damage is observed. This makes ET1 an additional useful marker for severe intestinal strangulation than other hitherto reported markers including procalcitonin.⁴ According to these results, measurement of plasma ET1 in a clinical setting is justified to further evaluate its value in the early diagnosis of intestinal ischaemia due to strangulation.

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The RANTES -28 g polymorphism is associated with primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disorder commonly associated with inflammatory bowel disease (IBD). The pathogenesis of PSC remains unknown, but bacterial translocation from the gut to the portal circulation, resulting in activation of an immune cascade and subsequent bile duct injury, is believed to be one of the triggering factors. In a previous study,¹ we found a significantly lower frequency of the Δ32 deletion in the CC-type chemokine receptor 5 (CCR5) gene in patients

Figure 1 The RANTES (*Regulated on Activation Normal T Expressed and Secreted*) gene and the position of the different studied polymorphisms.

with PSC compared with patients with IBD and healthy controls (HC), suggesting a protective effect of this mutation on the development of PSC. Given this association in our population, we further investigated the role of RANTES (*Regulated on Activation Normal T Expressed and Secreted*, also known as CC-motif chemokine ligand 5 (CCL5)), one of the ligands for the CCR5 receptor.

RANTES, localised to the cytokine cluster on chromosome 17q11.2-q12, is a plausible candidate gene for PSC, given its proinflammatory properties both independent of and as a ligand for the CCR5 receptor. A higher expression of RANTES has been reported in the gut epithelium and lymphocytes of patients with IBD.² Moreover, in an animal model of colitis, treatment with RANTES antagonists resulted in decreased bacterial translocation, as measured by portal blood endotoxin levels.³

Two promoter polymorphisms in RANTES (-28G and -403A) result in increased transcription of the gene, whereas a single-nucleotide polymorphism (SNP) in the first intron (In1.1C) results in reduced transcription of RANTES.⁴ We studied these three SNPs together with a fourth known SNP of as yet unknown function in the 3'UTR (3'222), for their role in susceptibility to PSC, and behaviour and progression of PSC (fig 1).

We genotyped 124 patients with PSC (63 without IBD, 25 with Crohn's disease (CD), 31 with ulcerative colitis (UC) and 5 with indeterminate colitis (IC)) for the -403G/A, -28C/G, In1.1T/C and 3'222T/C variants in the RANTES gene. Patients with PSC and IBD were recruited from the hepatology and gastroenterology departments of the same tertiary care referral centre. Table 1 summarises and compares the disease characteristics of IBD in patients with and without PSC. Genotype and

allele frequencies were compared with 595 patients with IBD without PSC (418 CD, 160 UC, 17 IC), and with 362 HC. SPSS V.14.0 software was used for statistical analysis, Haploview for calculation of linkage disequilibrium (LD)⁵ and fastPHASE 1.1.4 for haplotype estimation.⁶

Allele frequencies for the studied polymorphisms are summarised in table 2. All studied polymorphisms were in Hardy-Weinberg equilibrium. The -28G allele was significantly more frequent in patients with PSC (5.9%) compared with those with IBD (3.4%, $p=0.05$) and HC (2.2%, $p=0.005$). Furthermore, in patients with CD, the -28G allele was significantly more frequent in those patients who developed PSC (10.4%) compared with those who did not develop PSC (3%, $p=0.005$), with an odds ratio (OR) of 4.16 (95% CI 1.4 to 12). The allele frequency for the RANTES 3'222 allele was <1% in our cohort. The -403, -28 and In1.1 SNPs were all in strong LD (D' 0.838 for -403/-28, 0.946 for -403/In1.1 and 0.78 for -28/In1.1). Haplotype analysis could not identify differences between the studied groups. There was no association between any of the studied RANTES SNPs and location and behaviour of IBD or PSC in the different subgroups, nor with the CCR5Δ32 mutation.

In conclusion, this is the first report of an association between a functional promoter polymorphism in the RANTES gene, with an OR of 4.16 for the development of PSC in patients with CD. This -28G promoter polymorphism is known to result in increased RANTES transcription and expression. Given its known proinflammatory properties, and taking the data on the action of RANTES antagonists in experimental colitis into account,³ a possible mechanism to explain the

Table 1 Characteristics of patients with IBD and of patients with PSC with concomitant IBD

	Crohn's disease		Ulcerative colitis	
	CD with PSC n=25 (%)	CD without PSC n=418 (%)	UC with PSC n=31 (%)	UC without PSC n=160 (%)
Localisation of CD				
Ileal	1/25 (4)	107/396 (27)	—	—
Colonic	8/25 (32)	65/396 (16)		
Ileocolonic	15/25 (60)	177/396 (45)		
Upper	1/25 (4)	47/396 (12)		
Anal involvement	8/25 (35)	132/392 (34)		
Behaviour of CD				
Inflammatory	16/25 (64)	144/386 (37)	—	—
Strictureing	3/25 (12)	86/386 (22)		
Penetrating	6/25 (24)	156/386 (40)		
Localisation of UC				
Proctitis	—	—	3/31 (10)	33/146 (23)
Left-sided colitis			10/31 (32)	66/146 (45)
Extensive colitis			18/31 (58)	47/146 (32)

CD, Crohn's disease; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

Table 2 Allele frequencies for the -403, -28, in1.1 and 3'222 RANTES polymorphism in primary sclerosing cholangitis, inflammatory bowel disease and healthy controls

	PSC total n = 124 (%)	PSC without IBD n = 63 (%)	PSC CD n = 25 (%)	PSC UC n = 31 (%)	IBD total n = 595 (%)	CD without PSC n = 418 (%)	UC without PSC n = 160 v(%)	HC n = 362 (%)
RANTES-403A	18.1	14.9	25.0	20.0	18.6	19.1	17.9	19.7
RANTES-28G	5.9	3.4	10.4	6.5	3.3	3.0	4.2	2.2
RANTES in1.1C	15.3	12.9	22.9	14.5	13.8	15.0	10.6	14.6
RANTES 3'222C	0.0	0.0	0.0	0.0	0.7	0.9	0.3	0.0

CD, Crohn's disease; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; RANTES, Regulated on Activation Normal T Expressed and Secreted; UC, ulcerative colitis.

association between the RANTES -28G allele and PSC could be that an increased inflammatory response in the gut predisposes to bacterial translocation through the bowel wall.

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Increased risk of colorectal neoplasia in asymptomatic liver-transplant recipients

Liver-transplant recipients (LTRs) are known to carry an increased risk of cancer, including tumours of the skin and lymphoproliferative disorders.¹ Whether the risk of colorectal cancer (CRC) is increased after orthotopic liver transplantation (OLT) is controversial.² There is

also no consensus whether screening for colorectal neoplasia in asymptomatic LTRs is warranted, except for those with primary sclerosing cholangitis (PSC) with associated ulcerative colitis (UC).² In a previous study, we found an increased risk of CRC in patients after OLT compared with the general population.³ In this report, we examined the prevalence of colorectal adenomas and carcinomas in asymptomatic LTRs.

Between 1979 and 2001, 381 adult patients underwent OLT at the University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. For this retrospective study, all patients were included in which a colonoscopy had been performed for screening purposes, at least 5 years after OLT. Patients with symptoms suggestive of colorectal neoplasia and patients with previous colorectal neoplasia were excluded. Only complete colonoscopy reports including caecal inspection were included. Data on the presence, location and number of colorectal neoplastic lesions were collected. Patients with more than one lesion were categorised according to the most advanced lesion. All pathological specimens were reviewed by the study pathologist for assessment of the degree of dysplasia and the presence of villous architecture according to the World Health Organization criteria.⁴ Advanced neoplasia was defined as an adenoma of at least 1 cm in size, and/or (tubulo) villous architecture, and/or high-grade dysplasia, or cancer, in accordance with the literature.

In all, 92 asymptomatic patients, including 20 with PSC, had undergone colonoscopy at a median (range) age of 53.5 (35.8-71.2) years, after a median (range) interval of 11.1 (5.0-23.2) years after OLT. One or more adenomas were found in 20 of 92 (21.7%) patients (9 men, 11 women). Of these 20 patients, 4 had PSC, including 1 with concomitant UC. In 9 of 20 patients, one or more adenomas were located in the proximal colon. Advanced adenomas were found in 8 of 92 (8.7%) patients. Cancer was found in none of the patients.

These prevalence data in patients with OLT were compared with six asymptomatic cohorts from the literature (table 1). Although the prevalence of all neoplasia was comparable with other cohorts, advanced neoplasia was more often found in our population than in most studies. In addition, the relative proportion of advanced neoplasia, expressed as a ratio of all neoplasia, was 0.40 in our study, which is higher than in any other report. As the prevalence of colorectal neoplasia increases with age, data from our population were compared with data from the literature stratified in three groups (<50, 50-59 and >60 years). For patients aged <50 years and 50-59 years, the prevalence of advanced

neoplasia was higher in our study population than in any other study (table 1). Our data are probably best compared with the only other available Dutch study that was performed in a relatively young asymptomatic population.⁵ In patients aged <50 years, the relative risk in the population which underwent OLT was 3.6 (p<0.05) for overall neoplasia and 8.9 (p<0.01) for advanced neoplasia. Taken together, our data suggest that LTRs have a higher risk of colorectal neoplasia, particularly advanced neoplasia, compared with average-risk populations. The absence of a gender- and age-matched control group limits the strength of this retrospective study. We suggest designing larger and prospective studies including adequate control groups to better assess the risk of colorectal neoplasia in LTRs.

Currently, CRC screening is recommended in many countries worldwide for all patients aged ≥50 years. It was recently recommended that for the asymptomatic liver transplant population, CRC screening should be offered to those aged >50 years and those with PSC associated UC.² The results from our preliminary study suggest that CRC screening could be considered in all adult LTRs.

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