Original paper

Analysis of selected genetic variants in psoriasis susceptibility and response to treatment

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Abstract

Introduction: Aetiology of psoriasis is complex with risk factors involving both environmental triggers and genetic background. Although the best characterized genetic risk factor for psoriasis is HLA-C*06 allele, a number of other variants were associated with the disease.
Aim: In the current paper we have conducted a confirmation study for SNPs located in 9 gene regions in a case-control analysis of 507 psoriatic patients and 396 controls from the Polish population.
Material and methods: Subsequently the impact of genetic variants on response to topical and NB-UVB therapy (reduction in the Psoriasis Area and Severity Index) was analysed.
Results: Significant differences in genotype and/or allelic frequency were observed for the following SNPs: rs33980500 (TRAF3IP2), rs582757 (TNFAIP3I), rs12188300 (IL12B), rs28998802 (NOS2), and rs2233278 (TNIP1). None of the genetic factors was associated with treatment outcome.
Conclusions: Although the genetic variants have an impact on the disease risk, they are unlikely to be useful in personalization of topical therapy.

Key words: psoriasis, SNP, NB-UVB.

Introduction

Psoriasis (Ps) is a common inflammatory dermatologic condition that affects from 1% to 12% of population, depending on ethnicity and geographical location [1]. Aetiology of the disease is complex and it is generally considered a skin-specific T-cell mediated autoimmunological disease with risk factors involving genetic factors and environmental triggers [2]. The best characterized genetic risk factor for psoriasis is HLA-C*06 allele, encoding a variant of a major histocompatibility complex I (MHC I) antigen. However, HLA-C*06 does explain only a part of hereditability of psoriasis. Therefore, further investigations were undertaken in the last years to identify other genetic variants associated with the disease. Many single nucleotide polymorphisms (SNPs) were revealed by genome-wide association studies (GWAS), mostly localized in gene regions related to adaptive immunity, but including those connected with innate immune system pathways [3]. GWAS together with target genotyping performed in different ethnic populations resulted in identification of approximately 50 genetic markers associated with psoriasis [4]. Since reproducibility is very important in genetic investigations, in the current study we tried to verify an association between nine selected SNPs, previously linked to altered disease risk in GWAS. The investigated variants are located in genes encoding for proteins mainly involved in innate immunity. *IFNLR1* (interferon lambda receptor 1, also known as *IL28RA*) may have an essential role in anti-viral activity and immune regulation, and it has been recently reported that it inhibits human epidermal keratinocyte proliferation *in vitro* [5]. *STAT2*, encoding one of ubiquitous transcription factors, was associated with psoriasis vulgaris in one of the GWAS, and subsequently it was demonstrated that it can be involved in the pathogenesis of psoriasis [6, 7]. The *NFKBIA* gene product is an inhibitor of the nuclear factor κB (NF-κB) pathway that may play a role in psoriasis pathogenesis, as reported increased expression of

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NF-κB in psoriatic skin may drive the proliferation of immune cells [8]. Similarly, *TNFAIP3* (tumor necrosis factor, alpha-induced protein 3), *TNIP1* (TNFAIP3-interacting protein 1), *TRAF3IP2* (TRAF3 interacting protein 2) and *REL* (REL proto-oncogene, NF-kB subunit) are also involved in regulation of NF-κB associated inflammatory signalling pathways [3]. NOS2 encodes for inducible nitric oxide synthase playing an important role in metabolic and inflammatory processes, which is significantly upregulated in psoriatic lesional skin [9]. Finally, the *IL12B* gene product is a p40 subunit, shared by IL-23 and IL-12 cytokines. IL-23 induces differentiation of naïve T cells into Th17 and Th22 cells that in turn mediate the epidermal hyperplasia, keratinocyte immune activation and tissue inflammation [10].

Despite the strong evidence for an association between genetic factors with psoriasis, not many studies were focused on their impact on treatment efficacy up-to-date, and those published mostly refer to biopharmaceutics and psoriatic arthritis. Although the availability of monoclonal antibodies for psoriasis treatment is increasing, topical therapy combined with narrow-band ultraviolet B (NB-UVB) phototherapy is still one of the most effective treatments, especially in the case of mild or moderate disease severity, and an impact on genetic factors on the therapy outcome is unknown.

Aim

In the current paper we have investigated nine genetic variants in relation to their association with the disease, and subsequently in relation to response to topical and NB-UVB therapy in a cohort of Polish Caucasian patients with mild to moderate plaque psoriasis.

Material and methods

Study subjects

The current study involved 507 Polish psoriatic patients (361 type I and 146 type II psoriasis) and 396 healthy controls from the same geographical region, who were enrolled in the study after signing informed consent. The protocol of the study was approved by the local ethics committee. The diagnosis of psoriasis vulgaris was based on clinical examination and histopathological findings in selected cases. The main enrolment criteria included more than 1 year duration of psoriasis and presence of the active form of the disease. The patients were initially recruited for the purpose of our previous study [11]. More detailed characteristics of the subjects are presented in Table 1.

Evaluation of genetic factors in relation to treatment outcome was performed in a subset of 306 patients with complete clinical data (49.7% females, mean disease onset at 30.6 ±13.7 years). The patients were classified as mild (n = 154) or moderate (n = 152) psoriasis based on the Psoriasis Area and Severity Index at the start of therapy (PASI ≤ 12 or 12–18, respectively). All patients were subjected to topical therapy, which consisted of vitamin D analogues (calcipotriol), steroids (betamethasone dipropionate glycol 0.05% or clobetasol 17-propionate 0.05%), salicylic acid 5%, urea 5–10%, and dithranol, administered according to the recommendations [12]. Additionally, 155 from 306 (50.7%) patients received NB-UVB phototherapy (Cosmedico Medizintechnik GmbH, Germany, or Series 3 Daavlin Philips AG) 3 times a week throughout the study period, based on skin phototype according to the manufacturer's recommendations. Patients medicated with systemic immunosuppressive regimens and PUVA (psoralen + ultraviolet A) treatment were excluded from the study. Patients were evaluated at baseline, and then after 8 weeks of therapy. The percent reduction of PASI score was evaluated as a variable in the analysis of the treatment outcome. Mean PASI value (± SD) at the start of therapy was 11.52 ±4.52, range: 3.2–18.0, and after 8 weeks of therapy: 3.78 ±4.05, range: 0.0–17.2 (mean PASI reduction: 68.64 ±29.56%, 7.74 ±4.53 points, range: 2.52–100.0%, 0.2–19.6 points).

Genotyping

Genomic DNA was extracted from buccal swab samples using Genomic Micro AX SWAB Gravity kit (A&A Biotechnology, Gdynia, Poland) and from peripheral blood samples using a GeneMATRIX Quick Blood DNA Purification Kit (EURx, Poland) following the manufacturer's protocol. DNA was subsequently standardized to equal concentrations of 20 ng/µl, based on spectrophotometric absorbance measurement (260/280 nm). Genotyping for

Table 1. Clinical data of the study subjects.

Demographic data	Value	Range
Psoriasis patients, n = 507:	Mean ± SD	
Age [years]	45.1 ±15.6	13–82
BMI [kg/m^2]	26.3 ±4.6	16.9–40.3
Age at disease onset [years]	30.9 ±13.9	5–77
Disease duration [years]	14.2 ±11.4	0.5–57
PASI at therapy onset	11.9 ±5.3	3.2–18
	n	%
Female sex	240	47.3%
Type I psoriasis	361	71.2%
Type II psoriasis	146	28.8%
Control group, n = 396:	Mean ± SD	Range
Age [years]	42.6 ±16.9	17–97
	n	%
Female sex	210	52.9%

Type I psoriasis: disease onset at age < 40 years; Type II psoriasis: disease onset at age ≥ 40 years.

Table 2. Single nucleotide polymorphisms evaluated in the current study and TaqMan assays used for genotyping

SNP	Gene name	Gene symbol	SNP location	Nucleotide change	TaqMan Assay ID
rs7552167	Interferon l receptor 1	*IFNLR1*	1p36.11, intergenic	A>G	C__30618571_20
rs12188300	Interleukin 12B	*IL12B*	5q33.3, intergenic	A>T	C__31985572_10
rs2066819	Signal transducer and activator of transcription 2	*STAT2*	12q13.3, intronic	C>T	C__12055241_10
rs8016947	NF-κB inhibitor α	*NFKBIA*	14q13.2, intronic	T>G	C_____28885_20
rs28998802	Nitric oxide synthase 2	*NOS2*	17q11.2, intronic	G>A	C__60591573_10
rs702873	Proto-oncogene, NF-κB Subunit	*REL*	2p16.1, intronic	C>T	C___3219727_10
rs33980500	TRAF3 interacting protein 2	*TRAF3IP2*	6q21, missense variant	C>T	C___2473124_10
rs2233278	TNF induced protein 3, interacting protein 1	*TNIP1*	5q33.1, 5'UTR	G>C	C__15945494_10
rs582757	TNF-α induced protein 3	*TNFAIP3*	6q23.3, intronic	C>T	C___8300291_10

the following single nucleotide polymorphisms (SNPs): *IFNLR1* rs7552167, *IL12B* rs12188300, *STAT2* rs2066819, *NFKBIA* rs8016947, *NOS2* rs28998802, *REL* rs702873, *TRAF3IP2* rs33980500, *TNIP1* rs2233278 and *TNFAIP3* rs582757 was performed using a pre-validated allelic discrimination TaqMan real-time PCR assay (Life Technologies, USA), and TaqMan GTXpress Master Mix (Life Technologies, USA). Fluorescence data were captured using the ViiA7 Real-Time PCR System (Applied Biosystems, USA) after 40 reaction cycles. Specific genotypes were assigned to individual samples after analysis with TaqMan Genotyper software (Thermo Fisher Scientific, USA). The information about SNP location and TaqMan assay used is given in Table 2.

Statistical analysis

The χ^2 and Fisher's exact test was used to compare qualitative variables between genotype groups, alleles as well as clinical data in genotype groups, and accordance of genotypes with Hardy-Weinberg equilibrium was calculated. Analysis of PASI reduction was performed by means of the Kruskal-Wallis test. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using Statistica ver. 13.1 software (TIBCO Software Inc., Palo Alto, CA, USA).

Results and Discussion

Distribution of genotypes was in accordance with Hardy-Weinberg equilibrium for all studied SNPs, both in psoriatic patients and healthy controls ($p > 0.05$). Among the analysed variants, *IL12B* rs12188300, *TRAF3IP2* rs33980500 and *TNFAIP3* rs582757 minor alleles have been significantly more frequent among psoriatic patients ($p < 0.05$) (Table 3). When analysing genotypes we observed an association of the studied *IL12B*, *TRAF3IP2*, *TNIP1* polymorphisms in a dominant model (significantly higher frequency of carriers of at least one risk allele among psoriatic patients), while for *NOS2* the odds for disease were significantly increased only in homozygotes with two minor alleles (recessive model). A marginally significant difference was

Table 3. Association analysis of *IFNLR1*, *IL12B*, *STAT2*, *NFKBIA*, *NOS2*, *REL*, *TRAF3IP2*, *TNIP1*, *TNFAIP3* allele frequency and genotype distribution in psoriasis patients ($n = 507$) and healthy controls ($n = 396$)

Gene	SNP id	MAF psoriasis	MAF controls	*P*-value*	Genotypes – dominant model**		Genotypes – recessive model***	
					OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
IFNLR1	rs7552167:A>G	0.133	0.152	0.276	0.86 (0.64–1.17)	0.357	1.41 (0.62–3.23)	0.524
IL12B	rs12188300:A>T	0.118	0.087	**0.036**	1.53 (1.09–2.16)	**0.014**	1.29 (0.41–4.01)	0.773
STAT2	rs2066819:C>T	0.096	0.090	0.684	1.07 (0.75–1.51)	0.790	0.80 (0.26–2.46)	0.784
NFKBIA	rs8016947:T>G	0.437	0.455	0.474	1.07 (0.81–1.42)	0.664	1.37 (0.99–1.89)	0.066
NOS2	rs28998802:G>A	0.150	0.122	0.099	1.19 (0.88–1.62)	0.281	0.31 (0.10–0.94)	**0.038**
REL	rs702873:C>T	0.376	0.400	0.307	0.81 (0.61–1.06)	0.126	0.99 (0.68–1.45)	1.000
TRAF3IP2	rs33980500:C>T	0.130	0.095	**0.021**	1.42 (1.02–1.97)	**0.040**	0.42 (0.14–1.32)	0.137
TNIP1	rs2233278:G>C	0.083	0.059	0.067	1.49 (1.01–2.19)	**0.045**	1.28 (0.08–20.55)	1.000
TNFAIP3	rs582757:C>T	0.304	0.260	**0.046**	1.22 (0.94–1.59)	0.141	0.60 (0.37–0.99)	0.053

*MAF – minor allele frequency; *p-value for comparison of allele frequency (Fisher exact Test), **homozygotes + heterozygotes for minor allele vs. major homozygotes; ***homozygotes for minor allele vs. major homozygotes + heterozygotes; bold font indicates significant association (p < 0.05).*

Table 4. Genotype distribution of the studied *IFNLR1, IL12B, STAT2, NFKBI, NOS2, REL, TRAF3IP2, TNIP1* and *TNFAIP3* SNPs in psoriasis and healthy controls

Genotype	Psoriasis *N* = 507		Healthy controls *N* = 396		*p*1	*p*2	*p*3	*p*4
	n	(%)	*n*	(%)				
IFNLR1 rs7552167:A>G:								
GG	383	(75.5)	288	(72.7)	0.473	0.399	0.357	0.524
AG	113	(22.3)	96	(24.3)				
AA	11	(2.2)	12	(3.0)				
IL12B rs12188300:A>T:								
AA	393	(77.5)	333	(84.1)	**0.009**	0.780	**0.014**	0.773
AT	108	(21.3)	57	(14.4)				
TT	6	(1.2)	6	(1.5)				
STAT2 rs2066819:C>T:								
CC	418	(82.4)	330	(83.3)	0.854	0.783	0.790	0.784
CT	81	(16.0)	61	(15.4)				
TT	8	(1.6)	5	(1.3)				
NFKBIA rs8016947:T>G:								
TT	91	(18.0)	91	(23.0)	0.247	0.341	0.066	0.664
TG	261	(51.5)	178	(45.0)				
GG	155	(30.5)	127	(32.0)				
NOS2 rs28998802:G>A:								
GG	371	(73.2)	303	(76.5)	0.577	0.037	0.281	**0.038**
GA	120	(23.7)	89	(22.5)				
AA	16	(3.1)	4	(1.0)				
REL rs702873:C>T:								
CC	197	(38.9)	134	(33.8)	0.108	0.595	0.126	1.000
CT	239	(47.1)	207	(52.3)				
TT	71	(14.0)	55	(13.9)				
TRAF3IP2 rs33980500:C>T:								
CC	387	(76.3)	325	(82.1)	0.089	0.129	**0.040**	0.137
CT	108	(21.3)	67	(16.9)				
TT	12	(2.4)	4	(1.0)				
TNIP1 rs2233278:G>C:								
GG	424	(83.6)	350	(88.4)	**0.043**	1.000	**0.045**	1.000
GC	82	(16.2)	45	(11.4)				
CC	1	(0.2)	1	(0.2)				
TNFAIP3 rs582757:C>T:								
TT	250	(49.3)	215	(54.3)	0.398	**0.034**	0.141	0.053
CT	206	(40.6)	156	(39.4)				
CC	51	(10.1)	25	(6.3)				

P-values calculated by means of Fisher exact test, p1 – heterozygotes vs. major homozygotes, p2 – minor homozygotes vs. major homozygotes, p3 – heterozygotes + minor homozygotes vs. major homozygotes (dominant model), p4 – minor homozygotes vs. major homozygotes + heterozygotes (recessive model).

also observed in case of *TRAF3IP2* in the recessive model. Polymorphic variants of *IFNLR1*, *STAT2*, *NFKBIA* and *REL* genes did not show any association with psoriasis in the analysed population. More detailed results of genotype analysis is given in Table 4. The variants investigated in the current study were initially identified as psoriasis risk

Table 5. Analysis of response to the treatment (PASI reduction in %) of patients stratified by genotype data (n = 306)

Locus	Genotype			*P*-value
IFNLR1 rs7552167	GG (n = 235)	AG (n = 64)	AA (n = 7)	
	68.0 ±29.7	70.9 ±30.0	67.7 ±23.4	0.822
IL12B rs12188300	AA (n = 242)	AT (n = 62)	TT (n = 2)	
	67.8 ±29.7	72.7 ±28.6	49.8 ±44.8	0.360
STAT2 rs2066819	CC (n = 249)	CT (n = 51)	TT (n = 6)	
	69.2 ±29.7	67.9 ±28.2	53.4 ±33.9	0.474
NFKBIA rs8016947	GG (n = 83)	TG (n = 168)	TT (n = 55)	
	70.8 ±27.1	67.7 ±30.3	68.3 ±31.2	0.718
NOS2 rs28998802	GG (n = 233)	GA (n = 66)	AA (n = 7)	
	67.6 ±30.4	71.9 ±26.9	72.6 ±26.6	0.723
REL rs702873	CC (n = 117)	CT (n = 141)	TT (n = 48)	
	72.4 ±28.5	67.0 ±30.3	64.5 ±29.6	0.312
TRAF3IP2 rs33980500	CC (n = 230)	CT (n = 68)	TT (n = 8)	
	68.8 ±30.3	68.4 ±27.1	66.3 ±30.6	0.830
TNIP1 rs2233278	GG (n = 262)	CG (n = 44)	CC (n = 0)	
	68.6 ±29.5	69.0 ±30.1	–	0.957
TNFAIP3 rs582757	TT (n = 148)	CT (n = 123)	CC (n = 35)	
	67.7 ±29.4	69.6 ±29.8	69.4 ±29.9	0.755

PASI reduction is given in percentage with standard deviation; p-values calculated by means of the Kruskal-Wallis test.

modifiers in GWAS studies [13–19] and the associations were further investigated in many confirmation studies, where both positive and negative results were reported. Kisiel *et al.* confirmed association of *IFNLR1* rs7552167 (p = 0.017), *NFKBIA* rs8016947 ($p = 7.5 \times 10^{-3}$) and *REL* rs702873 ($p = 2.5 \times 10^{-4}$) in the Polish population [20]. However, we have not observed any difference in the frequency of genotypes or alleles between psoriatic patients and controls (p = 0.276, p = 0.474 and p = 0.307, respectively), it might be due to a less numerous control group in our study or due to exclusion of patients with psoriatic arthritis from the patient group. In the German population *IL12B* rs12188300 and *TRAF3IP2* rs33980500 SNPs were strongly associated with psoriasis vulgaris (p = 0.027, $p = 1.5 \times 10^{-9}$), as confirmed in the present study on the Polish population (p = 0.036, p = 0.021) [21]. Large scale meta-analysis of the psoriasis-associated *TNFAIP3* SNPs pointed rs582757 as top Ps variant ($p = 6.07 \times 10^{-12}$, OR = 1.23) [22]. Our results confirm the *TNFAIP3* rs582757 association with psoriasis vulgaris (p = 0.046). *STAT2* rs2066819, one of the novel Ps susceptibility SNP loci did not reach statistical significance in our study, possibly due to a limited sample size [4, 19]. Similar to our study, replicated GWAS analysis in the Japanese population showed *TNIP1* rs2233278 association with psoriasis ($p = 7.0 \times 10^{-6}$). TNFAIP3-interacting protein 1, *TNIP1* gene coded protein, is an inflammation regulator in autoimmune diseases, involved in internal signalling pathways, like regulation of an NF-κB pathway and microRNA [23, 24].

The vast majority of psoriasis risk SNP variants are situated near the genes encoding molecules involved in the innate immune system [4]. As many of them do not affect directly the protein sequence or function (intronic, intragenic and synonymous SNPs), it is probable that interethnic differences can affect the outcome of association studies. Hence, only extensive meta-analyses taking into account the results of many heterogeneous studies performed in different ethnic groups could finally verify the impact of individual SNPs on the psoriasis risk. For that reason the results of that study not only provide data for psoriasis genetics in the Polish population, but also could be of some value for future meta-analyses.

Subsequently, the response to therapy was analysed in relation to the patients' genotype. However, no significant impact on efficacy of topical therapy combined with NB-UVB was noted in case of any investigated SNPs (Table 5). Additional analysis was performed for possible association of genetic factors with the age of disease onset, but also in this case the results were negative (data not shown). Contrary to the current negative results in relation to topical therapy, some evidence was provided that the genetic polymorphism may be responsible for different patient response to treatment with biologic drugs that are targeted to inflammatory cytokines involved in developing psoriasis [25]. Among the genes

investigated in the current study, *IL12B, IFNLR1, TNFAIP3* polymorphisms were reported to affect treatment with anti-TNF (adalimumab, etanercept) or anti-IL-12/IL-23 (ustekinumab) agents. However, biologic therapy is much more specific, and the polymorphism within genes involved in pathogenesis can directly affect potency of therapeutic antibodies and their interaction with targets. On the contrary, topical treatment is generally less specific, and the relation between drugs and genes involved in psoriasis pathogenesis is not so clear. Possibly, other genetic variants may play a role, like it was described earlier in case of vitamin D receptor (*VDR)* and calcipotriol therapy [26].

Conclusions

The results of the current study confirmed an association of *IL12B, TNFAIP3, TRAF3IP2*, *TNIP1* and *NOS2* variants with psoriasis vulgaris in the Polish population. However, the analysed SNPs do not seem to have any impact on efficacy of topical/NB-UVB therapy, and are not potentially useful in personalized therapy.

Conflict of interest

The authors declare no conflict of interest.

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