Polymorphisms of Interleukin-23 Receptor in Patients with Inflammatory Bowel Disease in a Croatian Tertiary Center

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ABSTRACT

The Interleukin-23 signalling pathway is important for the differentiation of TH17 lymphocytes and is involved in the pathogenesis of Inflammatory bowel disease. Polymorphisms in the IL-23 receptor gene were previously found to be associated with Inflammatory bowel disease in various populations. The aim of this study was to determine whether the specific rs11209026 and rs7530511 single-nucleotide polymorphisms in the Interleukin-23 receptor gene are associated with Crohn's disease and ulcerative colitis in a Croatian patient population. A total of 50 patients with Crohn's disease and 93 patients with ulcerative colitis, as well as 99 healthy control subjects were included in the study. The results determined a significantly higher occurrence of rs11209026 in control group compared to patients with inflammatory bowel disease, suggesting a protective effect of this polymorphism. The rs11209026 variant was strongly associated with Crohn's disease, but it was absent in ulcerative colitis. However, there was no significant association between the rs7530511 polymorphism with either ulcerative colitis or Crohn's disease. Associations presented in this study give potentially important insight into the roles of specific Interleukin-23 receptor polymorphisms in Crohn's disease pathogenesis in the Croatian population.

***Key words**: Crohn's disease, ulcerative colitis, Inflammatory bowel disease, interleukin-23 receptor, single nucleotide polymorphism, genotype, population, inflammation, cytokine, autoimmune*

Introduction

Inflammatory bowel diseases (IBD) are chronic idiopathic inflammatory disorders of the gastrointestinal tract characterized by variable disease course with episodes of clinical activity as a result of active inflammation. The major phenotypes are Crohn's diseae (CD) and ulcerative colitis (UC) with IBD having a large spectrum of clinical presentations with different course and prognosis[1,2]. IBDs are multifactorial, polygenic diseases with genetic heterogenicity. Besides genetic predisposition, a number of host (epithelial, immune, nonimmune...) and environmental factors play major roles in the pathogenesis of IBD[3]. It is becoming more clear that IBD is a result of an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host[3]. Numerous genetic studies highlighted the importance of host-microbe interactions and among the identified ge-

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netic factors, nucleotide oligomerization domain 2 (NOD2), autophagy genes and components of the interleukin--23-type 17 helper T-cell (Th17) pathway play major roles in perpetuating the abnormal inflammatory response in IBD[3]. The strong genetic component as a major factor is illustrated in the fact that the lifetime risk to develop CD is about 10–20% in the presence of an affected first-degree relative[4–6]. Defining subgroups based on genetic mutations might therefore be a helpful marker, especially when planning personalized therapy in the future[4].

The interleukin-23 signalling pathway is recognized as a very important pathogenetic mechanism in IBD. Interleukin-23 is a pro-inflammatory cytokine belonging to the interleukin-12 cytokine family and is essential for the differentiation of Th17 lymphocytes – a subtype of T lymphocytes implicated in chronic inflammatory/autoimmune diseases[7]. Therefore, this pathway is considered an important therapeutic target and the monoclonal antibody Ustekinumab was developed to target the common p40 subunit of interleukin-23 and interleukin-12 (and currently licensed for psoriasis treatment)[7].

Duerr and co-workers identified, in a genome-wide association study, the interleukin-23 receptor (IL23R) gene on chromosome 1p31 as an IBD gene. This gene encodes a subunit of the receptor for the proinflammatory cytokine interleukin-23[8]. Furthermore, they found that the uncommon single-nucleotide polymorphism (SNP) coding variant rs11209026 (c.1142G>A, p.Arg381Gln) is associated with protection against CD in both Jewish and non-Jewish populations. Additional noncoding IL23R variants were independently associated[8]. Replication studies confirmed IL23R associations in independent cohorts of patients with CD or UC[8]. The rs11209026 SNP in IL23R gene had a protective effect for IBD in a Dutch case-control analysis[9] and both UC and CD were associated with IL23R[9]. Subsequently, among other studies, a German study confirmed the rs11209026 association to CD also in children IBD population, verifying a protective effect of the rs11209026 SNP for CD, but not for UC[10]. The rs11209026 SNP is part of a haplotype with rs7530511 that is associated with psoriasis[11] and psoriatic arthritis[12], but also with several other immune--pathological conditions including ankylosing spondylitis in Hungarian population samples[13].

The aim of this work was to determine whether specific SNPs rs11209026 and rs7530511 in the IL23R gene are linked to CD and/or UC in a Croatian IBD patient population. The research is crucial for gaining more insight into pathogenetic mechanisms of IBD in the Croatian population, as well as for optimization and efficient use of future therapies specifically targeting the IL-23 signalling pathway.

Materials and Methods

Patients

A total of 50 patients with CD (26 males, median age 35 yr, interquartile range 21–40 yr), 93 patients with UC (52 males, 47 (36–59) yr) and 99 ethnically and geographically matched healthy control subjects (84 males, 36 (26–47) yr) were included in the study. All were adults, Caucasian and living in eastern Croatia. Diagnosis of IBD (CD or UC) was established according to standard clinical criteria, including endoscopic, radiological and histopathological analysis at the University Hospital Centre Osijek, Croatia. Median follow-up for the entire cohort of IBD patients was six (interquartile range 3–12) years. The institutional ethical committee approved the study and all participants gave informed consent before testing.

SNP determination

The specific rs11209026 and rs7530511 SNPs of the IL23R gene were determined in the IBD patient group and in the healthy control group. Genomic DNA was extracted from 200 μL EDTA treated blood with High Pure PCR Template Preparation Kit (Roche Diagnostics, Mannheim, Germany) according to manufacturer's instructions. Genotyping was done with primers obtained from TIBMOLBIOL (Berlin, Germany) and LightCycler FastStart DNA Master SYBR Green Kit purchased from Roche Diagnostics, Mannheim, Germany in a LightCycler System (Roche Diagnostics Mannheim, Germany) with subsequent fluorescent probe melting point analysis. For the SNP IL-23R rs11209026 detection, a master mix contained 2 mM $MgCl_2$, 0.5 μM of the primers 5´-CCT TCC TTT CAT TAG ACA ACA GAG G-3´ and 5´-AAC TGA AAT GAC TAA ATT TTG GTG A-3´, and 0.2 μM of the probes: 5/-ACA GAT CAT TCC AAA cTG GGT-FL and LC640-GTT TTT GCA GAA TTT CTG TTT TCT GAT TT-PH, and 2 μL of FastStart (Roche Diagnostics, Mannheim, Germany) mixture. Obtained 194 bp PCR product was analyzed using melting curve analysis (54 °C for GG genotype, 54 °C and 61 °C for GA genotype, and 61 °C for AA genotype). The SNP IL-23R rs7530511 was analyzed by asymmetric PCR. A mastermix contained 2.65 mM $MgCl_2$, 0.9 μM forward (5´-GGA GCC AAA CAT TAA GTA CGT ATT T-3´) primer, 0.7 μM reverse (5´-CCT GCT TCc GGT GCT TTA TGA- 3´) and 0.2 μM hybridization probes 5´-AGG CAA AAG GTA CTG GCA GCC-FL and LC640-TGG AGT TCA CCG TTT TTT CA-PH. Amplified 105 bp PCR product was analyzed using melting curve analysis (63 °C for TT genotype, 53 °C and 63 °C for TC genotype, and 53 °C for CC genotype). To prevent genotyping errors DNA samples were genotyped in duplicate by RealTime PCR based method.

Statistical methods and analysis

Data are presented as medians with interquartile ranges (IQR), absolute and relative frequencies, depending on the scale of the measure. Departures from the Hardy-Weinberg equilibrium were analyzed by using an exact test[14]. Single marker effects were assessed simultaneously by Westfall-Young permutation procedures[15] giving P-values corrected for multiple testing (10000 replicates, PLINK 1.07[16], http://pngu.mgh.harvard.edu/pur-

cell/plink). Permutation-corrected P-values of <0.05 were taken as significant. Odds ratios (OR) and median unbiased estimates (MUE)[17] with their respective 95% confidence intervals (CI) were used to measure the strength of association (LogXAct 10, Cytel Inc., Cambridge, MA, USA).

Power calculations were performed using the Genetic Power Calculator program (http://pngu.mgh.harvard.edu/~purcell/gpc). Assuming a multiplicative model, a two-tailed type I error rate of $\alpha=0.05$ and a population disease prevalence of 0.005, the sample size employed in this study was sufficient to give 80% power to detect as significant an odds ratio of 2.6, 2.1 and 1.65 for 5, 10 and 35% minor allele frequency in the control population.

Results

All genotype distributions were in Hardy-Weinberg equilibrium (Table 1). The observed population allele frequencies in controls were similar to those reported in other Caucasian populations[18]. In the combined population (IBD, UC+CD), the rs11209026 A allele was differentially distributed between cases and controls (2.1 *vs.* 7.1%, p=0.014, Table 1), indicating a significant reduction in IBD risk for carriers (allelic OR 0.28; 95% CI 0.11–0.75). With respect to each of the populations, the prevalence of the uncommon rs11209026 p.381Gln variant was lower in CD, but not UC patients compared to healthy controls, suggesting a protective effect against CD (Table 2). The rs7530511 variant, in contrast, was associated neither with CD nor with UC.

The genotype distributions of the rs11209026 and rs7530511 variant in the IL23R gene are shown in Table 3 and Table 4. For the rs11209026 SNP, a significantly reduced risk of IBD (OR 0.27, 95% CI 0.1–0.72), limited most likely to the CD phenotype only (MUE 0.09, 95% CI 0–0.54), was observed for heterozygous A/G carriers as compared with the homozygous G/G genotype (Table 3). No minor allele homozygotes or heterozygotes were observed for CD cases, nor were rare AA homozygotes observed in any other study group. For the rs753051 SNP, no significant effect on disease susceptibility was observed. The IL23R variants did not influence the age at diagnosis (data not shown).

Discussion

The results presented in this work associate the rs 11209026 SNP (minor allele A) in the IL23R gene with CD in the manner that the SNP represents a protective factor for CD development. It is impressive that no case of CD was found to have the rs11209026 SNP. The GA genotype was found to be relevant in this link with CD protection. On the other hand, there was no such association of this SNP with UC. When all IBD patients are analyzed together, there is a significant association of rs11209026 with IBD (conferring a protective effect). The rs7530511 SNP of the IL23R was not by itself associated with CD or UC, and also when all IBD patients were analyzed together there was no statistically significant link in this Croatian IBD patient population.

A protective effect of rs11209026 of the IL23R in the Croatian population is in accordance with previously published results of other populations where this SNP was found to be significantly less represented in CD patients[8–10]. In some of those other works, there was also no evident link to UC, reflecting a potential difference in pathogenetic factors between the two IBD phenotypes, and this lack of UC-association was confirmed in the Croatian population of this study. Interestingly, some stud-

TABLE 1
ALLELIC COMPARISONS BETWEEN IBD (CASE) AND HEALTHY (CONTROL) POPULATIONS FOR THE IL23R SNPS

SNP	Minor allele	Case	Control	OR (95% CI)	p*	HWE controls p	HWp
IL23R rs11209026	A	0.021	0.071	0.28 (0.11–0.75)	0.014	1	1
IL23R rs7530511	T	0.105	0.101	1.04 (0.57–1.9)	1	0.054	0.727

OR – Odds ratio, CI – confidence interval, HWE – Hardy-Weinberg equilibrium, * – Empirical p-value, 10^4 permutations, Westfall-Young correction

TABLE 2
ALLELIC COMPARISONS BETWEEN IBD (CASE) AND HEALTHY (CONTROL) POPULATIONS FOR THE IL23R SNPS, SEPARATED BY DISEASE (CD AND UC)

Disease	SNP	Minor allele	Case	Control	OR (95% CI)	p*
CD	IL23R rs11209026	A	0	0.071	0.09 (0–0.57)**	0.013
	IL23R rs7530511	T	0.12	0.101	1.21 (0.57–2.6)	0.871
UC	IL23R rs11209026	A	0.032	0.071	0.44 (0.16–1.17)	0.185
	IL23R rs7530511	T	0.097	0.101	0.95 (0.49–1.87)	1

OR – Odds ratio, CI – confidence interval, * – Empirical p-value, 10^4 permutations, Westfall-Young correction, ** – median unbiased estimate

TABLE 3
COMPARISON OF IL23R SNPS BY GENOTYPE AND SEPARATED BY DISEASE (CD AND UC)

Disease	SNP	Genotype	Case N (%)	Control N (%)	p*	OR (95% CI)
CD	IL23R rs11209026	AA	0	0		–
		GA	0	14 (14.1)	0.012	0.09 (0–0.54)**
		GG	50 (100)	85 (85.9)		1***
	IL23R rs7530511	TT	0	3 (3.1)		0.57 (0–5.43)
		CT	12 (24)	14 (14.1)	0.38	1.85 (0.78–4.38)
		CC	38 (76)	82 (82.8)		1***
UC	IL23R rs11209026	AA	0	0		–
		GA	6 (6.5)	14 (14.1)	0.288	0.42 (0.15–1.14)
		GG	87 (93.5)	85 (85.9)		1***
	IL23R rs7530511	TT	0	3 (3.1)		0.29 (0–2.73)
		CT	18 (19.4)	14 (14.1)	0.381	1.41 (0.65–3.02)
		CC	75 (80.6)	82 (82.8)		1***

OR – Odds ratio, CI – confidence interval, N – number of subjects, * – Empirical p-value, 10^4 permutations, Westfall-Young correction, ** – median unbiased estimate, *** – reference genotype

TABLE 4
GENOTYPE ASSOCIATIONS

SNP	Genotype	Case N (%)	Control N (%)	p*	OR (95% CI)
IL-23R rs11209026	AA	0	0		–
	GA	6 (4.2)	14 (14.1)	0.015	0.27 (0.1–0.72)**
	GG	137 (95.8)	85 (85.9)		1***
IL–23R rs7530511	TT	0	3 (3.1)		0.19 (0–1.8)**
	CT	30 (21)	14 (14.1)	0.128	1.56 (0.78–3.12)
	CC	113 (79)	82 (82.8)		1***

OR – odds ratio, CI – confidence interval, N – number of subjects, * – Empirical p-value, 10^4 permutations, Westfall-Young correction ** – median unbiased estimate, *** – reference genotype

ies, including the work of Büning and coworkers[19] found that the rs11209026 variant of the IL23R confers a protective effect not only against CD, but also against UC. Such a protective effect for UC alone was not evident in our Croatian cohort, based on the presented results. There was, however, not enough statistical power to confirm an effect of such a proportion in a sample of this size.

Although the ultimate goal of such research investigating genetic susceptibility to certain chronic diseases is to foster personalized medicine in which an individual genetic profile would help direct further diagnostic workup and optimize therapy, the realistic clinical utility of the presently known genetic associations remains unclear. A large French case-control study by Jung and co-workers looked into 53 CD-associated genetic polymorphisms of 798 CD patients from referring paediatric and adult gastroenterology centres, linking predominantly NOD2 variants with CD, but also accentuating some significant associations with rs11209026 of the IL23R gene[20]. The patient population in that study included cases of most severe CD comparable to subjects in our study, included at a tertiary clinical center where the most severe IBD cases are followed up. The authors concluded, however, that it cannot be recommended to genotype the studied polymorphisms in routine practice because the interpretation of the number, nature and strength of the associations did not argue for their usefulness in clinical practice[20].

A number of other studies looked into the link between IL23R polymorphisms and IBD in various populations. Weersma et al. confirmed the association of the rs11209026 SNP with CD in a Dutch-Belgian cohort, but also found associations with a number of other polymorphisms[21]. An association of rs11209026 with CD was confirmed in the Czech population by Dusatkova and coworkers[22], in Spanish populations by Oliver et al.[23] and Marquez et al.[24], in a German population by Glas et al.[25], in New Zealand Caucasians by Roberts et al.[26], in a Brazilian population by Baptista et al.[27], in a Hungarian population by Lakatos[28] and in a British cohort by Cotterill et al.[29]. On the contrary, Venegas et al. researching a Chilean cohort of a similar size as the one investigated in our study found no association of the rs11209026 SNP of the IL23R with either CD or UC. The polymorphism was present in about 5.2% of the control group and 5% of IBD

patients (7.9% for CD and 3.2% for UC)[30]. This lack of rs11209026 involvement in the genetic predisposition to IBD in this Chilean population highlights ethnic differences in the genetic background of IBD[30] and raises the need to explore such associations in various populations to draw a complete picture about IBD predisposition and pathogenesis. A study of polymorphisms in Lithuanian IBD patients found as well no association between rs 11209026 and either CD or UC[31].

Besides such discussed cohort studies, there were several large meta-analyses determining associations of IL23R variants with IBD. These meta-analyses should be accentuated, because the differences found in small cohort studies may reflect differences in statistical power due to small sample sizes, imbalances in allelic links, allelic frequency differences or differences in the composition of recruited subject groups. Meta-analysis conducted by Li et al. supported the polymorphisms rs 11209026 and rs7517847 within the IL23R gene as protective factors against developing CD[32]. But the authors concluded that further case-control studies especially concerning ethnicity differences should be performed to clarify possible roles of IL-23R in CD[32]. The presented case-control study on a Croatian IBD patient population is an example of the necessary additional research. A meta-analysis by Cotterill et al. on 13,000 cases provided more strong evidence that the rs11209026 polymorphism alters susceptibility to CD across populations of European ancestry[29].

There are also other immune-related diseases with an association to rs11209026, including ankylosing spondylitis[33], chronic sarcoidosis[34], rheumatoid arthritis[35], psoriasis[36] and systemic sclerosis[37]. The rs7530511 polymorphism was also linked to some of those immune-related conditions, such as psoriasis[38] and psoriatic arthritis[39], as well as ankylosing spondylitis[40]. The rs7530511 is part of a haplotype with rs11209026, but Szabo et al. found evidence for the need of haplotype analysis instead of just single standing SNP analysis when susceptibility to or protection against a disease is investigated[41]. The rs 7530511 SNP could certainly be a potentially interesting research target. However, there is a lack of studies confirming a link of rs7530511 to CD or UC, and our results did not find such an association either.

The IL-23 signalling pathway and its importance for the differentiation of TH17 lymphocytes is becoming more and more clearly implicated in various autoimmune and chronic inflammatory diseases and is also recognized as an important pathogenetic pathway in IBD[7]. The molecular location of the IL23R gene is on chromosome 1. The receptor IL23R, consisting of an IL-12β1 and an IL-23R chain, is highly expressed on the cell membrane of memory T cells and other immune cells, such as natural killer cells, monocytes, and dendritic cells and interacts with IL-23[42]. It is involved in the mediation of proinflammatory activities by the production of IL-17 via the activation of Th17 lymphocytes, and the role of this axis in CD pathogenesis was supported in human patients and animal models of colitis[42]. It makes it therefore an interesting subject for better understanding of the underlying pathologic processes in IBD and certainly is becoming a valid therapeutic target. One of the first drugs specifically targeting IL23R is Ustekinumab, a monoclonal antibody for the common p40 subunit of interleukin-23 and interleukin-12[7]. It is already recognized as an effective future treatment option for psoriasis[7], and trials are under way to test its efficacy in CD. The efficacy of treatments targeting the IL-23 signalling system in psoriasis is also interesting in the context of the previously discussed links of rs11209026 and rs 7530511 to psoriasis. In context of IBD, the rs11209026 of the IL23R could be exploited to define clinical outcomes, such as a pharmacological approach to mimic the rs11209026 polymorphism[42]. In general, the prospect of diagnostic and therapeutic personalization based on individual genetic profiles seems feasible, but further translational research and abundant replication studies are needed to extend pioneering findings into clinical practice[43,44].

In conclusion, current clinical usefulness of genetic associations with IBD as discussed here and investigated in this work is at the present somewhat limited, further research is necessary to make final judgements about possible individualized diagnostic approaches. To the best of our knowledge, this is the first study exploring the specific IL23R SNPs in a Croatian IBD patient population and broadens the insight into genetic implications of IBD pathogenesis in the Croatian population. Perhaps with a combined future use of multiple genetic markers, where IL23R variants would be interpreted in context of several other significant markers, a potential diagnostic or therapeutic benefit could become apparent. Since specific therapies targeting the IL-23 signalling pathway are on the verge of clinical use in IBD (such as Ustekinumab), investigation of the IL-23 signalling components in Croatian IBD patients is interesting and might provide useful information for more efficient treatment choices in the future.

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POLIMORFIZMI INTERLEUKIN-23 RECEPTORA U PACIJENATA S UPALNIM BOLESTIMA CRIJEVA U HRVATSKOM TERCIJARNOM CENTRU

S A Ž E T A K

Interleukin-23 signalni put je važan u diferencijaciji TH17 limfocita i uključen je u patogenezu upalnih bolesti crijeva. Polimorfizmi interleukin-23 receptora u ranijim istraživanjima povezivani su s upalnim bolestima crijeva u različitim populacijama. Cilj ovog istraživanja bio je odrediti povezanost specifinih rs11209026 i rs7530511 polimorfizama pojedinačnog nukleotida (eng. single nucleotide polymorphism) interleukin-23 receptora s Crohnovom bolešću i ulceroznim kolitisom u hrvatskoj populaciji pacijenata tercijarnog kliničkog centra. Ukupno 50 pacijenata s Crohnovom bolešću i 93 pacijenta s ulceroznim kolitisom, kao i 99 zdravih kontrolnih ispitanika uključeno je prospektivno. Rezultati ukazuju na značajno veću pojavnost rs11209026 polimorfizma u zdravih ispitanika u odnosu na pacijente s upalnim bolestima crijeva, što sugerira protektivan učinak ovog polimorfizma. Kada se analiziraju posebno pacijenti s Crohnovom bolešću i s ulceroznim kolitisom, povezanost je bila značajna za Crohnovu bolest, ali odsutna za ulcerozni kolitis. rs7530511 polimorfizam, međutim, nije bio značajno povezan niti s Crohnovom bolešću niti s ulceroznim kolitisom. Povezanosti s polimorfizmima prikazane u ovom istraživanju predstavljaju potencijalno važan uvid u uloge polimorfizama interleukin-23 receptora u patogenezi Crohnove bolesti u hrvatskoj populaciji.