by restoring endothelial cell function of the portal vein in patients. However, the present study suggests that L-arginine deficiency in LPI can cause impairment of portal circulation via a decrease in NO production.

T Takeda, H Watanabe, T Saito, K Saito, H Takeda, H Togashi
Department of Gastroenterology, Faculty of Medicine, Yamagata University, Yamagata, Japan

J Fujii
Department of Biochemistry, Faculty of Medicine, Yamagata University, Yamagata, Japan

Y Takasago
Morioka Children's Hospital, Morioka, Japan

S Kawata
Department of Gastroenterology, Faculty of Medicine, Yamagata University, Yamagata, Japan

Correspondence to: Professor S Kawata, Department of Gastroenterology, Faculty of Medicine, Yamagata University, 2-2-2 Iida-nishi, Yamagata 990-9585, Japan; kawata@med.id.yamagata-u.ac.jp

doi: 10.1136/gut.2005.086603

Conflict of interest: None declared.

References

1 **Simell O**. Lysinuric protein intolerance and other aminocidurias. In: Scriver CR, Beaudet AL, Sly WS, *et al*. *The metabolic and molecular bases of inherited disease, vol 3*, 7th edn. New York: McGraw-Hill, 1995:3603–27.
2 **Sakuma I**, Stuehr DJ, Gross SS, *et al*. Identification of arginine as a precursor of endothelium-derived relaxing factor. *Proc Natl Acad Sci U S A* 1988;**85**:8664–7.
3 **Kilbourn RG**, Belloni P. Endothelial cell production of nitrogen oxides in response to interferon γ in combination with tumor necrosis factor, inteleukin-1, and endotoxin. *J Natl Cancer Inst* 1990;**82**:772–6.
4 **Palmer RMJ**, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987;**327**:524–6.
5 **Rubanyi GM**, Romero JC, Vanhoutte PM. Flow-induced release of endothelium-derived relaxing factor. *Am J Physiol* 1986;**250**:H1145–9.
6 **Kamada Y**, Nagaretani H, Tamura S, *et al*. Vascular endothelial dysfunction resulting from L-arginine deficiency in a patients with lysinuric protein intolerance. *J Clin Invest* 2001;**108**:717–24.
7 **Noguchi A**, Shoji Y, Koizumi A, *et al*. SLC7A7 genomic structure and novel variants in three Japanese lysinuric protein intolerance families. *Human Mutat* 2000;**15**:357–72.
8 **Koizumi A**, Shoji Y, Nozaki J, *et al*. A cluster of lysinuric protein intolerance (LPI) patients in a northern part of Iwate, Japan due to a founder effect. *Human Mutat* 2000;**16**:270–1.
9 **Taourel P**, Blanc P, Dauzat M, *et al*. Doppler study of mesenteric, hepatic, and portal measurements and the severity of portal hypertension and hepatic failure. *Hepatology* 1998;**28**:932–6.
10 **Piscaglia F**, Zironi G, Gaiani S, *et al*. Systemic and splanchnic hemodynamic changes after liver transplantation for cirrhosis: A long-term prospective study. *Hepatology* 1999;**30**:58–64.

Association study of *TNFSF15* polymorphisms in Japanese patients with inflammatory bowel disease

Tumour necrosis factor superfamily (TNFSF) 15 is a novel member of the TNFSF and its mRNA and protein expression is upregulated in inflammatory bowel disease (IBD), particularly in Crohn's disease (CD).[1 2] Recently, Yamazaki *et al* performed a large scale case control study using single nucleotide polymorphism (SNP) markers and reported that polymorphisms in *TNFSF15* conferred susceptibility to CD in both Japanese and UK populations.[3] They also suggested a potential association between a Caucasian ulcerative colitis (UC) cohort and *TNFSF15*, but this association was not studied in Japanese patients. To investigate this possible association between *TNFSF15* and Japanese UC, and to replicate this association with CD in Japanese, we performed a case control association study in Japanese patients with CD and UC.

We selected six SNPs—tnfsf15_26, tnfsf15_28, tnfsf15_31, tnfsf15_33, tnfsf15_35, tnfsf15_36—which were reported to show a strong association ($p<10^{-10}$), and genotyped these six SNPs in 286 patients with CD, 263 patients with UC, and 277 healthy controls (HCs) by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. All patients and HCs were Japanese, and none had a family history of IBD.

We replicated all six SNPs that were significantly associated with the Japanese CD cohort (table 1). On the other hand, in contrast with Caucasians,[3] none of the SNPs were associated with the Japanese UC cohort. Risk allele frequencies of tnfsf15_35, tnfsf15_36, and tnfsf15_31 were higher in the CD group with anal lesions than in those without, but the associations were statistically weak ($p = 0.019$, 0.019, and 0.037, respectively). No significant differences were found in allele frequencies between the CD subgroups classified by age at diagnosis, location of disease, existence of fistula, stenosis, need for steroid therapy, and past history of surgical treatment, and also the UC subgroups classified by age at diagnosis, extent of disease, need for intensive intravenous steroid therapy, and need for surgical treatment.

In this study, we confirmed the findings of a previous report concerning a significant association between *TNFSF15* and CD. On the other hand, no evidence for an association with Japanese UC was observed, although a potential association with Caucasian UC was reported. It is generally accepted that UC and CD may share some susceptibility genes. Ethnic differences in genetic susceptibility may be explained by differences in the haplotypic background. Some *TNFSF15* polymorphisms identified in the Japanese were monomorphic or nearly monomorphic in the Caucasian population.[3] Thus it seems likely that population specific patterns of haplotypes may contribute to differences in UC susceptibility.

Although a previous report described that tnfsf15_28 showed the lowest p value and highest odds ratio among the SNPs in *TNFSF15*,[3] our results showed that p values and odds ratios of tnfsf15_36 and tnfsf15_35 were similar to those of tnfsf15_28. Thus to identify the pathogenic SNP, a functional study is clearly needed. We analysed the transcription factor binding sites in the promoter region of *TNFSF15* by TFSEARCH[4] and found that GATA-1, 2, and 3 possibly bind the tnfsf15_35-T allele while the GATA binding *cis* element is absent in the tnfsf15_35-C allele (risk associated). It is well known that GATA-3 promotes a Th2 mediated immunological state and suppresses expression of Th1 mediated cytokines.[5 6] These findings have raised the possibility that GATA-3 may not bind the promoter region with the tnfsf15_35-C risk allele resulting in lack of suppression of TNFSF15 expression. Consequently, overexpressed TNFSF15 promotes a Th1 mediated immunological state and initiates or exacerbates the severity of CD. Although we do not have experimental evidence for this hypothesis, we intend to elucidate the functional significance in the future.

Y Kakuta, Y Kinouchi, K Negoro, S Takahashi, T Shimosegawa
Division of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai, Japan

Correspondence to: Dr Y Kakuta, Division of Gastroenterology, Tohoku University Graduate School of Medicine, 1-1 Seiryo, Aoba, Sendai, 980-8574, Japan; ykakuta@mail.tains.tohoku.ac.jp

doi: 10.1136/gut.2006.100297

Conflict of interest: None declared.

References

1 **Migone TS**, Zhang J, Luo X, *et al*. TL1A is a TNF-like ligand for DR3 and TR6/DcR3 and functions as a T cell costimulator. *Immunity* 2002;**16**:479–92.

Table 1 Allele frequencies of *TNFSF15*

SNP	dbSNP	Location	Allele1	Allele2	Frequency of allele2 (%)/OR/p value HCs (n = 277)	CD (n = 286)	UC (n = 263)
tnfsf15_36	rs7848647	5′-flanking region	G	A	39.0	25.7 (OR = 1.85, $p = 1.84\times10^{-6}$)	36.3 (NS)
tnfsf15_35	rs6478109	5′-flanking region	C	T	39.0	25.7 (OR = 1.85, $p = 1.84\times10^{-6}$)	36.3 (NS)
tnfsf15_33	rs6478108	Intron 1	A	G	51.8	37.6 (OR = 1.78, $p = 1.60\times10^{-6}$)	52.3 (NS)
tnfsf15_31	rs4979462	Intron 1	A	G	39.5	26.2 (OR = 1.84, $p = 1.98\times10^{-6}$)	36.5 (NS)
tnfsf15_28	–	Intron 3	C	T	53.1	38.8 (OR = 1.78, $p = 1.58\times10^{-6}$)	52.3 (NS)
tnfsf15_26	rs3810936	Exon 4 (Val201Val)	G	A	40.3	26.9 (OR = 1.83, $p = 2.15\times10^{-6}$)	36.3 (NS)

SNP, single nucleotide polymorphism; HCs, healthy controls; CD, Crohn's disease; UC, ulcerative colitis; NS, no significant. OR, odds ratio.

2 **Bamias G**, Martin C iii, Marini M, et al. Expression, localization, and functional activity of TL1A, a novel Th1-polarizing cytokine in inflammatory bowel disease. *J Immunol* 2003;**171**:4868–74.
3 **Yamazaki K**, McGovern D, Ragoussis J, *et al*. Single nucleotide polymorphisms in TNFSF15 confer susceptibility to Crohn's disease. *Hum Mol Genet* 2005;**14**:3499–506.
4 **Heinemeyer T**, Wingender E, Reuter I, *et al*. Databases on transcriptional regulation: TRANSFAC, TRRD and COMPEL. *Nucleic Acids Res* 1998;**26**:362–7.
5 **Zheng W**, Flavell RA. The transcription factor GATA-3 is necessary and sufficient for Th2 cytokine gene expression in CD4 T cells. *Cell* 1997;**89**:587–96.
6 **Ferber IA**, Lee HJ, Zonin F, *et al*. GATA-3 significantly downregulates IFN-gamma production from developing Th1 cells in addition to inducing IL-4 and IL-5 levels. *Clin Immunol* 1999;**91**:134–44.

NOTICE

The XXXI Pan American Congress of Digestive Diseases: Global challenges in gastroenterology from the end of the world

This conference will be held in Santiago, Chile, on 11–14 November 2008.

EDITOR'S QUIZ: GI SNAPSHOT

Answer

From question on page 1422

An abdominal operation revealed a hard whitish tumour. The tumour involved that part of the small intestine (fig 2). On pathological examination it was diagnosed as a metastasis from a pleomorphic carcinoma of the lung (fig 3). Metastasis of lung carcinoma to the small intestine has been reported to be in the range 2.6–10.7% in autopsy studies.[1 2] Some cases of small intestine metastasis showed various symptoms, such as obstruction, malabsorption, haemorrhage, and perforation. Berger *et al* reported that 0.5% of patients operated on for lung carcinoma developed symptomatic small intestine metastases.[3] In this case, the shape of the small intestine metastasis was unusual. Cancer cells were substituted for normal cells all round the intestinal wall. Intestinal fluid passed through inside the tumour so that, although he had slight abdominal pain after meals, he did not have obstruction. Fortunately, it did not perforate.

Careful examination for intra-abdominal lesions is needed after resection of primary lung carcinoma. If acute abdomen occurs in patients with a known history of lung carcinoma, gastrointestinal metastasis must be considered.

doi: 10.1136/gut.2005.090035

References

1 **McNeill PM**, Wagman LD, Neifeild JP. Small bowel metastases from carcinoma of the lung. *Cancer* 1987;**59**:1486–9.
2 **Antler AS**, Ough Y, Pitchumoni CS, *et al*. Gastrointestinal metastases from malignant tumor of the lung. *Cancer* 1982;**49**:170–2.
3 **Berger A**, Cellier C, Daniel C, *et al*. Small bowel metastases from primary carcinoma of the lung: clinical findings and outcome. *Am J Gastroenterol* 1999;**94**:1884–7.

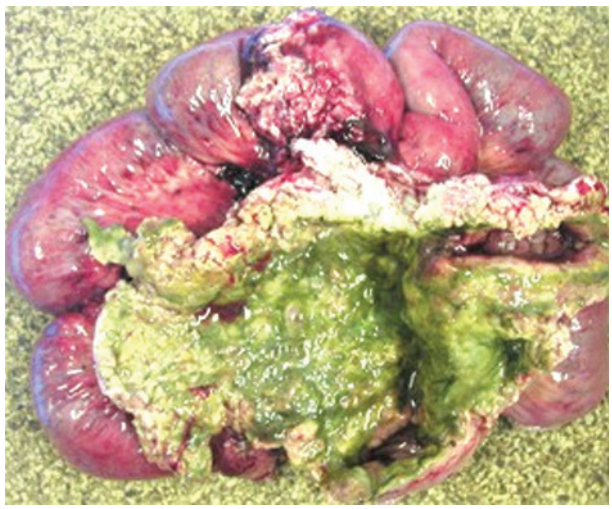

Figure 2 The tumour. The small intestine was segmented by the tumour but intestinal juice passed through the lumen of the tumour.

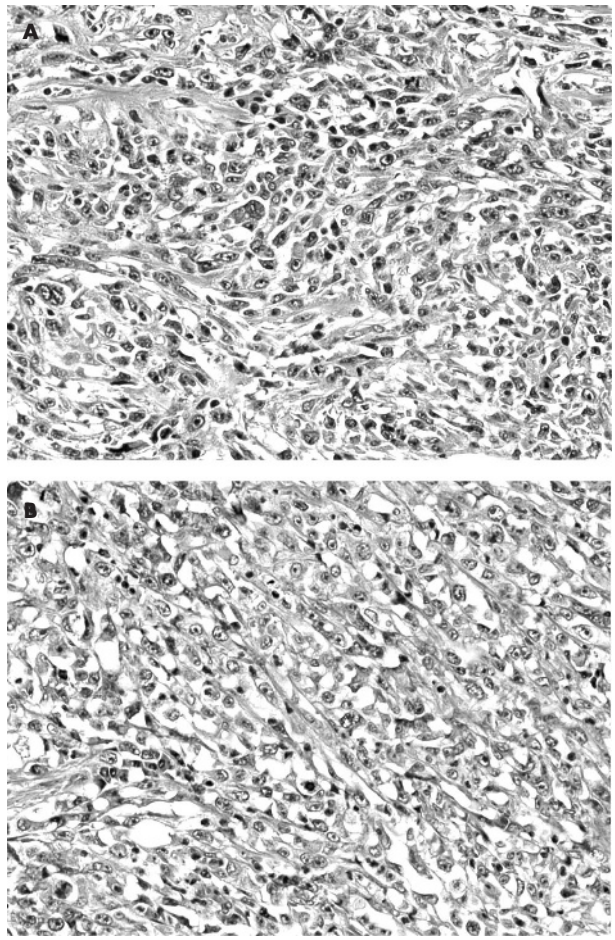

Figure 3 Pathological findings. On pathological examination, the structures of both the primary tumour (A) and metastatic tumour (B) were made of spindle cells and giant cell carcinoma. The similarity of the two tumours strongly supports the idea that the abdominal mass is a secondary.