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ANALYSIS OF ASSOCIATION BETWEEN CYTOKINE GENE POLYMORPHISMS AND PSORIATIC DISEASE IN RUSSIANS OF EAST SIBERIA

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Abstract

Psoriasis (PS) and psoriatic arthritis (PsA) are subtypes of psoriatic disease (PD), a chronic inflammatory disorder with predominantly cutaneous manifestations. PsA is developed in approximately one third of patients with PS. These two phenotypes are immune-mediated

diseases with different heredity that might in part be explained by different genetic factors. We carried out an analysis of association between haplotypes of cytokine genes (*TNFA*, *IL4* and *IL10*) and PD in Russians from East Siberian region of Russia. The haplotypes were not found to be associated with either PS or PsA. However, meta-analyses with published data suggested associations between PS and *IL4* rs2243250 and *TNFA* rs1800629 polymorphisms, while PsA was found to be associated with *IL4* rs2243250 only. The results provide further insight into understanding of genetic factors predisposing to PD.

Abbreviations: PS, Psoriasis; PsA, Psoriatic arthritis, PD, Psoriatic disease; TNFα, Tumor necrosis factor-alpha; SNPs, Single nucleotide polymorphisms; DNA, Desoxyribonucleic acid; RFLP, Restriction fragment lengths polymorphism; PASI, Psoriasis Area and Severity Index.

Keywords: Psoriatic disease; Psoriasis; Psoriatic arthritis; Haplotype; Cytokines

1. Introduction

Psoriasis (PS) is a common and stigmatizing chronic immune-mediated inflammatory skin disease characterized by the altered proliferation and differentiation of keratinocytes and affecting about 2% of the population worldwide with a high burden of disability and increased mortality (Boehncke and Schön, 2015; Bowcock and Krueger, 2005; Nestle et al., 2009). The main characteristics of psoriasis are excessive proliferation of keratinocytes and being easy to relapse; however, it was reported that the disease can affect many tissues in the muscles, joints, digestive tract and even eyes. Therefore, it is agreed that PS is one of the forms of psoriatic disease (PD) (Ritchlin, 2007; Meng et al., 2018). Psoriasis possesses a major social and economic burden on society as the existent therapies only relieve symptoms and cannot cure disease. Therefore, a better understanding of the immunopathogenesis of PS is essential for the development of improved therapies.

Approximately one third of patients with PS develop psoriatic arthritis (PsA), a chronic inflammatory heterogeneous disease that can affect various distinct anatomical sites including peripheral and axial joints, entheses, skin and nails. Both PS and PsA are T-cell-mediated autoimmune diseases united under the term of psoriatic disease (Baliwag et al., 2015; Loft et al., 2018; Sakkas and Bogdanos, 2017). Their pathogenesis is largely driven by the dysregulation of pro-inflammatory and anti-inflammatory cytokines production.

Psoriatic disease has a strong hereditary character and has a complex genetic background. Genome-wide association studies have identified polymorphisms within or near a number of genes encoding cytokines, cytokine receptors or elements of their signal transduction pathways, further implicating these cytokines in the pathogenesis. A considerable number of inflammatory cytokines have been shown to be elevated in lesioned psoriatic skin, and the serum concentrations of a subset of these also correlate with PD severity (Baliwag et al., 2015). According to the Phenopedia data (https://phgkb.cdc.gov/PHGKB/startPagePhenoPedia.action), the spectrum of genes involved in the pathogenesis of PS and PsA is diverse and distinguishes them from each other. Moreover, because of the complexity and heterogeneity of disease, pathogenetic links between PS and PsA are unclear (Ruiz et al., 2012).

The identification of cytokine gene polymorphisms and the study of their involvement in the pathogenesis of PD have been carried out in different populations with contradictory results, so as there is no completed picture of the association of the polymorphisms with PS and PsA. By far, no such studies have been carried out in Russian populations. The greatest interest for such studies is the polymorphisms of the *TNFA* gene, since TNF-α is the main mediator of inflammation in PD, which is confirmed not only by its participation in the cytokine regulation of cells interactions, but also by the success of anti-TNFα therapy (Mease, 2004). Despite the fact of undoubtful importance of cytokines produced by Th2 cells in the pathogenesis of PS, studies of the effect of polymorphism of their genes on predisposition to PS and PsA are limited. Until now, the role of the *IL4* and *IL10* genes in the development of PS and PsA is unclear.

The aim of current study was to analyse associations between PD and haplotypes of the *TNFA*, *IL4*, and *IL10* cytokine genes in ethnic Russians from East Siberian region of Russia.

2. Material and Methods

2.1. Study subjects

The study was approved by the Ethics Committee of the Scientific Research Institute of Medical Problems of the North (#12 of 10.12.2013). Signed informed consent was obtained from all participants.

Blood samples from 279 ethnic Russians (West Slavs, Caucasians) were obtained to study the haplotypes of single nucleotide polymorphisms (SNPs) of *TNFA*, *IL4*, and *IL10* genes. The sample comprised 77 patients with psoriasis (mean age 32.0±1.92); 99 patients with psoriatic arthritis (mean age 48.0±1.79); and 103 healthy control individuals (mean age

29.0±0.92) from the city of Krasnoyarsk, Russia. All patients were examined by specialists dermatologists in the progressing stage of PS, the degree of severity of the skin process was assessed by the PASI (Psoriasis Area and Severity Index). The diagnosis of PsA was assigned according to the Classification for Psoriatic Arthritis (CASPAR) criteria (Taylor et al., 2006). According to the demographic characteristics, PsA was more often diagnosed in women, and psoriasis in men. In the PS group, there were 54 men (70.1%) and 23 women (29.9%), in PsA group there were 39 men (39.4%) and 60 women (60.6%). The mean age of psoriatic skin rash in PS was 22±1.24 years and in PsA it was 25±1.34 years. Mean age of psoriatic arthritis onset was 36±1,39 years. Patients with PsA had a higher rate of severe psoriasis with a Psoriasis Area and Severity Index (PASI) than those PS patients: 17.9±0.95 vs 13.6±0.83 ($p = 0.0007$). Psoriasis duration in PS was 8±1.15 years and 17±1.38 years in PsA.

2.2. DNA isolation and genotyping

DNA was extracted from the blood using DIAtom™ DNA Prep kits ("IzoGen", Russia). Genotyping was carried out using restriction fragment lengths polymorphism (RFLP) approach with visualization of the results in agarose gel stained with ethidium bromide. Six polymorphisms were studied: *TNFA* (rs1800629, rs1800630), *IL4* (rs2070874, rs2243250) and *IL10* (rs1800872, rs1800896) (Table 1). The accuracy of the genotyping has been assessed by repeated genotyping of a randomly selected 10% of the sample. In all cases, the genotypes were concordant upon repeated analysis.

2.3. Statistical analysis

The compliance of the genotype frequencies with Hardy-Weinberg equilibrium was tested using Fisher's exact tests. Linkage disequilibrium (LD) between SNPs was calculated using package *genetics* for R programming environment. The association between haplotypes and psoriasis were analyzed using the *haplo.stats* package for R. Haplotype score test was applied with 1000 permutations to calculate p-values and logistic regression to obtain odds ratios (OR) and respective 95% confidence intervals. Meta-analysis with published data was carried out using Mantel-Haenszel approach as implemented in *meta* package for R.

3. Results and Discussion

The prevalence of alleles in the studied control sample was in keeping with other world's European populations (according www.ensemble.org data; Table 2). No deviation from HWE was observed for *TNFA* and *IL10* in the control group; however, there was the deviation from

HWE for *IL4* SNPs ($p<0.05$). The studied SNPs in *IL4*, *IL10*, and *TNF* were in high LD according to D' statistics (Table 3).

We analyzed associations between PD (PS and PsA) and genotypes and haplotypes of cytokine genes *TNFA*, *IL4*, *IL10* genes. No statistically significant associations were found (Supplementary Tables 1A-C). Due to the small number of patients and controls in the current study, the results are preliminary. The estimated power to find associations with three haplotypes with the given sample size was 41%. Therefore, we set out to carry out meta-analysis of the data from previous studies for individual SNPs for *TNFA* rs1800629, *IL4* rs2243250 and *IL10* rs1800896 SNPs.

For *IL4*, two study have been published so far to the best of our knowledge: one in a Chinese population (Indhumathi et al., 2017) and one in South Indian Tamils (Li et al., 2014). Meta-analysis with fixed-effects showed a significant association between PS and *IL4* rs2243250 (OR = 1.27 [1.07-1.50] and OR = 1.23 [1.05-1.46]; Supplementary Figures 1, 2); however, in case of PsA, a remarkable heterogeneity between the studies was seen, with the current study effects direction being opposite to other two studies. In both cases, random effects model was insignificant, though very close to such in case of PS (C vs T allele OR = 1.23 [0.99-1.53]).

For *TNFA*, several meta-analyses have been published so far; therefore, we have chosen one that provided all necessary tabulated data (Jia et al., 2013) and updated it with the results of our study as well as with the results of tree other recent studies (Karam et al., 2014; Cardili et al., 2015; Popa et al., 2011). For PS, the data were stratified by Caucasian and Asian cohorts, while for PsA, only Caucasian cohorts were included because only one small Asian study data were provided. Meta-analysis provided evidences for association between PS and *TNFA* rs1800629 using both fixed and random effects models: G vs A allele OR = 1.43 [1.26-1.62] and 1.42 [1.22-1.66], respectively (Supplementary Figure 3). At the same time, no associations between PsA and *TNFA* rs1800629 was observed (Supplementary Figure 4).

For *IL10* rs1800896 we used the studies reported in a meta-analysis by Lee et al. (2012) as well as from our study and another recent study (Karam et al., 2014). For PS we used all the studies, while for PsA we only used another Caucasian cohort due to the lack of Asian cohorts (only one was available). Neither PS nor PsA were found to be associated with the *IL10* polymorphism (Supplementary Figures 5, 6).

The results of our study provide evidence about positive association between promoter polymorphisms of the *TNFA* gene and PS, but not PsA. It is well known that TNF-α plays a

crucial role in autoimmune and infectious diseases as a proinflammatory cytokine; however, the mechanism of altered PS and PsA risk owing to SNPs in the *TNFA* gene promoter region remains unknown. A possible explanation is abnormal expression of the TNF-α gene mediated by variations in the TNF-α promoter (Zhu et al., 2013). Expression of the TNF-α has been shown to be increased in psoriatic lesions (Baran et al., 2006). *TNFA* gene is located on chromosome 6p21.231 in the polymorphic region of MHC III. SNPs in promoter of the *TNFA* gene at positions -238 and -308 have been associated with psoriasis vulgaris and PsA, though due to strong LD at chromosome 6p21, the region known to harbor risk factors for psoriasis susceptibility (PSORS1), the interpretation of these findings is difficult (Reich et al., 2007). Some studies have shown association of *TNFA* gene polymorphism and the development of PS (Karam et al., 2014), while other studies have reported that G-308A (rs1800629) polymorphism decreases the risk of psoriasis (Li et al., 2007) and yet other studies reported no significant association between G-308A and PS (Baran et al., 2006; Kim et al., 2003; Tsunemi et al., 2003). Similarly, there are conflicting results about association between another polymorphism of *TNFA* gene (rs361525) and PS or PsA (Loft et al., 2018). The curative effect of TNF-α blockers in patients with PS and PsA indicates that, to a certain degree, they share common immunopathogenesis (Mease, 2004). Therefore, both PS and PsA may have a common risk of onset with regard to TNF-α promoter SNPs. The results of a meta-analysis confirmed this hypothesis via showing that TNFα -238A/G and TNFα -308A/G polymorphisms are associated with susceptibility to both PS and PsA. In Brazilian population, the TNFα −308A/G polymorphism was found to be associated with generalized forms of psoriasis (erythrodermic and generalized pustular psoriasis) (Cardili et al., 2016). Furthermore, this meta-analysis shows that the TNFα -857T/C variant increases the risk of PsA significantly, whereas TNFα -857T/C and TNFα -238A/G polymorphisms exhibit risk effects in the pooled analysis of PS and PsA. In contrast, the TNFα -308A/G polymorphism has a protective effect for PS and PsA. The -857C/T polymorphism was associated with susceptibility to PsA in Romanian population individually (p = 0.03, OR 1.65, 95% CI 1.05–2.57) and in haplotypes with the −238G/A and −308G/A SNPs (Popa et al., 2011). No significant association between TNFα-308A/G, -1031C/T, or -863A/C polymorphism and to PsA alone was revealed (Zhu et al., 2013, Murdaca et al., 2014).

The results of our meta-analysis provide further evidence about positive association between promoter polymorphisms of the *IL4* gene and PD. IL-4 plays an important role in the pathogenesis of PS and PsA, via suppressing Th1 and Th17 cells and promoting Th2, thus preventing the maintenance of IL-17–producing Th17 cells by abrogating the expression and production of the Th17 cell-associated cytokine in psoriatic epidermal cells (Ghoreschi et al.,

2003; Hahn and Ghoreschi, 2017). It was shown that IL-4 treatment improves the course of PS (Jain et al., 2009; Hahn and Ghoreschi, 2017, Lotti and Hercogova, 2015). It was supposed that the IL4/IL13 gene locus is associated with PS [Nair, 2009]. The gene encoding the IL-4 product is located on 5q31.1 chromosome; it exhibits strong association with the development of PS and its expression is almost absent in psoriatic skin (Bidwell et al., 1999, Hahn and Ghoreschi, 2017). The *IL4* gene is one of susceptibility genes to PS and PsA, identified in subjects of European ethnicity, but not in subjects of Chinese ethnicity (Chandran, 2013). The C-590T (rs2243250) polymorphism of the IL4 gene has the greatest functional significance for PS and PsA due to its effect on the levels of IL-4 production with the rs2243250*T associated with hyperproduction of IL-4 (Chang et al., 2007). The results of the study in South Indian Tamils suggest that IL4 (rs2243250) polymorphism is protective against psoriasis and the heterozygous C/T genotype demonstrated significant high IL-4 levels in blood (Indhumathi et al., 2017). In contrast, the rs2243250*C allele is associated with the increased risk of PS in another studies (Munir et al., 2015; Kim et al., 2007).

The results of our study of *IL10* gene provide no evidence about association between its promoter polymorphisms and PS or PsA both in Russians and in other world populations. IL-10 is a pluripotent anti-inflammatory and immunosuppressive cytokine that plays an important role in the regulation of the immune response, including the PS and PsA. Deficiency of IL-10 in PS and PsA promotes the launch of autoregulative process of polarization of Th0 cells towards the Th2 lymphocytes, which triggers the autoimmune mechanisms of formation of inflammatory processes in skin and joints in PS and PsA thereby affecting the phenotype of the disease (Karam et al., 2014, Al-Balbeesi et al., 2015). It was found that prolonged use of cytokine therapy of IL-10 in PS reduces the frequency of exacerbations of the disease, but no similar effect was observed with PsA (Lotti and Hercogova, 2015). The *IL10* gene is located on 1q31-32 chromosome (Bidwell et al., 1999, Bowcock and Krueger, 2005). Genetic variants in promotor region of *IL10* gene are known which affect the level of IL-10 in serum (rs1800890, rs1800896, rs1800871, rs1800872) and have the greatest functional role in PS and PsA (Karam et al., 2014; Trifunović et al., 2015). The results of the meta-analysis of these polymorphisms showed the association of G-1082A polymorphism with the susceptibility to PS in Asians, but not in Caucasians, suggesting ethnic-specific effect (Lee et al., 2012). This corroborates with our findings in Russians of East Siberia.

4. Conclusion

Genetic polymorphism of the cytokine network affects the level of cytokine concentration in the serum, thus mediating the development of psoriatic disease. In the current study, we did not establish association between the haplotypes of promoter polymorphisms of *TNFA*, *IL4* and *IL10* genes in Russians of East Siberia. However, meta-analysis using our new data on the Russians and other world populations strengthen the argument about associations between PD and the polymorphisms of *TNFA* and *IL4* genes. Thus, the results of the study add value to the accumulating data about the impact of cytokine genes polymorphism on the development of psoriatic disease.

Conflict of interest

The authors declare that they have no conflicts of interest, financial or otherwise associated with the manuscript.

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Table 1 – Oligonucleotide primers, annealing temperature, restriction endonucleases and products of endonuclease hydrolysis for the studied polymorphisms of the cytokine genes

Gene	Polymorphism (SNP)	Sequence of primers	Annealing temperature, °C	Restriction enzyme	Products of restriction enzyme hydrolisis (bp), allelic variants
TNFA	G-308A rs1800629	5'-aggcaataggttttgagggccat-3' 5'-acactccccatcctcccggct-3'	58	Bsp19 I	G: 97, 20 A: 117
TNFA	C-863A *rs*1800630	5'-ggctctgaggaatgggttac-3' 5'-ctacatggccctgtcttcgttacg-3'	60	BstBA I	C: 125 A: 102, 23
IL4	C-33T rs2070874	5'- caagttactgacaatctggtgt-3' 5'- cggcacatgctagcaggaa-3'	60	BstMA I	C: 178, 45 T: 140,45, 38
IL4	C-590T rs2243250	5'-cacctaaacttgggagaacatggt-3' 5'-gttgtaatgcagtcctcctg-3'	60	Bme 18I	C: 192, 60 T: 252
IL10	C-592A rs1800872	5'-atccaagacaacactactaa-3' 5'-taaatatcctcaaagttcc-3'	54	Rsa I	C: 306, 232, 42 A: 240, 232, 66, 42
IL10	G-1082A *rs*1800896	5'-aaggcaacactactaaggcttcctt-3' 5'-taaatatcctcaaagttcc-3'	53	BstEN I	G: 310, 280 A: 310, 252, 28

Table 2 – Frequencies of allelic polymorphisms of cytokine genes (%)

Genotype	PS (n=77)	PsA (n=99)	Control group (n=103)
		TNFA (rs1800629)	
GG	87.0	80.8	85.4
GA	13.0	18.2	11.7
AA	0	1.0	2.9
		TNFA (rs1800630)	
CC	84.4	77.8	76.7
CA	15.6	19.2	23.3
AA	0	3.0	0
		IL4(rs2070874)	
CC	62.3	63.6	66.0
CT	33.8	27.3	25.3
TT	3.9	9.1	8.7
		IL4 (rs2243250)	
CC	55.8	67.7	67.0
CT	39.0	24.2	24.3
TT	5.2	8.1	8.7
		IL10 (rs1800872)	
CC	58.4	57.6	57.3
CA	36.4	39.4	34.0
AA	5.2	3.0	8.7
		IL10 (rs1800896)	
AA	29.8	26.3	28.2
GA	48.1	51.5	57.3
GG	22.1	22.2	14.5

Table 3 – Linkage disequilibrium between the studies SNPs

Gene	SNP1	SNP2	Lewontin's D'	r^2	χ^2	p-value
IL4	rs2070874	rs2243250	0.893	0.797	444.8375	<0.0001
IL10	rs1800872	rs1800896	0.950	0.238	132.7267	<0.0001
TNF	rs1800629	rs1800630	0.994	0.011	6.218431	0.0126

Note: According to D' there is strong LD between all the studies SNP (also confirmed by significant p-values), but r2 gives low values. Such the situation with r2 may happen when minor allele frequencies (MAF) are rather low or when there is a remarkable discrepancy in MAFs for the SNPs (the case in our study).

Psoriasis (PS) and psoriatic arthritis (PsA) are immune-mediated diseases with different heredity that might in part be explained by different genetic factors.

We carried out an analysis of association between haplotypes of cytokine genes (*TNFA*, *IL4* and *IL10*) and PD in Russians from East Siberian region of Russia.

The haplotypes were not found to be associated with either PS or PsA.

Meta-analyses with published data suggested associations between PS and *IL4* rs2243250 and *TNFA* rs1800629 polymorphisms, while PsA was found to be associated with *IL4* rs2243250 only.