REVIEW

Genetic contributions to the pathogenesis of functional dyspepsia

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ABSTRACT

Functional dyspepsia (FD) is a common gastrointestinal (GI) disorder in the community and in clinical practice. The pathogenesis of FD is largely unknown. However, abnormal gut motility, visceral hypersensitivity, low-grade inflammation, and abnormal brain-gut interaction have been incriminated in its pathogenesis. Accumulating evidence, including the occurrence of these conditions in family members, suggested that functional gastrointestinal disorders (FGIDs), including FD, might be influenced by genetic factors. Several studies have explored the contribution of genetic factors to FD. However, genetic factors contributing to the development of FD remain largely unknown. It appears to be a multi-factorial polygenic disorder. Since gut motility, visceral sensation, and degree of inflammation are all mediated by neuro-peptides, hormones and cytokines and various other proteins, which are transcribed from different genes, alterations in these genes may lead to alterations in these physiological processes. Recent studies showed a host of genetic factors playing important roles in the pathogenesis of FD. We conducted a literature search using the keywords "functional dyspepsia AND gene polymorphisms", "functional dyspepsia AND host genetic factors", and "functional dyspepsia AND gene pathogenesis" to review the major studies on association between FD and gene polymorphisms [*G-protein beta polypeptide-3 (GNβ3), Cholecystokinin-A receptor (CCK-AR), interleukin-17F* (*IL-17F),* and *interleukin-10 (IL-10)*].

KEYWORDS: Visceral hypersensitivity, gut-motor dysfunction, low-grade inflammation, functional gastrointestinal disorders; gene polymorphisms

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INTRODUCTION

Splice variant GNβ3s is associated with increased intra-cellular signal transduction (Tahara et al; 2008). 825C allele (CC genotype) results in the synthesis of the GNβ3 wild-type protein predominantly and only minute amounts of the GNβ3 splice variant (Lin et al; 2001). Also, the homozygous CC genotype is associated with diminished G-protein activity and reduced signal transduction responses (van Lelyveld et al; 2008). Thus, *GNβ3* C825T polymorphism alters intra-cellular signal transduction, which may lead to motor or sensory abnormalities in the GI-tract.

Studies on the association between *GNβ3* C825T and FD have produced inconsistent results. A study from our centre on *GNβ3* C825T polymorphism showed that the homozygous variant TT genotype was more common among patients with FD than HC and conferred up to the two-fold higher risk of FD in reference to homozygous wild CC genotype (Singh et al; 2016). This is perhaps the first study on an Indian population showing an association between *GNβ3* C825T polymorphism and FD. Our findings are consistent with previous studies from Japan, US, Germany, and the Netherlands, showing significant association between this polymorphism and FD (Kim et al; 2012, Oshima et al; 2010, Tahara et al; 2008, van Lelyveld et al; 2008, Camilleri et al; 2006, Chung et al; 2014, Park et al; 2012). Recently, a meta-analysis on eight studies showed a significant association between this polymorphism and FD (Dai et al; 2014). In contrast, studies from Korea showed no association between this polymorphism and FD (Park et al; 2012, Park, 2011). The sample size of patients and controls was small in these studies; hence, the possibility of type II statistical error is quite likely. Inconsistent results have been reported on *GNβ3* C825T polymorphism from the Western countries (Camilleri et al; 2009, van Lelyveld et al; 2008, Camilleri et al; 2006). A study from the Netherlands demonstrated that T allele carriage of *GNβ3* 825C>T polymorphism was associated with dyspepsia (van Lelyveld et al; 2008). A German study showed that homozygous GNβ3 825C status was associated with unexplained dyspepsia (Holtmann et al; 2004). Furthermore, studies from the USA revealed that meal-unrelated dyspepsia was associated with both homozygous *GNβ3* 825TT and CC genotypes (Camilleri et al; 2009, Camilleri et al; 2006). We evaluated this polymorphism in various sub-types of FD [(EPS; epigastric pain syndrome, PDS; post-prandial distress syndrome)]; however, we did not find any association between this polymorphism and various sub-types of FD (It might be due small sample size (Type II error) of EPS and PDS sub-group or due to the fact that patient-reported symptoms might not always correlate with the pathophysiology of FD.) (Singh et al; 2016). Some studies reported a significant association between *GNβ3* C825T polymorphism and sub-types of FD. A study from Japan showed that TT genotype of *GNβ3* C825T was significantly Functional dyspepsia (FD) is a common clinical syndrome characterized by the presence of recurrent or chronic upper abdominal symptoms, such as epigastric pain, early satiety, and fullness, without any structural abnormalities upon upper gastrointestinal (UGI) endoscopy explaining these symptoms (Table 1 and Figure 1) (Drossman, 2006, Stanghellini et al; 2016, Ghoshal et al; 2018, Bhatia et al; 2016, Ghoshal et al; 2011, Shah et al; 2001). FD is a heterogeneous disorder in which different pathophysiological mechanisms underlie specific symptom patterns. Studies have identified several pathophysiological mechanisms, including visceral hypersensitivity, gastric motor dysfunction, and low-grade mucosal inflammation as possible etiological factors (Figure 2) (Li et al; 2013, Takeda et al; 2014, Walker et al; 2014). Visceral hypersensitivity, abnormal gastric motility (impaired gastric accommodation and delayed gastric emptying) and low-grade mucosal inflammation have been considered major pathophysiological mechanisms in FD (Figure 3 and 4) (Mazur et al; 2004, Miwa et al; 2012, Tandon, 2012, Tack et al; 2013, Vanheel; et al, 2013,

Powell et al; 2017). Several studies showed that the patients with FD display exaggerated

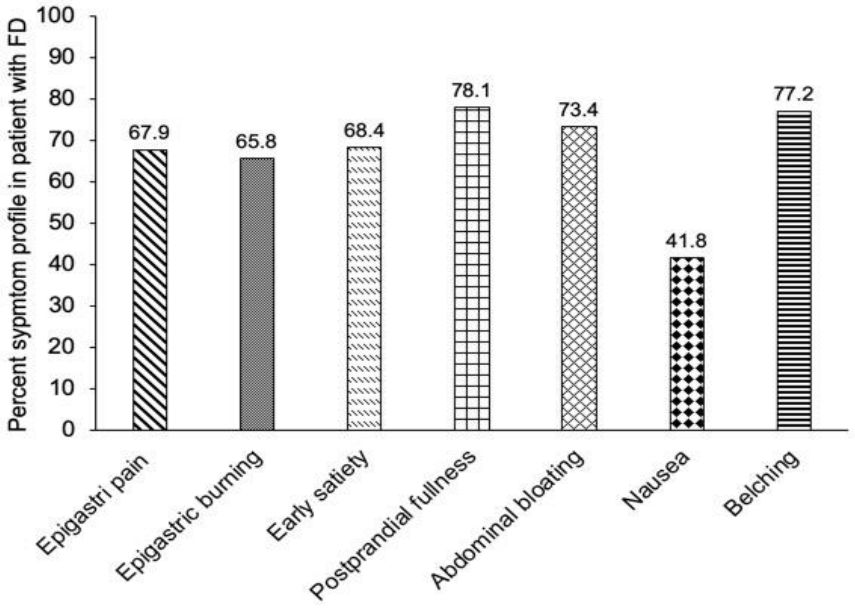

Figure 1. Symptom profile of patients with functional dyspepsia

Table 1: Diagnosis of functional dyspepsia: Rome III criteria		
Diagnostic criteria* for functional dyspepsia must include		
1	One or more of	Bothersome postprandial fullness
		Early satiation
		Epigastric pain
		Epigastric burning
2	No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms	

sensitivity to gastric distension, chemical stimulation and duodenal hypersensitivity to acids (Lee et al; 2010, Vanheel et al; 2013, Vanheel et al; 2014, Mayer et al; 2013). Also, a number of studies implicated inflammatory mechanisms in the pathogenesis of FD (Hughes et al; 2013, Vanheel et al; 2014).

The occurrence of FD might be influenced by multiple genetic factors (Sarnelli et al; 2013). The identification of the genetic factors may improve understanding of the underlying pathophysiological mechanisms. Accumulating evidence, including the occurrence of these conditions in family members, suggested that

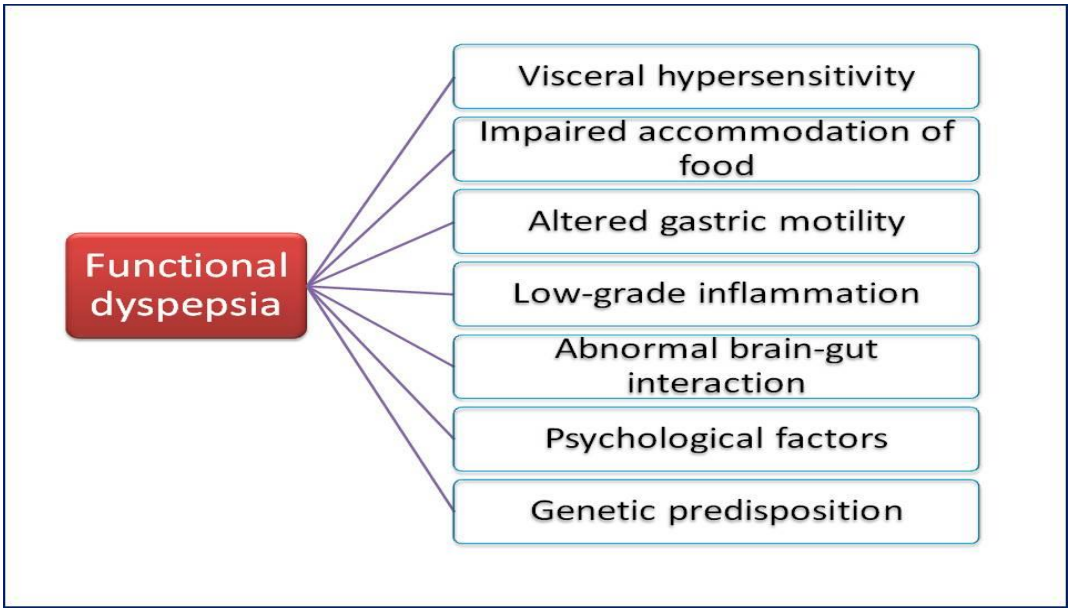

Figure 2. Pathophysiology of functional dyspepsia

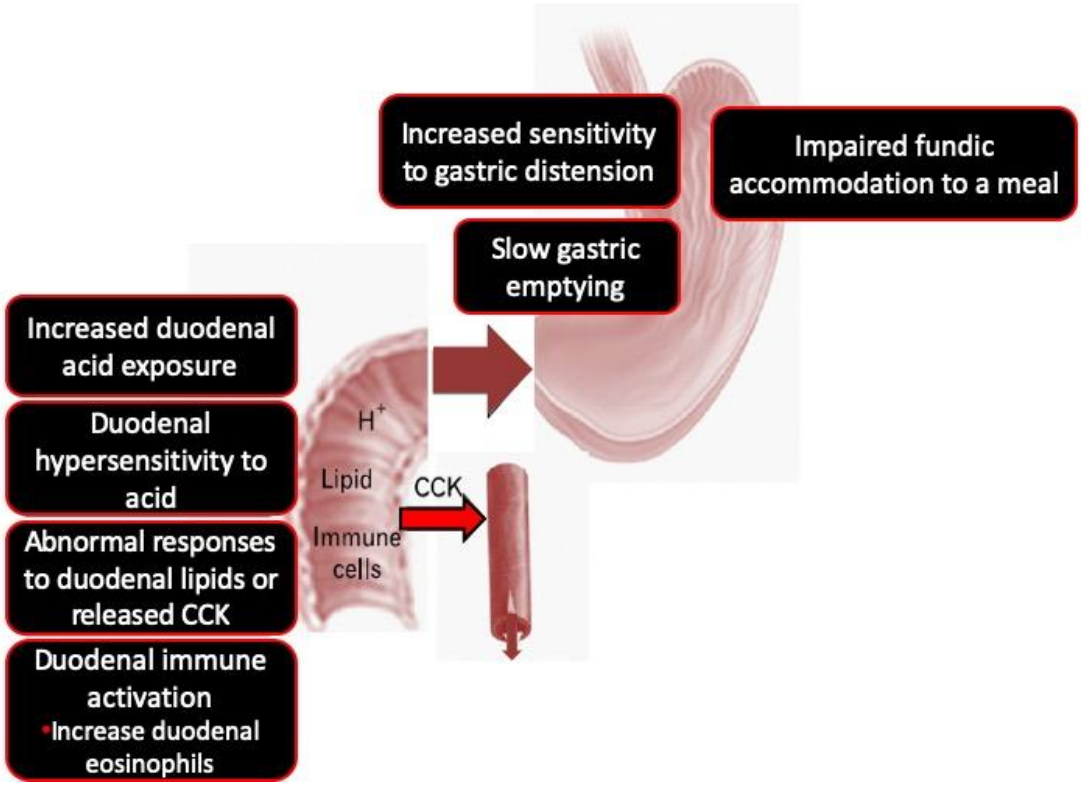

Figure 3. Duodenal visceral hypersensitivity in the pathophysiology of functional dyspepsia

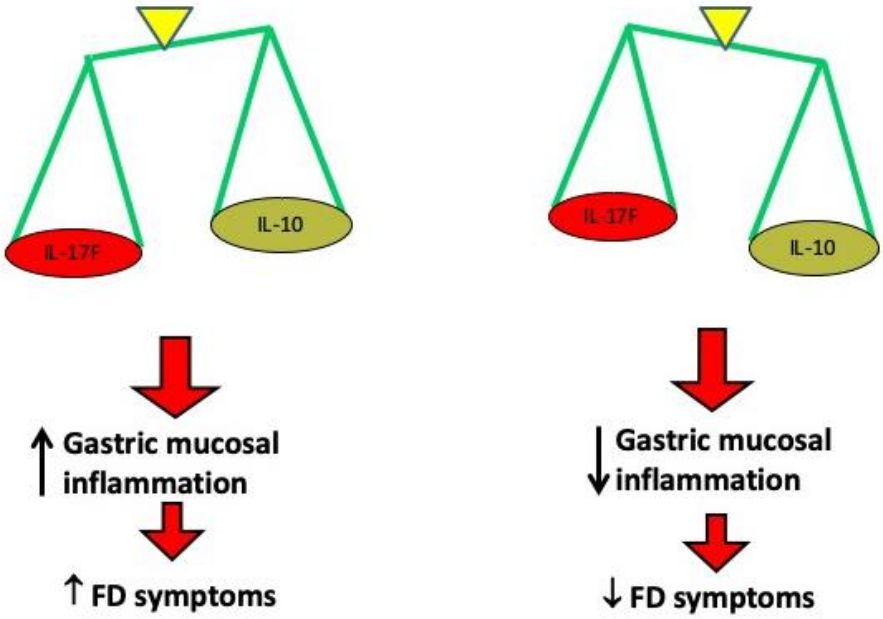

Figure 4. Cytokine gene polymorphism and varying cytokine expression may alter the degree of gastric mucosal inflammation

functional gastrointestinal disorders (FGIDs), including FD, might be influenced by genetic factors (Vanheel et al; 2014, Sarnelli et al, 2013, Adam et al; 2007, Locke et al; 2000, Camilleri et al; 2009). However, genetic factors contributing to the development of FD remain largely unknown. Since, FD might result from altered visceral sensation, gastric motor abnormalities, and low-grade mucosal inflammation in GI, genes influencing it might contribute to the occurrence of FD.

GNβ3 in the pathogenesis of FD

Guanine nucleotide-binding proteins (G-proteins) are essential for stimulus-response in approximately 80% of all known membrane receptors that are linked to intra-cellular signal transduction pathways (Rozengurt et al; 2002, Jankowski et al; 2009). The *G-protein beta polypeptide-3 (GNβ3)* gene encodes the Gβ3 subunit of G proteins, which are key components of intra-cellular signal transduction (Kim et al; 2012). *GNβ3* gene shows common 825C>T polymorphism (rs5443) (Oshima et al; 2010). This substitution 825C>T (TC or TT genotype) is associated with alternative splicing of the gene in exon 9 and the formation of a truncated splice variant GNβ3s, a protein product with 41 amino acids less than in the GNβ3 wild-type protein associated with EPS (Oshima et al; 2010). Another Japanese study showed that CC genotype at this locus was associated with PDS (Shimpuku et al; 2011).

CCK-AR in the pathogenesis of FD

Cholecystokinin (CCK) is an established brain-gut peptide (33-amino acid) that plays an important regulatory role in the GI motility (Pilichiewicz et al; 2008). CCK is released by endocrine I cells within the duodenal and jejunal mucosa in response to various nutrients in the lumen (Pilichiewicz et al; 2008). Biological actions of CCK in the alimentary canal are mediated by CCK-AR (Srivastava et al;

2008). A study showed that fasting and post-fatty meal plasma CCK levels were higher among patients with FD than HC (Pilichiewicz et al; 2008, van Boxel et al; 2014). Intra-venous administration of a CCK-AR antagonist reduced the effects of duodenal lipid on gastric relaxation and gastrointestinal sensations during distension (Maselli et al; 2003). Thus, CCK-AR is involved in the modulation of satiety signal and delayed gastric emptying, which is associated with FD (Fried et al; 2002, Lehmann et al; 2003). *CCK-AR* gene is located on chromosome 4p15. A single nucleotide polymorphism, rs1800857 is located in intron 1 at the intron 1 / exon 2 boundary in the vicinity of the mRNA splice acceptor site consensus sequence (Koefoed et al; 2009). Thus, it might result in an alteration of the splicing mechanism, resulting in alteration in the protein (Srivastava et al; 2008, Koefoed et al; 2009). Also, this polymorphism has been widely proposed to play an important role in the regulation of functional mRNA levels of CCK-AR. It is important to study variations in the *CCK-AR* gene, which might alter the response to endogenous CCK and to pharmacologic agents that target these receptors (Srivastava et al; 2008, Chua et al; 2006). There are scant studies on this polymorphism in relation to FD. A study from our centre showed significant an association between *CCK-AR* T/C polymorphism and FD (Singh et al; 2016). A study from Japan reported that this polymorphism was associated with an increased risk of PDS in male subjects (Tahara et al; 2009). Another study from Korea on patients with irritable bowel syndrome-constipation predominant (IBS-C) revealed that *CCK-AR* gene (779T>C) could be functionally important because 779C variant is associated with slower gastric emptying (Park et al; 2010). This observation might suggest that, compared with 779T variant, 779C substitution could result in a greater response to endogenous cholecystokinin, which is known to delay gastric emptying. A study from the US failed to show significant association between *CCK-AR* (779T>C) polymorphism and FD (Camilleri et al; 2009). CCK-AR T/C polymorphism might be associated with reduced levels of CCK-AR. Reduced level of CCK-AR via its ligand CCK might accelerate gastric emptying. Hence, lower FD risk in the presence of this polymorphism is quite expected.

IL-17F in the pathogenesis of FD

Genes encoding cytokines have been reported to be associated with FD (Adam et al; 2007). Moreover, these cytokine genes have polymorphic sites, which are considered to alter gene transcription influencing the degree of the inflammatory response (Adam et al; 2007, Tripathi et al; 2011, Ghoshal U et al; 2013). Allelic variations in their genes may result in high or low production of the cytokines. Therefore, individuals can be classified by their allele status as high, intermediate or low producers of a particular cytokine. A genetic predisposition to produce high or low amounts of a particular cytokine might alter individual susceptibility to FD (Adam et al; 2007, Andersen et al; 2005, Qin et al; 2013). The genetic basis of FD in relation to cytokine production is poorly understood. *IL17F*, a pro-inflammatory molecule, belongs to the IL17 family, which plays a role in coordinating tissue inflammation by inducing the release of other pro-inflammatory and neutrophil-mobilizing cytokines (Gu et al; 2013, Wu et al; 2010). This cytokine is important in neutrophil recruitment and activation causing gastric mucosal inflammation (Arisawa et al; 2007). Since gastritis is associated with symptoms of FD, it is important to study the role of immune related gene polymorphism, such as that of *IL17F*, in the pathophysiology of FD. Cytogenetic location of *IL17F* is on 6p12 (Paradowska-Gorycka et al; 2010). This gene exhibits common single nucleotide polymorphisms (SNPs) rs2397084: A/G and rs763780: T/C. The functional role of *IL17F* (rs2397084) polymorphism is not well known. However, some studies suggest that it may alter *IL17F* expression (Paradowska-Gorycka et al; 2010). *IL17F (*rs763780) polymorphism causes His-to-Arg substitution at amino acid 161 (H161R), which leads

to the reduction of *IL17-F* cytokines level (Wu et al; 2010).

In a study from our centre, we found that *GG* (variant) genotype of *IL17F* (rs2397084) was associated with FD as compared to the presence of AA (wild) genotype (Singh et al; 2017). Such a high frequency of variant genotype in FD suggests that high production of IL17F (a pro-inflammatory cytokine) may have some risk for FD. Such genetic predisposition to higher pro-inflammatory cytokine production among patients with FD might mean that exaggerated inflammatory response may predispose to FD. This is perhaps the first study on *IL17F* (rs2397084) polymorphism in FD. This SNP has been studied in other inflammatory disorders such as lung cancer and rheumatoid arthritis; however, no significant association was found in those diseases (Paradowska-Gorycka et al; 2010, Kaabachi et al; 2014). Our study supported the recently proposed hypothesis that FD may be related to mucosal low-grade inflammation (Barbara et al; 2016, Enck et al; 2017). Thus, a genetic predisposition to produce high amounts of pro-inflammatory cytokines might alter individual susceptibility to FD. Another gene polymorphism we studied, *IL17F* (rs763780), was comparable among patients with FD and with HS (Singh et al; 2017). This polymorphism causes His-to-Arg substitution at amino acid 161 (H161R), which leads to reduction of *IL17F* cytokines level (Arisawa et al; 2007). In contrast, one Japanese study showed that the *T* allele of *IL17F* (rs763780) was significantly associated with EPS, a subgroup of FD (Arisawa et al; 2007). Another study from Japan showed that *IL17F* (rs763780) polymorphism was comparable among patients with duodenal ulcer disease and HS (Hayashi et al; 2012). Also, some studies reported an association between *IL17F* (rs763780) and ulcerative colitis, another inflammatory gastrointestinal condition (Li et al; 2014).

IL10 in the pathogenesis of FD

IL10 is an immune-regulatory cytokine that inhibits cell-mediated immune response (Olszak et al; 2014). It has been shown to exert potent anti-inflammatory activity by down regulating pro-inflammatory cytokines such as *TNF- α*, *IL1*, *IL12*, and chemokines (Olszak et al; 2014, Bodger et al; 2001). A genetic predisposition to produce low levels of anti-inflammatory cytokines may result in an inability to control the inflammatory response, which may be associated with the development of some types of FGIDs including FD (Adam et al; 2007, Qin et al; 2013).

IL10 gene is located on chromosome 1q31-32 and consists of five exons and four introns (Rad et al; 2004). Two commonly studied polymorphisms in the *IL10* gene are rs1800896: G/A and rs1800871: C/T (Rad et al; 2004, Zhao et al; 2014). *IL10 -819 C/T* and *-592 A/C* showed 100% linkage disequilibrium in their genotype distribution (Rad et al; 2004). It has been reported that *IL10* SNPs markedly influenced mucosal *IL10* expression in the course of chronic *H. pylori* infection: GCC haplotype carriers (*IL10* -1082G; -819C; -592C) were associated with high and ATA carriers with low *IL10* expression (Rad et al; 2004).

In a study from our centre, we showed that *IL10* (rs1800896) polymorphism was comparable among patients with FD and HS (Singh et al; 2017). However, TT (under-producers) genotype of *IL10* (rs1800871) was more common among patients than HS. Such a high frequency of the under-producer genotype in FD suggests that lowers the production of *IL10* (an anti-inflammatory cytokine) may have some risk for FD. Several studies have shown that serum *IL10* levels are significantly lower among patients with IBS (another common FGID) than HS, suggesting that altered *IL10* levels may be involved in the pathogenesis of FGIDs (Qin et al; 2013, Zhao et al; 2014, Bashashati et al; 2014. Also, it has been reported that *IL10* polymorphisms markedly influenced mucosal IL-10 expression in the course of chronic *H. pylori* infection: GCC haplotype carriers (*IL-10* -1082G; -819C; -592C) were associated with high and ATA carriers with low *IL10* expression (Rad et al; 2004). A study by Wang BM et al showed that *IL10* genotypes, -819 T/T and -592 A/A were associated

with diarrhea-predominant irritable bowel syndrome (D-IBS) (Wang et al; 2006). In another study, low prevalence of high-producer genotype in patients with IBS suggested that high levels of *IL10* might have some protective role and low producers of this cytokine might be more likely to develop IBS (Qin et al; 2013, Gonsalkorale et al; 2003, Bashashati et al; 2012). A genetic predisposition to produce low levels of anti-inflammatory cytokines could mean a compromised control of the inflammatory response, which may lead to continuing problems.

Conclusion and future directions

Several studies showed *GNβ3* C825T polymorphism was associated with FD. Homozygous CC genotype of *CCK-AR* T/C polymorphism (associated with lower expression of CCKAR) is protective against FD. The importance of visceral hypersensitivity and gut motility related gene polymorphisms in FD has been emphasized. In addition, these results provide some support to the concept that 'altered gastrointestinal motor and sensory function' may contribute to the pathogenesis of this condition. Polymorphisms in immune related genes are involved in the development of FD. *IL17F* (rs2397084) and *IL10* (rs1800871) are associated with a higher risk for FD. These studies provided evidence that the genetic polymorphisms in genes associated with inflammation or immune response may be involved in the development of FD (Figure 5).

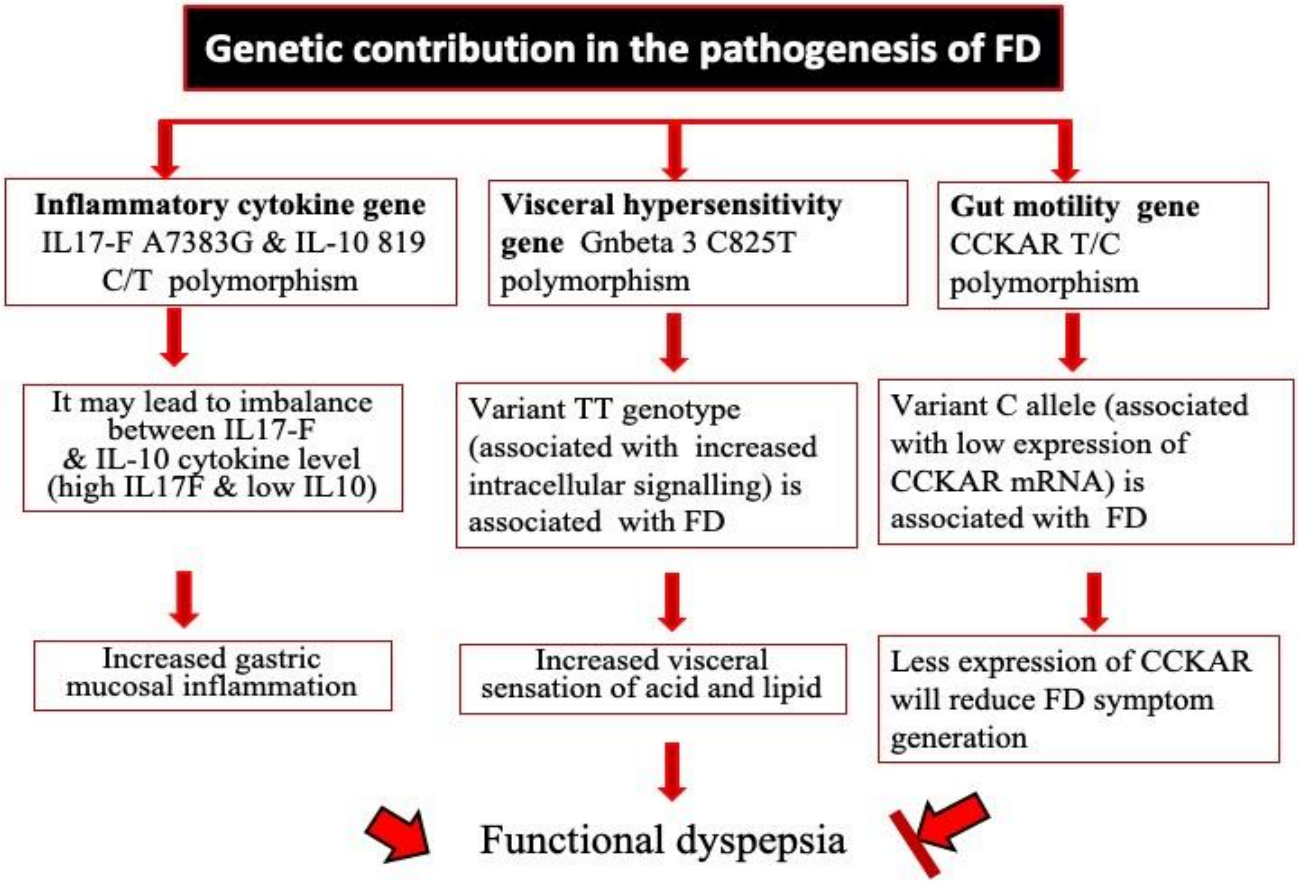

Figure 5. Summary of genetic polymorphism study

In addition, these studies provided some support to the concept that 'low-grade inflammation' might contribute to the pathogenesis of this condition. Future studies should replicate these association studies in different populations and also explain the molecular mechanisms of pathogenesis of the condition. Animal studies related to an individual gene knock down/knock out/knock in warrant further studies to explore the exact molecular mechanisms in sub-types of FD and disease progression.

Conflict of interest statement

The authors declared to have no competing or conflict of interest.

Authors' contributions

RS and UCG conceived, designed and drafted the manuscript.

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