ERAP1 and HLA-C*06 are strongly associated with the risk of psoriasis in the population of northern Poland

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Abstract

Introduction: HLA-C*06 is a major psoriasis genetic risk marker. Recent reports have been focused on the role of different polymorphisms within genes involved in the functioning of the epidermal barrier and antigen processing in the pathogenesis of psoriasis. Data on the association between genetic variants of LCE3B_LCE3C, CSTA, ERAP1, ZAP70 and this dermatosis in the population from Eastern Europe are lacking.

Aim: To compare the association between known genetic risk markers and psoriasis in a cohort of northern Polish patients with psoriasis and healthy controls.

Material and methods: Based on previous studies’ results, five susceptibility loci: HLA-C, LCE3C_LCE3B, ERAP1, ZAP70 and CSTA were selected for genotyping in 148 patients with chronic plaque psoriasis and 146 healthy controls. Each patient with this disease was clinically assessed with the Psoriasis Area and Severity Index.

Results: The study population showed a significant association of psoriasis and a single nucleotide polymorphism in the ERAP1 – rs26653 (p = 3.11 × 10⁻⁵) and HLA-C*06 allele (p = 1.02 × 10⁻¹¹) when compared with the control group. The presence of HLA-C*06 or rs26653 G allele significantly increased the risk of psoriasis by 2.4 times or twice, respectively. Carrying rs26653 C allele considerably decreased the risk of psoriasis by 1.5 times.

Conclusions: In the context of pathogenesis of psoriasis, our findings might give the evidence on disturbances in the proteolytic processing of N-terminal fragments of antigens presented via major histocompatibility complex class I to T cells.

Key words: psoriasis, genetic polymorphism, genome-wide association studies.

Introduction

Psoriasis is a common, inflammatory skin disease. It affects from 2% to 4% of the Caucasian population [1, 2]. Genetic background plays a key role in the pathogenesis of psoriasis. It is classified as a complex disease with polygenic and multifactorial mode of inheritance. Its heterogeneous clinical manifestation depends on interactions between numerous susceptibility genes as well as genetic and environmental factors.

Linkage analysis of large family cohorts and genome-wide association studies (GWAS) have led to identification of more than 46 susceptibility loci located on different autosomal chromosomes. Up to date, the strongest association with psoriasis has been proven in psoriasis susceptibility 1 (PSORS1) locus on chromosome 6p21 [2]. The region consists of 300 kilobase-fragment (kb) within the major histocompatibility complex class I (MHC class I), from corneodesmosin gene (CDSN) to HLA-C. Among genes identified in PSORS1 locus, HLA-C*06 allele presents the strongest association with psoriasis, which has been demonstrated in the studies on various ethnic populations [3–9]. As in other disorders characterized by polygenic mode of inheritance with a low penetrance power of genes involved in the process, HLA-C*06 is responsible for 35–50% of genetic predisposition to the early-onset type of psoriasis in Caucasians [10–12]. The latest research results have confirmed the association of genes involved in the functioning of the epidermal barrier (LCE3 and CSTA) and genetic variants involved in the processing of antigens in the context of MHC class I and regulation of CD8+ cells activation.
ERAP1 and HLA-C*06 are strongly associated with the risk of psoriasis in the population of northern Poland

(ERAP1 and ZAP70) with psoriasis [13–21]. With respect to psoriasis pathogenesis, epistasis has been described with reference to HLA-C*06 and polymorphisms, such as: LCE3C_LCE3B-del and single nucleotide polymorphisms (SNPs): rs26653 located within the ERAP1 gene, rs17695937 linked to the ZAP70 gene and rs17589 located within the CSTA gene [13, 14, 16, 21–25]. On the other hand, the reports on interactions of these genetic markers with HLA-C*06 are inconsistent and differ among ethnically diverse populations.

Aim

In this study, we compared the incidence of HLA-C*06, LCE3C_LCE3B-del and three SNPs: rs26653 located within the ERAP1 gene, rs17695937 linked to the ZAP70 gene and rs17589 located within the CSTA gene in the population of patients with psoriasis and healthy controls from northern Poland. We compared the coincidence of LCE3C_LCE3B-del, rs26653, rs17695937 and rs17589 with HLA-C*06 in the northern Polish population of patients with psoriasis and the control group. We analyzed the relationship between HLA-C, LCE3C_LCE3B, CSTA, ERAP1 and ZAP70 genotypes and the severity of this dermatosis, provided by Psoriasis Area and Severity Index (PASI) score.

Material and methods

Selection of genetic risk markers

The selection of the genetic risk markers included into the research was based on previous GWAS and large cohort studies’ results demonstrating the strongest association with the risk of psoriasis at \( p < 0.05 \) [13, 14, 16, 21, 23, 24, 26, 27].

Sample collection

DNA was obtained from 148 patients with chronic plaque psoriasis and 146 unrelated healthy individuals. The study population included 79 (53.38%) men and 69 (46.62%) women. The mean age of the study population was 43.3 (range: 18–83) years. Patients with guttate psoriasis, pustular psoriasis and psoriatic erythroderma were not included in the study. The control group consisted of 83 (56.64%) men and 63 (43.16%) women, gender- and age-matched with the psoriasis patients. The mean age of the control group was 42.0 (range: 19–84) years. There were neither personal nor family history of psoriasis or psoriatic arthritis in the healthy controls.

All participants provided written informed consent and the study was approved by the ethical committee of the Medical University of Gdansk (NKBBN/181/2012).

Clinical assessment

The disease severity was evaluated by PASI score, which was applied to each patient with psoriasis. The index is based on a quantitative assessment of three clinical features of psoriatic lesions (erythema, desquamation and infiltration) combined with the skin surface area involved. In each patient, PASI score was calculated by the same clinical assessor.

Genotyping

DNA samples were extracted from EDTA-treated peripheral blood, using a modified non-organic method by Lahiri and Nurnberger [28]. The yield and purity of DNA were checked by measuring absorbance at 260 nm.

HLA-C*06 genotypes were determined by the optimized three-step procedure. Polymerase chain reaction (PCR) with sequence-specific primers (PCR-SSP) was used for specific detection of HLA-C*06. PCR with analysis of restriction fragment length polymorphism (PCR-RFLP) was used to distinguish HLA-C*06 homozygous and heterozygous subjects. Homozygous genotypes were additionally analyzed for nonspecific digestion by PCR-SSP [29, 30]. The sequences of primers used for genotyping of HLA-C*06 (HLA-CF and HLA-CA) are presented in Table 1. Alleles with LCE3C_LCE3B-del were identified by PCR with evaluation of amplified fragment length polymorphism (PCR-AFLP), described in the study of de Cid et al. [14]. Three different primers were used for the reaction (Table 1). A specific product of 240 base pairs (bp) in length without the deletion was amplified with LCE3C_F and LCE3C_R primers. LCE3C_LCE3B-del allele of 199 bp in length was detected by LCE3C_F and LCE3CR2D primers.

After optimization of temperature of hybridization of specific primers used to detect SNPs within the ERAP1 and the CSTA genes and linked to the ZAP70 gene, dis-

Table 1. Sequences of primers used for genotyping of HLA-C*06, LCE3C_LCE3B-del, ERAP1, ZAP70 and CSTA polymorphisms

| Primer name | Primer sequence |
|-------------|-----------------|
| HLA-CF      | 5’TITAGGATTCTCCACTCCCCCTGAG3’ |
| LCE3C_R     | 5’TGGGGAACCACGAAAGTAG3’ |
| LCE3CR2D    | 5’CATCCCACTGATGCTCATG3’ |
| ERAP1-FC    | 5’GACGGCATTGGTCCTTAACG3’ |
| ERAP1-R     | 5’GACGGCATTGGTCCTTAACG3’ |
| ZAP70-FA    | 5’CCITCGGAGAGATTTTTCA3’ |
| ZAP70-FG    | 5’CCITCGGAGAGATTTTTCA3’ |
| CSTA-FC     | 5’GAAGAAAAAAACATGACGTGAC3’ |
| CSTA-FT     | 5’GAAGAAAAAAACATGACGTGAC3’ |
| CSTA-R      | 5’TGAGATGCCACACTGG3’ |
crimination of rs26653, rs17589 and rs17695937 alleles was performed by PCR-SSP method (Table 1).

In order to ensure quality control in all cases, a negative non-template control as well as an internal positive control of amplification were used to eliminate genotype mistakes.

The PCR products were analyzed by polyacrylamide gel electrophoresis and stained with silver.

Statistical analysis

No deviations from Hardy-Weinberg equilibrium were found. The frequencies of genetic variants and genotypes of HLA-C, LCE3C_LCE3B, CSTA, ERAP1 and ZAP70 in patients with psoriasis and healthy controls were compared with the use of Fisher’s exact test for 2 × 2 contingency tables and χ² test for large tables. The analysis of coincidence of selected psoriasis susceptibility markers with HLA-C*06 was performed by Fisher’s exact test. The relationship between mean PASI score and studied genotypes was calculated by U Mann-Whitney test. The calculations were performed with the use of Statistica 12 package (StatSoft Inc.). Relative risks (RRs) and their 95% confidence intervals (CIs) were estimated with the use of MedCalc 16 (MedCalc Software bvba). Relative risk is defined as a ratio of probability of developing psoriasis in carriers of the tested allele to probability of developing the disease in non-carriers of the allele and is given by the following formula: \( \frac{a/(a + b)}{c/(c + d)} \), where \( a \) is the number of carriers who developed psoriasis, \( b \) is the number of carriers who did not develop psoriasis, \( c \) is the number of non-carriers who developed psoriasis and \( d \) is the number of non-carriers who did not develop psoriasis.

Results

In the population of patients with psoriasis studied in this work, 296 alleles were genotyped for HLA-C*06. There were 101 alleles with HLA-C*06 (34.1%), whereas in 195 (65.9%) HLA-C*06 was not identified. In the control group, 292 alleles were genotyped for HLA-C*06. In 32 alleles HLA-C*06 was observed (11.0%), whereas in 260 (89.0%) HLA-C*06 was not present. The frequency of HLA-C*06 allele was significantly higher in the group of patients with psoriasis compared with the control group (\( p = 1.02 \times 10^{-3} \)). In the group of patients with psoriasis, 296 alleles were genotyped for LCE3C_LCE3B-del. One hundred eighty-one (61.1%) alleles presented LCE3C_LCE3B-del, whereas in 115 (38.9%) the deletion was not detected. In healthy controls, 292 alleles were genotyped for LCE3C_LCE3B-del. In 167 (57.2%) alleles LCE3C_LCE3B-del was identified, whereas in 125 (42.8%) it was not present. The results did not reveal a statistically significant difference between patients with psoriasis and the control group in LCE3C_LCE3B-del frequency (\( p = 0.356 \)).

In the group of patients with psoriasis, 254 alleles were genotyped for rs26653 G and rs26653 C at ERAP1. In 210 (82.7%) alleles rs26653 G was identified, whereas in 44 (17.3%) alleles rs26653 C was detected. In the control group, 202 alleles were genotyped for rs26653 G and rs26653 C at ERAP1. In 132 (65.3%) alleles rs26653 G was observed, whereas in 70 (34.7%) alleles rs26653 C was present. Psoriatic patients presented a significantly higher incidence of rs26653 G allele compared with healthy individuals, whereas a statistically significant higher frequency of rs26653 C allele was observed in the control group compared with the group of patients with psoriasis (\( p = 3.11 \times 10^{-3} \)).

There were no significant differences between patients with psoriasis and the control group in rs17589 alleles at CTA (\( p = 1.00 \)) and CTA genotype frequencies (\( p = 0.193 \)). Statistically significant differences between patients with psoriasis and the control group in rs17695937 alleles at ZAP70 (\( p = 0.300 \)) and ZAP70 genotype frequencies (\( p = 0.468 \)) were not found.

Psoriatic patients presenting heterozygous LCE3C_LCE3B-del genotype showed a statistically higher mean PASI score compared to patients having both copies of the LCE3B and LCE3C. There was a statistically higher mean PASI score in patients with psoriasis carrying at least one rs17695937 G copy at ZAP70 (either heterozygous or homozygous) compared with the patients without this allele. Psoriatic patients presenting homozygous rs17695937 A genotype demonstrated a statistically lower PASI score compared to the patients with heterozygous ZAP70 genotype. There were no statistically significant differences in mean PASI score between ERAP1 and CSTA genotypes. Table 2 presents the relationship between mean PASI score and different genotypes of HLA-C, LCE3C_LCE3B, CSTA, ERAP1 and ZAP70.

The group of individuals carrying HLA-C*06 allele demonstrated a statistically higher frequency of rs26653 G allele at ERAP1 in the population of patients with psoriasis compared with the control group. In HLA-C*06-positive group, a statistically higher incidence of rs26653 C allele at ERAP1 was observed in the control group compared with patients with psoriasis. In the group of individuals carrying at least one copy of HLA-C*06, no significant differences between patients with psoriasis and healthy controls in the frequencies of LCE3C_LCE3B-del, CSTA and ZAP70 alleles were found. Table 3 demonstrates the comparison of frequencies of LCE3C_LCE3B-del, rs17589 at CSTA, rs26653 at ERAP1, rs17695937 at ZAP70 in HLA-C*06-positive group in the population of patients with psoriasis and healthy individuals. Carrying at least one copy of HLA-C*06 increased significantly the risk of psoriasis 2.4 times in the study population. Carrying an allele other than HLA-C*06 allele decreased significantly the risk of psoriasis twice in the study population. Individuals with rs26653 G allele at ERAP1 demonstrated a significantly higher risk of psoriasis development com-
ERAP1 and HLA-C*06 are strongly associated with the risk of psoriasis in the population of northern Poland.

Table 2. The relationship between mean PASI score and different genotypes of HLA-C, LCE3C_LCE3B, CSTA, ERAP1 and ZAP70

| Gene       | Genotypes compared     | Mean PASI score | P-value* |
|------------|------------------------|-----------------|----------|
| **Group 1** | **Group 2**            | Group 1 | Group 2 | Group 1 | Group 2 |
| HLA-C      | C*06 (+)               | 17.7     | 14.6          | 0.13       |
|            | Non-C*06 (+)           | 16.2     | 31.4          | 0.04       |
|            | C*06/C*06 Heterozygotes | 31.4     | 17.1          | 0.05       |
|            | Non-C*06/non-C*06 Heterozygotes | 14.6 | 17.1          | 0.20       |
| LCE3C_LCE3B | del(+)                | 17.2     | 13.8          | 0.06       |
|            | wt(+)                 | 17.2     | 15.8          | 0.46       |
|            | del/del Heterozygotes | 15.8     | 18.2          | 0.15       |
|            | wt/wt Heterozygotes   | 13.8     | 18.2          | 0.03       |
| CSTA       | C(+)                  | 16.6     | 18.0          | 0.61       |
|            | T(+)                  | 17.0     | 15.3          | 0.64       |
|            | CC Heterozygotes      | 15.3     | 16.9          | 0.69       |
|            | TT Heterozygotes      | 18.0     | 16.9          | 0.66       |
| ERAP1      | G(+)                  | 16.7     | 15.2          | 0.79       |
|            | C(+)                  | 15.8     | 16.9          | 0.89       |
|            | GG Heterozygotes      | 16.7     | 16.6          | 0.73       |
|            | CC Heterozygotes      | 15.2     | 16.6          | 0.89       |
| ZAP70      | G(+)                  | 18.5     | 15.4          | 0.03       |
|            | A(+)                  | 16.6     | 18.7          | 0.97       |
|            | GG Heterozygotes      | 18.7     | 18.5          | 0.74       |
|            | AA Heterozygotes      | 15.4     | 18.5          | 0.02       |

*U Mann-Whitney test.

Table 3. Comparison of LCE3C_LCE3B, CSTA, ERAP1 and ZAP70 allele frequencies in the HLA-C*06-positive group in the population of psoriatic patients and controls

| Parameter | HLA-C*06(+)(n) | LCE3C_LCE3B-del(n) | Non-LCE3C_LCE3B-del(n) | P-value* |
|-----------|----------------|-------------------|------------------------|----------|
| Psoriasis | 97             | 0.603             | 0.397                  | 0.770    |
| Control   | 32             | 0.578             | 0.422                  |          |
| HLA-C*06(+)(n) | rs17589 C (n) | rs17589 T (n)    |                        |          |
| Psoriasis | 96             | 0.547             | 0.453                  | 0.885    |
| Control   | 32             | 0.531             | 0.469                  |          |
| HLA-C*06(+)(n) | rs26653 G (n) | rs26653 C (n)    |                        |          |
| Psoriasis | 85             | 0.800             | 0.200                  | 0.019855 |
| Control   | 23             | 0.630             | 0.370                  |          |
| HLA-C*06(+)(n) | rs17695937 G (n) | rs17695937 A (n) |                        |          |
| Psoriasis | 97             | 0.242             | 0.758                  | 0.301    |
| Control   | 32             | 0.172             | 0.828                  |          |

*Fisher’s exact test.
Table 4. Relative risk score for each of the analyzed psoriasis genetic markers in the case-control samples from northern Poland

| Genotype                  | Relative risk | 95% CI          |
|---------------------------|---------------|-----------------|
| HLA-C*06 (+)              | 2.4327        | 1.8970–3.1197   |
| Non-HLA-C*06 (+)          | 0.4966        | 0.4422–0.5576   |
| LCE3C_LCE3B-del (+)       | 1.0898        | 0.7848–1.5134   |
| Non-LCE3C_LCE3B-del (+)   | 0.8849        | 0.7026–1.1145   |
| rs17589 C (+)             | 0.7093        | 0.4843–1.0388   |
| rs17589 T (+)             | 0.8540        | 0.6383–1.1425   |
| rs26653 G (+)             | 1.9865        | 1.1364–3.4726   |
| rs26653 C (+)             | 0.6522        | 0.4923–0.8640   |
| rs17695937 G (+)          | 1.1343        | 0.9035–1.4241   |
| rs17695937 A (+)          | 0.7526        | 0.4225–1.3407   |

Discussion

In the context of disorders with polygenic mode of inheritance, where single genes present a modest impact on the phenotype, GWAS became an extremely useful tool used for molecular analysis. With genotyping of hundreds of thousands of polymorphisms it led in the last decade to identification of novel genetic risk markers associated with psoriasis. The latest results of genetic analyses including patients with psoriasis from northern Poland have demonstrated the association of the −2518 A/G monocyte chemoattractant protein-1 (MCP-1) and −403 G/A regulated on activation, normal T-cell expressed and secreted (RANTES) promoter gene polymorphisms with an increased risk of psoriasis and suggested the influence of polymorphisms in the Toll-like receptor 2 (TLR2) and Toll-like receptor 9 (TLR9) genes on the clinical manifestation of this dermatosis [31, 32]. Among different genetic markers identified in the context of psoriasis susceptibility, HLA-C*06 still presents the strongest association with the early-onset type of the disease in Caucasians [3, 7, 8, 33–35]. This fact has been also confirmed by the studies performed in the Polish population of patients with psoriasis from north and south regions [8, 29, 36]. On the other hand, psoriasis susceptibility genes located within PSORS1 locus are estimated to be responsible for less than 50% of genetic predisposition to the disease, which indicates the presence of other markers outside the MHC region, which may predispose to psoriasis [10–12]. In this study, the frequency of HLA-C*06 was found to be significantly higher in patients with psoriasis than in the control group, which is in agreement with other cohorts’ results, as well as with earlier studies performed in the northern Polish population [3–9, 36]. The incidence of HLA-C*06 in the group of psoriatic patients involved in this research was 65.5% which does not differ from other findings [37–39].

Recent GWAS results showed the association of novel genetic markers involved in the skin barrier functioning with psoriasis. Numerous observations within ethnically diverse populations have proven a common deletion in LCE3B and LCE3C genes (LCE3C_LCE3B-del) to predispose to psoriasis [14, 17, 19, 20, 23, 40]. Our study is the first analysis on frequency of LCE3C_LCE3B-del in patients with psoriasis from Eastern Europe. Herein a higher incidence of LCE3C_LCE3B-del in the population of psoriatic patients compared to the control group was found although the difference was not statistically significant. Our findings revealed a significant higher mean PASI score in patients carrying LCE3C_LCE3B-del compared to the patients with both copies of LCE3B and LCE3C genes. This might refer to the influence of LCE3C_LCE3B-del on the clinical course of the disease. There are only a few reports on higher frequency of LCE3C_LCE3B-del in patients with the early-onset type of the disease, but the relationship with PASI score has never been analyzed so far [20, 24].

Another protein arranged in the process of cornified envelope formation and proper skin barrier functioning is cystatin A, encoded by CSTA gene on 3q21 chromosome. Vasilopoulos et al. investigated three genetic markers in the CSTA gene, but the strongest effect on the psoriasis risk was found in rs17589 (p < 0.001) [21, 25]. A higher expression of cystatin A was also observed in psoriasis plaques compared to healthy skin [41]. Our research is the first study on frequency of rs17589 at CSTA in the population of patients with psoriasis from Eastern Europe. No differences in frequencies of genetic variants in CSTA gene between psoriatic patients and the control group were found. These observations are in agreement with the results reported by Samuelsson et al. [42]. Different findings might be explained by genetic variations between Polish and British populations, which needs further research.

Numerous SNPs within the ERAP1 gene have been proven to have an effect on genetic predisposition to psoriasis, but the strongest association with the disease in the European population has been found in rs26653 marker (p = 0.00006) [26]. These observations were confirmed by Tang et al. for the Chinese population (p = 5.27 × 10^{-12}) [27]. Various polymorphisms at ZAP70 were analyzed in the context of predisposition to psoriasis [13, 43]. The strongest association with the disease has been shown by Strange et al. in rs17695937 marker (p = 2.37
ERAP1 and HLA-C*06 are strongly associated with the risk of psoriasis in the population of northern Poland

The proteins encoded by ERAP1 and ZAP70 genes play an important role in antigen processing and its presentation in the context of MHC class I that results in the activation of CD8+ lymphocytes. What is more, the study by Strange et al. proved an association of SNPs at ERAP1 (rs27524) and linked to ZAP70 (rs17695937) with psoriasis only in the group of patients carrying HLA-C*06 allele, which is evidence on interaction between these genetic markers [13]. Our report is the first study on frequency of genetic risk variants at ERAP1 and ZAP70 genes in the population of patients with psoriasis from Eastern Europe. We found a significant higher frequency of rs26653 G allele in the group of psoriatic patients compared with the healthy controls. On the other hand, rs26653 C allele was significantly more frequent among healthy individuals compared with the patients with psoriasis, which may indicate the protective effect of this genetic marker. The evaluation of frequencies of particular ERAP1 genotypes, revealed a significant higher incidence of homozygous rs26653 G genotype in the population of patients with psoriasis compared with the control group. Up to date, this has been the first report in the literature. A significant higher mean PASI score was observed in patients with psoriasis carrying at least one copy of rs17695937 G allele compared to the patients with homozygous genotype of rs17695937 A. On the contrary, patients with two copies of rs17695937 A allele presented a significant lower mean PASI score compared to the patients with one copy of rs17695937 G allele. These findings may indicate the existence of the protective effect of rs17695937 A regarding less severe clinical course of the disease, but only in the group of patients carrying both copies of this allele. On the other hand, the presence of rs17695937 G allele may be considered as a negative prognostic factor, correlated with more severe psoriasis clinical course.

The results of single reports on interaction between polymorphisms within the ERAP1 gene and the major psoriasis susceptibility allele – HLA-C*06 were not confirmed in the present study [13, 24]. Although we found a statistically significant difference between the patients with psoriasis and the control group in the frequencies of ERAP1 alleles in the population of C*06-positive individuals, the difference was also shown in the whole group of subjects without limitation to HLA-C*06 carriers. This result presents a lack of interaction between ERAP1 and HLA-C*06, which might be explained by a low number of healthy individuals carrying HLA-C*06 in the control group. To compare, the analysis made by Strange et al., which is evidence of such interaction, included 2,622 psoriasis patients and 5,667 healthy controls [13].

In the study population, rs26653 G allele proved to be almost as strong psoriasis genetic risk marker as HLA-C*06. Although in the present research, we did not show a statistically significant interaction between these genetic variants, the results seem to be reflected in the biological functions of the proteins encoded by HLA-C*06 and ERAP1. Based on our findings, we assume that genetically determined change in ERAP1 and Cw6 protein function in patients with psoriasis is related and might play an important role in the pathogenesis of the disease. One of the current hypotheses on the induction of the psoriatic process is based on presentation of an unknown antigen to CD8+ T-cells. We consider that the excessive activation of CD8+ T-cells is due to the presentation of proteins in the context of MHC class I, which N-terminal fragments underwent previously an abnormal proteolysis catalyzed by ERAP1.

Conclusions
Among genetic markers (analyzed in the present study): HLA-C*06, LCE3C_LCE3B-del, rs17589 located within the CSTA gene, rs26653 located within the ERAP1 gene, rs17695937 linked to the ZAP70 gene, we confirmed the strong association of HLA-C*06 and rs26653 G alleles with the risk of psoriasis in the northern Polish population. Our findings suggest a protective role of rs26653 C allele at ERAP1 in the study population. None of analyzed CSTA alleles presented an effect on genetic predisposition to psoriasis. It has been shown that severity of the disease might be determined by HLA-C, LCE3C_LCE3B and ZAP70 genotypes, which has not been previously reported.

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Conflict of interest
The authors declare no conflict of interest.

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Advances in Dermatology and Allergology 3, June / 2018

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