Original paper

Coexistence of 2282del4 FLG gene mutation and IL-18 –137G/C gene polymorphism enhances the risk of atopic dermatitis

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Abstract

Introduction: Atopic dermatitis (AD) pathogenesis appears in the context of the correlation between cornified envelope proteins and immunological factors.
Aim: To estimate the association between FLG R501X and 2282del4 gene mutations, –137 G/C IL-18 and –1112 C/T IL-13 gene polymorphisms and their influence on AD course and the risk in the Polish population.
Material and methods: One hundred and fifty-two AD patients and 123 healthy volunteers were included into the study. Amplification refractory mutation system – polymerase chain reaction method was used.
Results: 2282del4 FLG mutation, predominant (p = 0.04) in Polish AD patients, enhanced the risk of AD (OR = 2.35; p = 0.01) and was associated with itch (p = 0.023). GG genotype of IL-18 was prevailing in AD (p < 0.0001), associated with elevated IgE levels (p = 0.00074) and pruritus (p < 0.0001). GG genotype and G-allele in –137 position of IL-18 increased AD risk (OR = 5.4; p = 0.0001, respectively, OR = 5.3; p = 0.000029). –1112 C/T polymorphism of IL-13 was associated with elevated IgE levels (p = 0.00049), pruritus (p = 0.0005), SCORAD score (p = 0.02), concomitant asthma (p = 0.0087) and AD risk (OR = 2.02; p = 0.012). Coexistence of 2282del4 or R501X FLG gene mutation with GG genotype of IL-18 was associated with a 6-fold higher risk of AD (OR = 5.8; p = 0.00013), contrary to combined occurrence of FLG mutations with T-allele in –1112 position of IL-13 gene (OR = 0.12; p = 0.1).
Conclusions: 2282del4 FLG mutation similarly to GG genotype and G-allele in –137 position of IL-18 gene enhance the risk of AD in the Polish population. Coexistence of FLG mutations with GG genotype of IL-18 may be helpful to estimate chances of AD development.

Key words: filaggrin, interleukin 18, interleukin 13, atopic dermatitis.

Introduction

Atopic dermatitis (AD) is common, chronic inflammatory skin disease [1, 2] with increasing socio-economical influences [3–5]. The clinical picture, the course of the disease, pruritus and sleep disturbances have a significant impact on occupational activity of the patients, worsen their social relations and decrease quality of life of the patients and their families [6]. Atopic dermatitis pathogenesis is multi-factorial. Beside immunological, environmental and genetic factors, the role of the epidermal barrier dysfunction is strongly underlined. Last year researches revealed that in the European population, 2282del4 and R501X filaggrin null mutation are the major predisposing factor in AD development [7–9]. On the other hand, Th2 cytokines like: IL-4, IL-13, IL-25, IL-31 decrease FLG expression even if there is no FLG mutation [10]. Ethnic differences in FLG mutations are also observed [11]. Interleukin 18 (IL-18) is a pleiotropic cytokine, whose activities depend on cytokine milieu and genetic background [12–15]. Recently a key role of this cytokine was raised in allergic diseases. Interleukin 18 induces IgE synthesis by enhancing production of IL-4 and IL-13 [12, 14], but it can also lead to AD-like inflammation in an IgE-independent manner [14, 15]. Interleukin 18 was suggested as a marker of AD severity [12, 16, 17]. The gene encod-

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ing IL-18 is located on chromosome 11q22.2–22.3, which has been designated as a candidate region for atopy [12, 13, 18, 19]. The crucial role of interleukin 13 (IL-13) in AD was confirmed by different studies [20–22]. This cytokine is mainly responsible for enhanced IgE levels. Expression of IL-13 correlates with elevated IgE levels and AD severity [23]. It is thought that the polymorphism of IL-13 gene in the promoter region may be related to the increased transcription of that gene and susceptibility to development of AD and increased serum levels of IgE [24].

In the light of recent publications, pathogenesis of AD appears in the context of two major groups of genes: encoding epidermal proteins and major elements of the immune system [2]. Taking this into account, the association between cornified envelope protein gene mutations and cytokine genotyped gene polymorphisms and their influence on AD risk seems to be interesting.

Aim

The aim of this study is to estimate the association of –137 G/C IL-18 gene polymorphism, –1112 C/T IL-13 gene polymorphism, FLG R501X and 2282del4 gene mutations with AD risk and course of the disease in the Polish population and answer whether –137 G/C IL-18 polymorphism or –1112C/T polymorphism of IL-13 enhances the risk of AD development in AD patients with FLG R501X or 2282del4 mutations.

Material and methods

Two hundred and seventy-five subjects were included into the study: 152 AD patients diagnosed according to current criteria and 123 healthy volunteers with no previous history of allergic diseases. The M : F (male and female) ratio was 0.8 : 1. The average age of the AD patients was 23.2 ±11.57 (age range: 5–56 years) and of the controls was 24.9 ±8.02 (age range: 8–52 years). Assessment of pruritus severity was performed using the visual analogue scale (VAS: 0–3 – mild pruritus, > 3–7 – moderate pruritus, > 7–9 – severe pruritus, > 9 – very severe pruritus). Atopic dermatitis severity was rated by SCORAD index (severe (SCORAD > 60, $n = 67$), moderate (SCORAD 25–60, $n = 50$), and mild (SCORAD < 25, $n = 35$)). The average SCORAD score was 47.5 (11.5–85). The patients taking immunosuppressive treatment or other immunotherapy were excluded from the study. Informed consent was obtained prior to enrollment in the study. The study was conducted with the consent of the local ethics committee.

Genomic DNA was isolated from peripheral blood samples using Blood DNA Prep Plus according to the instructions of the manufacturer (A&A Biotechnology, Gdansk, Poland).

Analysis of polymorphic variants of IL-18, IL-13 gene and FLG mutations was performed by the amplification refractory mutation system – polymerase chain reaction method (ARMS-PCR) using designed specific sequences of oligonucleotides. The samples tested in our study were evaluated (genotyping) with internal amplification control of growth hormone 1 (GH1). Serum total IgE levels were measured by fluoroimmunoenzyme assay using the Uni-CAP 100 System (Phadia, Uppsala, Sweden). The cut-off point for serum IgE was 100 kU/l.

All analyses were performed according to the manufacturer's protocols.

Statistical analysis

The data from inquiry prepared specially for this study were statistically worked out using Excel 2003 (Microsoft Corp., Redmond, WA, USA), Statistica (Version 8.0; StatSoft, Tulsa, OK, USA). The *W* Shapiro-Wilk, *U* Mann-Whitney, Kruskal-Wallis and χ^2 were performed. A logistic regression model was used to calculate the odds ratio (OR) and 95% confidence intervals (CIs). The statistical significance were established for the $p < 0.05$.

Results

Filaggrin

2282del4 FLG mutation was the predominant one in AD patients with FLG mutations ($p = 0.04$). We have found 42 (28.6%) patients that were heterozygotes, and no homozygotes (Table 1). 2282del4 of FLG mutation coexisted with allergic rhinitis ($p = 0.001$) and pruritus ($p = 0.03$). There was no association of FLG 2282del4 mutation with elevated IgE levels ($p = 0.16$), early onset of the disease ($p = 0.97$), concomitant asthma ($p = 0.14$), SCORAD score ($p = 0.97$), eosinophilia ($p = 0.65$). 2282del4 FLG mutation enhanced the risk of AD over twofold (OR = 2.35; $p = 0.01$) (Table 2).

R501X heterozygous mutation was observed in 20 (13.2%) AD patients ($p = 0.18$) (Table 1). We have not disclosed any homozygous mutation. There was no association of R501X FLG mutation with pruritus ($p = 0.14$), elevated IgE levels ($p = 0.09$), early onset of the disease ($p = 0.35$), SCORAD score ($p = 0.91$), eosinophilia ($p = 0.21$). We have only observed the association of R501X mutation with concomitant asthma ($p = 0.0047$). R501X mutation had no influence on the AD risk (OR = 0.68; $p = 0.38$) (Table 2).

The presence of R501X or 2282del4 FLG mutation in AD patients was associated with: pruritus ($p = 0.009$), elevated IgE levels ($p = 0.025$), concomitant asthma ($p = 0.01$) and allergic rhinitis ($p = 0.0014$). The presence of any of FLG mutations enhanced the risk of AD (OR = 1.88; $p = 0.016$) (Table 2).

–137 G/C polymorphism of IL-18

GG genotype of IL-18 was prevailing in AD ($p < 0.0001$). It was observed in 94 (61.8%) AD patients (Table 1). GG genotype of IL-18 was dominant in the

Table 1. The occurrence of FLG mutations, genotypes of IL-18 –137 G/C promoter gene polymorphism and –1112 C/T IL-13 promoter gene polymorphism in atopic dermatitis patients and control group

		Controls	AD	*P*-value V^2
		***N* = 123**	***N* = 147**	
2282del4 FLG mutation	Heterozygotes	23 (18.7%)	42 (28.6%)	0.04
	Wild type	100 (81.3%)	105 (71.4%)	
		***N* = 123**	***N* = 152**	
R501X FLG mutation	CT	10 (8.1%)	20 (13.2%)	0.18
	CC	113 (91.9%)	132 (86.8%)	
		***N* = 123**	***N* = 152**	
IL-18	GG	41 (33.3%)	94 (61.8%)	< 0.0001
	GC	51 (41.5%)	49 (32.2%)	
	CC	31 (25.2%)	9 (5.9%)	
		***N* = 123**	***N* = 146**	
IL-13	CC	52 (42.3%)	34 (23.3%)	0.00028
	CT	70 (56.9%)	102 (69.9%)	
	TT	1 (0.8%)	10 (6.8%)	

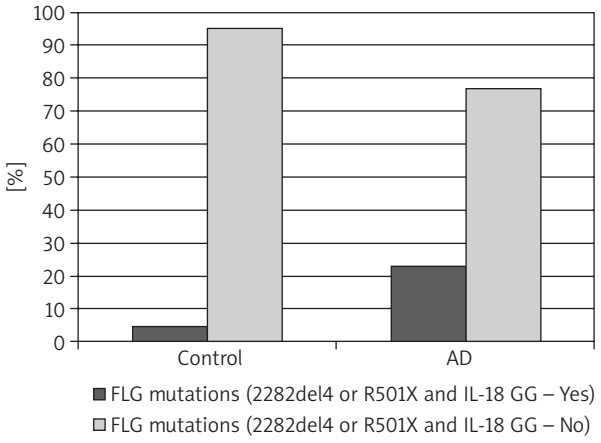
Table 2. The influence of FLG mutations, IL-18 and IL-13 genotypes and alleles on the AD risk

Variable	*P*-value	OR	–95% CL	+95% CL
2282del4 FLG mutation	0.01	2.35	4.519	1.223
R501X FLG mutation	0.39	0.684	0.289	1.616
2282del4 or R501X FLG mutations	0.016	1.885	3.179	1.118
IL-18	< 0.0001	2.672	3.861	1.849
GG genotype of IL-18	< 0.0001	5.412	2.761	10.608
G-allele of IL-18	0.000029	5.351	2.429	11.804
C-allele of IL-18	< 0.0001	0.308	0.508	0.178
–1112 C/T IL-13	0.013	2.021	1.159	3.526
T-allele of IL-13	0.001	2.319	3.940	1.365
C-allele of Il-13	0.038	0.111	0.014	0.892
2282del4 or R501X mutation and GG genotype of IL-18	0.00013	5.815	2.342	14.439
2282del4 or R501X mutation and T-allele of IL-13	0.12	0.625	0.348	1.123

group of patients with pruritus in contrast to CC genotype ($p < 0.0001$). We have observed the association of –137G/C IL-18 polymorphism with elevated IgE levels. GG genotype of IL-18 dominated in the group with enhanced IgE serum concentration comparing to CC genotype that dominated in the group with normal IgE level ($p = 0.00074$). We have observed an association of –137G/C IL-18 gene polymorphism with allergic rhinitis ($p = 0.00027$). We have not found any association of –137 G/C polymorphism of IL-18 with early onset of the disease ($p = 0.48$), concomitant asthma ($p = 0.15$) or eosinophilia ($p = 0.26$). –137G/C polymorphism of IL-18 gene enhanced the risk of AD, especially GG genotype (OR = 5.14; $p < 0.0001$) and G allele (OR = 5.35; $p = 0.000029$) over 5 times (Table 2).

–1112 C/T polymorphism of IL-13

CT genotype of IL-13 was predominant in AD (69.9%, $p = 0.00028$) (Table 1). T-allele was dominant in the AD group: 61.2% vs. 38.8% in controls ($p = 0.0015$). –1112 C/T IL-13 gene polymorphism was associated with pruritus ($p = 0.0005$) and elevated IgE levels ($p = 0.00049$),



FLG – filaggrin, IL-18 GG – GG genotype of IL-18 in position –137 of the promotor gene, AD – atopic dermatitis patients.

Figure 1. FLG mutations together with GG genotype of IL-18 is more frequent in AD patients than in the healthy control group (p = 0.03)

SCORAD score (p = 0.022), eosinophilia (p = 0.00029) and concomitant asthma (p = 0.0087). We have not found any association of –1112C/T polymorphism of IL-13 with early onset of AD (p = 0.07), allergic rhinitis (p = 0.08). –1112 C/T IL-13 gene polymorphism was associated with the AD risk (OR = 2.02; p = 0.013). C allele decreased the risk of AD (OR = 0.111; p = 0.038), T allele increased the risk of AD (OR = 2.319; p = 0.001) (Table 2).

FLG mutations and GG genotype of IL-18, serum levels of IL-18, –1112 T allele of IL-13

FLG mutations (2228del4 and R501X) together with GG genotype of IL-18 were more frequent in AD patients than in controls (p = 0.03) (Figure 1). There is no such a phenomenon between FLG mutations (2282del4 or R501X) and T allele of IL-13 (p = 0.1). Coexistence of 2282del4 or R501X FLG gene mutation with GG genotype of IL-18 increased the AD risk nearly 6 times (OR = 5.8; p = 0.00013). Coexistence of 2282del4 or R501X FLG gene mutation with T allele in –1112 position of IL-13 gene had no statistically significant influence on the AD risk (p = 0.12) (Table 2).

We have found no associations between elevated serum levels of IL-18 and presence of 2282del4 mutation as well as for R501X FLG mutation (p = 0.1).

Discussion

The phenotype of AD is a result of genetic, immunological and environmental influences [25]. Analysis of such a multifactorial disease like AD poses different difficulties. Last year's research have identified some genes responsible for AD susceptibility and provided a number of valuable clues that let us better understand the genetic background of AD. The FLG mutation is the risk factor for AD in European populations [7–9]. Our data are in accordance with previously reported findings for 2282del4 FLG mutation [8, 9], which was associated with the AD risk in our population, too. In turn, R501X FLG mutation does not contribute to AD in Polish patients, which is in contrast to observations in other European populations such as Irish, British, or German [8, 9]. It was confirmed by most of the authors [7, 11, 26] that carriers of FLG gene mutations manifest a more severe course of AD. This trend was not noted in our group. Similarly to Poninska *et al*. [27], we have not found any association between 2282del4 FLG gene mutation and elevated serum IgE levels, what was in contrast to others [7–9, 26]. These differences may be explained by effect size or ethnic limitations. We have not observed any association of 2282del4 of FLG gene mutation with early onset of AD like Lesiak *et al*. [28], but some researches in European and Asian populations have indicated such a correlation [7, 11, 26].

Similarly to our studies, in the Danish population [29], a relationship between a polymorphic variant of the IL-13 gene and AD occurrence was indicated. In the Japanese population [30], significant differences in the frequency of each allele and genotype of the IL-13 gene between the AD patients and healthy subjects were not found, in spite to our data. The association of IL-13 polymorphisms with the increased serum IgE levels was demonstrated in a group of 1399 children with atopic diseases [31] and in the German population [32], as well as in our results. On the other hand, the scientists at several European centers studied a group of 453 AD children and did not demonstrate any associations between polymorphism in the promoter region of IL-13 and the IgE level for the TT homozygotes, while they observed slightly increased IgE levels for the CT heterozygotes [33].

Results of our study are consistent with the the one carried out in the German population [13], which revealed a significant association of SNPs in –137G/C of IL-18 gene with AD. We have previously published the data, which have indicated that G-allele reveals susceptibility to AD development and C-allele seems to have protective properties [34]. Now we have more proofs because GG genotype of IL-18 is associated with elevated IgE levels and pruritus in contrast to CC genotype. Kruse *et al*. [19] have also observed an association of –137 G/C IL-18 gene polymorphism with high IgE levels. By the way, we have found no association with SCORAD score, similarly to Novak *et al*. [13]. According to the latter study, the association of –137 G/C SNP of IL-18 with AD was not directly dependent on concomitant manifestation of allergic rhinitis or asthma. We have noticed the associations of –137G/C IL-18 polymorphism with concomitant allergic rhinitis, but not with asthma. The association of IL-18 serum levels with AD course was previously published [16, 17]. Now, in the context of FLG mutations, we have found no associations between elevated serum levels of IL-18 and 2282del4 FLG mutation as well as for R501X FLG

mutation. Anyway, it is well documented that Th2 cytokines like IL-13, IL-4 influence the FLG expression even if no FLG mutation exists [10]. It seems to be interesting if IL-18 also inhibits FLG expression in AD patients, while they are not FLG mutations carriers. On the other hand, in our study AD 2282del4 carriers with homozygous GG genotype for –137 G/C polymorphism of IL-18 have a nearly 6-fold higher risk of AD development. We have previously published that elevated levels of IL-18 were associated with GG genotype and G allele [34]. Additionally, although –1112 C/T polymorphism of IL-13 gene and T allele enhance the risk of AD according to previous data [35], coexistence of T allele with any FLG mutation does not increase susceptibility to AD.

These results seem to indirectly indicate that there must be an interaction between FLG decreased expression and Th2 cytokines over-expression, as it was previously suggested [4, 36] and AD emerges in the light of innate and acquired immune response [37], genes and immunology interactive net.

Conclusions

2282del4 FLG mutation that dominates in the Polish population is a risk factor for AD development. GG genotype and G allele of IL-18, similarly to T allele of IL-13, seem to promote AD development. In contrast to combined occurrence of FLG mutations with T allele of IL-13, coexistence of FLG mutations with GG genotype of IL-18 is associated with a 6-fold higher risk of AD. Thus, our results indicate that this combined occurrence may be helpful to estimate chances of AD development and seems to be a useful parameter in separating patients from healthy persons.

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Conflict of interest

The authors declare no conflict of interest.

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