MSI tumours and also think that we should spare no efforts in trying to understand the molecular basis of the response to chemotherapy in that kind of tumour. The importance of DNA methylation in prognosis and chemotherapy response is not completely known, and, in our opinion, research in that area is scarce and inconclusive. In our own and other published studies, most of the tumours that show a lack of efficacy of 5-FU in MMR-deficient tumours are sporadic (and therefore with MSI caused by hypermethylation of the promoter region of *MLH1*), suggesting that the lack of efficacy of adjuvant 5-FU on MSI tumours could happen in both hereditary and sporadic MSI tumours. Further studies on the role of hypermethylation in prognosis and chemotherapy response in colorectal cancer are under way in our series. Soon, we will be able to report the 5-year follow-up analysis in these series, which will bring forth new and interesting data on this topic.

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Paraoxonase 1, 2 and 3 DNA variants and susceptibility to childhood inflammatory bowel disease

Inflammatory bowel disease (IBD) is characterised by an imbalance between pro-oxidant and anti-oxidant mechanisms. Cellular detoxification systems in IBD seem unable to adequately control the amplified generation of reactive oxygen species, put a stop to free radical injury and repair damaged cellular elements, suggesting that an increase in oxidative stress might be involved in the pathogenesis of IBD,^{1,2} although the underlying molecular mechanisms remain largely undefined. Human paraoxonase family members (PON1, PON2, PON3) possess anti-oxidant and anti-inflammatory properties.^{3–5} Despite the large impact of genetic variation on PON activity, its important role in controlling oxidative stress and inflammation,^{5–8} as well as its association with several pathophysiological conditions,⁴ no

information is available on the relationship between PON genetic variants and IBD.

Here, we wanted to assess whether the genotype or haplotype distribution of PON polymorphisms was different in patients with IBD during childhood compared with healthy controls. Eight common variants in PON1, PON2 and PON3 were genotyped by polymerase chain reaction allele-specific oligonucleotide hybridisation assays in 192 incident cases of childhood IBD (mean SD age of onset 11.03 (3.9) years) diagnosed and treated at Ste-Justine Hospital (Montreal, Ontario, Canada) and in 92 controls, all of French-Canadian origin. In PON1, three promoter polymorphisms (–107 C→T, –824 A→G and –907 C→G) and two coding polymorphisms (L55M and Q192R) were genotyped. Although their distribution did not differ significantly between patients with IBD and controls, overall the frequency of the 192R (ex6 +78G) allele that seems to alter the structure of PON1 and influence enzyme activity in a substrate-dependent manner⁹ was consistently higher in patients with Crohn's disease (table 1). The structures of 11 haplotypes in French-Canadians, including seven with a frequency >7%, were inferred from the genotypic frequencies of the five PON1 variants (table 2). No significant differences were observed in the distribution of common haplotypes between patients with IBD and controls. The assessment of two linked PON2 polymorphisms (A148G and S311C) showed that people homozygous for 148GG and 311CC were less frequently found in patients with IBD than in controls (52% v 69%) suggesting a protective effect (odds ratio 0.5, 95% confidence interval 0.3 to 0.8, p = 0.011) against childhood IBD (table 3). No difference was observed in the frequency of PON2 variants in relation to the patient's characteristics (data not shown). The physiological role of PON2 is still unknown, but it was suggested that it may exert its anti-oxidant role by decreasing intracellular oxidative stress.³ Hence, it is plausible that subsequent to exposure to toxic

Table 1 Genotype distribution of paraoxonase 1 polymorphisms

Position	Controls (%)	IBD (%)	OR (95% CI)	CD (%)	OR (95% CI)	UC (%)	OR (95% CI)	IC (%)	OR (95% CI)
–907 G→C									
GG	19 (21)	37 (20)	0.97 (0.5 to 1.8)	26 (20)	0.93 (0.4 to 1.8)	6 (40)	2.4 (0.7 to 7.7)	5 (16)	0.7 (0.2 to 2.0)
GC	45 (50)	104 (59)		76 (59)		5 (33)		22 (71)	
CC	25 (28)	36 (20)		27 (20)		4 (27)		4 (13)	
–824 A→G									
AA	5 (6)	13 (7)	1.3 (0.4 to 3.8)	8 (6)	1.0 (0.3 to 3.5)	2 (13)	2.5 (0.4 to 14)	3 (10)	1.8 (0.4 to 8.0)
AG	42 (47)	83 (47)		64 (50)		4 (27)		15 (48)	
GG	42 (47)	80 (45)		56 (44)		9 (60)		13 (42)	
–107 C→T									
CC	22 (25)	44 (25)	1.0 (0.5 to 1.8)	33 (26)	1.0 (0.5 to 1.9)	6 (40)	2.0 (0.6 to 6.3)	5 (16)	0.5 (0.2 to 1.7)
CT	45 (50)	101 (57)		71 (55)		7 (47)		22 (71)	
TT	22 (25)	32 (18)		25 (19)		2 (13)		4 (13)	
Ex3+18T→A (L55M)									
TT	34 (38)	70 (38)	0.9 (0.4 to 2.0)	53 (39)	0.8 (0.3 to 1.9)	8 (53)	1.7 (0.4 to 7.3)	9 (29)	0.7 (0.2 to 3.0)
TA	45 (50)	93 (50)		69 (51)		4 (27)		19 (61)	
AA	11 (12)	22 (12)		14 (10)		3 (20)		3 (10)	
Ex6+78 A→G (Q192R)									
AA	46 (52)	81 (46)	1.1 (0.4–2.6)	51 (40)	1.3 (0.6–3.1)	10 (67)	0.6 (0.07–5.3)	20 (65)	0.6 (0.1 to 2.9)
AG	33 (38)	74 (42)		60 (47)		4 (27)		9 (29)	
GG	9 (10)	20 (11)		17 (13)		1 (7)		2 (6)	

CD, Crohn's disease; IBD, inflammatory bowel disease; IC, indeterminate colitis; UC, ulcerative colitis. The oligonucleotides and polymerase chain reaction assay conditions are available on request.

Table 2 Distribution of paraoxonase 1 haplotypes in patients with inflammatory bowel disease and in controls

Haplotype*	Controls (%) (n† = 178)	IBD (%) (n† = 354)	CD (%) (n† = 258)	UC (%) (n† = 30)	IC (%) (n† = 62)
CGTAA	32	30	30	23	34
GACTA	20	19	17	23	24
CGTTG	11	10	11	7	6
GACTG	9	9	12	3	5
GGCTA	7	8	7	13	8
CGTTA	7	6	5	7	8
CGCTG	1	2	2	—	—
CGCAA	2	1	1	3	—
GGCAA	3	1	0.4	7	—
GGCTG	7	9	10	10	8
GACAA	0.5	2	2	—	5
GGCAG	0	1	0.4	—	2
CGTAG	0	0.3	0.8	—	—

CD, Crohn's disease; IBD, inflammatory bowel disease; IC, indeterminate colitis; UC, ulcerative colitis.

*The single nucleotide polymorphism positions in a haplotype (inferred using the software PHASE) are the following: -907G→C, -824A→G, -107C→T, ex3+18T→A, ex6+78A→G.

†Number of chromosomes.

environmental factors, people carrying PON2 variants may be less likely to exhibit disease susceptibility. Five PON3 polymorphisms (G51G, G73G, A99A, S311T and G324D) were genotyped, but only A99A showed a minor allele frequency (>5%), which did not differ from controls (data not shown), suggesting that this allelic variant does not independently modify the overall risk of IBD.

In summary, we found that genetic variants in PON2 might contribute to the risk of developing childhood IBD, although additional studies must tackle the role of PON2 polymorphisms in childhood IBD in view of their potential effect on the expression of PON2 activity as an antioxidant.

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British Society of Gastroenterology guidelines for the diagnosis of Barrett's oesophagus: are we casting the net too wide?

We read with interest the British Society of Gastroenterology guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus¹ and the related commentary by Professor Playford (*Gut* 2006;55:442-3). One of the new recommendations in these guidelines relates to the diagnosis of Barrett's oesophagus. The guidelines state that "the presence of areas of intestinal metaplasia, although often present, is not a requirement for diagnosis". This is out of step with guidelines from the US, where intestinal metaplasia is required to establish a diagnosis of Barrett's oesophagus.² The rationale for the British guidelines is that sampling errors at initial endoscopy may miss areas affected with intestinal metaplasia. The evidence used to support this is an article from a Continuing Professional Development bulletin.³ The authors in this bulletin conclude that "if a sufficient number of biopsies are taken over an adequate period of time, IM can usually be demonstrated (in the majority of these patients)". Although this may at first seem logical, the results of a study from Northern Ireland do not support this logic.

We carried out a population-based study of Barrett's oesophagus and examined pathology reports relating to all sets of oesophageal biopsies carried out in Northern Ireland (population 1.7 million) between January 1993 and December 1999.⁴ Biopsy specimens of Barrett's oesophagus were subdivided into those in which intestinal metaplasia was present and those in which it was absent. Patients in the cohort were followed up until death or development of oesophageal malignancy. A total of 4955 sets of biopsy specimens from 2969 patients met the criteria for Barrett's oesophagus. After a mean follow-up of 3.7 (range 1-8) years, 29 oesophageal malignancies were found to have developed

Table 3 Genotype distribution of paraoxonase 2 polymorphisms

Position	Controls (%)	IBD (%)	OR (95% CI)	CD (%)	OR (95% CI)	UC (%)	OR (95% CI)	IC (%)	OR (95% CI)
Ex5+76 C→G (G148A)									
CC	61 (69)	91 (52)*	0.5 (0.3 to 0.8)	69 (55)**	0.5 (0.3 to 0.9)	7 (47)	0.4 (0.1 to 1.1)	13 (42)***	0.3 (0.1 to 0.7)
CG	24 (27)	73 (42)		49 (39)		7 (47)		16 (52)	
GG	3 (3)	10 (6)		7 (6)		1 (7)		2 (6)	
Ex9+25 C→G (S311C)									
CC	61 (69)	79 (52)*	0.5 (0.3 to 0.8)	60 (57)**	0.6 (0.3 to 1.0)	5 (38)***	0.3 (0.08 to 0.9)	13 (43)****	0.3 (0.1 to 0.8)
CG	24 (27)	62 (41)		39 (37)		7 (54)		15 (50)	
GG	3 (3)	10 (7)		7 (7)		1 (8)		2 (7)	

CD, Crohn's disease; IBD, inflammatory bowel disease; IC, indeterminate colitis; UC, ulcerative colitis.

*p=0.011. **p=0.045. ***p=0.001. ****p=0.015.

The oligonucleotides and polymerase chain reaction assay conditions are available on request.