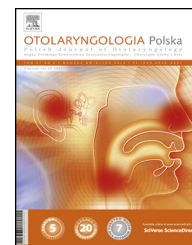


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High-affinity IgE receptor gene polymorphism and allergic rhinitis in a Polish population



Wariant polimorficzny receptora FcεRIβ i występowanie alergicznego nieżyty nosa w populacji polskiej

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ABSTRACT

Introduction: The high-affinity IgE receptor (FcεRIβ subunit int 2) gene polymorphism is a candidate gene in atopic diseases and is associated with atopy. The aim of this biochemical study was to investigate the association of its intronic mutation and allergic rhinitis in a Polish population. **Materials and methods:** 100 atopic patients and 85 controls were included in the study. Polymerase chain reaction-based analysis for FcεRIβ subunit int 2 gene polymorphism was used for genotyping and detection. **Results:** There was a difference in the frequencies of genotypes of FcεRIβ subunit int 2 in allergic rhinitis patients and controls. The FcεRIβ subunit int 2 gene polymorphism was found to be associated with allergic rhinitis in the Polish cohort. **Conclusion:** The results indicate that genetic factors may play an important role in the allergic rhinitis development in the investigated group.

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Introduction

Genetic and environmental factors play a crucial role in the development of atopy. Atopic asthma, allergic rhinitis and atopic dermatitis are frequent chronic diseases and still rise in prevalence worldwide [1, 2]. Atopy is caused by an increased production of IgE immunoglobulins against allergens and

cross-linking of the mast cell-bound IgE leads to inflammation in the nasal cavity, lungs and skin [3].

Many genetic studies were performed in the several populations and the number of chromosomal locations were considered to be associated with atopy. The high affinity IgE receptor (FcεRIβ subunit int 2) gene is localized on chromosome 11q13. It was shown that coding and non-coding variants of this gene are associated with an increased risk

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of atopic status but its correlation with allergic rhinitis is not well proved [4]. The purpose of this paper is to estimate the frequency of FcεRIβ int 2 gene polymorphism and its association with allergic rhinitis in Polish population. The ranges of total IgE confirming atopic status differ in similar papers (100 IU–400 IU or higher) [5]. We decided to choose a positive RAST as greater than 2 to at least one allergen and elevated total IgE, over 200 IU, to underlay the IgE overproduction.

Materials and methods

We recruited 185 unrelated subjects, Lodz citizens, 100 atopic patients and 85 controls, the average age being 30 yrs. Atopic status was confirmed by at least one positive skin prick test to house dust mite (hdm)/mixed grass pollen (mgrp) – *Artemisia*, *Timothy grass*, *Rye grass* allergens, total/specific IgE concentrations and clinical history of allergic rhinitis, a positive RAST (greater than 2) test to at least one allergen and elevated total IgE (normal range up to 120 IU). Total and specific IgE levels were measured by Pharmacia Cap System.

Genomic DNA was extracted from peripheral white blood cells, using the standard phenol/chloroform method. Polymerase chain reaction (PCR) for FcεRIβ subunit int 2 gene polymorphism was used for genotyping. PCR mixture consisted of 20 μM of 3' and 5' primers: gAATggCCAACAgAgTgAAggAT and CAAGTACAgAgCAGACAAGTg, 200 ng of template DNA, 25 nM of each dNTPs, PCR buffer, 2 U Taq polymerase and 100 μl of mineral oil. PCR reaction mixture consisted of preliminary cycle: 94 °C (5 min), 60 °C (1 min), 72 °C (2 min) and 34 cycles: 94 °C (30 s), 60 °C (30 s), 72 °C (1 min). Amplification product was digested with restriction enzyme, *Rsa* 1 with a restriction site: 5'...gT/AC...3' and 3'...CA/Tg...5'. Restriction was performed for 2 hours at 37 °C. The DNA fragments were visualized on agarose gel in UV light. In data analysis, the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated and Fisher's test was used in the probability calculation. The t-test and Mann–Whitney test were used to compare parameters (Statistica 6.0; Statsoft).

Results

Atopic patients had positive skin prick tests to hdm: 28%, to mgrp: 27% or hdm/mgrp: 43%. Total IgE levels greater than

200 IU/mL and hdm/mgrp specific IgE RAST classes greater than 2 were considered as positive. Raised total IgE level (>200 IU) was observed in 62% of atopic patients. Maximum level noted was 1860,0 IU in allergic rhinitis patient. The total IgE level, raised above 200 IU was associated with a clinical manifestation of allergic rhinitis and was observed in a half of patients, $p = 0.4$. There was a strong correlation between atopic status and raised total IgE level, OR = 16.3 95%CI (7.0–37.51). The polymorphic variant FcεRI β int 2 was observed in an allergic rhinitis group with the frequency 0,16. It was strongly correlated with allergic rhinitis clinical manifestation, OR = 2.95 95%CI (1.15–8.51) and elevated total IgE level, OR = 4.73 95%CI (1.02–22.34). The polymorphic variant FcεRI β int 2 was associated with the positive skin prick tests to mgrp and hdm/mgrp (Tab. I). There was no correlation of the investigated polymorphic variant FcεRI β int 2 with hdm skin prick tests only and specific IgE concentrations, OR = 0.71 95% 0.08–6.41 (Tab. I).

Discussion

Many authors indicate the association of genetic variants of the high affinity IgE receptor with atopic diseases. The polymorphic variant FcεRI β int 2 and its linkage to atopy, mainly atopic asthma, were investigated in several populations [6]. Studies on the genetic polymorphisms in allergic rhinitis have been started in the last 6 years worldwide [7]. A positive association to allergic rhinitis has been described for polymorphic sites of IL-4, IL-13 and IL-4RA genes, ACE gene and polymorphisms in genes encoding for leukotrienes/lipoxygenase pathway [8]. The high affinity IgE receptor and its role in IgE regulation are well known [9, 10]. We confirmed the strong association of the investigated genetic variant and the raised levels of total and specific IgE and positive skin prick tests to mixed grass pollens. Some authors underlay the significant influence of a polymorphism in a coding region of the FcεRI β gene on allergic rhinitis development [11].

Young in his early studies showed the association of the polymorphic variants of FcεRIβ with positive skin prick tests and raised specific IgE level to house dust mite in the investigated group of patients [12]. Cardaba described the correlation of the same genetic region with the elevated specific IgE levels and positive skin prick tests to olive in individuals exposed to this allergen [13]. These findings may underlay the environmental influence in the atopic diseases development and progress. Many genes

Table I – FcεRIβ int 2 variant vs positive spt to hdm, mgrp and hdm/mgrp in allergic rhinitis patients

Allergic rhinitis	FcεRI int 2				OR	95%CI
	Positive		Negative			
	n	%	n	%		
–	5	6	82	94	Ref.	–
hdm	1	4	23	96	0.71	0.08–6.41
mgp	5	13	33	87	2.50	0.66–9.13
hdm + mgp	9	25	27	75	5.46	1.68–17.74

were studied due to association of the development and severity of atopic diseases, mainly atopic asthma, but the genetics of allergic rhinitis was not evaluated so well. Atopic diseases are closely related and allergic rhinitis is often present in asthmatics and the risk of asthma development raised five times in individuals suffered from allergic rhinitis.

Atopic asthma candidate genes may be also the predisposing factors for allergic rhinitis. In Andiapan meta-analysis, investigated genetic loci in the majority of the highly replicated asthma genes were not associated to allergic rhinitis. However, the authors underlined genetic links between allergic rhinitis and asthma and associations of polymorphisms in NPSR1 and CTLA4 [14].

In recent years Japanese cedar pollinosis has been increasing rapidly in Japan. Sakaida et al. [15] made an analysis, concerning the factors influencing the development of the cedar pollinosis. The study did not focus on genetics investigations, but however showed an interesting data. One third of examined individuals were sensitized to the Japanese cedar pollen and among the eleven factors examined, only sensitization to house dust mites significantly influenced the sensitization rate to Japanese cedar pollen.

Tanaka [16] studied the association of polymorphisms in the genes for IL-4 receptor alpha chain with atopic dermatitis and Japanese cedar pollinosis, common allergic diseases associated with the activation of T-helper 2 cells. They indicated that investigated genetic loci: promoter region and Ile50Val in interleukin-4 receptor alpha chain gene were risk factor for atopic dermatitis and Japanese cedar pollinosis and play an important role in modulating severity of allergy.

Recent reports have demonstrated the critical role of antigen presentation by basophils for the induction of Th2 responses. Basophils are responsible for the initial Th2 priming and clinical allergy manifestation. FcεRI-dependent allergen presentation has the critical role [17, 18].

Sallmann et al. [19] indicated that in the presence of IgE and allergen, FcεRI on dendritic cells might instruct naive T cells to differentiate into Th2 cells and influenced allergen-specific Th2 response and Th2-dependent eosinophilia at the site of allergen exposure *in vivo*. This might begin the cascade of pathogenic reactions, linking the allergen capture by IgE. They also demonstrated that FcεRI in the presence of IgE instructed dendritic cells to influence activated naive Th cells into the Th2.

Conclusion

Our studies showed the correlation of the polymorphism of intron 2 of FcεRI β occurrence and allergic rhinitis in the investigated group. The FcεRI β plays an important role in IgE-mediated allergic reactions and is one of the genes linked with atopy and may also regulate the development of allergic rhinitis. The results support other authors' findings and indicate that genetic factors may play an important role in the allergic rhinitis development in the investigated group.

Authors' contributions/Wkład autorów

BK-Z – study design, statistical analysis. JM – data collection. HZ-B – data interpretation, literature search. JO – acceptance of final manuscript version.

Conflict of interest/Konflikt interesu

None declared.

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None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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