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Difference of interleukin-23 receptor gene haplotype variants in ulcerative colitis compared to Crohn's disease and psoriasis

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Abstract
Objective Polymorphisms of the interleukin-23 receptor (IL23R) gene have been found to play a role in the development of several autoimmune diseases. Our aim was to examine the possible effect of not only simple individual variants, but of haplotypes composed of them.

Subjects We analysed 263 patients with psoriasis, 199 patients with Crohn's disease (CD), 282 patients with ulcerative colitis (UC), and 253 controls for rs1884444, rs11805303, rs7517847, rs2201841, rs10889677 and rs11209032 variants.
Methods The genotypes were determined by using PCR/RFLP assay. Logistic regression analysis was used to compare the genotype distribution of the polymorphisms and haplotypes between the examined autoimmune diseases and healthy controls.
Results Rs1884444 was found to confer risk for UC and psoriasis, rs10889677 for CD and psoriasis, while rs2201841 and rs7517847 had effect only in CD. Using these SNPs we could study the susceptibility haplotype profiles in these diseases with special attention to UC. Eight different haplotypes could be differentiated. We found that the SNPs exert their susceptibility character in specific haplotype blocks, and the frequency of one haplotype differed significantly in UC compared with both other diseases and also with healthy controls. This haplotype conferred risk for UC, even while it had a somewhat lower frequency in the other diseases than in controls.
Conclusions The data presented here serve as evidence for the need of haplotype analysis instead of just single standing SNP analysis when susceptibility is interpreted.

Keywords IL23R · Ulcerative colitis · Crohn's disease · Psoriasis · IBD

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Introduction

Interleukin-23 (IL-23) is a heterodimeric cytokine that shows similar functions to IL-12 in promoting cellular immunity and enhancing lymphocyte proliferation. However, unlike IL-12, IL-23 develops $CD4^+$ T cells into IL-17

producing Th17 cells, instead of Th1 cells [1]. The Th17 cells produce several proinflammatory cytokines, like IL-17, IL-6 and tumor necrosis factor (TNF-α) [2]. IL-23 is recognized by its specific receptor-complex, IL23R. The IL23R gene is located on chromosome 1p31, and the encoded protein forms a receptor for IL23, together with the β1 subunit of IL12 receptor (IL12Rβ1) [3, 4]. These two subunits compose the IL23R receptor-complex.

Crohn's disease (CD) is a common form of inflammatory bowel disease (IBD). CD is a chronic inflammation of uncertain etiology, in which inflammation occurs primarily in the ileum and colon, although any portion of the intestinal tract can be affected. Ulcerative colitis (UC) is another form of IBD that leads to chronic inflammation of the digestive tract [5]. UC is restricted to the colon, characteristically starting in the rectum and then spreading proximally in a continuous fashion with mucosal ulcerations [6]. The risk of colorectal cancer increases 2 % after 10 years, 8 % after 20 years, and 18 % after 30 years [7]. Psoriasis is a chronic inflammatory disease that affects the skin and the 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 [8]. Prevalence rates vary from 0–5 % to 4–6 % between countries and races, affecting 2–3 % of whites of European descent [9]. The lesions are caused by abnormal keratinocyte proliferation driven by the activation of T lymphocytes, which leads to release of cytokines.

IL23R polymorphisms were first associated with IBD [10], and theoretical considerations immediately suggested their role in other autoimmune and immune-mediated diseases. In several cases, different research groups obtained contradictory results in different populations regarding the same disease. Moreover, it soon became clear that not only the individual polymorphisms, but also the haplotypes composed of them, can have significant effects. Our research group found association of IL23R SNPs with CD and psoriasis in a Hungarian population in former studies [11, 12]. As the significance of the haplotype (ht) analysis has already been revealed in previous studies in relation with some diseases [13–15], in the current study we performed comparative haplotype analysis of CD, psoriasis, and with special attention to UC.

Materials and methods

The DNA samples of the control group and of the patients with CD and ulcerative colitis originated from the central Biobank governed by the University of Pécs, as part of the National Biobank Network of Hungary (http://www.biobank.hu), which belongs also to the pan-European Biobanking and Biomolecular Resources Research Infrastructure preparatory phase project (http://bbmri.eu/bbmri/). The governance, maintenance and management principles of the Biobank had been approved by the National Scientific Research Ethics Committee, Budapest (ETT TUKEB). The DNA samples of the patients with psoriasis were collected at the Department of Dermatology and Allergology, University of Szeged. During the entire investigation period, the guidelines and regulations of the 1975 Helsinki Declaration and the currently operative national laws were followed; the patients gave their informed consent for use of their collected, anonymized DNA samples for research purposes.

We analysed a total of 263 psoriasis (126 males, 137 females), 199 CD (82 males, 117 females), 282 UC patients (103 males, 179 females), and 253 control subjects (104 males, 149 females).

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 IL-23 receptor gene (GenBank NM_144701, GeneID 149233), using the following forward and reverse primers: 5′-CAG TCT TTT CCT GCT TCC AGA CAT-3′ and 5′-AAT AAA ATC ATA CTC TTG CCA ATG GCC C-3′ for rs1884444; 5′-TCT TCC CAG TCT CCA GTG TG-3′ and 5′-CCG AAC AAT TTT TGT TTC CC-3′ for rs11805303; 5′-AAA CAT TGA CAT TCC CTT CAT AC-3′ and 5′-GAA ATG AGT CAC CAA TAA TCC AC-3′ for rs7517847; 5′-GGC AAA AGG GAA TTG AGA GG-3′ and 5′-GGC CTA TGA TTA TGC TTT TTC CTG-3′ for rs2201841; 5′-ATC GTG AAT GAG GAG TTG CC-3′ and 5′-TGT GCC TGT ATG TGT GAC CA-3′ for rs10889677 and 5′-TTG TTA CTG GAG TTA AAC CTC TTG C-3′ and 5′-AGG AAT AAT TGC TGA GAT GCA ATG-3′ for rs11209032 alleles. For RFLP tests PscI (rs1884444), MnlI (rs11805303 and rs10889677), BseMII (rs7517847), HpyF3I (rs2201841) and BseMI (rs11209032) restriction endonucleases were used, respectively; each of the primer sets were designed to make an obligate cleavage site on the amplicon to enable us to control the efficacy of the digestion. The digestion of the amplicon of rs1884444G resulted in 191 and 318 bp bands, while the T allele was indicated by 28, 191 and 290 bp digestion products. The rs11805303C allele resulted in 39, 136 and 198 bp fragments, and the T allele in 136 and 237 bp bands. The rs7517847T allele was characterized by bands with 29, 91 and 410 bp, while for the G allele 29 and 501 bp digestion products could be detected. The rs2201841T allele resulted in 163 and 257 bp fragments, while the C allele in 25, 163 and 232 bp bands. For the rs10889677C allele, the restriction endonuclease cleaves the PCR product into 61, 185 and 224 bp fragments. If the A allele was present, 185 and 285 bp fragments could be detected. For the rs11209032G allele, the restriction

endonuclease cleaves the PCR product into 24, 67 and 174 bp fragments. If the A allele was present 24 and 242 bp fragments could be seen.

Associations of the diseases and the examined genetic variants were tested using binary logistic regression analysis using SPSS 11.5 for Windows. Haploview 4.1 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. Haplotype frequencies were estimated using PHASE version 2.1 [16, 17].

The allele composition of some frequent haplotypes is shown in Table 1.

Results

The genotypes and minor allele frequencies (MAFs) of the examined *IL23R* variants are shown in Table 2. The rs1884444 SNP TT genotype showed a strong susceptibility nature in UC patients ($p = 0.001$; OR = 3.13; 95 % CI: 1.60–6.13) and in psoriasis patients ($p = 0.005$; OR = 2.68; 95 % CI: 1.35–5.35) as well. The rs7517847 GG genotype has a protective effect against the development of CD ($p = 0.017$; OR = 0.48; 95 % CI: 0.27–0.88), while the rs2201841 and rs10889677 homozygous variants confer risk for the disease ($p = 0.007$; OR = 2.43; 95 % CI: 1.27–4.62 and $p = 0.016$; OR = 2.28; 95 % CI:

Table 1 Major haplotypes (ht) of the examined IL23R variants

	rs1884444	rs11805303	rs7517847	rs2201841	rs10889677	rs11209032
ht1	G	C	G	T	C	G
ht2	G	C	T	T	C	G
ht3	T	T	T	C	A	A
ht4	T	C	T	T	C	G
ht5	T	C	G	T	C	G
ht6	G	T	T	C	A	A
ht7	G	C	G	T	C	A
ht8	T	T	T	C	A	G

Table 2 Genotypes and minor allele frequencies

		CD ($n = 199$)	UC ($n = 282$)	Psoriasis ($n = 263$)	Controls ($n = 253$)
rs1884444	GG	60 (30.2)	68 (24.1)	75 (28.5)	61 (24.1)
	GT	133 (66.8)	176 (62.4)	157 (59.7)	180 (71.1)
	TT	6 (3.00)	38 (13.5)*	31 (11.8)*	12 (4.74)
	MAF	0.36	0.45	0.42	0.40
rs11805303	CC	80 (40.2)	135 (47.9)	111 (42.2)	129 (51.0)
	CT	99 (49.7)	124 (44.0)	126 (47.9)	102 (40.3)
	TT	20 (10.1)	23 (8.16)	26 (9.98)	22 (8.70)
	MAF	0.35	0.30	0.34	0.29
rs7517847	TT	72 (36.2)	115 (40.8)	89 (33.8)	74 (29.2)
	TG	110 (55.3)	122 (43.3)	128 (48.7)	138 (54.5)
	GG	17 (8.54)*	45 (16.0)	46 (17.5)	41 (16.2)
	MAF	0.36	0.38	0.42	0.43
rs2201841	TT	77 (38.7)	132 (46.8)	89 (33.8)	123 (48.6)
	TC	94 (47.2)	129 (45.7)	128 (48.7)	114 (45.1)
	CC	28 (14.1)*	21 (7.45)	46 (17.5)	16 (6.32)
	MAF	0.38	0.30	0.42	0.29
rs10889677	CC	77 (38.7)	128 (45.4)	128 (48.5)	117 (46.2)
	CA	97 (48.7)	133 (47.2)	106 (40.3)	121 (47.8)
	AA	25 (12.6)*	21 (7.45)	29 (11.0)*	15 (5.93)
	MAF	0.37	0.24	0.31	0.30
rs11209032	GG	69 (34.7)	134 (47.5)	127 (48.3)	109 (43.1)
	GA	107 (53.8)	122 (43.3)	107 (40.7)	120 (47.4)
	AA	23 (11.6)	26 (9.22)	29 (11.0)	24 (9.49)
	MAF	0.38	0.31	0.31	0.33

* $p < 0.05$ versus controls

Table 3 Haplotype frequencies of the examined IL23R variants

	CD (%)	UC (%)	Psoriasis (%)	Controls (%)
ht1	21.1	21.0	24.7	24.7
ht2	19.9	20.1	17.0	17.4
ht3	12.8	15.1	14.3	12.9
ht4	5.50	9.47[§]	9.33	8.42
ht5	4.83	9.72*,§,#	5.91	6.55
ht6	10.4*	6.14[§]	6.71[§]	4.99
ht7	2.32	1.27	1.68	2.44
ht8	3.62*	3.41	2.07	1.67

* $p < 0.05$ compared to controls

§ $p < 0.05$ compared to CD patients

# $p < 0.05$ compared to psoriasis patients

1.17–4.45, respectively). The later SNP is associated with psoriasis also ($p = 0.041$; OR = 1.97; 95 % CI: 1.03–3.76).

Four haplotypes were associated with the examined diseases; the major haplotype frequencies can be seen in Table 3. A total of three haplotypes conferred risk for the development of either of the examined diseases. Ht5 occurred significantly more frequently in UC than in healthy controls ($p = 0.003$; OR = 2.50; 95 % CI: 1.36–4.58). Two haplotypes, ht6 and ht8, showed a strong susceptibility effect for the development of CD, with ht6 showing the highest level of significance among all (for ht6 $p < 0.001$; OR = 3.04; 95 % CI: 1.69–5.46 and for ht8 $p = 0.020$; OR = 2.62; 95 % CI: 1.16–5.89).

When the profile of the major haplotypes was studied, several strongly significant differences between UC and the other two examined diseases were verified (shown in Table 3.). Ht5 was accumulated in UC compared to both CD ($p < 0.001$) and psoriasis ($p = 0.045$). Ht6 was found less frequently in UC than in CD ($p = 0.002$), while ht4 was, on the contrary, elevated in UC compared to CD ($p = 0.021$). The frequency of ht6 also showed a significant difference between psoriasis and CD ($p = 0.006$).

Discussion

In the last few years the IL23R molecule and its variants have been subjects of thorough investigation in autoimmune diseases. Its associations have been described with several diseases, like IBD [10, 18–20], psoriasis [21, 22], and AS [23–25], and have been studied also in Sjögren syndrome [24] and systemic lupus erythematosus [26, 27]. Very recently, a study of the association of IL23R haplotypes with some of these diseases had also been initiated [12, 28, 29].

Results concerning the role of IL23R SNPs in UC are contradictory. Duerr et al. [10] were the first to report association of the gene with UC. Soon after, a replication study performed on Chilean IBD patients did not find any association [30], while in Spanish patients, even though a tendency could be observed, it did not reach the required level of significance [31]. These observations prompted us to investigate the effects of IL23R SNPs in a Hungarian UC population and to carry out a haplotype analysis too. We genotyped the same polymorphisms for CD, the other form of IBD, and also for a distinct autoimmune disorder, namely psoriasis, in which IL23R has been previously shown to play an important role [12, 21, 22].

We detected an association with rs1884444 in UC and psoriasis, however interestingly not in CD. Three major haplotypes consisting of the six investigated SNPs showed association with either of the studied diseases, and one haplotype (ht5) only with UC—a fact which calls attention to how different are the effects that haplotypes and single polymorphisms can have.

During the analysis of our data, very different distributions of haplotypes in the three investigated diseases could be identified. We found a statistically significant difference between CD and psoriasis in the case of one haplotype, but very interestingly, between the two forms of IBD, the frequency of three haplotypes showed a significant difference. Ht5 was elevated in UC compared to all studied populations. The elevation of ht6 frequency seems to be a distinct marker for CD. These results underline not only the different effects of individual SNPs and compound haplotypes, but also how seemingly similar diseases can differ from one another in the details of their genetic background.

The exact nature of how the haplotypes exert their effect is still not known. For SNPs involving or directly affecting coding regions, like the rs1884444 variant here, when the G→T variant in position 94 associates with His→Gln, there is usually strong effect on the helical structure of the protein product that can be detected using different in vitro approaches. Several roles in IL23R gene expression have been attributed to the untranslated regions. The rs10889677 C→A change in position 2284 can affect mRNA stability, mRNA localization, and translational efficiency. The intronic variants of IL23R rs11805303 C→T change in position 48348, rs7517847 T→G change in position 54501, rs2201841 T→C change in position 67034 may influence mRNA length and protein product. However, for other allelic sites (like rs11209032 G→A) encoding no amino acids in the intergenic region in haplotypes can modify regulatory nucleic acid binding reactions, siRNA interactions, and can have an influence on position effects. As recent studies have identified, IL-23 is a key player in both innate and adaptive immune systems, and most IL-23 is secreted by activated dendritic cells, monocytes and

macrophages following their exposure to pathogen-derived molecules that bind to toll-like receptors; moreover, IL-23 stimulates a unique $CD4^{+}$helper T-cell population characterized by the production of IL-17, tumor necrosis factor and IL-6, known as Th17 cells; in this complex cascade of events, several regulatory points can be supposed [32, 33]. As there are clinical and immunological differences and concurrent overlaps in the diseases we investigated, complex and even different actions can be supposed for the individual haplotypic variants.

Taken together, the data presented here show how important it is to study SNPs together, and not only the separate SNPs themselves, since some effects can only be detected this way, and it seems that some polymorphisms tend to act only in specific blocks.

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