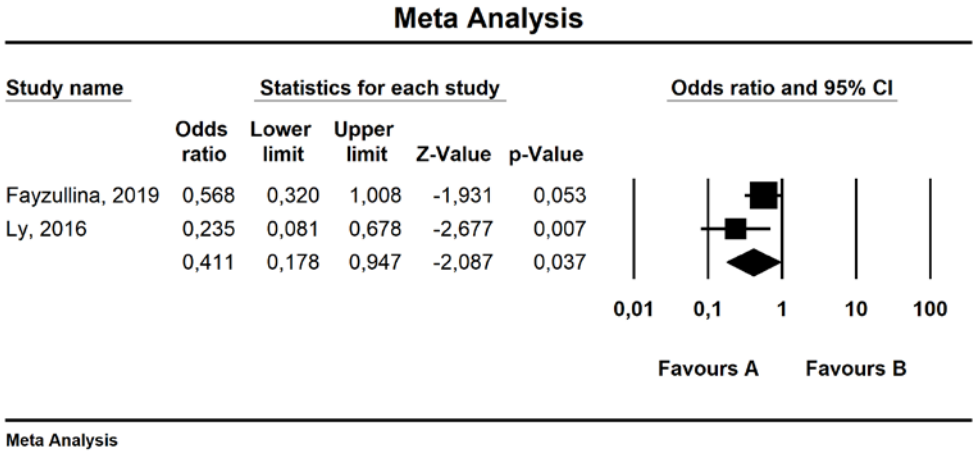

Figure 3. Forest plot of the association between FCER2 rs28364072 and risk of asthma: TC+CC vs. TT

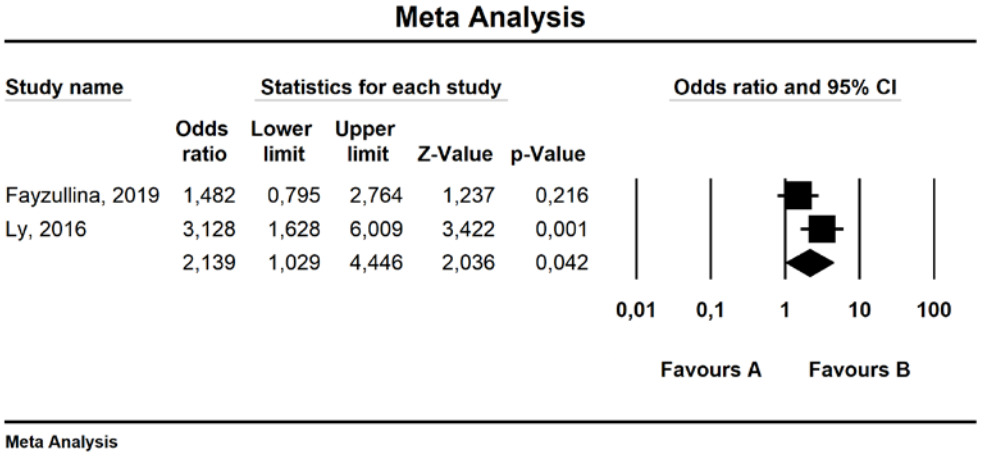

Figure 4. Forest plot of the association between FCER2 rs28364072 and risk of asthma: T allele vs. C allele

Meta-analysis of the relationship between the ADAM33 (rs528557) gene polymorphism and risk of asthma

According to the meta-analysis, there is no association between ADAM33 (rs528557) gene polymorphism with asthma in dominant, recessive and additive model (GG+GC versus CC: OR = 0.730, 95 % CI 0.062-2.630, p = 0.334; GC+CC versus GG: OR = 1.577, 95 % CI 0.542-13.109, p = 0.142; GG versus CC: OR = 0.604, 95 % CI 0.021-3.074, p = 0.306). However, the significant association was found under allele contrast model (G allele versus C allele: OR = 0.293, 95 % CI 0.121-0.360, p = 0.009 and C allele versus G allele: OR = 3.413, 95 % CI 0.909-8.272, p =0.009) (p < 0.05). All data of meta-analysis concerning associations between the ADAM33 (rs528557) polymorphism and risk of asthma is shown in Table 6.

Table 6

Meta-analysis of the association between ADAM33 (rs528557) polymorphism and risk of asthma

Polymorphism	OR	95 % CI	P-value	I^2	Egger P
Dominant model GG+GC vs. CC	0.730	0.062-2.630	0.334	93.112	0.32
Recessive model GC+CC vs. GG	1.577	0.542-13.109	0.142	94.931	0.08
Additive model GG versus CC	0.604	0.021-3.074	0.306	95.026	0.40
Allele contrast model G allele versus C allele	0.293	0.121-0.360	0.009	95.431	0.06
Allele contrast model C allele versus G allele	3.413	0.909-8.272	0.009	95.431	0.06

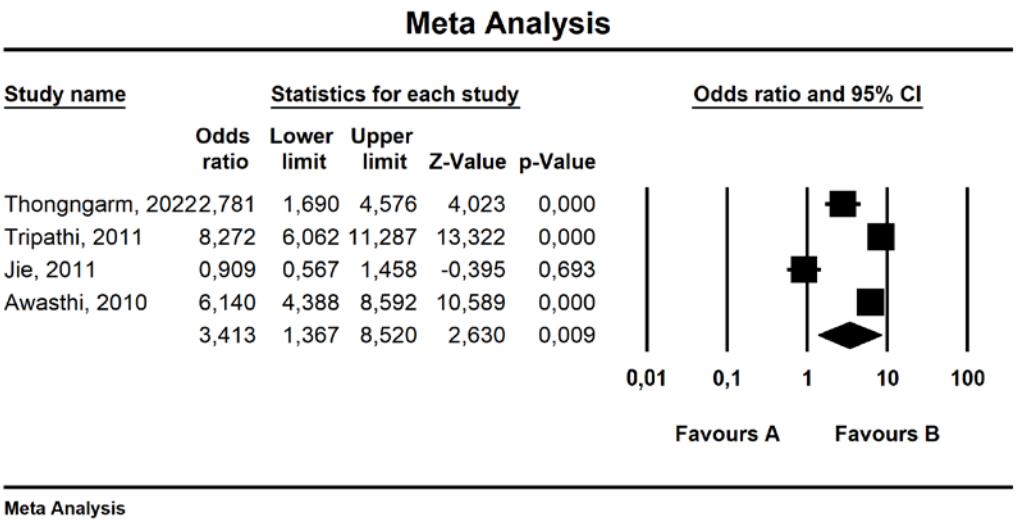

Figure 4. Forest plot of the association between ADAM33 rs528557 and risk of asthma: C allele vs. G allele

Discussion

Asthma is a common respiratory disease characterized by a significant decrease in the quality of life and a high rate of mortality from complications. An important feature of asthma is heterogeneity. It manifests itself in various phenotypes and genotypes arising from the activation of the different gene networks and the development of molecular patterns. As previously reported, genetic factors largely

determine the course of the disease. The contribution of heredity in asthma is about 75% [4]. Genetic variations or single nucleotide polymorphisms are widespread genetic factors that are found in the studies of many researchers in recent decades. Despite the fact that many studies have shown reliably statistically significant results, the contribution of genetic variations to the risk of asthma is still the subject of discussion. However, meta-analysis, which collects quantitative data from individual studies and combines their results, has a number of advantages in improving accuracy, providing reliable estimates, and solving problems that are not effective enough in studies of individual associations. Thus, in this study, we focused on the contribution of several genetic polymorphisms predisposing to the development of asthma.

The development of IgE-mediated inflammatory response is the central component of allergy asthma. IgE is secreted from B cells into blood circulation, where it binds to FCER1 on the surfaces of effector cells of allergic reactions, such as mast cells and basophils [41]. FCER1B combines with an IgE-binding alpha subunit and a gamma-subunit dimer to compose an FCER1 tetramer complex, which is essential for IgE-mediated allergic responses. FCER1B functions as an expression and signaling enhancer that enhances mast cell and basophil activation and activates IgE-mediated inflammatory responses [42].

One of the first described polymorphisms of the FCER1B gene in position -109 was the replacement of cytosine with thymine (rs1441586) [28]. Later, several studies showed that this polymorphism is not associated with the risk of developing asthma [25-27]. However, Kim et el., reported that patients carrying the homozygous TT genotype showed a high level of IgE compared to the patients with the homozygous CC genotype and the heterozygous CT genotype [23]. According to our results, there is no significant association between rs1441586 FCER1b gene polymorphism and the risk of asthma for all models.

The next candidate gene in our study was the FGFR2. The previous case-control study didn't find differences in the frequency distribution of alleles and genotypes of SNP rs28364072 in patients with asthma and healthy controls. But Tastisira et al., showed that rs28364072 of FCER2 gene was associated with high IgE levels in the blood serum of patients with asthma [40]. But in our case, it was found that the homozygous TT genotype increased the risk of developing asthma, whereas the homozygous CC genotype, on the contrary, decreased the risk of asthma. Since the number of studies is not enough to make an appropriate conclusion, in our opinion, further research is necessary to understand the role of this SNP in asthma.

One of the common SNPs of the ADAM33 gene, which is considered a potential biomarker of asthma, is the rs528557 polymorphism. As previously assumed rs528557 SNP can affect the activity of the ADAM33 gene and cause the occurrence of bronchial hyperreactivity and airway obstruction, which in turn can lead to the development of asthma [43].

However, our results indicated that rs528557 plays a potential role in the allelic contrast model. In other models, the role of this polymorphism is not statistically significant due to high heterogeneity.

Nonetheless, this meta-analysis had a number of limitations. First of all, our results may not provide sufficient statistical power to assess the correlation between FCER2 (rs28364072), and ADAM33 (rs528557) polymorphisms with asthma due to the small number of studies included. Secondly, single nucleotide polymorphisms vary between populations and have a different effects on bronchial hyperreactivity. Further case-control studies of SNPs in FCER2 and ADAM33 genes are needed in different populations.

Conclusion

In summary, our meta-analysis suggests that the polymorphisms rs28364072 of the FCER2 and rs528557 of the ADAM33 gene may contribute to the risk development of asthma and can be the potential biomarkers for the early diagnosis of asthma. However, gene polymorphism rs1441586 of FCER1b is not associated with asthma. Taking into consideration all mentioned limitations, further detailed research is required to confirm our data.

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. [Electronic resource] – Available at: www.ginasthma.org/reports (Accessed: Sept 2021).

2. Asthma. [Electronic resource] – Available at: https://www.who.int/ru/news-room/fact-sheets/detail/asthma (Accessed: Sept 2021).

3. Eva Morales, David Duffy. Genetics and Gene-Environment Interactions in Childhood and Adult Onset Asthma. Front. Pediatr. – 2019. – Vol. 7. – P. 499. DOI: 10.3389/fped.2019.00499.

4. Kabesch M., Tost J. Recent findings in the genetics and epigenetics of asthma and allergy. Semin. Immunopathol. – 2020. – Vol. 42. – P. 43-60.

5. Gautam Y., Afanador Y., Ghandikota S., Mersha T.B. Comprehensive functional annotation of susceptibility variants associated with asthma. Hum. Genet. – 2020. – Vol. 139. – P. 1037-1053.

6. Polyxeni Ntontsi, Andreas Photiades, Eleftherios Zervas, Georgina Xanthou and Konstantinos Samitas. Genetics and Epigenetics in Asthma. *Int. J. Mol. Sci.* – 2021. – Vol. 22(5). – P. 2412. DOI: https://doi.org/10.3390/ijms22052412.

7. Kraft S., Rana S., Jouvin M.H., Kinet J.P. The role of the FcepsilonRI beta-chain in allergic diseases. Int Arch Allergy Immunol. – 2004. – Vol. 135. – P. 62-72.

8. Ishizawa M., Shibasaki M., Yokouchi Y., Noguchi E., Arinami T., Yamakawa-Kobayashi K. No association between atopic asthma and a coding variant of Fc epsilon R1 beta in a Japanese population. J Hum Genet. – 1999. – Vol. 44. – P. 308-11.

9. Shirakawa T., Mao X.Q., Sasaki S., Enomoto T., Kawai M., Morimoto K. Association between atopic asthma and a coding variant of Fc epsilon RI beta in a Japanese population. Hum Mol Genet. – 1996. – Vol. 5. – P. 1129-30.

10. Green S.L., Gaillard M.C., Song E., Dewar J.B., Halkas A. Polymorphisms of the beta chain of the high-affinity immunoglobulin E receptor (Fcepsilon RI-beta) in South African black and white asthmatic and nonasthmatic individuals. Am J Respir Crit Care Med. – 1998. – Vol. 158. – P. 1487-92.

11. Rohrbach M., Kraemer R., Liechti-Gallati S. Screening of the Fc epsilon RI-beta-gene in a Swiss population of asthmatic children: no association with E237G and identification of new sequence variations. Dis Markers. – 1998. – Vol. 14. – P. 177-86.

12. Koster S.E., Maitland-van der Zee A.H., Tavendale R., Mukhopadhyay S., Vijverberg S.J., Raaijmakers J.A., Palmer C.N. FCER2 T2206C variant associated with chronic symptoms and exacerbations in steroid-treated asthmatic children. Allergy. – 2011. – Vol. 66. – P. 1546-1552.

13. Tantisira K. FCER2: A pharmacogenetic basis for severe exacerbations in children with asthma. J. Allergy ClinImmunol. – 2007. – Vol. 120. – P. 1285-91.

14. Tse S.M., Tantisira K., Weiss S.T. The Pharmacogenetics and Pharmacogenomics of Asthma Therapy. Pharmacogenomics J. – 2011. – Vol. 11. – P. 383-392.

15. Zastrozhina A.K. Farmakogeneticheskie aspekty effektivnosti i bezopasnosti ingalyacionnyh glyukokortikosteroidov v lechenii bronhial'noj astmy // Klinicheskaya farmakologiya i terapiya. – 2018. – № 27(5). – P. 64-68.

16. Tantisira K.G. FCER2: a pharma cogenetic basis for severeexa cerbationsin children with asthma // J. Allergy Clin. Immunol. – 2007. – Vol. 120, № 6. – P. 1285-1291.

17. Van Eerdewegh P., Little R., Dupuis J. et al. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness // Nature. – 2012. – Vol. 418. – P. 426-430.

18. Bazzi M., Al-Anazi M., Al-Tassan N.A. Genetic variations of ADAM33 in normal versus asthmatic Saudi patients. [Electronic resource] – Available at: http:// biotechcentersa.org/asthma-genetics/ (Accessed:).

19. Higgins J.P., Thompson. Quantifying heterogeneity in a meta-analysis. Statist. Med. – 2002. – Vol. 21. – P. 1539-1558. DOI: 10.1002/sim.1186.

20. Egger M., Smith G., Schneider M., Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. – 1997. – Vol. 315(7109). – P. 629-634. DOI: 10.1136/bmj.315.7109.629.

21. Li Hua, Quanhua Liu, Jing Li, Xianbo Zuo, Qian Chen, Jingyang Li, Yuwei Wang, Haipei Liu, Zhaobo Shen, Yi Li, Zenan Ma, Shengdong Dong, Ruoxu Ji, Dingzhu Fang, Yi Chen, Wenwei Zhong, Jun Zhang, Jianhua Zhang and Yixiao Bao. Gene–gene and gene-environment interactions on cord blood total IgE in Chinese Han children. Allergy Asthma Clin Immunol. – 2021. – Vol. 17. – P. 69.

22. Li Hua, Xian-Bo Zuo, Yi-Xiao Bao, Quan-Hua Liu, Jing-Yang Li, Jie Lv, Ding-Zhu Fang, Qian Lin, Jun Bao, and Ruo-Xu Ji. Four-Locus Gene Interaction Between IL13, IL4, FCER1B, and ADRB2 for Asthma in Chinese Han Children. Pediatric Pulmonology. – 2016. – Vol. 51. – P. 364-371.

23. Tikhonova V., Voitovich A., Korostovsev D., Larionova V. The-109C>T Polymorphism of the FCER1B gene in children with asthma. Article in Pediatric Research. – 2010. – Vol. 68. – P. 413-413. DOI: 10.1203/00006450-201011001-00821.

24. Eun Soo Kim, Seung-Hyun Kim, Kyung Won Kim, Hae-Sim Park, Eun Soon Shin, Jong Eun Lee, Myung Hyun Sohn, Kyu-Earn Kim. Involvement of FcεR1β gene polymorphisms in susceptibility to atopy in Korean children with asthma. Eur J Pediatr. – 2009. – Vol. 168(12). – P. 1483-90. DOI: 10.1007/s00431-009-0960-x.

25. Li H., Xiaoyan D., Quanhua L., Jie L., Yixiao B. Single-Nucleotide Polymorphisms in Genes Predisposing to Asthma in Children of Chinese Han Nationality. J Investig Allergol Clin Immunol. – 2009. – Vol. 19(5). – P. 391-395.

26. Potaczek D.P., Sanak M., Szczeklik A. Additive association between FCER1A and FCER1B genetic polymorphism and total serum Ige levels. Allergy. – 2007. – Vol. 62. – P. 1095-1099.

27. Kim S.-H., Bae J.-S., Holloway J.W., Leez J.-T., Suh C.-H., Nahm D.-H., Park H.-S. A polymorphism of MS4A2 (-109T>C) encoding the b-chain of the high-affinity immunoglobulin E receptor (FceR1b) is associated with a susceptibility to aspirin-intolerant asthma. Clinical and Experimental Allergy. – 2006. – Vol. 36. – P. 877-883.

28. Nobuyuki Hizawa, Etsuro Yamaguchi, Eisei Jinuchi, and Yoshikazu Kawakami. A Common FCER1B Gene Promoter Polymorphism Influences Total Serum IgE Levels in a Japanese Population. Am J Respir Crit Care Med. – 2000. – Vol. 161. – P. 906-909.

29. Fayzullina R.M., Viktorov V.V., Shangareeva Z.A., Gafurova R.R., Danilko K.V., Mukhametzyanov A.M. Search for association of clinical and anamnestic data in children with bronchial asthma with rs28364072 (T2206C) polymorphism of FCER2 gene. Medical Bulletin of Bashkortostan. –2019. – Volume 14, № 5(83).

30. Duong Thi Ly H., Pham Thi Hong N., Vu Thi T., Nguyen Thi Bich H., Le Thi Minh H., Duong-Quy S. The frequency of FCER2 genotype distributions related to corticosteroid response in asthma patients treated at the National Hospital of Paediatrics. J Fran Viet Pneu. – 2016. – Vol. 20(7). – P. 1-78.

31. Torpong Thongngarm, Aree Jameekornrak, Nachol Chaiyaratana, Wanna Thongnoppakhun,Atik Sangasapaviliya, Orathai Jirapongsananuruk, Chanin Limwongse. Effect of gene polymorphisms in ADAM33, TGFβ1, VEGFA, and PLAUR on asthma in Thai population. Asian Pac J Allergy Immunol. – 2022. DOI: 10.12932/AP-010419-0532.

32. Bo Shen, Rong Lin, Cai-Chun Wang, Jing rei, Yan Sun, Young-Le Yang and Ying-Ying Lin. ADAM33 gene polymorphisms identified to be associated with asthma in a Chinese Li population. Biomedical Reports. – 2017. – Vol. 6. – P. 323-328.

33. Miyake Y., Tanaka K., Arakawa M. ADAM33 polymorphisms, smoking and asthma in Japanese women: the Kyushu Okinawa Maternal and Child Health Study. Int J Tuberc Lung Dis. – 2012. – Vol. 16(7). – P. 974-979.

34. Priya Tripathi, Shally Awasthi, Rajendra Prasad, Nuzhat Husain and Subramaniam Ganesh. Association of ADAM33 gene polymorphisms with adult-onset asthma and its severity in an Indian adult population. J. Genet. – 2011. – Vol. 90. – P. 265-273.

35. Zhijun Jie, Zhilin Hu, Chunxue Bai and Meiling Jin. ADAM33 Gene Polymorphisms Associate with Asthma Susceptibility and Severity in East China Han Population. Journal of Asthma. – 2011. – Vol. 48. – P. 979-985.

36. Shally Awasthi, Priya Tripathi, Subramaniam Ganesh, and Nuzhat Husain. Association of ADAM33 gene polymorphisms with asthma in Indian children. Journal of Human Genetics. – 2011. – Vol. 56. – P. 188-195.

37. Blakey J.D., Sayers I., Ring S.M., Strachan D.P., Hall I.P. Positionally cloned asthma susceptibility gene polymorphisms and disease risk in the British 1958 Birth Cohort. Thorax. – 2009. – Vol. 64. – P. 381-387.

38. Torpong Thongngarm, Aree Jameekornrak, Chanin Limwongse, Atik Sangasapaviliya, Orathai Jirapongsananuruk, Anunchai Assawamakin, Nachol Chaiyaratana, Voravich Luangwedchakarn and Wanna Thongnoppakhun. Association between ADAM33 Polymorphisms and Asthma in a Thai Population. Asian Pacific Journal of Allergy and Immunology. – 2008. – Vol. 26. – P. 205-211.

39. Hirota T., Hasegawaz K., Obara K., Matsuda A., Akahoshi M., Nakashima K., Shirakawa T., Doi S., Fujitaz K., Suzukik Y., Nakamura Y., Tamari M. Association between ADAM33 polymorphisms and adult asthma in the Japanese population. Clinical and Experimental Allergy. – 2006. – Vol. 36. – P. 884-891.

40. Timothy D. Howard, Dirkje S. Postma, Hajo Jongepier, Wendy C. Moore, Gerard H. Koppelman, Siqun L. Zheng, Jianfeng Xu, Eugene R. Bleecker, and Deborah A. Meyers. Association of a disintegrin and metalloprotease 33 (ADAM33) gene with asthma in ethnically diverse populations. J Allergy Clin Immunol. – 2003. – Volume 112, Number 4.

41. Levine S.J., Wenzel S.E. Narrative review: the role of Th2 immune pathway modulation in the treatment of severe asthma and its phenotypes. Ann Intern Med. – 2010. – Vol. 152. – P. 232-237.

42. Kraft S., Rana S., Jouvin M.H., Kinet J.P. The role of the FcepsilonRI beta-chain in allergic diseases. Int Arch Allergy Immunol. – 2004. – Vol. 135. – P. 62-72.

43. Lambrecht B., Hammad H. The airway epithelium in asthma. Nat Med. – 2012. – Vol. 18(5). – P. 684-92.

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Бронх демікпесімен FCER1B, FCER2 және ADAM33 гендері полиморфизмі ассоциациясына мета-анализ

Аңдатпа. Бронх демікпесі - күрделі гетерогенді ауру, оның дамуы көптеген бейімділік гендері мен қоршаған орта факторларының күрделі өзара әрекеттесуімен анықталады. Көптеген эпидемиологиялық зерттеулер FCER1B (rs1441586), FCER2 (28364072) және ADAM33 (rs528557) гендеріндегі бір нуклеотидті полиморфизмдер (SNP) демікпе қаупімен байланысты екенін көрсетті. Алайда, нәтижелер қайшылықты және сенімсіз болды. Бұл зерттеудің мақсаты FCER1B

(rs1441586), FCER2 (28364072) және ADAM33 (rs528557) полиморфизмдерінің бронх демікпесіне бейімділігін анықтау болды. Дәлірек бағалау үшін мета-анализ жүргізілді. Мета-анализ жағдай-бақылау қауымдастығының зерттеу деректерін қолдана отырып жүргізілді (9954 бақылау және 8261 жағдайды қамтитын 20 зерттеу). Статистикалық талдау кешенді Comprehensive Meta-Analysis бағдарламалық жасақтамасын қолдану арқылы жүргізілді. Кездейсоқ эффект моделі жалпы ықтималдық коэффициенттерді (ORs) есептеу үшін қолданылды. Мета-анализ FCER1b rs1441586 нұсқасы мен бронх демікпесі арасында ешқандай генетикалық модельде байланыс көрсеткен жоқ. FCER2 (rs28364072) гендік нұсқасы үшін барлық субъектілердегі өкпе демікпесімен бейімділікпен маңызды байланысы үш түрлі модельде (аллельді модель, гомозиготалық модель (аддитивті) және доминантты) байқалды. Сонымен қатар, ADAM33 полиморфизмі үшін аллельдік контраст моделінде статистикалық маңызды нәтижелер алынды. Бұл мета-анализ көрсеткендей, FCER2 (rs28364072) және ADAM33 (rs528557) полиморфизмдері бронх демікпесіне сезімталдықты арттыруы мүмкін.

Түйін сөздер: бронх демікпесі, SNPs, FCER1B, FCER2, ADAM33, мета-анализ.

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Мета-анализ ассоциации полиморфизмов генов FCER1B, FCER2 и ADAM33 с бронхиальной астмой

Аннотация. Бронхиальная астма - сложное гетерогенное заболевание, развитие которого определяется сложным взаимодействием многих генов предрасположенности и факторов окружающей среды. Многие эпидемиологические исследования показали, что однонуклеотидные полиморфизмы (SNP) в генах FCER1B (rs1441586), FCER2 (28364072) и ADAM33 (rs528557) связаны с риском развития астмы. Однако результаты предыдущих исследований противоречивы и неубедительны. Целью этого исследования было определить, обусловливают ли полиморфизмы FCER1B (rs1441586), FCER2 (28364072) и ADAM33 (rs528557) предрасположенность к астме. Для получения более точной оценки был проведен мета-анализ с использованием данных исследований ассоциации случай-контроль (20 исследований с 9954 контрольными и 8261 случаями). Для статистического анализа использовалось программное обеспечение Comprehensive Meta-Analysis. Для расчета суммарных коэффициентов шансов (ORs) использовалась модель случайных эффектов. Мета-анализ не показал статистически значимой связи между астмой и вариантом FCER1B rs1441586 во всех трех генетических моделях. Заметная связь полиморфизма FCER2 (rs28364072) с предрасположенностью к астме у всех объединенных субъектов наблюдалась в моделях доминантного, рецессивного и аллельного контраста. Более того, были получены статистически значимые результаты для полиморфизма ADAM33 в модели аллельного контраста. Данный мета-анализ показывает, что полиморфизмы FCER2 (rs28364072) и ADAM33 (rs528557) могут повышать восприимчивость к астме.

Ключевые слова: астма, SNPs, FCER1B, FCER2, ADAM33, мета-анализ.

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