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Polymorphisms of the *IL23R* Gene Are Associated with Psoriasis but not with Immunoglobulin A Nephropathy in a Hungarian Population

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Abstract—Recently, associations were found between autoimmune diseases and variants of interleukin-23 receptor (*IL23R*) gene; here, we analyzed the association of nine *IL23R* polymorphisms with psoriasis and with immunoglobulin A nephropathy (IgAN). Groups of patients with psoriasis, IgAN, and controls were genotyped using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) methods. We observed a significant increase in the carriage of the minor allele of rs11805303 in psoriasis patients compared to controls. Similarly, for rs2201841 prevalence of the CC genotype and for rs10889677, the AA genotype showed a more than two- and threefold increase, respectively in patients compared to controls. There was no difference in the distribution of *IL23R* variants between controls and IgAN patients. We confirmed the association of *IL23R* with psoriasis in a Hungarian population and demonstrated the effect of the rs11805303 SNP, which was tested so far only for other autoimmune diseases. We could not detect any association between the *IL23R* variants and IgAN.

KEY WORDS: IL23R; psoriasis; IgAN; Hungarian; susceptibility.

INTRODUCTION

Psoriasis is a chronic inflammatory disease that affects skin and joints. It is characterized by red, scaly skin patches that appear mostly on the elbows, knees, and scalp but can be present on any body surface and may be associated with severe arthritis [1]. Prevalence rates vary from 0–5% to 4–6% between countries and races, affecting 2–3% of whites of European descent [2]. The lesions are caused by abnormal keratinocyte proliferation driven by the activation of T lymphocytes, which leads to the release of cytokines [3]. The usual age of onset of psoriasis is between 15 and 30 years, although it can present at any age [4]. Immunoglobulin A nephropathy (IgAN) is the most common form of glomerulonephritis, a principal cause of end-stage renal disease worldwide, affecting up to 1.3% of the population [5]. Kidneys of patients with IgA nephropathy show deposits of IgA-containing immune complexes with proliferation of the glomerular mesangium [6]. Typical clinical features include onset before age 40 with hematuria and proteinuria, and episodes of gross hematuria following mucosal infections are common; 10–20% of patients progress to end-stage renal disease [7].

Interleukin-23 (IL-23), a heterodimeric cytokine, shows similar functions to IL-12 in promoting cellular immunity and enhancing lymphocyte proliferation; however, unlike IL-12, IL-23 develops CD^+ T cells into IL-17 producing Th17 cells instead of Th1 cells [8]. In chronic inflammation, the antigen-stimulated macrophages and dendritic cells produce IL-23, which promotes the development of Th17 cells, which enhances T cell priming and triggers potent inflammatory responses by

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inducing the production of several inflammatory mediators. IL-23 also stimulates dendritic cells and macrophages in an autocrin manner to generate other pro-inflammatory cytokines, like IL-1, IL-6, and TNF-α. Upon bacterial infection, IL-23 is rapidly produced by activated macrophages and dendritic cells at the infection site. Then it activates the local Th17 cells to produce IL-17, which induces granulocyte colony-stimulating factor production from stromal cells. The generated neutrophils can then migrate into tissues. Apoptotic neutrophils are then phagocytosed by the macrophages and dendritic cells which reduce IL-23 production [9]. This process is in agreement with the supposed evolutionary significance of the IL-23/IL-17 pathway. The rapid IL-17 response to microbial products and the consecutive recruitment of neutrophils to the site of acute infection concludes in an early immune response to pathogens. This assumes that IL-23 is important for survival following catastrophic injuries where an immediate protective response is required to prevent sepsis and thus gains time for the induction of a Th1-IFN-γ response [10]; however, the dysregulation of the IL-23/IL-17 axis can lead to severe autoimmune diseases like Crohn's disease, rheumatoid arthritis and multiple sclerosis [11–13].

Here, we report an analysis of nine single nucleotide polymorphisms (SNPs) of the interleukin-23 receptor gene (*IL23R*) which has recently been identified to associate with psoriasis [14].

MATERIALS AND METHODS

The DNA samples of the patients with psoriasis were collected at the Department of Dermatology and Allergology, University of Szeged. The IgAN patients are from the Second Department of Internal Medicine and Nephrology Center, University of Pécs; the samples of the control group were obtained from a central pool governed by our department as part of the Central National Biobank Network of Hungary. During the collection and use of DNA samples and clinical data, guidelines and regulations of the local ethics committee and the Helsinki Declaration in 1975 were followed; at the blood collection, the patients gave their informed consent for the future use of their anonymized DNA. In general, the samples originated from an average Hungarian Caucasian population, the minorities were thereby randomly included at their normal distribution rate. The IgAN population represented a total of 143 clinically well-characterized subjects (mean age, 49.9±13.4 years). The psoriasis group consisted of 214 patients (mean age, 47.5±12.3 years). A total of 189 Caucasian subjects served as controls (mean age, 45.3±11.0 years). They were healthy and had no clinical history for any systemic illness, including autoimmune diseases.

The molecular analyses were performed using DNA extracted from peripheral blood leukocytes with a routine salting out procedure. PCR-RFLP methods were applied to test the alleles of the *IL23R* gene (GeneBank NM_144701; GeneID 149233) using the forward and reverse primers as shown in Table 1. Ten microliters of PCR products were digested with 1 U of appropriate restriction endonuclease and electrophoresed through an ethidium bromide-stained 3% agarose gel. The primers were designed to create obligatory cleavage sites of the proper restriction enzymes in the amplicons to control the accuracy of the digestion. In one primer, we had to introduce mismatch bases to generate artificial cleavage sites (underlined in the sequence). The restriction endonucleases, PCR product lengths, and the restriction patterns are also shown in Table 1.

Differences between the patient and control groups were examined by χ^2 test. Associations of the studied diseases and the examined genetic variants were tested using binary logistic regression analysis using SPSS 11.5 for Windows. Odds ratios refer to the patient population *vs*. controls and are calculated with 95% confidence intervals (95% CI), indicated in brackets. Haploview 4.1 [15] was used to study linkage disequilibrium (LD) patterns. We required the minor allele frequency at each locus to be >0.05, with an R^2 value of <0.8 between pairs of loci, based on the default settings in Haploview. After applying these criteria, six of the nine SNPs were retained for haplotype analysis. Haplotype frequencies were estimated using PHASE version 2.1 [16, 17].

RESULTS

The prevalence rates of the examined *IL23R* variants are shown in Table 2. All the genotype and allele distributions were in Hardy–Weinberg equilibrium both in the patient and control groups. The linkage disequilibrium patterns for the combined case–control data are shown in Fig. 1.

The presence of the mutant T allele of rs11805303 was significantly increased in patients with psoriasis compared to the healthy controls (p=0.019). The logistic regression analysis revealed that carrying the minor

Table 1. Primer Sequences, PCR Product Lengths, Restriction Endonucleases, and Restriction Patterns for the Analyzed Genetic Variants

	Forward primer	Reverse primer	Product length (bp)	Restriction endonuclease	Fragments of frequent allele genotype (bp)	Fragments of heterozygous genotype (bp)	Fragments of rare allele genotype (bp)
rs1004819	ATCTGGTGGAAATATGTGAAACCTA	GCATTCTAGGACCGTTTTGG	270	*Taa*I	13+71+185	13+71+185+257	13+257
rs11805303	TCTTCCCAGTCTCCAGTGTG	CCGAACAATTTTTGTTTCCC	373	*Mnl*I	39+136+198	39+136+198+237	136+237
rs7517847	AAACATTGACATTCCCTTCATAC	GAAATGAGTCACCAATAATCCAC	530	*BseM*II	29+91+410	29+91+410+501	29+501
rs7530511	TACCCATCCATTTTAGGTTAAAGAA	GTCTTGAAGTCCTGACCTAAGGTAATC	614	*Hph*I	51+134+429	51+134+185+429	185+429
rs10489629	TATAAGCTTGTTTGATTATGATGTCAGCAA	CCACACCTCGCCAAGACTTT	348	*Ssp*I	31+119+198	31+119+150+198	150+198
rs2201841	GGCCTATGATTATGCTTTTTCCTG	GGCAAAAGGGAATTGAGAGG	420	*HpyF*3I	163+257	25+163+232+257	25+163+232
rs11209026	AGTCACTCTGTGGCCTAAAGTAAAG	AGATTTTTCTAGTAAACAACTGAAATGA	350	*Hpy*188I	35+65+250	35+65+250+287	65+287
rs10889677	ATCGTGAATGAGGAGTTGCC	TGTGCCTGTATGTGTGACCA	470	*Mnl*I	61+185+224	61+185+224+285	185+285
rs11209032	TTGTTACTGGAGTTAAACCTCTTGC	AGGAATAATTGCTGAGATGCAATG	265	*BseM*I	24+67+174	24+67+174+242	24+242

Table 2. Genotype Distribution and MAF of the Examined Interleukin-23 Receptor Variants in the Groups of Patients with Psoriasis and Healthy Controls

	Alleles		Psoriasis patients (n=214) Genotypes					Controls (n=189) Genotypes						
IL23R SNPs	1	2	11	12	22	12+22	MAF	11	12	22	12+22	MAF	P	OR (95% CI)
rs1004819	G	A	107 (50.0)	81 (37.9)	26 (12.1)	107 (50.0)	0.31	103 (54.5)	73 (38.6)	13 (6.88)	86 (45.5)	0.26	0.367 [a]	1.20 (0.81–1.77)
rs11805303	C	T	96 (44.9)	100 (46.7)	18 (8.41)	118 (55.1)*	0.32*	107 (56.6)	69 (36.5)	13 (6.88)	82 (43. 4)	0.25	0.019 [a]	1.60 (1.08–2.38)
rs7517847	T	G	70 (32.7)	111 (51.9)	33 (15.4)	144 (67.3)	0.41	55 (29.1)	101 (53.4)	33 (17.5)	134 (70.9)	0.44	0.435 [a]	0.84 (0.55–1.29)
rs7530511	C	T	167 (78.0)	46 (21.5)	1 (0.47)	47 (22.0)	0.11	140 (74.1)	45 (23.8)	4 (2.12)	49 (25.9)	0.14	0.352 [a]	0.80 (0.51–1.27)
rs10489629	A	G	55 (25.7)	119 (55.6)	40 (18.7)	159 (74.3)	0.47	54 (28.6)	96 (50.8)	39 (20.6)	135 (71.4)	0.46	0.518 [a]	1.16 (0.75–1.80)
rs2201841	T	C	102 (47.7)	87 (40.7)	25 (11.7)*	112 (52.3)	0.32*	101 (53.4)	79 (41.8)	9 (4.76)	88 (46.6)	0.26	0.016 [b]	2.64 (1.20–5.81)
rs11209026	G	A	201 (94.7)	13 (6.07)	0	13 (6.07)	0.03	167 (88.4)	22 (11.6)	0	22 (11.6)	0.06	0.051 [a]	0.49 (0.24–1.00)
rs10889677	C	A	101 (47.2)	88 (41.1)	25 (11.7)*	113 (52.8)	0.32*	99 (52.4)	83 (43.9)	7 (3.70)	90 (47.6)	0.26	0.005 [b]	3.44 (1.45–8.15)
rs11209032	G	A	94 (43.9)	91 (42.5)	29 (13.6)	120 (56.1)	0.35	90 (47.6)	84 (44.4)	15 (7.94)	99 (52.4)	0.30	0.458 [a]	1.16 (0.78–1.72)

P<0.05 was considered significant
MAF minor allele frequency
[a] P value for presence of minor allele (heterozygous plus homozygous subjects together in both groups)
[b] P value for homozygosity of minor allele
*P<0.05

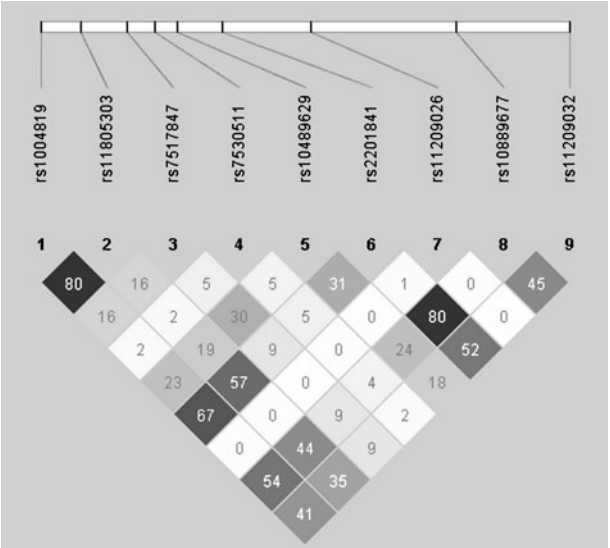

Fig. 1. Linkage disequilibrium patterns for combined case–control dataset. *Dark color* indicates high LD, *light color* indicates less LD. *Numbers* in the *squares* indicate correlation coefficient (R^2) value.

allele confers a 1.55-fold risk for the development of psoriasis (OR=1.60; 95% CI: 1.08–2.38). We performed a χ^2 test to investigate the dissimilarity between the allele frequencies of the patient and control group and found a statistically significant difference (p=0.037; OR=1.39; 95% CI: 1.02–1.89).

For the rs10889677 variant, the prevalence of the AA genotype showed a more than threefold increase in the psoriasis group compared to the controls (p=0.005; OR=3.44; 95% CI: 1.45–8.15). The homozygous form of the minor allele of rs2201841 was also significantly increased in psoriasis patients, conferring a 2.4-fold risk for the disease (p=0.016; OR=2.64; 95% CI: 1.20–5.81). The allele frequencies showed also significant differences between the psoriasis patients and controls (rs10889677, p=0.040; OR=1.38; 95% CI: 1.01–1.87 and rs2201841, p=0.048; OR=1.36; 95% CI: 1.01–1.86).

Association of *IL23R* haplotypes with psoriasis is shown in Table 3. SNP rs11209026 had a minor allele frequency less than 0.05 so it was not taken into account in the haplotype analysis. The R^2 values between rs11805303 and rs1004819, furthermore between rs10889677 and rs2201841, were 0.8 so rs1004819 and rs2201841 were removed from the haplotype analysis. The haplotypes CTCACG, CGCACG, and TTCACA were associated with protection against psoriasis in Hungarian patients (p=0.021, OR=0.54; p=0.001, OR=0.13; and p=0.042, OR=0.26; respectively). The TTCAAA haplotype was associated with the risk of psoriasis (p=0.003, OR=1.76).

Contrary to psoriasis, there was no difference in the distribution of any of the examined *IL23R* variants and haplotypes between the controls and the IgAN patients (data not shown).

DISCUSSION

The *IL23R* gene is located on chromosome 1p31 and the encoded protein forms a receptor for IL-23, together with the β1 subunit of IL-12 (IL12Rβ1) [18]. IL-23, a member of the IL-12 cytokine family, is a pro-inflammatory cytokine and is composed of the IL-23-specific p19 subunit and a p40 subunit, which is also part of IL-12 [19]. IL-23 plays a central role in the differentiation of native $CD4^+$ T cells into IL-17 producing T helper cells [20]. Polymorphisms of *IL23R* have been shown to associate with numerous different autoimmune diseases like inflammatory bowel disease, ankylosing spondylitis, rheumatoid arthritis, Graves' ophthalmopathy, and also psoriasis [21–25].

In our present study, we examined the possible effect of nine SNPs of the *IL23R* gene on two autoimmune diseases, namely psoriasis and immunoglobulin A nephropathy. We analyzed the rs11805303, rs10889677, rs1004819, rs2201841, rs11209032, rs7530511, rs7517847, rs10489629, and rs11209026 SNPs of which the latter has been previously shown to hold a protective effect for the development of psoriasis [14, 26]. The rs11805303 polymorphism has been identified by the Wellcome Trust Case Control Consortium as a susceptibility variant to Crohn's disease,

Table 3. *IL23R* Haplotypes Associated with Psoriasis

	CTCACG			CGCACG			TTCACA			TTCAAA		
	P value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI
psoriasis patients	0.021*	0.54	0.32–0.91	0.001*	0.13	0.04–0.43	0.042*	0.26	0.07–0.95	0.003*	1.76	1.22–2.54

P<0.05 was considered significant
*P<0.05

another complex autoimmune disease [27], while the others were first shown by Duerr *et al*. to either confer risk (rs10889677, rs1004819, rs2201841, rs11209032), be neutral (rs7530511), or have a protective effect (rs7517847, rs10489629, rs11209026) for the development of Crohn's disease [11].

Our findings are partly in contrast with previous studies, since we could not demonstrate a significant association between psoriasis and the rs11209026 Arg381Gln variant [14, 26, 28, 29], probably due to the fact that we were not able to find a homozygous mutant form of the rs11209026 polymorphism in any of our examined groups. Nevertheless, the heterozygous phenotype showed a noticeable increase among the patients compared to the control group, proposing a protective effect; however, it did not reach the level of significance. A larger study population would be required to precisely examine the precise effect of polymorphisms with extreme genotype distributions. The rs2201841 variant was also associated with psoriasis in a recent genome-wide scan performed on a study population containing almost 6,500 patients and similar number of controls, all North Americans of European ancestry [30].

In the absence of functional studies regarding these variants, their impact on the functionality and expression of *IL23R* is not clear, but it is obvious that the SNPs represent an important factor in the development of psoriasis; however, several assumptions can be made: SNPs like rs10889677 located in the 3′-UTR can probably cause over expression of the receptor (*e.g.*, by increasing mRNA stability) driving differentiation of T cells towards the Th17 direction resulting in an increased release of other inflammatory cytokines. The rs2201841 is an intronic variant and is in significant linkage disequilibrium with rs10889677 (correlation coefficient R^2=0.80 in the case–control data) and therefore is unlikely to confer independent risk. As the *IL23R* gene is expressed in at least six alternatively spliced mRNAs, which generate diverse isoforms of the receptor protein [31], intronic polymorphisms like rs11805303 can perhaps influence the regulation of the differential splicing. Anti-p40 therapies, which inhibit both IL-12 and IL-23, due to their shared p40 subunit, showed promising results in human trials for Crohn's disease, another organ specific autoimmune disease [32]. With the recognition of the role of IL-23 functional variants in inflammatory diseases, it is clear that further differentiations are required to verify the patients who could benefit from the selective suppression of the IL-23 signaling. With the current observations, this can be extended also for rheumatoid arthritis as well that would represent a new perspective toward a personalized therapy for patients with this disease.

In conclusion, similar to previous studies, we confirmed the effect of *IL23R* polymorphisms on the development of psoriasis in a Hungarian population, and we were the first to perform a haplotype analysis regarding polymorphisms of the gene and psoriasis. We investigated for the first time, in literature, the effect of the shared susceptibility allele *IL23R* on an autoimmune disease with, so far, no clear background, namely immunoglobulin A nephropathy; however, we could not show any association with it.

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