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Reference

1 **Miele VJ**, Nigam A. Obstructive jaundice and pancreatitis secondary to percutaneous endoscopic gastrostomy tube migration. *J Gastroenterol Hepatol* 2005;**20**:1799–804.

Does delayed gastric emptying really cause symptoms in functional dyspepsia? We still doubt it!

We enjoyed reading the provocative commentary by Camilleri (*Gut* 2006;**55**:909–10) on our large study of patients with functional dyspepsia (*Gut* 2006;**55**:933–9). We completely agree that delayed gastric emptying is a marker of disturbed pathophysiology in functional dyspepsia; indeed, we first reported this observation in 1989.[1] However, we remain unconvinced, based on the available data, that this abnormality alone is linked to upper gastrointestinal symptoms.[1–3] Factor analysis studies from the general population, in the absence of objective testing, do not provide insights into this issue,[4 5] although we have shown that non-consulters with dysmotility-like dyspepsia are more likely to have gastric emptying delay.[6] Studies from selected tertiary care patients are of interest, but Camilleri has previously reported negative results.[3] Importantly, in a previous study of 551 patients with functional dyspepsia and 247 patients with type I diabetes and postprandial dyspepsia, gastric emptying, as measured by C^{13} octanoic acid breath testing, was also not linked to any specific upper gastrointestinal tract symptomatology.[2]

Interpretation of the symptom associations identified does need clarification, as statistical significance in a large study does not equate with clinical relevance. Our primary goal was to determine whether delayed gastric emptying was inducing symptom disturbances that, in turn, impair quality of life. The results from the models clearly suggest that while symptoms are associated with impaired quality of life in functional dyspepsia, gastric emptying is, at best, a very minor contributor and arguably has little clinical relevance.

We therefore dispute the view that there is overwhelming evidence of an association between symptoms and delayed gastric emptying. Indeed, we would argue that there continues to be accumulating evidence that there is often a disconnection between symptoms and slow gastric emptying. This does not negate the fact that delayed gastric emptying is an important biomarker, but it does strongly suggest that the symptom experience is related to other key factors that remain to be accurately identified.

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References

1 **Talley NJ**, Shuter B, McCrudden G, *et al*. Lack of association between gastric emptying of solids and symptoms in nonulcer dyspepsia. *J Clin Gastroenterol* 1989;**11**:625–30.
2 **Talley NJ**, Verlinden M, Jones M. Can symptoms discriminate among those with delayed or normal gastric emptying in dysmotility-like dyspepsia? *Am J Gastroenterol* 2001;**96**:1422–8.
3 **Bredenoord AJ**, Chial HJ, Camilleri M, *et al*. Gastric accommodation and emptying in evaluation of patients with upper gastrointestinal symptoms. *Clin Gastroenterol Hepatol* 2003;**1**:264–72.
4 **Camilleri M**, Dubois D, Coulie B, *et al*. Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: results of the US Upper Gastrointestinal Study. *Clin Gastroenterol Hepatol* 2005;**3**:543–52.
5 **Talley NJ**, Holtmann G, Agreus L, *et al*. Gastrointestinal symptoms and subjects cluster into distinct upper and lower groupings in the community: a four nations study. *Am J Gastroenterol* 2000;**95**:1439–47.
6 **Haag S**, Talley NJ, Holtmann G. Symptom patterns in functional dyspepsia and irritable bowel syndrome: relationship to disturbances in gastric emptying and response to a nutrient challenge in consulters and non-consulters. *Gut* 2004;**53**:1445–51.

Author's reply

The first demonstration of impaired gastric emptying in functional dyspepsia should be attributed to Rees and colleagues.[1] Additional information provided does not specifically counter the solid arguments offered in the commentary.

In response to the points raised I would like to put forth the following.

Firstly, the reason for dismissing in the published study a positive and significant association between postprandial fullness and gastric emptying is still not provided and appears arbitrary.

Secondly, reference number 2 (Talley *et al* 2001) in the letter was also an observational study of patients with functional dyspepsia and postprandial diabetic dyspepsia (clearly different conditions) participating in a multicentre drug study using a stable isotope gastric emptying test. The latter was subsequently shown to require more sophisticated mathematical analysis to provide accurate estimates of gastric emptying.[2 3] As the gastric emptying data in reference number 2 (Talley *et al* 2001) are suspect, they cannot be used to support the claim that gastric emptying does not contribute to symptoms.

Thirdly, the strongest observational data in functional dyspepsia are in the approximately 800 consecutive patients diagnosed and studied in a uniform manner at a single centre by Tack and colleagues.[4] In this study, a significant association between gastric emptying delay and symptoms of early satiety, nausea, vomiting, and fullness was convincingly demonstrated. It is possible that discrepancies between the studies may reflect the wide spectrum of patients included under ''epigastric pain and discomfort'' in the Rome I and II criteria for dyspepsia. The reference to Bredenoord *et al* (reference No 3 in the letter) is quoted out of context as that study had a different aim, and symptoms were evaluated by patient history rather than in response to a standardised meal.

Fourthly, my commentary never claimed that there was overwhelming evidence that gastric emptying *alone* was responsible for symptoms. Rather, the literature (summarised in Tack's review[4]) shows that combinations of symptoms (typically those now grouped in the ''postprandial distress syndrome'' in the Rome III criteria for functional dyspepsia[5]) are associated with abnormal gastric functions, including abnormal gastric emptying.

Controlled perturbations of physiology provide a more meaningful appraisal of the causative relationship between pathophysiology and symptom generation. Abnormal gastric emptying is not just a biomarker. Our studies show that several physiological perturbations (for example, gastric emptying, sensitivity, and dysaccommodation) also contribute to the variance in symptoms.[6] In studies to date, no single factor has explained more than 25% of the variance in symptoms of patients with dyspepsia.[6] However, this does not justify dismissal of gastric emptying as a causative cofactor in dyspepsia.

The statement that ''gastric emptying has arguably little clinical relevance'' by Talley *et al* is not based on a fair global interpretation of the available literature.

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References

1 **Rees WD**, Miller LJ, Malagelada JR. Dyspepsia, antral motor dysfunction, and gastric stasis of solids. *Gastroenterology* 1980;**78**:360–5.
2 **Choi MG**, Camilleri M, Burton DD, *et al*. [13C]octanoic acid breath test for gastric emptying of solids: accuracy, reproducibility, and comparison with scintigraphy. *Gastroenterology* 1997;**112**:1155–62.
3 **Maes BD**, Mys G, Geypens BJ, *et al*. Gastric emptying flow curves separated from carbon-labeled octanoic acid breath test results. *Am J Physiol* 1998;**275**:G169–75.
4 **Tack J**, Bisschops R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. *Gastroenterology* 2004;**127**:1239–55.
5 **Tack J**, Talley NJ, Camilleri M, *et al*. Functional gastroduodenal disorders. *Gastroenterology* 2006;**130**:1466–79.
6 **Delgado-Aros S**, Camilleri M, Cremonini F, *et al*. Contributions of gastric volumes and gastric emptying to meal size and postmeal symptoms in functional dyspepsia. *Gastroenterology* 2004;**127**:1685–94.

Association of tumour necrosis factor α promoter haplotype with chronic pancreatitis

Genetic risk factors are attributed an important role in the pathogenesis of chronic pancreatitis.[1] The genetic basis of chronic pancreatitis is complex. The cationic trypsinogen gene,[2] serine

Table 1 Five locus haplotype (−1031/−863/−857/−308/−238) frequency estimates of tumour necrosis factor α promoter in patients with chronic pancreatitis and controls and significance levels of comparison from permutation tests

Haplotype	Overall (n = 270)	CP (n = 70)	Controls (n = 200)	χ^2	p Value	OR
TCCGG	0.595860	0.540880	0.621680	2.82249	Ref	Ref
CACGG	0.141300	0.144350	0.142340	0.00342	0.946	1.016498
TCTGG	0.081810	0.059120	0.087790	1.15374	0.336	0.650546
TCCAG	0.053060	0.000000	0.068920	10.16847	0.002*	ND
TACGG	0.049970	0.128310	0.017020	29.3496	<0.0000001	8.503401
CACAG	0.018230	0.048120	0.004580	12.5827	0.006*	10.975743
TATGG	0.009870	0.007410	0.010530	0.10515	0.819	0.701090
CCCGG	0.009380	0.000000	0.012110	1.71025	0.292	ND
CATGG	0.009030	0.027080	0.002370	7.28342	0.131	11.735711
CCCGA	0.007490	0.000000	0.010100	1.42439	0.232	ND
TCTAG	0.005060	0.000000	0.005810	0.81674	0.666	ND
TACAG	0.004240	0.024060	0.000660	8.49643	0.015*	37.271710
TCCGA	0.003810	0.000000	0.005090	0.71562	0.452	ND
CATGA	0.003520	0.007140	0.002310	0.68242	0.223	3.107713
CATAG	0.002710	0.001880	0.005200	0.26332	0.747	0.361452
TATAG	0.001880	0.011660	0.000000	4.67664	0.05*	ND
CCTAG	0.001860	0.000000	0.002330	0.32635	0.997	ND
CCTGG	0.000930	0.000000	0.001170	0.16449	0.894	ND
Log likelihood				58.28461	0.00100	

CP, chronic pancreatitis; OR, odds ratio; ND, not done.

protease inhibitor Kazal type 1 (SPINK1),[3] and cystic fibrosis transmembrane conductance regulator[4] genes have been most extensively studied in chronic pancreatitis. However, the frequency of hereditary pancreatitis, which may be related to the trypsinogen gene and SPINK1 in Orientals, is regarded as relatively low and hardly explains the genetic susceptibility of chronic pancreatitis in Chinese.[5] Chronic pancreatitis is a progressive chronic inflammatory disease characterised by irreversible destruction of exocrine pancreatic tissue and extensive fibrosis. Tumour necrosis factor (TNF)-α, a prototype proinflammatory cytokine, has been implicated as an important pathogenic mediator in a variety of inflammatory diseases. Several biallelic polymorphisms have been described within the *TNF*-α promoter region upstream of the transcriptional start site.[6] In the past, limited and conflicting data on the associations between TNF-α promoter polymorphisms and the pathogenesis of chronic pancreatitis have been reported in Western countries.[7]

In this study, cases with chronic pancreatitis and controls were recruited consecutively from the National Taiwan University Hospital from July 2000 to June 2003. They were the so-called ''Taiwanese'' or ''Taiwan Chinese.'' Most of their ancestors moved to Taiwan from southeastern China approximately 500 years ago. They were not Taiwanese aborigines. Chronic pancreatitis was defined histopathologically or by the occurrence of pancreatic parenchymal calcifications demonstrated in imaging studies. All patients were negative for the trypsinogen gene (PRSS1) and SPINK1 mutations. Patients who had pancreatic adenocarcinoma or any malignancies were also excluded. The aetiology of chronic pancreatitis was classified using the TIGAR-O system.[1] We genotyped 70 cases (48 men and 22 women) and 286 control subjects (151 men and 135 women) for five TNF-α promoter polymorphisms (−1031, −863, −857, −308, and −238) using direct sequencing. The study was approved by the local institution committee, and subjects gave their informed consent. Age and sex were not statistically different. All of the study subjects were followed up for at least three years and no malignancy was diagnosed during this period.

Allele frequencies of TNF-α promoter −1031C, −863A, −857T, −308A, and −238A were 19%, 19.25%, 26%, 8.25%, and 1.75%, respectively, and were consistent with previous reports in the Chinese population. The −863A allele of the TNF-α promoter conferred an increased risk for chronic pancreatitis (odds ratio (OR) 4.949 (95% confidence interval (CI) 2.678–9.035)). In multivariate analysis, −863A and −1031C were independently associated with higher susceptibility to chronic pancreatitis ($p<0.0001$).

We also determined the haplotypes for chronic pancreatitis risk by EM based haplotype frequency estimations and permutation based hypothesis testing procedures based on previous work in our institution.[8] Table 1 displays the results of five locus estimated haplotype frequency analyses for the TNF-α promoter. The omnibus haplotype profile test was highly significant ($\chi^2 = 58.28461$, $p = 0.001$). TACAG, CACAG, and TACGG haplotypes were associated with ORs (37.27, 10.97, and 8.50) that indicated a large association effect ($p<0.05$).

Here we report for the first time associations between TNF-α promoter polymorphisms and TNF-α promoter haplotype in non-hereditary chronic pancreatitis. Our findings provide the possibility that TNF-α promoters are candidate genes for non-hereditary chronic pancreatitis in Chinese. In Taiwanese Chinese, the −863 and −1031 alleles of the TNF-α promoter were also reported to determine the severity of benign ulcerations after *Helicobacter pylori* infection.[9] Moreover, the −1031/−863/−857 three locus haplotype was associated with a higher risk of Alzheimer's disease in Chinese patients in Hong Kong.[10] These findings support the fact that the TNF-α promoter polymorphism/haplotype is truly associated with some disease entities and phenotypes in our population.

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References

1 **Etemad B**, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001;**120**:682–707.
2 **Gorry MC**, Gabbaizedeh D, Furey W, *et al*. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. *Gastroenterology* 1997;**113**:1063–8.
3 **Witt H**, Luck W, Hennies HC, *et al*. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. *Nat Genet* 2000;**25**:213–16.
4 **Cohn JA**, Mitchell RM, Jowell PS. The role of cystic fibrosis gene mutations in determining susceptibility to chronic pancreatitis. *Gastroenterol Clin North Am* 2004;**33**:817–37.
5 **Gu ZY**, Zhang KH. Chronic pancreatitis in China: etiology and management. *World J Surg* 1990;**14**:28–31.
6 **Wilson AG**, Symons JA, McDowell TL, *et al*. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. *Proc Natl Acad Sci U S A* 1997;**94**:3195–9.
7 **Schneider A**, Pogue-Geile K, Barmada MM, *et al*. Hereditary, familial, and idiopathic chronic pancreatitis are not associated with polymorphisms in the tumor necrosis factor alpha (TNF-alpha) promoter region or the TNF receptor 1 (TNFR1) gene. *Genet Med* 2003;**5**:120–5.
8 **Tsai CT**, Lai LP, Lin JL, *et al*. Renin-angiotensin system gene polymorphisms and atrial fibrillation. *Circulation* 2004;**109**:1640–6.

9 **Lu CC**, Sheu BS, Chen TW, *et al*. Host TNF-alpha-1031 and −863 promoter single nucleotide polymorphisms determine the risk of benign ulceration after H. pylori infection. *Am J Gastroenterol* 2005;**100**:1274–82.
10 **Ma SL**, Tang NL, Lam LC, *et al*. Association between tumor necrosis factor-alpha promoter polymorphism and Alzheimer's disease. *Neurology* 2004;**62**:307–9.

Lack of association of the pregnane X receptor (PXR/NR1I2) gene with inflammatory bowel disease: parallel allelic association study and gene wide haplotype analysis

The pregnane X receptor gene (PXR/NR1I2) regulates an array of genes involved in the response to xenobiotics.[1 2] Dysregulation of this gene may critically influence intestinal barrier defence and susceptibility to inflammatory bowel disease (IBD).[3] Recent data from Ireland have suggested strong associations between polymorphisms within the PXR/NR1I2 gene and IBD. Dring *et al* performed a case control study involving 422 patients with IBD (185 ulcerative colitis (UC) and 237 (Crohn's disease (CD)) and 350 healthy controls, using eight candidate polymorphisms in this gene.[4] Highly significant associations were demonstrated with UC, CD, and IBD as a whole. This effect was most significant for the two individual single nucleotide polymorphisms (SNPs) in the promoter region of this gene; compared between the IBD cohort and controls, rs3814055/−23585 ($p = 0.000008$; odds ratio (OR) 1.62 (95% confidence interval (CI) 1.31–2.00)) and rs1523127/−24381 ($p = 0.0002$; OR 1.50 (95% CI 1.21–1.84)).

We have critically re-evaluated the contribution of these allelic variants of rs1523127/−24381 of the PXR/NR1I2 gene as determinants of disease susceptibility and phenotype in the Scottish population. In addition, we also performed a gene wide association study using a haplotype tagging strategy to assess in detail the overall contribution of this gene to disease susceptibility. A total of 387 UC and 328 CD patients, together with 338 healthy controls (HC), were studied. This study was designed to have 98% power to replicate the previous association with the rs1523127/−24381 variant ($p<0.05$). In the haplotype analysis, five tagging SNPs (tSNPs) were selected using a multimarker criterion, haplotype $r^2>0.80$ to predict all SNPs/haplotypes. This approach was described by Weale and Goldstein and was successfully applied in our previous study of the ABCB1/MDR1 gene.[5–8] The exons,

Table 1 Allelic and genotype frequencies of the selected five tagging single nucleotide polymorphisms (tSNPs)

dbSNP ID position	Allele (1/2)	UC	CD	IBD	HC	UC *v* HC 1 *v* 2 p value odds ratio 95% CI	UC *v* HC 1/1 *v* 2/2 p value odds ratio 95% CI	CD *v* HC 1 *v* 2 p value odds ratio 95% CI	CD *v* HC 1/1 *v* 2/2 p value odds ratio 95% CI	IBD *v* HC 1 *v* 2 p value odds ratio 95% CI	IBD *v* HC 1/1 *v* 2/2 p value odds ratio 95% CI
rs1523127	AA	139 (35.9%)	102 (31.1%)	241 (33.7%)	119 (35.6%)	0.96	0.91	0.69	1.00	0.82	1.00
120983729	AG	190 (49.1%)	186 (56.7%)	376 (52.6%)	167 (50.0%)	0.99	0.97	0.95	1.03	0.97	0.99
	GG	58 (15.0%)	40 (12.2%)	98 (13.7%)	48 (14.4%)	0.80–1.22	0.61–1.52	0.76–1.19	0.62–1.69	0.81–1.17	0.66–1.49
	A	468 (60.5%)	390 (59.5%)	858 (60.0%)	405 (60.6%)						
	G	306 (39.5%)	266 (40.5%)	572 (40.0%)	263 (39.4%)						
rs2461823	CC	152 (40.9%)	132 (40.2%)	284 (40.6%)	119 (35.8%)	0.38	0.71	0.46	0.80	0.38	0.66
121002815	CT	175 (47.0%)	157 (47.9%)	332 (47.4%)	174 (52.4%)	1.11	1.11	1.09	1.10	1.09	1.10
	TT	45 (12.1%)	39 (11.9%)	84 (12.0%)	39 (11.7%)	0.88–1.37	0.68–1.81	0.87–1.37	0.66–1.82	0.90–1.32	0.71–1.70
	C	479 (64.4%)	421 (64.2%)	900 (64.3%)	412 (62.0%)						
	T	265 (35.6%)	235 (35.8%)	500 (35.7%)	252 (38.0%)						
rs7643645	TT	143 (39.7%)	128 (43.2%)	271 (41.3%)	128 (38.5%)	0.79	0.90	0.82	0.62	0.73	0.91
121008187	TC	172 (47.8%)	120 (40.5%)	292 (44.5%)	168 (50.6%)	1.04	1.04	1.04	0.87	1.04	0.96
	CC	45 (12.5%)	48 (16.2%)	93 (14.2%)	42 (12.6%)	0.84–1.29	0.64–1.69	0.82–1.30	0.54–1.42	0.86–1.26	0.63–1.46
	T	458 (63.6%)	376 (63.5%)	834 (63.6%)	424 (62.7%)						
	C	262 (36.4%)	216 (36.5%)	478 (36.4%)	252 (37.3%)						
rs1464603	AA	172 (45.9%)	153 (46.6%)	325 (46.3%)	167 (49.4%)	0.61	1.00	0.72	1.00	0.62	1.00
121009039	AG	159 (42.5%)	138 (42.1%)	297 (42.3%)	130 (38.5%)	0.94	0.98	0.96	1.01	0.95	0.99
	GG	43 (11.5%)	37 (11.3%)	80 (11.4%)	41 (12.1%)	0.75–1.17	0.61–1.58	0.76–1.21	0.62–1.67	0.78–1.15	0.65–1.52
	A	503 (67.2%)	444 (67.7%)	947 (67.5%)	464 (68.6%)						
	G	245 (32.8%)	212 (32.3%)	457 (32.5%)	212 (31.4%)						
rs2472682	TT	42 (11.0%)	35 (11.1%)	77 (11.0%)	39 (11.7%)	0.65	1.00	0.63	0.70	0.97	0.82
121015342	TG	177 (46.2%)	129 (40.8%)	306 (43.8%)	140 (42.2%)	1.06	1.00	0.94	0.90	1.00	0.96
	GG	164 (42.8%)	152 (48.1%)	316 (45.2%)	153 (46.1%)	0.84–1.32	0.62–1.64	0.74–1.19	0.54–1.50	0.82–1.22	0.62–1.47
	T	261 (34.1%)	199 (31.5%)	460 (32.9%)	218 (32.8%)						
	G	505 (65.9%)	433 (68.5%)	938 (67.1%)	446 (67.2%)						

UC, ulcerative colitis; CD, Crohn's disease; HC, healthy controls; 95% CI, 95% confidence interval.