Dig Dis Sci (2014) 59:1823–1830
DOI 10.1007/s10620-014-3057-y

ORIGINAL ARTICLE

Association of Genetic Variants in *GNβ3* with Functional Dyspepsia: A Meta-Analysis

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Received: 8 October 2013 / Accepted: 5 February 2014 / Published online: 21 February 2014

Abstract
Background Functional dyspepsia (FD) is a functional upper gastrointestinal disorder. The etiology and pathogenesis of FD remain unclear, with genetic factors playing an important role. Previous studies investigated the association of C825T in GNβ3 with FD, with conflicting results reported.
Aims The aim of this meta-analysis is to assess the association of genetic variants in GNβ3 with FD.
Methods We performed a systematic literature search in PubMed, Cochrane Library, Google Scholar, and Web of Knowledge, and conducted a meta-analysis to assess the association of C825T in *GNβ3* with FD. For sensitivity analysis, we analyzed the association between C825T and subtypes of FD. We also performed meta-analyses separately for individual ethnic groups/countries of origin.
Results A total of eight studies met the eligibility criteria and were included in our analyses. Our meta-analysis finds no association between 825CC and FD (OR 1.19, 95 % CI 0.84–1.67, $p = 0.328$). However, the association is significant under an additive model (OR 0.59, 95 % CI 0.38–0.92, $p = 0.018$). Sensitivity analysis indicated a significant association of C825T with FD in participants from Korea but not in those from Japan, Europe, or the United States. We also detected a significant association of this SNP with dysmotility.
Conclusions The genetic variant C825T in *GNβ3* is significantly associated with FD under an additive model and the association is race-specific. Further studies with larger samples sizes are needed to validate our findings and to explore the potential mechanism underlying the association.

Keywords Functional dyspepsia · Meta-analysis · GNβ3 · Polymorphism

Electronic supplementary material The online version of this article (doi:10.1007/s10620-014-3057-y) contains supplementary material, which is available to authorized users.

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Introduction

Functional dyspepsia (FD) is a functional upper gastrointestinal disorder characterized by recurrent or chronic abdominal symptoms in the absence of anatomical or biochemical abnormality [1]. It has been reported that up to 25 % of the population experiences symptoms of FD, including postprandial discomfort, early satiety, or upper abdominal burning or discomfort [1]. FD is a chronic disease, with over 80 % of affected patients showing

persistent symptoms after long-term follow-up [2, 3]. FD has two subtypes under the Rome III classification: postprandial distress syndrome (PDS), which refers to meal-induced dyspeptic symptoms characterized by postprandial fullness and early satiation, and epigastric pain syndrome (EPS) characterized by epigastric pain and burning [4].

The etiology and pathophysiology of FD remain unclear. Studies have identified several pathophysiology mechanisms, including delayed gastric emptying [5], visceral hypersensitivity [6], and dysfunction of the autonomic nervous system [7] as possible etiological factors. Previous studies also indicate that age, gender, smoking, *Helicobacter pylori* (*H. pylori*) infection, and psychological disturbances could be potential risk factors for FD [8–11]. Recently, familial aggregation of FD has been reported, suggesting that genetic factors may play a role in the pathophysiology of FD [12, 13]. Many studies have been conducted to search for susceptibility genes for FD, including guanine nucleotide binding protein beta polypeptide 3 (*GNβ3*) [14], the serotonin transporter promoter (*SERT-P*) [15], the cyclooxygenase-1 (*COX-1*) [16], and the catechol-*o*-methyltransferase (*COMT*) [17].

Guanine nucleotide-binding proteins (G-proteins), membrane receptors and signal transduction molecules are involved in intracellular signal transduction pathways. The Gβ3 protein is encoded by the GNβ3 gene, in which there is a common polymorphism C825T (rs5443), located on chromosome 12, with an exchange from cytosine to thymidine, producing three possible genotypes (i.e., CC, TC, and TT). The 825T allele is associated with alternative splicing of the gene and its protein activity [18]. Previous studies investigated the association of C825T with FD, with conflicting results reported [14, 15, 19, 20]. Therefore, in this study, we performed meta-analysis to assess the association of C825T with FD.

Methods

Search Strategy and Study Selection

We did an extensive literature search in PubMed, Cochrane Library, Google Scholar, and Web of Knowledge in November, 2012 for studies on the association of genetic variants in *GNβ3* with FD. Search terms can be found in the supplementary file. The following inclusion criteria were used in determining study eligibility: (1) studies on human subjects; (2) outcomes of interest include FD; and (3) report of genotype data of individual genetic variants in *GNβ3* in participants with and without FD [or provided odds ratios (OR) and their variances]. All potentially relevant publications were retrieved and evaluated for inclusion. We also hand-searched references of all relevant publications for additional studies missed by the database search. Only studies published in the English language were included in our analysis. Two authors (F.D. and Y.L.) performed the search independently. Disagreement over eligibility of a study was resolved by discussion until a consensus was reached.

Data Extraction

Two reviewers (Y.L. and S.G.) independently extracted the following data according to a pre-specified protocol: first author's name, year of publication, characteristics of the study participants (sample size, mean age, percentage of male and race/country of participants), genotype data for subjects with and without FD (or OR, and the corresponding variances), and the genetic model used (additive, allelic, dominant, or recessive). Discrepancies were resolved by discussion, and extracted data were entered into a computerized spreadsheet for analysis.

Statistical Analysis

We used OR as a measure of the association between the genetic variants in *GNβ3* and FD. We used a random-effects model to calculate OR and the corresponding 95 % confidence interval (CI) if there was significant heterogeneity between the studies; otherwise, a fixed-effect model was used. For random-effects meta-analysis, the inverse of the variance of each study was used as the weight for the study. A forest plot was used to graphically represent the calculated pooled ORs and their 95 % CIs. Each study was represented by a square in the plot, the area of which is proportional to the weight of the study. The overall effect from the meta-analysis is represented by a diamond, with its width representing the 95 % CI for the estimate. Between-study heterogeneity was assessed using a Q test, and publication bias was assessed using Egger's regression test [21].

Sensitivity Analysis

We analyzed the association between C825T and subtypes of FD (PDS, EPS, ulcer, dysmotility, and non-specific FD). Meta-analyses were conducted when there were multiple studies for the analysis of each subtype. We also performed meta-analysis separately for individual ethnic groups/countries of origin (Korea, Japan, and Europe/United States).

Meta-analysis was performed using Stata 11.2 (StataCorp LP, College Station, TX, USA). All other analyses were performed using SAS v.9.3 (SAS Institute, Cary, NC, USA).

Results

Literature Search and Eligible Studies

The flow diagram in Fig. 1 adheres to the QUOROM statement and shows the selection of studies to be included in our analysis [22]. Using our pre-defined search strategy, we identified a total of 286 potential publications through our initial search. After screening the abstracts of these studies, 208 were excluded either because they were not genetic studies, not about human subjects, or not published in English. The remaining 78 studies were retrieved for more detailed evaluations, which excluded an additional 70 studies because they were not about FD or subtypes of FD, there were not sufficient data, they were meta-analyses or review studies, or the full text was unavailable despite efforts to contact the authors. This left eight potentially relevant publications (with nine studies) to be included in our analysis. Further exploration of the data from these studies excluded one more study with insufficient data. A total of eight studies met the eligibility criteria and were included in our analyses [14, 15, 19, 20, 23–26].

All qualified publications were published since 2004 and had sample sizes ranging from 89 to 829 (See Table 1). A total of 2,706 participants (718 with FD and 1,988 controls) were included in the meta-analysis. Prevalence of FD ranged from 8.2 to 56 %. Of these eight studies, three used Japanese participants, two used Korean participants, and three used participants from the USA or Europe.

Assessment of Publication Bias

Examination of the funnel plot did not reveal severe deviance from symmetry (Fig. 2). Egger's test was also used to assess publication bias, and we found no publication bias for the meta-analysis ($p = 0.572$). Assessment of

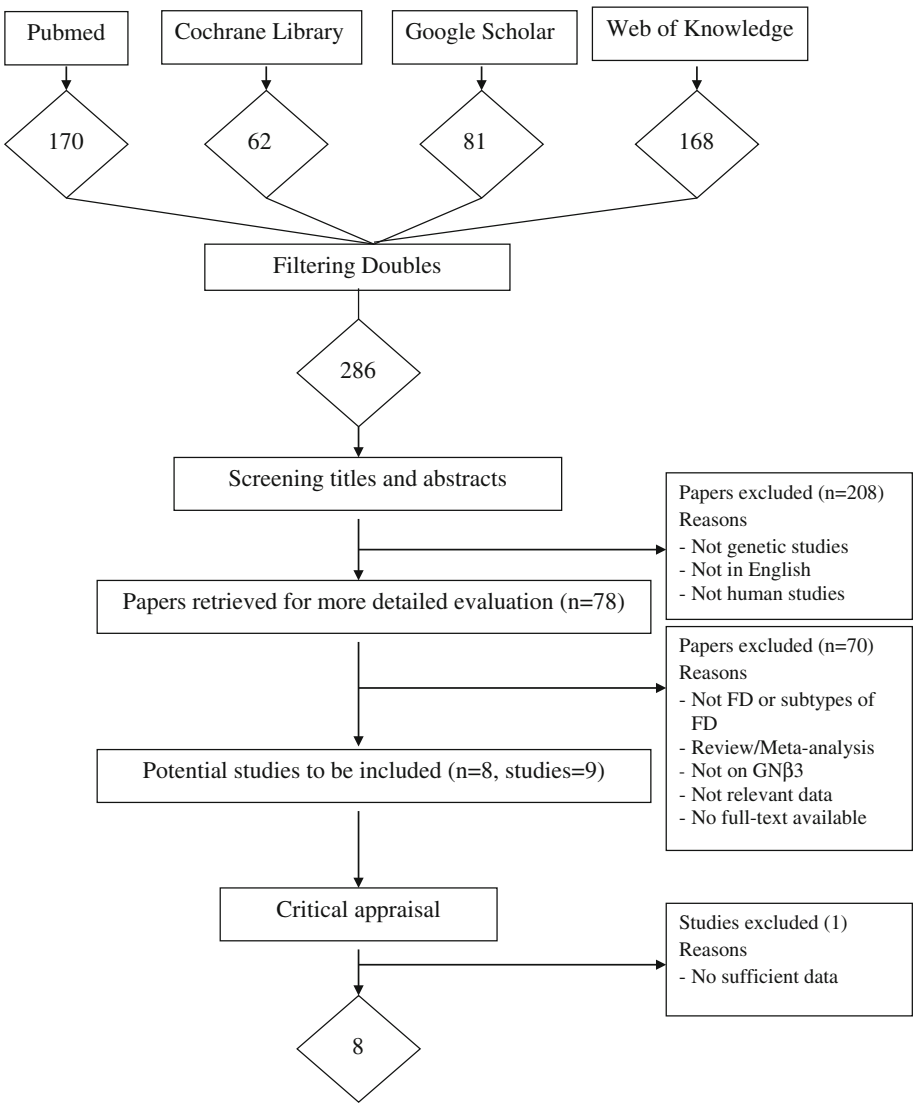

Fig. 1 Flow diagram of the selection process of the studies included in the meta-analyses. Please see "Methods" for additional details

Table 1 Basic characteristics of all studies

Study	Race/country	Definition of FD	FD			Control		
			n	Age (mean ± SD)	Male (%)	*n*	Age (mean ± SD)	Male (%)
Park et al. [26, 27]	Korean	Rome III	102	11.2 ± 3.6	31.3	148	10.8 ± 3.9	54.7
Kim et al. [20]	Korean	Rome III	167	49 ± 15	37.1	434	47 ± 15	38.5
Shimpuku et al. [23]	Japanese	Rome III	74	59.2 ± 14.2	48.6	64	37.2 ± 9.13	89.1
Oshima et al. [19]	Japanese	Rome III	68	43 (23–69)[a]	36.8	761	45 (19–83)[a]	42.7
Van-Lelyveld et al. [24]	Netherlands/ Caucasian	Rome II	112	42.3 ± 1	28	336	41.9 ± 1	28
Tahara et al. [17, 25]	Japanese	Rome II	89	60.1 ± 13.1	73	94	61.1 ± 13.1	69
Camilleri et al. [15]	USA	Rome II	50	55 (34–79)[a]	54	39	60 (37–81)[a]	44
Holtmann et al. [14]	Germany/Caucasian	Rome II	56	46.4 ± 1.9	35.7	112	44.4 ± 1.3	35.7

FD functional dyspepsia, *SD* standard deviation

[a] Range of age

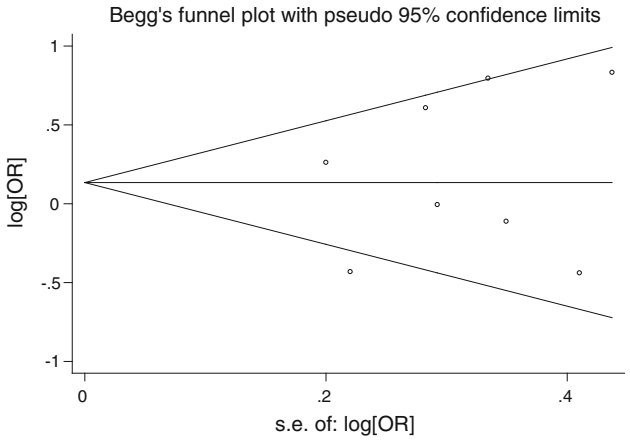

Fig. 2 Funnel plot for meta-analysis of C825T in *GNB3*. The *x*-axis is the standard error of the log-transformed odds ratio *s.e. of log[OR]*, and the *y*-axis is *log[OR]*. The *horizontal line* in the figure represents the overall estimated log-transformed OR. The two *diagonal lines* represent the pseudo 95 % confidence limits of the effect estimate

publication bias for the meta-analysis of the association of C825T with subtypes of FD is not very meaningful due to limited number of studies included in the corresponding meta-analysis.

Association of C825T with FD

We calculated the association between C825T and FD assuming four different genetic models (additive, allelic, dominant, and recessive). Due to space limits, we present the results for CC versus TC and TT, which was used by many studies. Results obtained using other models can be found in the supplementary file.

Of the eight studies included in our meta-analysis, only two show significant association between C825T and FD,

Table 2 Meta-analysis of the association of FD and C825T in *GNB3*

Study	Case	Control	OR	*p*
Park et al. [26, 27]	102	148	1.84 (1.06–3.20)	0.031
Kim et al. [20]	167	434	1.30 (0.88–1.92)	0.187
Shimpuku et al. [23]	74	64	0.65 (0.29–1.44)	0.292
Oshima et al. [19]	68	761	0.99 (0.56–1.76)	0.973
Van-Lelyveld et al. [24]	112	336	0.65 (0.42–1.00)	0.052
Tahara et al. [17, 25]	89	94	0.89 (0.45–1.77)	0.739
Camilleri et al. [15]	50	39	2.30 (0.98–5.42)	0.056
Holtmann et al. [14]	56	112	2.22 (1.15–4.27)	0.017
Total	718	1,988	1.19 (0.84–1.67)	0.328

CC versus TC and TT

with another two studies indicting marginal association (Table 2). Specifically, one study [14] indicated that CC carriers had increased risk of FD (OR 2.22, 95 % CI 1.15–2.47), as confirmed by a recent study (OR 1.84, 95 % CI 1.06–3.20) [26]. The other two studies reported marginal association of C825T with FD, but the direction of effect is inconsistent [15, 24]. Our meta-analysis indicates no significant association of C825T with FD (OR 1.19, 95 % CI 0.84–1.67, $p = 0.328$; Fig. 3). However, the association is significant under an additive model (reference genotype: CC; OR 0.59, 95 % CI 0.38–0.92, $p = 0.018$; Supplementary Table 1).

Sensitivity Analysis

Sensitivity analysis reveals significant association between C825T and dysmotility ($p = 0.001$), but the association with other subtypes of FD is not significant, probably due to limited sample size in the calculation. We found significant association of C825T with FD in Korean participants (OR 1.46, 95 % CI 1.06–2.01, $p = 0.021$) but not in

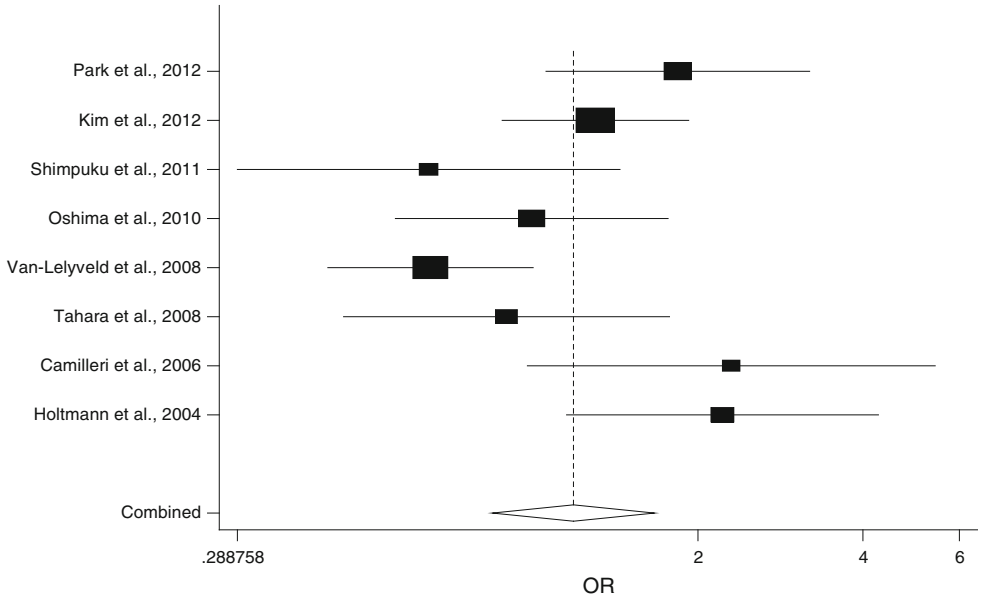

Fig. 3 Forest plot for meta-analysis of C825T in *GNB3*. Each study is represented by a *square* and a *line*. The mid-point of the *square* is the point estimate of that study, and the area of the *square* is proportional to the weight of the study. The width of the *line* represents the 95 % confidence interval (CI) of the estimate of the study. The overall effect from meta-analysis is represented by a *diamond* whose width represents the 95 % CI for the estimated OR. The *vertical dashed line* is the line of no effect

Japanese (OR 0.87, 95 % CI 0.59–1.28, $p = 0.481$) or Europe/United States participants (OR 1.43, 95 % CI 0.56–3.61, $p = 0.453$).

Discussion

In this paper, we conducted a systematic literature search for publications on the association of genetic variants in GNβ3 with FD. Our results show no evidence for the association between 825CC genotype and FD. The association is, however, significant under the additive model. We also detected a significant association of this SNP with dysmotility. To the best of our knowledge, this is the first meta-analysis on the potential association of C825T with FD.

Studies on the association between C825T and FD have reported inconsistent results. The most significant results were reported in a study comprising 56 patients with FD and 112 controls ($p = 0.017$) [14]. This study recruited Caucasian participants from across Germany. The positive findings in this study could not be replicated by most other subsequent studies except for a recent one which reported a similar effect size in participants from Korea [26]. Inconsistencies of the results among these studies might also be due to the different genetic models used by individual studies. Although most studies compared the frequency of homozygous CC carriers versus T-allele carriers, other studies also reported results using other genetic models [19, 20, 25]. Our meta-analysis found no significant association of 825CC with FD. However, C825T shows significant association with FD under an additive model (Supplementary Table 1). Another explanation for the inconsistencies might be the adjustment for different confounding factors: some studies did not control for any confounding factors, while others controlled for age and/or sex [14, 20]. Factors such as sample size, heterogeneity of the disease, or sample selection might also contribute to the conflicting results [27]. Specifically, one study recruited very young participants (aged 4–18 years) [26] while other studies used data from older participants. Another important factor accounting for the conflicting results might be the difference in genetic composition of participants among different races/ethnic groups. The frequency of the C825TT allele is approximately 50 % in Canadian Oi-Cree Indians [28], almost twice as high as in Germany [29]. Consequently, our sensitivity analysis found significant association of C825T with FD in Korean participants, but not in participants from Japan or Europe/United States. However, these results should be interpreted with caution because limited sample size may lead to insufficient power in detecting a significant association.

Although the two subtypes of FD (dysmolitity and PDS) employed different criteria in diagnosis, they share the same disturbed gastric motor function, including antral hypomotility, delay in gastric emptying, and impaired gastric accommodation. The two studies on dysmotility both reported significant and consistent association with

Table 3 Association of C825T with subtypes of FD: (a) Rome III, (b) Rome II

Symptom	Study	Case	Control	OR (95 % CI)	*p*
(a) Rome III					
PDS	Oshima et al. [19]	40	761	0.99 (0.48–2.07)	0.989
EPS	Oshima et al. [19]	43	761	0.68 (0.31–1.50)	0.340
(b) Rome II					
Ulcer	Holtmann et al. [14]	16	112	1.84 (0.64–5.31)	0.256
	Camilleri et al. [15]	3	39	9.00 (0.44–185.96)	0.155
	Total	19	151	2.19 (0.81–5.94)	0.123
Dysmotility	Holtmann et al. [14]	40	112	2.66 (1.26–5.65)	0.011
	Camilleri et al. [15]	21	39	4.14 (1.26–3.57)	0.019
	Total	61	151	3.02 (1.60–5.70)	0.001
Non-specific	Camilleri et al. [15]	26	39	1.29 (0.48–3.50)	0.612

CC versus TC and TT

C825T, and meta-analysis indicates that CC genotype carriers had a twofold increased risk of having dysmotility (Table 3b) [14, 15]. Only one study examined the genetic association of C825T with PDS and found no significant association [19]. The study on PDS was limited to participants in Japan, while the studies on dysmotility were done in the USA, and therefore might represent different genetic architectures across populations. More studies are certainly needed to quantify the association of C825T with PDS.

Few other genetic variants in *GNβ3* have ever been studied. Our extensive literature search found only one study that reported the genotype data of an additional SNP A814G in *GNβ3* with FD [15]. There was no significant association of A814G with FD (OR 1.42, 95 % CI 0.39–5.26, $p = 0.596$). The finding is not conclusive because of limited sample size ($n = 89$). Knowledge about this genetic variant is scarce.

Heterotrimeric G-proteins, composed of α, β, and γ subunits, are essential for stimulus–response coupling of a majority of known membrane receptors that are linked to intracellular effector systems [30–33]. Many hormones, neurotransmitters, and sensory stimuli, which have been implicated in the generation of dyspeptic symptoms, exert their effects on cells through binding to G-protein coupled receptors [24]. Changes in G-proteins could lead to disease by blocking or enhancing intracellular signal transduction [34]. The common polymorphism C825T in *GNβ3* has been reported to be associated with a number of disorders, including obesity [35, 36], hypertension [29, 37, 38], coronary heart disease [39], stroke [40], insulin resistance [41], and depression [42]. The 825T allele is associated with enhanced G-protein activation and thereby altered signal transduction response [29]. It is associated with alternative splicing of the gene, resulting in a truncated deletion—but functionally active splicing variant—of 41 amino acids [29]. This can result in motor or sensory abnormalities of the gastrointestinal tract, which might be the pathophysiological mechanism underlying FD [43]. It was also reported that the T allele in C825T was associated with lower fasting gastric volume [44], which was found to contribute to symptoms in patients with FD [45]. The effect of C825T on gastrointestinal motor and sensory functions warrants further research to uncover the physiologic mechanism underlying the association.

Our study has some limitations. Although we conducted an extensive literature search, the number of participants included in our meta-analysis is limited, especially in the sensitivity meta-analysis to assess the association with FD subtypes. We would like to emphasize that the findings from these small number of studies are not conclusive and warrant further validation. Specifically, although we detected significant association of C825T with dysmotility, the sample size (total participants: 212) is too limited to reach a conclusive finding. Further studies are warranted to validate our findings and to explore the potential mechanisms underlying the association, particularly studies with larger sample sizes that more intensively re-sequence genetic variants in *GNβ3* to rigorously evaluate their cumulative contribution to disease pathogenesis. The definition of FD is different across studies, with earlier publications adopting Rome II criteria and later ones adopting Rome III criteria (Table 1). We cannot test the publication bias for sensitivity analyses due to the limited number of studies. This might lead to bias in the data and possibly influence the results of our analysis. The appropriate model for testing the genetic association of *GNβ3* with FD is not clear. Further biological studies are needed to elucidate the mechanism linking *GNβ3* to FD in order to provide more evidence on the correct functional genetic model.

In summary, we did a systematic literature search and performed the first meta-analysis on the association of C825T in *GNβ3* with FD. Under a dominant genetic model, we found no evidence of association between C825T and FD, but the association is significant if an additive model is used. We found that this genetic variant is significantly associated with dysmotility-like symptoms and symptoms in PDS.

Further studies, particularly studies with larger samples sizes, are needed to validate our findings and to explore the potential mechanisms underlying the association.

Acknowledgments Dr. Yang's research was supported by R01AG036042 and the Illinois Department of Public Health.

Conflict of interest None.

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