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Intercellular adhesion molecule 1 gene polymorphisms in inflammatory bowel disease

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Abstract. – **Intercellular adhesion molecule (ICAM)-1 is a single-chain cell surface glycoprotein that plays an important role in the recruitment of leukocytes at sites of inflammation and is up-regulated in intestinal mucosa of inflammatory bowel disease (IBD). ICAM-1 gene lies on chromosome 19p13, implicated in determining susceptibility to IBD. The human ICAM-1 gene contains two polymorphic sites in codon 241 (G241R) and 469 (K469E) which have been implicated in the susceptibility to a range of degenerative and inflammatory diseases. Recently, several reports have shown discordant data regarding the association of these polymorphisms with IBD. In particular, we found an association of IBD with the E/E genotype while allele E469 was associated with a subgroup of patients with more extensive location of Crohn's disease and penetrating behaviour. However, other studies reached different conclusions. A possible explanation for the discrepancy of results is probably the influence of the different geographic distribution of the genetic mutations.**

Key Words:

Inflammatory bowel disease, Intercellular adhesion molecule 1.

Introduction

The etiologies of Crohn's disease (CD) and ulcerative colitis (UC), the two major forms of chronic inflammatory bowel disease (IBD), are unknown. However, genetic predisposition seems to play a crucial role as evidenced by the increased familial prevalence of IBD and increased concordance rates in siblings or twins[1]. Epidemiological data provide evidence that this predisposition to both CD and UC depends on the contribution of multiple genes instead of a single genetic factor and genetic heterogeneity could explain different clinical features of the disease. In fact, in the last years, several association studies and linkage analyses have been performed to identify susceptibility genes in the whole genome[2-5]. IBD are characterized by immune dysregulation and leukocyte recruitment into gastrointestinal tissue[6]. Thus, polymorphisms of genes codifying for proteins involved in initiation and regulation of the immune response, such as cytokines and adhesion molecules, were investigated in order to show an association with IBD. Recently, Rioux et al. have identified a linkage between IBD and chromosome 19p13, where intercellular adhesion molecule (ICAM)-1 gene is located[7]. ICAM-1 is a surface glycoprotein that belongs to the immunoglobulin superfamily and plays an important role in the trafficking and activation of leukocytes[8]. It serves as a receptor for the leukocyte function-associated antigen-1 (LFA-1) and the macrophage differentiation antigen-1 (Mac-1)[9-10]. The up-regulation of ICAM-1 on endothelial cells by proinflammatory cytokines is a central event in regulating leukocyte localization at inflammatory sites and can play an important role also in the regulation and amplification of the inflammatory response observed in IBD[11-14]. Thus, an anti- ICAM-1 therapeutic strategy with antisense oligonucleotide has been used in steroid dependent or refractory CD with conflicting efficacy data[15-16]. Genetic variation in ICAM-1 gene structure may result in altered expression and/or function of the resulting adhesion molecule, thus potentially contributing to a genetic predisposition to in-

Table I. ICAM-1 genotype and allele distribution in IBD patients overall, CD and UC patients separately, and in controls.

	Controls	IBD		CD		UC	
	N = 187	N = 165	P(p_c)	N = 75	P(p_c)	N = 90	P(p_c)
Genotype							
K/K	61 (32.6)*	51 (30.9)		19 (25.3)		32 (35.6)	
E/K	104 (55.6)	73 (44.2)		38 (50.7)		35 (38.9)	
E/E	22 (11.8)	41 (24.9)	0.00023	18 (24.0)	0.00065	23 (25.5)	0.00002
Allele							
K	226 (60.4)	175 (53)		76 (50.7)		99 (55)	
E	148 (39.6)	155 (47)	0.0479 (0.0958)	74 (49.3)	0.041 (0.082)	81 (45)	0.224 (0.448)

*Numbers in parentheses are % of total.

flammatory and immunomediated events. Two polymorphisms in the ICAM-1 gene have been identified, one at position 241 of the coding region (exon 4) and the other at position 469 (exon 6), the first determining Gly/Arg substitution and the second a Lys/Glu variation[17]. The K469E polymorphism of the ICAM-1 gene might be functionally important and has been reported to affect interactions between ICAM-1 and the leukocyte function-associated antigen-1 (LFA-1)[18]. It is located in the fifth immunoglobulin-like domain of ICAM-1. This domain has been shown to play a role for adhesion of B cells and dendritic cells[19] and has also been demonstrated to be the ICAM-1 immunodominant epitope[20]. Aim of this report is to summarize all the available studies regarding the association between IBD and ICAM-1 gene polymorphisms.

Epidemiological Studies

ICAM-1 genetic polymorphisms have been implicated in the susceptibility to a range of degenerative and inflammatory diseases. Several reports have shown discordant data regarding the association of these polymorphisms with IBD[21-25]. Matsuzawa et al., reported an association between the K469 allele of ICAM-1 gene and IBD in a Japanese population[23]. The Author found that the allelic frequency of K469 was significantly higher in

Table II. ICAM-1 genotype and allele distribution according to CD location of disease.

	Controls	Small bowel		Small bowel plus colon		Colon	
	N = 187	N = 22	P(pc)	N = 42	P(pc)	N = 11	P(pc)
Genotype							
K/K	61 (32.6)*	4 (18.2)		10 (23.8)		5 (45.5%)	
E/K	104 (55.6)	13 (59.1)		20 (47.6)		5 (45.5%)	
E/E	22 (11.8)	5 (22.7)	0.00022	12 (28.6)	0.00072	1 (9%)	0.035
Allele							
K	226 (60.4)	21 (47.7)		40 (47.6%)		15 (68.2%)	
E	148 (39.6)	23 (52.3)	0.105 (0.21)	44 (52.4%)	0.0217 (0.0434)	7 (31.8%)	0.51 (NS)

*Numbers in parentheses are % of total. NS, not significant compared to controls.

Table III. ICAM-1 genotype and allele distribution according to CD clinical behaviour.

	Controls	Penetrating		Stricturing		Non-stricturing, non-penetrating	
	N = 187	N = 23	P(pc)	N = 16	P(pc)	N = 36	P(pc)
Genotype							
K/K	61 (32.6)*	2 (8.7)		2 (12.5)		15 (41.7)	
E/K	104 (55.6)	15 (65.2)		9 (56.3)		14 (38.9)	
E/E	22 (11.8)	6 (26.1)	< 0.00001	5 (31.2)	< 0 .00001	7 (19.4)	0.0023
Allele							
K	226 (60.4)	19 (41.3)		13 (40.6)		44 (61.1)	
E	148 (39.6)	27 (58.7)	0.013 (0.026)	19 (59.4)	0.0289 (0.0578)	28 (38.9)	0.913 (NS)

*Numbers in parentheses are % of total. NS, not significant compared to controls.

both CD and UC patients than controls[23]. Braun et al. found that the E/E genotype was significantly associated with both UC and CD patients with respect to controls, but no significant difference was observed in alleles frequencies between patients and controls[22]. The third study performed in United States did not show any significant association between the K469E polymorphism and IBD[21]. In the last two studies was investigated also the G241R polymorphism of ICAM-1 gene and IBD patients were stratified by antineutrophil cytoplasmic antibodies (ANCA) status[21-22]. In particular, Yang et al. found a significantly increased frequency of the G241R polymorphism both in ANCA-negative UC and in ANCA-positive CD patients[21], while Braun et al. showed an association between the R241 allele and UC independently of the ANCA status[22]. A recent report from the Oxford group included 228 CD patients, 243 UC patients and 407 controls[24]. They found a significant association between K469 homozygosity and CD overall (39.9% vs. 29.4%) and between E469 and fistulating disease (21.8% vs. 10.0%)[24]. In the UC group, limited disease extent was associated with homozygosity of the G241 allele (82.7% vs. 64.7%)[24]. Also our group investigated the prevalence of the K469E polymorphism in a population of Italian IBD patients[25]. We studied 165 consecutive patients with IBD (90 had UC and 75 CD) and 187 healthy subjects. The distribution of ICAM-1 genotypes and alleles in IBD and controls is shown in Table I. In particular, the prevalence of the homozygous E/E genotype

Table IV. ICAM-1 genotype and allele distribution according to UC location of disease.

	Controls	Entire colitis		Left sided colitis		Proctitis	
	N = 187	N = 23	P(p_c)	N = 48	P(p_c)	N = 19	P(p_c)
Genotype							
K/K	61 (32.6)*	10 (43.5)		18 (37.5)		4 (21)	
E/K	104 (55.6)	9 (39.1)		17 (35.4)		9 (47.4)	
E/E	22 (11.8)	4 (17.4)	0.0031	13 (27.1)	0.00003	6 (31.6)	0.00043
Allele							
K	226 (60.4)	28 (63.6)		53 (55.2)		17 (44.7)	
E	148 (39.6)	16 (36.4)	0.732 (NS)	43 (44.8)	0.353 (0.706)	21 (55.3)	0.061 (0.122)

*Numbers in parentheses are % of total. NS, not significant compared to controls.

was significantly higher in IBD than in controls. Also considering CD and UC patients separately the E/E genotype resulted more frequent than in controls. On the contrary, the alleles frequency did not differ between groups of patients (CD and UC) and controls. Subdividing CD patients according to disease extension (small bowel, small bowel plus colon or colon) (Table II) and clinical behaviour (penetrating, structuring, and not-stricturing not-penetrating) (Table III) we found that the E/E genotype occurred more frequently in all subgroups of CD patients, independently by disease location and clinical behaviour, while the frequency of E469 allele was significantly higher only in patients with small bowel plus colon disease and penetrating behaviour. In UC patients, after stratification according to disease extension (proctitis, left sided colitis or entire colitis) (Table IV), we found that only the frequency of the E/E genotype was increased in all subgroups of patients compared to controls, while no difference was observed in the frequency of the allele E469 between subgroups of UC patients and controls. The G241R polymorphism is extremely rare in the general Italian population, since the frequency of the RR genotype and the R241 allele have been reported to be 0.4 and 3.1, respectively, in healthy controls[26], thus, it was not analysed in our study. A possible explanation for the discrepancy of results in the reported studies is probably the influence of the different geographic distribution of the genetic mutation. Indeed, Japanese patients have a genetic background that differs from Western patients as also recently showed for the NOD2/CARD15 gene polymorphisms[27-28] while the IBD population studied by Yang et al. was in part constituted by patients of Jewish ethnicity[21].

The prevalence of ICAM-1 gene polymorphisms was also analysed in an extra-intestinal condition associated to UC: primary sclerosing cholangitis (PSC)[29]. The Authors found that the EE frequency of K469E was significantly lower in PSC than in controls (12% vs. 24%) and thus associated with protection against PSC[29].

Conclusions

In the last years several reports studied the association between ICAM-1 gene polymorphisms and IBD with conflicting results. Thus, multi-centre studies including a wide IBD population are needed to definitely clarify the role of ICAM-1 polymorphisms in IBD and in different clinical subgroup, also in association with other genetic and immunological markers.

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