

## Gene polymorphisms associated with functional dyspepsia

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### Abstract

Functional dyspepsia (FD) is a constellation of functional upper abdominal complaints with poorly elucidated pathophysiology. However, there is increasing evidence that susceptibility to FD is influenced by hereditary factors. Genetic association studies in FD have examined genotypes related to gastrointestinal motility or sensation, as well as those related to inflammation or immune response. G-protein b3 subunit gene polymorphisms were first reported as being associated with FD. Thereafter, several gene polymorphisms including serotonin transporter promoter, interleukin-17F, migration inhibitory factor, cholecystocynine-1 intron 1, cyclooxygenase-1, catechol-o-methyltransferase, transient receptor potential vanilloid 1 receptor, regulated upon activation normal T cell expressed and secreted, p22PHOX, Toll like receptor 2, SCN10A, CD14 and adrenoreceptors have been investigated in relation to FD; however, the results are contradictory. Several limitations underscore the value of current studies. Among others, inconsistencies in the definitions of FD and controls, subject composition differences regarding FD subtypes, inadequate samples, geographical and ethnical differences, as well as unadjusted environmental factors. Further well-designed studies are necessary to determine how targeted genes polymorphisms, influence the clinical manifestations and potentially the therapeutic response in FD.

**Key words:** Functional dyspepsia; Gene polymorphism; Genetic susceptibility; Pathophysiology

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**Core tip:** Functional dyspepsia is a common disorder with complex pathophysiology. Recent evidence has shown that certain gene polymorphisms might be implicated in its pathogenesis; however, results are inconsistent.

Further studies are required to develop new data that provide novel insights regarding the mechanisms of genetic susceptibility in functional dyspepsia.

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## INTRODUCTION

Functional dyspepsia (FD) is a common clinical condition, up to 25% of the population experience symptoms, characterized by the presence of one or more of the following: epigastric pain or burning, postprandial fullness, early satiation, with no anatomical abnormality (detected by gastroscopy) to explain the symptoms. These symptoms should be present for the last three months with symptom onset at least six months before diagnosis. Functional dyspepsia is classified into postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS); however, these two syndromes may overlap<sup>[1-3]</sup>.

While FD pathophysiology is not yet well elucidated<sup>[4]</sup>, several pathogenetic mechanisms have been proposed, including gastric motility and compliance dysfunctions (antral hypomotility, delayed or rapid gastric emptying, impaired gastric accommodation)<sup>[5-9]</sup>, visceral hypersensitivity<sup>[10-14]</sup>, and psychosocial disorders<sup>[15-18]</sup>. Moreover, evidence from randomized controlled trials suggests that eradication of *Helicobacter pylori* (*H. pylori*) leads to relief of dyspeptic symptoms in some patients. At the same time, studies have failed to confirm a temporal correlation between *H. pylori* infection and FD or the relation between *H. pylori* and FD subgroups<sup>[19-22]</sup>.

There is growing evidence that susceptibility to functional gastrointestinal disorders is influenced by hereditary factors. Genetic association studies in patients with FD have investigated candidate genes associated with G protein functions, inflammation and immune response, gastrointestinal sensation and control of adrenergic, serotonergic and cholecystokinergic functions; however, studies have shown inconsistent results in different populations. The results of currently available studies are summarized in Tables 1 and 2.

The aim of this review is to provide insights and critical appraisal on the existing evidence of certain gene polymorphisms implicated in FD pathogenesis.

## FAMILIAL AGGREGATION

Locke *et al.*<sup>[23]</sup> reported familial aggregation in adults with functional gastrointestinal disorders. Among 643

American subjects, the presence of a first-degree relative with abdominal pain or bowel problems was significantly associated with the diagnosis of either irritable bowel syndrome (OR = 2.3; 95%CI: 1.3-3.9) or dyspepsia (OR = 1.8; 95%CI: 1.05-3.0). Gathaiya *et al.*<sup>[24]</sup> showed that a positive family history of abdominal pain (OR = 4.7, 95%CI: 1.5-14.9; *P* = 0.008) and indigestion (OR = 3.4, 95%CI: 1.0-11.5; *P* = 0.04) were independently associated with FD raising the possibility of a genetic component in the disease, although shared environmental factors need to be considered. On the contrary, one study of 986 twin pairs in the United States showed a genetic contribution to gastro-esophageal reflux disease (GERD) and irritable bowel syndrome (IBS), but not to dyspepsia<sup>[25]</sup>. However, this study was limited by the inclusion of uninvestigated dyspeptics only.

## GENE POLYMORPHISMS AND FUNCTIONAL GASTROINTESTINAL DISORDERS

Evidence suggests that alterations in the brain-gut axis functionality is the main mechanism related to motor disorders, visceral hypersensitivity and autonomic dysfunction<sup>[26,27]</sup>. Several neurotransmitters such as serotonin 5-hydroxytryptamine (5-HT), substance P, VIP and CCK participate in the regulation of this axis. These mechanisms that affect both central and peripheral levels of brain-gut interaction may be influenced by genetic factors and some reports have suggested that genes and substances involved in the brain-gut axis might be the keys to unlock the mystery of IBS pathogenesis<sup>[27,28]</sup>.

Certain gene polymorphisms encoding adrenergic, serotonergic and opioidergic receptors, as well as genes involving proteins with immunomodulatory and/or neuromodulatory features have been investigated in functional disorders<sup>[29,30]</sup>. These studies have highlighted the importance of G-protein beta 3 subunit gene (C825T), polymorphisms in the promoter region of the serotonin reuptake transporter gene, cholecystokinin receptor (CCKAR), and high-producer tumor necrosis factor genotype in IBS<sup>[31]</sup>. Genetic variation in the *NPSR1* gene, which encodes neuropeptide S receptor, affects children's predisposition to recurrent abdominal pain (RAP), and the NPS-NPSR1 system which acts along the gut-brain axis to regulate inflammation, anxiety and nociception is suggested as a modulator of intestinal function that may influence individual risk for the development of functional gastrointestinal disorders<sup>[32]</sup>.

Candidate genotypes for FD have also been tested, leading to inconsistent results in different populations. GABARA6 genotypes have been associated with susceptibility to stress and gastric acid secretion. In a Chinese study, a positive correlation between

**Table 1 Genetic association studies in functional dyspepsia involving gene polymorphisms related to gastrointestinal motility or sensation**

Ref.	Study origin	FD subjects/controls, <i>n</i>	Studied gene polymorphism	Disease association
Holtmann <i>et al</i> <sup>[39]</sup>	United States	STUDY A: 67/259 STUDY B: 56/112	GNB3 C825T (CC)	FD
Camilleri <i>et al</i> <sup>[40]</sup>	United States	41/47	GNB3 C825T (CC) or (TT)	Meal unrelated dyspepsia
van Lelyveld <i>et al</i> <sup>[42]</sup>	The Netherlands	112/336	GNB3 C825T 825T	FD
Tahara <i>et al</i> <sup>[41]</sup>	Japan	89/94	GNB3 C825T 825TT	FD in <i>H. pylori</i> (-)
Oshima <i>et al</i> <sup>[43]</sup>	Japan	68/761	GNB3 C825T 825TT	EPS
Shimpuku <i>et al</i> <sup>[44]</sup>	Japan	74/64	GNB3 C825T 825CC	PDS with impaired gastric emptying and feeling of hunger in FD
Park <i>et al</i> <sup>[45]</sup>	South Korea	102/148	GNB3 C825T 825CC	FD in children
Hwang <i>et al</i> <sup>[46]</sup>	South Korea	112/269	GNB3 C825T	No association
Camilleri <i>et al</i> <sup>[40]</sup>	United States	41/47	SERT-P(SLC6A4)	No association
van Lelyveld <i>et al</i> <sup>[42]</sup>	The Netherlands	112/336	SERT-P(SLC6A4)	No association
Toyoshima <i>et al</i> <sup>[62]</sup>	Japan	53/646	SLC6A45-HTTLPR allele	PDS
Arisawa <i>et al</i> <sup>[63]</sup>	Japan	223/172	SERT-P(SLC6A4)	No association
Park <i>et al</i> <sup>[45]</sup>	South Korea	102/148	SERT-P(SLC6A4)	No association
Hwang <i>et al</i> <sup>[46]</sup>	South Korea	112/269	SLC6A45-HTTLPR (S/S)	Inverse association with EPS in <i>H. pylori</i> (+)
Arisawa <i>et al</i> <sup>[63]</sup>	Japan	223/172	Pri-microRNA-325	FD Interacts with SLC6A4 in increasing susceptibility to FD, especially in <i>H. pylori</i> (-)
Camilleri <i>et al</i> <sup>[40]</sup>	United States	41/47	5-HT1A, 5-HT2A, 5HT2C	No association
van Lelyveld <i>et al</i> <sup>[42]</sup>	The Netherlands	112/336	HTR3A C178T	No association
Mujakovic <i>et al</i> <sup>[69]</sup>		NA	HTR3Ac-42C>T HTR3Ac-42T	Severe FD
Tahara <i>et al</i> <sup>[68]</sup>	Japan	91/93	5HTR2A C 102T	No association
Camilleri <i>et al</i> <sup>[40]</sup>	United States	41/47	a2a, a2c adrenoreceptor	No association
Hwang <i>et al</i> <sup>[46]</sup>	South Korea	112/269	a2a	No association
Camilleri <i>et al</i> <sup>[40]</sup>	United States	41/47	CCK1, CCK promoter	No association
Hwang <i>et al</i> <sup>[46]</sup>	South Korea	112/269	CCK1R intron 779 T>C	No association
Tahara <i>et al</i> <sup>[73]</sup>	Japan	124/119	CCK-1 intron 1 779T	PDS in males
Tahara <i>et al</i> <sup>[107]</sup>	Japan	109/98	TRPV1 G315C 315CC	Inverse association with FD, EPS, PDS, <i>H. pylori</i> (+)
Hwang <i>et al</i> <sup>[46]</sup>	South Korea	112/269	TRPV1 G945C CC	Inverse association with FD, PDS, EPS especially in <i>H. pylori</i> (+)
Arisawa <i>et al</i> <sup>[108]</sup>	Japan	297/345	SCN10A 3218CC	Inverse association with FD
Arisawa <i>et al</i> <sup>[108]</sup>	Japan	297/345	SCN10A 2884A>G	Inverse association with FD, EPS, PDS especially in <i>H. pylori</i> (-)
Arisawa <i>et al</i> <sup>[108]</sup>	Japan	297/345	SCN10A 3275T>5	Inverse association with FD, EPS, PDS especially in <i>H. pylori</i> (-)
Tahara <i>et al</i> <sup>[100]</sup>	Japan	91/94	COMT	FD

FD: Functional dyspepsia; EPS: Epigastric pain syndrome; PDS: Postprandial distress syndrome.

GABARA6 genotypes and functional heartburn provides an insight into the contribution of genetic factors to disease development<sup>[33]</sup>.

### G-protein b3 subunit gene polymorphism (C825T)

G-proteins are important in stimulus-response coupling of almost 80% of membrane receptors that are linked to intracellular effector systems<sup>[34]</sup>. G-protein B3 (GNB3) subunit gene polymorphism (C825T) is related to alternative G-protein activity and signal transduction. The 825T allele is associated with enhanced G-protein activation, while the C allele

is predictive of diminished G-protein activation<sup>[35,36]</sup>. Studies have shown an association between GNB3 status and depression<sup>[37]</sup>, altered activation of  $\alpha$ 2-adrenoreceptors<sup>[36]</sup> and increased immune cell activation<sup>[38]</sup>. The altered signal transduction related to the CC or TT allele may contribute to the abnormalities in gastroduodenal sensory and motor function observed in FD.

Holtmann *et al*<sup>[39]</sup> suggested, for the first time, a role for the homozygous 825CC GNB3 genotype in dyspepsia in Caucasians. Blood donors with gastrointestinal symptoms and two different clinic-

**Table 2 Genetic association studies in functional dyspepsia involving gene polymorphisms related to inflammation or immune response**

Ref.	Study origin	FD subjects/ controls, <i>n</i>	Studied gene polymorphism	Disease association
Tahara <i>et al</i> <sup>[78]</sup>	Japan	108/99	CD 14	No association
Arisawa <i>et al</i> <sup>[82]</sup>	Japan	90/188	MIF G173C	EPS, especially in <i>H. pylori</i> (+)
Arisawa <i>et al</i> <sup>[82]</sup>	Japan	90/188	173C	No association
Arisawa <i>et al</i> <sup>[82]</sup>	Japan	90/188	IL-17A	EPS in <i>H. pylori</i> (+)
Arisawa <i>et al</i> <sup>[82]</sup>	Japan	90/188	IL17F	
			7488T	
Tahara <i>et al</i> <sup>[86]</sup>	Japan	134/112	RANTES promoter C-28G	Reduced risk for PDS, especially in <i>H. pylori</i> (+)
			G carrier	
Tahara <i>et al</i> <sup>[94]</sup>	Japan	111/106	TLR2	Inverse association with FD and PDS in <i>H. pylori</i> (+)
			-196 to -174	
Tahara <i>et al</i> <sup>[94]</sup>	Japan	111/106	MBL2	No association
Tahara <i>et al</i> <sup>[95]</sup>	Japan	89/95	C242T p22PHOX	Inversely related to FD in <i>H. pylori</i> (+)
Arisawa <i>et al</i> <sup>[96]</sup>	Japan	87/185	COX-1	EPS in females
Park <i>et al</i> <sup>[99]</sup>	South Korea	89/180	NOS	FD
			T allele	

FD: Functional dyspepsia; EPS: Epigastric pain syndrome; PDS: Postprandial distress syndrome.

based groups of patients with dyspepsia showed an association between homozygous 825C carrier status and unexplained upper abdominal complaints (OR = 2.2, 95%CI: 1.4-3.3). Furthermore, Camilleri *et al*<sup>[40]</sup> showed that meal-unrelated dyspepsia was associated with the homozygous 825 T or C alleles of GNB3 protein in a United States community study. In this study, DNA was extracted from 41 dyspeptic patients and 47 healthy controls. Homozygous C genotype was identified in 67% of meal-unrelated dyspeptics vs 43% of controls, and homozygous T genotype in 20% of meal-unrelated dyspeptics and 3% of controls. On the other hand, a Japanese study<sup>[41]</sup> with 89 dyspeptic and 94 asymptomatic individuals concluded that homozygous GNB3 825T status was associated with dyspepsia in the absence of *H. pylori* infection (CC vs TT, OR = 5.73, 95%CI: 1.27-25.82; CC vs others, OR = 3.08, 95%CI: 1.02-9.25 after adjustment for sex and age). van Lelyveld *et al*<sup>[42]</sup> reported that T allele carriers of GNB3 C825T polymorphism were associated with dyspepsia (OR = 1.60, 95%CI: 1.03-2.49) in a population study in the Netherlands that enrolled 112 FD patients and 336 sex- and age-matched controls. Furthermore, Oshima *et al*<sup>[43]</sup> showed that the homozygous 825T allele status influences the susceptibility to epigastric pain syndrome-like dyspepsia (OR = 2.00, 95%CI: 1.07-3.76, adjusted for gender and age) in a population of 68 dyspeptics and 761 controls. However, no significant relationship was found between GNB3 polymorphism and PDS-like symptoms. On the contrary, Shimpuku *et al*<sup>[44]</sup> detected a significant relationship ( $P = 0.045$ ) between GNB3 825CC genotype and PDS in 74 FD patients with impaired gastric emptying compared to 64 controls. GNB3 825CC genotype was also significantly associated ( $P = 0.0485$ ) with a feeling of hunger compared with the other GNB3 825 genotypes. Furthermore, Park *et al*<sup>[45]</sup> reported that the CC genotype of GNB3 C825T

may be associated with FD and diarrhea-predominant IBS in Korean children. However, Hwang *et al*<sup>[46]</sup>, found no association between this genotype and FD in another Korean study.

These contrasting observations might be explained by the different genotypic composition of populations in different countries and different racial groups. The frequency of 825TT allele seems to be higher in Japanese subjects than in Caucasians. In addition, the definition of FD or sample selection may also affect the outcome and may at least partially explain the differences detected in the aforementioned two Korean studies<sup>[45,46]</sup>. Moreover, the effect of type II error cannot be excluded in relatively small sample sizes. Conclusively, even though the association between GNB3 C825T polymorphism and FD has been investigated by various studies, its role in FD pathogenesis is not yet clear.

### Genes of the serotonergic system

#### Serotonin transporter protein (SERT or SLC6A4):

Serotonin (5-HT) is a brain neurotransmitter linked to the development of migraine, depression and other neuropsychiatric disorders. 95% of the body's serotonin is found in the gut, synthesized in enterochromaffin cells and this hormone affects motor and sensory functions in the GI tract<sup>[47]</sup> due to seven subclasses of 5-HT receptors, differentiated on the basis of molecular mechanisms, structure and function<sup>[48]</sup>. The action of 5-HT in the gut is terminated by reuptake *via* the 5-HT transporter (SERT) which is encoded by a single gene on chromosome 17q11 composed of 14 exons<sup>[49]</sup>. There is a 44-bp insertion/deletion in the 5'-flanking promoter region which generates a short and a long allele. The short (S) allele of SERT gene has been implicated with lower transcriptional efficiency and lower reuptake of serotonin than the long allele (L)<sup>[50]</sup>.

Several studies have investigated the relationship between SERT polymorphisms and both behavioral and psychological disorders<sup>[51-55]</sup>, and IBS<sup>[56-61]</sup>. Few studies have investigated the association between the SERT gene and FD. Among these studies, no significant association was detected in studies from the United States<sup>[40]</sup> and the Netherlands<sup>[42]</sup>. On the contrary, in a Japanese study<sup>[62]</sup> that included 53 dyspeptics and 646 controls, the SERT L carriers were at increased risk of PDS (OR = 2.32, 95%CI: 1.23-4.37) compared to the SS genotype, when adjusted for sex and age. However, in another larger Japanese study<sup>[63]</sup>, neither SLC6A4 -185 A>C nor 463 G>T was associated with susceptibility to FD. However, the authors found that the rs5981521 T allele in pri-miR-325, targeting the SLC6A4 3'-untranslated region (UTR) was a risk factor for the development of FD, especially in *H. pylori* negative patients. This allele also interacts with SLC6A4 polymorphisms in increasing susceptibility to dyspepsia in Japan. At the same period, a study from Korea<sup>[45]</sup> showed that polymorphisms of the 5'-flanking controlled SERT gene linked polymorphic region (5HTTLPR) gene were not associated with FD in Korean children. In another Korean study<sup>[46]</sup> that recruited 112 FD patients and 269 controls, the frequency of S/S genotype of SLC6A4 5-HTTLPR polymorphism, was significantly lower than that of L/L + L/S genotype in FD compared to controls ( $P < 0.05$ ). After stratification according to *H. pylori* infection status, the S/S genotype was protective for EPS subtype in *H. pylori*-positive patients compared to controls (adjusted OR 0.46; 95% CI 0.22-0.99;  $P = 0.048$ ).

**5-HT receptor genes:** Of special interest among the seven subclasses of 5-HT receptors<sup>[48]</sup> is 5-HT3 receptor, as 5-HT3 receptor antagonism leads to a reduction in dyspeptic symptoms and anxiety relief. It is present in central nervous system and enteric neurons, as well as in the mucosal terminals of extrinsic primary afferents. Five different subunit genes have been identified for this receptor, termed A-E; the 5-HT3A subunit being the most important in the receptor formation<sup>[64-67]</sup>.

Very few studies have investigated the association between genes controlling serotonergic functions and FD. Camilleri *et al.*<sup>[40]</sup> found no association for 5-HT1A, 5-HT2A, 5-HT2C, while van Lelyveld *et al.*<sup>[42]</sup> did not reveal any association between HTR3A C178T polymorphism and FD. In addition, Tahara *et al.*<sup>[68]</sup> suggested that 5-HT2A receptor T102C polymorphism is unlikely to be associated with susceptibility to dyspeptic symptoms. On the contrary, a study in a Caucasian population of 592 dyspeptics<sup>[69]</sup> showed that HTR3A c.-42T allele carriers of HTR3A c.-42C>T Single Nucleotide Polymorphism were more prevalent in patients with severe dyspepsia (OR = 1.50, 95%CI: 1.06-2.20). This association appeared to be stronger in females (OR = 2.05, 95%CI: 1.25-3.39) and patients

homozygous for the long (L) variant of the 5-HTTLPR genotype (OR = 2.00, 95%CI: 1.01-3.94); females with 5-HTTLPR LL genotype showed the strongest association (OR = 3.50, 95%CI: 1.37-8.90).

### Genotypes altering adrenergic and cholecystokinergic functions

**Adrenergic agents**, mainly  $\alpha 2$  agents, affect motor and sensory function of the human gastrointestinal tract. Three  $\alpha 2$  adrenoceptor (AR) subtypes have been identified: 2A, 2B and 2C. Prejunctional  $\alpha 2A$ - and  $\alpha 2C$ -adrenoreceptors contribute to a negative feedback regulation of norepinephrine release from sympathetic nerves. Genetic disorders of  $\alpha 2$  mechanisms can influence functions such as intestinal motility and pain sensation, as well as anxiety and somatization<sup>[70,71]</sup>.

Cholecystokinin (CCK) is a hormone secreted after meal ingestion and signals satiation through peripheral or central actions. CCK receptors found in the gastrointestinal tract and the central nervous system also influence gastric emptying and accommodation, while they regulate satiety *via* the same connections<sup>[72]</sup>.

Camilleri *et al.*<sup>[40]</sup> detected no association between polymorphisms of candidate genes for  $\alpha 2A$ ,  $\alpha 2C$  adrenoreceptors or CCK-1 receptors and CCK promoter with FD. In addition, Hwang *et al.*<sup>[46]</sup>, also found no significant association between ADRA2A- 1291C>G or CCK-1R intron 779T>C with dyspeptic symptoms. In contrast to the aforementioned observations, Tahara *et al.*<sup>[73]</sup> suggested that Japanese male 779 T carriers of CCK-1 intron 1 are exposed to a higher risk of PDS.

### Genes associated with inflammation or immune response

**CD14:** CD14 mediates the inflammatory response in the first line of host defense by recognition of Lipopolysaccharide, a main component of the outer cell wall of *H. pylori*<sup>[74]</sup>. Soluble CD14 levels tend to be higher in *H. pylori* positive than in *H. pylori* negative patients<sup>[75]</sup>. In addition, FD patients with extensive gastric mucosal inflammation accompanied by a high density of *H. pylori* show increased CD14 expression<sup>[76]</sup>. The TT genotype of the CD14 C-159T polymorphism has been related to high density of the CD14 receptor and high soluble CD14 levels<sup>[77]</sup>. Due to the important role of CD14 in inflammation, polymorphisms in the CD14 gene promoter may influence gastric inflammation and susceptibility to FD. Tahara *et al.*<sup>[78]</sup> investigated the association between CD14 promoter C-159T polymorphism and FD among 108 dyspeptic and 99 non-dyspeptic Japanese individuals. They suggested that this CD14 polymorphism is not associated with dyspepsia, while there was a weak correlation between TT genotype and PDS in male patients. There has been no study so far in Caucasians investigating the association between CD14 gene polymorphisms and FD.

**Macrophage migration inhibitory factor:** Macrophage migration inhibitory factor (MIF), isolated from T lymphocytes, inhibits the random migration of macrophages<sup>[79]</sup>. MIF is an important regulator of innate immunity both directly and *via* stimulation of the expression of proinflammatory cytokines by immune cells<sup>[80]</sup>. Polymorphisms (G-173C and -794 CATT) identified in the *MIF* gene promoter, were correlated with alteration of MIF genes transcription levels *in vitro*. It seems that MIF also plays a significant role in inflammation related to *H. pylori* infection<sup>[81]</sup>. A study from Japan<sup>[82]</sup> examined the association between MIF gene polymorphisms and FD. Investigators showed that MIF-173C allele carriers were at significantly increased risk of developing epigastric pain syndrome; this association being more prominent in *H. pylori* infected subjects.

**Interleukin-17:** Interleukin-17 (IL-17) family members coordinate local tissue inflammation by inducing the release of proinflammatory and neutrophil-mobilizing cytokines. Furthermore, IL-17A and -17F function in a similar way: they are involved in the recruitment and activation of neutrophils<sup>[83]</sup>. On the basis of this pathophysiology, Arisawa *et al.*<sup>[82]</sup> revealed that polymorphisms of the IL-17A and IL-17F genes were not related to FD susceptibility, overall. However, the IL-17F 7488T allele was positively associated with developing EPS in *H. pylori* infected subjects.

**RANTES promoter:** RANTES is a powerful chemotactic agent for T lymphocytes and monocytes<sup>[84]</sup> contributing to the inflammatory response in *H. pylori* gastritis<sup>[85]</sup>. The effect of RANTES promoter C-28G polymorphism on the risk of functional dyspepsia has been investigated in 134 dyspeptic and 112 non-symptomatic Japanese subjects<sup>[86]</sup>. Although the frequency of RANTES promoter polymorphisms did not differ among dyspeptics and controls, overall, a significant association was revealed between G carriers and a reduced risk of PDS; this association being more prominent in *H. pylori* positive subjects.

**Toll like receptor 2 and mannan-binding lectin genes:** Toll like receptor 2 (TLR2) and mannan-binding lectin (MBL) protein play significant roles in innate immune system activation<sup>[87]</sup>. It was reported that TLR2 is expressed in gastric epithelial cells infected by *H. pylori*<sup>[88]</sup>. MBL activates complement and also functions as an opsonin<sup>[89,90]</sup>.

The expression of MBL in the mucosa is up-regulated in *H. pylori*-related gastric mucosa inflammation<sup>[91]</sup> and two studies reported a possible association between MBL2 haplotype and susceptibility to *H. pylori* infection, as well as an increased risk of gastric malignancy<sup>[92,93]</sup>. With regard to FD, absence of the correlation between TLR2 -196 to -174 del and MBL2 codon 54 G/A polymorphisms and the syndrome has been shown in a Japanese population<sup>[94]</sup>. However, it was suggested

that TLR2 -196 to -174 del carrier status, but not MBL2 codon 54 G/A, was inversely related to the risk of PDS in *H. pylori*-infected subjects.

**C242T p22PHOX:** Superoxide has been associated with the pathogenesis of *H. pylori*-related diseases through induction of inflammation. Nicotinamide adenine dinucleotide phosphate oxidase, a major source of superoxide plays a crucial role in *H. pylori* gastritis. Tahara *et al.*<sup>[95]</sup> did not identify any significant association between C242T polymorphism of p22PHOX, an essential component of nicotinamide adenine dinucleotide phosphate oxidase and FD. However, C242T carriers were at lower risk of developing FD in the sub-group of *H. pylori*-infected patients.

**Cyclooxygenase-1:** Cyclooxygenase (COX) is the key enzyme in the conversion of arachidonic acid to prostaglandins (PGs), which are implicated in many physiological gastric processes and contribute to gastrointestinal integrity. There is only one study investigating COX-1 genotypes and dyspepsia. Arisawa *et al.*<sup>[96]</sup> revealed that T-1676C polymorphism in the *COX-1* gene promoter was significantly associated with the development of EPS in female subjects.

**Nitric oxide synthase:** Nitric oxide (NO) is a major neurotransmitter that mediates gastric accommodation or relaxation and meal-induced satiety<sup>[97]</sup>. Therefore, it has been postulated that impairment of this system can lead to FD. There are three different NOS isoforms: neuronal NOS (nNOS), inducible (iNOS), and endothelial NOS (eNOS)<sup>[98]</sup>. In the only available study of FD, Park *et al.*<sup>[99]</sup> suggested that the genotype frequencies of eNOS and iNOS were not significantly different between FD patients and controls. However, the nNOS gene polymorphism was associated with susceptibility to FD and influences satiation in dyspeptics.

#### **Catechol-o-methyltransferase gene**

Catechol-o-methyltransferase (COMT) is an important enzyme in the brain-gut axis regulating pain sensitivity, and the presence of COMT gene val158met has been associated with dyspepsia<sup>[100]</sup>.

#### **Capsaicin/vanilloid receptor (transient receptor potential vanilloid 1 receptor)**

TRPV1 receptor is expressed in the gastrointestinal tract, and is a member of the sensory ion channel superfamily. Studies using capsaicin provide evidence that TRPV1 regulates gastrointestinal sensation. Capsaicin administration into the alimentary tract causes pain in humans<sup>[101]</sup> and mice<sup>[102]</sup>. Hammer *et al.*<sup>[103]</sup> suggested that capsaicin application produces symptoms originating from the upper abdomen; being more severe in FD. Continuous capsaicin desensitization has also been reported to be beneficial in patients with FD<sup>[104]</sup>. Capsaicin suppresses gastrointestinal hyperalgesia by desensitization/inactivation and

downregulation of TRPV1<sup>[105]</sup>, indicating that the up-regulation of TRPV1 may be implicated in the pathogenesis of FD.

G315C gene polymorphism alters TRPV1 protein levels and the variant 315C of TRPV1 G315C increases TRPV1 mRNA and protein expression and results in maximal response to capsaicin<sup>[106]</sup>. However, a significant inverse association was detected between TRPV1 315CC genotype and FD, EPS, PDS and *H. pylori* positive FD in Japan<sup>[107]</sup>. Furthermore, a significant inverse correlation between C carrier of TRPV1 945G>C polymorphism status and PDS has been detected and C/C genotype *H. pylori*-positive subjects were at reduced risk of EPS<sup>[46]</sup>.

### SCN10A

Visceral hypersensitivity has been implicated in the pathogenesis of functional gastrointestinal disorders. C-fibers contribute to visceral sensory impulse transmission from the gastrointestinal tract to the central nervous system. SCN10A gene encodes the tetrodotoxin-resistant (TTX-r) sodium channel, Na(V) 1.8/SNS (sensory-neuron specific), which has been identified on C-fibers. Arisawa *et al.*<sup>[108]</sup> investigated the association between FD and SCN10A non-synonymous polymorphisms (2884 A>G, 3218 C>T and 3275 T>C) among 297 dyspeptics and 345 symptom-free controls. They concluded that subjects with the 2884 G allele, 3275 T allele and no 3218 T allele of SCN10A were at reduced risk of FD, for both the EPS and PDS subtypes, especially in *H. pylori*-negative patients.

### LIMITATIONS OF THE AVAILABLE STUDIES

Genetic association studies in FD have yielded diverse and inconsistent results for the investigated candidate genes. These inconsistencies might be explained by subject composition differences and can be influenced by unadjusted environmental factors. In addition, the definition of FD has changed over time and FD patients were inconsistently defined. The selection procedure for controls is also questionable in functional disease studies, as symptom-free subjects are not necessarily equal to healthy controls<sup>[109]</sup>. Moreover, in most of these studies the association between the candidate genotype and FD has been investigated in small samples without appropriate sample size estimation; therefore type II error cannot be excluded. Finally, the majority of the studies have been conducted in Asia, and Western populations are underrepresented.

### CONCLUSION

Functional dyspepsia is a disorder with complex pathophysiology including gastrointestinal motor abnormalities, altered visceral sensation, psychosocial and genetic factors. Genetic factors may influence

susceptibility to FD in the presence of exogenous factors, such as *H. pylori* infection. Studies investigating possible associations between FD and genotypes related to gastrointestinal motility and sensation, as well as to inflammation or immune response are limited by several caveats and they have reached inconclusive results. Properly designed, multicenter, adequately powered, worldwide conducted studies enrolling well defined disease subjects and controls are warranted to investigate potential associations between pre-specified gene polymorphisms and FD. The results of such studies may shed light on the pathogenesis of the syndrome and may potentially lead to genetic diagnostic tools and ultimately to novel therapeutic options for FD.

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